Essentials of Anatomic Pathology

Edited by

Liang Cheng, MD

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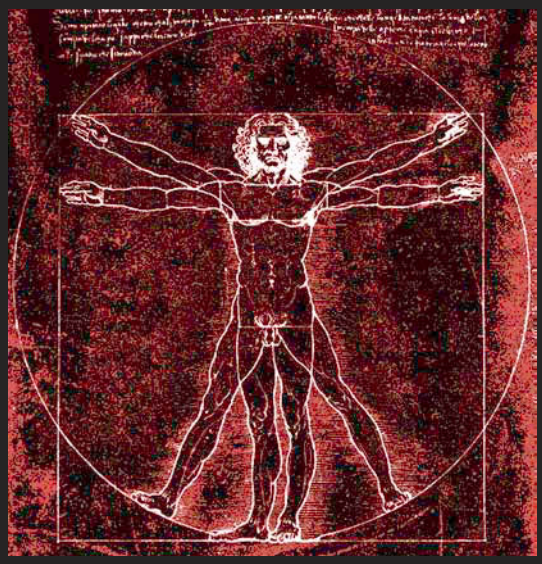

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PREFACE

The past decade has witnessed remarkable progress in surgical pathology. The ability of contemporary surgical pathologists to reach a definite diagnosis has been greatly enhanced by innovative immunohistochemical techniques and markers. Information useful in the practice of pathology may not be readily accessible in the daily sign-out. An up-to-date handbook that contains information relevant to the establishment of accurate diagnoses would be of immense practical value. Therefore, we have concentrated on setting forth basic diagnostic criteria and differential diagnoses that will help our readers ensure accurate diagnoses.

Essentials of Anatomic Pathology is intended to provide a concise review of anatomic pathology for all pathologists in training as well as practicing pathologists, integrating the many recent advances in diagnostic surgical pathology. The book is organized to allow easy reference for daily practice, and is intended to aid residents who are preparing for Anatomic Pathology Boards and in-service examinations. It will prove a useful resource not only for medical students, but also for anyone interested in pathology.

Part I covers general anatomic pathology, including diagnostic molecular pathology, human genetic disorders, microbiology for surgical pathologists, diagnostic electron microscopy, forensic pathology, and cytopathology. Part II is classified by organ system, and covers all the important diagnostic features of common medical diseases and tumors. The pertinent clinical information, salient diagnostic features, relevant ancillary data (for example, immunohistochemical profiles), main differential diagnoses, and most recent tumor-staging information are presented for each disease, in a consistently user-friendly format. We believe that this approach will provide easy access to information essential for sign-out. It is not meant as a substitute for lavishly illustrated, comprehensive textbooks, but to complement them as a practical aid. We hope that this text will materially aid in continuing efforts to recognize, understand, and accurately interpret the gross and light microscopic findings in anatomic pathology specimens.

We thank the staff at Humana Press, Thomas H. Moore, James Geronimo, Mary Jo Casey, Wendy Kopf, and Humana Press' composition department, for their assistance in the preparation of this work.

We earnestly solicit constructive criticism from colleagues so that the utility of our book can be expanded and improved to its maximum potential in future editions.

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Part I

General Pathology

Chapter 1

Molecular Diagnostic Pathology

Richard Press, MD, PhD,
and Charli Nesbitt, MS, CGC

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MOLECULAR DIAGNOSIS IN ONCOLOGY

Introduction

- Consistent nonrandom genetic alterations are the hallmark of the majority of hematopoietic tumors (Table 1–1) (also see Chapters 7 and 8)
- Standard histologic and immunophenotypic analyses are sufficient for the diagnosis of the vast majority of leukemias and lymphomas. However, diagnostically difficult cases may require molecular tools to assist with:
  - Diagnostic subclassification: B versus T cell, diffuse versus follicular, etc.
  - Prognostic subclassification: to predict responses to appropriate therapy
  - Detection of minimal residual disease: unique molecular markers often useful to monitor response to therapy, early detection of relapse, or appropriate "purging" of pre-transplant therapeutic bone marrow
- Tumor-specific genetic rearrangement events can be detected by:
  - Standard cytogenetic methods
    - Low-sensitivity detection method
    - Nonspecific: target genes determining biologic behavior not analyzed
    - Tumor cell metaphase spreads are typically of poor quality
    - Slow turnaround time: for cell growth and analysis

DNA Diagnostic Methodologies

- Southern blot assay and/or polymerase chain reaction (PCR) assay

Southern Blot Assay

- Requires microgram amounts of good-quality, high-molecular-weight DNA
- DNA is digested with a restriction enzyme to produce fragments of known size
- Fragments are size-separated on a gel and transferred to a membrane
- Membrane is hybridized to a labeled DNA probe that is specific to the disease-causing gene. The size of the hybridizing fragment is determined by the migration length through the gel
- Fragment size differences between control and patient samples can yield information about genetic alterations causing disease

Benefits

- Useful to detect and measure gross size changes in genes

Limitations

- Unable to accurately determine small changes or point mutations
- Need relatively large amounts of high-quality non-degraded DNA

PCR Assay

- Rapid enzymatic amplification of a fragment of DNA using short oligonucleotides that sequentially anneal to opposite strands and prime synthesis of the complementary DNA
- Requires nanogram amounts of intact or partially degraded DNA (from blood or fresh frozen or fixed tissue)
- Products of PCR are visualized directly on a gel (or after Southern blot hybridization with a gene-specific probe). The size of the PCR product yields information about the gene region between the 2 primers

Benefits

- Less DNA required (compared to Southern blot)
- DNA can be of poorer quality (i.e., fixed tissue)
- Turnaround time for results is generally shorter
- Accurate sizing

Limitations

- Not useful for large gene expansions, which may fail to amplify with enzyme-mediated PCR

Immunoglobulin and T-Cell Receptor Gene Rearrangements

Theory

- Genetic rearrangements in the immunoglobulin and T-cell receptor genes determine the diversity of the immune response (Table 1–2)
  - Cell-specific gene rearrangements can be used as a molecular "signature" of a clone of B or T cells
  - Molecular methods to detect these gene rearrangements can determine the presence of a "clone" of identical lymphocytes—a hallmark of neoplasia
    - Useful for both primary diagnosis and post-therapy disease monitoring

Immunoglobulin Heavy Chain (IgH) Gene Rearrangements

- Unique V, D, and J region DNA rearrangements in each B cell generate the variable regions (antigen-binding domains) of the Ig light and heavy chain
- 1st rearrangement: DH to JH
  - With the insertion of a random number of nucleotides (N) between DH and JH
- The VH gene then joins to the DHNJH segment

Table 1–1. Genetic Alterations in Hematopoietic Tumors Amenable to Molecular Diagnosis

Translocation	*Disease correlation*	*Genes involved*
Chromosome 14q32 rearrangements	B-cell lymphomas	IgH (Jh) with multiple partners (oncogenes)
Ig light chain rearrangements: κ (chrom 2) or λ (chrom 22)	B-cell lymphomas	κ or λ light chains with multiple partners
t(8;14)	Burkitt's lymphoma (high grade)	c-myc/IgH
t(14;18)	Follicular B-cell lymphomas (~90%); Diffuse B cell lymphomas (~20%)	IgH-bcl-2
Bcl-6 translocations (chromosome 3q27)	Diffuse large-cell lymphomas (~40%); Diffuse mixed lymphomas (10%)	Bcl-6 with IgH and other partners
t(11;14)	Specific for mantle-cell lymphoma	Bcl-1 (cyclin D1)- IgH
T cell receptor α or δ (chromosome14q11–12)	T-cell lymphomas	TCR α or δ with multiple partners
T cell receptor β or γ (chromosome 7)	T-cell lymphomas	TCR β or γ with multiple partners
t(2;5)	Anaplastic large-cell lymphomas (Ki-1/ CD30 positive)	Alk-NPM
t(9;22) (Philadelphia chromosome)	CML (95%); ALL (25%) (poor prognosis)	Abl–bcr (tyrosine kinase)
Inversion (16)	AML M4Eo (good prognosis)	CBFβ-MYH11 (transcription factor)
t(1;19)	Pre-B ALL (poor prognosis)	PBX1-E2A (transcription factor)
11q23 rearrangements	Infant ALL (80%); Post-therapy AML; Poor prognostic indicator	MLL (aka HRX) joined to multiple loci (chrom 19, 4, others)
t(8;21)	AML (15%) (often M2) (good prognosis)	ETO-AML1 (transcription factor)
t(12;21)	B lineage ALL (good prognosis)	TEL-AML1 (transcription factor)
t(15;17)	AML M3 (APL) (retinoid responsive)	PML-RARα (transcription factor)

  - With the insertion of a random number of nucleotides (N) between VH and DH
- The VHNDHNJH segment then joins with a CH constant region gene and its switch region to generate VHNDHNJHCH
- VDJC is transcribed and translated into an Ig heavy chain
- Failed rearrangements are followed by attempts at rearranging the second IgH allele
- Approximately 10^{14} different variable region configurations exist (for immune diversity)

T-Cell Receptor (β) *Gene Rearrangements*

- Mechanism of TCRβ VDJC rearrangement is very similar to IgH (above)
- TCRβ VDJC is transcribed and translated into a T-cell receptor β protein
- Failed rearrangements are followed by attempts at rearranging the second T-cell receptor β allele

Antigen Receptor Gene Rearrangements as Markers of Clonality

Table 1–2. Ig and T-cell Receptor Gene Rearrangements in Normal Lymphocyte Development

In the germline (non-rearranged state), the Ig and TCR genes are composed of discontinuous coding regions:

Gene	*B-Cell IgH Locus (heavy chain) (chromosome 14q32)*	*T-Cell Receptor β Locus (chromosome 7q34)*
V (variable region)	>200 V_H genes	~100 V_b genes
D (diversity region)	30–40 D_H genes	2 D_b genes
J (joining region)	6 J_H genes	13 J_b genes
C (constant region)	12 C_H genes	2 C_b genes

Principle: Each individual lymphocyte contains a uniquely rearranged DNA pattern within the IgH or TCRβ genes

- Routine molecular methods (Southern blot and/or PCR) are not sufficiently sensitive to detect VDJ genetic rearrangements in a single cell
- Molecular analysis of polyclonal lymphocyte populations (reactive lymph nodes) will then show a heterogeneous mixture of unique (each individually invisible) "single-cell" signals
  - The gel electrophoresis pattern will reveal a very faint "smear" consisting of many hundreds of heterogeneously sized DNA fragments
  - The size heterogeneity in the VDJ DNA fragments of non-clonal lymphocytes results from:
    - Many differently sized V, D, J, or C genes being represented
    - Insertion of a random number of N nucleotides between VD and DJ
    - Imprecise exonuclease-mediated gene recombination
- Clonal lymphocyte populations (i.e., lymphoma) contain, by definition, thousands of cells with the identical IgH (B-cell) or TCRβ (T-cell) gene rearrangement
  - Molecular analysis (Southern or PCR) will then show a single detectable non-germline VDJ rearrangement (from the predominant clone of cells)
  - The gel electrophoresis pattern will reveal a distinct BAND (reflecting the predominant clone) often together with a faint "smear" (the background polyclonal lymphocyte population)

Southern Blot Detection of IgH and TCR Gene Rearrangements

- Requires fresh or frozen tissue (not fixed)
  - Tissues should be trimmed of "non-tumor" tissue in order to increase diagnostic sensitivity
- Requires >10^7 cells (>1 mg tissue)
- Tissue DNA is digested with restriction enzyme and electrophoresed
  - Typically use 2–3 simultaneous enzymes to increase diagnostic sensitivity
  - Southern blot probed with immunoglobulin heavy chain probe (for suspected B-cell lesions) and/or T-cell receptor β probe (for suspected T-cell lesions)
    - Usually both probes are used simultaneously
- Distinct non-germline rearranged bands (not smears) imply a monoclonal lymphocyte population, suggesting malignancy
- Sensitivity: Southern blot will detect a rearranged band if the lymphocyte clone represents >1% to 5% of the cells analyzed
  - Tumor cell load of <1% of total cells will yield a false negative signal
  - Rearrangement with IgH or TCR probe usually (not always) suggests tumor cell lineage (B- or T-cell origin)
  - Intensity of rearranged band reflects the quantity of tumor cells
    - May be useful for estimating tumor burden
  - Southerns can also be probed with immunoglobulin light chain gene (κ or λ) probes
  - κ and λ undergo VJC gene rearrangements similar to heavy chain genes (except no D regions for light chain genes)
  - κ light chain genes rearrange after successful Ig heavy chain gene rearrangement
  - λ light chain genes rearrange only after both κ alleles fail to successfully rearrange

Limitations

- Low sensitivity: tumor cell burden below 1% to 5% may not be detected
- Long turnaround time: 2–5 days
- Requires significant amounts of DNA (can be problem-

atic for skin and other small lesions)

- These limitations can be overcome with PCR methods

PCR-Based Detection of IgH and TCR Gene Rearrangements

- Requires fresh, frozen, or fixed tissue
- Tissues should be trimmed of "non-tumor" tissue to increase diagnostic sensitivity
- Requires only >104–105 cells (not many)

IgH PCR for B Cell Clonality Determinations

- Sense PCR primers: from conserved sequences within VH region (framework I, II, or III)
- Antisense PCR primers: from conserved sequences within JH region
- Depending on primer pair chosen, PCR product band from a clone of rearranged B cells will be 70–380 bp in length
- VH and JH regions in germline (unrearranged) cells are too distant for successful PCR amplification and yield no PCR product
  - Only rearranged cells (clones) yield detectable PCR bands
  - Gel interpretation: detectable PCR band between 70–380 bp suggests clonal B-cell population
  - Analytical sensitivity: clones of B cells representing >0.1% to 10% of all cells will yield detectable PCR band (dependent on primers, tissue source, PCR conditions)
  - Diagnostic sensitivity: only ~70% to 90% of known lymphomas will yield detectable IgH PCR products (dependent on primers, tissue source, PCR conditions, tumor type)
    - Sequence heterogeneity in VH and JH regions may prevent primer binding in some clones

T-Cell Receptor β PCR for T-Cell Clonality Determinations

- Sense PCR primers: from conserved sequences within Vβ or Dβ regions
- Antisense PCR primers: from conserved sequences within Jβ region
- Typically, a panel of multiple primer pairs is used, as any one primer pair will fail to bind to a significant minority of TCR genes
- Depending on the primer pairs chosen, the PCR product band from a clone of rearranged T cells will be 55–100 bp in length
- Vβ and Jβ regions in germline (unrearranged) cells are too distant for successful PCR amplification and yield no PCR product
  - Only rearranged cells (clones) yield detectable PCR bands
  - Gel interpretation: detectable PCR band between 55–100 bp suggests clonal T-cell population
  - Analytical sensitivity: clones of T cells representing >0.05% to 5% of all cells will yield detectable PCR band (dependent on primers, tissue source, PCR conditions)
  - Diagnostic sensitivity: only ~70% to 90% of known T-cell lymphomas will yield detectable TCR PCR products (dependent on primers, tissue source, PCR conditions, tumor type)

Advantages of PCR-Based Methods for Lymphoid Gene Rearrangements

- Rapid result—often same day as biopsy
- Increased diagnostic sensitivity (afforded by amplification technology)
- Can be used on small amounts of DNA (from smaller biopsies)
- DNA integrity can be somewhat compromised (fixed or archival tissue)

Disadvantages of PCR-Based Methods for Lymphoid Gene Rearrangements

- Consensus primers may fail to amplify some VDJ clones
- Oligoclonal cells of questionable clinical significance may generate specific bands
- No quantitative information

Clinical Utility of IgH and T-Cell Receptor Gene Rearrangement Studies

Primary Diagnosis of Hematopoietic Neoplasms

- For determining clonality in hematopoietic lesions with uncertain diagnostic criteria by standard morphology, flow cytometry, and immunohistochemistry
- Clonality usually (not always) indicates malignancy
- Benign (reactive) lesions are usually (not always) nonclonal
- Other methods to assess clonality:
  - Light chain restriction: kappa versus lambda by immunohistochemistry or flow cytometry
  - Clonal B- or T-cell markers by flow cytometry
  - Nonrandom X chromosome inactivation (females only)

IgH and TCR Gene Rearrangements in Leukemias

- B lineage ALL: ~95% have clonal IgH gene rearrangements
  ~20% have TCRβ gene rearrangements
- T lineage ALL: most have TCRβ gene rearrangements

~20% have clonal IgH gene rearrangements

- AML: ~20% have clonal IgH or TCRβ gene rearrangements (typically TdT positive cases)

Monitoring Disease Progress

- Once a clone of lymphocytes has been discovered, PCR and/or Southern blotting can be used to continually track the tumor cell clone to evaluate response to therapy (minimal residual disease)
  - Disappearance of the "tumor-specific" gel band may correlate with successful therapy
  - Reappearance of the "tumor-specific" gel band may correlate with disease relapse
  - PCR clearly more sensitive than Southern blotting for minimal residual disease determinations
- A diagnosis of lymphoma should NEVER be made using only the gene rearrangement data
- Gene rearrangement data should always be interpreted along with the accompanying clinical, histologic, and immunophenotypic data

Molecular Methods for Lymphoma Diagnosis (also see Chapters 7 and 8)

Introduction

Translocations Within the Immunoglobulin Gene in B-Cell Lymphomas

- VDJ rearrangements in IgH locus are essential for B-cell development
- Aberrant recombination events, between the IgH gene and one of a group of characteristic oncogenes, characterize many B-cell lymphoma tumors
  - Oncogene localization to "active" IgH locus causes inappropriate oncoprotein synthesis and stimulation of cell growth (or suppression of cell death) and leads directly to tumorigenesis
  - Probably involves promiscuous gene rearrangement catalyzed by the B-cell active VDJ recombinase enzyme
  - Chromosomal translocations involving chromosome 14q32 (IgH locus) are therefore common in B-cell lymphomas
    - Identification of the IgH "partner" gene aids in diagnosis and defines a tumor-specific genetic marker for future disease monitoring

Burkitt's Lymphoma (BL): t(8;14)

- 90% of BLs have characteristic t(8;14) chromosomal translocation
- t(8;14) juxtaposes IgH gene to c-myc oncogene on chromosome 8
- Some BLs have translocations between c-myc (chromosome 8) and either the κ (chromosome 2) or λ (chromosome 22) light chain genes
- Inappropriate c-myc synthesis promotes lymphomagenesis
- Diagnosis is usually apparent by histology and immuno-phenotype
  - Molecular methods are typically not required for clinical practice
  - t(8;14) detection by cytogenetic or molecular methods denotes an aggressive high-grade B-cell lymphoma with a high proliferative rate

Follicular Lymphoma: t(14;18) and the bcl-2 Gene

- t(14;18) is the most common translocation in human lymphoid tumors
  - Present in ~90% of follicular B-cell lymphomas
  - Present in ~20% of diffuse B-cell lymphomas
  - Juxtaposes IgH gene with the bcl-2 gene on chromosome 18
- bcl-2
  - lymphomas show two predominant breakpoint regions within bcl-2
    - Major breakpoint region (MBR) utilized in ~60% to 70% of tumors
    - Minor cluster region (MCR) breakpoints used in most of the other tumors
    - bcl-2 coding regions left intact by translocations
    - IgH regulatory controls stimulate inappropriate overproduction of bcl-2 protein
  - bcl-2 normal function is the suppression of apoptosis (programmed cell death)
    - B-cell bcl-2 overproduction suppresses cell death, promotes inappropriate cell survival, and thus increases the chances for secondary oncogenic genetic aberrations
- Molecular diagnosis of lymphomas with t(14:18)
  - Southern blot with MBR and/or MCR bcl-2 probe will show "novel" rearranged bands
    - May be insensitive for low tumor cell burdens
  - PCR with primer for bcl-2 (MBR and/or MCR) and primer for Jh (IgH)
    - Only cells with rearrangements (i.e., tumor cells) will show a PCR product
      - Highly sensitive: typical detection limit is 1 lymphoma cell in 10^4–10^5 background cells
      - Useful for monitoring for minimal residual disease after therapy
      - Useful for checking "purged" bone marrow prior to transplantation
    - May be overly sensitive

- Some benign lymphoid tissue (tonsils, nodes) may contain RARE bcl-2-JH positive cells: below the sensitivity limit of most PCR assays

Diffuse Large-Cell Lymphoma: Chromosome 3q27 Translocations and the bcl-6 Gene

- bcl-6 gene on chromosome 3q27 is translocated to a partner chromosome in:
  - ~40% of diffuse large-cell lymphomas
  - ~10% of diffuse mixed-cell lymphomas (large-cell component)
  - ~5% of follicular lymphomas
  - Also associated with immunodeficiency-associated lymphomas
- bcl-6 partner genes in 3q27 translocations include:
  - IgH (chromosome 14), λ light chain gene (chromosome 22q11), and others
- bcl-6 encodes a likely transcription factor that may regulate B-cell growth when inappropriately overexpressed

Mantle-Cell Lymphoma: t(11;14) and the bcl-1 Gene

- Approximately 50% of mantle-cell lymphomas carry characteristic t(11;14)(q13;q32)
  - partner genes are IgH (chromosome 14) and bcl-1 (chromosome 11)
- bcl-1 is also known as cyclin D1
  - juxtapositioning near IgH causes inappropriate overexpression of bcl-1/cyclin D1
  - Cyclin D1 normally functions to inactivate (phosphorylate) the tumor-suppressing retinoblastoma protein Rb, thus preventing its suppression of cell cycle progression
    - Overexpressed cyclin D1 thus promotes inappropriate cell growth
  - Overexpressed cyclin D1 may be a specific (but insensitive) marker for mantle-cell lymphoma
    - Alterations can be detected by immunohistochemistry or molecular methods (PCR and/or Southern blot)

Genetic Rearrangements in T-Cell Lymphomas

- T-cell lymphomas: typically less common, more aggressive than B-cell lymphomas
  - A consistent theme in T-cell lymphomas is translocation events involving one of the highly expressed T-cell receptors
    - TCR α or δ on chromosome 14
    - TCR β or γ on chromosome 7
    - Partner genes are typically transcription factors whose expression is dysregulated by TCR juxtapositioning

Anaplastic Large-Cell Lymphoma: t(2;5) and the ALK-NPM Fusion Gene

- t(2;5) is found in many cases of anaplastic large-cell lymphoma
- Typical advanced disease stage, skin involvement, chemotherapeutic responsiveness
- These tumors typically express Ki-1 or CD30
- NPM is a chromosome 5 nucleolar phosphoprotein gene (with lymphoid expression)
- ALK is a chromosome 2 insulin receptor-like protein kinase (normally not expressed in T cells)
- NPM-ALK fusion protein in tumor cells has active kinase activity
  - aberrantly overexpressed NPM-ALK kinase has direct transforming activity
- Gene rearrangement can be detected by cytogenetics or molecular methods (PCR and/or Southern blot)
- Useful for proper diagnosis and proper therapy

Molecular Methods for Leukemia Diagnosis (also see Chapters 7 and 8)

- Specific chromosomal abnormalities can be identified in over 90% of ALL, AML, and CML cases (but in only ~60% of CLL cases)
- Chromosomal translocations can be identified by cytogenetic or molecular diagnostic methods

t(9;22)(q34;q11) (Philadelphia Chromosome): bcr-abl and CML

- t(9;22) occurs in ~95% of CML cases
  - Also present in ~25% of adult B lineage ALL and 5% of childhood ALL
    - Presence of t(9;22) in ALL predicts poor prognosis
  - Translocation involves the ABL tyrosine kinase proto-oncogene on 9q34 and the BCR gene (breakpoint cluster region) on 22q11
  - Results in aberrant expression of a bcr-abl fusion protein with enhanced tyrosine kinase (and transforming) activity
- Two predominant breakpoint regions within bcr:
  - Major breakpoint cluster region (M-bcr) in most CML cases and approximately half of ALL cases
    - Leads to synthesis of a 210 kD bcr-abl kinase
  - Minor breakpoint cluster region (m-bcr) (further upstream in bcr) in most pediatric ALL cases and approximately half of adult ALL cases
    - Leads to synthesis of shorter 190 kD bcr-abl kinase

Diagnostic Methods

- Routine cytogenetics
  - Insensitive, slow, nonspecific, technically difficult

- Fluorescence in situ hybridization (FISH) with bcr and abl probes
- Southern blot analysis with bcr probes
  - bcr-abl translocation creates novel tumor-specific Southern blot bands
  - Useful for primary diagnosis in "difficult" cases (cytogenetically negative)
  - Slow, relatively insensitive (1% to 5% tumor cell load) and requires abundant DNA
- RT-PCR from tumor cell RNA
  - with an abl primer and a bcr primer (M-bcr and/or m-bcr)
    - Only tumor cells (with juxtaposed bcr and abl) yield PCR signal
    - Requires only small amounts of tissue RNA; fast turnaround
    - Extremely sensitive tumor cell detection
      - Useful for monitoring minimal residual disease
      - bcr-abl reappearance after therapy predicts clinical relapse

t(1;19)(q23;p13): E2A/PBX1 and Pre-B Cell ALL

- t(1;19) occurs in ~25% of ALLs with pre-B (cytoplasmic Ig) immunophenotype
  - Most common nonrandom translocation in pediatric B-lineage ALL
  - Predicts poor prognosis and need for more aggressive treatment
- t(1;19) fuses the E2A transcription factor (chromosome 19) with the PBX1 transcription factor (chromosome 1)
  - Creates E2A-PBX1 fusion protein, a transcription factor with direct transforming activity
- Detected by cytogenetics (less sensitive) or RT-PCR
  - Some cases have t(1;19) by cytogenetics but no E2A-PBX1 (by RT-PCR)
    - These cytogenetic false positives (unlike those with detectable E2A-PBX1) have a good response to standard therapies

Chromosome 11q23 Rearrangements

- 11q23 rearrangements are found in ~80% of ALL cases in infants
- 11q23 rearrangements are also common in post-chemotherapy secondary AMLs
  - Especially after topoisomerase inhibitor therapy
  - Secondary AMLs often show monocytic features (M4 or M5)
  - Presence of 11q23 rearrangements predicts poor response to standard therapies
- Breakpoint locus on 11q23 codes for the MLL transcription factor (also known as HRX)
- Common reciprocal translocation loci include 19p13 (ENL gene) and 4q21
  - The resulting chimeric transcription factors contribute to cell transformation
- Detectable by cytogenetics, Southern blots (as partner proteins often heterogeneous), or RT-PCR (if partner gene is known)
- Cytogenetics are often negative in infant ALLs with MLL gene rearrangements by Southern blot

AML1 Gene Rearrangements: t(8;21) (AML1-ET0) and t(12;21) (TEL-AML1)

- Chromosome 21q22 is a common site for rearrangements in both ALL and AML
  - Breakpoint locus is AML1, a transcription factor
- t(8;21) fuses AML1 with ETO (chromosome 8) to create AML1-ETO fusion protein
  - Also an aberrant transcription factor
  - AML1-ETO rearrangements found in ~15% of AML cases (often M2)
  - Predicts good response to therapy
  - Detectable by cytogenetics, Southern blot, or RT-PCR
- t(12;21) fuses AML1 with TEL (chromosome 12) to create TEL-AML1 fusion protein
  - TEL-AML1 rearrangements found in ~25% of B lineage ALLs
    - A common genetic lesion in pediatric ALL (~20%)
    - Imparts good prognostic features
    - Only rarely detectable by standard cytogenetics (submicroscopic)
    - Requires molecular methods (PCR and/or Southern) for sensitive detection

Inversion 16: CBFb–MYH11

- Inv(16)(p13q22) is found in ~10% of AML cases
  - Typically associated with myelo-monocytic differentiation with bone marrow eosinophilia (FAB M4Eo)
  - Usually a good prognostic indicator
  - inv(16) fuses CBFβ gene (q22) (a transcription factor) with MYH11 (p13) (smooth muscle myosin heavy chain)
    - Dysregulation of transcription promotes leukemogenesis
  - Detected by cytogenetics or RT-PCR

t(15;17): PML-RARa and Acute Promyelocytic Leukemia

- t(15;17) is the hallmark of acute promyelocytic leukemia (APL or AML M-3)
  - Patients often have coagulopathies

- M3 subtype typically responds favorably to retinoid therapy
- t(15;17) joins the gene for the retinoic acid receptor alpha (RARα) (on 17q21) (a retinoid regulated transcription factor) with the promyelocytic leukemia (pml or myl) gene (chromosome 15q21)
- the PML-RARα fusion transcription factor has altered activity and promotes leukemogenesis

- Primary diagnosis is by cytogenetics (typically) or molecular methods
- RT-PCR (with primers spanning the breakpoints) is useful for detecting minimal residual disease after all-trans retinoic acid therapy
  - Persistent PCR positivity after treatment predicts relapse
  - Persistent PCR negativity after treatment predicts continued remission

BRCA1, BRCA2 (Breast Cancer Susceptibility Genes)

Introduction

- Mutations in the breast cancer susceptibility genes, BRCA1 and BRCA2, account for approximately 5% to 10% of all cases of breast cancer
- Diagnosis of breast cancer is (and will continue to be) based solely on histopathology
- Identification of a mutation in one of the two breast cancer susceptibility genes, BRCA1 or BRCA2, increases the risk of an individual developing breast cancer over the course of a lifetime, but certainly does not guarantee an eventual tumor
- Mutations are identified by direct DNA-based methods. Because the spectrum of different possible mutations is so high, DNA testing requires "gene-scanning" methods such as allele-specific oligonucleotide testing, protein truncation testing, conformation sensitive chromatography or gel electrophoresis, single-strand conformation polymorphism analysis, direct gene sequencing, or a combination of the above methodologies

Genetics

BRCA1

- Inheritance: autosomal dominant (i.e., a single mutant allele predisposes to increased cancer risk)
- Locus: BRCA1 gene mapped to chromosome 17q21
- Protein product: BRCA1 is a nuclear protein with a functional role in DNA damage repair and maintenance of genomic stability
- BRCA1 is a classic tumor suppressor protein that is capable of inhibiting both cell growth and tumorigenesis
- Mutations that abolish this normal growth-suppressive and genome "gatekeeper" function lead to an inherited cancer predisposition syndrome
- 20% to 50% of women with early onset familial (generally described as two or more first degree relatives affected) breast cancer have BRCA1 mutations
- Up to 70% of women with familial breast/ovarian cancer have BRCA1 mutations

BRCA2

- Inheritance: autosomal dominant
- Locus: BRCA2 gene mapped to chromosome 13q12
- Approximately 15% of women with familial breast/ovarian cancer have BRCA2 mutations
- BRCA2 is also (like BRCA1) involved in DNA repair and maintenance of genomic stability

Prevalence

- Normal population prevalence of BRCA1/2 mutations is unknown (but is much higher in certain ethnic minorities such as Ashkenazi Jews, as indicated in Table 1–3)
- In families with >3 cases of early onset breast cancer, disease was linked to BRCA1 in an estimated 50% of families, to BRCA2 in ~30% of families, and to neither gene in ~20%, suggesting other predisposition genes
- In total, approximately 5% to 10% of all cases of breast cancer are thought to be due to mutations in the breast cancer susceptibility genes
- Other combinations or patterns of expression of multiple other genes (shown with gene arrays) may predispose to breast cancer.

Mutations

- >300 different mutations have been identified in BRCA1 in cancer patients
  - These mutations abolish normal BRCA1 function
- >100 different mutations have been identified in BRCA2 in cancer patients

Phenotype: Genotype Correlation

- Breast cancers in BRCA1/2 carriers are a higher overall histologic grade (on average) than other sporadic cases, and are more likely to be estrogen receptor and progesterone receptor negative
- Medullary or atypical medullary carcinoma may be found more often in BRCA1 mutation carriers
- There is increased risk for bilateral breast cancer in BRCA1/2 mutation carriers

Onset/Progression

- BRCA1/2 asymptomatic carriers have an approximate 80% lifetime risk of developing breast cancer:
  - 1/200 risk by the age of 40
  - 1/50 by the age of 50
  - 1/25 by the age of 60
- BRCA1/2 asymptomatic carriers have an approximate 40% lifetime risk of developing ovarian cancer

Table 1–3. BRCA1 and BRCA2 Mutations in Ashkenazi Jewish Women

Gene	*Mutation*	*Frequency in normal Ashkenazi Jewish population*
BRCA1	185delAG*	1.0%
	5382insC	0.1%
BRCA2	6174delT*	1.4%

**Either the 185delAG or 6174delT mutation has been found in approximately 25% of Jewish women with early-onset (i.e., before age 45–50 years) breast cancer and in approximately 60% of Jewish women with early-onset ovarian cancer*

Criteria for Direct DNA–Based Testing (High-Risk Patients)

- Patient with breast or ovarian cancer:
  - Diagnosed < age 45
  - With >2 first or second degree relatives with breast or ovarian cancer
  - With one relative with breast or ovarian cancer diagnosed < age 45
  - With multiple primary cancers or bilateral disease
- Men with breast cancer at any age
- Relatives of a person with documented BRCA1/2 mutations

Surveillance for Unaffected Carriers (Those With Documented Heterozygous Mutations)

- Monthly breast self-exam
- Annual or semiannual clinical breast exam starting at age 25–35
- Annual mammography starting at age 25–35
- Discuss prophylactic mastectomy option
- Consider ovarian cancer screening
- Tamoxifen prophylaxis may (?) reduce risk of cancers in BRCA1/2 carrier
- *Note*: There are multiple ethical, legal, and social issues surrounding predisposition testing for adult-onset cancer disorders such as breast cancer. Pretest and post-test counseling in the adherence to genetic counseling protocols is routinely required

Other Solid Tumor Genetics*

- Frequent genetic alterations in selected solid tumors (also see Chapter 2 "Familial Cancer Syndrome" section):
  - Ewing's sarcoma and primitive neuroectodermal tumor (PNET): **t(11,22)**(q24;q12)(the translocation results in the fusion of the EWS gene at 22q12 with a truncated transcription factor FL11 gene at 11q24)
  - Intra-abdominal desmoplastic small cell tumor: t(11;21)(q13;q12)
  - Clear cell sarcoma (melanoma of soft part): **t:(12;22)**(q13;q12)
  - Synovial sarcoma: **t(X;18)**(p11;q11)
  - Aleolar rhabdomyosarcoma: **t(2;13)**(q35;q14); t(1;13)(p36;q14)
  - Myxoid chondrosarcoma: t(9;22)(q13;q12)
  - Myxoid and round cell liposarcoma: **t(12;16)**(q13;p11) (the translocation results in the fusion of the CHOP gene at 12q13 with the FUS gene at 16p11)
  - Well differentiated liposarcoma (atypical lipoma): marker ring and giant chromosome; ring chromosome 12
  - **Lipoma: t(3;12) and t(12q13)**
  - Lipoblastoma: 8q rearrangement
  - Dermatofibrosarcoma protuberans: ring chromosome 17
  - Pleomorphic adenoma: **t(3;8)**(p12;q12)
  - Glioblastoma (GBM) and glioma: double minutes (EGF receptor); trisomy 7; 9p rearrangement; monosomy 10; monosomy 22
  - Pheochromocytoma: del(22); del (1p)
  - Meningioma: **del(22)**(q11-q13); monosomy 22; t(14;22)
  - Medulloblastoma: i(17q) or del(17q)
  - Neuroblastoma: HSR/dmin (homogenous staining region and double minutes) for N-myc (2p) amplification; de(1)(p31-32)
  - Retinoblastoma: del(13q14)(RB gene) (also seen in osteocarscoma); struct abn 1; i(6p); del (3)(p14p23)

- Papillary cystadenocarcinoma of ovary: **t(6;14)**
- Ovarian carcinoma: struct abn 1; t(6;14); del(3)(p13-p21); del(6q)
- Uterine leiomyoma: **t(12;14)**
- Leiomyosarcoma: del(1p)
- Uterine carcinoma: struct abn 1
- Breast carcinoma; struct abn 1; (t16q) or del (16q); LOH of 11p; INT gene amplification (11q); Her-2/neu gene amplifications (17q); BRCA-1 (17q21) and BRCA-2 (13q12)
- Prostate carcinoma: del 8p(12-21); del (10q24); trisomy 7, loss of chromosome Y
- Non-papillary renal cell carcinoma: deletion and rearrangement of **3p**11-21; somatic mutation or inactivation of von Hippel-Lindau gene (3p25)
- Papillary renal cell carcinoma: gain of chromosomes 7 and 17: loss of chromosomes Y and 4
- Bladder carcinoma: monosomy 9 or del(**9q)**
- Wilms' tumor: del(11p13)(WT-1 gene); LOH at 11p15.5 (WT-s); struct abn 1; trisomy 18; del (8)
- Mesothelioma: del(3)(p21p23)
- Papillary thyroid carcinoma: 10q11-13 (RET tyrosine kinase gene)
- Melanoma: del(22q); monosomy 22: trisomy 7
- Granulosa cell tumor and Brenner tumor: trisomy 12 or i(12)
- Intraubular germ cell neoplasia and testicular germ cell tumors: i(12p)
- Small cell carcinoma of lung: **del(3)**(p14p23)
- Colon cancer: struct abn1, 17; del(17p); t(17); DCC ("deleted in colon carcinoma"; 18q21; encode transmembrane adhesion molecule); APC (5q21-22) (also see Chapter 2 "Familial Cancer Syndrome")
- Li-Fraumeni syndrome: p53 gene mutation (17p13.1)(also see Chapter 2)
- von Hippel-Lindau syndrome: VHL gene (3p25-26)(also see Chapter 2)
- Multile endocrine neoplasia (MEN): 11q13 (MEN Type 1); 10q11.2(MEN Type 2)(also see Chapters 2 and 11)

*Those highlighted are especially important for Pathology Board Examination

MOLECULAR DIAGNOSIS IN HEMATOLOGY

Hereditary Hemochromatosis

♦ Hereditary hemochromatosis (HH) is a common inherited (autosomal recessive) iron overload disorder that is caused by a mutation in the transferrin receptor binding protein, HFE, leading to excessive iron absorption from the GI tract

Clinical

♦ Clinical symptoms from excessive iron ultimately accumulating and damaging the:
- Liver: cirrhosis and liver failure
- Heart: arrythmias and heart failure
- Endocrine organs: diabetes, hypogonadism, hypothyroidism, impotence, infertility
- Skin: "bronze" coloration
- Joints: arthropathy (often chondrocalcinosis)
- Pancreas: diabetes
- Miscellaneous: fatigue, weakness
- Symptoms usually after age 20–30 (typical onset ~middle age)

Differential Diagnosis

♦ Must distinguish from:
- Secondary Fe overload: transfusions, hemolytic anemias, hemodialysis
- African Fe overload (genetic versus dietary)

Prevalence

♦ Normal population frequency of:
- ~0.2% to 0.5% (1/20–1/500) for symptomatic homozygotes
- ~10% to 13% (1/10–1/ 12) for heterozygote carriers
- ~5% to 7% (1/10–1/15) for the mutant allele
- Perhaps the most common single-gene disorder in European Caucasians

Diagnosis

♦ Clinical signs/symptoms: nonspecific

♦ Family history

♦ Serum-based iron overload: increased transferrin saturation (Fe/TIBC) and ferritin

♦ Liver biopsy with increased hepatic iron (by iron stain or quantitative analysis)

♦ New gold standard: direct DNA-based detection of the HFE C282Y mutation
- Must exclude secondary Fe overload causes

Therapy

♦ Phlebotomy (effective in most cases)

♦ Bleed until iron deficient (ferritin <10–50 ng/ mL)

- Continue maintenance phlebotomies to maintain subnormal ferritin

Genetics

- Autosomal recessive with gender-dependent penetrance (M>F)
- Primarily restricted to Northern European Caucasians
- Linked to HLA locus on chromosome 6 (6p21.3)
- ~75% of HH patients (vs 30% controls) have HLA-A3 serotype

The Hemochromatosis Gene

- HFE (also known as HLA-H)
- Homologous to MHC class I proteins
- Binds to transferrin receptor and reduces its affinity for iron bound transferrin
- Mechanism of action in controlling GI iron absorption unknown

Hemochromatosis-Specific Mutations in HFE

- Single homozygous C282Y point mutation in 80% to 90% of HH patients
- Homozygous C282Y mutation in 0.3% of controls (population prevalence)
- Heterozygous C282Y mutation (i.e., HH carrier status) in 10% to 15% of normal Caucasians: mildly increased iron loads
- C282Y mutation abrogates transferrin receptor binding
- Mutation is detectable by direct DNA-based analyses
- PCR amplify the region surrounding the mutation site
- Mutant allele is detectable by differential restriction enzyme analysis (RFLP), allele-specific hybridization, allele-specific PCR, etc.

Clinical Utility of HFE C282Y DNA Test

- Confirm HH diagnosis in patients with elevated iron studies
- Replace liver biopsy as "gold standard" diagnostic test
- Sensitivity ~80% to 90%
- Specificity: penetrance dependent
- C282Y homozygosity highly penetrant for laboratory iron overload; but clinical iron overload (symptoms) may only develop in 50–80% of homozygotes

Factor V Leiden (R506Q)

- Factor V Leiden is a common predispositional hereditary hypercoagulable syndrome in which a point mutation in factor V (R506Q) creates a coagulation factor that is resistant to inactivation by activated protein C (APC resistance)

Clinical

- Venous thrombotic events (deep vein thrombosis, pulmonary embolism)
- As with all hypercoagulable states, the clinical clues to an inherited predispositional hypercoagulable syndrome include:
  - Recurrent thrombotic episodes
  - Thrombosis at a young age
  - Thrombosis at unusual anatomic sites (not pelvis, leg, or lung)
  - Family history of similar thrombotic events

Acquired Risk Factors for Venous Thrombosis (Synergistic With Factor V Leiden)

- Pregnancy
- Prolonged immobility
- Postsurgical state
- Oral contraceptives
- Trauma
- Cancer

Prevalence

- By far the most common cause of inherited thrombophilia in whites
- APC resistance caused by factor V Leiden is found in:
  - ~20% of patients with first episode of DVT
  - ~60% of patients with recurrent or pregnancy-associated thrombotic events
- In comparison, in hypercoagulable families, the combined prevalence of other inherited hypercoagulable states is only ~10% to 20%, including:
  - Protein C deficiency (rule out by activity or antigenic assay)
  - Protein S deficiency (rule out by activity or antigenic assay)
  - Antithrombin III deficiency (rule out by activity or antigenic assay)
- Must rule out other causes of thrombophilia:
  - Lupus anticoagulant (by aPTT and mix)
  - Myeloproliferative syndromes (CBC and diff)
  - Acquired hypercoagulable states (listed above)

Genetics and Biochemistry

- Factor V Leiden is caused by well-conserved point mutation in the gene for coagulation factor V
  - G to A substitution at nucleotide 1691 changing Arg 506 to Glutamine
  - Codon 506 is normal cleavage site for inactivation of activated factor V by activated protein C (APC)
  - Mutant (506Q) factor V cleaved much less efficiently by APC
  - Hypercoagulable state caused by long-lived activated factor V (resistant to APC)
- An extremely common mutation in Caucasians

- Factor V Leiden heterozygotes make up ~2% to 10% of the NORMAL POPULATION in Northern European Caucasians

Relative Risk

- Heterozygotes have an ~5–10 fold increased risk of venous thrombosis
- This is a predispositional syndrome: Although heterozygotes are PREDISPOSED to getting clots, most heterozygotes will NOT get clots
- Homozygotes have an ~50–100 fold increased risk of venous thrombosis

Diagnosis

- Conventional laboratory diagnosis:
  - screening lab test for Factor V Leiden: functional APC resistance test
    - Ratio of PTTs measured in the absence and presence of exogenous APC (+APC/-APC)
    - Failure of added APC to adequately prolong the PTT suggests "APC resistance"
    - Low APC ratio (cutoff is method dependent) suggests "APC resistance"
      - Homozygotes usually with very low APC ratio (< 1.5, often near 1.0)
    - 90% to 95% of patients with functional APC resistance will have a factor V Leiden mutation (hetero or homozygous)
    - Low APC ratio functional test may not be accurate if baseline PTT is prolonged (heparin Rx, lupus anticoagulant, etc.)
    - Dilution into factor V deficient plasma allows increased diagnostic accuracy (with baseline PTT elevation)

DNA Diagnosis

- Gold standard direct DNA-based test for factor V Leiden
  - Excellent correlation with APC resistance test
  - PCR amplify the region surrounding the mutation site
  - Mutant allele detectable by differential restriction enzyme analysis (RFLP), allele-specific hybridization, allele-specific PCR, etc.
- Indications for direct DNA-based diagnostic test:
  - To confirm diagnosis in those with functional APC resistance
  - Primary screen for family members
  - Patients with baseline prolonged PTTs

Functional Test (APC Resistance) Versus DNA Test

- Functional test is less costly and more widely available (for now)
- Functional test can be inaccurate if baseline PTT is prolonged
- DNA test is more definitive and gives unambiguous result: ~100% specific, 90% sensitive
- DNA test may miss 5% to 10% of those with "APC resistance" due to other causes (unknown)

Management of Factor V Leiden Carriers (Anti-Coagulation)

Homozygotes

- Acute thrombotic episode: treat with heparin, followed by warfarin
- Homozygotes should probably be treated long-term with warfarin to prevent recurrent thrombosis

Heterozygotes

- Those with first DVT event and another reversible thrombotic cofactor (pregnancy, oral contraceptives, immobility, surgery, trauma) may not require long-term warfarin
- First DVT with NO identifiable thrombotic cofactor: consider unknown "genetic" cofactor and consider long-term prophylaxis
- Those with recurrent thrombotic events probably require long-term prophylactic anticoagulation
- Family members must be screened
- Counsel patients to avoid prothrombotic tendencies or to get prophylactic anticoagulants BEFORE exposure to: pregnancy, oral contraceptives, immobility, surgery, trauma

Thrombosis Probably Requires at Least "Two Hits": Factor V Leiden Heterozygosity Plus One of:

- Protein C, S, or antithrombin III deficiency
- An "acquired" prothrombotic tendency (pregnancy, surgery, immobilization, cancer, etc.)
- Lupus anticoagulant
- Hyperhomocysteinemia
- Prothrombin G20210A mutation
- 2nd Factor Leiden mutation (i.e., homozygote)

Prothrombin G20210A Mutation

- Point mutation at nucleotide 20210 in the 3' untranslated region of the factor II (prothrombin) gene
- Very common in healthy control population: 1% to 2% of controls are heterozygotes
- Overrepresented in those with venous thrombotic histories
- Heterozygotes represent 18% of patients with personal and family histories of venous thrombosis
- Heterozygotes represent 6% to 8% of patients with

confirmed DVT/PE
- Carriers of the mutation have 3–5 fold increased thrombotic risk
- Probably synergistic with factor V Leiden for thrombotic risk
- Mutation increases efficiency of mRNA 3' end processing and causes increased factor II (prothrombin) protein levels
- Detectable with direct PCR-based assays for the mutated 20210 nucleotide
- High prevalence suggests that it should be a first-line screening test in hypercoagulable evaluations

MOLECULAR DIAGNOSIS IN MICROBIOLOGY

Introduction

- Molecular microbiology uses the technology of molecular genetics for the clinical diagnosis of infectious diseases

Uses

- Primary detection of infectious organisms—qualitative and quantitative
- Epidemiologic typing: comparing "clonality" between epidemiologically related isolates
- Determining virulence: i.e., antibiotic/antiviral resistance

Nucleic Acid Structure

- Complementary base-pairing of G/C and A/T pairs
- Principal of complementary strand hybridization crucial to all molecular diagnostic assays

Nucleic Acid Isolation and Purification

- DNA and RNA can be made from blood, tissue, body fluids, or paraffin blocks
  - classic DNA extraction method: organic extraction
  - new, quick DNA preparation methods
    - Salt precipitation
    - Quick-spin affinity columns
    - Automated robotic workstations

Major Diagnostic Methods

- Direct probe hybridization
- Nucleic acid amplification
  - Polymerase chain reaction (PCR)
  - Other amplification technologies

Polymerase Chain Reaction (PCR)

- Allows billion fold amplification of any target DNA sequence
- Three steps of a typical PCR reaction
  - Denaturation: separates the double helix into single-stranded DNA—typically ~94°C
  - Annealing: allow primers to anneal to complementary target gene sequences—typically ~55–60°C
  - Extension: extends the ssDNA to dsDNA (copying the template sequence)—typically ~72ϒC
- Repeated cycles of annealing, extension, denaturation generate exponential amplification of DNA between the two primers
- Typical PCR reaction requires 20–40 amplification cycles

Advantages of PCR as a Microbiologic Detection Tool

- Target amplification provides extreme sensitivity
- 1–100 molecules of target nucleic acid can be detected
- Excellent specificity
- Only targets homologous to both primers will be amplified
- Applicable to the detection of any infectious organism: particularly useful for those that cannot be easily cultured

Disadvantages of PCR

- Requires specialized equipment and personnel and workspace
- Not presently well-standardized
- Risk of false positives from PCR product contamination carry-over

Detection of PCR Products

Ethidium bromide (EtBr) staining of gels
- Intercalates specifically into duplex DNA
- Fluoresces under UV light to yield visible DNA "band" of a particular size
- Low sensitivity: requires ~10 ng PCR product DNA
- Will detect specific and nonspecific PCR products
- Useful for detecting "abundant" organisms after PCR

Southern Blotting
- Electrophorese PCR products to separate by size
- Denature to make single stranded DNA
- Transfer to solid support (membrane)
- Hybridize to labeled probe DNA: radioactive or chemiluminescent

- Probe binds to complementary sequences to generate specific bands, observable on X-ray film
- Approximately 10,000 times more sensitive than ethidium bromide and also highly specific

Semi-Automated PCR Product Detection

- Routine clinical utility of diagnostic PCR will require rapid, nonradioactive, semi-automated detection methodologies
- Several competing technologies exist
  - Widely divergent; none predominant as yet
  - Popular format is solid-phase capture of PCR products and microplate colorimetric readout: PCR-ELISA
- Faster, more precise, more economical than tedious manual gel-based detections
  - Can be as sensitive and specific (or more so) as manual gel-based detections

Non-PCR Amplification Methodologies

- Ligase chain reaction
- Transcription-mediated amplification (TMA)
- NASBA
- Branched chain DNA (bDNA)
- A variety of others

Clinical Microbiologic Applications of Amplification Technologies

- Rapid detection of organisms not optimally identifiable by routine methods—culture and serology
- Applicable to virtually any organism for which some DNA sequence information is available
- Tests available now for a multitude of organisms

Pathogen Detection: PCR Versus Culture and/or Serology

- Culture often impossible: HCV, pneumocystis, toxoplasma
- Culture often slow and insensitive: HIV, MTB, enterovirus
- Sensitivity may be crucial: HSV or MTB in the CNS

Infectious Agents for which PCR-Based Tests Have Clear Clinical Utility

- Viruses
  - Hepatitis C virus
  - Herpes family viruses (CMV, HSV, EBV)
  - HIV
  - Many others: enterovirus, rotavirus, adenovirus
- Mycobacteria
  - Rapid ID of Mycobacteria from clinical sample
  - Rapid speciation of mycobacterial culture: TB versus non-TB
- Spirochetes: Borrelia Burgdorferi (Lyme Disease) and T. Pallidum (Syphilis)
- Sexually transmitted disease agents
  - Chlamydia, N. gonorrhoea, treponema pallidum
- Immunodeficiency-associated pathogens
  - Fungi: dimorphic fungi, aspergillus, pneumocystis
  - Parasitic: toxoplasma
- Respiratory pathogens
  - Mycoplasma
  - Legionella
- Novel organisms
  - Universal amplification of 16s rDNA

Hepatitis C Virus (HCV)

- Primary etiologic agent of non-A, non-B hepatitis
- Member of the Flavivirus family: RNA genome of 9.4 kb
- Transmitted parenterally, perinatally, sexually
- Very high frequency of chronic hepatitis (50% to 90%) in infected patients
- Increased risk of cirrhosis and hepatocellular carcinoma
- PCR-based diagnostic test is a model for analogous tests of many other organisms

Laboratory Diagnosis

HCV Serologic Tests

- Tests to detect antibodies to HCV
  - ELISA immunoassay is primary screening test
    - Detects serum antibodies to viral proteins (c22–3, c100–3, c33c)
    - ~90% sensitive
    - Specificity: 70% to 100% in high-risk groups; ~50% in low-risk groups (blood donors)
  - Recombinant immunoblot assay (RIBA, western blot)
    - Primarily a supplemental, confirmatory test
    - Serum reacted with four recombinant HCV antigens immobilized on a strip:
      - c22–3, c33c, c100–3, c100–3 (5–1–1)
    - Positivity defined as reactivity with at least two different HCV antigens
    - Reactivity with only one HCV antigen defined as indeterminate
  - Seroconversion ~11 weeks after exposure
    - Symptoms (and increased LFTs) often present after 6–8 weeks

    - Window of seronegativity: 6–11 weeks after infection
  - Tests to detect HCV antigens—NONE
- Weaknesses of Antibody Tests
  - Acute disease may precede seroconversion by 3–5 weeks
  - Low specificity in low-risk populations
  - False negative test in immunocompromised patients
  - False positive test in patients with autoimmune disease (many have hepatitis)
  - Antibody test remains positive indefinitely irrespective of hepatitis

Direct Detection of HCV by RNA-PCR

- Only available method for directly measuring virus (rather than an antibody response)
- Methodology:
  - Extract RNA from serum or plasma
  - Copy RNA into cDNA with reverse transcriptase
  - PCR amplify the cDNA with oligonucleotide primers to a conserved region of the HCV genome (such as the 5' nontranslated region)
- Qualitatively or quantitatively detect the amplified HCV DNA:
  - Southern blot analysis with an HCV-specific probe
  - PCR-ELISA (colorimetric detection)
  - Real-time fluorescent PCR

Controls for the HCV RNA PCR Assay

- Strict physical containment of PCR products to avoid contamination
- RNA mixed with HCV-positive RNA ("spiked" control) to detect potential PCR inhibitors in clinical specimens
- Multiple water controls to detect reagent contaminations
- Positive and negative "RNA extraction" controls

Semi-automated Quantitative HCV RNA methods

- bDNA (branched chain): signal (not target) amplification
- Quantitative competitive PCR-ELISA
- NASBA (nucleic acid sequence based amplification)
- Real-time fluorescent PCR

Clinical Utility of HCV RNA PCR (Qualitative)

- Primary diagnosis of acute hepatitis C before seroconversion (~11 weeks)
- HCV hepatitis in patients with no antibody response (immune-compromised)
- Patients with indeterminate or ambiguous serologic assays
- To monitor efficacy of interferon therapy
  - Loss of HCV RNA after therapy confirms effective antiviral response

Clinical Utility of HCV RNA PCR (Quantitative)

- To predict efficacy of interferon therapy:
  - Pretreatment HCV RNA level is a significant predictor of sustained IFN responsiveness
  - Initial low level viremia correlates with sustained antiviral response
  - High pre-therapy viral load predicts poor response to IFN therapy
- To monitor viral load after therapy:
  - Successful therapy correlates with reduced or undetectable HCV RNA
- To determine disease severity:
  - High viral titers correlate with advanced disease stage

Cytomegalovirus (CMV)

- Cytomegalovirus (CMV) is a complex DNA virus of the Herpes family
- Produces latent infections (often asymptomatic in immunocompetent hosts)
- Common cause of life- or sight-threatening systemic disease in immunocompromised patients:
  - Transplant recipients: pneumonitis, enteritis
  - AIDS/HIV: retinitis, CNS infection, polyradiculitis
  - Neonates—congenital CMV

Prevalence

- 30% to 70% of U.S. population is infected (seropositive): immunocompetent are not typically symptomatic:

Diagnostic Tests

- Serology:
  - IgG antibody indicates past exposure
  - IgM antibody indicates recent exposure or reactivation
  - Serologic tests have limited utility for the diagnosis of clinically active disease
- Histopathologic changes:
  - Characteristic basophilic intranuclear inclusions (owl's eye) in infected cells
  - Specific for CMV, but not very sensitive
  - Requires biopsy specimen
- CMV antigenemia assay:
  - Direct immunostain of peripheral blood WBCs
  - Specific and rapid, but less sensitive than culture or PCR

Viral Culture

- Traditional diagnostic "gold standard" (before PCR)
- Sensitive and specific, but may require 3–4 weeks of culture

- Rapid shell vial (centrifuge-assisted) viral culture: more rapid but less sensitive
  - Culture followed by CMV-specific immunostain after 1–2 culture days

Detection: PCR Versus Culture

- PCR is more sensitive, more rapid, and more expensive than viral culture
  - Results typically available within 1–3 days
- PCR may be a better predictor of active CMV disease in some patient groups, particularly bone marrow transplant recipients
- Earlier, more sensitive detection of CMV may lead to earlier, more effective therapy in transplant and AIDS patients

PCR Test

- Specimen: whole blood (or plasma or white cells), body fluid, tissue
- Extract DNA
- PCR with CMV-specific primers
  - Internal control: co-amplify patient DNA with primers to an endogenous human gene to ensure the presence of "amplifiable" DNA and to detect potential PCR inhibitors
  - Usual positive, negative, sensitivity controls
- Detect by Southern blot w/CMV probe (or by PCR-ELISA or real-time fluorescent PCR)
- Sensitivity: typically <1000 molecules/mL

Clinical Utility of CMV PCR

Bone Marrow Transplant Patients

- Screen all post-transplant patients with weekly PCRs (culture not necessary)
- Give preemptive ganciclovir therapy when PCR is positive; do not treat if PCR is negative
  - Spares most patients ganciclovir-mediated bone marrow toxicity
- Most BMT centers use similar protocols
  - In BMT, PCR is consensus best test for CMV—detects active disease earlier and with higher sensitivity than either viral culture or antigenemia assays

Solid Organ Transplants and HIV Patients

- PCR is clearly the most sensitive test for pre-symptomatic disease detection
- Perhaps too sensitive?
  - May detect "asymptomatic" viremia
  - Conflicting reports: highly method- and lab-dependent
- Lesson: know your lab's capabilities

MOLECULAR DIAGNOSIS OF TRINUCLEOTIDE REPEAT DISORDERS

Introduction to Trinucleotide Repeat Disease

- A growing number of inherited disease syndromes (primarily neurologic) are caused by the abnormal presence of an expanded tract of trinucleotide repeats within disease-specific genes (Table 1–2)
- The clinical hallmark of these trinucleotide repeat diseases is anticipation. Anticipation may be defined as an amplification in the number of expanded repeats in successive generations and the clinical observance of an earlier age of onset and increased rate of disease progression
- Diagnosis is by determining the number of trinucleotide repeats within a specific disease-causing expandable allele (within the proper clinical context). The normal allele will have a "normal range" of trinucleotide repeats, whereas the disease-associated (expanded) allele will contain an increased number of repeats (in the hundreds, for some diseases)
- Also see Chapter 2

Fragile X Syndrome

- Fragile X syndrome is an X-linked mental retardation disorder that is caused by a trinucleotide repeat expansion in the FMR1 gene at chromosome Xq27.3. It is the leading hereditary cause of learning and developmental disabilities in males

Clinical

(Nonspecific and Non-Diagnostic)

- Developmental delay
- Mental retardation
- Characteristic craniofacial features
- Macroorchidism in males

Prevalence

- 1/4,000 males

Genetics

- Inheritance: X-linked dominant with reduced penetrance
  - Virtually all males with an expanded mutant allele are affected with the clinical status of fragile X
  - 50% of females with a mutant expanded allele are affected, 50% of females are not affected

Table 1–4. Common Trinucleotide Repeat Diseases

Disease	*Gene*	*Repeat sequence*	*Repeat location, type of region*	*Normal allele size (# repeats)*	*Expanded mutant allele (fully penetrant)*
Fragile X Syndrome	FMR1	CGG	exon 1, 5′ untranslated region	6–54	>230
Myotonic Dystrophy	DMPK	CTG	exon 15, 3′ untranslated region	5–37	50–>2000
Friedreich Ataxia	X25	GAA	intron 1	7–10, 12–38	≥66
Huntington's Disease	IT15	CAG	exon 1, polyglutamine coding	9–26	≥40
Dentatorubral Pallidoluysian Atrophy	DRPLA	CAG	exon 5, polyglutamine coding	7–35	49–88
Spinocerebellar Ataxia Type 1	SCA1	CAG	exon 8, polyglutamine coding	6–39	40–81
Spinocerebellar Ataxia Type 2	SCA2	CAG	exon 1, polyglutamine coding	14–31	34–64
Spinocerebellar Ataxia Type 3	SCA3/MJD1	CAG	exon ?, polyglutamine coding	12–43	56–86
Spinocerebellar Ataxia Type 6	CACNA1A	CAG	3′ end of gene, polyglutamine coding	4–18	21–33
Spinocerebellar Ataxia Type 7	SCA7	CAG	exon 1, polyglutamine coding	4–19	37–≥200

- Locus: FMR1 locus at the FRAXA folate sensitive fragile site mapped to chromosome Xq27.3
- Gene product: FMR1
- Protein function: FMRP (fragile X mental retardation protein) unknown, but is associated with mRNA in translating polyribosomes
- Mutation: expansion of a CGG repeat upstream of exon 1 in the 5' untranslated region of the FMR1 gene
  - Normal allele sizes: 6–54 CGG repeats
  - Premutation allele sizes: 55–230 CGG repeats
  - Mutant allele sizes: >230 CGG repeats
  - The vast majority of males with >230 repeats are clinically affected
    - The trinucleotide repeat expansion is associated with inactivation of the FMR1 gene and absence of the protein product, which is presumably responsible for the neurologic phenotype
  - The inactivation of the FMR1 gene is associated with excessive methylation of the expanded CGG repeats
- Premutation:
  - Allele sizes ~55 to ~230 repeats
  - Premutation males and females have normal intellect and appearance
    - Premutation females have a 50% chance of transmitting the premutation in pregnancy, which may expand to a full mutation in the fetus (Table 1–3)

Diagnosis

- Prior to the widespread use of direct DNA testing, fragile X syndrome was often diagnosed cytogenetically by the demonstration, on karyotypic analysis, of a characteristic "fragile" site on the X chromosome (at Xq27.3, the site of the FMR1 trinucleotide repeat expansion)

DNA-Based Diagnosis

- Virtually all cases of full mutations will be identified using genomic Southern blot analysis with an FMR1 specific probe. Expanded trinucleotide repeats will appear as larger sized Southern blot bands, whose size is proportional to the number of repeats

Table 1–5. Risk of Maternal Meiotic Trinucleotide Repeat Expansion

Maternal CGG premutation (# of repeats)	*Risk of expansion into mutant allele size (>230 repeats)*
56–69	13%
60–69	21%
70–79	58%
80–89	73%
90–99	94%
>100	>99%

- The PCR-based assay is useful to identify normal and pre-mutation size repeats, but will not detect alleles with high repeat numbers because PCR may often fail to amplify across the very large repeat

Huntington's Disease

- Huntington's disease is an autosomal dominant progressive disorder of motor, cognitive, and psychiatric disturbances that is caused by a trinucleotide repeat expansion in the huntington gene at chromosome 4p16.3

Clinical

- Diagnosis based on clinical presentation is accurate in 85% to 93% of cases
- Diagnosis may be suspected in the presence of:
  - Positive family history consistent with an autosomal dominant inheritance pattern
  - Progressive motor disability (see below)
  - Mental disturbances (decline in cognitive skills or psychiatric changes, see below)

Onset/Progression

- Mean age of onset: 35–44 years
- Median survival after onset: 15–18 years
- Average age at death: 54–55 years
- Common causes of death: pneumonia, cardiovascular disease, suicide, choking, accident

Prevalence

- 3/100,000 to 7/100,000 in populations of Western European descent
- Less common in Japan, China, Finland, and African blacks

Clinical

- Originating presentation: 2/3 neurological, 1/3 psychiatric
  - Voluntary and involuntary movement disturbances (progressive):
    - Choreic movement (>90% of patients)
    - Hyperreflexia (90% of patients)
    - Saccadic difficulties/disturbances (75% of patients)
  - Cognitive changes (progressive):
    - Forgetfulness
    - Slowness of thought processes
    - Impaired visuospatial abilities
    - Cortical speech abnormalities
  - Psychiatric/behavioral changes (usually regress with disease advancement):
    - Personality changes
    - Affective psychosis

Radiologic

- CT and MRI scans show atrophy of the caudate and putamen
- PET findings show a decrease in the uptake and metabolism of glucose in the caudate nucleus

Macroscopic

- Small brain
- Striking atrophy of caudate nucleus and putamen
- Secondary atrophy of globus pallidus
- Dilated lateral and third ventricles

Microscopic

- Severe loss of striatal neurons, most severe in caudate nucleus
- Large and small neurons affected
- Spiny neurons using GABA and enkephalin or GABA and substance P as neurotransmitters are prominently affected

Differential Diagnosis

- Neuroacanthocytosis
- Benign hereditary chorea

- Hereditary cerebellar ataxia
- Creutzfeld-Jakob disease

Genetics

- Inheritance: autosomal dominant
- Locus: HD gene mapped to chromosome 4p16.3
- Protein function: unknown
- Mutation: CAG trinucleotide repeat expansion in protein-coding exon 1 yielding a polyglutamine tract
  - Normal allele sizes: 9–26 CAG repeats
  - Intermediate allele sizes: 27–35 CAG repeats
  - Mutant allele sizes: >36 CAG repeats
- An inverse correlation exists between repeat size and age of onset
- Homozygotes are no more severely affected than heterozygotes

DNA-Based Diagnosis

- "Gold standard" test to be used to confirm diagnosis in suspected clinical cases
- PCR and/or Southern blot methods to quantitate the number of trinucleotide repeats within the huntington gene on chromosome 4p16.3
- Detection of >36 CAG repeats is diagnostic of Huntington's disease
- Sensitivity: 99%
- Specificity: 100%
- *Note*: There are multiple ethical, legal, and social issues surrounding predictive testing for adult-onset disorders such as Huntington's disease. Pretest and post-test counseling in the adherence to genetic counseling protocols is routinely required

Myotonic Dystrophy

- Myotonic dystrophy is a degenerative musculoskeletal disease that is caused by a trinucleotide repeat expansion in the DMPK gene on chromosome 19q13.3

Clinical

- Myotonia
- Progressive muscle weakness and wasting
- Cataracts
- Hypogonadism
- Frontal balding
- Cardiac conduction defects

Prevalence

- 1/8,500

Onset/Progression

- Onset: variable (birth to 2nd decade)
- Progression: correlates with size of expansion

Microscopic

- Skeletal muscle:
  - Increase in the number of internal nuclei, possibly forming conspicuous chains
  - Ring fiber, possibly associated with sarcoplasmic mass
  - Fiber splitting, necrosis, and regeneration of intrafusal fibers of muscle spindles
  - Hypotrophy of Type I muscle fibers

Endocrine/Laboratory

- High insulin secretion in response to glucose load
- Diabetes (uncommon)
- Depressed IgG levels
- Elevated serum CPK

Genetics

- Inheritance: autosomal dominant
- Locus: DMPK gene mapped to chromosome 19q13.3
- Gene product: DMPK
- Protein function: novel protein, myotonin, with strong homology to the protein kinases
- Mutation: expansion of a CTG repeat of exon 15 in the 3' untranslated region of the DMPK gene
  - Normal allele sizes: 5–37 CTG repeats
  - Mutant allele sizes (predictive of disease in heterozygous form): 50–>2000 CTG repeats
- Direct correlation between severity and repeat size

DNA-Based Diagnosis

- Diagnostic testing by Southern blotting with DMPK specific probes using different restriction enzymes for various expansion sizes
- Accurate sizing of expansions is performed by PCR
- Detection of >50 CTG repeats is diagnostic of myotonic dystrophy
- Some patients with the clinical presentation may not be found to have the trinucleotide repeat expansion, indicating a possible deletion or point mutation

Spinocerebellar Ataxias (SCAs)

- The spinocerebellar ataxias (SCAs) are a set of clinically indistinguishable inherited neuro-degenerative disorders that are characterized by poor movement coordination (from dysfunction of the cerebellum) and are caused by a characteristic trinucleotide repeat expansion in one of a series of unique disease-specific genes
- Direct DNA tests are clinically available for SCA type 1, 2, 3, 6, 7 and 8 to detect the presence of the trinucleotide repeat expansion

- Much clinical overlap exists among the SCAs and they may be considered clinically indistinguishable
- Some clinical features may be somewhat suggestive or common to an SCA subtype, for example:
  - Slow saccadic eye movements in SCA2
  - Later onset and slower disease progression in SCA6
  - Visual loss with retinopathy in SCA7
- There is generally an inverse correlation in the number of expanded trinucleotide repeats and the clinical age of onset
- Anticipation in many cases of SCA is defined as:
  - Increased rate of progression
  - Earlier age of onset
  - Amplification in the number of expanded repeats in successive generations
- Disease frequency varies between different ethnogeographical groups

Spinocerebellar Ataxia Type 1

- SCA1 is an autosomal dominant neurological syndrome with cerebellar ataxia and peripheral neuropathy that is caused by a CAG trinucleotide repeat expansion in the SCA1 gene

Clinical

- Ataxia
- Dysarthria
- Bulbar dysfunction

Onset/Progression

- Onset: third or fourth decade (childhood onset has been reported)
- Duration: variable (10–30 years)
- Inverse correlation between age of onset and the number of trinucleotide repeats

Prevalence

- 1/100,000 to 2/100,000

Radiologic

- Brain CT and MRI:
  - Atrophy of the brachia pontis and anterior lobe of the cerebellum
  - Enlargement of the fourth ventricle

Microscopic

- Cerebellar atrophy with loss of Purkinje cells and dentate nucleus neurons
- Eosinophilic spheres in the axons of degenerating Purkinje cells
- Severe neuronal degeneration in the inferior olive
- Mild neuronal loss in cranial nerve nuclei III, IV, IX, X, and XII
- Demyelination of the restiform body and brachium conjunctivum, dorsal and ventral spinocerebellar tracts

Genetics

- Inheritance: autosomal dominant
- Locus: SCA1 gene mapped to chromosome 6p22–23
- Gene product: ataxin-1
- Protein function: unknown, but accumulated ataxin forms nuclear inclusions (probably insoluble aggregates that disrupt neuronal function)
- Mutation: expansion of an uninterrupted CAG repeat within protein-coding exon 8 of the SCA1 gene yielding a polyglutamine tract
  - Normal allele sizes: 6–39 CAG repeats
  - Mutant allele sizes (predictive of disease in heterozygous form): 40–81 CAG repeats

DNA-Based Diagnosis

- Progressive ataxia, dysarthria, and a suspected family history are criteria for confirmational DNA-based testing for a mutation in the SCA1 gene Direct DNA-based detection of the expanded SCA1 CAG uninterrupted repeat detects 100% of affected patients
- PCR and/or Southern blot methods for the direct detection (and approximate quantitation of the number) of trinucleotide repeats within the SCA1/ataxin-1gene

Spinocerebellar Ataxia Type 2

- SCA2 is an autosomal dominant neurological syndrome with cerebellar ataxia including nystagmus and slow saccadic eye movements that is caused by a CAG trinucleotide repeat expansion in the SCA2 gene at chromosome 12q24

Clinical

- Slowly progressive ataxia
- Ocular findings of: nystagmus, slow saccadic eye movements, ophthalmoparesis

Onset/Progression

- Onset: highly variable (<10 to >60 years)
- Duration: highly variable (1–30 years)
- Inverse correlation between age of onset and trinucleotide repeat length

Prevalence

- Unknown, accounts for approximately 15% of autosomal dominant cerebellar ataxias

Microscopic

- Marked reduction in the number of cerebellar Purkinje cells

- Purkinje cell dendrites with poor arborization and torpedo-like formation of axons
- Decreased number of granule cells
- Demyelination in posterior columns of spinal cord
- Reduction in the size and number of motor neurons and neurons in Clarke's column
- Severe gyral atrophy
- Thin cerebral cortex
- Strophic and gliotic cerebral white matter

Radiologic

- Marked neuronal loss in inferior olive and pontocerebellar nuclei
- Marked loss in substantia nigra

Genetics

- Inheritance: autosomal dominant
- Locus: SCA2 gene mapped to chromosome 12q24
- Gene product: ataxin-2
- Protein function: unknown; no identified homologies with proteins of known function
- Mutation: expansion of a CAG repeat within protein-coding exon 1 of the SCA2 gene yielding a polyglutamine tract
  - Normal allele sizes: 14–31 CAG repeats
  - Mutant allele sizes (predictive of disease in heterozygous form): 34–64 CAG repeats

DNA-Based Diagnosis

- PCR and/or Southern blot methods for the direct detection (and approximate quantitation of the number) of trinucleotide repeats within the SCA2/ataxin-2 gene
- Direct DNA-based detection of the expanded SCA2 CAG repeat detects 100% of affected patients

Spinocerebellar Ataxia Type 3 (Machado-Joseph)

- SCA3 is an autosomal dominant neurological syndrome with cerebellar ataxia that is caused by a CAG trinucleotide repeat expansion in the SCA3/MJD1 gene

Clinical

- Cerebellar ataxia
- Pyramidal and extrapyramidal signs
- Amyotrophy

Onset/Progression

- Onset: 2nd to 4th decade
- Progression: 6–30 years

Prevalence

- Unknown, ethno-geographic variation exists
- Brain imaging: pontocerebellar atrophy
- Neuropathology: prominent loss of pontine neurons, neurons of the substantia nigra, anterior horn cells, and Clarke's column in the spinal cord

Genetics

- Inheritance: autosomal dominant
- Locus: SCA3 or MJD1 mapped to chromosome 14q24.3–32
- Gene product: ataxin-3
- Protein function: unknown
- Mutation: expansion of a CAG repeat within a protein-coding exon of the SCA3 gene yielding a polyglutamine tract
  - Normal allele sizes: 12–43 CAG repeats
  - Mutant allele sizes (predictive of disease in heterozygous form): 56–86 CAG repeats

DNA-Based Diagnosis

- PCR and/or Southern blot methods for the direct detection (and approximate quantitation of the number) of trinucleotide repeats within the SCA3/ataxin-3 gene

Spinocerebellar Ataxia Type 6

- SCA6 is an autosomal dominant neurological syndrome with cerebellar ataxia that is caused by a CAG trinucleotide repeat expansion in the CACNA1A gene at chromosome 19p13.1-p13.2

Clinical

- Very slow progression of ataxia, sometimes episodic
- Visual disturbances

Onset/Progression

- Onset: highly variable (19–70 years)
- Progression: >25 years

Prevalence

- .02/100,000 to .31/100,000

Differential Diagnosis

- Dominantly inherited ataxia due to missense mutation in the CACNA1A gene
- Episodic ataxia type-2 due to protein truncation mutations in the CACNA1A gene
- Familial hemiplegic migraine due to missense mutations in the CACNA1A gene

Microscopic

- Selective Purkinje cell degeneration or a combined degeneration of Purkinje cells and granule cells

Genetics

- Inheritance: autosomal dominant
- Locus: CACNA1A mapped to chromosome 19p13.1-p13.2

- Gene product: 1 A voltage-gated calcium channel
- Protein function: alpha 1A subunit that serves as the pore-forming subunit of a voltage-gated calcium channel
- Mutation: expansion of a CAG repeat within the 3' end of the CACNA1A gene yielding a polyglutamine tract
  - Normal allele sizes: 4–18 CAG repeats
  - Mutant allele sizes (predictive of disease in heterozygous form): 21–33 CAG repeats

DNA-Based Diagnosis

- PCR and/or Southern blot methods for the direct detection (and approximate quantitation of the number) of trinucleotide repeats within the CACNA1A/ataxin-6 gene

Spinocerebellar Ataxia Type 7

- SCA7 is an autosomal dominant neurological syndrome with cerebellar ataxia and retinal degeneration that is caused by a CAG trinucleotide repeat expansion in the SCA7 gene at chromosome 3p12-p13

Clinical

- Cerebellar ataxia
- Ophthalmology
  - Visual problems progressing to complete blindness
  - ERG reveals abnormalities of cone and rod function
  - Fundoscope reveals macular changes

Onset/Progression

- Onset: highly variable (<1–60 years)
- Progression: highly variable (1–45 years)

Prevalence

- <1/100,000

Differential Diagnosis

- Mitochondrial encephalopathies presenting with ataxia

Genetics

- Inheritance: autosomal dominant
- Locus: SCA7 gene mapped to chromosome 3p12-p13
- Gene product: ataxin-7
- Protein function: unknown
- Mutation: expansion of a CAG repeat within protein coding exon 1 of the SCA7 gene yielding a polyglutamine tract
  - Normal allele sizes: 4–19 CAG repeats
  - Mutant allele sizes (predictive of disease in heterozygous form): 37–≥200 CAG repeats
  - High meiotic instability in paternal transmission leading to increased expansions

DNA-Based Diagnosis

- PCR and/or Southern blot methods for the direct detection (and approximate quantitation of the number) of CAG trinucleotide repeats within the SCA7/ataxin-7 gene

OTHER GENETIC DISEASES

Cystic Fibrosis

- Cystic fibrosis is a multisystem disease that is caused by defective chloride transport in epithelia (dehydrated secretory processes) due to a heterogeneous array of mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene (also see Chapter 2)

Clinical

Lungs (also see Chapter 17)

- Bronchi obstructed by dehydrated secretions, bronchiectosis
- Pulmonary infections
  - Pseudomonas aeruginosa
  - Staphylococcus aureus

Pancreas (85% to 90% patients)

- Mucus accumulations and/or plugs in small ducts
- Dilatation and/or atrophy and/or fibrosis of exocrine glands
- Pancreatic insufficiency resulting in malabsorption of nutrients due to inability to deliver pancreatic enzymes to the bowel (65%)

Liver (5%)

- Obstructed bile canaliculi

Other

- Skin: increased sweat chloride concentration
- Small intestine: small bowel obstruction, meconium ileus (in infants)
- Male reproduction:
  - Congenital bilateral absence of the vas deferens (CBAVD)
  - Infertility from abnormal secretion of electrolytes and water by epididymal epithelieum (for sperm maturation and transport)

Laboratory

- CFTR dysfunction assays:
  - Elevated sweat chloride concentrations, diagnostic

sensitivity ~96%
  - Abnormal nasal transepithelial potential difference measurements

Onset/Progression

- Median age at clinical diagnosis: 6–8 months
- Median life-span: 30.1 years
- Mortality due to respiratory failure from pulmonary complications/infections

Prevalence

- Approximately 1/3000 Caucasians are homozygotes
- Carrier frequency (heterozygotes): approximately 1/25 Caucasians (phenotypically normal)

Genetics (also see Chapter 2)

- Inheritance: autosomal recessive
- Locus: 7q31
- Gene product: CFTR (cystic fibrosis transmembrane conductance regulator)
  - Multiple domains:
    - Two transmembrane
    - Two cytoplasmic nucleotide binding
    - One regulatory
- Protein function: cyclic AMP-dependent chloride channel
- Mutations:
  - > 900 mutations have been described in the CFTR gene in CF patients in widely varying locations within the CFTR gene
  - Most mutations involve a single nucleotide:
    - 40% missense
    - 20% nonsense
    - 10% RNA splicing
- The single most common disease-causing allele is deltaF508, which is seen in virtually all populations
- The deltaF508 mutation is a deletion of 3 nucleotides (encoding a single phenylalanine codon), creating a loss of function in the CFTR chloride channel
- There are 15 to 20 other "common" mutations that in total account for 2% to 15% of CF alleles (depending on the population ethnicity)

DNA Diagnostic Methods

- The great heterogeneity in the spectrum of mutations makes DNA-based diagnostic methods non-routine
- The sensitivity of detection will depend on how many mutations are specifically assessed—typically by PCR-based methods
- Because of the large spectrum of possible mutations, DNA testing requires "gene-scanning" methods such as:
  - Multiplex PCR, multiplex allele-specific oligonucleotide hybridization, protein truncation testing, conformation sensitive gel electrophoresis, single-strand conformation polymorphism analysis, direct gene sequencing, or a combination of the above methodologies
  - High-density oligonucleotide gene-chip testing may soon simplify the analysis
- The diagnostic sensitivity varies according to the population of interest and the number of mutations assessed (Table 1–6)
  - The addition of ~40 extra mutations to the DNA testing panel will moderately increase the diagnostic sensitivity for African Americans (to ~60%), but will not significantly increase the diagnostic sensitivity for other ethnic groups (as most of these rare mutations are found in only one or a few families throughout the world)

Achondroplasia

Clinical

- Achondroplasia is a type of skeletal dysplasia that is characterized by short stature, a large head, and characteristic facial features. It is caused by a mutation in the fibroblast growth factor receptor 3 gene
- Clinical findings include:
  - Short stature
  - Rhizomelic shortening of limbs (shortened proximal extremities) with redundant skin folds
  - Genu varum (bowleg)
  - Trident hands
  - Limited elbow extension
  - Thoracolumbar gibbus present at birth, but resolves
  - Lumbar lordosis
  - Large head with frontal bossing
  - Midface hypoplasia
  - Hyperextensibility of joints

Differential Diagnosis

- Severe hypochondroplasia
- Cartilage hair hypoplasia
- Thanatophoric dysplasia

Prevalence

- 1/15,000–1/40,000 live births

Genetics (see Tables 1–6 and 1–7)

- Inheritance:
  - Autosomal dominant
  - >80% of cases represent new mutations (i.e., usually no family history)

Table 1–6. Diagnostic Sensitivity Factors of Cystic Fibrosis DNA Testing

Ethnic Group	*30 Mutation Allele Analysis Diagnostic Sensitivity*
Ashkenazi Jews	97%
Caucasians	~90%
Hispanics	57%
African Americans	52%

Table 1–7. Delta F508 Allele Frequency in Cystic Fibrosis Patients

Ethnic group	*Delta F508 Allele Frequency in CF Patients (%)*
Caucasians	70
Hispanics	46
Ashkenazi Jews	30
African Americans	48
Asian Americans	30

  - Germline mosaicism accounts for rare cases in which both parents are of normal stature
  - Homozygotes are more severely affected than heterozygotes (may be considered a lethal disorder)
- Locus: FGFR3 gene mapped to chromosome 4p16.3
- Gene product: fibroblast growth factor receptor 3 (FGFR3) protein
- Protein function: membrane-spanning tyrosine kinase receptor with an extracellular ligand-binding domain
- Mutations:
  - >99% of cases are caused by a glycine to arginine substitution at codon 380 of FGFR3, the vast majority of which are a G to A transition at nucleotide 1138, (the remainder being a G to C transversion at nucleotide 1138)
  - Rare cases have been reported of other mutations in other amino acid positions within FGFR3

Radiologic

- Narrowing of interpedicular distance caudally in the spine
- Notch-like sacroiliac groove
- Squared iliac wings
- Flat vertebral bodies
- Short ribs

Microscopic

- Growth plate anomalies:
  - Shortened growth plate
  - Zones of proliferation and hypertrophy:
    - Narrowed and disorganized
    - Contain clusters of large chondroctyes
  - Base contains premature deposition of horizontal struts of bone that seals the plate and prevents growth

Diagnosis

- DNA-based testing to directly detect the codon 380 mutation in FGFR3:
  - Typically by PCR amplification and restriction enzyme analysis (using enzymes that differentially cleave the mutation [or wild type] specific allele)
  - Sensitivity to detect mutations in FGFR3 gene is 97% to 99%
- Diagnosis based on clinical and radiographic evidence is reliable for most individuals

Ataxia-Telangiectasia (also see Chapter 2)

Clinical

- Ataxia-telangiectasia is a progressive cerebellar ataxia that occurs in childhood and is characterized by oculocutaneous telangiectasias, radiosensitivity, immu-

nodeficiency, and a predisposition to malignancy.

- It is caused by loss of function mutations in the ATM gene
- Clinical features may not be apparent in very young children
- Typical clinical findings include:
  - Progressive cerebellar ataxia in childhood
  - Ocular motor apraxia (loss of voluntary eye movement)
  - Dysarthria
  - Telangiectasias of the conjuctivae

Differential Diagnosis

- A-T like variants
- Cerebral palsy
- Nijmegan Breakage syndrome
- Friedrich ataxia

Prevalence

- 1/40,000–1/100,000 live births

Onset/Progression

- Cerebellar dysfunction at 1 to 3 years
- Confined to wheelchair by age 10

Genetics

- Inheritance: autosomal recessive
- Locus: ATM gene mapped to chromosome 11q22–23 (accounts for >99% of the cases)
- Gene product: ATM
- Protein function: part of mulit-protein complex functioning to sense and respond to DNA damage

Mutations

- >300 known disease associated mutations within the ATM gene
- <1% of unrelated patients share a common mutation
- 70% of the mutations truncate the normal protein product (with resultant loss of function)
- Founder effect mutations have been described for the following populations:
  - Amish (100%)
  - Costa Rica (96%)
  - Sardinia (>95%)
  - England (73%)
  - Norway (55%)
  - Japanese (>50%)
  - Italy (35%)
  - Poland (>30%)

Microscopic

- Loss of Purkinje and granule cells in the cerebellum
- Combined T-Cell and B-Cell deficiency
- Nucleomegaly in cells throughout the body
- Predisposed to malignancy (usually leukemia or lymphoma)

Laboratory

- Elevated serum alpha-fetoprotein (AFP) (90% to 95% of patients)
- Decreased cerebellar size on MRI
- DNA repair defects, classically, 7;14 chromosome translocations
- In vitro radiosensitivity (>99% of patients)
- IgE and IgA deficiency

Diagnosis

- Clinical DNA testing is not routinely recommended because:
  - <1% of patients share a common (i.e. easily detectable) mutation
  - Detecting the "uncommon" mutation requires intensive (i.e. extensive) testing with sequence-based or "gene-scanning" methods
  - DNA chips may allow more cost-effective primary diagnosis
- DNA testing may be recommended for:
  - Families with a known mutation
  - Certain ethnic groups with a high prevalence of a single mutation
- Test sensitivity <100%

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Chapter 2

Human Genetic Disorders

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Table of Contents

CHROMOSOMAL DISORDERS

Chromosomal Aneusomy

Trisomy 21 (Down Syndrome)

Chromosome and Gene Location

- Additional chromosome 21
- Trisomy of the bottom 1/3 of chromosome 21 is sufficient for the clinical phenotype (21q22 is the critical region)

Inheritance

- 95% meiotic nondisjunction (47 chromosomes present)
- 80–90% maternal, increases with maternal age
- 10–20% paternal
- 1% risk of recurrence or maternal age related risk (whichever is greater)
- 3–4% unbalanced translocation (46 chromosomes with an extra chromosome 21 fused to another chromosome
  - 50% sporadic (not inherited)
  - 50% balanced translocation in one parent, often translocation of acrocentric chromosomes (13,14,15,21,22)
- 1–2% mosaicism (at least two different cell lines)
  - Results from post zygotic nondisjunction or loss of the extra 21 in one cell line

Incidence

- 1/800 live births

Clinical

- Phenotype:
  - Flat facial profile, thick nuchal fold, upward slanting palpebral fissures, depressed nasal bridge, single transverse palmar crease, gap between 1st and 2nd toe, epicanthal folds, Brushfield spots of iris, low set c-shaped ears
- Neurologic:
  - Learning disabled (IQ=40–80), poor Moro reflex, infantile hypotonia, developmental delay, joint hyperflexibility, increased risk for Alzheimer disease
- Other:
  - 40% congenital heart defects (endocardial cushion defects including atrioventricular canal defect, and ventricular septal defects), increased risk for childhood acute leukemia, hypothyroidism, obesity, short stature, increased incidence of pulmonary hypoplasia, duodenal atresia
- Life Expectancy:
  - 75% spontaneously abort in first trimester. If live born, 80% survival at age 30

Laboratory

- Cytogenetics:
  - Chromosome analysis identifies extra chromosome 21
- Prenatal:
  - Altered maternal serum markers (decreased alpha-fetoprotein and unconjugated estriol, increased human chorionic gonadotrophin)
- Ultrasound:
  - Thickened nuchal fold, congenital heart defects, duodenal atresia ("double bubble" sign), short humerus and femur, short middle phalanx of 5th finger
- Treatment:
  - Not curable, supportive/symptomatic

Trisomy 13 (Patau syndrome)

Chromosome and Gene Location

- Additional chromosome 13

Inheritance

- 80% meiotic nondisjunction
- 80–90% maternal, increases with maternal age
- 10–20% paternal
- 20% unbalanced translocations (derived from parental carrier of balanced chromosomal translocation involving chromosome 13)a

Incidence

- 1/10,000 births

Clinical

- Phenotype:
  - Spectrum of mid-line abnormalities ranging from simple ocular hypotelorism to cyclopia to complete absence of eyes. Other features include, prominent occiput, microcephaly, malformed low set ears, cleft lip and palate, polydactyly of hands and feet, clenched hands, rocker bottom feet, transverse palmar crease
- Neurologic:
  - Complete or incomplete holoprosencephaly, severe mental retardation, seizures, deafness, hypotonia, apneic spells
- Other:
  - Congenital heart defects (hypoplastic left heart & ventricular septal defects), urogenital defects, cryptorchidism (males), bicornuate uterus & hypoplastic ovaries (females), polycystic kidneys, umbilical hernia, omphalocele
- Life Expectancy:
  - 90% die in first year of life (2/3 by 6 months)

Laboratory

- Cytogenetics:
  - Chromosome analysis identifies extra chromosome 13
- Prenatal:
  - Maternal serum markers are not useful
- Ultrasound:
  - Holoprosencephaly, cleft lip and palate, cystic hygroma, polydactyly, congenital heart defects, cystic kidneys, omphalocele

Treatment

- Not curable, supportive/symptomatic

Trisomy 18 (Edward Syndrome)

Chromosome and Gene Location

- Additional chromosome 18

Inheritance

- Meiotic nondisjunction
  - 95% maternal, increases with maternal age
  - 5% paternal

Incidence

- 1/5000–1/10,000 births

Clinical

- Phenotype:
  - Microcephaly with prominent occiput, micrognathia, malformed ears, cleft lip and palate, clenched hands, 2nd and 5th digits overlapping 3rd and 4th, rocker bottom feet, single transverse palmar crease, hypoplastic nails
- Neurologic:
  - Severe mental retardation, seizures, hypertonia
- Other:
  - Severe intrauterine growth retardation, congenital heart defects (ventricular septal defects), urogenital defects, cryptorchidism, horseshoe kidney, diaphragmatic hernia, omphalocele
- Life Expectancy:
  - 95% spontaneously abort. Of those live born, 90% die within first year of life

Laboratory

- Cytogenetics:
  - Chromosome analysis identifies extra chromosome 18
- Prenatal:
  - Altered maternal serum markers (decreased alpha-fetoprotein, unconjugated estriol, and human chorionic gonadotrophin) may detect 80% of cases
- Ultrasound:
  - Clenched hands, club and rocker-bottom feet, micrognathia, cleft lip and/or palate, congenital heart defects, omphalocele, diaphragmatic hernia, neural tube defects, choroid plexus cysts, cystic hygroma

Treatment

- Not curable, supportive/symptomatic

Klinefelter Syndrome (XXY)

Chromosome and Gene Location

- Extra X chromosome

Inheritance

- 55% Maternal nondisjunction
- 45% Paternal nondisjunction
- Also may be mosaic XY/XXY

Incidence

- 1/800 males

Clinical

- Phenotype:
  - Tall habitus, small testes in older boys, gynecomastia, poor musculature
- Neurologic:
  - Mild delay, behavioral immaturity, shyness, learning disabilities (reading) speech delay
- Other:
  - Infertile
- Life Expectancy:
  - Normal

Laboratory

- Cytogenetics:
  - Chromosome analysis identifies XXY
  - Leydig cell hyperplasia, absence of spermatogenesis, increased follicular stimulating hormone and estradiol, and decreased testosterone

Treatment

- Testosterone supplementation for development of secondary sexual characteristics

Turner Syndrome (45,X)

Inheritancexs

- 55% 45,X
  - 80% loss of paternal X chromosome
  - 20% loss of maternal X (no maternal age effect)
- 25% 46,XX
  - Structural alteration in one X chromosome
- 15% mosaic
  - 45X with 46XX, 46XY or other

Chromosome and Gene Location

- X chromosome

Incidence

- 1/2000–1/5000 female births: most common single chromosome finding in spontaneous abortions

Clinical

- Phenotype:
  - Short stature, webbed neck, lymphedema of hands and feet, high arched palate, cystic hygroma, low posterior hairline, hypoplastic widely-spaced nipples
- Neurologic:
  - Normal or near normal intelligence; may have delay in speech, neuromotor behaviors, and learning abilities
- Other:
  - Gonadal dysgenesis (infertility, primary amenorrhea), renal malformations (horseshoe kidney), cardiovascular malformations (coarctation of aorta, hypoplastic left heart), increased risk for gonadoblastoma if mosaic for some Y chromatin
- Life Expectancy:
  - 99% spontaneously abort prior to 28 weeks, those who survive infancy usually reach adulthood

Laboratory

- Cytogenetics:
  - Chromosome analysis indicates monosomy X or other variant
- Prenatal:
  - Elevated alpha-fetoprotein (only in cases of cystic hygroma and hydrops)
- Ultrasound:
  - Cystic hygroma (detectable after 10 weeks), lymph collections (ascites, pleural effusion), congenital heart disease, renal anomalies

Treatment

- Estrogen and thyroid hormone replacement therapy for secondary sexual characteristic and growth

Microdeletion Syndromes

Angelman Syndrome

Chromosome and Gene Location

- 15q11.2

Inheritance

- 60–70% deletion of maternal 15q11.2
- 5% paternal uniparental disomy (2 copies of the paternal chromosome)
- Remainder are point mutations and imprinting defects

Incidence

- 1/20,000

Clinical

- Phenotype:
  - Prominent mandible, open-mouthed expression, hyperflexia, microcephaly, brachycephaly, optic atrophy
- Neurologic:
  - Ataxia, severe mental retardation, seizures, gross motor developmental delay
- Other:
  - Absent speech, inappropriate laughter, arm flapping, feeding difficulties
- Life Expectancy:
  - Most survive into adulthood

Laboratory

- Cytogenetic analysis and/or Fluorescent In Situ Hybridization (FISH) detects deletion
- Molecular methylation analysis identifies missing maternal allele
- Uniparental disomy studies identify 2 copies of paternal allele

Treatment

- Not curable, supportive/symptomatic

Prader Willi Syndrome

Chromosome and Gene Location

- 15q11.2

Inheritance

- 70–75% deletion of paternal 15q11.2
- 20% maternal uniparental disomy (2 copies of maternal chromosome 15)
- Remainder are point mutations and imprinting defects

Incidence

- 1/10,000–1/25,000

Clinical

- Phenotype:
  - Hypotonia, hypogonadism, obesity, small hands and feet, almond shaped eyes, short stature
- Neurologic:
  - Mild to moderate mental retardation
- Other:
  - Failure to thrive, hyperphagia
- Life Expectancy:
  - Most survive into adulthood

Laboratory

- Cytogenetic analysis and/or Fluorescent In Situ Hybridization (FISH) detects deletion
- Molecular methylation analysis identifies missing paternal allele
- Uniparental disomy studies identify 2 copies of maternal allele

Treatment

- Not curable, supportive/symptomatic

Cri du Chat Syndrome

Chromosome and Gene Location

- 5p15

Inheritance

- 85% sporadic (85% deletion, 4% mosaics, 3% ring chromosomes, 4% translocations)
- 12% familial translocations, inversions & parental mosaicism

Incidence

- 1/50,000

Clinical

- Phenotype:
  - "Cat-like" cry, microcephaly, hypertelorism, micrognathia, transverse palmar crease, hypotonia
- Neurologic:
  - Mental retardation
- Other:
  - 50% no speech, growth failure
- Life Expectancy:
  - Most survive into adulthood

Laboratory

- Cytogenetic and/or Fluorescent In Situ Hybridization (FISH) identifies abnormality of 5p15

Treatment

- Not curable, supportive/symptomatic

DiGeorge (DGS)/ Velo-Cardio-Facial Syndrome (VCF)

Chromosome and Gene Location

- 22q11.2

Inheritance

- 90% are deletions involving multiple genes, most cases are sporadic
- Approximately 10–15% are familial (autosomal dominant)

Incidence

- 1/4000

Clinical

- The disturbance of neural crest migration of pharyngeal pouches is thought to cause clinical features
- Interpatient variability is dependent on extent of deletion
- Phenotype:
  - Hypertelorism, down slanting eyes, high arched palate, micrognathia, low set ears, bulbous nose, square nasal tip, cleft palate (VCF), small open mouth, retrognathia, microcephaly, slender hands and digits
- Cardiac Manifestations:
  - Tetralogy of Fallot, outflow tract defect, right sided aortic arch, interrupted aortic arch, ventricular septal defect
- Neurologic:
  - Mild-moderate learning difficulties, seizures, tetany, emotional and behavioral problems
- Other:
  - Hypoparathyroidism, neonatal hypocalcemia (DGS), immune /T-cell deficit (DGS), hypernasal speech, hypospadius, short stature
- Life Expectancy:
  - Most reach adulthood if cardiac lesion is not life threatening

Laboratory

- Biochemical:
  - Hypocalcemia, decreased T-Cells
- Cytogenetics:
  - Deletion 22q11 usually not visible on routine chromosome studies Fluorescent In Situ Hybridization (FISH) studies demonstrate deletion

Treatment

- Cardiac surgery, calcium supplements, supportive care

Smith-Magenis Syndrome

Chromosome and Gene Location

- 17p11.2

Inheritance

- Most are sporadic interstitial deletions, a few cases of pericentric inversions with breakpoints in 17p11

Incidence

- 1/50,000

Clinical

- Phenotype:
  - Brachycephaly, flat, broad mid-face, prominent forehead
- Neurologic:
  - Seizures, mental retardation

- Other:
  - Hyperactivity behavioral problems including: screaming outburst, speech delay, self-mutilation
- Life Expectancy:
  - Most survive into adulthood

Laboratory x

- Cytogenetic analysis and/or Fluorescent In Situ Hybridization (FISH) detects deletion

Treatment

- Not curable, supportive/symptomatic

Beckwith Wiedemann Syndrome

Chromosome and Gene Location

- 11p15, Insulin-like growth factor II is a candidate gene

Inheritance

- 85% sporadic (20% of these have paternal uniparental disomy [two copies of paternal segment of chromosome 11], arises from somatic recombination)
- 10–15% familial-linkage to 11p15, autosomal dominant with incomplete penetrance and variable expressivity, increased transmission through females

Incidence

- 1/14,000

Clinical

- Phenotype:
  - Macroglossia, macrosomia, nephromegaly, splenomegaly, mid-face hypoplasia, cryptorchidism
- Neurologic:
  - Seizures, developmental delay
- Other:
  - Omphalocele, increased risk for embryonal tumors (Wilms tumor, adrenal cortical carcinoma, hepatoblastoma, rhabdomysosarcoma, neuroblastoma)
- Life Expectancy:
  - Most survive into adulthood

Laboratory

- Cytogenetic analysis identifies paternal duplications, translocations or inversions of 11p15 (fewer than 15% of cases)

Treatment

- Not curable, supportive/symptomatic

Miller-Dieker Syndrome

Chromosome and Gene Location

- 17p13.3

Inheritance

- 90% are sporadic deletions of 17p13.3

Incidence

- 1/100,000

Clinical

- Phenotype:
  - Lissencephaly (smooth brain), microcephaly, anteverted nostrils, carp mouth, agenesis of corpus callosum
- Neurologic:
  - Seizures, mental retardation
- Other:
  - Failure to thrive, absent speech
- Life Expectancy:
  - Variable, but most die in childhood

Laboratory

- Cytogenetic analysis and/or Fluorescent in situ Hybridization (FISH) detects deletion of 17p13.3

Treatment

- Not curable, supportive/symptomatic

William Syndrome

Chromosome and Gene Location

- 7q11.23

Inheritance

- Mostly sporadic, a few cases of autosomal dominant inheritance have been reported

Incidence

- 1/20,000 live births

Clinical

- Phenotype:
  - Elfin facies, broad forehead, bitemporal narrowness, periorbital fullness, wide mouth, broad nasal tip, long philtrum, micrognathia, supravalvular aortic stenosis, peripheral pulmonary stenosis, growth retardation, small widely spaced teeth
- Neurologic:
  - Mental retardation
- Other:
  - Gregarious personality, joint limitations, hypercalcemia
- Life Expectancy:
  - Most survive into adulthood

Molecular Genetics

- Contiguous gene syndrome with deletion of 7q11.23. Elastin gene locus is deleted in approximately 90%, which most likely accounts for widespread abnormal connective tissue vasculature

Laboratory

- Deletion usually not visible by routine chromosome analysis, Fluorescent In Situ Hybridization (FISH) analysis is usually necessary to identify deletion. Elevated serum calcium

Treatment

- Not curable, supportive/symptomatic
- Elimination of vitamin D and calcium from the diet

Chromosome Breakage Syndromes

Fanconi Anemia

Chromosome and Gene Location

- Genetically heterogeneous (multiple gene loci involved)
- The majority of families show linkage to 16q24.3

Inheritance

- Autosomal Recessive

Incidence

- 1/22,000

Clinical

- Short stature
- Absent or hypoplastic radii and thumbs
- Brown skin pigmentation
- Pancytopenia
- Anemia
- Increased incidence of leukemia
- Kidney defects
  - Absent
  - Duplication of kidney or collecting system
  - Horseshoe kidney
- Cryptorchidism
- Mental retardation (onset usually by 15 years)

Molecular Genetics

- Cells are defective in ability to excise ultraviolet induced pyrimidine dimers but are capable of single strand break production and unscheduled DNA synthesis-specific exonuclease which corrects distortions in the tertiary structure of DNA

Laboratory

- Increased chromosomal breakage, gaps, and rearrangements after exposure to diepoxybutane or mitomycin C (DNA alkylating agents)

Treatment

- Supportive
- Transfusions
- Steroid therapy
- Bone marrow transplantation for anemia and leukemia

Bloom Syndrome

Chromosome and Gene Location

- 15q26.1

Inheritance

- Autosomal Recessive

Incidence

- Rare

Clinical

- Short stature
- Facial erythema
- Increased susceptibility to infections
- Increase incidence of leukemia
- High pitched voice
- Normal intelligence
- Most frequent in Ashkenazi Jewish population

Molecular Genetics

- Decreased activity of DNA ligase I leads to genomic instability and multi-system anomalies

Laboratory

- Increased chromosomal sister chromatid exchange (12X normal)
- Quadrilateral formation is increased as are random breaks and translocations between non-homologous chromosomes

Treatment

- Not curable, supportive/symptomatic
- Minimize exposure to radiation/mutagenic agents

Ataxia Telangiectasia

Chromosome and Gene Location

- 11q22–q23

Inheritance

- Autosomal Recessive

Incidence

- 1/40,000 – 1/100,000

Clinical

- Cerebellar ataxia, conjunctival telangiectasia, IgA deficiency
- Predisposition to malignancy
- Increased infections
- Growth failure, onset first 2 years of life

- Death usually occurs in 2nd or 3rd decade

Molecular Genetics

- Defect in X-ray induced DNA repair mechanisms

Laboratory

- Increased chromosomal breakage and X-radiation sensitivity; especially with breakpoints at sites of immunoglobin genes or receptors

Treatment

- Not curable, supportive/symptomatic
- Treatment of infections and neoplasms, avoidance of radiation

Xeroderma Pigmentosum

Chromosome and Gene Location

- Multiple loci

Inheritance

- Autosomal Recessive

Incidence

- 1/250,000

Clinical

- Sensitivity to sunlight (blistering and freckling with little exposure)
- Predisposition to malignancy (especially skin cancer)
- In some, mental deterioration
- Death usually occurs before adulthood

Molecular Genetics

- Defective in ultraviolet-induced DNA repair mechanisms
- Skin cells unable to repair sunlight induced DNA damage

Laboratory

- Cytogenetic analysis identifies clones of cells with chromosome abnormalities, increased ultraviolet induced chromosome breaks and sister chromatin exchanges

Treatment

- Not curable, supportive/symptomatic
- Avoidance of ultraviolet light

SINGLE GENE DISORDERS

Neuromuscular Disorders

Huntington Disease

Chromosome and Gene Location

- 4p16.3

Inheritance

- Autosomal Dominant

Incidence

- 3/100,000 –7/100,000

Clinical

- Slowly progressive disorder with onset usually in mid-life
- Manifestations include any combination of mental impairment, restlessness, choreiform movements, psychiatric changes, and dysarthria
- Life expectancy is approximately 50 to 60 years

Molecular Genetics

- Disease results from an expansion of a trinucleotide CAG repeat in the Huntington gene
- Normal alleles range from 10–26 repeats
- Individuals with Huntington Disease have greater than 36 repeats
- Allele sizes of 27–35 are intermediate, not associated with symptoms, but may have risk of expansion in next generation

Laboratory

- Molecular analysis identifies expanded repeat
- Computed tomography and magnetic resonance imaging identifies atrophy of the caudate nucleus and putamen

Treatment

- Not curable, supportive/symptomatic

Duchenne/Becker Muscular Dystrophy (DMD/BMD)

Chromosome and Gene Location

- Xp21

Inheritance

- X-linked Recessive

Incidence

- 1/3500 (male) 1/1500 (female carriers)
- 30% of cases are new mutations
- 5–15% of sporadic cases are result of mother being gonadal mosaic (carries a subpopulation of oocytes with the mutation)

Clinical

- Duchenne Muscular Dystrophy:
  - Difficulties involving gait, jumping, and climbing stairs
  - Gower sign (use of arms to push themselves into standing position by moving their hands up their thighs, indicative of hip weakness)
  - Pseudohypertrophy of the calf muscles, muscle weakness
  - Dilated cardiomyopathy
  - Gastrointestinal dilation
  - 25%–35% with mental retardation
  - Loss of ability to walk by age 10–15 years
  - Death usually occurs in the 2nd decade
- Becker Muscular Dystrophy:
  - Milder course with onset in 1st or 2nd decade
  - Slower progression
  - Survival into 30's and 40's
  - Cardiac and mental problems are rare

Molecular Genetics

- Dystrophin is a protein found in the sarcolemma of normal muscle. It is thought to be involved in the anchoring of the cytoskeleton of the muscle cell to extracellular proteins
- DMD and BMD result from alterations within the dystrophin gene [deletions (60%), duplications (5%) point mutations (35%)]
- Deletions which disrupt the reading frame of the triplet code (frameshift mutations) lead to DMD
- Deletions which do not disrupt the reading frame (in-frame mutations) most often lead to BMD

Laboratory

- Pathology:
  - Variability in size of muscle fibers, degeneration, atrophy of individual fibers and proliferation of endomysial and perimysial connective tissue Antidystrophin antibodies detect <3% of normal dystrophin in DMD, 3–10% in mild DMD or severe BMD, >20% normal dystrophin correlates with BMD
- Creatine Kinase (CK):
  - 50–100X the normal range, 2/3 of carriers have elevated CK. Caution must be used as CK levels vary with age, pregnancy , and activity
- Genetics:
  - Deletions and duplications detected directly by molecular analysis, linkage analysis available when deletion/duplication negative

Treatment

- Not curable, supportive/symptomatic

Myotonic Dystrophy

Chromosome and Gene Location:

- 19p13.3

Inheritance

- Autosomal Dominant

Incidence

- 1/8000

Clinical

- Myotonia (impaired muscle relaxation)
- Muscle wasting
- Cataracts
- Frontal balding
- Cardiac conduction disturbances
- Swallowing and speech disability
- Facial weakness
- Neonatal hypotonia
- Delayed motor development
- Wide phenotypic range from severely affected infants to minimally symptomatic elderly

Molecular Genetics

- Expansion of a trinucleotide CTG repeat in the Myotonic Dystrophy Protein Kinase gene
  - 5–40—normal allele size
  - 50–100—minimally affected
  - 2000+—severely affected (congenital form)
- Expansion occurs preferentially through maternal transmission

Laboratory

- Molecular analysis identifies expanded repeat
- Electromyogram shows slow nerve conduction velocities

Treatment

- Not curable, supportive/symptomatic
- Monitor for cataracts, cardiac conduction disturbances, diabetes, sleep apnea and other endocrine problems

Friedreich Ataxia

Chromosome and Gene Location

- 9q13

Inheritance

- Autosomal Recessive

Incidence

- 1/100,000

Clinical

- Age of onset is approximately 10 to 16 years
- Ataxia, muscle weakness, dysarthria, absent deep tendon reflexes, scoliosis, hypertrophic cardiomyopathy, hammer toes, pes cavus, diabetes (10–20%)
- Normal intelligence

Life Expectancy

- 30–60y

Molecular Genetics

- Expansion in a trinucleotide GAA repeat in the Frataxin gene
- Normal alleles range from 7–22 repeats, affected individuals have >200 repeats

Laboratory

- Molecular analysis identifies expanded repeat
- Electromyogram shows slow nerve conduction velocities

Treatment

- Not curable, supportive/symptomatic

Spinal Cerebellar Ataxia (SCA) (Types I–VIII)

Chromosome and Gene Location

- See Table 2–1

Inheritance

- Autosomal Dominant

Incidence

- 1/20,000

Clinical Findings

- Adult onset gait ataxia, dysarthria, dysphagia, ophthalmoplegia
- Decreased vibrations sense and sphincter disturbances
- Death usually occurs 10–20 years following age of onset

Molecular Genetics

- See Table 2–1

Laboratory

- Molecular analysis identifies expanded trinucleotide repeat
- Molecular genetic testing available for most subtypes

Treatment

- Not curable, supportive/symptomatic

Spinal and Bulbar Muscular Atrophy (SBMA, Kennedy Disease)

Chromosome and Gene Location

- Xq11–q12

Inheritance

- X-linked Recessive

Incidence

- 1/50,000 males

Clinical

- Teen to adult onset of muscle weakness, atrophy and fasciculations with bulbar involvement
- Androgen insensitivity (gynecomastia, reduced fertility, testicular atrophy)

Molecular Genetics

- Expansion of trinucleotide CAG repeat in the human androgen receptor gene
- Normal allele size ranges from 11–34 repeats, affected individuals have repeat sizes of 36–62

Laboratory

- Molecular analysis identifies expanded repeat

Treatment

- Not curable, supportive/symptomatic
- Hormone replacement as needed

Spinal Muscular Atrophy (SMA), Types I, II, and III

Chromosome and Gene Location

- 5q

Inheritance

- Autosomal Recessive

Incidence

- 1/25,000

Clinical

- See Table 2–2

Molecular Genetics

- Survival Motor Neuron (SMN) is homozyously deleted in nearly all of Type I and II and about 80% of type III SMA

Laboratory

- Atrophy of anterior horn cells
- Molecular analysis for deletions in exon 7 and/or exon 8 of SMN gene

Treatment

- Not curable, supportive/symptomatic

Charcot Marie Tooth Disease

Chromosome and Gene Location

- At least 9 loci have been identified, see table for most common

Table 2–1. Expansion of Trinucleotide CAG Repeat in Spinal Cerebellar Ataxia

	SCA1	*SCA2*	*SCA3*	*SCA4*	*SCA5*	*SCA6*	*SCA7*	*SCA8*
Gene Location	6p	12q	14q	16q	11cen	19p	3p	13q21
Normal Allele	19–39	14–31	14–34	NA	NA	4–16	14-35	16–91
Mutant Allele	39–81	34–57	61–85	NA	NA	21–27	37-200	>100

NA - information not yet available

Table 2–2. Spinal Muscular Atrophy

Type I (Werdnig-Hoffmann)	***Type II (Intermediate Type)***	***Type III (Kugelberg-Welander)***
Reduced fetal movements	Mild/arrested type 1	Waddling gait
General muscle weakness	Non-ambulatory	Muscle weakness
Respiratory muscle weakness	Increased life span when respiratory function preserved	Fasciculations
Arthrogryposis		Contractures
Tongue fasciculations		Ambulation feasible
Contractures		
Death often by 1 year		

Inheritance

- Autosomal Dominant
- Autosomal Recessive
- X-linked

Incidence

- 1/2500

Clinical

- Progressive muscular atrophy and weakness of feet and legs (during first 2 decades), pes cavus, central nervous system involvement includes optic and cochlear nerve
- CMT1 is differentiated on the basis of being a demyelinating neuropathy, with decreased nerve conduction velocities and absent deep tendon reflexes
- CMT2 is an axonal neuropathy with normal or slightly decreased conduction velocities, deep tendon reflexes are preserved

Molecular Genetics

- See Table 2–3

Laboratory

- Molecular testing is available for 17p duplication for CMT1A, and connexin 32 for X-linked CMT

Treatment

- Not curable, supportive/symptomatic

Hereditary Neuropathy with Liability to Pressure Palsies

Chromosome and Gene Location

- 17p11.2

Inheritance

- Autosomal Dominant

Incidence

- Unknown

Clinical

- Recurrent transient palsies
- Sensory dysfunction (result of compression to peripheral nerve)

Table 2–3. Molecular Genetics of Charcot Marie Tooth Disease

Disorder (% of CMT)	*CMT1A (57%)*	*CMT2 (19%)*	*X-linked CMT (21%)*
Gene location	17p	1q36-p35	X
Inheritance	Autosomal Dominant	Autosomal Dominant	X-linked dominant
Molecular genetics	1.5kb duplication, candidate gene peripheral myelin protein 22	?	Point mutations in connexin 32

- ♦ Pes cavus
- ♦ Scoliosis

Molecular Genetics

- ♦ Deletion of peripheral myelin protein 22 gene at 17p11.2. Repetitive elements surround this region
- ♦ Unequal crossing over between misaligned repetitive elements leads to the HNPP deletion and the CMT1A duplication
- ♦ De novo mutations are most often paternally derived

Laboratory

- ♦ Sausage shaped swellings of myelin sheath (tomacula)
- ♦ Reduced motor and sensory conduction velocity
- ♦ Cytogenetics using fluorescent in situ hybridization or molecular genetics analysis identifies deletion of 17p11.2

Treatment

- ♦ Not curable, supportive/symptomatic

Skeletal Disorders

Achondroplasia

Chromosome and Gene Location

- ♦ 4p16.3

Inheritance

- ♦ Autosomal Dominant; 50–80% result from a new mutation

Incidence

- ♦ 1/25,000

Clinical

- ♦ Short stature, due to shortened limbs
- ♦ Genu varum
- ♦ Large head
- ♦ Frontal bossing
- ♦ Hypoplasia of mid-face
- ♦ Infantile hypotonia
- ♦ Gross motor developmental delay
- ♦ Normal intelligence
- ♦ Normal life expectancy
- ♦ Also at risk for cord compression due to odontoid hypoplasia

Molecular Genetics

- ♦ Mutation in transmembrane domain of Fibroblast Growth Factor transmembrane receptor (FGFR-3)

Laboratory

- ♦ X-ray implicates skeletal involvement
- ♦ Molecular testing for FGFR-3 mutation is available

Treatment

- ♦ Not curable, supportive/symptomatic

Osteogenesis Imperfecta (Types I–IV)

Chromosome and Gene Location

- ♦ COL1A1 gene (Chromosome 17)
- ♦ COL1A2 gene (Chromosome 7)

Inheritance

- ♦ Autosomal dominant, often due to new mutation

Incidence

- ♦ 1/5000–1/10,000

Clinical

- ♦ See Table 2–4

Molecular Genetics

- ♦ Collagen is the major protein of the white fibers of connective tissue, cartilage, and bone
- ♦ There have been numerous types of collagen identified

- Mutations in the pro-collagen genes, whose products make up the triple helix of Type 1 collagen, lead to the various types of Osteogenesis Imperfecta
- Clinical presentation is dependent on the extent to which the mutation alters the protein product

Laboratory

- X-ray implicates skeletal involvement
- Direct molecular analysis of pro-collagen genes available

Treatment

- Not curable, supportive/symptomatic
- Surgical intervention when indicated

Connective Tissue Disorders

Fibrillin Related

Marfan Syndrome

Chromosome and Gene Location

- 15q

Inheritance

- Autosomal Dominant
- 15–30% result from a new mutation

Incidence

- 1/10,000

Clinical

- Diagnosis based on clinical criteria
- Tall, thin habitus
- Long extremities
- Arachnodactyly
- Pectus deformity
- Scoliosis
- Ectopia lentis
- Retinal detachment
- Mitral valve prolapse
- Aortic dilation
- Aortic aneurysm
- Life expectancy is reduced to about 2/3 normal life span

Molecular Genetics

- Mutations in gene for fibrillin, a structural protein which is the major constituent of microfibrils

Laboratory

- Molecular linkage analysis to 15q for familial cases

Treatment

- Surgical intervention when indicated
- Close monitoring of heart defects as they can lead to sudden death
- Use of beta adrenergic blockade

Collagen Related

Ehlers-Danlos Syndrome

Chromosome and Gene Location

- Multiple loci for collagen genes. (1q, 2q, 7q, 9q)

Table 2–4. Clinical Findings of Osteogenesis Imperfecta

	Inheritance	*Clinical Findings*	*Abnormal Collagen Chains*
Type I	Autosomal Dominant	Bone fragility, blue sclera, hearing loss	Pro-α2(1) Pro-α1(1)
Type II	Autosomal dominant, but usually new germline mutation.	Perinatal lethal, calvarial under-mineralization, beaded ribs, compressed femurs, 6-7% recurrence risk due to parental gonadal mosaicism	Pro-α2(1) Pro-α1(1)
Type III	Autosomal Dominant/ Recessive	Multiple prenatal bone fractures, limb shortening, limb deformities, deafness, blue sclera	Pro-α2(1)
Type IV	Autosomal Dominant	Mild, short stature, mild deformity, dentinogenesis imperfecta, white sclera	Pro-α2(1)

Inheritance

- Most are Autosomal Dominant
- Some Autosomal Recessive and X linked recessive

Incidence

- 1/5000–1/10,000

Clinical

- Dependent on which type of Ehlers-Danlos is present. Features common to most types include:
  - Joint hypermobility
  - Skin fragility
  - Skin hyperextensibility
  - Blue sclera
  - Papyraceous scars
  - Kyphoscoliosis
  - Hernias
  - Short stature
  - Joint dislocation
  - Ocular fragility
- Type IV (the arterial form) is the most serious subtype, with a predisposition to arterial rupture and perforation of a hollow viscus

Molecular Genetics

- Collagen is the major protein of the white fibers of connective tissue, cartilage, and bone
- Mutations in collagen genes leads to decreased synthesis, altered secretion, and instability of collagen
- The defect for some types is unknown

Laboratory

- Direct analysis available for types, IV, VI and some forms of VII
- Histological features are non-diagnostic

Treatment

- Not curable, supportive/symptomatic

Stickler Syndrome

Chromosome and Gene Location

- 12q13, 6p21.3

Inheritance

- Autosomal Dominant

Incidence

- Unknown

Clinical

- Progressive myopia, retinal detachment, blindness
- Pierre Robin syndrome (micrognathia and abnormal smallness of the tongue, often with cleft palate)
- Severe myopia, congenital glaucoma, and retinal detachment
- Premature degenerative changes in various joints with abnormal epiphyseal development
- Mitral valve prolapse
- Cataracts

Molecular Genetics

- Genetic heterogeneity
- Some cases of Stickler syndrome result from mutations in the gene for type II collagen (COL2A1)
- A second form is caused by mutations in the gene for type VII collagen (COL11A2)

Laboratory

- Skeletal x-rays show changes of a skeletal dysplasia
- Direct molecular analysis available for COL2A1

Treatment

- Not curable, supportive/symptomatic

Alport Syndrome

Chromosome and Gene Location

- Xq13. Xq22, 2q36

Inheritance

- X-linked, Autosomal Reecessive

Incidence

- Unknown

Clinical

- Renal failure
- Sensorineural deafness,
- Lenticonus
- Macular changes

Molecular Genetics

- Alport syndrome is thought to result from mutations in the gene for type IV collagen gene
- Molecular testing on research basis

Laboratory

- Microscopic hematuria
- Urinary red cell casts
- Proteinuria
- Leukocyturia
- Abnormal glomerular basement membrane on electron microscopy

Treatment

- Not curable, supportive/symptomatic
- Kidney transplant as indicated

Hematologic Disorders

Alpha Thalassemia

- The normal adult hemoglobin is a tetramer of 2 alpha and 2 beta chains
- The alpha-thalassemias are a group of inherited conditions characterized by decreased synthesis of alpha-globin chains resulting in an imbalance of chains for the formation of the hemoglobin tetramer

Chromosome and Gene Location

- 16p13.1-pter (there are 2 alpha-globin genes present on each chromosome at this locus)

Inheritance

- Complex: individuals with alpha-thalassemia may have alterations in two, three or four alpha globin genes

Incidence

- Varies by population, being most common in African American, Southeast Asian, Mediterranean and Indian populations
- Severe forms occur almost exclusively among Asians

Clinical

- An individual with one altered gene is a silent carrier and does not have any clinical symptoms
- Individuals with two altered genes are referred as having "alpha-thalassemia trait", which is manifested by mild anemia with microcytosis, hyperplasia of marrow red cells, increased iron, and modest splenomegaly
- Hemoglobin H disease results when three alpha-globin genes are altered. This is characterized by moderate to marked anemia, enlarged liver and spleen, and marrow expansion
- Hydrops fetalis results when all four alpha genes are not functional
- The hemoglobin is formed without alpha chains and is called Hemoglobin Barts. The oxygen affinity of Hemoglobin Barts is so high that it cannot release oxygen to the tissues
- Death occurs from anoxia in utero

Molecular Genetics

- Numerous mutations have been found
- The most common type of mutation is a deletion which results from the misalignment and subsequent recombination of the alpha thalassemia genes

Laboratory

- Abnormal cell morphology
- Hemoglobin electrophoreses shows abnormal proportion of alternate hemoglobins
- Reticulocytes are used to evaluate globin chain synthesis
- Molecular genetic analysis available

Treatment

- Transfusion
- Splenectomy
- Iron chelation therapy
- Bone marrow transplantation

Beta Thalassemia

Chromosome and Gene Location

- 11p15.5

Inheritance

- Autosomal Recessive

Incidence

- Most common in Mediterranean, Middle East, South and Southeast Asia

Clinical

- Beta thalassemia becomes clinically evident as the fetal hemoglobin production decreases and adult hemoglobin is supposed to replace it (around 6 months of age)
- Normally, both alpha and beta globin chains are produced in roughly equal amounts. When beta globin synthesis is decreased, alpha globin synthesis increases
- Free alpha chains are very unstable and precipitate in the red cell
- Erythropoiesis is ineffective and results in anemia
- There is a phenomenal increase in erythropoiesis with marrow expansion and persistence of erythropoiesis in the liver and spleen
- There are numerous classes of Beta thalassemia based on the extent to which beta chain production is decreased
- Beta Thalassemia Major results from the homozygous or compound heterozygous state and is characterized by anemia, failure to thrive, fever, diarrhea, stunted growth if untreated
  - Features secondary to extramedullary hematopoiesis, chipmunk face, skeletal deformities, liver and spleen enlargement
  - Another feature is increased pigmentation
  - Death often occurs in second or third decade due to cardiac complications
- Beta Thalassemia Intermedia has milder phenotype and results from homozygosity or compound heterozygosity of alleles with a reduced beta chain production
  - May result from co-inheritance of alpha and beta thalassemia
  - Variable presentation

Molecular Genetics

- Numerous alterations have been described including:
  - Deletions
  - Transcriptional mutations

- RNA processing mutations
- Nonsense and frameshift mutations

Laboratory

- Abnormal cell morphology
- Elevated iron
- Hyperplastic marrow with hyperplasia of red cell precursors
- Hemoglobin electrophoreses shows increases in minor hemoglobins
- Molecular analysis available

Treatment

- Frequent transfusions
- Splenectomy
- Chelation therapy
- Bone marrow transplantation

Sickle Cell Anemia

Chromosome and Gene Location

- 11p15.5

Inheritance

- Autosomal Recessive

Incidence

- 1/500 African American births

Clinical

- Failure to thrive
- Repeated infections
- Pallor
- Palpable spleen
- Painful swelling
- Splenomegaly
- Painful crisis due to vasoocclusive episodes usually affecting the limbs, back, abdomen and chest
- Chronic organ damage (renal, hepatic, retinopathy, leg ulcerations)

Molecular Genetics

- Glutamic acid to valine substitution in Beta chain alters the configuration of the hemoglobin molecule
  - This causes the cells to sickle and obstruct blood flow in small vessels leading to ischemia of tissues and organs

Laboratory

- Sickling and reduced oxygen tension of red cells
- Hemoglobin electrophoresis and /or isoelectric focusing identifies abnormal hemoglobin (part of many state's newborn screening programs)
- Direct molecular testing for nucleotide substitution

Treatment

- Prophylactic penicillin in infants and children
- Transfusion during splenic or hepatic sequestration crises

Hemophilia A

Chromosome and Gene Location

- Xq28

Inheritance

- X-linked recessive

Incidence

- 1/5000 to 1/10,000

Clinical

- The clinical severity is related to the level of Factor VIII coagulant activity in the plasma. If level is <1% of normal the disease is severe and is characterized by spontaneous recurrent bleeds into the hip, shoulder, knee, ankle and elbow
- If untreated, severe pain and loss of cartilage may result
- Bleeding into muscles may result in nerve compression
- Intracranial bleeding may occur and may be fatal
- In moderate hemophilia (1–5% of normal Factor VIII activity), bleeding usually occurs following mild trauma, excessive bruising and some arthrosis may also be present
- In mild hemophilia (>6% Factor VIII activity) bleeding usually follows severe trauma, dental work or surgery

Molecular Genetics

- Numerous mutations have been identified:
  - Approximately 45% of severe hemophiliacs have an inversion within the gene
  - Point mutations are also common (32% of all hemophilia A)
  - Mutations result in decreased Factor VIII coagulant activity

Laboratory

- Prolonged partial thromboplastin time (PTT)
- Normal prothrombin time(PT)
- Normal thrombin clotting time (TCT)
- Normal von Willebrand factor and ristocetin cofactor
- Decreased Factor VIII clotting activity
- Molecular genetic analysis for mutation detection and linkage analysis

Treatment

- Avoid trauma and anitcoagulants
- Factor VIII replacement therapy to raise Factor VIII activity (approximately 10–15% of patients develop inhibitors against Factor VIII)

Hemophilia B

Chromosome and Gene Location

- Xq27.1-q27.2

Inheritance

- X-linked recessive

Incidence

- 1/40,000

Clinical

- The clinical severity is related to the level of Factor IX coagulant activity in the plasma and is very similar to classical Hemophilia A
- If level is <1% of normal, the disease is severe and is characterized by spontaneous recurrent bleeds
- Intracranial bleeding may occur and may be fatal
- In moderate hemophilia (1–5% of normal Factor IX activity), bleeding usually occurs following mild trauma, excessive bruising and some arthrosis may also be present
- In mild hemophilia (>6% Factor IX activity) bleeding usually follows only severe trauma, dental work or surgery

Molecular Genetics

- Almost 500 unique mutations have been described including many deletions and point mutations, however no common recurrent mutation
- Mutations result in decrease Factor IX activity

Laboratory

- Prolonged partial thromboplastin time (PTT)
- Normal prothrombin time (PT)
- Normal thrombin clotting time (TCT)
- Normal von Willebrand factor and ristocetin cofactor
- Decreased Factor IX clotting activity
- Molecular genetic analysis for mutation detection and linkage analysis

Treatment

- Avoid trauma and anticoagulants
- Apply pressure and cold compresses to bleeding sites
- Factor replacement therapy to raise Factor IX

von Willebrand Disease

Chromosome and Gene Location

- 12p

Inheritance

- Autosomal Dominant (70%) and Autosomal Recessive

Incidence

- 1/8000 for Autosomal dominant type
- Autosomal recessive inheritance:
  - 1/ 2,000,000–1/300,000 in Western Europeans and Scandinavians
  - 1/200,000 in Middle Eastern Arabs

Clinical

- Bleeding from mucous membranes (nose, gums)
- Menorrhagia
- Prolonged bleeding after injury

Molecular Genetics

- Numerous mutations characterized including deletions, missense and nonsense mutations, leading to decreased activity of von Willebrand factor

Laboratory

- Prolonged bleeding time
- Decreased Factor activity (von Willebrand and Factor VIII)
- Reduced ristocetin cofactor, normal or prolonged PTT
- Normal PT, thrombin time and platelet count

Treatment

- Avoid trauma and anticoagulants
- Apply pressure and cold compresses to bleeding sites
- Replacement therapy for von Willebrand factor

Other Genetic Disorders

Cystic Fibrosis

Chromosome and Gene Location

- 7q31

Inheritance

- Autosomal Recessive

Incidence

- 1/2500 in the Caucasian population, lower in other ethnic groups

Clinical

- Chronic pulmonary disease
- Pancreatic insufficiency
- Elevated sweat electrolytes
- Males generally infertile due to absence of the vasdeferens
- Meconium ileus in neonate (10–16% of patients)
- 50% survival at age 30

Molecular Genetics

- Defect in the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) gene results in:
  - Abnormal electrolyte transport
  - Excessive sodium absorption
  - Decreased chloride secretion

- Over 600 mutations described:
  - DeltaF508 most common in Caucasian (75% of carriers)
  - W1282X most common in Ashkenazi Jews (60% of carriers)

Laboratory

- Molecular analysis identifies approximately 90% of CF mutations
- Elevated sweat chloride (>60mmol/l)

Treatment

- Antibiotics for control of respiratory infections
- Postural drainage and inhalation therapy
- Pancreatic enzyme-replacement therapy

Albinism (Oculocutaneous Albinism) (OCA type 1)

Chromosome and Gene Location

- 11q14–21 (OCA1)
- There are numerous other types of Albinism

Inheritance

- Autosomal Recessive

Incidence

- 1/30,000

Clinical

- Hypopigmented skin and hair
- Nystagmus
- Reduced iris and retinal pigment
- Foveal hypoplasia

Molecular Genetics

- Melanin is the dark brown to black pigment that is normally produced in the skin, hair, pigmented coat of the retina, and in the medulla and zona reticularis of the adrenal gland
- Tyrosinase is an enzyme critical to melanin production
- Mutations in the tyrosinase gene therefore alter melanin production and lead to hypopigmentation and ocular changes
- Mutations in other genes involved in melanocyte production, transportation, or proliferation lead to various other types of Albinism

Laboratory

- Deficient tyrosinase activity on hairbulb
- Molecular genetic analysis available

Treatment

- Not correctable, supportive/symptomatic
- Avoidance of direct sunlight

Fragile X Syndrome

Chromosome and Gene Location

- Xq27.3

Inheritance

- X-linked dominant

Incidence

- 1/1500 males (accounts for up to 5% of male mental retardation)
- 1/2500 females

Clinical

- Mental retardation (IQ 50–60)
- Large narrow face with moderately increased head circumference
- Macroorchidism (80%)
- Large ears

Molecular Genetics

- Expanded CGG repetitive element within FMR-1 gene
- 6–50—Normal
- 50–200—Premutation (meiotic instability), no associated phenotype
- 250–4000—Full mutation, leads to abnormal methylation and transcriptional suppression of FMR-1 gene and absence of FMRP (RNA binding protein)
- CGG repeat expansion is through female germline (males transmit premutation repeat without much change)
- Sherman's Paradox:
  - Describes apparent deviation from traditional Mendelian inheritance and varies according to whether the causative gene is transmitted through a male or female
  - In Fragile X, this is the result of expansion from premutation to full mutation through the female germline

Laboratory

- Molecular analysis detects expanded CGG repeat and is now the test of choice
- Chromosomal fragile site is apparent when cultured in folate deficient /thymidine inhibiting

Treatment

- Not curable
- Supportive/symptomatic

Neurofibromatosis Type I (von Recklinghausen)

Chromosome and Gene Location

- 17q11.2

Inheritance

- Autosomal Dominant. 50% are due to new mutation and 50% are inherited from a parent

Incidence

- 1/4000

Clinical

- Diagnosis based on established clinical criteria
- Neurofibromas
- Café au lait spots
- Axillary freckling
- Lisch nodules
- Optic gliomas
- Intellectual handicap (40%)

Molecular Genetics

- The NF1 gene appears to be a tumor-suppressor gene. Its product,called neurofibromin, is a GTPase activating protein (GAP)-like polypeptide that appears to down-regulate the RAS oncogene
- Protein truncating mutations have been found in approximately 70% of affected patients

Laboratory

- Molecular testing identifies mutation in approximately 70% of individuals

Treatment

- Surgical intervention when indicated

Neurofibromatosis Type II

Chromosome and Gene Location

- 22q

Inheritance

- Autosomal Dominant
- 50% are new mutations

Incidence

- 1/50,000

Clinical

- Diagnosis based on established clinical criteria
- Vestibular schwannomas (bilateral acoustic neuromas)
- Loss of hearing, presenile lens opacities
- Subcapsular cataracts

Molecular Genetics

- The NF2 gene appears to be a tumor-suppressor gene
- Numerous mutations have been identified

Laboratory

- Molecular analysis available
- Bilateral eighth-nerve masses on computerized tomography or magnetic resonance imaging

Treatment

- Surgical intervention when indicated

Tuberous Sclerosis

Chromosome and Gene Location

- 9q33–34
- 16p13.3

Inheritance

- Autosomal dominant, with reduced penetrance
- 60–75% are new mutations in the family

Incidence

- 1/30,000

Clinical

- Diagnosis based on established clinical criteria
- Highly variable
- Facial angiofibromas
- Hypopigmented or leaf shape spots (by Woodslamp)
- Shagreen patches
- Seizures
- Mental retardation
- Subependymal giant-cell astrocytomas
- Renal cell cancer or renal cysts
- Angiomyolipomas
- Cardiac rhabdomyomas
- Cortical tubers
- Subependymal nodules
- Retinal hamartomas
- Dental enamel pits

Molecular Genetics

- Approximately half of the families are linked to TSC1 on chromosome 9 and half are linked to TSC2 on chromosome 16
- Numerous mutations have been reported in both genes

Laboratory

- Linkage analysis is available, but may not be informative for some families

Treatment

- Not curable, supportive/symptomatic
- Surgical removal of tumors

METABOLIC DISORDERS

Amino Acid Disorders

Phenylketonuria

Chromosome and Gene Location

- 12q24

Inheritance

- Autosomal Recessive

Incidence

- 1/10,000 to 1/25000 (lower in African Americans and Ashkenazi Jews)

Clinical

- Mental retardation
- Seizures
- Hyperactivity
- Eczema
- Hypopigmentation
- ”Mousey” odor
- Maternal PKU - Children born to mothers with PKU have a high risk (90%) of having mental retardation, microcephaly, impaired growth and cardiac malformations if mothers have not received dietary restriction of phenylalanine during pregnancy

Molecular Genetics

- Mutations in phenylalanine hydroxylase gene causes:
  - Inactivation of enzyme (more than 100 described)
  - Disrupting the conversion of phenylalanine to tyrosine with subsequent hyperphenylalaninemia

Laboratory

- Newborn screening detects blood phenylalanine (>1.0–1.2mM) using fluorometric or Guthrie Bacterial inhibition assay
- Molecular genetic analysis available for positive screens

Treatment

- Low phenylalanine diet supplemented with tyrosine throughout life

Tyrosinemia Type 1 (most prevalent)

Chromosome and Gene Location

- 15q23–q25

Inheritance

- Autosomal Recessive

Incidence

- Varies by population, highest incidence along the St. Laurence waterway in Canada (1/1846)

Clinical

- Vomiting, acidosis
- Diarrhea
- Failure to thrive
- Rickets
- Hepatic cirrhosis
- Fanconi renotubular syndrome
- Urine odor of rotten cabbage (caused from methionine metabolites)
- Increased risk for hepatocellular carcinoma

Molecular Genetics

- Mutations in the gene for Tyrosinemia inactivate the enzyme fumarylacetoacetate hydrolase which results in the accumulation of tyrosine and its metabolites (succinylacetoacetate, succinylacetone, and fumarylacetone) in the liver and kidney
- Numerous mutations have been found and are generally population specific

Laboratory

- Increased urine tyrosine and metabolites and succinyl acetone
- Decreased fumarylacetoacetate hydrolase activity in liver biopsy specimens or cultured fibroblasts or chorionic villi sample
- Elevated succinylacetone in amniotic fluid
- Molecular analysis also available

Treatment

- Low phenylalanine, tyrosine, and methionine diet delays but does not stop progression of disease

Maple Syrup Urine Disease

Chromosome and Gene Location

- 19q13.1–q13.2, (type 1-E1a subunit)
- 1p31 (type 2-E2 subunit)
- 6p22-p21 (type 3-E1b subunit)

Inheritance

- Autosomal Recessive

Incidence

- 1/125,000–1/300,000

Clinical

- Variable based on type, level of enzyme deficiency and management of acute episodes
- Features include:
  - Apnea
  - Hypoglycemia

- Poor feeding
- Maple syrup odor of urine and sweat
- Vomiting
- Lethargy
- Hypertonicity
- Muscle rigidity
- Seizures
- Bilateral ptosis

Molecular Genetics

- The branched chain alpha-ketoacid dehydrogenase is a mitochrondrial enzyme consisting of 4 subunits; E1a, E1b, E2, and E3 (each subunit is located on a different chromosome, see above.)
- The enzyme system is responsible for the decarboxylation of the branched-chain amino acids; leucine, isoleucine, and valine
- Mutations in the genes encoding the various subunits result in defective expression and build up of the branched chain amino acids and their metabolites in the blood, urine, and cerebral spinal fluid

Laboratory

- Deficiency of branched chain alpha ketoacid dehydrogenase activity in leukocytes
- Cultured skin fibroblasts (also chorionic villi and amniocytes for prenatal diagnosis)
- Elevation of leucine, isoleucine, valine, alloisoleucine, depressed alanine in serum and urine

Treatment

- Not curable, supportive/symptomatic
- Manage acute episodes
- Reduce intake of branched chain amino acids by using special formulas and reducing protein intake

Homocystinuria

Chromosome and Gene Location

- 21q22.3

Inheritance

- Autosomal recessive

Incidence

- 1/100,000

Clinical

- Dislocation of ocular lens
- Myopia
- Strabismus
- Cataract
- Glaucoma
- Thinning and lengthening of the long bones
- Osteoporosis
- Scoliosis
- High arched palate
- Pes cavus
- Genu valgum
- Biconcave vertebrae
- Thromboembolism
- Bluish mottling of the skin on legs and hands
- Mental retardation and seizures

Molecular Genetics

- The enzyme cystathionine-B-synthase (CBS) converts homocysteine to serine and cystathionine
- Mutations in the gene encoding the enzyme result in an inactivation of this enzyme which leads to elevated methionine and homocysteine levels, and low cysteine levels

Laboratory

- Homocysteine in urine
- Hyperhomocystinemia with reduced cysteine and increased methionine in plasma or serum. Decreased enzyme activity in fibroblasts, liver biopsy specimens or PHA stimulated lymphocytes (also amniocytes for prenatal diagnosis)
- Obligate carriers have 20–50% enzyme activity
- Molecular analysis available for mutation detection

Treatment

- High doses of pyridoxine (vitamin B6), which is a cofactor of CBS are given to decrease homocysteine levels (increases conversion of homocysteine to cysteine)
- Folic acid permits response to pyridoxine
- Betaine is used in pyroxidine unresponsive patients to lower plasma homocysteine levels by allowing conversion to methionine
- Low methionine diets reduce accumulation of methionine and homocysteine and their metabolites
- Patients treated from newborn period have had fewer complications than those treated late or untreated

Urea Cycle Disorders

- The urea cycle functions to prevent the accumulation of toxic nitrogenous compounds and also contains several reactions required for the synthesis of arginine
- The urea cycle consists of five biochemical reactions. Defects in the biosynthesis of any of the 5 expressed enzymes in this pathway lead to disease

Chromosome and Gene Location

- See Table 2–5

Inheritance

- See Table 2–5

Incidence

- See Table 2–5

Clinical

- All defects with the exception of arginase deficiency result in a similar clinical phenotype which includes:
  - Lethargy
  - Coma
  - Hypotonia
  - Seizures
  - Persistent vomiting
  - Poor feeding
  - Hepatomegaly
- The onset usually occurs after feeding in newborn period or after infections or protein overload
- In arginase deficiency, children are often asymptomatic for the first few months to years of life
- Clinical features include:
  - Loss of developmental milestones
  - Increased clumsiness
  - Spastic quadriplegia with loss of ambulation
  - Loss of speech
  - Seizures
  - Progressive mental retardation

Molecular Genetics

- See table for enzyme involved. Enzyme defects lead to the accumulation of ammonia and alters levels of other amino acids
- Ammonia is a neurotoxin that adversely affects the CNS

Laboratory

- Hyperammonia, altered amino acids levels specific to each reaction
- Deficient enzyme activity
- Prenatal diagnosis is also available through enzyme analysis or molecular testing (see table)

Treatment

- Not curable, supportive/symptomatic
- Control of and avoidance of acute episodes
- Restrict protein, high caloric diet to minimize break-down of protein
- Prognosis is better if disorder is treated promptly

Organic Acidemias

Isovaleric Acidemia

Chromosome and Gene Location

- 15q14-q15

Inheritance

- Autosomal Recessive

Incidence

- Rare

Clinical

- Usually presents within the first few days of life

Table 2-5. Urea Cycle Disorders

	Chromosome	*Enzyme*	*Inheritance*	*Incidence*	*Molecular Analysis*
Carbamyl Phosphate Synthetase Deficiency	2q35	Carbamyl phosphate synthetase	Autosomal recessive	1/60,000	Linkage
Orithine Transcarbamylase Deficiency	Xp21.1	Orithine transcarbamylase	X-linked recessive	1/30,000	Direct and linkage
Citrullinemia	9q34	Argininosuccinate sunthetase	Autosomal recessive	Rare	Linkage
Arginosuccininc Aciduria	7cen-q11.2	Argininosuccinate lyase	Autosomal recessive	1/70,000	Not available
Argininemia	6q23	Arginase	Autosomal recessive	Rare	Not available

Symptoms include:
- Acute attacks of vomiting
- Acidosis
- Ataxia
- Lethargy
- Coma
- Seizures
- Mental retardation

♦ Attacks are usually triggered by stresses such as infections or surgery

Molecular Genetics

♦ Isovaleryl CoA dehydrogenase catalyzes the conversion of isovaleric acid to 3-methylcrotonic acid in the branch-chain amino acid leucine degradation pathway

♦ Deficient isovaleryl CoA dehydrogenase results in the accumulation of isovaleric acid and its metabolites, which are toxic to the body

Laboratory

♦ Elevated isovaleric acid

♦ Hyperammonemia

♦ Hypocalcemia pancytopenia

♦ Neutropenia

♦ Thrombocytopenia

♦ Anemia

♦ Elevated urine isovalerylglycine in acute attack

♦ Deficiency of isovaleryl CoA dehydrogenase in leukocytes or cultured skin fibroblasts (chorionic villi or amniocytes may be used for prenatal diagnosis)

Treatment

♦ Not curable, supportive/symptomatic

♦ Avoidance of and symptomatic control of acute episodes

♦ Correct dehydration, electrolyte disturbances, and metabolic acidosis

♦ Reduce protein intake

♦ Remove excess isovalerylic acid by use of glycine and carnitine (allows for urinary excretion)

Propionic Acidemia

Chromosome and Gene Location

♦ 13q32

Inheritance

♦ Autosomal Recessive

Incidence

♦ Rare

Clinical

♦ Onset occurs within the first few weeks of life

♦ Symptoms include:
- Apnea
- Hypoglycemia
- Poor feeding
- Vomiting
- Lethargy
- Coma
- Hypotonia
- Seizures
- Frequent infections
- Osteoporosis
- Mental retardation

♦ Symptoms may be triggered by infections, constipation, and protein overload

Molecular Genetics

♦ Propionyl-CoA-Carboxylase (PCCA) is a mitochondrial enzyme consisting of 12 subunits (6 alpha-subunits and 6 beta-subunits)

♦ The gene for each subunit is located on different chromosomes: Chromosome 13 (alpha) and chromosome 3q (beta)

♦ Propionic Acidemia can arise from mutations in either the alpha or beta subunit

♦ PCAA is involved in the catabolic pathway for the odd chain length fatty acids; threonine, methionine, isoleucine and valine

♦ Deficiencies of PCAA lead to the accumulation of propionic acid which results in the inhibition of citric acid cycle enzymes, acetylglutamate synthetase, granulocytes, and T and B cell development

♦ Numerous mutations have been described in the Beta subunit

Laboratory

♦ Metabolic acidosis

♦ Hypoglycemia

♦ Hyperammonemia

♦ Carnitine deficiency

♦ Elevated glycine

♦ Elevated propionic and methylcitric acids

♦ Neutropenia

♦ Thrombocytopenia

♦ Deficiency of PCAA activity in leukocytes or cultured skin fibroblasts (chorionic villi or amniocytes for prenatal)

Treatment

♦ Not curative. Avoidance of and symptomatic control of acute episodes

♦ Correct dehydration, electrolytes disturbances, and metabolic acidosis (bicarbonate)

- Decrease protein intake
- Antibiotics prevent production of propionic acid by intestinal bacteria

Methylmalonic Acidemia

Chromosome and Gene Location

- 6p21

Inheritance

- Autosomal Recessive

Incidence

- 1/50,000

Clinical

- Lethargy
- Failure to thrive
- Recurrent vomiting
- Dehydration
- Respiratory distress
- Muscular hypotonia
- Growth retardation
- Psychomotor retardation
- Impairment of renal function
- Neurological abnormalities

Molecular Genetics

- Methylmalonic Acid is derived from propionic acid as part of the catabolic pathway of isoleucine, valine, threonine, methionine, cholesterol and odd-chain fatty acids
- Methylmalonic acid is converted to succinic acid by methylmalonyl-CoA mutase and a coalbumin cofactor
- Defects in the mutase or its cofactor result in the accumulation of methylmalonic acidemia and its precursors
- Six complementation groups have been identified indicating multiple alleles
- Numerous mutations within the mutase gene on chromosome 6 have been reported

Laboratory

- Ketosis, acidosis, anemia, elevated urinary and serum methylmalonic acid
- Decreased or absent mutase activity in cultured fibroblasts
- Prenatal diagnosis by measuring MMA in amniotic fluid, methylcitric acid, or methylmalonyl-CoA mutase in cultured fibroblasts from amniocytes or chorionic villi samples

Treatment

- Restricted protein
- Vitamin B12 supplements to lower MMA levels

Carbohydrate Metabolism Disorders

Glycogen Storage Disease (Type I)

Chromosome and Gene Location

- 17q21

Inheritance

- Autosomal Recessive

Incidence

- 1/120,000

Clinical

- Hypoglycemia
- Hypertension
- Excessive perspiration
- Bruising
- Nose bleeds
- Short stature
- Delayed puberty
- Protuberant abdomen
- Liver adenomas
- Hepatomegaly
- Hepatoblastoma
- Hepatocellular carcinoma
- Chronic pancreatitis
- Renal insufficiency

Molecular Genetics

- The enzyme glucose-6-phosphatase catalyzes the conversion of glucose-6-phosphate to glucose
- Mutations in the gene encoding glucose-6-phosphatase result in a deficiency of this enzyme and the subsequent inability to free glucose for use in the body
- Mutations have been found in about 75% of patients studied
- There are various other types of glycogen storage diseases which result from deficiencies of other enzymes involved in the glycogen metabolism pathway

Laboratory

- Deficiency of glucose-6-phosphatase in liver biopsy (enzyme not present in skin fibroblasts)
- Lipidemia
- Hyperuricemia
- Hhyperlacticacidemia
- Ketonemia
- Metabolic acidosis
- Molecular analysis available

Treatment

- Maintenance of normal blood glucose concentration, by

supplementation of glucose, pancreatic enzymes and cornstarch
- Limit intake of fructose and galactose
- Low fat diet
- Liver transplantation if necessary

Galactosemia

Chromosome and Gene Location

- 9p13

Inheritance

- Autosomal Recessive

Incidence

- 1/60,000

Clinical

- Babies with galactosemia may appear normal at birth. Symptoms begin soon after milk feedings have begun. Symptoms include:
  - Lethargy
  - Irritability
  - Vomiting
  - Seizures
  - Feeding difficulties
  - Poor weight gain
  - Failure to thrive
  - Jaundice
  - Hepatomegaly
  - Hypoglycemia
  - Ascites
  - Splenomegaly
  - Hepatic cirrhosis
  - Lens opacities
  - Increased susceptibility to infections
  - Seizures
- Long term complications include:
  - Speech deficits
  - Ataxia
  - Dysmetria
  - Diminished bone density
  - Premature ovarian failure

Molecular Genetics

- Galactose-1-P uridyl transferase (GPUT) catalyzes the conversion of galactose-1-phosphate to glucose-1-phosphate
- Deficiency of GPUT results in the accumulation of galactose -1-phosphate which causes injury to the parenchymal cells of the kidney, liver, brain, ovaries and eyes
- One mutation (Q188R) accounts for about 70% of galactosemia alleles
- 12% of Caucasian population carry Duarte variant which decreases enzyme activity, but does not result in phenotypic consequence

Laboratory

- Newborn screening uses dot enzyme fluorescent assay and/or measurement of galactose -1- phosphate in the blood
- Classic and variant alleles can be detected with isoelectric focusing
- Molecular analysis is used in conjunction with biochemical testing for prognostication, heterozygote detection and prenatal diagnosis
- Serum in affected individual shows, elevated transaminase, follicular stimulating hormone, and leutenizing hormone, decreased estrogen, and anemia
- E.coli septacemia results in hyperbilirubinemia

Treatment

- Eliminate lactose and galactose from the diet, special formula is necessary
- Even with good dietary control there may be poor intellectual function, speech problems, and ovarian dysfunction

Galatokinase Deficiency

Chromosome and Gene Location

- 17q24

Inheritance

- Autosomal Recessive

Incidence

- 1/40,000

Clinical

- Cataracts
- Neonatal jaundice
- Normal intelligence

Molecular Genetics

- Galactokinase catalyzes the conversion of galactose to galactose-1-phosphate
- Galactokinase deficiency results in the accumulation of galactose
- Some galactose is converted to galacticol which may be responsible for the cataract formation

Laboratory

- Deficiency of galactokinase activity in red blood cells

Treatment

- Elimination of lactose and galactose from the diet

Transport Disorders

Familial Hypophosphatemic Rickets

Chromosome and Gene Location

- Xp22.2-p22.1

Inheritance

- X-linked dominant (also autosomal recessive and sporadic forms)

Incidence

- 1/1,000,000

Clinical

- Bowing of lower extremities
- Waddling gait
- Short stature
- Decreased femur/shaft angle
- Dolichocephaly
- Tooth deformities

Molecular Genetics

- Deficiency interferes with phosphate reabsorption in kidney and conversion of 25-hydroxy-D to 1,25-hydroxy-2D

Laboratory

- Hyperphosphaturia
- Normal amino acids
- X-rays show metaphyseal widening and fraying, cupping of metaphyses at tibia, femur, radius, and ulna

Treatment

- Phosphate supplements, surgery for limb deformities

Cystinuria

Chromosome and Gene Location

- 2p16.3

Inheritance

- Complex autosomal recessive with genetic compounds of multiple alleles producing three clinical types

Incidence

- 1/2000 in England to 1/100,000 in Sweden
- Overall approximately 1/7000

Clinical

- Urinary tract calculus
- Cystine stones are formed and crystals appear in the urine
- Increased risk for impaired cerebral function

Molecular Genetics

- Six missense mutations have been identified in the SLC3A1 gene on chromosome 2p, accounting for approximately 30% of the cystinuria chromosomes studied
- The relationship between the genetic compounds has not been elucidated

Laboratory

- Dibasic aminoaciduria (excess excretion of cystine)
- Increased urinary lysine, arginine and ornathine
- Molecular testing available

Treatment

- Dietary therapy to reduce cystine excretion and increase solubility
- Decreased methionine
- Low-sodium diets
- High fluid intake
- Drugs which increase solubility
- Surgery to remove stones

Hartnup's Disease

Chromosome and Gene Location

- 11q13

Inheritance

- Autosomal Recessive

Incidence

- 1/30,000

Clinical

- Cerebellar ataxia
- Emotional instability
- Delayed development
- Severe retardation
- Photosensitive skin rash

Molecular Genetics

- Thought to be caused by a genetic defect in neutral amino acid transport across the brush-border membrane of the renal and intestinal epithelium
- Gene has not been identified

Laboratory

- Characteristic pattern of increased secretion of the monoaminomonocarboxylic acids (alanine, serine, threonine, valine, leucine, isoleucine, phenylalanine, tyrosine, tryptophan, histidine, glutamine, and asparagine)

Treatment

- Nicotinic acid or nicotinamide for deficiency of this vitamin, reduces rash, ataxia and psychotic behavior
- High protein diet or supplementation

Cystinosis

Chromosome and Gene Location

- 17p

Inheritance

- Autosomal Recessive

Incidence

- 1/100,000 and 1/200,000

Clinical

- There appears to be three types of cystinosis with varying degrees of involvement:
  - Nephrotic-classic renal and systemic disease in which children develop dehydration, acidosis, vomiting, electrolyte imbalances, hypophosphatemic rickets, failure to grow, photophobia, corneal crystals, hypothyroidism, myopathy, decreased ability to sweat and renal failure by age 9–10
  - Intermediate late onset of nephrotic cystinosis
  - Non-nephrotic, clinically affecting only the corneas

Molecular Genetics

- Defective carrier mediated transport of cystine causes accumulation of cystine and formation of crystals in the lysosomes of most tissues
- Genetic defect has not been found
- Mutations in the CTNS gene are responsible for all 3 types of cystinosis

Laboratory

- Cystine crystals in blood buffy coat and bone marrow, cystine storage in pancreatic islet cells, aorta, atrophic ovaries, and brain
- Diagnosis in utero by cystine measurements in amniocytes or chorionic villi is possible
- Molecular testing available

Treatment

- Management of electrolyte imbalance
- Renal allografts
- Growth hormones
- Therapy with cysteamine averts the otherwise inevitable renal failure, but systemic therapy does not improve the corneal keratopathy

Metal Metabolism Disorders

Wilson's Disease

Chromosome and Gene Location

- 13q14

Inheritance

- Autosomal Recessive

Incidence

- 1/100,000–500,000 live births

Clinical

- Liver disease
- Neurologic disturbance
- Acute jaundice
- Hemolysis
- Dysarthria
- Involuntary movement
- Renal tubular acidosis
- Osteoarthropathy
- Cardiomyopathy
- Golden-brown granular pigmentation is seen in the outer crescent of the iris ("Kayser Fleischer"rings)

Molecular Genetics

- The gene encodes a Copper-binding P-type ATPase
- Expression occurs primarily in the liver, kidney, and placenta
- Defects in the gene lead to defective liver-specific copper transportion and defective copper excretion into the bile
- Copper accumulates in the liver and other tissues and inhibits various enzymatic reactions
- Numerous mutations have been identified

Laboratory

- Reduced serum copper level and ceruloplasmin, increased urinary copper excretion
- Elevated copper in liver biopsy
- Diagnosis by quantitating hepatic copper stores which are increased

Treatment

- Penicillamine, which increases urinary copper excretion
- Liver transplantation when necessary

Acrodermatitis Enteropathica

Chromosome and Gene Location

- Unknown

Inheritance

- Autosomal Recessive

Incidence

- Rare

Clinical

- Symptoms most often occur early in infancy after transition from breast milk to cows milk
- Features include:

- Dry, scaly, reddish skin lesions on face, knees, elbows and perineal areas
- Reddish hair
- Hair loss
- Photophobia
- Conjunctivitis
- Corneal dystrophy
- Chronic diarrhea
- Growth retardation
- Delayed wound healing
- Immune defects

Molecular Genetics

- Impaired zinc absorption due to an absent or defective ligand which facilitates zinc absorption
- The genetic defect is not currently known
- The variety of clinical features is likely due to the fact that zinc plays a role in numerous metabolic pathways

Laboratory

- Without therapy, plasma zinc concentration and serum alkaline phosphatase, as well as urinary excretion of zinc, are very low

Treatment

- Oral zinc compounds abolish the manifestations of the disease

Menkes Disease

Chromosome and Gene Location

- Xq13

Inheritance

- X-linked recessive

Incidence

- 1/300,000

Clinical

- Hypothermia
- Hypotonia
- Myoclonic seizures
- Chubby, rosy cheeks
- Kinky, colorless friable hair
- Failure to thrive
- Severe mental retardation
- Optic atrophy
- Osteopenia with pathologic fractures (may be mistaken for child abuse)

Molecular Genetics

- The gene product is predicted to be a copper binding ATPase
- Mutations in this gene result in defective copper absorption and transport
- A wide spectrum of mutations have been identified, most are single base pair changes, but deletions and rearrangements have also been described

Laboratory

- Low serum copper and ceruloplasmin levels
- Intracellular accumulation of copper in cultured cells (amniocytes and chorionic villi samples for prenatal)
- Direct molecular analysis is available

Treatment

- Copper histidine treatment prevents neurologic deterioration

Hemochromatosis

Chromosome and Gene Location

- 6p21.3

Inheritance

- Autosomal Recessive

Incidence

- Varies by population:
  - 1/200 to 1/300 in Northern European populations
  - Lower in others

Clinical

- Fatigue
- Palpitations
- Premature arthritis
- Impotence in males
- Amenorrhea in females
- Cardiac arrhythmias
- Congestive heart failure due to cardiomyopathy
- Cirrhosis with hepatosplenomegaly
- Ascites
- Hyperpigmentation
- Onset is generally between ages 40–60
- Females have later onset due to menses/child birthing

Molecular Genetics

- A candidate gene called HLA-H or HFE has been shown to be altered in the majority of hemochromatosis patients
- The most common mutation causes an amino acid substitution at codon 282 (C282Y)
- Approximately 85% of hemochromatosis patients of Northern European descent are homozygous, 5–10% are heterozygous and an additional 5–10% do not carry the C282Y mutation

- A second less frequent alteration is an amino acid substitution at codon 63 (H63D), its role in this disease is controversial, but may increase ones risk for developing hemochromatosis
- It has been hypothesized that the C282Y mutation results in an abnormal protein trafficking or cell surface expression of the HFE gene

Laboratory

- Elevated serum transferrin saturation and concentration
- Elevated hepatic iron concentration on liver biopsy
- Molecular testing available

Treatment

- Venesection reduces iron stores to normal
- Chelating agents remove smaller amounts of iron but are not as effective as phlebotomy

Purine Metabolism Disorders

Lesch-Nyhan

Chromosome and Gene Location

- Xq26-q27

Inheritance

- X-linked recessive

Incidence

- 1/300,000

Clinical

- Delayed motor development
- Choreoathetosis
- Spastic movements
- Hyper-reflexia
- Self-injurious behavior
- Gouty arthritis
- Kidney stones composed of uric acid

Molecular Genetics

- The enzyme hypoxanthine guanine phosphoribosyltransferase converts hypoxanthine and xanthine to nucleotides, inosinic acid, and guanylic acid
- Deficiency in enzyme activity results in accelerated purine production de novo and increased uric acid
- Deficiencies may also result in decreased synthesis of nucleotides

Laboratory

- Elevated serum uric acid concentration
- Marked increases in the production and excretion of uric acid
- Absence of hypoxanthine guanine phosphoribosyltransferase activity in erythrocytes and fibroblasts (amniocytes and chorionic villi samples)
- Heterozygote detection is possible in fibroblasts

Treatment

- Avoidance of dehydration
- Adequate nutrition
- Behavior control and modification
- Allopurinol to prevent damage to kidneys Experimental gene therapy

Adenosine Deaminase

Chromosome and Gene Location

- 20q13

Inheritance

- Autosomal Recessive

Incidence

- 1/200,000–1,000,000

Clinical

- Severe immunodeficiency
- Complete impairment of T-cell function
- Rib cage abnormalities
- Chondro-osseous dysplasia

Molecular Genetics

- Mutations in the gene encoding the enzyme adenosine deaminase result in the accumulation of adenosine, 2' deoxyadenosine and 2'-O-methyladenosine, which leads to lymphocyte toxicity and subsequent immunodeficiency

Laboratory

- Absence of adenosine deaminase in red cell, or cultured fibroblasts or lymphocytes (chorionic villi samples for prenatal)

Treatment

- Enzyme replacement therapy has resulted in clinical and immunologic improvement in some patients
- Bone marrow transplantation

Peroxisomal Disease

Zellweger Syndrome

Chromosome and Gene Location

- 7q11.23 (also chromosomes 1,2,6,8, and 12)

Inheritance

- Autosomal Recessive

Incidence

- 1/25,000–1/50,000

Clinical

- High forehead
- Unslanting palpebral fissures
- Hypoplastic supraorbital ridges
- Epicanthal folds
- Severe weakness
- Hypotonia
- Seizures
- Eye abnormalities
- Profound mental retardation
- Early lethality

Molecular Genetics

- Zellweger syndrome is caused by mutations in several different genes involved in peroxisome biogenesis
- Mutations have been identified in PEX1 gene on chromosome 7

Laboratory

- Reduced or absent peroxisomes
- Catalase in cytosol
- Reduced plasmalogens
- Accumulation of very long chain fatty acids
- Phytanic acid
- Bile acid intermediates
- L-pipecolic acid
- Increased urinary excretion of dicarboxylic acids

Treatment

- Not curable, supportive/symptomatic

Refsum Sundrome

Chromosome and Gene Location

- 10pter-p11.2

Inheritance

- Autosomal recessive

Incidence

- Rare

Clinical

- Epicanthal folds
- Flat bridge of nose
- Low-set ears
- Hypotonia
- Enlarged liver with impaired function
- Ataxic gait
- Severely retarded
- Hearing loss
- Pigmentary degeneration of the retina

Molecular Genetics

- Mutations in the gene encoding phytanoyl-CoA hydroxylase result in inability to metabolize phytanic acid
- Phytanic acid then accumulates in tissues and body fluids of patients with Refsum disease

Laboratory

- Deficiency of phytanoyl - CoA hydroxylase activity in cultured fibroblasts or amniocytes
- Elevated blood and tissue phytanic acid

Treatment

- Reduced intake of foods which might contain phytol, phytanic acid or their precursors, phytanic acid
- Plasmaphoresis performed once or twice a month effectively removes phytanic acid from the body prevents progression of the clinical features

Adrenoleukodystrophy

Chromosome and Gene Location

- Xq28

Inheritance

- X-linked recessive

Incidence

- 1/20,000–1/50,000

Clinical

- Progressive spastic paresis
- Loss of hearing and vision
- Dementia
- Demyelination of cerebral hemispheres

Molecular Genetics

- Mutations in the ALD-gene are thought to result in defective peroxisomal B-oxidation of very long chain fatty acids (VLCFAs)
- Deficiency results in the accumulation of VLCFAs in the adrenal cortex and brain gangliosides, plasma, blood cells and cultured fibroblasts
- Over 100 mutations have been identified, testing currently being done by linkage

Laboratory

- Accumulation of unbranched saturated fatty acids with a chain length of 24–30 carbons in plasma, cultured skin fibroblasts and amniocytes

Treatment

- Combined oleic acid, VLCFA-restricted diet, bone marrow transplantation

LYSOSOMAL STORAGE DISEASES

Mucopolysaccharidoses

- The mucopolysaccharidoses are a group of lysosomal storage disorders caused by the deficiency of any of the enzymes involved in the stepwise degradation of dermatan sulfate, heparan sulfate, keratan sulfate, or chondroitin sulfate (glycosaminoglycans)
- Glycosaminoglycans are constituents of connective tissue and are also present in mitochondria, nuclear and cell membranes
- Accumulation of glycosaminoglycans interferes with the normal functioning of cells, tissues and organs

Chromosome and Gene Location

- See Table 2–6

Inheritance

- See Table 2–6

Incidence

- See Table 2–6

Clinical

- See table: Clinical manifestations of enzyme deficiency leading to glycosaminoglycan storage includes:
  - Coarse facial features
  - Thick skin
  - Corneal clouding
  - Organomegaly
- Features characteristic of defective cell function include:
  - Skeletal dysplasia
  - Mental retardation
  - Growth deficiency and hearing loss
- Joint contractures, heart valve abnormalities, and hernias result from abnormal conective tissue formation

Laboratory

- Decreased enzyme activity in cultured fibroblasts, amniocytes, chorionic villi, leukocytes, serum or plasma
- Radiographs show skeletal abnormalities
- Direct molecular genetic analysis available for some (see table)

Treatment

- Not curable, supportive/symptomatic
- Bone marrow transplantation has been reported to improve clinical features in some
- Prophylaxis for patients with cardiac abnormalities

Mucolipidoses

- Mucolipidoses are a group of disorders which result from abnormal lysosomal enzyme transport, in which lysosomal enzymes are inappropriately secreted into the extracellular medium instead of being targeted to the lysosomes

I-Cell Disease

Chromosome and Gene Location

- 4q21-q23

Inheritance

- Autosomal Recessive

Incidence

- Rare

Clinical

- Low birth weight
- Plump swollen face
- Hernias
- Clubfoot
- Dislocation of hips
- Kyphosis
- Hypotonia
- Severe growth failure
- Stiffening of all joints
- Protuberant abdomen
- Coarse facial features
- Psychomotor retardation

Molecular Genetics

- The primary deficiency is in the enzyme GlcNac-1 phosphotransferase, which catalyzes the first step in the synthesis of the mannose-6-phosphtase recognition marker on lysosomal hydrolases. Mannose-6-phosphate serves as a specific recognition marker for targeting these enzyme to lysosomes
- Mutations within the gene disrupt interactions and recognition of the phosphotransferase, results in disproportionally high extracellular partioning of nearly all lysosomal enzymes

Laboratory

- Cytoplasmic granular inclusions in skin fibroblasts (swollen lysosomes), also seen in amniocytes and chorionic villi samples
- Decreased activity of lysosomal acid hydrolases in I cells with increased activity in culture media and extracellular fluid
- Numerous membrane bound vacuoles in connective tissue cells
- Molecular genetic testing is not yet available

Table 2–6. Mucopolysaccharidoses

Name	*Inheritance*	*Chromo-some*	*Enzyme Deficiency*	*Excess Excretion*	*Clinical Features*	*Incidence*	*Molecular Testing*
Hurler's Syndrome (MPS 1 H)	Autosomal Recessive	4p16.3	alpha-L-iduronidase retardation, death in childhood	dermatan and heparan sulfate disease, mental	Corneal clouding, dysostosis multiplex, organomegaly, heart	1/100,000	Direct
Scheie (MPS 1 S)	Autosomal Recessive	4p16.3	alpha-L-iduronidase sulfate	dermatan and heparan intelligence, normal life span	Corneal clouding, stiff joints, normal	Unknown	Direct
Hunter Syndrome (MPS II)	X-linked Recessive	Xq28	iduronate 2-sulfatase	dermatan and heparan sulfate before 15 years	Dysostosis multiplex, organomegaly, mental retardation, death	1/100,00 male births	Direct and linkage
Sanfilippo	Autosomal Syndrome (MPS III)	17q25.3 Recessive	1. Sulfamidase 2. Alpha-N-acetyl-glucosaminidase 3. Acetyl-CoA alpha-glucosaminide N-acetyltransferase 4. N-aceglucosamine-6-sulfate sulfatase	heparan sulfate	Profound mental deterioration, hyperactivity	Unknown	Available for some subtypes
Morquio Syndrome (MPS IV)	Autosomal Recessive	16q24.3 (TypeIV -A), 3(type IV-B)	1. N-acetyl-galactosamine-6-sulfate sulfatase (Type IV-A) 2. B-galactosidase (Type IV B)	keratan sulfate	Skeletal abnormalities, corneal clouding, odontoid hypoplasia	1/300,000	Direct (on limited basis)
Maroteaux -Lamy Syndrome (MPS VI)	Autosomal Recessive	5q13.3	N-acetylgalactosamine-4 -sulfate sulfatase	dermatan sulfate normal intellgence	Dysostosis multiplex, corneal clouding,	1/200,000	Not available

Treatment

- Not curable, supportive/symptomatic

Pseudo-Hurler Polydystrophy

Chromosome and Gene Location

- 4q21-q23

Inheritance

- Autosomal Recessive

Incidence

- Rare

Clinical

- Joint stiffness
- Decreased mental development
- Plump face
- Reduced growth rate
- Mild mental deficiency
- Osteoporosis
- Dysostosis multiplex

Molecular Genetics

- The same enzyme defect as in I-cell disease, except a milder allelic variant

Laboratory

- Cytoplasmic granular inclusions in skin fibroblasts (swollen lysosomes), also seen in amniocytes and Chorionic Villi samples
- Decreased activity of lysosomal acid hydrolases in I cells with increased activity in culture media and extracellular fluid
- Numerous membrane bound vacuoles in connective tissue cells

Treatment

- Not curable, supportive/symptomatic

Sphingolipidoses

GM1 Gangliosidosis

Chromosome and Gene Location

- 3p21.33

Inheritance

- Autosomal recessive

Incidence

- Unknown

Clinical

- Onset is generally in childhood
- Psychomotor retardation
- Hepatosplenomegaly
- Bony abnormalities (widening of the long bones and ribs, broad short stubby fingers, contractures)
- Failure to thrive
- Gum hypertrophy
- Macroglossia
- Macrocephaly
- Protuberant abdomen
- Coarse facies
- Frontal bossing
- Depressed nasal bridge
- Hypertelorism
- Cherry red spot on macula
- Exaggerated startle response
- Also other forms with onset between ages 3–50

Molecular Genetics

- Beta-galactosidase cleaves terminal galactose from a number of compounds including GM1 ganglioside, galactose oligosaccharides and derivatives of keratan sulfate
- Mutations lead to deficiency of the enzyme and result in the accumulation of GM1-gangliosides, oligosaccharides and keratan sulfate derivatives

Laboratory

- Empty appearing vacuoles on electron microscopy
- Large foam cells in bone marrow
- Skeletal changed on X-ray
- Deficient B-galactosidase in cultured fibroblasts and leukocytes

Treatment

- Not curable, supportive/symptomatic

GM2 Gangliosidosis (Tay Sachs)

Chromosome and Gene Location

- 15q

Inheritance

- Autosomal Recessive

Incidence

- 1/3600 (Ashkenazi Jewish)

Clinical

- Hypotonia
- Exaggerated startle response
- Inability to hold head up or sit
- Cherry red spot on macula
- Convulsions
- Optic atrophy

- Blindness
- Mental retardation
- Macrocephaly
- Fatal by 4 years of age

Molecular Genetics

- The enzyme hexosaminidase A catalyzes the degradation of gangliosides (constituents of neuronal cell membranes)
- Deficiency results in the accumulation of GM2-ganliosides in the brain, nervous system lever, spleen, and heart, leading to the disruption of cell function and death
- Hexosaminidase A is made up of an alpha and a beta chain
- The alpha chain is encoded on chromosome 15, mutations lead to a deficiency of hexosaminidase A. (Mutations in the beta chain lead to Sandhoff disease, see below)
- Three common mutations in Ashkenazi Jewish population, (1277insTATC, 1421+1G-C, G269S) account for approximately 94% of mutations in this population

Laboratory

- Decreased hexosaminidase A in serum, leukocytes and/or cultured fibroblasts, amniocytes, or chorionic villi samples
- Very effective for carrier screening as well
- Direct mutation analysis also available
- Pseudodeficiency alleles (more common in non-Jewish population), may falsely indicate carrier status

Treatment

- Not curable, supportive/symptomatic

Sandhoff Disease

Chromosome and Gene Location

- 5q13

Inheritance

- Autosomal Recessive

Incidence

- 1/75,000 (non-Jewish)
- 1/250,000 (Jewish)

Clinical

- Hypotonia
- Exaggerated startle response
- Inability to hold head up or sit
- Cherry red spot on macula
- Convulsions
- Hepatosplenomegaly
- Blindness
- Mental retardation
- Macrocephaly
- Fatal by 4 years of age

Molecular Genetics

- The enzymes hexosaminidase A and hexosaminidase B catalyze the degradation of gangliosides (constituents of cell membranes)
- Hexosaminidase A is made up of an alpha and a beta chain, hexosaminidase B is made of two beta chains
- The beta chain is encoded from a gene on chromosome 5, mutations in this gene therefore result in a deficiency of both hexosaminidase A and hexosaminidase B
- Deficiency results in the accumulation of GM2-gangliosides in the brain, nervous system, liver, spleen, and heart, leading to the disruption of cell function and death
- Mutations have been identified with the most common being a 16 kb deletion in the 5' end of the gene

Laboratory

- Deficient hexosaminidase A and hexosaminidase B in serum, leukocytes and/or cultured fibroblasts, amniocytes, and chorionic villi

Treatment

- Not curable, supportive/symptomatic

Niemann-Pick, Types A and B

Chromosome and Gene Location

- 11p15.1-p15.4

Inheritance

- Autosomal Recessive

Incidence

- Type A - 1/40,000 (Ashkenazi Jewish)

Clinical

- Type A - failure to thrive, hepatosplenomegaly, progressive neurodegeneration, death by age 3
- Type B - Hepatosplenomegaly, respiratory insufficiency, little or no neurologic involvement, may survive into adolescence or adulthood

Molecular Genetics

- Deficiency of the lysosomal hydrolase acid sphingomyelinase, causes accumulation of sphingomyelin in cells and tissues
- Three common mutations have been found in Ashkenazi Jewish population(L302P, R496L, and fsP330) and account for >95% of the mutations in this population; other more rare mutations have been found in other ethnic groups

Laboratory

- Deficiency of acid sphingomyelinase, increased tissue cholesterol levels

Treatment

- Not curable, supportive/symptomatic

Niemann-Pick, Type C (NP-C)

Chromosome and Gene Location

18q11

Inheritance

- Autosomal recessive

Incidence

- As frequent as NP-A and NP-B combined

Clinical

- Neonatal jaundice
- Histiocytosis
- Neurological evidence depends on variant (infantile-adult)
- Progressive neurological deterioration. Ataxia, dyarthria, dystonia
- Vertical supranuclear gaze

Molecular Genetics

- Mutation causes impaired homeostatic regulation of cholesterol levels within cells
- Mutation prevents egress of freed cholesterol from the lysomal compartment

Laboratory

- Delayed induction of cholesterol esterification following LDL uptake
- Filipin staining of accumulated choleserol in fiboblasts

Treatment

- No current treatent to change natural progression
- Supportive pharmacologic care for CNS symptoms

Gaucher Disease

Chromosome and Gene Location

- 1q21

Inheritance

- Autosomal Recessive

Incidence

- Type 1: 1/600 (Ashkenazi Jewish), 1/60,000–1/360,000 non-Jewish
- Type 2: <1/500,000 live births
- Type 3: 1/100,000

Clinical

- Type 1 - Age of onset varies widely, from children to adults. Disease severity is also variable. Symptoms include:
  - Enlarged liver and spleen (causes abdominal protuberance)
  - Fatigue
  - Anemia
  - Excessive bleeding
  - Pain in lower extremities
  - Fractures
  - Bronzed complexion
  - Growth failure
  - Bone disease
- Type 2 - Onset is within first few months of life
  - Inattentiveness
  - Loss of head control
  - Poor sucking and swallowing
  - Failure to thrive
  - Spasticity
  - Tonic arching of back
  - Strabismus
  - Seizures
  - Enlargement of liver and spleen
  - Progression of disease is rapid, death from respiratory complications usually occurs within several months
- Type 3 - Clinically heterogeneous
  - Presentation in mid to late childhood
  - Myoclonus
  - Dementia
  - Ataxia
  - Horizontal supranuclear gaze palsy
  - Seizures
  - Spasticity
  - Enlarged spleen and liver
  - Death from neurologic degeneration in 2nd or 3rd decade

Molecular Genetics

- Glucocerebrosidase hydrolyzes glucosylceramide to glucose and ceramide
- Mutations in the gene encoding glucocerebrosidase result in the accumulation of glucosylceramide in the lysosomes
- There are four common mutations, N370S, L444P, 84GG, IVS2(+1), which account for >90% of the mutations in the Ashkenazi Jewish population
- N370S is not found in Type 2 or 3 and is thought to confer a less severe phenotype when compounded with other mutations

Laboratory

- Deficiency of glucocerebrosidase activity (not accurate for carrier determination) in cultured fibroblasts, amniocytes, and chronic villi
- Anemia
- Leukopenia
- Thrombocytopenia
- Increase iron stores
- Prolonged bleeding time
- Deficiency of factor IX, XI and von Willebrand
- Presence of Gaucher storage cells in bone marrow
- Molecular genetic analysis is available for the above mutations

Treatment

- Enzyme replacement therapy (most effective on patients with Type 1 disease)
- Transfusions may be required for hypersplenism or bone marrow failure
- Skeletal problems are treated with limitation of activity, prostheses, analgesics, and surgical intervention
- Liver transplant sometimes necessary

Krabbe Disease

Chromosome and Gene Location

- 14q

Inheritance

- Autosomal recessive

Incidence

1/100,000–1/200,000

Clinical

- Onset within first six months
  - Feeding difficulty
  - Irritability
  - Fever
  - Failure of development
  - Spasticity
  - Cortical blindness
  - Optic atrophy
  - Deafness
  - Cherry red macula
  - Death by age 2
- Also late onset variants

Molecular Genetics

- Galactosylceramide B-galactosidase is a lysosomal enzyme which degrades galactocerebroside to ceramide and galactose
- Mutations in the gene cause deficient activity and result in the accumulation of enzyme substrates which lead to the early destruction of oligodendroglia (type of glial cell that forms the myelin sheath of nerve fibers in the central nervous system)
- Mutations in gene have been identified

Laboratory

- Deficient galactosylceramide B-galactosidase activity in amniocytes or chorionic villi
- Elevated protein in cerebral spinal fluid, decreased nerve conduction velocity
- Accumulation of globoid cells and calcium on magnetic resonance, white matter abnormalities, small brain, glial cell proliferation
- Peripheral nerves show segmental demyelination
- Molecular testing available

Treatment

- Not curable, supportive/symptomatic

Metachromatic Leukodystrophy

Chromosome and Gene Location

- 22q13.31-qter

Inheritance:

- Autosomal Recessive

Incidence

- 1/100,000

Clinical

- Loss of developmental milestones
- Gait difficulty
- Hypotonia
- Decline in speech, and mentation
- Cherry-red macula
- Spasticity
- Death by age 6
- Juvenile and adult onset also seen

Molecular Genetics

- Arylsulfatase A with sphingolipid activator protein (SAP1) metabolize cerbroside sulfate
- Mutations lead to enzyme deficiency which results in accumulation of galactosyl-3-sulfate cerebroside, and metachromatic material in neural and non-neural tissues
- A few common mutations have been found

Laboratory

- Arylsulfatase A deficiency in cultured fibroblasts in leukocytes, fibroblasts, amniocytes, or chorionic villi (pseudodeficient alleles complicate assay)

- Increased protein in the cerebrospinal fluid and decrease in nerve conduction velocity
- Demyelination and deposits of metachromatic granules in central and peripheral nervous system
- Increase in sulfatides in white matter
- Decrease in other myelin lipids (cholesterol and sphingomyelin)
- Molecular genetic studies are also available

Treatment

- Not curable, supportive/symptomatic
- Bone marrow transplantation slows progression of symptoms

Fabry Disease

Chromosome and Gene Location

- Xq22.1

Inheritance

- X-linked recessive

Incidence

- 1/40,000 males

Clinical

- Childhood or adolescent onset
- Pain in distal extremities
- Fever
- Elevation of erythrocyte sedimentation
- Vascular lesions
- Central nervous system usually spared
- Peripheral edema
- Corneal opacities
- Skin lesions
- Reduced motor nerve conduction velocities
- Renal failure later as disease progresses
- Carrier females are usually asymptomatic some may have an attenuated form of the disease

Molecular Genetics

- Alpha galactosidase is an enzyme involved in the degradation of glycosphingolipids
- Mutations in the gene result in the accumulation and deposition of glycosphingolipids with terminal alpha-galactosyl moieties in body fluids and nonneuronal tissues of the body

Laboratory

- Deficient alpha galactosidase A activity in plasma or serum, tears, fibroblasts, amniocytes and chorionic villi
- Tissue deposition of crystalline glycosphingolipids
- Molecular genetic testing is available

Treatment

- Peripheral neuropathy may respond to carbamazepin, phenytoin, or neurotropin
- Renal transplantation
- Enzyme replacement therapy

FAMILIAL CANCER SYNDROMES

Familial Adenomatous Polyposis

Chromosome and Gene Location

- 5q21-q22

Inheritance

- Autosomal Dominant
- 1/3 are the result of new mutations

Incidence

- 1/6000–1/13,000

Clinical

- Multiple (>100) polyps early in life (by age 20 over 90% of gene carriers will develop polyps)
- Polyps progress to colonic carcinoma by age 40
- Additional features include: congenital hypertrophy of the retinal pigment epithelium (CHRPE) and supernumerary teeth
- Other tumors may occur (duodenal, thyroid, brain, liver, desmoid tumors, childhood hepatoblastomas)
- "Gardner syndrome" refers to individuals with FAP who have extracolonic manifestations such as tumors of the jaw, lipomas and fibromas

Molecular Genetics

- Numerous mutations have been identified in the Adenomatous Polyposis coli (APC) gene, most mutations lead to truncated protein product
- The protein is thought to be involved in cell adhesion

Laboratory

- Linkage testing and direct mutational analysis by protein truncation assay are available

Treatment/Surveillance

- Genetic consultation is necessary to determine the utility of genetic testing in these families

- For individuals with a diagnosis of FAP, colectomy is advised when polyps become too numerous to remove or watch
- For individuals who have a positive gene test or who have not had genetic testing and are at risk, flexible sigmoidoscopy every 2–3 years beginning at age 10–12 years through age 35
- Annual thyroid palpation and ophthalmologic examination for CHRPE
- For children at risk, alpha-fetoprotein testing and abdominal palpation is recommended for hepatoblastoma every 6 months until age 6

Basal Cell Nevus Syndrome (Gorlin Syndrome)

Chromosome and Gene Location

- 9q22.3, 9q31, 1p32

Inheritance

- Autosomal Dominant

Incidence

- 1/55,000 (in United Kingdom)

Clinical

- The following criteria have been proposed for a making a diagnosis. (The sensitivity and specificity are not known). A diagnosis is made when two major or two minor and one major criteria are fulfilled:
  - Major criteria:
    - Multiple basal cell carcinomas
    - Basal cell nevi
    - Odontogenic keratocyst
    - Polyostotic bone cyst
    - Palmar or plantar pits
    - Ectopic calcification
    - Family history of Basal Cell Nevus syndrome
  - Minor criteria:
    - Congenital skeletal anomaly:
      - Bifid, fused, splayed or missing rib
      - Bifid wedged or fused vertebra
      - Head circumference in the 97th %
      - Cardiac or ovarian fibroma
      - Medulloblastoma
      - Lymphomesenteric cysts
    - Congenital malformation:
      - Cleft lip and/or palate
      - Polydactyly
      - Eye anomaly
  - Other:
    - Tall stature
    - Frontal bossing with large head
    - Ocular hypertelorism
    - Broad nasal root
    - Enlarged jaw

Molecular Genetics

- Mutations in PTCH or PTCH2 gene leads to premature stop or frameshift
- The protein is thought to be involved in controlling cell fates, patterning and growth in numerous tissues

Laboratory

- Molecular genetic testing available by direct DNA or linkage

Treatment/Surveillance

- Early excision of basal cell tumors
- Annual screening by dermatologist in puberty and more frequently as needed
- Gynecologic exam annually in adulthood

Breast/Ovarian Cancer

Chromosome and Gene Location

- 17q12 (BRCA1)
- 13q12 (BRCA2)

Inheritance

- Autosomal Dominant

Incidence

- Varies by population:
  - 1/1000 BRCA1 mutation in general Caucasian population
  - 1/100 carrier frequency of 185delAG mutation in Ashkenazi Jewish women
  - 8/100 carrier frequency for 6174delT in Ashkenazi Jewish women diagnosed with breast cancer < age 42
  - Overall carrier frequency for either BRCA1 or BRCA2, estimated to be 1/100–1/2500 across different populations

Clinical

- Early onset (premenopausal) adenocarcinoma of the breast, often bilateral disease
- Additionally, ovarian cancer is a prominent feature of BRCA1 families, but not BRCA2
- Breast cancer in males is more common in BRCA2 families but also present in BRCA1 families
- Males carrying a mutated BRCA1 gene are at an increased risk (3.3 relative risk) of developing prostate cancer
- Males and females carrying BRCA1 gene are at an increased risk (4.1 relative risk) for colon cancer

- BRCA1 is thought to account for 50% of all familial early-onset cases (2.5–5% of all breast cancer) and about 80% of inherited breast and ovarian cancer
- BRCA2 is estimated to account for 17–35% of hereditary breast cancer
- It is estimated that individuals who carry BRCA1 gene may have as high as an 56–87% risk of developing breast cancer and 27–44% risk of developing ovarian cancer by age 70
- Lifetime population risk is 1/8 and 1/70 for breast and ovarian cancer respectively

Molecular Genetics

- Various mutations (deletions, insertion, point mutations) have been identified, most result in truncation or absence of BRCA1 and BRCA2 proteins
- Both are thought to be a tumor suppressor genes

Laboratory

- Molecular testing available for BRCA1 and BRCA2

Treatment/Surveillance

- Prophylactic mastectomy and/or oophorectomy have been undertaken to reduce risk
- Chemoprophylaxis with tamoxifen or related compounds
- Screening recommendations include monthly breast self examination ages 18–21, annual or semiannual clinical breast exam for ages 25–35
- Mammography suggested beginning by ages 25–35
- Annual or semiannual screening using transvaginal ultrasound and serum CA-125 ages 25–35 (caution: less than half of early stage ovarian tumors produce elevated levels of CA-125)
- For prostate cancer surveillance in BRCA1 carriers only, rectal examination and PSA level should be offered annually
- For colon cancer, annual fecal occult blood test and flexible sigmoidoscopy every 3–5 years starting at age 50

Colon Cancer (Hereditary Non-Polyposis)

Chromosome and Gene Location

- 3p21.3 (hMLH1)
- 2p22-p21 (hMSH2)
- 2q31-q33 (hPMS1)
- 7p22 (hPMS2)
- 2p16 (hMSH6)

Inheritance

- Autosomal Dominant

Incidence

- May account for 3–5% of all colon cancer

Clinical

- Colorectal cancer:
  - 2/3 in right colon
  - Average age at diagnosis is 45
- Endometrial adenocarcinoma
  - Increased risk for ovarian, transitional cell renal collecting system, ureter, stomach, small bowel, hepatobiliary tract and pancreatic cancers
  - Also at an increased risk for sebaceous carcinomas, basal and squamous cell carcinomas of the skin
- Muir-Torre syndrome is a variant form of HNPCC characterized by a combination of benign or malignant sebaceous skin tumors and internal malignancy Linkage analysis and mutations have been found in hMSH2 and hMLH1
- Turcot syndrome is characterized by brain tumor (glioblastoma multiforme) and colorectal tumors and is also associated with HNPCC
- The following Amsterdam criterion were developed to assist in the definition of HNPCC. All four conditions need to be fulfilled to meet the Amsterdam criterion. However, the criterion have been found to be overrestrictive for clinical use:
  - Three cases of colon cancer of which two people are first degree relatives of the third person
  - Colon cancer occur in two generations
  - One colon cancer diagnosed before age 50
  - The family does not have FAP

Molecular Genetics

- The products of the genes hMLH1, hMSH2, hPMS1, hPMS2 and hMSH6 participate in a DNA mismatch repair complex
- The hMLH1 and hMSH2 account for most of the mutations found in HNPCC families to date
- Most mutations are thought to result in a truncated protein
- Colon cancer is a multi-step process, meaning that a number of mutations in different genes need to occur before the onset of colon cancer
- When a mutation occurs in a mismatch repair complex, the ability to repair other random mutations is compromised, thus leading to an accumulation of mutations (microsatellite instability)
- The mutations may inactivate tumor suppresser genes and lead to the subsequent penetrance of colon cancer

Laboratory

- Mutational analysis available
- Histological appearance of tumors is non-diagnostic

- Nearly all tumors show widespread microsatellite instability

Treatment/Surveillance

- Prophylactic subtotal colectomy has been used to reduce risk
- Prophylactic hysterectomy and oophorectomy after childbearing may reduce risk
- For asymptomatic, suspected or known gene carriers, a full colonoscopy every 1–3 years beginning at ages 20–25
- Annual screening for endometrial cancer beginning ages 25–35
- Annual urinalysis and cytology beginning at age 25
- Annual skin surveillance
- Periodic upper gastrointestinal endoscopy beginning age 35 for families in which gastric cancer has occurred
- Endometrial biopsy and urinalysis with cytology every 2 years beginning age 35

Cowden's Syndrome (MultipleHamartoma Syndrome)

Chromosome and Gene Location

- 10q23 (PTEN)

Inheritance

- Autosomal Dominant

Incidence

- Unknown

Clinical

- Multiple hamartomas including:
  - Cobblestone-like hyperkeratotic papules of gingiva and buccal mucosa
  - Fibroadenomatous breast enlargement
  - Hamartomatous polyps of the stomach, small bowel and colon
  - Cerebellar gangliocytomatosis
  - Breast cancer in 30% of female gene carriers
  - May also be increased risk for thyroid adenoma and carcinomas
- In children:
  - Mucocutaneous lesions
  - Lipomas
  - Fibromas
  - Hemangiomas and progressive macrocephaly
  - Mild to moderate delay may be present at an early age

Molecular Genetics

- Mutations in PTEN gene thought to disrupt the tyrosine/dual-specificity phosphatase domain of this gene

Laboratory

- None known

Treatment/Surveillance

- Surveillance for thyroid masses, breast cancer beginning age 20
- May consider prophylactic mastectomy for women at risk

Li Fraumeni Syndrome

Chromosome and Gene Location

- 17p13.1 (plus other currently unidentified)

Inheritance

- Autosomal Dominant

Incidence

- Unknown

Clinical

- Soft tissue sarcomas
- Early onset breast cancer
- Adrenocortical and brain tumors
- Osteosarcomas
- Leukemia
- Risk of developing invasive cancer is approximately 50% by age 30 and 90% by age 70
- Classical definition requires one patient with sarcoma under age 45; a 1st degree relative under age 45 with any cancer, and a third affected 1st or 2nd degree relative with either sarcoma at any age or any cancer under age 45

Molecular Genetics

- Approximately 50% of Li Fraumeni families have mutations in the p53 tumor suppressor gene
- Mutation types include nonsense mutations, and splice site mutations which generate truncated protein products

Laboratory

- Mutations in p53, otherwise no other specific laboratory findings

Treatment/Surveillance

- Screening includes annual mammogram
- Physical exam of breasts every 6 months
- Monthly self breast exam beginning in adulthood
- Annual blood count and review of peripheral smear for leukemia

- Annual exam beginning in infancy for all related findings

Multiple Endocrine Neoplasia Type 1

Chromosome and Gene Location

- 11q13

Inheritance

- Autosomal Dominant

Incidence

- 1/5000–1/50,000 live births

Clinical (also see Chpater 11)

- Hyperparathyroidism
- Peptic ulcer disease
- Parathyroid adenomas
- Pancreatic islet cell tumors (most commonly gastrinomas)
- Insulinoma
- Pituitary adenoma (prolactinoma)
- Features are relatively consistent within families

Molecular Genetics

- MEN1 gene encodes a transcript called menin
- Numerous frameshift, nonsense, missense, and in-frame deletions have been reported
- Function of protein is not known

Laboratory

- Elevated ACTH
- Abnormal secretin test
- Hypoglycemia
- Hypergastrinism
- Hyperparathyroidism
- Glucose intolerance
- Molecular linkage analysis is available

Treatment/Surveillance

- Screening recommendations include an annual evaluation for prolactin, cortisol, glucose, calcium, phosphorus
- Physical exam with endocrinologic review of systems

Multiple Endocrine Neoplasia Types 2A, 2B and Familial Medullary Thyroid Carcinoma (FMTC)

Chromosome and Gene Location

- 10q11.2

Inheritance

- Autosomal Dominant

Incidence

- 5–10% of thyroid cancers are of the medullary type, of these, 20% are due to germline RET mutations

Clinical (also see Chapter 11)

- MEN2A
  - Medullary thyroid carcinoma (>95%)
  - Pheochromocytoma (>50%)
  - Hyperparathyroidism (parathyroid hyperplasia or adenoma)(15–30%)
- MEN2B
  - Same features as MEN2A but earlier onset (10 years)
  - Parathyroid disease is rare
  - Additional findings include:
    - Mucosal neuromas
    - Thickened corneal nerves
    - Marfanoid habitus
    - Gastrointestinal involvement
- FMTC
  - Medullary thyroid carcinoma only
  - More benign than MEN2A or 2B

Molecular Genetics

- Mutations in cystiene residues of extracellular binding domain in exons 10 and 11 of the RET protooncogene account for most of the cases of MEN2A and FMTC
- A single point mutation in exon 16 accounts for MEN2B
- RET mutations account for approximately 95% of MEN2A families, 85% of FMTC, and 95% of MEN2B families

Laboratory

- Mutations in RET protooncogene
- Elevated calcitonin after pentagastrin stimulation
- Metanephrines may be elevated if pheochromocytoma is present
- Parathyroid hormone and calcium elevation may also be present

Treatment/Surveillance

- Screening recommendations include genetic testing for at risk individuals
- For positive individuals, prophylactic thyroidectomy and screening for pheochromocytoma and hyperparathyroidism is indicated

Peutz-Jeghers Syndrome

Chromosome and Gene Location

- 19p13.3

Inheritance

- Autosomal Dominant

Incidence

- 1/125,000–1/50,000 births

Clinical

- Numerous pigmented spots on lips and buccal mucosa (more rarely on face, forearms hands, feet, and perianal area)
- Multiple gastrointestinal hamartomatous polyps in the jejunum (malignant transformation not common)
- Risk of any malignancy estimated is 50%
- Most reported cancers are in stomach or duodenum in patients under 40 years
- Also associated with cancers of the breast, cervix, ovaries, testis, and pancreas

Molecular Genetics

- Disorder is due to mutations in the serine threonine kinase STK11 gene
- 50% are due to a new mutation

Laboratory

- Polyps can have a unique cellular morphology imparting branching tree-like appearance of mucosa with interdigiting smooth muscle
- Molecular testing available

Treatment/Surveillance

- Removal of polyps if feasible
- Screening includes upper and lower GI endoscopy and small bowel x-rays when GI symptoms are present (repeated every 2–3 years for those with a diagnosis)
- Regular breast and gynecologic screening after age 20
- Mammography between age 20 and 30 repeated every 2–3 years
- Regular testicular exam for at risk males
- Periodic colon cancer screening after age 35

Retinoblastoma (RB)

Chromosome and Gene Location

- 13q14

Inheritance

- Approximately 60% are unilateral and sporadic
- 15% are unilateral and hereditary
- 25% are bilateral and hereditary and autosomal dominant with 90% penetrance
- In inherited cases, an affected individual will have a 50% risk of passing the gene on the their offspring
- One altered gene is NOT sufficient to cause RB
- Another sporadic event needs to occur in this gene to cause RB (thus incomplete penetrance)
- Individuals who carry the gene and do not have RB still have a 50% risk of passing the gene on their offspring

Incidence

- 1/15,000 to 1/20,000 live births

Clinical

- Strabismus and/or leukocoria, multifocal, and bilateral tumors of the retina
- Other secondary cancers include:
  - Osteosarcomas
  - Fibrosarcomas
  - Melanomas
- May also be at an increased risk for lung, prostate and breast cancer

Molecular Genetics

- Numerous large and small deletions as well as point mutations have been found in the RB1 gene
- The protein is involved in cell cycle and cell growth regulation

Laboratory

- Deletions and point mutations in RB gene

Treatment/Surveillance

- Surgery options include:
  - Enucleation (removal of entire eye)
  - Cryosurgery (kills cancer by freezing it)
  - Photocoagulation (uses narrow beam of strong light to kill blood vessels that feed the tumor)
- Chemotherapy and radiation are also options
- Screening includes ophthalmologic examination at birth and every 8–12 weeks to age 2 every 6 months from age 2 to 12, annually there after

von Hippel-Lindau (VHL)

Chromosome and Gene Location

- 3p25–26

Inheritance

- Autosomal Dominant
- 100% penetrant by age 65

Incidence

- 1/36,000

Clinical

- Diagnosis of VHL if patient has one symptom from Section A plus one symptom from Section B or two symptoms from Section A or a family history of VHL and one symptom from either column

- Section A:
  - Retinal hemangioblastomas (45–59%)
  - Cerebellar hemangioma (44%–72%)
  - Spinal hemangiomas (13–59%)
- Section B:
  - Pheochromocytoma (15%)
  - Pancreatic cystic disease
  - Cystadenoma of the epididymis (10–26%)
  - Renal cysts (60%)
  - Renal carcinoma

Molecular Genetics

- Numerous deletion, insertion, nonsense and missense mutations in the VHL gene
- VHL gene is a tumor suppressor gene
- The gene product functions to negatively regulate transcription

Laboratory

- Mutation analysis of VHL gene
- Linkage analysis also available for suitable pedigrees

Treatment/Surveillance

- Laser therapy
- Cryotherapy
- Photocoagulation
- Radiation
- Surgery
- Screening recommendations include:
  - Annual physical exam with neurologic evaluation for signs of cerebellar or cord lesions
  - Annual ophthalmologic examination
  - Red blood cell count for polycythemia
  - Annual urinalysis
  - Urine cytology, and urinary metanephrines
  - MRI imaging of CNS and cord at age 11
  - Annual imaging no later than age 18 for kidneys and pancreas by CT and /or ultrasound

Wilms' Tumor

Chromosome and Gene Location

- 11p13 (WT1)
- 11p15.5 (WT2)
- Plus an additional unidentified locus

Inheritance

- Mostly sporadic, autosomal dominant with reduced penetrance (60%) and variable expressivity

Incidence

- 1/10,000
- 10–30% have germline mutation in WT1
- Less than 1% of all cases of Wilms' tumor are thought to result from a gene mutation inherited from a parent

Clinical

- Wilms' tumor is a tumor affecting the kidney
- Tumor development requires two hits to the WT1 gene, one germline mutation and another somatic mutation
- Deletions which lead to hemizygosity (one copy) of the gene WT1 are associated with WAGR syndrome (Wilms tumor, aniridia, genitourinary malformations, and mental retardation)
- Missense mutations in WT1 zinc finger region lead to Denys-Drash syndrome which includes male pseudohermaphrodism and nephropathy progressing to renal failure
- WT2 gene is subject to genomic imprinting, (promoter on paternal allele, suppressor on maternal allele)
- Paternal uniparental disomy (2 copies of the gene from the father) leads to Beckwith-Weidemann syndrome (overgrown condition with hemihypertrophy, macroglossia, omphalocele, abdominal organomegaly, ear pits and creases and predisposition to Wilms' tumor)

Molecular Genetics

- The WT1 gene product is a developmentally regulated transcription factor of the zinc finger family which is expressed primarily in the gonads and kidneys, it is thought to be a tumor suppressor gene which binds to p53 gene and suppresses expression
- The WT2 locus is thought to be an imprinted growth promoter on paternal allele, and an imprinted growth suppressor on maternal allele

Laboratory

- Molecular testing available

Treatment/Surveilance

- Surgery, chemotherapy and radiation therapy
- Screening includes abdominal exams every one to two months and ultrasound every four to six months through age 6

MITOCHONDRIAL DISORDERS

- Mitochondria are the cellular organelles which generate energy for cellular processes by producing ATP through oxidative phosphorylation
- The mitochondria contain their own DNA, separate for genomic DNA
- Mitochondrial DNA is a double stranded circular molecule, which encodes 13 protein subunits of 4 biochemical complexes and 24 structural RNA's required within the mitochondria for translation of the protein-coding units
- Although the mitochondria can replicate, transcribe and translate their DNA independent of nuclear DNA, the mitochondria are dependent on imported proteins coded by nuclear DNA for their structure and function
- Each mitochondria contains 2–10 molecules of DNA, and each cell contains numerous mitochondria

Chromosome and Gene Location

- Mitochondrial DNA

Inheritance

- Mitochondrial DNA (and therefore alterations within the mtDNA) is inherited through the maternal germline (transmitted in the ovum, not in sperm). Therefore mitochondrial diseases will show only maternal inheritance; both males and females can be affected
- Mitochondria replicate and segregate into daughter cells randomly
- During this process, the proportion of normal and mutant cells in a given cell may shift
- The term heteroplasmy refers to the coexistence of normal and mutant mitochondrial DNA in the same cell
- Homoplamsy refers to the presence of all normal or all mutant mitochondrial DNA
- Whether a person is affected by mitochondrial disease and to what extent is dependent on the proportion of mitochondria which contain mutant mitochondrial DNA
- The proportion of mutant mitochondrial DNA required for a particular disease varies among individuals, organ systems, and tissues, and in general is based upon the balance between oxidative supply and demand

Incidence

- Unknown

Clinical

- Nearly all tissues depend on oxidative metabolism
- Therefore, mitochondrial diseases are complex multi-system disorders which include a variety of neurologic, ophthalmologic, cardiac, endocrine, gastrointestinal, and pulmonary manifestations
- Below are examples of some of the mitochondrial diseases:
  - Mitochondrial encephalomyopathy, Lactic Acidosis and Stroke-Like Episodes (MELAS):
    - Seizures
    - Stroke like episodes
    - Brain dysfunction
    - Cerebral structural changes short stature
  - Myoclonic Epilepsy with Ragged-Red Fibers (MERRF):
    - Myoclonus
    - Seizures
    - Cerebellar ataxia
    - Mitochondrial myopathy
  - Leber's Hereditary Optic Neuropathy (LHON):
    - Bilateral visual loss
    - Central scotomas
    - Abnormal color vision
  - Kearns-Sayre syndrome (KSS):
    - Chronic progressive external ophthalmoplegia
    - Retinal degeneration
    - Heart block

Molecular Genetics

- Numerous deletions and point mutations have been identified
- Mitochondrial DNA is thought to mutate more than 10 times as frequently as nuclear DNA
- Additionally, mtDNA does not have the protective effect of introns, histones or repair systems
- Sequencing of the entire mtDNA is available

Laboratory

- Ragged-red fibers in skeletal muscle
- Elevated serum and cerebrospinal fluid lactate
- Myopathic potentials
- Axonal and demyelinating peripheral neuropathy on conduction studies
- Cardiac conduction defects
- Defective oxidative phosphorylation
- Mitochondrial DNA mutations

Treatment

- Not curable, supportive/symptomatic

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Chromosomal Disorders

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Chapter 3

Microbiology for the Surgical Pathologist

Melanie Triffet Treviño, MD

Table of Contents

VIRAL INFECTIONS

Herpesvirus Group

Herpes Simplex Virus 1 and 2 (HSV)

Clinical

- HSV1 is associated with orofacial infections and HSV2 with genital infections
- HSV1 primary infection is usually asymptomatic; 10% develop gingivostomatitis
- HSV1 primary infection rarely will cause keratoconjunctivitis, respiratory infection, Kaposi's varicelliform eruption, or fatal disseminated disease (neonatal)
- HSV1 may infect any part of the skin or mucosa and can be acquired venereally
- Recurrent HSV1 usually occurs on the vermillion border of the lips:
  - Recurrence may be triggered by sunlight, fever, or illness
- HSV2 is acquired through sexual contact; rarely by infants during vaginal delivery
- HSV2 has a higher rate of genital recurrence than HSV1

Cutaneous Variants

- Kaposi's varicelliform eruption: secondary herpetic infection of a preexistent skin disease (such as atopic dermatitis or Darier's disease)
- Herpetic whitlow: painful paronychial HSV1 or HSV2 infection of the distal finger; usually occurs in medical or dental personnel
- Herpetic folliculitis of the bearded skin
- Recurrent HSV has been associated with recurrent erythema multiforme; herpetic DNA has been identified in the cutaneous lesions of erythema multiforme
- Patients with immunocompromise are susceptible to severe recalcitrant infection

Herpetic Infections in the Immunocompromised Host

- Chronic cutaneous or mucosal ulceration: face, perineum, and perianal
- Systemic disseminated disease: widespread organ involvement with focal necrosis, including pancreas, liver, brain, and adrenals
- Generalized mucocutaneous disease: widespread vesicopustular lesions

Herpetic Infections in Pregnancy

- When a woman has recurrent HSV2 during pregnancy, the risk to the fetus is low; however, if she has genital lesions at the time of vaginal delivery, the infant may acquire neonatal herpetic infection:
  - Neonatal herpetic infection is associated with generalized cutaneous disease, encephalitis, widespread organ necrosis, and death
- When a woman acquires primary HSV2 during pregnancy, a lack of maternal antibodies leads to transplacental infection of the fetus and congenital HSV:
  - Congenital HSV acquired during the first trimester is associated with severe malformations; when it is acquired later in the pregnancy, the malformations are less severe but still include motor and mental retardation, microcephaly, and a recurrent vesiculopustular eruption

Microscopic

- Epidermal disruption leading to acantholysis and ulceration
- Disruption is either by ballooning degeneration or reticular degeneration
- Careful examination of hair follicle epithelia may reveal viral cytopathic change
- A variable lymphocytic inflammatory infiltrate is present in the dermis
- Vascular damage with necrosis, thrombosis, and hemorrhage may be present

Ballooning Degeneration

- Keratinocyte nuclear swelling is followed by cellular swelling
- The cytoplasm become eosinophilic and multinucleate cells form
- Swelling leads to detachment of intercellular bridges and acantholysis
- Occurs mainly in the deep epidermis and may extend down hair follicles
- Eosinophilic inclusion bodies may be seen in the nucleus of the balloon cells

Reticular Degeneration

- Cellular swelling leads to rupture of cell membranes
- A multilocular vesicle forms, separated by resistant cell membranes
- Older lesions degenerate more and form unilocular vesicles
- Occurs mainly in the superficial epidermis
- Not specific for viral vesicles; occurs in spongiotic dermatitis as well

Virus

- Member of the herpesvirus group; a DNA virus
- Electronmicroscopy demonstrates a 135 μm spheric virion
- Viral culture is the gold standard and involves identification of viral cytopathic change in the culture cells
- Viral antigens can be identified using direct immunofluorecence on infected cells

- Tzanck smear involves examination of Wright stain of cells scraped from the base of a new blister, looking for multinucleate cells and viral cytopathic change
- Virus can also be demonstrated with immunoperoxidase stains using antibodies to HSV1 or HSV2 antigens, or by in situ hybridization
- Complement fixation can be used to determine the patient's antibody titer

Varicella-Zoster Virus (VZV)

Clinical

- VZV is the causative agent of varicella (chicken pox) and herpes zoster (shingles)
- Varicella usually occurs in childhood and results in a mild generalized vesicular eruption; sometimes subclinical
- Primary infection with varicella is more severe and complications (including varicella pneumonia) are more likely in adult patients
- After primary infection, virus moves to a spinal or cranial sensory ganglion and becomes dormant
- Reactivation usually occurs in older adults; however, ~5% of patients are children under 15 years of age
- Impaired cellular immunity is a risk factor for reactivation as well as for severe and recalcitrant disease
- After reactivation, the virus moves along the sensory nerves of the involved ganglion and causes a vesicular eruption in the corresponding dermatome; occasionally a few lesions occur outside of the dermatome
- Disease course is usually mild in immunocompetent hosts and involves grouped vesicles on a hemorrhagic base; erosion or ulceration often follows, followed by crust formation
- Rarely in immunocompetent hosts and more commonly in immunocompromised patients, there is generalized disease that looks like varicella, including mucosal lesions
- Widespread necrosis and eosinophilic inclusions in many organs (lungs, kidneys, liver, and adrenal glands) may lead to death in patients with impaired cellular immunity
- Involvement of the central nervous system (CNS) usually only occurs in cases of neonatal varicella

Microscopic

- Pathology is very similar to HSV, although there is more vascular involvement with necrosis and hemorrhage in varicella and especially in zoster
- In severe varicella and disseminated zoster, there are eosinophilic inclusion bodies in dermal endothelial cells and perivascular fibroblasts
- In zoster, there are inclusion bodies in the neurilemmal cells of the small dermal nerves supplying the involved skin

Virus

- Member of the herpesvirus group; a DNA virus
- Electron microscopy demonstrates a 150 μm virion
- Virus can be identified in epidermal nuclei occasionally forming crystalloid aggregates, as well as in capillary endothelial cells (in varicella) and in dermal nerves (in herpes zoster)
- As with herpes simplex, viral infection can be demonstrated by Tzanck smear, immunohistochemistry, serologic studies, in situ hybridization, or culture

Cytomegalovirus (CMV)

Clinical

- Associated with cytomegalovirus inclusion disease
- CMV is a ubiquitous organism that can produce serious and systemic disease in immunocompromised patients; especially common in human immunodeficiency virus (HIV) disease
- It is not always a cause of end-organ disease
- Viral cytopathic change may be identified in some biopsies, but may be an epiphenomenon
- Skin is uncommonly affected; two types of cutaneous involvement occur
  - A generalized viral exanthem (macules and papules) that may become purpuric
  - A chronic perianal ulcer

Microscopic

- Perivascular and interstitial mixed inflammation with prominent vessels
- Enlarged pleomorphic endothelial cells with basophilic intranuclear inclusions admixed with normal endothelial cells; often surrounded by a clear halo
- May see focal leukocytoclasis

Virus

- Member of the herpesvirus group; a DNA virus
- Electronmicroscopy reveals a 110 μm viral particle that resembles HSV
- Virus may be demonstrated with immunoperoxidase stains using antibodies to CMV antigens or by in situ hybridization

Epstein-Barr Virus (EBV)

Clinical

- Lymphotropic virus that is the causative agent of infectious mononucleosis and is strongly associated with oral hairy leukoplakia, Gianotti-Crosti syndrome in children, nasopharyngeal carcinoma, Burkitt's lymphoma, and other lymphomas and lymphoproliferative diseases
- Infection is nearly ubiquitous in poverty-stricken countries with crowded living conditions; usually acquired in childhood

- In affluent countries, infection is still common but not universal; often acquired by young adults
- Primary infection is often subclinical in children and symptomatic in older children and adults
- Primary infection is transmitted when virus present in the saliva invades B lymphocytes in the oral cavity
- Virus is shed in the saliva during acute infection and in smaller quantities throughout life
- Parotid duct epithelium, oropharyngeal squamous epithelium, and uterine cervical epithelium are sites of viral replication and release
- A 30 to 50 day incubation period is followed by dissemination of EBV, which is associated with a prodrome of headache and malaise
- Most common symptoms are fever, sore throat, and tender lymphadenopathy, usually in cervical nodes but also in other locations (axillary, inguinal, etc.)
- Other manifestations include periorbital edema, exudative tonsillitis, oropharyngeal lymphoid hyperplasia, palatal petechiae, and elevation of liver function studies
- Splenomegaly and less often hepatomegaly are also associated
- A wide variety of skin manifestations occur, including morbilliform viral eruption, petechiae and purpura, and urticaria (may be associated with cold agglutinins)
- Increased incidence of skin rashes following treatment with ampicillin or ampicillin analogs is related to high levels of IgM and IgG antibodies to ampicillin documented during acute EBV infection
- Rare CNS complications include encephalitis, cerebellar ataxia, and Bell's palsy
- Rare hematologic complications include hemolytic anemia, thrombocytopenia, and neutropenia

Laboratory Findings
(Necessary for the Diagnosis)

- Increased lymphocytes and atypical B-lymphocytes early in the disease and T cells later
- IgM heterophile antibodies and EBV-specific antibodies, including anti-VCA IgM and IgG (viral capsid) and anti-EBV-EA (associated with viral replication) during acute infection
- Persistent antibodies include anti-EBV-R (a component of the EA complex) and anti-EBNA (nuclear antigens)

Microscopic

- Widespread reactive lymphoid hyperplasia, including lymph nodes, spleen, and nasopharynx
- Non-lymphoid organs (heart, liver, kidneys, and lungs) have focal lymphoid aggregates
- Bone marrow hyperplasia with occasional granulomatous inflammation

Virus

- Member of the herpesvirus group; a DNA virus

Poxvirus Group

Molluscum Contagiosum

Clinical

- Characterized by skin-colored umbilicated papules, 1–3 mm in size
- A fairly common infection in children
- Numerous or large recalcitrant lesions develop in immunosuppressed patients
- Lesions occurring on the perineum or buttocks in a sexually active patient may be considered a sexually transmitted disease; partner should be examined
- In immunocompetent patients (especially children), disease is self-limited; lesions will involute spontaneously in time
- Involution is clinically characterized by erythema, warmth, and tenderness
- Resolution is hastened by locally destructive treatments, such as curretage

Microscopic

- Acanthotic and endophytic lesion, with a central crater corresponding to clinical umbilication
- Keratinocytes contain large cytoplasmic eosinophilic inclusion bodies referred to as molluscum bodies or Henderson-Patterson bodies
- Inclusions increase in size as the infected cells move up from the stratum malpighii (first area to demonstrate changes) to the granular layer
- In the granular layer, inclusions change from eosinophilic to basophilic
- The stratum corneum disintegrates in the center of the lesion, releasing the molluscum bodies and forming the central crater
- May see minimal inflammation in the dermis, or a mononuclear cell infiltrate (during the involution phase)

Virus

- Member of the poxvirus group; a DNA virus
- Electron microscopy demonstrates a very large (~200 by 300 μm) "brick-shaped" virus
- Organism may be identified in tissue by in situ hybridization; has not been grown in tissue culture

Paravaccinia and Parapox

Clinical

- Clinically similar group of diseases produced by poxviruses, including orf, milker's nodules, and bovine papular stomatitis:
  - Orf, or ecthyma contagiosum (parapox), is transmit-

ted by infected ruminants (sheep and goats); disease is manifested in the animal as crusts or nodules around the nose or mouth

– Milker's nodules (paravaccinia) are acquired from infected nodules on the udder or from calves with oral lesions secondary to nursing from an infected udder (called bovine papular stomatitis in the calf)

- Clinically characterized by a painful nodule on the digit; multiple lesions can occur; may arise in other sites (autoinoculation)
- Six clinical stages over the course of 6 weeks; each phase lasts ~1 week
  1. Papular stage
  2. Target stage: nodule in the red center, white middle ring, red peripheral rim
  3. Acute stage: weeping serum
  4. Nodular or regenerative stage: painless hard nodule
  5. Papillomatous stage: nodule develops papillomatosis
  6. Regression or resolution: involution of the nodule; heals without scarring

Microscopic

- Papular and target stages have vacuolar change in upper stratum malpighii leading to intraepidermal vesicles
- Intracytoplasmic and occasional intranuclear eosinophilic inclusion bodies are present in the vacuolated cells
- With progression through the stages, see more acanthosis and papillomatosis with a mononuclear cell infiltrate and dilation of blood vessels in the upper dermis

Virus

- Members of the poxvirus group; all are DNA viruses
- Electron microscopy demonstrates a very large (~200 by 300 μm) virus; ovoid or cylindrical in shape, with a wide capsid
- Organism may be cultured from lesions during the first 2 weeks or demonstrated by in situ hybridization in the later stages

Human Cowpox

Clinical

- Disease is actually carried by rodents and cats rather than cows
- In patients unvaccinated for variola, see crusted lesions and ulcers on exposed skin surfaces with lymphadenopathy in some cases

Pathology

- Reticular degeneration and intracytoplasmic eosinophilic inclusion bodies
- Indistinguishable from orf and milker's nodules

Virus

- Member of the orthopox group; a DNA virus

Papovavirus Group

Human Papillomavirus

Clinical

- > 67 types identified to date

Basic Clinical Subtypes

- Common warts, filiform warts
- Deep palmar-plantar warts
- Mosaic warts
- Flat warts
- Condyloma acuminatum

Selected Clinical Forms and Associated HPV Types

- Verruca vulgaris (common wart): HPV types 2 and 4 (also 7)
- Deep palmoplantar warts (myrmecia): HPV type 1
- Verruca plana (flat warts): HPV type 3 (also 10)
- Butcher's warts: HPV type 7
- Epidermodysplasia verruciformis (high cancer risk in sun-exposed skin): HPV types 3, 5, 8–10, 12, 14, 15, 17, 19–29, 38, and 47
- Condyloma acuminatum with low cancer risk: HPV types 6 and 11
- Condyloma acuminatum with high cancer risk: HPV types 16, 18, 31, 33, and 51
- Bowenoid papulosis: HPV types 16, 18, 31, 33, and 51
- Laryngeal carcinoma: HPV type 30
- Verrucous carcinoma (Buschke-Loewenstein tumor: perineum): HPV type 6
- Verrucous carcinoma (epithelioma cuniculatum: foot): HPV type 2
- Common, flat, and mosaic warts are common in children
- Immunosuppression increases the frequency and severity of papillomavirus infection (HIV infection, transplant patients)

Bowenoid Papulosis

- Presents as small red papules or verrucal papules on the glans and shaft of the penis in men or the vulva and perineum in women
- May spontaneously regress or persist unchanged for years; rarely develop invasive squamous cell carcinoma
- Strongly associated with cervical or perianal neoplasia in the partner of an infected patient

Epidermodysplasia Verruciformis

- Usually an inherited disease that often begins in childhood and is characterized by a widespread verrucal eruption

- Lesions include verruca plana-like papules with confluence into plaques, tinea versicolor-like macules, and seborrheic keratosis-like lesions
- Lesions occurring in sun-exposed sites frequently develop squamous cell carcinoma in situ (Bowen's disease) and occasionally invasive squamous cell carcinoma

Microscopic

Verruca Vulgaris

- Epidermal hyperkeratosis, papillomatosis, acanthosis and radial orientation
- Hypergranulosis with clumped keratohyaline granules
- Vertical columns of parakeratosis surmounting the crests of the papillae
- Often located below the parakeratotic column, there are viral cytopathic changes or koilocytotic cells: shrunken "raisin-like" nuclei with condensed chromatin and irregular nuclear outline; vacuolated cytoplasm with a perinuclear halo
- Dilated capillaries in the upper dermal papillae

Deep Palmoplantar Warts

- Endophytic growth with marked hyperkeratosis and papillomatosis
- Distinctive cytoplasmic eosinophilic granules that appear in the lower epidermis and coalesce as the cells move upward to form large eosinophilic "inclusion bodies"
- Some of the cells in the stratum malpighii contain eosinophilic intranuclear inclusion bodies; approximately the same size as the nucleolus
- True granular layer is absent

Verruca Plana

- Acanthosis and basket-weave hyperkeratosis but no papillomatosis or parakeratosis
- Marked viral cytopathic change in upper stratum spinosum and granular layer; confluence of vacuolated cells with irregular, basophilic shrunken nuclei
- Dermis is normal; no dilated capillaries

Condyloma Acuminatum

- Parakeratosis and mild hyperkeratosis on mucosal surfaces
- Marked acanthosis and papillomatosis
- Perinuclear vacuolization with shrunken and basophilic nuclei (koilocytic cells) that extend into the deeper levels of the stratum malpighii are necessary for the diagnosis
- Lesions that have recently been treated with podophyllum may have pleomorphic and necrotic epithelial cells and bizarre mitotic figures

Bowenoid Papulosis

- Dysplasia with crowding of keratinocytes, loss of epithelial architecture, increased mitotic activity, and cytologic atypia that varies from mild to severe (carcinoma in situ)
- Rarely, invasive squamous cell carcinoma can be seen in association with bowenoid papulosis
- Koilocytic cells are often present

Virus

- Member of the papovavirus group; a DNA virus
- Does not grow in tissue culture; can be demonstrated by in situ hybridization

Picornavirus Group

Coxsackievirus: Hand-Foot-and-Mouth Disease

Clinical

- Most commonly occurs in children; often as a small epidemic
- Small vesicles in the mouth are the most common sign
- Less often see palmar and plantar vesicles with surrounding erythema; lesions also occur on the sides of the fingers
- Disease is mild; lasts <1 week
- Diagnosis is usually made clinically but, if necessary, virus may be cultured from stool and occasionally from the vesicles

Microscopic

- Marked reticular degeneration leads to multilocular intraepidermal vesiculation; old vesicles may appear subepidermal
- Ballooning degeneration is sometimes seen in the deeper levels of the epidermis

Virus

- Coxsackie type A16 is most commonly associated; types A5 and A9 have also been found
- An enterovirus that is a member of the picornavirus group; an RNA virus
- May be grown on human epithelial cells or monkey kidney

Retrovirus Group

Human Immunodeficiency Virus (HIV)

Clinical

- The retroviral causative agent of acquired immunodeficiency syndrome (AIDS)
- Transmission exclusively by blood, semen, or transplacentally
- The virus infects T helper cells and destroys them, bringing about the destruction of cellular immunity

- Death results from opportunistic infection or malignancy

Associated Infections

- Pneumocystis carinii pneumonia
- Oral hairy leukoplakia: Epstein-Barr virus
- Bacillary angiomatosis: rochalimaea henselae or rochalimaea quintana
- Bacterial: folliculitis, impetigo, mycobacterium avium-intracellulare
- Viral: molluscum contagiosum, cytomegalovirus, HSV, and VZV
- Fungal: candidiasis, dermatophytosis, cryptococcosis, histoplasmosis, coccidioidomycosis

Associated Malignancies

- Kaposi's sarcoma: associated with human herpes virus 8
- Body-cavity-based lymphoma
- Nonmelanoma skin cancer

Associated Inflammatory Skin Conditions

- Seborrheic dermatitis:
  - In addition to typical histology of common seborrheic dermatitis, there is more keratinocyte necrosis and leukocyte exocytosis, and there are more plasma cells in the dermal inflammatory infiltrate
- Eosinophilic folliculitis:
  - Chronic pruritic papular eruption histologically showing folliculitis with eosinophils and mixed inflammation
- Poorly characterized and nonspecific interface dermatitis:
  - Generalized pink to red papules and plaques histologically demonstrating basal vacuolar change, necrotic keratinocytes, and a perivascular lymphocytic infiltrate
- Exanthem of primary HIV infection:
  - A nonspecific and widespread eruption of pink to red macules and small papules; biopsy has a lymphohistiocytic infiltrate and mild epidermal spongiosis
- Psoriasis vulgaris and Reiter's syndrome also appear or worsen with AIDS

Human T-Cell Leukemia Virus Types I and II (HTLV I and II)

Clinical

- HTLV-I and HTLV-II are related but distinct Type C human retroviruses
- Endemic in southern Japan, the Caribbean islands, equatorial Africa, and South America; recently reported in IV drug users in the United States
- HTLV-I has been better studied than HTLV-2, but most of the properties that are known about HTLV-I (such as transformation of T cells in vitro) are also true for HTLV-II
- The vast majority of associated diseases are associated with HTLV-I
- HTLV-I brings about immunosuppression and subsequent opportunistic infections
- HTLV-I has been implicated in a variety of diseases, including adult T-cell leukemia (ATL), infective dermatitis, polymyositis, neurologic disorders, tropical spastic paraparesis, peripheral neuropathy, and HTLV-I associated myelopathy
- The incidence rate of ATL in HTLV-1 carriers is ~2% to 5%

Four Different Courses of ATL

Acute Prototypic ATL

- Fatal disease with involvement of multiple organ systems, including bone marrow, spleen, liver, lung, CNS, skin, and bone
- Many patients experience refractory hypercalcemia and lytic bone lesions resembling those of multiple myeloma, possibly due to cytokines produced by the leukemic cells that signal osteoclast activation

Chronic ATL

- Indolent disease that may transform into acute form

Smoldering ATL

- Indolent disease that may transform into acute form

Cutaneous-Type ATL

- Controversial subtype characterized by skin manifestations without involvement of other organs

Microscopic

- In prototypic acute ATL, the peripheral blood has characteristic leukemic cells with multilobate nuclei ("flower cells")
- The phenotype of these cells is CD2+, CD3+, CD4+, CD8–, and CD25+; CD25 positivity distinguishes the cells from Sézary syndrome
- Cells indistinguishable from Sézary cells are also found in the peripheral blood
- Far fewer multilobate cells are seen in the blood of chronic and smoldering ATL
- The pathology of other organs involved is variable and not distinctive
- Skin lesions may show changes similar to mycosis fungoides and Sézary syndrome with epidermotropism of atypical lymphocytes and Pautrier's microabscesses
- ATL is associated with several different lymphomas, including small cell, mixed small, large cell, and large cell immunoblastic, among others

- Distinction from other peripheral T-cell lymphomas is based on a combination of pathology, clinical features, disease course, and the presence of multilobate cells
- The diagnosis is established by documentation of seropositivity for HTLV-I and the presence of HTLV-I provirus in leukemic or lymphoma cells

FUNGAL INFECTIONS

Classification and Terminology

- See Table 3-1

Superficial Infections

Pityriasis (Tinea) Versicolor

- Other names include Malassezia furfur, Pitysporon orbiculare, and Pitysporon ovale
- Lipophilic yeast
- Associated with seborrheic dermatitis and, to a lesser degree, with perioral dermatitis
- On potassium hydroxide (KOH) and hematoxylin-eosin (H&E) stained sections: short true hyphae and yeast = "spaghetti and meatballs"

Tinea Nigra Palmaris (Phaeannelomyces wernickii)

- Name literally means black yeast
- Old name was Exophialia wernickii
- Clinically can be mistaken for acral nevus or melanoma
- KOH: Black septate hyphae
- H&E: Black hyphae in stratum corneum of acral skin

Black Piedra (Piedraia hortai)

- Seen on hair of unwashed heads in Amazon, Congo, Africa, and South America
- Ascospores (nodules along the hair); the only time sexual spores are seen in a clinical specimen

White Piedra (Trichosporon beigelii)

- Axillary and pubic hair
- White soft nodules along the hair shaft
- May see a break in the hair at the nodule
- KOH: A mixture of yeast, hyphae, pseudohyphae, and arthroconidia

Dermatophytes

Large Smooth Walled Club Macroconidia; No Microconidia

Epidermophyton Floccosum

- Colony: fine granular or grainy to suede-like and flat; can have a feathery edge
- Colony pigment: khaki
- Club-shaped macroconidia
- Colony exhibits pleomorphism: white fluffy sterile hyphae that form when the medium is not optimal

Large Rough Walled Macroconidia; Few or No Microconidia

Microsporum canis

- Colony: wooly or fluffy, heaped and white
- Colony pigment (reverse): "canary" yellow; older colonies are more orange
- Distinguished from *M. audounii* by its ability to grow on rice media
- Pectinate (nobby) macroconidia with a "pointy snout"
- Macroconidia are thick walled, with 5–6 or more septae

Microsporum distortum

- Similar to *M. canis* in its colony growth and appearance
- Macroconidia are very similar to those of *M. canis* except they are bent and distorted.

Microsporum gypseum

- Colony: granular, with a feathered edge
- Colony pigment: cinnamon
- Smooth macroconidia with rounded ends that are thin walled and have fewer septae than *M. canis* (<5)

Microsporum audouinii

- Colony: white and fluffy
- Colony pigment: salmon
- Does NOT grow on rice media
- Terminal chlamydospores
- Rare "antler" and pectinate hyphae

Many Microconidia; Rare Smooth Elongated Macroconidia

Urease Positive

Trichophyton mentagrophytes Var. Interdigitale

- Colony: white heaped and fluffy

T. mentagrophytes Var. mentagrophytes

- Colony: white, flat, and granular or "powdery"
- Colony pigment (reverse): sparse red, if present at all

Table 3-1. Classification of Fungal Infections

Sexual Reproduction

Sexual spore	*Septation*	*Asexual spore*
Zygomycetes	aseptate	sporangiospore
Ascomycetes (histoplasma, blastomyces)	septate	conidia
Basidiomycetes (mushrooms, toadstools, cryptococcus)	septate	conidia

Nonsexual "imperfect fungi"

Deuteromycetes (most human pathogens)	septate	conidia

Asexual Reproduction: Types of spores

Conidia: dermatophytes

Arthroconidia: coccidioides

Chlamydoconidia: resting spore (most fungi)

Blastoconidia: budding spore (yeasts)

Sporangiospore: spores in a spherule or sporangium (coccidioides, rhizopus)

Anamorphic or Telemorphic State

Some dermatophytes have a sexual (stable) state = "arthroderma state"

Example: M. gypseum = Arthroderma gypseum

Anthropophilic Fungi: infection with anthropophilic species causes less inflammation than infection with zoophilic or geophilic species.

Worldwide	**Geographically limited**
E. floccosum	*M. ferrugineum*
M. audouinii	*T. concentricum*
T. mentagrophytes	*T. gourvilli*
var. interdigitale	*T. menignii*
T. rubrum	*T. soudanense*
T. schoenleinii	*T. yaoundei*
T. tonsurans	
T. violaceum	

Zoophilic Fungi	**Geophilic Fungi**
M. canis	*M. gypseum*
M. distortum	*M. cookei*
M. gallinae	*M. nanum*
M. and T. equinum	*M. fulvum*
T. mentagrophytes	*M. vanbreuseghemii*
var. mentagrophytes	*T. terrestre*
T. verrucosum	*T. ajelloi*

(continued on next page)

(Table 3-1 continued)

Colony Requirements

Thiamine	Inosital	Niacin	Histidine
T. verrucosum	*T. verrucosum*	*M. equinum*	*T. menignii*
T. violaceum			
T. concentricum			
T. tonsurans			

Species' Ability to Cause Infection

	Hair	Skin	Nails
Trichophyton	+	+	+
Microsporum	+	+	NO
Epidermophyton	NO	+	+

Hair Flourescence (With wood's lamp)

M. distortum *M. audouinii* *M. canis* *M. ferrugineum* *T. schoenleinii*

Favus (hyphae inside hair)

Look like "tunnels filled with air"

Caused by *T. schoenleinii*

Endothrix

Organisms are inside the hair shaft; all are non-fluorescing

T. soudanense *T. violaceum* *T. tonsurans* (most common in USA)
+ adenopathy
+ "black dot" tinea capitus

Ectothrix

Organisms are on the outside of the hair shaft

Small spore: DO fluoresce	Large spore: do NOT fluoresce
M. canis	*T. mentagrophytes*
M. audouinii	*T. verrucosum*
M. ferrugineum	*M. gypseum*
M. distortum	

Lactophenol Cotton Blue Tape Prep

Lactic acid makes cell wall permeable to cotton blue dye

Phenol kill the fungus

Cotton blue dye colors the organism to assist visualization

- Growth on cornmeal agar
- Round grape-like clusters of microconidia
- Occasionally see spiral hyphae
- Rarely see slender macroconidia with smooth walls and narrow attachment at base
- Penetrates hair

Urease Negative

Trichophyton rubrum

- Colony: white, heaped, and fluffy, sometimes moist
- Colony pigment: red; may see a "bullseye" with dark red center and yellow outside
- Tear-drop shaped microconidia likened to "birds on a wire"
- Rare smooth-walled macroconidia
- NO spiral hyphae

Trichophyton tonsurans

- Colony: flat and grainy, slow growing
- Colony pigment: mahogany brown, also white and yellow
- Colony growth requires thiamine
- Wide variety of microconidia; "balloon forms" are characteristic
- Hyphae become swollen with age
- Macroconidia are rare and distorted

Only Hyphae Seen; Conidia Usually Absent

Trichophyton violaceum

- Colony: wrinkled and leathery or waxy
- Colony pigment: violet
- Colony growth requires thiamine (VERY slow growth without it)
- Intercalary chlamydoconidia are characteristic
- Swollen hyphae with cytoplasmic granules

Trichophyton schoenleinii

- Colony: wrinkled, heaped, and leathery or waxy
- Colony pigment: white
- "Antler" hyphae are characteristic
- Chlamydospores

Trichophyton verrucosum

- Colony: moist and leathery, ± submerged in media
- Colony pigment: none
- Colony growth requires thiamine ± inositol
- Colony grows very slowly at 25°
- The only species that has increased growth at 37°
- Conidia absent in routine cultures
- Sometimes see "antler" and "chandalier" hyphae

Miscellaneous

Microsporum nanum

- Colony: flat and granular
- Colony pigment (reverse): yellow-red to brown
- "Pig snout" macroconidia with 1–3 septae

Trichophyton concentricum

- Colony: very wrinkled, referred to as "cerebriform"
- Colony pigment (reverse): orange to brown
- Colony growth requires thiamine
- Tangled hyphae, no spores

Microsporum ferrugineum

- Prominent septate "bamboo" hyphae
- Colony pigment: white to orange-yellow

Pigmented Nail Disease

Scytilidium dermatiadum (Syn. Hendersonula toruloidea)

- Common in the Caribbean and Thailand; USA 6% to 7% of nail infections
- Can also be a plant pathogen (bananas)
- Sexual phase: nattrassia mangiferse
- Very fast growing; doesn't grow with cyclohexamide
- Black mold with black septate hyphae
- Break up into two-celled arthroconidia

Schyilidium hyalinum

- White (albino) type

Subcutaneous Infections

Sporotrichosis: Sporothrix schenkii

- Agent: found worldwide in soil, rose thorns, shrubs, trees, bark, mulch, and moss
- More common in florists and gardeners; usual transmission via inoculation injury

Clinical Forms

Lymphocutaneous

- Most common form
- Demonstrates "sporotrichoid spread" with inoculation site nodule and secondary nodules along the lymphatics to the draining lymph node

Fixed Cutaneous

- Occasional
- May indicate a high degree of immunity

Pulmonary/Disseminated Cutaneous

- Rare
- Acquired by inhalation or aspiration

- Risk factors include immunosuppression, alcoholism, diabetes, sarcoidosis, chronic steroid use, AIDS, and tuberculosis

Dimorphic

- Different growth patterns at 25 and 37 degrees

25°: Saprobic Form

- Colony: wrinkled to leathery
- Colony pigment: cream-tan-black; can be "dark and greasy"
- Microscopic: clear delicate septate and branching hyphae with "daisy-like" conidia or conidiophores at right angles

37°: Parasitic (Tissue) Form

- Colony pigment and form: white-tan yeast
- Microscopic: round-oval or "cigar-shaped" yeast; rarely seen in tissue
- Histology: pseudoepitheliomatous hyperplasia, neutrophilic abscesses surrounded by granulomatous inflammation; VERY rare organisms
- Splendor-Hopley reaction: high host resistance due to previous exposure; see the organism surrounded by radiating eosinophilic spokes
- HIV/AIDS: sporotrichosis is not common; when it does occur, see more cigar bodies and fewer asteroid bodies

Chromomycosis

Fonsecaea pedrosoi: Most common cause; 97%
Phialophora verrucosa
Cladosporium carrioni
Rhinocladiella aquaspora
Fonsecaea compacta

- Clinical setting: adult male agricultural workers in Third World (Central America and Caribbean); contamination of skin break with soil or plant
- Usually affects lower extremities: chronic and indolent, verrucous to nodular
- KOH of skin scales and tissue H&E: sclerotic bodies, copper pennies, or medlar bodies; all refer to thick-walled septate copper-colored fungal cells (5–10 μm)
- Histology: epidermal acanthosis to pseudo-epitheliomatous hyperplasia, dermal abscess with surrounding granulomatous inflammation and dermal fibrosis
- Culture: dematiaceous (black) mold; identification based on type of sporulation

Types of Sporulation

- Rhinocladiella: "bottle brush"
- Phialophora: "flask shaped" or "vase of flowers"
- Cladosporium: "tree-like" chains of flowers
- Fonseca: all three types are present; must see 2/3

Phaeohyphomycosis

Exophiala jeanselmeii: Most common cause
Bipolaris species
Alternaria
Curvilaria
Wangiella dermatitidis

- Dematiacious (black) fungi; numerous forms, >60 species
- Opportunistic pathogen with a worldwide distribution
- Present in soil and decaying organic material
- Most commonly introduced via trauma
- Clinical: nodular dermal cysts and abscesses; disseminated forms in immunocompromised (transplant patients); IV drug abusers can get fatal brain abscesses
- Direct exam: pigmented hyphae; if organism is young, may be without pigment (can visualize with PAS or Fontana Masson)
- Histology: necrotic dermal abscess surrounded by granulomatous inflammation and peripheral dense fibrosis
- Both yeast and hyphal forms can be seen in tissue
- Hyphae are septate, irregular, and swollen, branched or unbranched; yeast may form chains
- Culture: All are black; difficult to identify

Mycetoma

- Chronic infection of the skin characterized by draining sinuses that discharge exudate with granules
- Infection begins with repetitive inoculation, usually on the lower extremity
- Clinically begins as a papule that progresses to a nodule (with sinus tracts) and ultimately causes a grossly misshapen and swollen limb
- May be caused by bacteria (actinomycetes mycetoma) or fungi (maduromycotic mycetoma)

Actinomycetes mycetoma: 98%

Actinomycetes Group

- Note that the group contains nocardia species, NOT Actinomycosis
- Nocardia braziliensis (aerobic): most common cause
- Nocardia caviae
- Nocardia asteroides

Streptomyces Group

- Streptomyces pelletieri
- Streptomyces somaliensis
- Actinomadura madurae

Actinomycosis israelii

- Note that while *A. israelii* may cause infection with draining sinuses and granule formation, it is not a true mycetoma

Maduromycotic Mycetoma: 2%

- True mycotic mycetoma: "eumycotic mycetoma" NOT = "madurella"
- Pseudoallescheria boydii: most common fungal cause of mycetoma
- Asexual names: scedosporium or apiospermum
- Culture: rapid growth, fluffy and "mouse grey"
- Madurella mycetomatis: rarely seen in USA
- Culture: diffusable pigment; rare conidia

Grain Color Differential

- Black: fungal
- Red: bacterial: streptomyces pelletieri
- Yellow: actinomycosis (not true mycetoma)
- White: CRUSH then GRAM STAIN:
  - Bacteria and fungus: GRAM +
  - If filamentous, do ACID FAST: nocardia is +; actinomycosis (or other) is –

Rhinosporidiosis: Rhinosporium seeberi

- The nature of the agent is unknown; fungus? protozoan?
- Clinical setting: soil and stagnant water; presumably acquired by inoculation
- Reported in East Asia, Ceylon, India, and rural Georgia
- Clinical: nasal polyps appear pink-red with "salt dots;" ocular lesions also reported
- Pathology: huge spherules with endospores
- Culture: organism has never been cultured

Lobomycosis: Paracoccidioides Glenosporella) loboi or Loboa loboi

- Confined to Central and South America
- Affects males more commonly; seen in all races
- Natural habitat unknown, but has been cultured from the bottle-neck dolphin
- Lesions are usually confined to the skin; slow progressive growth
- Presumably related to inoculation injury
- Lesions may be associated with a keloid-like scar
- Histopathology: large spores (10–20 μm) with a thick capsule; "lemon-like":
  - Organism free in tissue and in giant cells
  - Granulomatous inflammation, lymphocytes, and plasma cells; no neutrophils
  - Spores do not stain with H&E, leave unstained "holes" in biopsy

Entomophthoromycosis

Basidiobolus Haptosporus (ranarum)

Conidiobolus Coronatus

- Clinical setting: found in feces of reptiles and amphibians; Central Africa and Indonesia
- Infection in adults: *C. coronatus*; hard swelling of the face
- Infection in children: *B. haptosporus*; hard swelling of the legs and thighs
- Pathology: eosinophilic sleeve
- Direct exam: broad septate hyphae
- Culture: short broad hyphae; zygospores, ballistic conidia

Protothecosis

- Rare infection caused by achloric algae Prototheca, usually *P. wickerhamii*
- Organism is ubiquitous; found in lakes, ponds, rivers, and on many animals
- Infection probably caused by inoculation into skin by minor trauma
- Clinical: hard verrucal plaques, cellulitis, or olecranon bursitis
- 60% normal hosts, 40% immunocompromised
- May see an eczematous dermatitis in immunocompromised hosts
- Pathology (localized lesion): central necrosis surrounded by granulation and granulomatous inflammation; organism found in necrotic center
- Pathology (dermatitic lesion): epidermal acanthosis and papillomatosis with dermal mixed inflammation including few multinucleate giant cells; organism found throughout the epidermis and in the dermis
- The organism (2–15 μm) has characteristic sporangia with symmetric endospores, likened to a "morula" or "soccer ball"
- Culture: white creamy colony, looks like any yeast; no pigment

Disseminated Diseases

Histoplasmosis: Histoplasma capsulatum

- Found in soil with high nitrogen content (bird and bat guano)
- Worldwide distribution; increased in Ohio and Mississippi river valleys
- Disease acquired by inhalation, which then leads to pulmonary disease
- Pulmonary disease heals partially but leaves areas of calcification in parenchyma and lymph nodes
- Increased risk for disseminated disease: immunocompromised (AIDS) and patients with lymphoid malignancy

- Disseminated form: goes to reticuloendothelial system (RES), skin, and mucous membranes (tongue and palate)
- Skin lesions: papular to pustular
- Dimorphic: different growth patterns at 25° and 37°

25°: Saprobic Form

- Colony: filamentous mold
- Large (10–20 μm), tuberculate macroconidia
- ± microconidia

37°: Parasitic Form (Tissue)

- Colony: soft and creamy
- Pathology: tiny (2–5 μm) intracellular yeast in histiocytes
- Organism best visualized with Giemsa or Wright stain

African Histoplasmosis: Histoplasma duboisii

- Organism and disease not well understood
- Found in soil of Central Africa
- Clinical: subcutaneous lesions and osteomyelitis; little or no lung disease
- Dimorphic: different growth patterns at 25° and 37°

37° (Tissue)

- 10–15 yeast cells with a narrow base
- Resembles *Paracoccidioides* at 37° or *Histoplasma* at 25°

Blastomycosis: Blastomyces dermatididus

- Found in soil of southeastern and eastern USA, Canada, and Africa
- Disease acquired by inhalation, which then leads to pulmonary disease
- Infection may then be:
  - Controlled by cell mediated immunity (CMI)
  - Partially controlled by CMI: chronic flu-like illness and pulmonary cavitary lesions
  - Widely disseminated (lung, bone, skin, prostate): increased incidence in immunosuppressed patients or patients with large inhalation inoculum
- Direct exam (KOH) of crusted lesion: may see large yeast
- Dimorphic: different growth patterns at 25° and 37°

25° (Saprobic Form)

- Colony: white-buff filamentous mold
- Branching septate hyphae
- Conidia: smooth walled; oval to round

37° (Parasitic Tissue Form)

- Thick walled spores; 8–10 μm
- Broad-based budding

Coccidioidomycosis: Coccidiodes immitis

- Found worldwide, increased incidence in California and southwest United States (arid)
- Disease acquired by inhalation, which then leads to pulmonary disease
- Infection May Then Be:
  - Controlled by CMI (most common)
  - Partially controlled by CMI: chronic cutaneous lesions (abscesses, fistulae)
  - Widely disseminated to skin, viscera, and bones (increased risk in black and dark-skinned patients)
- Dimorphic: different growth patterns at 25° and 37°

25° (Saprobic Form)

- Entire culture is highly infectious
- Barrel-shaped alternating arthroconidia (highly infectious)
- White inoculum; peripheral "ground glass" growth

37° (Parasitic Tissue Form)

- Grows sparsely at 37°; colony appears same as above
- In tissue biopsy, see large thick-walled spherules with many endospores

Paracoccidioidomycosis: Paracoccidiodes brasiliensis

- Found in soil in Brazil (most commonly), South and Central America, and Mexico
- Disease acquired by inhalation, which then leads to pulmonary disease
- Lung disease is bilateral, bibasilar, and multinodular
- Lung disease has an equal incidence in men and women
- Infection May Then Be:
  - Contained by CMI (more common in females; due to an estrogen effect?)
  - Disseminated (much higher incidence in men)
- Clinical (disseminated): ulcerative granulomata and lymphangitis
- Affects skin (perioral), mucous membranes (palatal, buccal, nasal), and viscera
- Fatal if not treated
- Dimorphic: different growth patterns at 25° and 37°

25° (Saprobic Form)

- Fine septate hyphae lacking spores

37° (Parasitic Form)

- "Mariner's wheel" (looks like African Histoplasma)
- Thick-walled large (10–60 μm) yeast with small buds

Penicillinosis: Penicillium marnefii

- Acquired in Asia or the Far East; Thailand
- Found in soil; reservoir in bamboo rat
- Disease acquired by inhalation, which then leads to pulmonary disease
- Infection May Then Be:
  - Contained by CMI
  - Disseminated (increased risk in patients with AIDS and transplant patients)
- Dimorphic: different growth patterns at 25° and 37°
- Yeast-like cells that divide by fission or septation (NOT budding spores)
- Tissue: organisms are found within histiocytes

Disseminated Diseases in the Immunocompromised Patient

Cryptococcosis: Cryptococcus neoformans and C. gatti (Australia)

- Found in soil and pigeon droppings (attics, belfries, cornices)
- Can remain viable for years
- Disease acquired by inhalation, which then leads to mild pulmonary disease
- Infection May Then Be:
  - Contained by CMI
  - Disseminated (increased risk in AIDS, lymphoid malignancy, sarcoid, steroid use)
- Disseminated disease frequently involves the CNS (no phagocytic cells)
- Patients have chronic meningitis with alternating disease and remission
- Organism: NOT dimorphic; only has a yeast form
- Encapsulated, thin-walled, single budding, with a narrow attachment
- Distinguished by its large gelatinous capsule; variable sizes (2–15 μm)
- Direct examination of cerebrospinal fluid with India ink (stains capsule)
- Biopsy: minimal inflammatory response with gelatinous reaction
- Biopsy: patients with intact immunity have less gelatinous reaction and more granulomatous response
- Alcian blue stains the capsule blue, and periodic acid-Schiff (PAS) stains the organism pink
- Mucicarmine stains the capsule red
- Serology: complement fixation and FAb tests for antibody to organism
- Culture: rapid grower (delete cyclohexamide)
- Sabauroud's blood agar or bird seed (black) agar: organism uses precursors and makes melanin

Candidiasis: Candida albicans and Other Candida Species

- Most common of the severe fungal infections
- Normal flora of man (gastrointestinal, genitourinary, etc.)
- In the presence of certain risk factors, patients develop superinfection:
  - Risk factors: immunosuppression, steroids, antibacterials, obesity (intertriginous)
- Mucous membrane lesions: thrush, balanitis, vaginitis, esophagitis
- Cutaneous lesions: intertrigo, paronychia, diaper rash; erythematous plaques with peripheral pustules

Clinical Forms

Acute Mucocutaneous

- Benign and self-limited, very common

Chronic Mucocutaneous

- A heterogeneous group of disorders characterized by recurrent candidiasis (mucous membranes, nails, and skin) and immunodeficiency
- Systemic lesions do not occur
- Can be seen in AIDS, or as an inherited condition
- May be accompanied by endocrinopathy or thymic agenesis (di George syndrome)

Disseminated

- Hematogenous spread from urinary or gastrointestinal tract
- High mortality rate
- Polymorphic skin lesions, including macules, papules, nodules, and petechiae are present in <15% of patients
- Accompanied by diffuse muscle tenderness, caused by muscle infiltration by the yeast
- Candida tropicalis and Candida krusei are responsible for half of the cases of disseminated disease
- Polymorphic: pseudohyphae, yeast, and rare hyphae
- Commensal (harmless) form: yeast and oval elongated budding blastosperes
- Invasive form: blastospheres elongate and remain attached end to end to form pseudohyphae and rare true hyphae

Biopsy

- Dense neutrophilic infiltrate in the epidermis and superficial dermis; may see a spongiform subcorneal pustule indistinguishable from psoriasis
- Organisms (pseudohyphae and yeast) visible on H&E
- Pseudohyphae are septate with 90° branching; constriction at septae and septae at branch points
- Chronic inflammatory infiltrate in the deeper levels
- Yeast forms in mouth may not be pathogenic

- Chronic forms have acanthosis and hyperkeratosis
- Disseminated lesions have small numbers of organisms; may require step sectioning to identify; spores may show budding
- Disseminated forms may have leukocytoclastic vasculitis (*Candida tropicalis* in particular)
- Culture: white and creamy; pseudohyphae at the edge
- Cornmeal agar: chlamydospores
- Blood (37°): germ tube test—wait 2–3 hours, look for germ tubes

Aspergillosis

- Ubiquitous and worldwide (compost, decaying vegetable matter)
- Predisposing factors: neutropenia, malignancy (especially hematologic), AIDS, transplant patients, long-term steroid use
- Primary pulmonary infection may disseminate to skin, or skin may be primary

Clinical Forms

Disseminated Disease

- A. fumigatus: the most common human pathogen
- Skin lesions: red macules, papules, pustules, and nodules; rarely cellulitis, purpura, and ulceration

Primary Cutaneous Disease

- A. flavus is the most likely agent when the skin is primary, but all species may cause the disease
- Usually begins at the site of a previous trauma (IV infusion site)
- Skin lesions: hemorrhagic bullae, indurated plaques, cellulitis, and ulceration with black eschar
- May become disseminated and cause death

Secondary Cutaneous Disease

- Hematogenous embolic spread from invasive lung disease
- Poor prognosis
- Other subtypes: *A. niger*, *A. terreus*, and *A. nidulan*

Other Clinical Forms

- Fungal ball: acquired by inhalation; if wall breaks, may lead to dissemination
- Localized: sinusitis
- Invasive pulmonary
- Allergic bronchopulmonary
- Systemic: CNS (increased risk in IV drug users)

Organism

- NOT dimorphic; do not see yeast

Biopsy

- Septate hyphae (often in parallel), with 45° branching
- Hyphae may be seen invading blood vessels
- In disseminated disease/immunocompromised hosts, numerous organisms may be present with minimal inflammatory infiltrate
  - Acute and chronic inflammation with histiocytes may also be seen
- In cutaneous disease/immunocompetent hosts, see few organisms and granulomatous inflammation

Conidiophores (Fruiting Bodies)

- Allow speciation; rarely seen in tissue
- *A. flavus*: "dandelion"
- *A. fumigatus*: "plume of smoke"
- Culture:
  - *A. flavus*: yellow
  - *A. fumigatus*: smoky grey
  - *A. niger*: black
  - *A. terreus*: earth color

Zygomycosis: Mucor, Absidia, and Rhizopus

- Ubiquitous; present in soil, compost, decaying vegetable matter, and water
- Risk factors: uncontrolled diabetes, burns, surgery, severe illness

Clinical Forms

Rhinocerebral

- Begins in the sinuses and spreads rapidly to the nose, paranasal skin, orbit, and CNS
- Increased incidence in patients with uncontrolled diabetes/ketoacidosis and immunosuppression
- Fulminant course; usually fatal
- Death can be rapid, in <24 hours
- Organism has affinity for myelin; tracks along the optic nerve into the brain
- Clinical: nasal discharge and swelling with ulceration and necrotic eschar soon following

Primary Cutaneous

- Seen in burn and trauma victims, especially those with uncontrolled diabetes
- Also reported in IV drug abusers with AIDS
- Begins as blister or pustule that rapidly develops into ulceration with necrotic eschar

Secondary Cutaneous

- Develops from embolization of organisms in patients with systemic disease
- Lesions begin as papules or nodules that blister, ulcerate, and develop eschars

Chronic Subcutaneous

- Painless, progressively enlarging mass; usually on the face
- Patients are otherwise healthy
- May also see pulmonary disease and gastrointestinal ulcers

Biopsy

- Broad aseptate "ribbon-like" hyphae, with 90° branching
- Thin-walled hyphae that may be twisted and fragmented
- Spores are usually not present
- Often see vascular invasion with thrombosis and infarction

Colony

- VERY fast growers, fill entire volume of the container
- Mucor: no rhizoids
- Absidia: rhizoids in between the fruiting bodies
- Rhizopus: rhizoids directly adjacent to the fruiting bodies

Alternariosis: Alternaria Species

- Hyphae are pigmented; sometimes classified as a phaeohyphomycosis
- Organism commonly colonizes human skin but rarely causes disease
- Risk factors for disease include immunosuppression and severe illness
- May be acquired by inhalation, which then leads to pulmonary disease
- Patients with pulmonary disease may develop secondary cutaneous disease by hematogenous spread
- Cutaneous disease may also occur by colonization of an existing skin lesion (that has been treated with steroids), or by trauma with inoculation
- Skin lesions are nonspecific; include papules, nodules, bullae, pustules, verrucal or granulomatous lesions, and ulcers

Biopsy

- Location of organism depends on clinical form:
  - Found in epidermis when organism colonizes preexisting lesions
  - Found in dermis and panniculus in systemic and tauma-related disease
- Dermal abscess with ulceration and granulomatous inflammation; may see pseudoepitheliomatous hyperplasia

Culture

- May see spores and/or hyphae:
  - Spores are large and "hand grenade-shaped," with longitudinal and transverse cross walls; occur singly or in chains
  - Spores may be free in tissue or within histiocytes and giant cells
  - Hyphae are septate, branching, and broad, with brown pigmentation

PARASITIC INFECTIONS

- Parasite refers to organisms belonging to one of two groups, protozoa and helminths; most of the species of both groups are free living
- Protozoa: microscopic single-celled eukaryotes, like yeasts in size and simplicity
- Helminths: macroscopic multicellular worms with complex internal organs

Sporozoans

- See Table 3-2

Malaria

Clinical

- Causative agent is plasmodia
- Many different species exist, but four are known to infect humans: *P. falciparum*, *P. ovale*, *P. malariae* and *P. vivax*:
  - *P. falciparum* produces the most severe disease and is most commonly associated with death
- The reproductive phases are carried out in different hosts; the sexual phase (sporogony) occurs in the gut of the mosquito and the asexual phase (schizogony) takes place in red blood cells of the human
- The organisms multiply, eventually rupture the erythrocyte, and are released into the blood stream; this event corresponds to the intermittent fever that characterizes the disease and is known as malaria
- In the early stages of the disease, the fever is irregular due to red cell infection with parasites at different stages of sporulation
- With time, the sporulation becomes synchronized, resulting in a very regular fever cycle (72 hours for P. malariae and 48 hours for the others)
- The malarial paroxysm begins with a cold stage with chills; this is followed by the hot stage with fever from 40–41.7° C (104–107° F) and severe vasodilation with hypotension; the wet stage is marked by decreasing fever and profuse sweating
- Other clinical manifestations include anemia, thromb-

Table 3-2. Classification of Parasitic Infections

Classes of Protozoa	*Classes of Helminths*
Sporozoa	Intestinal nematodes (roundworms)
Plasmodia (malaria)	*Ancylostoma* (hookworm)
Toxoplasma	*Necator* (hookworm)
Cryptosporidia	*Enterobius* (pinworm)
Rhizopods (amebas)	*Ascaris* (roundworm)
Entamoeba histolytica	*Strongyloides* (roundworm)
Acanthamoeba	*Trichuris* (whipworm)
Naegleria	Tissue nematodes
Flagellates	*Ancylostoma* (cut. larva migrans)
Giardia	*Toxocara* (visceral larva migrans)
Trichomonas	*Trichinella* (trichinosis)
Leishmania	*Wuchereria* (elephantiasis)
Trypanosoma	Onchocerciasis
Ciliates	*Loa loa* (loiasis or eye worms)
Miscellaneous infestations	Cestodes (tapeworms)
Scabies	*Taenia saginata* (cysticercosis)
Myiasis	*Taenia solium* (cysticercosis)
Tungiasis	Trematodes (flukes)
	Schistosoma

ocytopenia, and splenomegaly

- Blackwater fever (seen with *P. falciparum*) refers to the syndrome of fever and dark urine produced when there is massive intravascular hemolysis and subsequent hemoglobinuria
- With *P. falciparum*, severe complications come from blockage of capillaries by the organism
- With blockage of CNS vessels, the patient develops delerium, seizures, coma, and death; acute pulmonary insufficiency is also reported with CNS involvement
- Involvement of visceral capillaries produces jaundice, abdominal pain, vomiting, diarrhea, and renal failure; these syndromes are associated with a high level of parasitemia

Pathology/Laboratory

- The diagnosis is made by demonstrating the parasite in stained smears of the peripheral blood
- The different species can be distinguished using intraerythrocytic morphologic differences
- Infection with *P. vivax* and *P. ovale* produces a large pale parasitized erythrocyte that contains abundant small granules (Schüffner's dots); *P. ovale* is oval-shaped and has a fringed appearance
- With *P. vivax*, *P. ovale*, and *P. malariae*, all the asexual phases are present
- With *P. malariae* infection, there are no granules and the size of the erythrocyte is not increased
- In *P. falciparum* infection, there is frequently more than one parasite in each erythrocyte and there may be a small number of cleft-shaped granules (Maurer's dots)
- It is sometimes necessary to collect several specimens in order to identify the parasite; parasitemia is highest during the febrile paroxysm
- Both thick or thin smears may be used
- In the thick smear, the erythrocyte is lysed with water and the organisms are concentrated; this method is more sensitive but is associated with many artifacts

Toxoplasmosis

Clinical

- The causative organism, Toxoplasma gondii, is an obligate intracellular sporozoan
- The definitive host is the domestic cat; both the asexual and sexual phases take place in the GI tract of the cat
- It affects almost all mammals and many birds; it occurs in all parts of the world but is more common in the tropics
- By adulthood, ~50% of Americans have antibodies to *T. gondii*
- The morphologic stages are the trophozoite, the oocyst, and the tissue cyst:
  - The oocyst has a thick wall that makes it resistant to many environmental challenges; it has an immature form without internal structure, and more mature forms with two sporocysts and later, two trophozoites within each sporocyst
  - The trophozoite is crescent-shaped; it is the form that invades the nucleated cells of the host
  - A tissue cyst is formed (in particular in the brain, heart, and skeletal muscle) when the trophozoites produce a membrane that surrounds and protects them; it is also resistant to environmental challenges, including digestive enzymes (like oocysts)
- The disease is transmitted to humans by ingestion of oocysts in the feces of the cat
- The disease may also be transmitted by ingestion of meat containing tissue cysts, most commonly pork and mutton; cysts are killed by cooking to well done
- Three clinical forms occur: self-limited febrile lymphadenopathy, severe lethal infection in the immunocompromised host, and congenital infection of the infant
- Congenital toxoplasma occurs when the pregnant woman acquires acute toxoplasma infection; the earlier the infection is acquired, the more severe are the manifestations, with devastating consequences in the first trimester
- In most patients with a normal immune system, the infection is asymptomatic
- Clinical manifestations include lymphadenopathy (most commonly cervical nodes), fever, hepatosplenomegaly, atypical lymphocytosis, rash, and sore throat
- Meningoencephalitis, hepatitis, pneumonitis, myocarditis, or unilateral chorioretinitis occasionally occur
- Congenital infection may cause microcephaly, hydrocephaly, cerebral calcifications, seizures, and psychomotor retardation; it may also lead to abortion or stillbirth
- Congenital infection may also cause chorioretinitis in the region of the macula (quite common), fever, lymphadenopathy, pneumonia, hepatosplenomegaly, hepatitis, and/or rash
- Congenital toxoplasma is in the differential of the "blueberry muffin baby" that has generalized blue to red papules and nodules due to dermal erythropoiesis
- In the immunocompromised host, there is dissemination of acute disease or reactivation of latent disease leading to widespread organ involvement including necrotizing encephalitis, pnemonitis, and myocarditis

Pathology/Laboratory

- The crescent-shaped trophozoite can be seen in Wright- or Giemsa-stained lymph node biopsies during the lymphadenopathy stage
- In chronic disease, tissue cysts can be seen in GMS-stained biopsies of many organs
- Serologic testing is the most common method of diagnosis, with the indirect fluorescent antibody test and indirect hemagglutination being very sensitive and specific; an enzyme-linked immunosorbant assay has also been developed
- An elevated titer of IgM (1:80 or higher) indicates acute infection or reactivation

Cryptosporidiosis

Clinical

- Cryptosporidia are obligate intracellular parasites that carry out both cycles of sexual and asexual reproduction in the GI tract of a single host
- The disease is transmitted when infective oocysts passed in the feces are ingested by the new host
- Although the primary mode of transmission is fecal-oral, indirect transmission via contaminated water, food, and fomites has been reported
- Clinical symptoms begin suddenly 1 to 2 weeks after exposure and abate rapidly
- The patient experiences explosive watery diarrhea and abdominal pain as well as nausea, vomiting, and low-grade fever in some cases
- The symptoms are similar to *Giardia* except for the lack of flatulence and more prominent abdominal pain; the course is shorter than *Giardia*
- The disease is especially severe in the very young and the immunocompromised:
  - In immunocompromised patients, the symptoms are more severe and prolonged; weight loss and malnutrition are prominent; the disease persists until the patient's death, usually of other causes

Pathology/Laboratory

- They appear as small, Giemsa + spherical structures in the microvilli of the intestinal epithelium; they are protected by a double membrane derived from the microvilli and are therefore considered to be intracellular
- The jejunum is usually the most heavily involved segment of the bowel

- There is mild to moderate villous atrophy, crypt dilation, and a lymphoplasmacytic infiltrate in the lamina propria
- The gold standard of diagnosis is the identification of oocysts in a diarrheal stool
- Oocysts found in the feces have cell walls that are acid-fast and can be visualized in the stool with acid-fast stains; it is one of the few acid-fast particles found in stool

Rhizopods (Amebas)

- The simplest of the protozoans; multiply by simple fission
- Move by pseudopodia and ingest food incidentally found in the way
- Usually exist in a trophozoite form but may form chitinous-walled cysts in response to environmental challenge
- There are several species that are obligate parasites of the human GI tract; only Entamoeba typically causes disease

Entamoeba histolytica

Clinical

- Usually the organism is present in the human gut as a harmless commensal
- In rare cases, it invades the gut wall, produces damage, and causes disease
- Some strains are more virulent than others (tropical strains); a strain's virulence can be estimated by analyzing the strain's trophozoitic enzymes (zymodenes)
- The amebic strain's ability to cause tissue invasion is dependent on its endocytic capacity, its production of collagenase and other cytotoxic proteins, and its ability to lyse target cells by production of a pore-forming protein
- Certain host factors increase the potential for invasion, such as pregnancy, protein malnutrition, and immunosuppression
- The infection is transmitted by ingestion of a cyst; cysts can withstand gastric pH and other challenges that would destroy the trophozoite form
- The organism tends to settle in areas of fecal stasis; the most common sites of involvement are the terminal ileum, appendix, cecum, ascending colon, sigmoid colon, and rectum
- The ameba can also enter the portal circulation and be carried to other organs (liver, spleen, lung, and brain), where they form abscess cavities
- Most infections are asymptomatic
- The most common manifestations of invasive disease are diarrhea, cramping abdominal pain, and flatulence; the stool is watery and contains mucus and blood
- An hepatic abscess occurs in ~5% of patients and may produce complications by extension into the surrounding tissue (lungs, heart, peritoneum)
- Amebic dysentary (in patients with risk factors for invasion) presents with an abrupt onset of high fever, severe abdominal pain and cramping, tenesmus, liver tenderness and enlargement, and profuse bloody diarrhea
- Possible complications of severe disease include massive GI hemorrhage and perforation with peritonitis, bowel obstruction due to circumferential growth of amebas, and postdysenteric colitis due to severe scarring causing chronic irritability

Pathology/Laboratory

- The gold standard of diagnosis is the identification of ameba in the diarrheal stool or endoscopic aspirate; the ameba must be distinguished from other harmless commensal Entameba species (E. hartmanni and others)
- *E. histolytica* is 10–20 μm in diameter and has a vacuolated granular endoplasm, directional motility, and finger-like projections of ectoplasm (pseudopods); invasive strains may contain ingested erythrocytes
- The nucleus is 3–5 μm and has a central nucleolus and peripheral chromatin
- Sigmoidoscopy demonstrates shallow ulcerations intermingled with normal mucosa; severe disease produces deeper and more extensive ulceration
- Colon biopsy will have mucosal ulceration with associated edema and vascular dilation but minimal inflammation; the adjacent mucosa is entirely normal
- The organism (in trophozoite form) resides in the greatest density at the junction between involved and uninvolved mucosa
- The ameba produces flask-shaped ulcerations by penetrating down to the muscularis and then invading laterally through the submucosa
- Ultimately, the blood supply is compromised, leading to sloughing of large regions of mucosa with subsequent granulation, fibrosis, scarring, and secondary infection
- Amebomas are nodular tumor-like growths of granulation tissue
- Serologic studies are usually only positive with symptomatic (invasive) disease
- Indirect hemagglutination and enzyme-linked immunosorbent assay testing are the most sensitive methods for detection of extraintestinal amebiasis

Acanthamoeba and Naegleria

- Primary amebic meningoencephalitis is associated with both *Acanthamoeba* and *Naegleria*, which are free-living genera of ameba

Clinical

Naegleria meningoencephalitis

- The disease is acquired from swimming in fresh water; typically affects children and young adults, and is usually fatal
- Cases have been reported in the southeastern United States, Great Britain, Czechoslovakia, Australia, and Africa
- The ameba apparently gains access to the CNS by migration across the nasal mucosa and cribiform plate
- The infection begins around the olfactory bulbs and progresses along vessels to other parts of the brain, where it produces intense inflammation and hemorrhage

Acanthamoeba meningoencephalitis

- The disease typically affects elderly, immunocompromised, or debilitated patients
- There is usually no history of swimming in fresh water;
- The ameba apparently gains access to the CNS by hematogenous dissemination from a primary infection site, such as the lungs or skin
- The clinical course is chronic and far less severe than that of Naegleria infection
- The disease can be fatal but spontaneous recovery is not uncommon

Pathology/Laboratory

- The CSF is hemorrhagic, with elevated protein, decreased glucose, and marked neutrophilia
- In the early stage of the disease, a wet mount of CSF will demonstrate diagnostic trophozoites
- Biopsy has necrotizing granulomatous lesions containing both trophozoites and cysts

Acanthamoeba Uveitis and Corneal Ulceration

- The infection is associated with corneal trauma and soft contact lenses
- Signs and symptoms include severe eye pain, corneal epithelial disruption, and a paracentral ring infiltrate of the cornea
- Diagnosis is confirmed by demonstration of double-walled cysts in wet mounts of corneal scrapings or biopsy; fluorescent antibody techniques have also been used
- Treatment usually requires corneal transplantation or enucleation of the eye

Flagellates

Giardiasis

Clinical

- The causative organism is *Giardia lamblia*
- *G. lamblia* is found worldwide and is associated with overcrowding and poor sanitation
- It is the most frequently identified intestinal parasite in the United States
- It is most common in children and young adults, but any age may be affected
- It is usually acquired by fecal-oral transmission that may occur in direct person-to-person contact (family members, male homosexuals, day-care workers) or less commonly as water- or food-borne disease (travelers)
- The likelihood of symptomatic infection is related to inoculum size, virulence of the strain, and host factors such as hypochlorhydria and immunosuppression
- In endemic areas, most patients are asymptomatic; this is not true in outbreaks
- It exists in both a cyst form and a trophozoite form:
  - The trophozoite prospers in the alkaline environment of the duodenum and jejunum:
    - Their tumbling movement through the mucus layer of the microvilli is distinctive and has been likened to a "falling leaf"
    - They use their large ventral sucker to attach to the brush border of the GI tract
    - Unattached trophozoites are carried to the large intestine, where they retract their flagella and secrete a cyst wall
  - The mature cyst is the infective form; it is resistant to many environmental challenges, including chlorine concentrations typically used in city water systems
- Clinically, patients usually experience sudden onset of explosive foul-smelling diarrhea with evidence of fat malabsorption (greasy appearance, floats); blood and mucus are absent
- Other symptoms/signs include abdominal distension due to intestinal gas, lactose intolerance, flatulence, and abdominal cramping
- Less commonly there is low-grade fever, nausea, and vomiting
- Some adults may experience a subacute form of the disease, with intermittent episodes of poorly formed stools, flatulence, reflux symptoms, and weight loss; this may follow the acute phase or may occur de novo
- The disease usually resolves in 1–4 weeks but may persist for months, especially in children
- Lactose intolerance may persist after the infection has resolved

Pathology/Laboratory

- The cyst occurs in formed stools; the trophozoite is found in diarrheal stools
  - With diarrhea, the transit time is too short for the organism to form a cyst
- The trophozoite can also be found in Giemsa-stained duodenal aspirates or biopsy specimens
- The organism can usually be found easily in acute

symptomatic disease but may be very difficult to identify in subacute or chronic disease

- The trophozoite is 10–20 μm in length and tear-drop-shaped; it is binucleated and has two central parabasal bodies and four flagella, giving the organism the appearance of a face with eyeglasses and whiskers
- The cyst is slightly smaller than the trophozoite and oval in shape
- During maturation, the internal structure of the immature cyst (which is a trophozoite with a cyst wall) divides to form a quadrinucleate organism with two ventral suckers and four parabasal bodies
- A characteristic feature of the cyst in fixed sections is the retraction of the cytoplasm from the cyst wall

Trichomonas

Clinical

- A common disease with a worldwide distribution; usually sexually transmitted
- 25% to 30% of woman will have the infection at some time during their life
- 40% to 70% of their male partners will also acquire the parasite; often transiently
- Transmission in the absence of sexual contact is rare but does occur; mechanisms include shared undergarments or washcloths, or neonatal transmission during the infant's passage through the mother's infected birth canal
- Susceptibility to infection and severity of the infection are mediated by the vaginal microbial population and pH, the patient's hormonal milieu, and the virulence of the infecting strain
- High estrogen levels of pregnancy increase the risk of acquiring infection as well as the severity of the infection; the same applies to menstruation, but to a lesser degree
- Although the parasite is not invasive, it does cause squamous epithelial destruction, leading to an intense inflammatory response
- Most women will have symptomatic chronic vaginitis, but some are asymptomatic
- Associated symptoms include an intermittent but persistent foul-smelling discharge, dyspareunia, vaginal pruritus, and dysuria
- On physical exam, there is erythema of the vaginal and cervical mucosa, a thin foamy white discharge and, in some cases, a friable granular cervix (strawberry cervix)
- In severe infection, there may be numerous erosions and petechiae
- In men, the most common sites of infection are the urethra and prostate
- Most men are asymptomatic but some will develop a mild discharge and/or dysuria; purulent urethritis will occasionally occur

Pathology/Laboratory

- Diagnosis is established by identification of the motile organism on a wet mount of vaginal discharge or, in men, urethral discharge after prostate massage
- It may be difficult to demonstrate the organism in asymptomatic patients
- A culture of secretions can improve the sensitivity of detection; it is grown under anaerobic conditions
- The organism exists in a trophozoite form only
- The trichomonas trophozoite is sturdier than most trophozoite forms; it can exist off the host for 1–2 hours, and in secretions, urine, and water for up to 24 hours
- It is oval in shape and 5–15 μm in length, but may be much larger
- There are four apical flagella, one flagella in association with an undulating membrane, and a single nucleus
- A characteristic feature is the axostyle, which is a microtuble with a pointed tip that runs longitudinally along the organism and protrudes from the posterior end; it is thought to mediate attachment and epithelial damage

Leishmaniasis

Clinical

- A variety of different species of the genus Leishmania produce three different clinical forms of the disease
- The vector of transmission is the sandfly (Simulian)

Cutaneous Leishmaniasis

- American (New World) cutaneous leishmaniasis is caused by L. brasiliensis or L. mexicana complex in the American continent
- Oriental (Old World) cutaneous leishmaniasis is caused by L. tropica or its subtypes L. major and L. aethiopia in Africa, Asia, Europe, and the Middle East
- Weeks to months after an infected sandfly bites the skin, the patient develops an erythematous papule (or papules), which enlarges to form a nodule that often ulcerates and frequently becomes secondarily infected
- Disease can be localized, diffuse, or in between, depending on the degree of host immunity
- Localized disease (host has an effective immunologic response to the organism) is characterized by a single or few cutaneous lesions with very few organisms and a good response to therapy; most common (>90% of cases)
- Diffuse disease (host has little or no immunologic response to the organism) has numerous lesions with many organisms and a poor response to treatment; very rare (<1% of cases)

- Patients with an intermediate degree of immunity may fall between these two poles and manifest one of several possible subtypes, including:
  - Chronic or verrucous: lesions last for longer than 2 years
  - Relapse (recidivans): new papules form at the edge of healed lesions

Mucocutaneous Leishmaniasis

- Mutilating involvement of the nose and oropharynx, which may extend to include the palate and tongue
- Only seen in New World disease; associated with L. brasiliensis in particular
- Represents an intermediate degree of immunity
- Very resistant to treatment

Visceral Leishmaniasis (Kala-Azar)

- Caused by L. donovani in Asia and Africa and occurs in large epidemics
- Caused by L. chagasi or L. infantum in Europe and Latin America and occurs in isolated cases
- Presents with fever, weight loss, hepatosplenomegaly, and anemia
- Can clinically resemble lepromatous leprosy
- Can have macules, plaques, or nodules; many more organisms are present in nodular lesions

Pathology/Laboratory

- The organism is nonencapsulated, 2–4 μm in size, and has an oval shape
- It possesses a nucleus and a kinetoplast (paranucleus)
- The presence of the kinetoplast distinguishes it from histoplasma capsulatum

Localized Cutaneous Leishmaniasis

- Early: epithelioid histiocytes with patchy lymphoid infiltrate; organisms are found in histiocytes and are relatively more numerous at this stage
- Intermediate to late stage, non-ulcerated: tuberculoid-type granuloma with lymphoid infiltrate; CD4 cells are present throughout the granuloma and in the interstitium, whereas CD8 cells are found at the periphery of the granuloma
- Intermediate to late stage, ulcerated: nonspecific inflammatory findings:
  - Variable degree of granulomatous versus lymphocytic inflammation
  - May have epithelial hyperplasia
  - May have necrosis, abscesses, and mixed acute and chronic infiltrates
  - Morphology influenced by presence and nature of secondary infection
  - Organisms are few in number; difficult to visualize histologically and grow on culture; may need PCR to confirm diagnosis at this stage

Cutaneous Disease With Intermediate Immunity (Mucocutaneous, Chronic, Relapse)

- Variable histology depending on degree of immunity, duration of lesion, and presence and nature of secondary infection
- Variable degree of granulomatous versus lymphoplasmacytic inflammation; unlike tuberculoid granuloma, there is no caseation necrosis
- May have necrosis, abscesses, and mixed acute and chronic infiltrates
- May have epithelial hyperplasia or even pseudoepitheliomatous hyperplasia in long-standing lesions
- Organisms are few in number and difficult to find, especially in late or chronic lesions; may need PCR to confirm diagnosis

Diffuse Cutaneous Disease

- Dense collection of epithelioid histiocytes with numerous organisms; minimal lymphoplasmacytic infiltrate

Visceral Disease (Kala-Azar)

- Histology of cutaneous lesions mirrors the clinical appearance; macular lesions have superficial inflammation, whereas nodular lesions extend to the deep dermis or panniculus
- As with cutaneous disease, there is a variable admixture of granulomatous inflammation, lymphoplasmacytic infiltrate, necrosis, and abscess formation
- Depending on the host's immunity, organisms may be numerous or rare
- In general, organisms are more abundant in nodules and plaques and more sparse in macular lesions

Trypanosoma

Clinical

- Two very different forms of trypanosoma infect humans, leading to either African sleeping sickness or Chaga's disease (American trypanosomiasis)

African Sleeping Sickness

- The infecting organism is different in different geographic locations
- *Trypanosoma brucei gambiense* is associated with the disease in West Africa and *Trypanosoma brucei rhodesiense* is seen in East Africa
- Clinical symptoms are similar, but the course of East African disease is more acute and fulminent
- The vector of disease transmission is the tsetse fly (Glossina species)
- Following the bite of an infected tsetse fly and a variable incubation period, the patient develops an

asymptomatic parasitemia, which may last from weeks to months

- After the period of parasitemia, the organism may be destroyed by the immune system (abortive infection) or it may invade the reticuloendothelial system, leading to systemic disease:
  - Systemic disease is characterized by attacks of fever with rigors, night sweats, malaise, weakness, headache, fleeting rash, anorexia, nausea, and vomiting
- Symptomatic attacks alternate with relatively asymptomatic periods:
  - During attacks, trypanosomes can be demonstrated in the blood
- Lymphadenopathy is a common feature, especially involving the posterior cervical lymph nodes (Winterbottom's sign); lymphadenopathy is seen less frequently in East African disease
- Following the interval of febrile attacks, the infection may resolve or may progress to involve the nervous system with meningoencephalitis:
  - Symptoms associated with progressive disease include increasing apathy and fatigue, somnolence, confusion, emaciation, and facial edema
- Neurologic signs develop in late stage disease and include ataxia, incoordination, slurred speech, muscular fibrillation (especially of facial muscles), and less often, sensory changes, including paresthesias
- The morbid stage of the disease is characterized by profound mental deterioration, incontinence, convulsions, paralysis, and progressive somnolence, culminating in coma and death

Chaga's Disease

- The causative trypanosome is *T. cruzi*
- It differs from other trypanosomes by having an intracellular amastigote form in cardiac muscle and other tissues, as well as trypanosome forms circulating in the blood
- The reservoir of disease is the wild rodent—opossums, armadillos, and others
- The vector of disease transmission is the reduviid bug (Panstrongylus)
- The organism is carried in the reduviid bug's feces; it defecates while feeding
- The victim scratches the bite (with adjacent infected feces) and introduces the organism into the break in the skin
- Congenital disease transmission is also possible
- The disease is more severe and more likely to involve the CNS in children; in adults, a chronic course follows the acute attack
- A chagoma, or erythematous nodule, forms at the site of infection, usually on the face; it gradually resolves over 2–3 months
- After the chagoma forms, the amastigotes are carried to the draining lymph nodes, which become enlarged and tender
- The organism may be phagocytosed by histiocytes or may actively penetrate them; they transform into the amastigote form in histiocytes
- Chagoma-like nodules or localized regions of edema may form over other parts of the body; they often involve one side of the face
- Unilateral facial edema (affecting the upper and lower eyelids) with conjunctivitis is referred to as Romaña's sign
- The oculoglandular syndrome describes clinical presentation of unilateral facial and ocular edema with involvement of the submaxillary lymph nodes
- The organism multiplies while in the amastigote form; it transforms to the trypanosome to invade the blood stream
- From the bloodstream, the organism travels to and infects numerous organs; Küpffer cells of the liver, macrophages of the cardiac muscle, and spleen are particularly prone to infection
- Signs of generalized infection (acute stage) include high fever and chills, malaise, myalgias, lymphadenopathy, mild hepatosplenomegaly, and an asymptomatic macular eruption over the chest and abdomen; infants often have signs of meningoencephalitis as well
- ECG abnormalities seen at this stage include prolongation of the P-R and Q-T intervals, T-wave inversion, S-T depression, and low-votage QRS complexes
- In the acute stage, organisms can only be found in the blood in infants
- The acute stage may culminate in death, recovery, or progression to chronic disease
- The chronic stage may be asymptomatic and diagnosed by ECG abnormalities
- ECG changes are very common in the chronic stage and include complete A-V block, right bundle branch block, and premature ventricular contractions, as well as abnormalities of the QRS complexes and T- and P-waves
- Signs of chronic infection include congestive heart failure (usually right sided) and syncope (likely due to heart block); sudden death may occur
- GI tract involvement also occurs, but less often than cardiac involvement
- Dilation of the GI tract is the cardinal sign, with esophageal enlargement giving dysphagia and megacolon characterized by constipation, fecal impaction, and volvulus
- Far less frequent is involvement of the CNS and/or thyroid

Pathology/Laboratory

African Sleeping Sickness

- There is generalized lymphoid hyperplasia due to proliferation of trypanosomes in the lymph nodes
- Hypergammaglobulinemia is common, with markedly increased IgM levels due to antigenic variation of the trypanosome
- Each febrile attack corresponds to a wave of parasitemia; the host produces IgM against the surface antigen of that particular wave, causing the parasitemia to diminish; the parasitemia recurs when the antigen changes
- During the attacks of parasitemia, the trypanosomes localize in the small blood vessels of the heart and CNS, causing endothelial proliferation and a perivascular lymphoplasmacytic infiltrate, with subsequent vasculitis
- Increased IgM in the CSF is diagnostic of CNS involvement
- Progressive leptomeningitis is characterized by a perivascular lymphocytic infiltrate in the Virchow-Robin spaces, an increased CSF protein level, and an increased CSF white cell count

Chaga's Disease

- The initial site of infection shows an acute localized inflammatory reaction with neutrophils, eosinophils, plasma cells, lymphocytes, and histiocytes; the organism is in the trypanosome form at this stage
- While in tissue, in particular heart, skeletal muscle, smooth muscle, and glial nerve cells, the amastigotes proliferate to form pseudocysts, which are massively enlarged host cells filled with amastigotes
- When the pseudocysts rupture, viable and nonviable organisms are released, bringing about an intense localized inflammatory reaction; with time, there is increased interstitial connective tissue, a chronic inflammatory infiltrate, and associated loss of muscle or nerve fibers
- In the late stages, when cardiomegaly occurs, there is diffuse inflammation of the myocardium with lymphocytes, plasma cells, and histiocytes, as well as interstitial fibrosis
- Similar changes are seen in the digestive tract; with destruction of Auerbach's plexus, there is a decrease in the number of ganglion cells
- While in the CNS, the organism causes a chronic inflammatory infiltrate of the cortex and meninges; there is a perivascular lymphocytic infiltrate with small granulomas adjacent to the blood vessels around the organism
- Circulating antibodies reactive against *T. cruzi* have been demonstrated to also be reactive against endocardium, blood vessels, and striated muscle

HELMINTHS

Intestinal Nematodes

Ancylostoma and Necator (Hookworms)

Clinical

- Infection occurs worldwide but is limited to warm climates with heavy rainfall
- *Ancylostoma duodenale* is the Old World hookworm and occurs in India, the Middle East, Asia, and the Mediterranean
- *Necator americanus* is the New World hookworm and occurs in the southern United States and tropical areas of the Americas
- An infected individual defecates and deposits feces containing eggs in the soil
- Eggs develop first into rhabditiform larvae, which migrate through the soil and feed on debris and microorganisms
- When the larvae double in size, they molt to become a filariform larvae, the infective form
- The disease is transmitted when an individual with unprotected skin comes in contact with filariform larvae
- The larvae penetrate the skin, most commonly between the toes
- The larvae migrate to the lymphatics and are carried to the right heart and then on to the lungs, where they penetrate the alveolar spaces
- Once in the lungs, they are coughed up by the host, swallowed, and are carried to the gut, where they mature into adult worms and begin to produce eggs
- The adult worm can live up to 15 years
- Because the worm burden is generally low, the majority of infections are asymptomatic
- An effective immune response leads to peripheral eosinophilia, as well as localized eosinophilia within the gut
- When the larvae penetrate skin, they can produce a localized pruritus and erythema, referred to as "ground itch"; this reaction is thought to be due to prior sensitization to larval antigens
- Cough, wheezing, and fever may also occur
- In the gut, the worms may cause abdominal pain and cramping, as well as impaired peristalsis and subsequent impaired digestion

- The most severe complication is microcytic anemia related to chronic blood loss caused by the attachment and feeding of the worm in the gut
- *Ancylostoma* extracts ~0.2 mL of blood each day, *Necator* ~.02 mL
- The blood loss may be clinically insignificant if the worm burden is very low or if the host ingests a diet high in iron
- In children, the anemia may be severe and lead to heart failure and impaired development

Pathology/Laboratory

- The adult worm is ~10 mm in length with a pinkish color; they are often curved into a hook shape
- The two species can be separated by the unique appearance of their mouth parts; *Ancylostoma* has four tooth-like structures whereas *Necator* has two cutting plates
- Diagnosis is made by identification of the eggs in the stool; they are ~50 μm, oval-shaped, have a thin shell, and contain two to four cells
- The eggs of the two species are essentially identical so exact subtyping is not usually done
- The worm burden may be estimated by quantitative egg counts
- Biopsy of the rash associated with larval penetration shows nonspecific inflammation with numerous eosinophils

Enterobius (Pinworm)

Clinical

- The causative organism, *Enterobius vermicularis*, has the simplest life cycle of the intestinal nematodes
- The pinworm is found worldwide and is one of the most common parasitic infections
- It can occur at any age, but it is more common in children and among the poor with crowded living conditions
- The organism most commonly causes pruritus ani that is worse at night; the excoriation may be so severe that secondary bacterial infection can follow
- In females, the worm can also migrate into the vagina and cause vaginitis; it has also reportedly entered the genital tract to cause endometritis and salpingitis
- The adult worms live in the cecum; the female migrates through the colon to the anus during the night and deposits her eggs on the perianal skin and the sheets
- The eggs are transferred to the host's fingers by scratching of the pruritic perianal skin; the eggs may also be airborne off sheets or clothing
- The eggs may remain viable and infectious for several days
- The infection is transmitted when the eggs are ingested or inhaled and swallowed
- The eggs are carried to the lumen of the small intestine, where they hatch
- The newly hatched worms then migrate to the cecum; on the way, they mature into adults and mate

Pathology/Laboratory

- The parent is sometimes able to identify and recover the adult worm from the child's perianal skin
- The adult female worm is ~1 cm in length and off-white in color; her tail is pointed (hence the name pinworm)
- The male worm is smaller; he is usually not seen
- The diagnosis is usually made by touching the sticky side of tape to the perianal skin, preferably first thing in the morning; the tape is then touched to a glass slide and the eggs are transferred to the slide
- The eggs are usually <50 μm in length and oval-shaped with a flattened side
- The infection does not usually cause eosinophilia or intestinal pathology
- When the worm migrates to the uterus, it can cause a granulomatous endometritis

Ascaris (Roundworm)

Clinical

- *Ascaris lumbricoides* is the largest of the intestinal nematodes; it is approximately the size and shape of an earthworm
- It occurs worldwide but is most common in warm climates
- It can occur at any age but it most commonly affects children, especially in areas with poor sanitation and crowded living conditions
- In underdeveloped countries, the intestinal worm loads may be very high; as many as 2,000 worms have been reported in a single child
- The infection is transmitted by ingestion of eggs, usually when the individual handles an object with eggs on it and then touches the mouth, or less commonly when food that has been contaminated by eggs is eaten
- The infection may also be acquired when the eggs are airborne and then inhaled and swallowed
- The eggs are deposited in soil when an infected individual defecates
- The eggs must then embryonate in the soil for at least 3 weeks before becoming infectious
- The eggs are extremely resistant to environmental conditions, and may remain infectious for >5 years
- After the eggs are swallowed, they are carried to the intestine, where they hatch, migrate through the mucosa, and enter the portal circulation

- The larvae are carried through the liver and into the hepatic vein, then on to the right heart and into the lungs
- By the time they reach the lungs, the larvae have grown too big to fit through the pulmonary capillaries, so they move out into the alveolar spaces
- Once in the lung, they are coughed up and swallowed and then carried to the small intestine
- In the upper intestine, the larvae mature into adults, mate, and produce eggs
- The clinical manifestations are most commonly related to the migration of the larvae into the pulmonary alveoli, but also may be due to the worm in the intestine
- Previous infection produces hypersensitivity to worm antigens on subsequent reinfection and increases the likelihood of pulmonary symptoms
- Symptoms include fever, shortness of breath, cough, wheezing, and rarely, death due to respiratory failure
- Primary infection may be asymptomatic, especially if the worm load is small
- The infection may come to attention when the worm is passed in the stool or vomited up, which occurs most commonly during an episode of fever
- If the worm load is large, the patient may have abdominal pain and malabsorption, which may be significant in an already undernourished child
- Occasionally, a worm can migrate to the appendix, bile duct, or pancreatic duct and cause obstruction
- Rarely, the worm load may be so large that there is obstruction of the intestinal lumen, especially in children

Pathology/Laboratory

- There is often peripheral eosinophilia, especially if the patient has been infected previously
- The diagnosis can be made when eggs are identified in the stool, or the larvae are found in the sputum
- The eggs are usually easy to find, as the female produces approximately 200,000 eggs each day; she produces eggs even when she has not been fertilized
- The eggs are oval in shape and ~50 μm in length; they have a rough coating on their outer shell

Strongyloidiasis

Clinical

- The causative agent is the intestinal round worm *Strongyloides stercoralis*, the smallest of the intestinal nematodes
- Although less common, the geographic distribution is similar to that of the hookworm
- This organism has three different possible life cycles:
  - The direct cycle occurs when the rhabditiform larvae are carried in the stool to the soil, where they mature into filariform larvae that can penetrate human skin; they are then carried to the lungs through the lymphatics, break through the alveoli, are coughed up and swallowed, and go on to mature into the adult worm in the small intestine
  - The autoinfective cycle occurs when there is a delay in transporting the larvae out in the stool and they mature into the infective form of larvae in the host instead of the soil; the larvae can penetrate the host's mucosa or perianal skin and then continue the cycle as above
  - The free-living cycle occurs when the larvae that are deposited in the soil develop into free-living adults that propagate; these adults can then produce infective larvae
- The intestinal infection is usually only symptomatic with large worm loads; there is an associated peptic ulcer-like pain that is aggravated by eating
- The organism in the intestine causes an inflammatory reaction, leading to ulcerations and abscesses that can eventuate in malabsorption and malnutrition
- Malnutrition and immunosuppression may speed the maturation of larvae to the infective stage and increase the chance of autoinfection
- The pulmonary phase may be similar to that of Ascaris, with fever, shortness of breath, cough, wheezing, and rarely, respiratory failure
- The term larva currens describes the migrating perianal linear and serpiginous urticarial lesions that occur with larval penetration of the perianal skin in autoinfection
- Disseminated disease may occur in immunosuppressed patients with larvae invading the CNS, heart, lungs and other organs; because the larvae can carry enteric bacteria with them, they may cause bacteremia and sepsis
- In the skin, disseminated disease is characterized by a rapidly progressive petechial and purpuric eruption over the trunk, proximal legs, and periumbilical skin; rapidly migrating larvae may leave numerous linear urticarial streaks

Pathology/Laboratory

- There is often a peripheral eosinophilia
- The diagnosis is made by the identification of larvae in the stool, in duodenal aspirates or jejunal biopsy; larvae are sometimes present in the sputum
- The larvae are very similar to those of hookworms, but may be distinguished by their shorter buccal cavity and longer primitive genitalia
- In disseminated disease, a skin biopsy has sections of many larvae at all levels of the dermis, associated with a variable mixed inflammatory infiltrate

Trichuris (Whipworm)

Clinical

- The disease occurs worldwide, but is more common in humid and warm locations; it affects ~2 million people in the southeastern United States

- It is more common in areas where defecation in the soil is a standard practice, in institutions, or in crowded communities with poor sanitation
- The worms are attached to and live in the colon, especially the cecum
- The females release their eggs, which are then carried in the stool and deposited in the soil
- The eggs must mature in the soil for 10 or more days before they are infectious
- Once mature, the eggs are transmitted by hands (usually children) to mouth, or on crops that have been fertilized with human feces
- After they are swallowed, the eggs travel to the duodenum, where they hatch and mature over the next few weeks before moving to the cecum
- The number of infecting worms ranges from a few to hundreds
- If the worm burden is low, the infection may be asymptomatic:
  - Symptoms occur with greater numbers of worms and include abdominal pain, nausea, and diarrhea; the patient may have significant blood loss and anemia
- If the worm burden is very high, there is a risk of colonic or rectal prolapse:
  - Prolapse through the anus can occur with increased intraabdominal pressure, especially during childbirth and less commonly defecation
  - With a high worm burden, the patient may have a peripheral eosinophilia

Pathology/Laboratory

- Infection is diagnosed by identification of the eggs in a stool sample
- The female produces 5,000 to 10,000 eggs daily
- The eggs are ~50 μm in length and oval shaped; they have a thick brown shell and translucent protrusions on each end
- The worm is ~50 mm in length and shaped like a whip; the anterior end is thin and the posterior end is rotund

Tissue Nematodes

Cutaneous Larva Migrans

Clinical

- Caused by the larvae of the cat and dog hookworms, *Ancylostoma braziliensis*, and *Ancylostoma caninum*, for which humans are incidental hosts
- Because humans are not natural hosts, the eruption is self-limited
- The larva penetrates the skin and migrates through the superficial epidermis, causing an urticarial serpiginous linear tract that migrates several millimeters each day
- It is most commonly seen on the feet and buttocks

Pathology/Laboratory

- The biopsy should be taken a few millimeters beyond the leading edge of the tract
- If the larva is present, it will appear in the superficial epidermis
- The adjacent epidermis will have spongiosis and necrotic keratinocytes
- There is a chronic inflammatory infiltrate with numerous eosinophils in the epidermis and dermis

Visceral Larva Migrans

Clinical

- The causative agent is *Toxocara canis*, a parasite of domestic and wild animals (dogs, wolves, and foxes); humans serve as an incidental host
- Other nematode larvae can occasionally cause the disease
- The disease occurs worldwide and is quite common in the United States, especially the southeastern states; it thrives in warm humid climates
- The disease may occur in any age group but is most common in children
- After the eggs are deposited in the soil by the infected canine, they must mature and embryonate for at least 2 weeks before becoming infectious
- Once mature, they remain infectious for months to years
- In humans and canines, the eggs hatch in the intestine, penetrate the mucosa, and are carried to the portal circulation, into the right heart and on to the lung
- In canines, the larvae burst through the alveolar spaces, are coughed up and swallowed; they then go on to mature in the small intestine
- In humans and occasionally in canines, the pulmonary capillaries are big enough to allow the larvae to pass into the circulation
- Once in the circulation, the larvae continue to grow until they reach a size that cannot pass through a vessel; they then migrate through the vessel and into the tissue
- Many infections are asymptomatic
- Manifestations in humans are related to invasion of tissues by larvae, most commonly skeletal muscle, heart, brain, liver, and lung; the eye may also be involved
- The severity of disease is related to the age of the patient (more severe in younger children), as well as the site and number of invading larvae and the degree of host sensitization to larval antigens
- Other symptoms and signs include (mostly depending on the infected organ) fever, hepatosplenomegaly, focal

neurologic deficits and seizures, pulmonary infiltrates and asthma, cardiac arrhythmias, decreased visual acuity, and strabismus

- A patchy urticarial or papular skin eruption can occur
- In the eye, the larvae (usually dead) can induce granulomatous endophthalmitis

Pathology/Laboratory

- In the tissue, the organism causes necrosis, hemorrhage, abscess formation, and subsequent granuloma formation with numerous eosinophils
- Peripheral eosinophila is fairly common
- Eggs or worms cannot be found in patient stool samples because the organism does not mature in humans
- The gold standard of diagnosis is the identification of organisms in a tissue biopsy (liver in particular)
- Diagnosis can be made using an enzyme-linked immunosorbent assay (ELISA) against larval antigens, although some patients may be seronegative

Trichinosis

Clinical

- The causative agent is *Trichinella spiralis*, a parasite of carnivorous animals including pigs, bears, rodents, domestic and wild felines and canines
- The disease is seen worldwide except it does not usually occur in Asia or Australia
- Slightly different strains are seen in different climates (arctic, tropical, etc.)
- Infection is fairly common in the United States; from 1 to 2 million people are infected
- Infection in humans is most commonly acquired by eating undercooked pork containing encysted larvae
- Once ingested, the encapsulated larvae are released and migrate to the small intestine, where they begin to mate
- The males die after mating and the females produce >1,000 larvae over the next several months
- The larvae move through the mucosa to the circulation and are carried to the right heart, through the pulmonary capillaries, and then widely disseminated
- The larvae that enter skeletal muscle survive, grow, encapsulate, and calcify; the larvae may live for up to 10 years
- Most often infected muscles include the diaphragm, the extraocular muscles of the eye, the tongue, the deltoid, and the intercostal muscles
- Clinical manifestations are related to the presence of encysted larvae or to the host's immune reaction to dead larvae and vary with the organ involved and the number of infecting larvae
- Most infections are asymptomatic (small worm load)
- Patients with larger worm loads may have abdominal pain and diarrhea during the migration of the larvae through the intestinal mucosa
- These patients also experience symptoms when the larvae penetrate the muscles (most commonly, fever, myalgia and weakness)
- Other signs and symptoms include subconjunctival hemorrhages, periorbital edema, splinter hemorrhages of the nails, and a nonspecific rash
- Serious complications occur when the heart or CNS are involved and include arrhythmias, heart failure, encephalitis, seizures, coma, and death

Pathology/Laboratory

- Peripheral eosinophilia commonly occurs and can be quite marked
- Muscle biopsy in the region of an encysted worm shows basophilic necrosis surrounded by an intense inflammatory infiltrate of eosinophils, neutrophils, and lymphocytes
- The earliest pathologic change is swelling of the muscle fibers and loss of striations
- Immune complex mediated leukocytoclastic vasculitis has also been reported
- Infection can also be diagnosed serologically by a number of different methods, including indirect fluorescent antibody identification, complement fixation and, for the earliest phase of the infection (before the formation of antibodies), ELISA

Filariasis

- A term that includes Onchocerciasis and Elephantiasis

Onchocerciasis

Clinical

- Causative agent *Onchocerca volvulus* is transmitted by Simulian black flies, which breed in and around fast-flowing rivers in Africa and Central and South America
- The larva enter human skin through the proboscis of the biting fly and move to the dermis or subcutaneous tissue to mature, where they form an asymptomatic or tender mobile nodule called an onchocercoma
- The adult worms (filariae) produce numerous microfilariae, which move to the papillary dermis; they can also move into the aqueous humor of the eye
- The microfilariae induce onchocercal dermatitis, an inflammatory reaction characterized initially by extreme pruritus, erythema, and scaling, and later by lichenification ("lizard skin") and pigmentary changes ("leopard skin"); it eventuates in atrophy, which produces "hanging skin"
- In the eye, microfilariae produce iritis, which leads to blindness ("river blindness")

- In some cases, the microfilariae can cause lymphatic obstruction and elephantiasis

Pathology/Laboratory

- Rarely, microfilariae can be found in urine, blood, or sputum

Subcutaneous Nodules (Onchocercomas)

- Consist of numerous worms
- The females can be up to 50 cm in length and the male is ~5 cm
- The worms are encased in a dense fibrous stroma
- Some are living, and some are dead
- The dead worms induce a granulomatous inflammatory reaction
- Infrequently, microfilariae can be seen in the adjacent lymphatics

Onchocercal Dermatitis

- Characterized by numerous microfilariae in the superficial dermis
- The microfilariae are from 5–10 μm in diameter and from 150–350 μm in length
- Older lesions have fewer organisms and a chronic inflammatory infiltrate with numerous eosinophils and dermal fibrosis; the epidermis has hyperkeratosis and hyperplasia with hypergranulosis
- Very old lesions have marked epidermal atrophy; very few organisms are present and may not be found in the biopsy

Elephantiasis

Clinical

- May be caused by *Wuchereria bancrofti* (Bancroftian type) or *Brugia malayi* (Malayan type)
- The Bancroftian type is seen worldwide in the tropics and subtropics; the Malayan type is found in India and Southeast Asia
- Mosquitos inject microfilariae, which find their way to the lymphatics, where they mature and produce more microfilariae
- Microfilariae are released into the bloodstream in large numbers, especially at night; the nocturnal blood film is the best way to identify organisms
- The adult worm can reach a size of 10 cm in length
- The adult worms in the lymphatics and lymph nodes cause chronic lymphangitis and lymphatic obstruction, which leads to lymphedema
- Massive lymphedema, especially of the lower extremities, incites the name elephantiasis

Pathology/Laboratory

- The tightly coiled worm may be found in a distended lymphatic vessel or node
- The worm is embedded in a fibrous stroma and surrounded by a chronic inflammatory infiltrate

Loiasis (Eye Worms)

Clinical

- The causative agent is *Loa loa*; the vector is the deer fly (*Chrysops*)
- The adult worm lives in the subcutaneous tissue or the eye and actively migrates at a rate of ~1 cm per hour
- In the tissue, the worm produces calabar swellings, which are subcutaneous nodules that are several centimeters in size
- The patient may experience fever, urticaria, and pruritus; calabar swellings may be tender, painful, or pruritic
- The worm may migrate across the eye below the conjunctiva and cause tearing and pain

Pathology/Laboratory

- The patient often has peripheral eosinophilia
- The diagnosis is made by identifying microfilariae in the blood, or the adult in the eye or calabar swelling

Cestodes (Tapeworms)

- The tapeworm is a long ribbon-like worm that is the largest of the intestinal parasites
- The adult is divided into three segments: the head (scolex), the neck, and a long segmented body (strobila):
  - The scolex has four suckers used to attach to the host's intestinal mucosa; some species also have a structure on the scolex called a rostellum, with numerous tiny hooks to further aid in attachment
  - The body is made up of many segments or proglottids that are produced one at a time; each proglottid is a complete hermaphroditic reproductive unit
- When the proglottid is ready to release its eggs, it ruptures or breaks down; some species release their eggs through a uterine pore
- The life cycle of all cestodes includes a definitive (primary) host that has the organism attached to intestinal mucosa, and at least one intermediate host that ingests the eggs
- The eggs are ingested (usually through fecal contamination of food) and the larvae hatch in the intestine, penetrate the mucosa of the intestine, and are hematogenously transmitted to multiple organs, where they encyst
- In some species, humans are the definitive host; in others, they are the intermediate host
- With *Taenia solium* and *Hymenolepis nana*, humans may be either the primary host or the intermediate host:
  - The primary host has mild disease because the

organism is confined to the gut; the intermediate host often has more severe consequences due to the encysted organism within tissues

- The more common organisms, the beef and the pork tapeworms, are discussed here; other cestodes include Diphyllobothrium latum, which is the fish tapeworm, and Echinococcus granulosus and Echinococcus multilocularis, which are the cause of hytadid disease

Cysticercosis: Beef Tapeworm

Clinical

- The causative agent is *Taenia saginata*
- The disease is fairly common in regions with overcrowding and poor sanitation, such as parts of Africa, South America, and Russia; it is rare in the United States but does occasionally occur in the southwestern states
- Humans are the definitive (primary) host and cattle are the intermediate host
- Intestinal infection is acquired after the intermediate host (a human) ingests undercooked beef containing the encysted larvae
- The larvae mature in the gut and then attach to the mucosa of the jejunum and produce eggs; the adult worm may live for 20 years and can reach a size of 10m
- When the proglottid is fully gravid, it breaks away and is passed in the stool or propels itself through the anus
- If the stool containing the proglottid is deposited on soil, the eggs are released and are then ready to be ingested by cattle
- As definitive hosts, most patients are asymptomatic and only become aware of the infection when they pass proglottids in the stool
- The patient may experience weight loss, nausea, and abdominal pain or discomfort; rarely, the proglottid causes obstruction of the biliary duct, pancreatic duct, or appendix
- Alcohol consumption may induce the release of proglottids

Pathology/Laboratory

- The diagnosis is made by the identification of proglottids or eggs in the stool
- Due to rupture of the proglottid during defecation, the eggs may be deposited on the perianal skin and can be recovered using cellophane tape that has been applied to the skin, as in pinworm diagnosis
- The recovery of a proglottid is necessary to distinguish *T. saginata* from *T. solium*, as their eggs are identical
- The proglottid is long (~15 mm) and narrow (5 mm) and has a large central uterus with numerous lateral branches; the scolex has suckers but no hooks
- The eggs are spherical and have a thick striated shell

Cysticercosis: Pork Tapeworm

Clinical

- The causative agent is *Taenia solium*
- The disease rarely occurs in the United States but is quite common in parts of Asia, Africa, Europe, and Central and South America
- Humans may be the definitive (primary) host, the intermediate host, or both
- Intestinal infection in the primary host is acquired by ingesting undercooked pork containing the encysted larvae
- The larvae are then released in the stomach and migrate to the jejunum, where they attach and produce eggs; the adult worm may live for many years
- In the intermediate host, the eggs are ingested (through fecal contamination of food) and the larvae hatch in the intestine, penetrate the wall of the intestine, and are hematogenously transmitted to multiple organs
- In the organs, most commonly eye, subcutaneous skin, brain, liver, lungs, heart, and skeletal muscle, the larvae encyst (develop into cysticerci), where they may remain for years
- The human becomes both the primary and intermediate host when an individual that has a worm attached to the gut (definitive host) becomes autoinoculated with eggs or proglottid segments; autoinoculation occurs when the eggs or proglottids are carried from the perianal area to the mouth on contaminated fingers
- When the larva is alive, there is minimal tissue reaction; when the larva dies, it induces an intense inflammatory reaction and the patient experiences fever, myalgias, arthralgias, and peripheral eosinophilia
- Subcutaneous lesions are usually asymptomatic firm 1–2 cm nodules; they have minimal associated morbidity but are often the key to diagnosis of the disease
- Brain cysticerci may cause significant morbidity (seizures and focal neurologic deficits) and mortality

Pathology/Laboratory

- When the patient is the primary host, the diagnosis is made by the identification of proglottids or eggs in the stool
- The scolex of the proglottid has a rostellum with a double row of hooklets; the strobila (body) is smaller than that of T saginata (~10 mm long and 5 mm wide) and the uterus has fewer lateral branches
- Encysted larvae in the intermediate host may be identified on x-rays as calcified cysts or nodules; CT scan of the head may reveal multiple small brain masses
- Serologic studies are sensitive but are not very specific
- The gold standard for diagnosis is biopsy of tissue containing cysticerci

- The cysticerca contains a central fluid-filled cavity containing the larva and is surrounded by a fibrous capsule

Trematodes (Flukes)

Schistosomiasis

Clinical

- Three species of *Schistosoma* cause disease in humans, including *S. haematobium* (India and Africa), *S. japonicum* (Asia and the Philippines), and *S. mansoni* (Africa, Asia, South America, and the Caribbean islands)
- The fresh water snail is the host to miracidia, which mature to the cercarial stage
- The snail releases the cercariae into fresh water, where they find their way to humans and penetrate the skin; this penetration causes a pruritic eruption known as dermatitis schistomastica or cercerial dermatitis
- After penetration, the cercariae migrate to the liver, where they mature into unisexual worms and begin mating
- After mating, the worms migrate to their target organ and begin to release numerous eggs (termed oviposition), eventually causing obstruction
- Schistosomides refers to a systemic reaction with features of serum sickness, urticaria, and petechiae
- *S. japonicum* inhabits the venous plexuses of the small intestine and releases eggs into the stool
- *S. mansoni* inhabits the venous plexuses of the large intestine and also releases eggs into the stool
- *S. haematobium* inhabits the pelvic and vesical veins and releases eggs into the urine
- The eggs are released in the fresh water when the infected human urinates or defecates; the eggs hatch to become miracidia, which penetrate snails and then mature to the cercarial stage
- Bilharziasis cutanea tarda is an eruption of papules and nodules that may become verrucous or ulcerative in the genital and perianal skin of a patient with visceral schistosomiasis; it is produced by ectopic deposition of eggs in dermal vessels
- Bilharziasis cutanea tarda usually occurs with S. haematobium, which produces a greater number of eggs
- *S. haematobium* is associated with hematuria and hydronephrosis, due to granulomas in the bladder
- *S. japonicum* and *S. mansoni* are associated with portal hypertension and esophageal varices, due to granulomas in the liver
- When the cercariae of schistosoma species nonpathogenic to humans penetrate human skin, they too can produce a mild pruritc eruption (referred to as "swimmer's itch"); the life cycle of these cercariae ends in the skin

Pathology/Laboratory

- Schistosomal egg granulomas can be found in genital and perianal skin
- The ovum has a PAS+ outer shell and is surrounded by a dermal necrotizing and palisading granulomatous infiltrate or microabscess
- At the periphery of the necrotic reaction, there are epithelioid histiocytes and plasma cells with occasional eosinophils
- The species can be identified based on the presence and location of a spine on the shell of the ova:
  - *S. japonicum* have no spine, *S. mansoni*'s spine is in a lateral position, and *S. haematobium*'s spine is at the apex of the shell
- Rarely, adult worms may be seen within dermal vessels

MISCELLANEOUS INFESTATIONS

Scabies

Clinical

- The causative agent, the mite sarcoptes scabiei, is transmitted by physical contact
- The characteristic burrow is formed as the female mite forces her way between the keratinocytes of the stratum corneum
- The mite may be found at the blind end of the burrow, which is located in the upper stratum malpighii
- Burrows are most commonly found in the web spaces of the hand and lateral aspects of the fingers, the flexor wrist, nipples, and scrotum
- A pruritic papular eruption without burrows is most marked on the buttocks, abdomen, and axillary folds
- A persistent nodular eruption may remain after successful treatment
- Norwegian scabies is a rare variant with hyperkeratotic crusted lesions and huge numbers of organisms; it is seen in debilitated patients who are unable to scratch
- In patients with immunosuppression (AIDS in particular),

there may be a severe generalized form with numerous papular lesions and high numbers of organisms

Pathology

- When present, the mite is found in the upper epidermis; eggs or fecal material are also sufficient to make the diagnosis
- There is significant epidermal spongiosis, which may form spongiotic vesicles
- In contrast to arthropod bite reactions, which are wedge shaped, the dermal infiltrate tends to fill the entire dermis as the mite migrates along the surface
- The infiltrate is chronic, with variable numbers of eosinophils
- In nodular scabies, there are generally more eosinophils and a denser infiltrate; there may even be focal vasculitis with fibrinoid necrosis and leukocytoclasis
- There may be a dense infiltrate with atypical appearing lymphocytes that can lead to the erroneous diagnosis of lymphoma
- In Norwegian scabies, there is hyperkeratosis and a large number of mites

Myiasis

Clinical

- Myiasis occurs when the larvae of flies inhabit the human body
- The disease occurs worldwide but is more common in the tropics; cases have also been reported in the southern United States
- The mosquito is the usual vector; the fly lays its eggs on the mosquito, and the mosquito deposits the eggs on the victim, who then scratches the area and implants the eggs into the skin
- *Dermatobia hominis*, the human botfly, is an obligate human parasite
- Opportunistic species, including musca domestica (the common housefly) and cochliomyia hominovorax (the screw worm), do not depend on human hosts
- Myiasis is classified according to the site of involvement, including skin, ear, eye, nasophayrnx, and sinuses
- Cutaneous lesions include wound myiasis and furuncular myiasis:
  - In wound myiasis, fly larvae (maggots) are deposited superficially on necrotic tissue
  - Wound myiasis can actually have a beneficial effect in debriding wounds and has been used experimentally with good results
- In nasopharyngeal myiasis, the screw worm larvae can penetrate the brain via the nose or ear and cause death

Pathology

- The larva is grossly visible and is often alive at the time of biopsy
- The cavity surrounding the larva has variable numbers of mixed inflammatory cells including neutrophils, eosinophils, lymphocytes, plasma cells, and histiocytes with giant cell formation

Tungiasis

Clinical

- The causative agent is *Tunga penetrans*, the sand flea (jigger flea)
- It is found in hot dry climates including Africa, India, and Central and South America
- The pregnant female burrows into the epidermis, most commonly on the feet (interdigital, subungual, and plantar)
- The intraepidermal flea enlarges and begins to produce eggs and expel them through an epidermal opening
- The flea feeds from the superficial vessels in the papillary dermis
- The flea produces a tender nodule up to 1 cm in size, with a central punctum
- Rarely, the skin lesion can lead to autoamputation of the digit or cellulitis

Pathology

- There is an intraepidermal flea; a communication through the stratum corneum may be seen in some cuts
- The superficial dermis contains a lymphoplasmacytic infiltrate with eosinophils

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Chapter 4

Diagnostic Electron Microscopy

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Table of Contents

INTRODUCTION

- In 1986 Ernst Ruska was awarded with the Nobel Prize in Physics for his pioneering work in the development of the electron microscope. The electron microscope, with its power of resolution, opened up the smaller new world of biology. Its diagnostic utility in anatomic pathology was contested by advanced immunohistochemical and molecular genetic techniques in recent years. The electron microscope still remains a useful tool in selected instances of tumor diagnosis and renal biopsy interpretation. The main contribution of the electron microscopy has been and will continue to be to the understanding of the structure-function relationships at the subcellular level
- In analyzing tumors, we must be always reminded of the fact that most of the diagnostically useful ultrastructures are phenotypic differentiation markers of a cell lineage, not tumor-specific, and that they are subject to inter-observer discordance, sample bias and technical artifact

THE NUCLEUS

- Chromatin pattern:
  - Euchromatin (finely and evenly dispersed):
    - Actively dividing immature cells
    - Examples: seminoma, Ewing's sarcoma, undifferentiated (lymphoepithelioma-like) carcinoma
  - Heterochromatin (condensed, clustering):
    - Resting, inactive cells
    - An increased number and size of condensed chromatin clumps in an enlarged nucleus and an enlarged nucleolus are a fairly common finding of various malignant neoplasms
- Nuclear configuration:
  - Extreme cerebriform irregularity:
    - Examples: Sézary syndrome and mycosis fungoides, dermatofibrosarcoma protuberans, fibroadenoma of the breast
  - Elongated and corrugated contour
    - Examples: smooth muscle neoplasms
  - Numerous nuclear pockets:
    - Examples: lymphoma and lymphocytic leukemia
  - Cleaved or cleft nuclear envelope:
    - Examples: lymphoma and lymphocytic leukemia, thyroid papillary carcinoma, Brenner tumor, granulosa cell tumor, urothelial (transitional cell) neoplasm
- Nuclear inclusions:
  - Viral particles (virions):
    - Round, elliptical or strand-like structures having a central dense core (nucleoid) and an outer shell (capsid)
    - Examples: Papovavirus (45-53 nm), Adenovirus (70-90 nm), Herpes (100-150 nm; simplex, Varicella-zoster, Cytomegalovirus, Epstein-Barr virus), Poxvirus (220-450 nm), hepatitis B virus (42 nm), human immunodeficiency virus (HIV, 100-130 nm)
    - For identification of a specific virus, an immunohistochemical or molecular genetic study (such as in situ hybridization) is needed
  - Intranuclear glycogen:
    - Examples: liver cells in diabetes, glycogen storage disease, Wilson's disease, and hepatocellular tumor
  - Intranuclear tubular inclusions:
    - Examples: hyperplastic or neoplastic type II pulmonary alveolar cells
- Nucleolus:
  - Multiple pleomorphic enlarged nucleoli:
    - A common finding in various malignant tumors
  - Inconspicuous nucleoli:
    - A common finding in resting, inactive cells
    - Examples of tumor: small cell carcinoma, neuroblastoma, Ewing's sarcoma
  - Anastomosing rope-like nucleolus:
    - An example: seminoma (dysgerminoma)

THE CYTOPLASM

- Mitochondria:
  - Tubulo-vesicular cristae
    - Typically seen in steroid producing cells, such as adrenal cortical adenoma, Leydig cell tumor,

ovarian hilus cell tumor, luteoma of pregnancy, thecoma, sex-cord stromal tumor and granulosa cell tumor

- Giant mitochondria (megamitochondria):
  - Certain adenomas of the pituitary, thyroid, salivary glands
  - Secretory endometrial glands
  - Alcoholic liver cells
- Abundant mitochondria:
  - Cells with excess mitochondria are called oncocytes
  - Oncocytoma of thyroid gland (also called Hürthle cell neoplasm), salivary gland, parathyroid, kidney and bronchial gland
  - Warthin's tumor
- Mitochondrial myopathies:
  - Increased numbers of mitochondria that are often unusually large and abnormally-shaped, having abnormal cristae and crystalloid inclusion bodies
  - A heterogeneous group of myopathies with mitochondrial abnormalities being a common denominator; a clinical correlation is always needed to reach a clinically relevant diagnosis

♦ Increased free ribosome and polyribosome:
- Immature blastic or undifferentiated tumor cells; e.g. Ewing's sarcoma, seminoma, lymphoblastic lymphoma, undifferentiated (lymphoepithelioma-like) carcinoma, Burkitt's lymphoma

♦ Increased granular endoplasmic reticulum:
- Cells synthesizing proteins for export; e.g. plasma cells, multiple myeloma, immunoblastic lymphoma, acinic or acinar cell carcinoma (salivary gland and pancreas), hepatocellular adenoma and carcinoma, fibroma, fibrosarcoma, malignant fibrous histiocytoma, chondroid tumors and osteoblastic tumors

♦ Tubulo-reticular structures (inclusions):
- Modified endoplasmic reticulum system, present often with cylindrical confronting cisternae
- Seen in vascular endothelial cells, lymphocytes, monocytes of patients with increased alpha and beta interferon; e.g. acquired immunodeficiency syndrome (AIDS), systemic lupus erythematosus and scleroderma

♦ Increased smooth endoplasmic reticulum:
- Steroid secreting cells; e.g. sex cord stromal tumors, granulosa cell tumor, thecoma, Sertoli-Leydig cell tumor, hilus cell tumor of the ovary, Leydig cell tumor of the testis and adrenal cortical tumors
- Hepatocellular adenoma and carcinoma
- Liver cells of patients with protracted use of barbiturate

♦ Lysosomes:
- Primary lysosomes (0.25–0.5 μm)— Membrane-limited dense bodies, sometimes mistaken as neurosecretory dense core granules
- Secondary lysosomes (autophagosome, heterophagic vacuoles, residual bodies or lipofuscin pigment):
  - Lysosomes containing intracellular metabolic products or phagocytosed extracellular material
- Abundant lysosomes:
  - Granular cell tumor, granular cell ameloblastoma, congenital epulis, thyroid follicular neoplasm, prostatic adenocarcinoma, myelocytic or monocytic leukemia
- Michaelis–Guttmann bodies:
  - Multilaminated, calcified spherules formed in secondary lysosomes, often containing calcium apatite crystals
  - Found in macrophages of malakoplakia
- Lamellar lysosomal inclusions or myelinosomes:
  - See below (lamellar inclusions)
- Lysosomal storage diseases:
  - Accumulation of secondary lysosomes containing various types of dense materials including myelinosomes, in parenchymal cells and/or macrophages, genetically transmitted as autosomal recessive disease; e.g. Tay-Sachs disease, Fabry's disease

♦ Ribosome-lamella complex:
- Several layers of parallel cylindrical lamellae, separated by ribosome like granules
- Most commonly seen in patients with hairy cell leukemia
- Also described in various other neoplasms and disorders; e.g. chronic lymphocytic leukemia, various lymphomas, reactive lymph node, adrenal cortical adenoma, insulinoma, Sertoli cell tumor, meningioma and glioma

♦ Mucous granules (0.7-1.8 μm):
- Membrane-limited granular, reticulated or flocculent material of various density
- Electron microscopy does not differentiate various types of mucins; for this purpose, histochemical and immunohistochemical studies are needed
- Seen in mucin-producing acinar or ductal epithelial cells of normal and neoplastic exocrine glands

♦ Serous or zymogen granules (0.5 – 1.5 μm):
- Membrane-limited, dense granular matrix, may or may not contain enzymes
- Exocrine gland (pancreatic acinar cells, serous acinic cells of salivary gland, serous glands of the upper respiratory tract) tumors, gastric chief cells, Paneth cells

- **Caveat**—*A histological designation of serous tumor does not necessarily mean that the cells have serous or zymogen granules. Ovarian serous tumors occasionally contain a few small mucous, rather than serous granules. Serous cystadenoma (microcystic) of the pancreas has abundant glycogen and rare apical seretory granules*

♦ Neurosecretory, dense core (or neuroendocrine) granules:
- – Membrane-limited dense core granules vary in size, shape and density (50-400 nm)
- – In neuroblastoma, esthesioneuroblastoma, ganglioneuroblastoma, 100 nm round dense core granules are more concentrated in cell processes than in cell bodies
- – Pheochromocytoma—two cell types, one with eccentric dense cores (norepinephrine) and the other (epinephrine) with centrally located spherical cores, resembling granules of neuroblastoma
- – Paraganglioma—spherical granules (100-200 nm)
- – Carcinoid tumor—serotonin-secreting pleomorphic granules
- – Medullary thyroid carcinoma—two types of calcitonin-containing granules, type I—large, medium-dense and with no halo, and type II—small, very dense and with halo
- – Merkel cell tumor (cutaneous neuroendocrine carcinoma)—small spherical granules (115–200 nm)
- – Pulmonary tumorlet—Dense core granules similar to those of carcinoid tumor
- – Small and large cell neuroendocrine carcinoma—sparse dense core granules
- – Renal juxtaglomerular cell tumor—spherical or rhomboid granules

♦ Glycogen:
- – Often washed away in routine preparation
- – Two-forms:
  - Beta glycogen; irregular shaped 15–30 nm particles
  - Alpha glycogen; rosette-like aggregates (prominent in the liver)
- – Abundant in Ewing's sarcoma, seminoma, rhabdomyosarcoma, yolk sac tumor, clear cell carcinoma of the breast, vagina, endometrium, salivary gland and kidney; clear cell sarcoma, sugar tumor of the lung, some hepatocellular adenoma and carcinoma
- **Caveat**—Water-clear cells of a parathyroid adenoma contain numerous small vesicles, not glycogen

♦ Lipids:
- – Lipid droplets are not limited by a membrane
- – In adipose tissue, normal and neoplastic
- – Hibernoma contains abundant lipid droplets and mitochondria
- – Steroid-secreting tumors – thecoma, ovarian hilus cell tumor, Leydig cell tumor, adrenal cortical tumors—contain numerous lipid droplets
- – Also present in sebaceous gland tumor, renal clear cell carcinoma, xanthoma, fibrohistiocytoma

♦ Crystals of Reinke:
- – Hexagonal prism-like, highly ordered 10 nm thick filaments, not limited by a membrane
- – Seen in Leydig cells, ovarian hilus cells
- – Crystals found in 35% of Leydig cell tumors

♦ Charcot-Böttcher "crystalloids":
- – Closely packed electron-dense, longitudinal arrays of fibrils or tubules lacking a geometric crystalline lattice in post-puberty Sertoli cells
- – Described in an occasional case of Sertoli cell tumor

♦ Lamellar inclusion body (myelinosome):
- – Concentrically arranged, stacked electron-dense membrane
- – Source of surfactant in type II alveolar cells
- – A metabolic (not necessarily toxic, as claimed initially) product of many drugs including amiodarone and gentamycin
- – Seen in bronchiolo-alveolar carcinoma and lysosomal storage diseases

♦ Langerhans cell granule (Birbeck granule):
- – A 34 nm wide rod-shaped structure of variable length with a periodic or striated zipper-like core
- – The limiting membrane is often dilated at one end giving the granule a tennis racket-like appearance
- – Positive for CD1 antigens and S-100 protein
- – Seen in Langerhans cell histiocytosis (eosinophilic granuloma, Letterer-Siwe disease, Hand-Schüller-Christian disease)
- – Absent in follicular dendritic and interdigitating dendritic cells

♦ Melanosome:
- – Matures stepwise from Stage I to IV
- – Stage II-III melanosomes are most characteristic, consisting of ovoid or ellipsoidal vesicles with striated internal structures
- – As melanin pigment deposits, the internal structure turns invisible
- – Seen in melanocytic neoplasms

♦ Weibel-Palade body:
- – A rod-shaped body with microtubular internal structures embedded in dense matrix
- – Seen in blood vessel endothelial cells but not in lymphatic endothelial cells
- – Seen in benign vasoformative tumors, and epithelioid hemangioendothelioma

- Not usually found in malignant vasoformative tumors, such as angiosarcoma, Kaposi's sarcoma

♦ Cytoplasmic fibrils/filaments:
- Microtubules; 25nm wide:
  - Axonemes of cilia
  - Neurotubules in neuronal cell tumors (neuroblastoma, ganglioneuroma, primitive neuroectodermal tumor), schwannoma
  - Intracisternal microtubules – described in melanoma and myxoid chondrosarcoma
- Thick filaments (muscle myosin); 15 nm wide:
  - In striated muscle cells, thick and thin myofilaments are set side by side
- Intermediate filaments; 10 nm wide:
  - Cytokeratin, vimentin, desmin, glial filaments, and neurofilaments; with the exception of tonofibrils (cytokeratin forming characteristic dense curvilinear bundles), they are not distinguishable by electron microscopy
- Actin microfilaments; 6 nm wide:
  - Found in smooth and striated muscle cells, myofibroblast, myoepithelial cell
- Nemaline rod:
  - First described in nemaline myopathy; it has been seen in muscular dystrophy and polymyositis
  - Thread-like or oblong structures having a lattice-like appearance, found beneath the sarcolemma
- Mallory's hyalin or body:
  - An irregularly shaped accumulation of cytokeratin intermediate filaments in liver cells
  - Seen in alcoholic and non-alcoholic steatohepatitis, Wilson's disease, various cholestatic conditions
  - Also described in hepatocellular carcinoma

THE CELL SURFACE (PLASMALEMMA)

♦ Interdigitating complex cell membranes:
- Common in glandular epithelial tumors (gastrointestinal adenocarcinomas, parathyroid adenomas and sweat gland tumors), epithelioid sarcoma, meningothelial meningioma and schwannoma

♦ Cilia:
- Respiratory epithelial cilia on cross section show a pair of centrally located microtubules and nine pairs of doublets at the periphery (9+2 pattern). Outer and inner dynein arms extend from each doublet
- In primary ciliary dyskinesia (or immotile cilia syndrome), outer and/or inner dynein arms are completely or almost completely absent. Those males with this defect are infertile, and other patients may have Kartagener's syndrome
- Cilia are lost in malignant tumors. Various abnormalities of the cilia are described in benign epithelial tumors. They are not useful in differential diagnosis

♦ Pinocytotic vesicles:
- Seen in well-differentiated smooth muscle, vascular endothelial and perineurial tumors

♦ Microvilli:
- Closely packed rigid microvilli (brush border), characteristic anchoring rootlets and glycocalyx; seen in adenocarcinoma of gastrointestinal tract and intestinal-type adenocarcinoma of other sites
- Long, branching, shaggy microvilli— in mesothelial cell and mesothelioma (epithelial type)
- Microvillus inclusion disease
  - An inherited, autosomal recessive condition, presenting with intractable diarrhea and steatorrhea
  - Usually fatal in 2 years
  - Histologically may resemble celiac sprue
  - Electron microscopy is diagnostic; 1) Abnormal microvilli at the luminal aspect of the enterocyte; 2) apical intracytoplasmic inclusions lined by microvilli

♦ Intracytoplasmic lumens:
- Their presence associated with microvilli is a useful marker for adenocarcinoma
- Prominent in breast carcinoma (both ductal and lobular)
- However, they are also found in adenocarcinomas of the lung, mesotheliomas, meningiomas and neuroendocrine tumors

♦ Cell Junctions:
- In general, the number of intercellular junctions are reduced in tumor cells compared with the normal counterpart; they tend to be rudimentary
- Cell junctions of various types are found in all benign and malignant epithelial tumors, meingothelial memingiomas, thymomas, mesotheliomas, endocrine gland tumors, neuroendocrine tumors, germ cell tumors, sex cord stromal tumors, epithelioid sarcoma, epithelial component of synovial sarcoma, and vascular endothelial cell and its tumors
- In most other mesenchymal tumors, cell junctions are poorly developed, primitive or inconspicuous
- In leukemia, granulocytic sarcoma and lymphoma, cell junctions are absent (one exception being follicular dendritic cell tumor)

THE EXTRACELLULAR CONSTITUENTS

- Luse bodies:
  - Fusiform long-spacing collagen fibers with a periodicity of 100-150 nm
  - Seen most characteristically in schwannoma
- Amianthoid fibers:
  - Giant collagen fibers with diameter up to 10 times of normal collagen fibrils (60 nm)
  - Detected in chondrosarcoma, synovial sarcoma, neurogenic sarcoma and meningioma
- Skeinoid fibers:
  - Tangles of curvilinear fibrils with a periodicity of 41-48 nm
  - Described in neurogenic spindle cell tumors and gastro-intestinal autonomic nerve tumors
- Amyloidosis and amyloidoma:
  - A beta-pleated sheet configuration
  - Congo-red positive, birefringent under polarized light
  - Haphazardly arranged, non-branching fibrils with a diameter of 7 to 10 nm
- Differential diagnosis between bullous pemphigoid and acquired epidermolysis bullosa:
  - The bulla in bullous pemphigoid lies in the lamina lucida, and the anchoring fibrils are normal; while the bulla in acquired epidermolysis bullosa occurs below the lamina densa, and the anchoring fibrils are totally absent or markedly reduced

DIAGNOSTICALLY USEFUL ULTRASTRUCTURAL FEATURES OF NEOPLASMS

- See Tables 4-1 and 4-2
- Acinic cell carcinoma of the salivary gland and acinar cell carcinoma of the pancreas:
  - Membrane-limited electron-dense round zymogen granules (0.3 to 1.5 μm)
  - Stacked rough endoplasmic reticulum
  - Well developed Golgi apparatus
  - Occasional small lumens lined by microvilli and juxtaluminal junction complexes
- Adenoid cystic carcinoma (salivary gland, breast, upper airway, skin):
  - Clusters of polygonal cells forming microcystic spaces containing multi-layered basal lamina, flocculent matrix and microfibrils
  - Three type of cells are identified:
    - Undifferentiated, with a high nucleus/cytoplasm ratio and organelle-poor cytoplasm
    - Myoepithelial cells, with thin (actin) filaments

Table 4-1 Small Round Cell Tumors

	Neuroblastoma	*Neuroendocrine tumor*	*Ewing's sarcoma*	*PNET*	*Rhadomyo-sarcoma*	*Lymphoma*	*DRCTDD*
Glycogen	±	±	+	+	+	±	±
Dense core Granules	+	+	–	±	–	–	±
Cell junctions	+	+	+	+	+	–	+
Cytoplasmic filaments	+	+	±	+	+ thick and thin	±	+
Microtubules	+	–	–	±	–	–	–
Basal lamina	–	±	–	–	+	–	+
Others	Neuropil				Z-band		

**** + present; - absent; ±occasionally present; PNET=primitive neuroectodermal tumor; DRCTDD=desmoplastic round cell tumor of divergent differentiation*

Table 4-2 Large Cell Tumors

	Squamous Cell Carcinoma	*Transitional Cell Carcinoma*	*Adeno-carcinoma*	*Neuro-endocrine tumor*	*Melanoma*	*Lymphoma*	*Sarcoma*
Cell Junctions	+	+	+	+	–	–	±
Microvilli with Lumen	–	–	+	±	–	–	±
Filaments	+ tonofibrils	+	+	+	+	±	+
Secretory Granules	–	–	+	+	–	–	–
Golgi RER	+	+	+	+	+	–	+
Basal Lamina	+	+	+	+	–	–	±

****RER=Rough Endoplasmic Reticulum*
**** + present; - absent; ± occasionally present*

condensed against cell membrane, facing the microcystic space that is lined by basal lamina
  - Ductular cells, forming true lumens lined by microvilli and held by junctional complexes

- Adenoma and adenocarcinoma (tumors of exocrine glandular epithelium in general):
  - True glandular lumen or intracytoplasmic lumen lined by microvilli (not specific; also seen in epithelial mesothelioma, choroid plexus papilloma, glandular component of synovial sarcoma, and neuroendocrine neoplasms)
  - Various cell junctions
  - A distinct basement membrane along the stromal interface
  - A well-developed Golgi apparatus and exocrine secretory granules (mucous, serous or zymogen)
  - Intermediate filaments (cytokeratin)
  - Interdigitation of cell membrane
  - In clear cell type, pools of glycogen particles
  - Characteristic features of intestinal type adenocarcinoma; rigid microvilli with prominent core rootlets, glycocalyx, junctional complex and mucous granules
- Adipose neoplasms (lipomas and liposarcomas):
  - Lipid droplets
  - Pinocytotic vesicles
  - Basal lamina
  - Varying amounts of rough endoplasmic reticulum, intermediate filaments, mitochondria and glycogen particles
- Adrenal cortical neoplasms:
  - Abundant smooth endoplasmic reticulum
  - Lipid droplets
  - Mitochondria with lamellar cristae (aldosteronoma), or with tubulovesicular cristae (cortisol-secreting tumor)
- Spironolactone bodies:
  - Spherical laminated whorls of smooth membrane resembling surfactant myelinosomes
  - Seen in zona granulosa cells of patients treated with the aldosterone antagonist, spironolactone
- Black adenoma of the adrenal cortex:
  - Abundant lipofuscin inclusions in zona reticularis type cells of a usually non-functioning adenoma
- Alveolar soft part sarcoma:
  - Golgi associated small dense granules (90 nm) and larger secretory granules (300 nm)
  - Rhomboid crystals in the larger granules in about 50% of the cases
  - Stacked rough endoplasmic reticulum, clusters of mitochondria, variable glycogen particles, lipid droplets and rare rudimentary cell junctions
  - Basal lamina around groups of tumor cells
- Brenner tumor:
  - Epithelial cells having the following features are

present in the fibroma–thecoma-like background:
  - Cleaved nuclei
  - Varying numbers of glycogen particles, lipid droplets, lysosomes and vesicles
  - Intercellular spaces containing prominent microvilli
  - Interdigitating cell membranes
  - Numerous small desmosomes
  - Basement membrane (basal lamina) enclosing the epithelial clusters
  - The borderline tumors have secretory (mucous) cells and ciliated cells along the cystic cavities

- Bronchiolo-alveolar carcinoma:
  - A pure or a mixture of type II pneumocytes, Clara cells and mucus-secreting cells:
    - Type II pneumocytes have surfactant myelinosomes and intranuclear microtubular inclusions
    - Clara cells are nonciliated secretory cells of the terminal bronchioles, having electron-dense, apical granules (350-1200 nm). Many of them contain fingerprint-like internal structures
    - Mucous cells with abundant apical mucous granules and intestinal type microvilli
- Carcinoid/islet cell tumors:
  - Nests of oval or spindle cells, surrounded by basal lamina
  - Occasionally the nests have a lumen with microvilli
  - Desmosomes and intermediate filaments
  - Numerous cytoplasmic neurosecretory dense-core granules
- Chondroid tumors (chondroma and chondrosarcoma):
  - Scalloped cell surface
  - Abundant rough endoplasmic reticulum
  - Occasional clusters of glycogen, lipid and intermediate filaments
  - No basal lamina
- Cholangiocarcinoma:
  - Intestinal type microvilli on the luminal surface
  - Mucous granules, abundant free ribosomes, scanty rough endoplasmic reticulum
  - No glycogen
  - A continuous basement membrane, often surrounded by a densely collagenous stroma
- Clear cell adenocarcinomas of the vagina, cervix, endometrium and ovary:
  - Abundant cytoplasmic glycogen
  - Short and blunt microvilli
  - Junction complexes
  - Stacks of rough endoplasmic reticulum
  - Microcysts, tubules and papillae lined by hobnail, cuboidal cells or solid areas of polygonal cells
- Clear cell renal carcinoma:
  - Rich in both cytoplasmic glycogen and lipid droplets
  - In contrast, chromophobe cell renal carcinoma contains numerous cytoplasmic vesicles of unknown origin
  - Microlumen formation, sparse microvilli, primitive cell junctions and basal lamina around groups of cells
- Clear cell sarcoma of tendons and aponeurosis:
  - Large pools of glycogen particles
  - In the majority, melanosomes are found
- Desmoplastic small cell tumor with divergent differentiation:
  - Small groups of epithelial cells joined by primitive desmosome-like junctions
  - Irregularly-shaped nuclei, heterochromatin, inconspicuous nucleoli
  - Abundant ribosomes, a prominent Golgi apparatus and bundles of intermediate filaments in the paranuclear region
  - Occasional cells with glycogen and neurosecretory granules
  - Basal lamina
  - Collagenous stroma containing fibroblasts and myofibroblasts
- Embryonal carcinoma:
  - A high nucleus/cytoplasm ratio, with large elongated or irregularly-shaped nuclei having clumped chromatin and large, often multiple nucleoli
  - Abundant free ribosomes
  - Mitochondria, aggregates of glycogen particles and intermediate filaments readily found
  - In better differentiated areas, smooth and rough endoplasmic reticulum, desmosomes, gland lumens, junction complexes, microvilli and basal lamina are seen
- Epithelioid sarcoma:
  - Clusters of large polygonal cells having round or indented nuclei with coarse chromatin, multiple nucleoli and abundant cytoplasm
  - Numerous intermediate filaments and occasional tonofibrils
  - A moderate amount of mitochondria, ribosomes and endoplasmic reticulum
  - Cell junctions including desmosomes
  - Rare discontinuous basal lamina around groups of tumor cells
- Ewing's sarcoma:

- Sheets of uniform cells with large oval nuclei with smooth nuclear contour and finely dispersed chromatin
- Nucleoli are small or inconspicuous
- Numerous free ribosomes and aggregates of glycogen particles
- An occasional cell showing cytoplasmic filaments
- Primitive cell junctions

♦ Fibromas and fibrosarcoma:
- Consisting of fibroblastic cells with abundant rough endoplasmic reticulum, a small number of mitochondria and a few bundles of intermediate filaments, and surrounded by collagen fibers

♦ Fibrous histiocytoma, benign and malignant:
- Tumors of fibroblastic cells and modified fibroblasts having histiocytic features, giant or multinucleate fibroblastic cells and histiocytic cells

♦ Follicular dendritic cell neoplasm:
- Oval or elongated nuclei with small amount of peripheral heterochromatin
- Scant cytoplasmic organelles
- Long cytoplasmic processes held together by desmosomes
- No Birbeck granules found

♦ Gastrointestinal autonomic nerve (GAN) tumor:
- A recently described, still controversial entity
- Presented as a subgroup of gastrointestinal stromal tumors (GIST)
- Consisting of spindle and epithelioid cells, often tightly arranged
- Long, interdigitating cytoplasmic processes resembling axons
- Intermediate filaments, microtubules and dense core granules
- Bulbous synaptic vesicle-like structures
- Small primitive cell junctions between the axonic processes
- Aggregates of curvilinear collagen fibrils ("skeinoid fibrils") in the intercellular space

♦ Gastrointestinal stromal tumor (GIST):
- A tumor consisting of spindle and epithelioid cells, tightly packed together, displaying ultrastructural features of muscle cell, Schwann cell, fibroblast, autonomic nerve cell or primitive mesenchymal cell
- A subgroup with features of autonomic nerve cell, described under the name of GAN tumor (see above)
- Skeinoid fibers may be seen between the cells
- The majority of the cases having features of smooth muscle

♦ Granular cell tumor:
- Clusters of polygonal cells having abundant cytoplasm
- Numerous pleomorphic phagolysosomes
- Slender cytoplasmic processes joined by rare rudimentary junctions
- Basal lamina around groups of tumor cells

♦ Granulosa cell tumor:
- Nests of oval cells in part surrounded by basal lamina, and joined by primitive desmosome-like junctions
- In adult form, nuclei tend to be deeply indented and the nucleus/cytoplasm ratio is high
- In juvenile form, the nucleus/cytoplasm ratio is low and the nucleus is not indented
- In both types, cytoplasm is rich in lipid droplets and smooth endoplasmic reticulum; mitochondria have tubular or tubulovesicular cristae

♦ Hemangiopericytoma:
- Spindle or polygonal cells arranged in a palisade around blood vessels
- Basal lamina around tumor cells
- Primitive cell junctions
- Pinocytotic vesicles
- Intermediate filaments in the cytoplasm

♦ Hepatocellular adenoma and carcinoma:
- Intercellular canaliculi and intra-luminal or cytoplasmic bile (homogeneous dense bodies, varying sized vesicles or membranous whorls)
- Well-developed smooth endoplasmic reticulum and abundant mitochondria
- Aggregates of intermediate filaments (Mallory bodies) or cytoplasmic dense, solid inclusions of alpha-1 antitrypsin in some cases
- Glycogen particles and lipid droplets may be conspicuous

♦ Hilus cell tumor (of the ovary):
- Ultrastructures are identical to those of testicular Leydig cells

♦ Interdigitating dendritic cell neoplasm:
- Large indented or pleomorphic nuclei with peripheral heterochromatin
- Sparse cytoplasmic organelles
- Interdigitating cytoplasmic processes with no desmosomes
- No Birbeck (or Langerhans) granules

♦ Langerhans cell histiocytosis:
- Large mononuclear cells with filopodia
- Birbeck or Langerhans granules (rod-shaped structures with striated core, sometimes with bulbous end giving a tennis racket-like appearance)
- Primary lysosomes present but secondary lysosomes (phago-lysosomes) usually absent

- Leukemia, myelocytic (granulocytic sarcoma) and myelomonocytic
  - Primary cytoplasmic (azurophil) granules
  - Myeloperoxidase activity in the cytoplasmic granules
  - Auer rods (rod-shaped, membrane-limited structures with dense lamellar internal substructure, resulting from coalescence of azurophilic granules)
  - Absence of cell junctions
- Leukemia, lymphocytic:
  - Peripherally condensed heterochromatin
  - Rare, myeloperoxidase-negative primary lysosomes, but no secretory granules in the cytoplasm
  - No cell junctions
- Leukemia, hairy cell:
  - Small lymphoid cells with villus-like (hairy) cytoplasmic projections, best seen in blood sample
  - In spleen and lymph node, filopodia or cell processes are interdigitating
  - Ribosome-lamellar complexes, usually in the paranuclear location, found in 50% of the cases
- Leydig cell tumor of testis (and hilus cell tumor of ovary):
  - Round nucleus, dispersed chromatin and medium-sized nucleolus
  - Abundant vesicles of smooth endoplasmic reticulum
  - Many lipid droplets
  - Mitochondria with tubulovesicular cristae
  - Microvilli covering the cell surface, basal lamina covering non-villous surface
  - Reinke crystals are diagnostic but present in a minority of cases (35%)
- Lymphoepithelial (lymphoepithelioma-like) carcinoma or undifferentiated carcinoma of nasopharynx:
  - Clusters of polygonal cells with small primitive desmosomes
  - Tonofibrils
  - Prominent free ribosomes
- Lymphomas:
  - Nucleus with peripheral heterochromatin
  - Abundant free ribosomes
  - Absence of intercellular junctions
  - Stacks of rough endoplasmic reticulum in plasmacytoid and immunoblastic cells
  - Various nuclear configurations, round to indented, multilobated, cleaved or cerebriform
  - In special types, the cell surface is covered with microvilli (filliform or anemone cell)
  - The cytoplasm may contain numerous vesicles (signet ring cell)
  - Nuclear pockets may be seen
- Malignant melanoma:
  - Stage II and III melanosomes (elliptical membrane-limited structures with striated lamellar core, without or with dense melanin deposition)
  - Stage I (vesicles) and stage IV (heavily pigmented) melanosomes, and atypical melanosomes are not as specific as stage II and III melanosomes for diagnosis
  - Unusual findings rarely described, include basal lamina, microvilli, primitive cell junctions and intracisternal microtubules
- Meningioma:
  - Long, interdigitating cell processes with desmosomes and other forms of cell junctions
  - Numerous intermediate filaments
- Merkel cell carcinoma (cutaneous neuroendocrine carcinoma):
  - Dense core granules
  - Intercellular junctions
  - Aggregates of paranuclear intermediate filaments or tonofibrils
- Mesothelioma, epithelial cell type:
  - Numerous, long slender microvilli with a height/width ratio of 10/1 or higher
  - No anchoring actin rootlets and no glycocalyx
  - Prominent intercellular junctions including desmosomes
  - Abundant intermediate filaments and tonofibrils
  - Basal lamina
  - Glycogen particles and intracytoplasmic lumens may be seen

  **In spindle cell type or sarcomatous mesothelioma, a spectrum of cells; fibroblastic, myofibroblastic, mesothelial and other hybrid cells are seen
- Neuroblastoma:
  - Oval cells with crowded cytoplasmic processes (neuropil)
  - Dense-core neurosecretory granules
  - Microtubules and intermediate filaments in cell processes
  - Primitive intercellular junctions and rare synaptic vesicles
- Neuroendocrine neoplasm, low grade (carcinoid, well differentiated neuroendocrine tumor)
- Neuroendocrine neoplasm, intermediate grade (atypical carcinoid, well differentiated neuroendocrine carcinoma)
- Neuroendocrine neoplasm, high grade (small cell or oat cell carcinoma, large cell neuroendocrine carcinoma, Merkel cell carcinoma):
  - Oval or spindle cells often with polar processes
  - Dense core neurosecretory granules

  - Intercellular junctions
  - Intermediate filaments
- Oncocytomas, oncocytic neoplasms. See Mitochondria
- Osteoblastic neoplasms (osteoma, osteoblastoma, osteosarcoma):
  - Polygonal cells with scalloped cell surface
  - Abundant dilated rough endoplasmic reticulum
  - Hydroxy-apatite deposits in the matrix containing woven type I collagen fibers (osteoid)
  - Variable numbers of intermediate filaments, glycogen particles, lipid droplets and mitochondria
- Ovarian surface epithelial neoplasms:
  - Serous tumors (benign, borderline and malignant)
    - Glandular lumens and papillae
    - Microvilli and cilia
    - Junctional complexes
    - Basal lamina
    - Glycogen and rare secretory granules may be present
  - Mucinous tumors:
    - Glandular lumens
    - Occasional papillae
    - Microvilli
    - Junctional complexes
    - Basal lamina
    - Mucous granules

    **Endocervical type (uniform small secretory granules, fibrillogranular bodies and basal nuclei)

    **Intestinal type (absorptive, goblet and neuroendocrine cells)
  - Endometrioid tumors:
    - Tubular glandular lumens
    - Microvilli
    - Junctional complexes
    - Basal lamina
    - Paranuclear filaments
    - Abundant glycogen
    - Desmosomes and tonofibrils in the squamous morules
  - Clear cell tumors (see clear cell adenocarcinoma above)
  - Transitional cell tumors (Brenner tumors):
    - Cystic structures or solid sheets of large polygonal cells
    - Basal lamina
    - Intercelluar spaces lined by numerous microvillus-like projections without desmosomal junctions
    - Numerous pinocytotic vesicles
    - Short microvilli on the luminal surface
    - Junctional complexes
    - Nuclear membrane occasionally invaginated
- Paraganglioma and pheochromocytoma:
  - Nests of polygonal cells surrounded by basal lamina
  - Round (in paraganglioma) and pleomorphic (in pheochromocytoma) dense core granules
  - Prominent Golgi apparatus
  - Sustentacular (supporting Schwann-like) cells seen in paraganglioma but not in pheochromocytoma
- Primitive neuroectodermal tumor:
  - Oval cells with polar processes
  - Cytoplasm mostly with free ribosomes, focal intermediate filaments, occasional microtubules and rare dense cored granules
  - Small intercellular junctions
  - Irregularly shaped nuclei with heterochromatin and varying-sized nucleoli
  - Glycogen may be found in the cytoplasm
- Rhabdoid tumor (renal and extrarenal):
  - Loosely arranged collection of oval cells with irregularly-shaped nuclei and large nucleoli
  - Large paranuclear whorls of intermediate filaments and occasional tonofibrils
  - Rudimentary cell junctions
- Rhabdomyosarcoma (alveolar and embryonal):
  - Thick (15 nm) myosin filaments with or without thin (6 nm) actin filaments
  - Thick filament-ribosomal complexes
  - Z-band formation
  - Basal lamina (in alveolar but not embryonal type)
  - Glycogen in the cytoplasm
- Schwannoma and malignant peripheral nerve sheath tumor:
  - Spindle nuclei with heterochromatin and numerous interwoven cell processes surrounded by basal lamina
  - No unique cytoplasmic organelles
  - Secondary lysosomes may be seen
  - Primitive cell junctions
  - Luse bodies (long-spacing type I collagen fibers) may be found in the matrix
- Seminoma and dysgerminoma:
  - Closely apposed large polygonal cells, held by various cell junctions, most often desmosome-like
  - Large euchromatic nuclei and large rope-like nucleoli
  - Abundant glycogen particles and scant organelles
- Sertoli cell tumor:
  - Tubules lined by basal lamina
  - Junctional complexes
  - Well-developed Golgi

  - Charcot-Böttcher filaments may be found
  - Lipid droplets common
- Small cell carcinoma, pulmonary type— see neuroendocrine cell neoplasms above
- Small cell carcinoma, ovarian hypercalcemic type:
  - No dense core granules and no glycogen found
  - Nests, cords, follicle-like groups of polygonal cells with intermediate junctions and desmosomes
  - Dilated rough endoplasmic reticulum and numerous free ribosomes
- Squamous cell carcinoma:
  - Demosomes
  - Tonofibrils
  - Keratohyalin granules in well differentiated carcinoma
  - Filopodia between cells, occasionally joined by desmosomes
  - Basal lamina
- Synovial sarcoma:
  - In a biphasic tumor, the epithelial components are surrounded by basal lamina
  - Luminal side has microvilli and junctional complexes
  - Spindle cells are closely apposed and rudimentary junctions present between them
  - Sparse collagen fibrils and dense stromal matrix in the background
- Thymoma:
  - Epithelial components are of squamous cell in ultrastructure
  - Lymphocytes of various quantity in the background
- Transitional cell carcinoma:
  - Desmosomes
  - Interdigitating, microvillus-like filopodia on lateral cell borders
  - Small invaginations of luminal cell membrane, and the presence of apical vesicles and filaments are characteristic of normal urothelium, and are seen rarely in tumors
  - Basal lamina

THE GLOMERULOPATHIES

- The readers are further referred to Chapter 23, Non-Neoplastic Renal Diseases, by Donna L. Lager, M.D.

Glomerulonephritides Characterized by Immune-type Dense Deposits

- Dense deposits are predominantly localized in the subepithelial space:
  - Membranous glomerulonephritis
    - Subepithelial dense deposits tend to be numerous and to affect every capillary loop
    - Deposits show early cupping, or appear sunken in the basement membrane
    - Extension of basal lamina material around the deposits gives the appearance of "spikes" on Jones' silver methenamine stain
    - Deposits become rarefied and buried in the basement membrane to be incorporated in it at the late stage
    - Epithelial foot processes are extensively effaced and the podocytes exhibit numerous microvillus-like projections
    - Dense deposits in the mesangium may coexist occasionally in idiopathic membranous glomerulonephritis, but almost always in membranous lupus nephritis (WHO Class V)
  - Acute postinfectious proliferative glomerulonephritis:
    - Subepithelial dense deposits tend to be fewer, larger (hump-like) and more variable in size than those of membranous glomerulonephritis
    - Small dense deposits are almost always present in the mesangium and in the subendothelial space of the capillary basement membrane
    - Effacement of epithelial foot processes is patchy
    - Granulocytes and monocytes are increased in the capillary lumen
- Dense deposits are primarily in the mesangium:
  - IgA nephropathy:
    - Large confluent deposits are found in the paramesangial space (at the base of capillary loops)
  - Henoch-Schönlein nephritis with purpura (HSP):
    - Morphologically the glomerular lesions are almost identical to those of IgA nephropathy
    - Patients with HSP have, in addition, leukocytoclastic vasculitis affecting skin, joints and intestine
    - Mesangial dense deposits may extend into the adjacent subendothelial space
    - Subepithelial deposits (sometimes hump-like) are also encountered but infrequently
  - Mesangial proliferative lupus nephritis (WHO Class II):

    - Mesangial deposits are positive for IgG and/or IgM, and C3
  - Idiopathic mesangial proliferative glomerulonephritis:
    - EM findings are similar to mesangial proliferative lupus nephritis
    - It is most often seen in children presenting with the nephrotic syndrome or with non-nephrotic range proteinuria and hematuria
  - Mesangial IgM nephropathy:
    - Mesangial dense deposits are usually small and inconspicuous
    - Patients present with proteinuria with or without edema
- Dense deposits are present predominantly in the subendothelial space of the capillary loops but also in the mesangium:
  - Membranoproliferative glomerulonephritis, Type1
  - Focal proliferative (WHO Class III) and diffuse proliferative (WHO Class IV) lupus nephritis

Glomerulopathies in which Immune-Type Dense Deposits Are Absent or Scant

- Minimal change glomerulopathy:
  - Extensive effacement of epithelial foot processes, associated with no demonstrable dense deposits
- Focal segmental glomerulosclerosis:
  - Sclerotic segments represent collapsed capillaries with wrinkled basement membrane, increased mesangial matrix, and sometimes deposition of collagen fibers
  - Electron dense deposits may be seen in the subendothelial or mesangial location of the sclerotic or hyalinized segments
  - The focus of hyalinosis corresponds to a capillary loop where the endothelial fenestrated membrane is denuded and the lumen is filled with amorphous dense material often containing lipid vacuoles
  - Detachment of a podocyte with the gap replaced by laminated, newly formed basement membrane-like material is a characteristic change in focal segmental glomerulosclerosis
  - An additional finding in HIV (human immunodeficiency virus)-associated nephropathy is the presence of tubuloreticular structures in the cytoplasm of capillary endothelial cells
- Anti-GBM (glomerular basement membrane) crescetic glomerulonephritis:
  - No discernable immune-type dense deposits are demonstrable, despite the fact that there exists characteristic smooth linear staining of immunoglobulins on the glomerular basement membrane
  - Disruption of the basement membrane is associated with proliferating parietal epithelial cells, accumulation of white blood cells and deposition of fibrin (active crescent)
  - Plasma proteins resembling immune-type dense deposits may be located in the area of capillary destruction
- ANCA (anti-neutrophil cytoplasm antibody)-positive or pauci-immune, crescentic glomerulonephritis, including Wegener's granulomatosis:
  - EM findings are similar to anti-GBM nephritis
- Diabetic glomerulopathy (intercapillary and nodular glomerulosclerosis):
  - It is characterized by widening of the lamina densa of the glomerular basement membrane, and an increase in mesangial cells and matrix A segmental lesion similar to that of focal segmental glomerulosclerosis may occur in diabetic glomerulopathy

Glomerulopathies Characterized by Distinctive Ultrastructural Deposits

- Dense deposit disease (type 2 membranoproliferative glomerulonephritis:)
  - Dense deposit (this one is not immune-type) lies on the lamina densa of the glomerular basement membrane but is much denser than the lamina densa itself
  - It is discontinuous, varying in width and length
  - It has a water color quality; it is homogeneous in density and finer than the granularity of the immune-type dense deposits
  - Round deposits of same quality occur in the mesangium as well
- Light chain deposition disease:
  - The deposits are denser and coarser than immune-type deposits
  - They precipitate on the basement membrane as a continuous band. The darkest zone corresponds to the lamina rara interna (subendothelial side of the basement membrane)
  - In tubules, the deposits are located on the outer part of the basement membrane
- Amyloidosis:
  - Regardless of their chemical nature, all amyloids consist of non-branching randomly oriented fibrils, 7 - 10 nm thick
  - The fibrils deposit in the mesangial matrix first, and later on the basement membrane. The amyloid fibrils also appear on the outer part of the tubular basement membrane as well as in the vascular wall
- Fibrillary (immunotactoid) glomerulopathy:
  - Some include fibrillary and immunotactoid glomerulopathies in the spectrum of an entity, while others consider them as separate entities
  - Both are Congo red negative, and appear to be

immune-type deposits in which organized fibrils or microtubules are formed
  - In fibrillary glomerulopathy, the fibrils are about 15–25 nm and in immunotactoid glomerulopathy, about 30–50 nm in diameter
  - As in amyloidosis, the fibrils accumulate in the mesangium first and then on the capillary basement membrane later
- In lupus nephritis and cryoglobulinemia-associated glomerulopathy, immune-type dense deposits may contain finger-print like or curvilinear microtubular substructures

Glomerulopathies with Structural Abnormalities of the Basement Membrane

- Alport's hereditary nephritis:
  - Widespread, irregular thinning and widening of the basement membrane with trabeculation or lamellation of the glomerular capillary basement membrane
- Thin glomerular basement membrane disease:
  - In benign familial recurrent hematuria, the sole abnormality found may be diffuse, extensive thinning of the glomerular capillary basement membrane (less than 130 nm in children and less than 200 nm in adults)

Glomerulopathies Associated with Vascular Endothelial Injury

- Detachment of endothelial cells from the glomerular capillary basement membrane, resulting in formation of micro-pseudoaneurysm, mesangiolysis and thrombosis (thrombotic microangiopathy):
  - Hemolytic uremic syndrome
  - Thrombotic thrombocytopenic purpura
  - Antiphospholipid syndrome
  - Scleroderma (systemic sclerosis)
  - Acute renal failure in pregnancy (eclampsia and postpartum acute renal failure)
  - Radiation nephritis
  - Cyclosporine and tacrolimus (FK506) associated nephropathy
  - Acute and chronic allograft glomerulopathy
  - Malignant hypertension

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Chapter 5

Forensic Pathology

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Table of Contents

GENERAL CONCEPTS

Cause of Death

- Injury, disease, or a combination of the two responsible for initiating the events leading to death; may be brief or prolonged
  - If prolonged with survival, sequelae may develop from the initiating or proximate cause, which leads to intermediate causes of death such as pneumonia, pulmonary embolism, or bronchopneumonia
- Examples of causes of death:
  - Coronary artery atherosclerosis
  - Blunt force injury of head
  - Gunshot wound of head
  - Hanging
  - Mixed drug intoxication

Manner of Death

- Circumstances in which the cause of death arose
- Separated into two categories:
  - Natural
  - Unnatural:
    - If unnatural, then further subdivided into accident, suicide, homicide, or undetermined (undetermined could be natural)

Mechanism of Death

- Physiologic derangement or biochemical disturbance that is incompatible with life and is initiated by the cause of death; does not appear on death certificate
- Examples of mechanism of death:
  - Ventricular fibrillation
  - Respiratory arrest
  - Exsanguination

IDENTIFICATION

Positive Identification

- Visual identification:
  - Family and friends
  - Personal identification (driver's license, social security card)
  - Tattoos, scars, congenital defects, fingerprints, dental examination (comparison of pre- and postmortem dental X-rays and charting), X-ray (pre- and postmortem X-ray comparison: frontal sinus, vertebral column, ribs, unique bony or therapeutic identifying features), foreign objects (orthopedic hardware)
  - DNA (blood, tissue, bone)

Circumstantial Identification

- For use on significantly altered decedents such as burned and decomposed bodies:
  - Secured residence or motor vehicle associated with suspected decedent
  - Personal effects on body or at scene (wallet, clothing, credit cards, etc.)

Anthropological Identification

- Age (range)
- Race (more complicated with interracial procreation)
- Sex (most consistent)
- Stature
- Hair examination (may help identify race as well as hair color)

TIME OF DEATH AND POSTMORTEM CHANGES

General

- No time of death test exists
- Eyewitness is best determination of time of death
- Generally give estimates and ranges for time of death:
  - Sepsis and heat accelerate decomposition
  - Cold delays decomposition

Livor Mortis (Lividity)

- Blue-purple discoloration in dependent areas of body
- Minimal with blood loss and dark pigmentation
- Usually visible within 24 hours following death, maximum usually 8–12 hours postmortem
  - After 8–12 hours postmortem, lividity becomes fixed and will no longer blanch

- Accelerated rate of fixation with increased temperature and decomposition
- Delayed with cool temperature
- Lividity may appear different from:
  - Refrigeration: pink to cherry red (retained oxygen cutaneous vessels)
  - Carbon monoxide: cherry red (carboxyhemoglobin)
  - Cyanide: pink to cherry red (excessive oxygen retention from inhibition of cytochrome oxidase)
  - Fluoroacetate: cherry red (excessive oxygen retention from inhibition of cytochrome oxidase)
  - Hydrogen sulfide: green (sulthemoglobin)
- Advanced livor mortis in which dependent capillaries and venules become over-extended, rupture, and coalesce, forming pinpoint hemorrhages called Tardieu spots

Rigor Mortis (Rigidity)

- Begins at death
- Due to cellular loss of ATP and accumulation of lactic acid with lowering of pH
- Occurs in all cells, but is externally manifested most prominently in the musculature
- Usually visible within 2–4 hours following death
- Fully developed 6–12 hours following death
- Accelerated in infants, febrile illnesses, increased environmental temperatures, electrocution, seizures, and any excessive muscular activity prior to death
- Reduced or delayed in emaciated, elderly, and cold
- Disappears with decomposition
- Loss of ATP prevents detachment of crossbridges between actin and myosin and increased free calcium ions
- Can affect involuntary muscles (pupil disparity postmortem)
- Cutis anserina: rigor mortis of arrector pili muscles (goose flesh)
- Cadaveric spasm: rigor mortis in agonal contraction (e.g., clenched fist, articles still held in hand)

Algor Mortis (Body Cooling)

- Postmortem cooling:
  - Conduction: heat transferred by direct contact to another object
  - Radiation: heat transferred to adjacent air by infrared rays
  - Convection: heat transferred through moving air currents adjacent to body
  - Heat loss decreased by an insulator such as clothing and increased body fat
  - Heat loss increased in cold water
  - Body temperature will approach environmental temperature
  - Body temperature prior to death may be increased by sepsis, hypothyroidism, exercise, heat stroke, seizures, drugs (cocaine, amphetamines, anticholinergics, phencyclidine), and head injuries
  - Body temperature may decrease prior to death due to shock, cold environment, and drugs (alcohol, sedatives, opiates, and phenothiazines)
  - No exact formula to calculate the time of death from body temperature:
    - Ideally, body temperature decreases 2–2.5° Fahrenheit per hour for the first few hours
    - Decreases at an average of 1.5–2° per hour Fahrenheit in first 12 hours
    - Following 12–18 hours, decreases an average of 1° Fahrenheit per hour

Decomposition

- Involves two processes:
  - Autolysis: breakdown of cells and organs by intracellular enzymes; accelerated by heat and slowed by cold
  - Putrefaction: process due to bacteria and fermentation; accelerated in patients with sepsis and increased temperature
- Decomposition is accelerated with higher environmental temperatures, obesity, heavy clothing, and sepsis
- Delayed by cold environment
- Generalized sequence of decomposition:
  - Decrease of rigor mortis and fixation of livor mortis
  - Green discoloration in the right lower quadrant of the abdomen
  - Green discoloration of the head, neck, and shoulders
  - Swelling of face (bacterial gas formation)
  - "Marbling" (hemolysis of blood with hemoglobin and hydrogen sulfide reaction, creating green-black discoloration along blood vessels)
  - Generalized bloating and skin slippage (body discoloration: green to black)
- Additional terminology:
  - Mummification: dehydration of body, most prominently seen in dry, hot climates in which skin develops a dry, leathery appearance
  - Miliaria: white-gray pinpoint discoloration seen below capsule of liver, kidney, and spleen, and below endocardium due to precipitation of calcium and other salts
  - Adipocere: gray-white, waxy material seen in bodies immersed in water or in damp warm environments in which neutral fats are converted to oleic, palmitic, and stearic acids

  - Tache noir: brown to black band of discoloration of the bulbar conjunctivae and sclerae from drying, in which eyes are open
  - Embalming: delays decomposition
  - Intrauterine maceration is a result of autolysis, not putrefaction

Gastric Emptying

- In general, there is variation from day to day in gastric emptying, even in healthy subjects
- Larger meals associated with longer emptying time than smaller meals
- Liquids empty faster than solids
- Mean half emptying time for liquids is ~1½ hours
- Mean half emptying time for solids is ~4½ hours
- Gastric emptying is delayed in diabetes mellitus, anorexia nervosa, illness, emotional stress, exercise, severe injury, and drugs (alcohols, narcotics, phenothiazines, atropine, and beta adrenergic drugs)
- Gastric emptying times are increased in certain medications (e.g., valium) and certain types of exercise

Forensic Entomology

- Different insects are attracted at different stages of decomposition and may aid in the determination of how long a body has been dead
- Temperature and humidity are major factors controlling the deposition of eggs and the rate of development of necrophagous insects
- Flies are the most common insect:
  - Eggs are deposited soon after death in the daytime and take 24–48 hours to hatch into maggots
  - Maggots grow larger to pupa stage (6–10 days); adult flies emerge in 12–18 days
- As body decomposes, insects settle on body
- The following factors determine how soon and how many insects appear:
  - Rate of decomposition
  - Burial
  - Immersion in water
  - Mummification
  - Geography
- Must differentiate injury postmortem artifacts created most commonly by:
  - Roaches
  - Ants
  - Mice and rats
- Scene markers, unscientific, but helpful:
  - Date of uncollected mail
  - Newspapers in front of house
  - Television guide open to specific date
  - Clothing attire
  - Sales receipts
  - Interviews with neighbors
- Vitreous humor:
  - Vitreous potassium not reliable for estimation of time of death
  - Intracellular potassium released after death, but not a reliable mathematical rate
  - Anything that accelerates decomposition increases the release of potassium

Postmortem Chemistry

- Vitreous humor:
  - Hypertonic dehydration pattern:
    - Increased sodium (>155 mEq/L)
    - Increased chloride (> 135 mEq/L)
    - Increased urea nitrogen (VUN) (40–100 mg/dL)
  - Uremia pattern:
    - Normal to minimal increase in sodium and chloride
    - VUN >150mg/dL
  - Low salt pattern (alcoholic, pyloric obstruction, diuretic treatment):
    - Sodium <130 mEqIL
    - Chloride <105 mEq/L
    - Potassium <15 mEq/L (low relative to decomposition pattern)
  - Decomposition pattern:
    - Sodium <130 mEqIL
    - Chloride <105 mEqIL
    - Potassium >20 mEq/L
  - Diabetic pattern:
    - Glucose >200
    - In ketoacidosis, may get acetone
    - Cannot diagnose hypoglycemia because glucose decreases postmortem
- Blood, postmortem stable:
  - Creatine stable
  - Total cholinesterase stable (can rule out organophosphate poisoning)
  - Cortisol stable
  - TSH stable
  - Calcium stable

- ♦ Blood, postmortem increase:
  - – Alkaline phosphatase, increase
  - – Creatine phosphokinase (CPK), increase
  - – Amylase, increase
  - – Catecholamines, increase
  - – Insulin, increase
  - – Magnesium, increase
  - – Potassium, increase
- ♦ Blood, postmortem decrease:
  - – T4, decrease
  - – Glucose, decrease
  - – Sodium, decrease
  - – Chloride, decrease

SUDDEN DEATH FROM NATURAL DISEASE

Classification

Classification in which an autopsy discloses the cause of death from disease with regard to certainty

- ♦ Class 1:
  - – Autopsy discloses cause of death with 100% certainty
  - – Accounts for ~5% of natural deaths in medicolegal population
  - – Examples:
    - • Myocardial infarct with rupture
    - • Dissecting aortic aneurysm with rupture
    - • Intracerebral hemorrhage
- ♦ Class 2:
  - – Does not have structural changes inconsistent with life, but advanced disease is present, sufficient for death
  - – Accounts for 90% of natural deaths in medicolegal population
  - – Examples:
    - • Advanced heart disease
    - • Chronic lung disease
    - • Complications of chronic alcoholism
- ♦ Class 3:
  - – A disease with lethal potential present, but not sufficiently advanced that under ordinary circumstances would be a competent cause of death:
    - • Requires a compelling history and exclusion of other causes to allow for marginal pathologic findings to be determined to be responsible for the fatality
  - – Infrequent in medicolegal population
  - – Example: witnessed collapse with moderate coronary artery disease present at autopsy and negative toxicology, with no other significant pathologic findings:
    - • Despite marginal findings at autopsy, one must conclude that death was due to heart disease
    - • Conduction disorders should be considered
- ♦ Class 4:
  - – Lethal structural disease is not readily demonstrable at autopsy
  - – Autopsy fails to disclose alternative explanation
  - – Example: epilepsy
- ♦ Class 5:
  - – Cause of death is undetermined after autopsy and toxicologic studies
  - – There is no evidence that death is due to unnatural causes

Cardiovascular Causes of Death

Atherosclerotic Heart Disease

Clinical

- ♦ Most common cause of unexpected natural death in the western world:

Autopsy

- ♦ Marked narrowing of coronary arteries, typically >75% of lumen, in which a thrombus may or may not be present

Microscopic

- ♦ Recent or remote myocardial infarct may be present:
  - – May see perivascular and interstitial fibrosis only
  - – In some cases, no significant microscopic findings are present
  - – Contraction band necrosis may be present in cases of ischemia, but may also be an artifact of resuscitation

Mechanism

- ♦ Pump failure
- ♦ Sudden arrhythmia

Hypertensive Cardiovascular Disease

Clinical

- May or may not have a history of hypertension
- No other symptoms, other than sudden cardiac arrest, may exist

Autopsy

- Concentric left ventricular hypertrophy
- Granular kidneys

Microscopic

- Myocardial fiber hypertrophy
- Sclerosis of mural cardiac arteries
- Arteriolar nephrosclerosis

Mechanism

- Sudden arrhythmia with an increased oxygen demand of hypertrophied muscle mass:
  - Hypertensive cardiovascular disease may co-exist with atherosclerotic heart disease and lead to the acceleration of coronary atherogenesis

Aortic Stenosis

Clinical

- Bicuspid aortic valve (males, 50–70 age group)
- Rheumatic valvular disease (women, 35–55; mitral involvement also)
- Degenerative (Monckeberg's calcification) changes (> age 60, involving all three cusps)

Autopsy

- Calcification and obstruction of aortic valve
- Left ventricular hypertrophy

Microscopic

- Calcification of valve
- Myocardial fiber hypertrophy

Mechanism

- No findings distinctive for aortic stenosis mechanism
- Sudden arrhythmia due to instability from obstructive blood flow to coronary arteries

Long QT Syndrome (LQTS)

Clinical

- Jervell and Lange-Nielson syndrome (rare):
  - Autosomal recessive (deafness)
  - Autosomal dominant (long QT) on same chromosome
- Romano-Ward syndrome:
  - Autosomal dominant
  - May have history of syncope or sudden death
  - Genetic linkage, chromosome 11 (KVLQT1), chromosome 7 (LQT2), chromosome 3 (LQT3), chromosome 4 (LQT4)
- Secondary or acquired QT prolongation
  - Generally later age onset
  - Secondary to other diseases or derangement (e.g., coronary artery disease, mitral valve prolapse, liquid or crash diets, cardiac or psychotropic medications)

Autopsy

- Associated pathology includes a fatty infiltration of atrioventricular pathways
- Focal fibrosis and chronic inflammation
- Attenuation of bundle branches
- Focal lymphocytic neuritis and neural degeneration

Mechanism

- Alteration of cardiac ion channels leading to lethal dysrhythmia

Hypertrophic Cardiomyopathy

Clinical

- Most common cause of sudden death in athletes <35 years of age
- Male:female = 2:1
- Autosomal dominant
- Affects 1 of every 500 people

Autopsy

- May be symmetrical or asymmetrical thickening of interventricular septum at distal outflow tract
- Wide range of phenotypes

Microscopic

- Myofiber disarray most prominent in septum
- Plexiform interstitial fibrosis mechanism of action
- Thickened intramural coronary arteries

Genetics

- Autosomal dominant with variable penetrance
- Mutations in genes that encode sarcomere proteins
- Gene defect for cardiac myosin-binding protein C may be late onset (middle age and favorable prognosis)

Dilated Cardiomyopathy

Clinical

- May be associated with progressive congestive heart failure with early death
- May be associated with sudden death
- May develop secondarily in viral myocarditis, chronic alcoholism, peri- or postpartum, or secondary to Duchenne's or myotonic dystrophy

Autopsy

- Enlarged dilated heart
- Flabby heart with all four chambers dilated
- Frequent endocardial thickening; may have mural thrombi

Microscopic

- Interstitial fibros
- Hypertrophied and attenuated myocytes

Restrictive Cardiomyopathy

Clinical

- Associated with systemic diseases such as amyloidosis, hemochromatosis, and glycogen storage diseases
- Clinically less common than hypertrophic and dilated cardiomyopathy; affects both sexes and all ages
- Decreased diastolic relaxation and elevated ventricular filling pressure

Autopsy

- Myocardium is stiff due to either infiltration from benign or malignant process, scarring, or intracellular accumulations

Microscopic

- Dependent on etiology of cardiomyopathy

Myocarditis

Clinical History

- May be associated with sudden death or progressive heart failure
- May be associated with virus, bacteria, fungus, protozoa, or autoimmune reaction
- Most common in forensic field is viral related
- May have history of recent viral-like symptoms

Autopsy

- Heart may be slightly dilated and flabby
- May have focal areas of mottling or may be grossly normal

Microscopic

- Diffuse or patchy cellular infiltration, mainly lymphocytes
- In some cases, accompanied by marked myocardial fiber necrosis

Mechanism

- Ectopic focal cardiac irritability leading to ventricular dysrhythmias

Mitral Valve Prolapse

Clinical

- Occurs in ~5–10% of general population
- Primary form may be inherited as autosomal dominant
- Mid systolic click
- Most common presenting symptom = palpitations (PVCs):
  - PVCs associated with Marfan's syndrome, Ehlers-Danlos syndrome, pseudoxanthoma elasticum, osteogenesis imperfecta, straight thoracic spine syndrome, and pectus excavatum
- Predisposed to infectious endocarditis and mitral regurgitation

Autopsy

- Redundancy of leaflets with prolapse into left atrium eventually get secondary fibrosis of leaflets
- Elongation of chordae tendineae
- Ventricular friction lesion

Microscopic

- Myxomatous prieration of acid mucopolysaccharides containing thickening and mucinous infiltration of zona fibrosa of mitral valve

Mechanism

- Frequent PVCs from impact of anterior mitral leaflet on atrial septum
- Rare progression to lethal dysrhythmia

Aortic Dissection

Clinical

- Hypertension (coexists in 70–90% of patients) and weakness of aortic wall (e.g., Marfan's syndrome)
- Male predominant (3:1)
- Increased incidence in pregnancy
- Dissection usually heralded by onset of severe chest pain or back pain

Autopsy

- Initiating event is a tear in the aortic intima in which blood dissects into the media
- Dissection propagates distally and proximally
- Most common cause of death is rupture of aortic dissection either in the pericardial space or into the left chest cavity

Microscopic

- Variation from medial necrosis to no specific pathologic changes

Mechanism of Action

- Exsanguination

Pulmonary Thromboembolism

Clinical

- Predisposing factors:
  - Cardiovascular disease (CVD)

- Malignant tumors
- Pregnancy
- Morbid obesity
- Immobility
- Postoperative bed rest
- Trauma

♦ Hereditary predispositions:
- Congenital deficiencies of antithrombin 111, Protein C, Protein S, and plasminogen
- Activated Protein C resistance (Factor V Leiden)
- Hyperhomocysteinemia
- Elevated levels of antiphospholipid antibody

♦ Prevalence of venous thromboembolism in antithrombin III, Protein C, or Protein S deficiency is >50%

♦ Clinical symptoms:
- Sudden death
- Chest pain
- Shortness of breath

Autopsy

♦ Coiled thrombi, not conforming to the shape of the pulmonary arterial tree

♦ >95% arise in the large deep veins of lower legs, including popliteal, femoral, and iliac vein

♦ Occasionally, thrombi are also recovered in pelvic veins, especially in pregnancy and periprostatic veins

♦ Rarely, thromboembolus may cross through interatrial or interventricular defect to systemic circulation (paradoxical embolus)

Microscopic

♦ Platelet-fibrin-red blood cell mass with lines of Zahn

♦ Thrombi within lower extremity

♦ Veins may demonstrate organization

♦ May see organizational changes in pulmonary arterial wall if survival for several days post-embolism

Mechanisms

♦ Occlusion of pulmonary trunk and right ventricle

♦ Minimal flow to left ventricle, leading to sudden death or cardiovascular collapse

♦ Occlusion of smaller arteries may lead to sudden death by vasospasm, sudden increase in blood pressure and right heart failure, or bradycardia due to vasovagal reflex

Cerebrovascular Disease

Intracerebral Hemorrhage (Apoplexy)

Clinical

♦ Associated with hypertension

♦ Most common in middle-aged and elderly

♦ May present with headaches and seizures

Autopsy

♦ Common sites of hemorrhage:
- External capsule with hemorrhage into basal ganglia
- Cerebellum
- Thalamus
- Pons

Microscopic

♦ Sharp demarcation of hematoma from surrounding brain with death of neurons and glia in adjacent tissue

♦ If survival >24 hours, cerebral edema present with early organizational changes consisting of monocytes and macrophages invading into edges of hematoma

♦ If pre-existing hemorrhage has occurred, hemosiderin may be present, and if small hematoma occurs with survival after several years, residual cysts with brown-orange discolored walls may be present with hemosiderin and gliosis (so-called apoplectic cyst)

Ruptured Berry Aneurysm

Clinical

♦ Accounts for 4–5% of sudden, rapid natural death; occurs at bifurcations of intracranial arteries

♦ Exists in 1–2% of population

♦ Median age of rupture = 50 years

♦ Increased incidence of saccular aneurysms in certain disorders:
- Fibromuscular dysplasia
- Polycystic kidney disease
- Moyamoya disease
- Coarctation of the aorta

Autopsy

♦ Large saccular aneurysm at branch points may be easily identified; however, in other cases, aneurysms may be small and destroyed when they rupture and may be difficult to detect at autopsy

♦ Aneurysms may rupture into and dissect into brain parenchyma

Preferential Locations

♦ 40% related to intracranial portion of internal carotid artery, usually at juncture of internal carotid and posterior communicating artery

♦ 30% anterior communicating artery

♦ 20% middle cerebral artery

♦ 5–10% associated with posterior cerebral arteries and basilar and vertebral artery

Microscopic

♦ Typically thin-walled pouch in which endothelium may be incomplete with adjacent blood clot

- Muscle coat and elastic lamina typically stop abruptly at neck of aneurysm, and wall of aneurysm is fibrotic

Mechanism of Action

- Cerebral ischemia with cerebral infarction

Non-Vascular Causes of Death

Chronic Alcoholism

Clinical

- May see in binge drinkers where alcohol can be a cardiac irritant and lead to sudden arrhythmia
- Long-term alcohol abuse with well-known complications
- Alcohol withdrawal with delirium tremens and Wernicke's disease

Autopsy

- May include a variety of findings:
  - Alcoholic cardiomyopathy
  - Acute pancreatitis
  - Cirrhosis of the liver
  - Wernicke's encephalopathy
  - Fatty metamorphosis of the liver
  - Central pontine myelinolysis (seen with rapid correction of hyponatremia)

Microscopic

- Specific to particular disease processes

Mechanism

- Alcohol may function as a cardiac irritant or may cause electrolyte abnormalities (e.g., magnesium deficiency)

Epilepsy

Clinical

- Must have antemortem diagnosis of epilepsy
- Agonal convulsive episode is not adequate for diagnosis of epilepsy

Autopsy Findings

- May be normal anatomic brain
- May have mesiotemoral sclerosis within Sommer's sector
- May find contusion of tongue
- May have nonspecific pulmonary edema

Microscopic Findings

- When present, cell loss may be seen in CA1 and CA4 sectors of hippocampus

Mechanism

- May have prolonged tonic-clonic seizures with cardiac and respiratory exhaustion
- May have non-visible seizure with paroxysmal autonomic dysfunction

Bronchial Asthma

Clinical

- History of asthmatic bronchitis; death typically occurs during acute asthmatic paroxysm
- Death may not correlate with the severity of the autopsy findings
- Death more common at night or in early morning
- Higher incidence of death in African Americans than Caucasians (rule out concommitant sickle cell disease trait)

Autopsy

- Mucoid plugging of bronchi
- Edema of mucosa
- Voluminous hyperexpanded lungs with indentation by ribs

Microscopic

- Prominent mucus in bronchus
- Goblet cells and eosinophils in mucus (Charcot-Leyden crystals)
- Hyaline thickening of basement membrane in bronchial mucosa
- Bronchiolar and bronchial smooth muscle hyperplasia
- Goblet cell hyperplasia
- Peribronchial neutrophilic lymphocytic and eosinophilic inflammation

Mechanism

- Decreased oxygenation
- Elevated carbon dioxide retention
- Increased pulmonary vascular resistance, metabolic acidosis
- Eventual exhaustion and death

Waterhouse-Friderichsen Syndrome

Clinical

- Toxic febrile illness of acute onset with rapid deterioration classically seen associated with Neisseria meningitidis

Autopsy

- Bilateral adrenal hemorrhages
- Petechiae to purpura on skin surface
- Cerebral hemispheres may or may not be visibly suppurative

Microscopic

- Adrenal glands with varying degrees of hemorrhage

- Affected skin and adrenal glands may show acute neutrophilic infiltrate

Mechanism

- Bacterial toxemia and adrenal insufficiency catastrophic rapid onset of shock

Colloid Cyst of Third Ventricle

Clinical

- Sudden episodes of headache associated with position of head
- Appearance in adult life

Autopsy

- Sudden acute hydrocephalus due to obstruction of foramen of Monroe
- 1–4 cm in diameter
- Cerebral edema
- Mass originates from anterior part of third ventricle
- Cross section of cyst reveals gelatinous hyaline material

Microscopic

- Epithelial layer of collagenous capsule
- Mucus goblet cells present
- + stain for mucin with mucicarmine and PAS

Mechanism

- Acute hydrocephalus with herniation and compression of brainstem

Diabetic Ketoacidosis

Clinical

- History of diabetes mellitus in most cases; however, onset may precede formal diagnosis of disease

Autopsy

- May be unremarkable
- Large amounts of glucose and acetone, often detected in vitreous humor
- Blood may contain acetone

Microscopic

- Hyperosmolar nephrosis of proximal tubules
- Kimmelstiel-Wilson glomerulopathy
- Pancreatic islet cell changes (rare)
- Armanni-Epstein lesion

Mechanism

- Metabolic acidosis
- Dehydration
- Cerebral edema (rarely)

Anaphylaxis

Clinical

- Sudden onset of shortness of breath and edema of face, hives, and vascular collapse
- May develop from insect bites, medication, or food

Autopsy

- Edema of epiglottis and airway obstruction

Microscopic

- Edema and eosinophilic infiltration in airway occasionally:
  - Hypereosinophilia within vasculature of liver and heart

Mechanism

- Cardiovascular collapse with sudden onset of shock from systemic vasodilatation that includes pulmonary edema and obstructive angioedema of upper airway

Toxicology

- Elevated total tryptase level with beta tryptase level > 1 ng/mL, indicating mast cell degranulation

Manner of Death

- Manner of death determined to be natural or accidental dependent on local convention

Sudden Infant Death Syndrome (SIDS)

- Sudden death of infant <1 year of age, which remains unexplained after performance of a complete postmortem investigation
- Investigation includes:
  - Review of the case history
  - Examination of the scene of death
  - Complete autopsy with toxicologic studies and metabolic screening

Clinical

- SIDS represents 10–12% of deaths in the first year of life
- Majority of deaths occur between 2–4 months of age
- Incidence is 1–2 per 1,000 infants
- Recurrence rate in a family is ~1–2%

Risk Factors Associated with SIDS

- Maternal risk factors:
  - Poor prenatal care
  - Multiparity at a young age
  - Unmarried mother
  - Low education level
  - Tobacco use

  - Drug use
  - Lack of breast-feeding
  - Maternal anemia
  - Low weight gain in pregnancy
- Neonatal risk factors:
  - Male gender
  - Prematurity
  - Small for gestational age infant
  - Low birth weight
  - Low Apgar scores (<7)
  - Respiratory distress
  - Tachycardia
  - Tachypnea
  - Cyanosis
  - Fever
  - Hypothermia
  - Irritability
  - Poor feeding
  - Prone sleeping position
  - Infant of twin birth
  - African American
  - Native American

Pathogenesis

- Theories proposed include:
  - Congenital apneic spells or abnormal respiratory control
  - Brainstem dysfunction
  - Abnormal sleep and arousal patterns
  - Upper airway or small airway disease
  - Cardiovascular abnormalities
  - Undetected metabolic defects
  - Abnormal temperature regulation
  - Infections that are undetected, especially botulism
  - "Developmental vulnerability"
- Preventative measure suggested is putting an infant to sleep on its side or back instead of on its stomach
- SIDS very likely represents a group of disorders that have not yet been delineated as causes of sudden death in infants
- Metabolic disorders and inapparent viral syndromes may comprise a significant part of this group of deaths
- A very small number of infant deaths diagnosed as due to SIDS are undoubtedly concealed homicides, particularly smotherings

Autopsy

- Petechiae of the thymus, pleura, or epicardium
- Gliosis of the brainstem and central nuclei
- Pulmonary edema or intra-alveolar hemorrhage
- Pulmonary hemosiderosis has been described
- Histologic evidence of recent viral illness
- Extramedullary hematopoesis
- Increased amounts of brown fat in periadrenal adipose tissues

Manner

- SIDS is a death due to natural causes
- A second death in the same family can be ruled "manner undetermined"
- A third death in the same family is extremely suspect, and one or more of the infants' deaths are probably homicides

Inborn Errors of Metabolism Resulting in Sudden Death

- Disorders of β-oxidation of fatty acids
- Glycogen storage disorders
- Other disorders

Disorders of β-oxidation of Fatty Acids

- Fatty acids are an important source of energy for neonates
- Enzymes necessary to carry out β-oxidation can be developmentally immature and inadequate in the perinatal period
- Infants usually present with sudden death or hypoketotic hypoglycemia
- Collapse of metabolic pathways due to concurrent illness or physiologic stress can precipitate symptoms after depletion of hepatic glycogen stores
- Myopathy, cardiomyopathy, and liver dysfunction result from the accumulation of fatty acids in the mitochondria and microsomes
- Fatty changes of the liver are indistinguishable from Reye's syndrome

Specific Disorders

- Medium-chain acyl-CoA dehydrogenase deficiency (MCAD):
  - MCAD is the first step in fatty acid oxidation:
    - MCAD deficiency may represent 1–10% of SIDS deaths
    - Autosomal recessive disorder
    - Carrier rate may be as high as 1 in 50 people, resulting in an incidence of 1 in 2,500 to 1 in 7,000 individuals
    - Two known DNA point mutations at positions 985 (A to G) and 583 (S to A)
  - Diagnosis:
    - Elevated levels of cis-4-decenoic acid and

dodecanoic acid in postmortem fluids
  - Organic acid analysis in urine or vitreous fluid
  - Fatty acid oxidation assay in fibroblasts, liver homogenate, or cells obtained at amniocentesis

- Long-chain acyl-CoA dehydrogenase deficiency (LCAD):
  - Inability to metabolize fatty acids longer than 12–14 carbons
- Short-chain acyl-CoA dehydrogenase deficiency (SCAD):
  - Inability to metabolize fatty acids smaller than 6 carbons
- Multiple acyl-CoA dehydrogenase deficiency (MADD)
  - Inability to metabolize fatty acids regardless of length
- Disorders of carnitine metabolism:
  - Carnitine is a required co-factor of fatty acid oxidation
  - Low maternal carnitine can result in deficiency in the neonate
  - Sudden death has been reported in infants with carnitine deficiency in the plasma membrane
  - Carnitine palmitoyl trarisferase type I deficiency
  - Carnitine palmitoyl transferase type 11 deficiency
  - Camitine palmitoyl translocase deficiency
- Diagnosis:
  - Camitine levels in blood
  - Bile acylcarnitine levels
  - Palmitoyl-carnitine oxidation assay using cultured fibroblasts
  - Therapy for carnitine-related disorders
- Therapy for carnitine-related disorders:
  - Carnitine supplementation
  - Diet modification
- Glycogen storage disorders:
  - Myophosphorylase deficiency (McArdle's disease)
  - Glycogen storage disease 1a (Glucose-6phosphatase deficiency)
  - Glycogen storage disease 1b (Transport protein T1 deficiency)
  - Glycogen storage disease 1c (Transport protein T2 deficiency)
- Other disorders:
  - Lactic acidemias
  - Aminoacidopathies
  - Disorders of carbohydrate metabolism
  - Hyperglycinemia
  - Urea cycle defects

PHYSICAL INJURIES

Mechanical Trauma

- When force applied to any part of the body results in harmful disturbance of function or structure

Principles and Effects

Amount of Force

- Wound-producing capacity for kinetic energy is determined by weight and velocity:
  - Formula: $KE = MV^2/2g$:
    - M = weight (mass)
    - V = velocity
    - g = acceleration of gravity
- Kinetic energy of a moving object increases arithmetically with weight, but geometrically with velocity (example: doubling the weight of a bullet doubles the kinetic energy, but doubling the velocity quadruples the kinetic energy)
- Further energy may be present if a rotational component exists, again best demonstrated in bullets
  - Formula: $RE = Mr^2/2g$:
    - M = weight (mass)
    - r = cross-section radius
    - g = acceleration of gravity
  - Or $RE = IW^2/2g$:
    - I = rotational inertia
    - W = angular velocity in radians/second:
      - Or W = 2 x number of rotations/second
    - g = acceleration of gravity

Rate of Energy Transfer

- The shorter the duration of impact, the greater energy transfer and the greater the potential for injury

Surface Area

- The larger the area through which force is transmitted, the less the intensity and potential for injury

Target Area

- Some tissues are more fragile than other tissues and a fixed amount of force applied to one tissue may cause no injury versus the same force applied to another tissue

Local Effects of Mechanical Injury

- Hemorrhage:
  - Once bleeding begins, it will continue until thrombosis, vasoconstriction, or equalization of intravascular and extravascular pressure occurs
  - Rate of hemorrhage is important in which a slower rate of blood loss may allow the body to adapt and tolerate greater accumulations prior to symptomatic development versus rapid rate of accumulation in similar locations may be lethal (example: rapid accumulation of 150mL of blood in the pericardium or 50ml of blood in the intracranial cavity may be lethal)
- Aseptic inflammation: non-infected inflammatory response to injury
- Local infection when protective layer of tissue is injured; infectious agent may be carried into wound during traumatic event

Systemic Effects of Mechanical Injury

- Primary shock:
  - Reflex vasodilatation
  - Decreased blood pressure and loss of consciousness (examples: dilatation of rectum, puncture of pleura, pressure to carotid sinuses)
- Secondary shock:
  - Excessive reduction of blood volume (hypovolemic shock)
  - Hemorrhage necessary to produce circulatory collapse governed by rate of loss
  - 1/3 blood volume lost rapidly leads to hemorrhagic shock
  - 1/2 blood volume lost rapidly leads to death
- Shock injuries to organs:
  - Shock kidney: ischemic damage (shunting of blood from cortex to medulla)
  - Shock lung: hyaline membranes, alveolar and interstitial edema, and interstitial inflammation
- Embolism:
  - Thromboembolism
  - Thrombus may occur as a result of direct venous injury or stasis of blood flow from edema or inactivity
  - Thrombus may detach, resulting in fatal pulmonary thromboembolism
- Fat embolism:
  - Occurs with fracture of long bones and injury to adipose tissue
- Fat embolism syndrome:
  - Progressive pulmonary insufficiency
  - Petechial rash
  - Mental deterioration 1–3 days following injury
  - May have fever, tachycardia, and renal failure
  - Occurs in 90–100% of cases with major fractures, especially in motor vehicle collisions
  - Usually lethal when brain involved and with massive fat embolism to lung, AV anastomoses in lung, tearing of lung parenchyma, or interartrial or interventricular defect
- Air embolism;
  - Air entrance into dilated veins of gravid uterus during oro-genital intercourse or instrumentation, through incision or laceration of veins (especially neck region), disconnection of catheters, and intraoperative procedures of posterior cranial fossa
  - Air enters right side of heart, forming air-lock; X-ray of chest may reveal right heart filled with air
  - Air may enter left side of heart with injury to lung in which air may then embolize to cerebral or coronary artery

Blunt Force Injuries

Abrasion

- A superficial scrape or scratch injuring the upper layers of skin:
  - Types of abrasions:
    - Linear abrasion: a scratch
    - Friction abrasion: a brush burn, such as from dragging on a road surface
    - Graze: superficial skin injury from a projectile such as a bullet
    - Impact abrasion: can result in a patterned injury that provides information about the object that caused the injury
  - Abrasions can occur antemortem or postmortem:
    - Postmortem abrasions:
      - Lack the vital reactions such as hemorrhage, hyperemia, and edema that occur antemortem
      - Postmortem loss of epithelium will result in a dried, parchment-like, yellow-tan lesion
      - Postmortem abrasions in areas involved by dependent lividity must be carefully examined

Contusion

- An area of hemorrhage into the tissues causes tearing of blood vessels by blunt trauma

- May be larger or smaller than the impacting object
- May be difficult to see in dark-skinned persons
- A deep bruise may not appear on the body surface if death follows a short time after the injury
- A contusion may appear at a location other than a point of impact
- Contusions due to accidents usually involve protuberant or prominent parts of the body, especially areas overlying bone
- Patterned contusions can provide information about the object that caused the injury

♦ Dating of contusions:
- Contusions resolve from the center outward and from the periphery inward
- Contusions are often of different ages due to separate episodes of trauma
- The coloration of contusions can provide a crude approximation of their age, but contusions of the same age can vary in their degree of resolution in a single individual:
  - Colors and their approximate ages are as follows:
    - Red: immediate
    - Blue-purple: 1–4 hours
    - Green: 4–7 days
    - Yellow: 7–10 days
    - Return to normal coloration: 14–21 days
- Microscopy can be used to identify hemosiderin in an injury that is 24 hours old
- Iron stains are helpful in identifying hemosiderin in an injury
- Hematoidin requires several days to be detected

Laceration

♦ A tear produced by a blunt instrument:
- The edges of the tear have:
  - Abraded margins
  - Ragged edges
  - Tissue bridging of the defect by vessels, nerves, and connective tissue
- The tear is produced by stretching the tissues beyond their elastic tensile strength or crushing and forcible separation of the tissues during compression between two hard surfaces, such as a weapon and the bone underlying the skin

Fractures

♦ Broken bones due to blunt force injury:
- Fractures are produced by a combination of compressive, tensile, and shearing forces acting on the bone
- Special types of fractures:
  - Spiral fractures are due to a twisting motion applied to a long bone of an extremity, usually the legs
  - Bucket handle fractures result from pulling on an extremity and fracturing the bone through a growth plate or pulling off the bone attached to a tendon or ligament that supports a joint
  - Spiral fractures and bucket handle fractures in children are highly suggestive of child abuse

♦ Motor vehicle accidents can cause massive blunt force injuries
- The most common cause of death is head injury

♦ A special type of injury known as a "dicing" abrasion is produced by the tempered side window glass of an automobile:
- The tempered glass shatters into small cubes as it breaks and can cause a patterned injury on the side of the face that is nearest the tempered window
- The safety glass of the front windshield of an automobile is laminated between two layers of plastic
  - Windshields do not cause dicing abrasions

Head Injuries

♦ Blunt force injuries of the head result in several interrelated traumatic lesions

External Scalp Injuries

♦ Laceration
♦ Contusions
♦ Abrasions
♦ Thermal injuries

Subscalpular Hemorrhage

♦ Occurs directly beneath the area of impact
♦ May be larger or smaller than the impacting object
♦ Can result in hematoma formation
♦ Can occur in the setting of consumptive coagulopathy

Skull Fractures

♦ Fracture seen in 80% of fatal head injuries
♦ Bone is more susceptible to tensile than compressive stress
♦ Skull fractures may occur without significant brain injury

Types of Skull Fractures

♦ Linear Fractures:
- Local deformation by an intermediate-sized (>5 cm^2) object
- Originate in the inner table of the skull after tensile failure

- Depressed Fractures:
  - Result from impacts with small objects that have areas of impact <5 cm^2
  - Cerebral injuries often occur due to intrusion of bone into the cranial cavity
- Comminuted Fractures:
  - Multiple fragments result from high-energy impacts
  - Fractures radiate from the site of impact
- Diastatic Fractures:
  - Separation of cranial sutures >2 mm
  - Primarily seen in children
- Contrecoup Fractures:
  - Fracture of bone away from the blow due to forces transmitted from the site of impact to the thin bones of the skull
  - Can occur with large impact areas or impacts of a fixed skull
- Basilar Fractures:
  - Fractures of the floor of the skull involving the anterior, middle, or posterior cranial fossa
  - Lateral impacts produce side-to-side fractures
  - Frontal or occipital impacts cause sagittal fractures
  - Result from significant impact injury
- Ring Fractures:
  - Basilar fractures that circumscribe the foramen magnum:
    - Can be caused by a vertex impact or a fall onto the buttocks, resulting in axial loading of the floor of the skull
    - Implies significant impact injury

Intracranial Hemorrhages

EPIDURAL HEMORRHAGE

- Usually underlies the temporal bone
- 85% of patients with epidural hemorrhage have skull fracture
- Caused by laceration of vessels on the inner table of the skull, most commonly the middle meningeal artery and its branches
- Hemorrhage dissects the dura away from the inner table
- Hernatoma compresses the underlying brain
- Fatal cases have >75 ml of blood clot
- Death occurs due to increased intracranial pressure and herniation

SUBDURAL HEMATOMA

- Caused by disruption of bridging veins between the cortical surface and dural sinuses
- Usually caused by rotational injury
- Atrophy of the cerebrum increases the distance spanned by bridging veins and promotes the occurrence of subdural hematoma
- Blood spreads freely in the subdural space and often covers the entire hemisphere
- Slow accumulation of blood clot is tolerated much better than rapid accumulation with sudden increases in intracranial contents:
  - The volumes of subdural hematoma that accumulate slowly can be quite large
- Clinically significant acute hemorrhage is >50 ml in an adult and >30 ml in children
- 100 mL of blood clot is often fatal in normal adults
- In contrast to flattening produced by epidural hemorrhage, subdural hemorrhage preserves the outline of the gyri because the blood is distributed over the hemisphere
- Older patients and chronic alcoholics, both of whom develop cerebral atrophy, can tolerate larger amounts of subdural blood clot

Classification of Subdural Hematomas

- Acute subdural hematoma: blood and clot present for the first 48 hours
- Subacute subdural hematoma: a mixture of clotted and fluid blood is present for 2–14 days
- Chronic subdural hematoma: only fluid blood is present after 14 days
  - Chronic subdural hematomas can be a cause of dementia

Autopsy

- Liquid clot for the first 1–3 days
- At 4 days, there is non-uniform adherence of the clot to the dura
- Neomembrane is visible at 7–10 days and well developed in 2–4 weeks

Microscopic

- Dating of subdural hematomas is inaccurate after 1 month of age
- Neutrophils are present in the clot at 24–48 hours
- Edematous nuclei are present at the dural edge in 2–3 days
- Macrophage infiltration occurs in 2–5 days
- Erythrocytolysis occurs at 4–5 days
- Two to five fibroblast layers are present at 2–5 days
- Angiogenesis is visible by 1 week
- Giant capillaries are present at 2 weeks
- Arachnoid neomembrane develops at 2 weeks
- The inner and outer neomembranes are well developed at 4 weeks

- Hyalinization occurs at 1–3 months
- Secondary hemorrhages into a subdural hematoma occur from the thin-walled giant capillaries ~1 month after the original injury
- Growth of chronic subdural hematomas is secondary to repeat episodes of bleeding from the giant capillaries

SUBARACHNOID HEMORRHAGE

- Blood is present in the subarachnoid space following localized trauma
- Often accompanies cerebral contusions
- May be due to rotation of the brain in the subarachnoid space
- Death can occur from pure subarachnoid hemorrhage due to vasospasm or acute hydrocephalus
- Posterior fossa subarachnoid hemorrhage can result from vertebral artery laceration following relatively minor injuries
- Examination of the vascular system for aneurysm, vascular malformation, or vessel lacerations should be performed at time of autopsy
- Small lesions can be obscured by adherent clot following fixation

Cerebral Contusions

COUP CONTUSIONS

- Result from temporary deformation of the skull at the site of impact
- Occur in a head that is at rest relative to a moving object
- The skull impacts the tips of the gyri with destruction of the molecular layer
- An alternative theory proposes that there is a local suction effect following temporary deformation of the skull
- The term should only be used when skull fractures are absent at the site of impact

CONTRECOUP CONTUSIONS

- Contusions occurring distant from the site of impact
- Occur in a moving head, often as it strikes a fixed object
- Typically involves the inferior frontal and temporal lobes and the anterior tips of the frontal and temporal poles
- Often accompanies falls with occipital impacts
- Proposed mechanisms include:
  - Cushioning of the brain by cerebrospinal fluid accumulation as the inertia of the brain causes it to lag behind the moving skull as the skull impacts
  - The CSF cushion minimizes coup injury and the lack of CSF in the contrecoup areas opposite the impact maximizes the contact of the brain with irregular bony surfaces of the floor of the skull and the skull opposite the impact
  - The development of cavitation and negative pressure opposite the site of impact
  - Tensile strain of the contrecoup areas as the brain moves toward the site of impact

FRACTURE CONTUSIONS

- Injuries of the brain surface underlying skull fracture
- Can be remote from the site of impact if skull fracture is present

HERNIATION

- Produced by subfacial, transentorial, or cerebellar tonsilar herniation
- Can result from herniation related to cerebral swelling or transitory motion of brain structures

Diffuse Axonal Injury

Clinical

- Symptoms can vary from transitory loss of consciousness with concussion to irreversible coma
- The white matter, especially the corpus callosum, is most involved
- Ethanol intoxication increases the clinical severity of the head injury

Autopsy

- Hemorrhages of corpus callosum on one side of the midline
- Can involve the interventricular septum and fornix
- Hemorrhage of the superior cerebellar peduncle
- Cerebral edema
- Hemorrhage of the basal ganglia

Microscopic

- Axonal retraction balls are visible in the white matter using routine H&E and silver stains within 24 hours of injury
- Groups of retraction balls of similarly oriented axons may be seen
- Immunohistochemical stains can detect axonal injury within 1–2 hours (GFAP, beta-amyloid precursor protein, ubiquitin)
- Astrocytes or microglia proliferate after a period of weeks

Pathophysiology

- Caused by rotational acceleration or deceleration resulting in sheer strain characterized by the change in acceleration over time (dA/dt)
- Transection of the axon at the time of injury is not necessary

- Mild injury may be limited to transmembrane ionic disturbances in the axon, which will spontaneously recover
- More severe injury produces reactive changes that result in delayed axotomy (Wallerian degeneration)
- Damage to structural elements of cytoskeleton
- Swelling of mitochondria occurs followed by increases in axonal diameter
- Microtubules become misaligned and are damaged, halting antegrade or retrograde axonal flow of organelles
- Cytoskeleton can also disintegrate at the point of damage
- The axolemma separates from the myelin sheath
- Proteins continue to be transported from the cell body to the site of injury
- Axonal bulb or swelling develops and axotomy occurs (Wallerian degeneration)
- Calcium influx into leaking axolemma may be responsible for cytoskeletal collapse

Brainstem Avulsion

- Laceration of the brainstem or avulsion related to severe hyperextension of the head due to facial impact
- Most common is a pontomedullary tear
- Often accompanied by atlanto-occipital dislocation, ring fracture, or high cervical fracture
- Most commonly produced by motor vehicle accidents

Complications of Head Injuries

Hypoxic Ischemic Encephalopathy

- Occurs in 90% of head injury deaths
- The brain is particularly sensitive to hypotension and inadequate perfusion
- Hypoxia and hypotension combine to cause particularly severe ischemic injury
- Trauma may sensitize the brain to ischemia mediated by increased glycosis, increased extracellular glutamate, and potassium flux
- Other organ injuries such as acute lung injury, systemic hypotension, and anemia related to trauma contribute to the cerebral insult

Cerebral Swelling

- Localized swelling can occur due to hemorrhage or contusion
- Diffuse swelling can occur related to hypoxic ischemic insults
- Vasogenic edema with increased hydrostatic pressure and damage to the blood-brain barrier can occur
- A cytotoxic component due to membrane pump failure and glutamate accumulation following ischemia is present
- Cerebral swelling may be increased by reperfusion injury following the restoration of blood pressure

Fat Embolism

Clinical Symptoms

- Occur 1–4 days following injury:
  - Petechial rash
  - Respiratory distress
  - Neuroloaic deterioration

Autopsy Findings

- Petechial hemorrhages of white matter
- Necrosis of foci in cortex, cerebellum, and brainstem
- Atrophy of white matter with long-term survival

Microscopic Findings

- Intravascular fat present in tissues stained with fat stains (ORO)
- Perivascular hemorrhages and/or infarcts of white matter
- Perivascular infarcts of gray matter

Shaken Baby Syndrome (SBS)

- Major cause of fatal child abuse deaths due to head injury
- Mortality rate = 20–25%
- Most children <1 year of age and almost all cases <2 years
- The major problem is diffuse axonal injury following stretching and tearing of axons during vigorous shaking
- Vigorous shaking is shaking that occurs 2–3 cycles per second

Clinical

- Unconsciousness
- Coma
- Seizures
- Respiratory depression
- Bradycardia
- Xanthochromic spinal fluid
- Intracranial hemorrhage
- Other injuries of child abuse are often present

Autopsy

- Cerebral edema
- Subdural and/or subarachnoid hemorrhages
- Retinal hemorrhages are seen in 75–90% of cases
- Evidence of head impact or skull fractures need not be present
- Detachment of the retina may occur
- Neck injuries can be present

Microscopic

- Diffuse axonal injury
- Cerebral edema

Associated Injuries

- Rib fractures can be present laterally or posteriorly just lateral to the spine, caused by squeezing the child's chest during shaking
- Victims of shaken baby syndrome with a prolonged survival interval develop:
  - Cerebral fluid collections
  - Cerebral atrophy
  - Cystic encephalomalacia
  - Cerebral infarcts due to hypoxic ischemic damage related to cerebral edema and intracranial hemorrhage

Firearms Injuries

General Principles

- Firing progression:
  - Trigger pull: firing pin strikes cartridge case
  - Primer detonates: ignites gunpowder
  - Gunpowder combustion: gas production
  - Pressure formation: expulsion of bullet
- Handguns and rifle barrels have spiral grooves in interior with elevated area between grooves called "lands":
  - Lands impart spin to projectile
- Typical primer material includes lead styphnate, barium nitrate, and antimony sulfide

Handguns

Revolvers and Pistols

Bullet Caliber

- Bullet diameter measured in hundredths of an inch or millimeters
- May be small caliber: .22 and .25; medium caliber: .32, .38, .357, 9mm; or large caliber: .40, .41, .44, and .45

Cutaneous Entrance Wound

- Diameter of defect not directly comparable to caliber of bullet
- Abraded marcrin, occurs when bullet impacts skin
- If impact to skin is perpendicular, abrasion will be symmetrical and uniform
- When skin impact is at an acute angle, asymmetrical abrasion is widest on the side from which the bullet approached

Range of Fire

Terminology

- Soot: black carbonaceous particles of residue consisting of completely burned gun powder and vaporized metals from primer, bullet, and cartridge case, which has a black disk-like appearance
- Powder tattooing or stippling: larger particles, mainly consisting of burning, partially burned, and unburned gunpowder, but also metal shavings and other debris from barrel and cartridge case:
  - Numerous red-brown to orange-red punctate lesions

Contact Range of Fire

- Barrel tip in contact with skin surface
- Soot on skin and in wound track
- If tight contact, then the majority of soot in depth of the wound with cherry red discoloration of surrounding skin where carbon monoxide from combustion of gases binds to muscle to form carboxymyoglobin
- If loose contact, then prominent soot on skin surface

Close Range of Fire

- Soot and gunpowder stippling surrounding wound
- Soot generally travels no more than 6–8 inches

Medium or Intermediate Range of Fire

- Gunpowder stippling only, no soot
- Gunpowder stipples routinely 3–3½ feet, but certain gunpowder may travel farther

Distant Range of Fire

- No residue on skin
- Indicates barrel tip to skin distance of at least 3–3½ feet

Indeterminate Range of Fire

- Cannot determine range of fire because of interposed target between barrel tip and skin
- Example of interposed target: doors, windows, metallic wall

Cutaneous Exit Wounds

- Typically larger than entrance wound, but may be slit-like
- Rarely has abrasions, but if skin is supported by elastic bands of undergarments or firm external surface, then may have a "shored" abrasion

Gunshot Wounds of Head

- Entrance wound in skull has internal beveling (larger on internal table than outer table)
- Exit wound has external beveling (defect larger on outer table than inner table)
- With gunshot wound through skull, there is energy propagation through bone with orbital plate fracture and subsequent spectacle hemorrhage from dissection of blood, which spares the supraorbital ridge, differentiating it from a blunt force injury

Shotguns

- Smooth bore weapon; no lands and grooves
- May fire more than one projectile: single projectile, slug; multiple projectiles, buckshot or birdshot
- "Gauge": number of lead balls of a given diameter equal to one pound:
  - Example: 12 gauge = 12 spherical lead balls of a bore diameter of 0.729 inches equal to one pound
- Shotgun bore diameter can also be described in thousandths of an inch:
  - Example: .410:= "4–10"
- Choke describes constriction of muzzle end of barrel used to reduce pellet dispersion:
  - Ranges from full to none
  - Is determined as percentage of shot falling, in 30 inch circle when weapon fired at distance of 40 yards:
    - Full choke: 60–75%
    - No choke (cylinder): 25–35%

Range of Fire

- Contact: round defect with soot on skin and in depths of wound
- Barrel tip 1½–2 feet from skin surface: single defect
- Barrel tip 3 feet from skin surface: single defect with slight discontinuous irregular margin
- Approximately 3½–4 feet, barrel tip to skin: central defect with individual satellite perforations
- As barrel tip is farther withdrawn, get more individual perforations until only separate perforations and no single central defect
- Broad rule of thumb is for every 1 inch of pattern, you have up to 3 feet of distance from barrel tip to skin
- Wadding enters central defect up to 5–10 feet, then drifts laterally, striking the skin and creating an abrasion
- Wadding marks the skin up to 15–20 feet
- Soot will travel out to 1 foot
- Gunpowder will travel up to 2–3 feet

Ammunition

- Shotgun shells consist of a plastic or paper body (the tube), a brass head, cardboard or composite wads, and lead shot
- Wadding in birdshot loads: small
- Winchester: cupwad with plastic shot cup
- Remington: power piston
- Federal: plastic wad column
- Buckshot: have white filler material that surrounds shot, can impact skin, and must be differentiated from gunpowder stippling

Rifles

- Rimfire rifles can fire projectiles at relatively low velocity, as seen in handguns (650–1,400 feet/second)
- Center fire rifles can fire projectiles at high velocity (2,400–4,000 feet/second)
- By increasing velocity, the kinetic energy and wounding potential is markedly increased
- Center fire rifle ammunition may be subdivided into hunting type ammunition and fall jacketed ammunition
- The goal of hunting ammunition is to expend all of its energy so that it frequently does not exit body, but fragments inside; has a characteristic "lead snowstorm" X-ray pattern
- Full metal jacketed ammunition usually exits body without fragmenting and its goal is to injure the victim, but not expend all of its energy
- Temporary cavity may be large and organs not directly perforated may still be injured
- Entrance wound is typically small and round, similar to a handgun entrance wound
- Exit wounds are often large and irregular

Sharp Force Injuries

- Sharp vs. blunt:
  - Sharp: mechanically cuts and divides tissue to depth of object inserted
  - Blunt: crushes and tears tissue with bridging in wound depth

Incised Wound

- Caused by a sharp-edged object drawn over tissue
- Wound defect is longer on skin than it is deep
- Edges may be straight or jagged
- No marginal abrasion
- No tissue bridging
- Bleeding may be extensive
- Typically seen on head, neck, and extremities
- If the wound is on the neck or through visible large vein, then X-ray for embolism
- On margin of wounds, may see superficial parallel incisions, consistent with serrated knife

Stab Wound

- Caused by pointed or sharp object being forced into tissue in a thrusting manner
- Wound track is deeper than the surface defect is long
- No tissue bridging and no marginal abrasions, with the exception of possible hilt mark
- Skin surface may reflect characteristics of weapon: single or double edged, Phillips screwdriver, serrated knife

- Skin defect appearance variable due to orientation with respect to Langer's lines
- Death may be caused by exsanguination, infection, or air embolism
- X-ray for knife tip fragments
- Depth of wound not equal to length of blade: wound may be shorter due to partial insertion or longer due to compressibility of body, especially in the abdominal area

Chop Wound

- Caused by sharp heavy instruments: ax, hatchet, cleaver; intermediate between sharp and blunt force injuries
- Deep gaping wounds that may have deep bruising and fracture
- May have marginal abrasion and contusion

Defense Wound

- Occurs when one is defending one's self from assailant
- Usually seen on upper extremities
- Appearance of wound varies with weapon
- May be seen in both stab and incised wounds

Asphyxia

- A condition in which there is an absence or reduction of oxygen in body tissues and increased carbon dioxide tension

Autopsy

- Tends to be fairly classical and non-specific (may be seen in other causes of death as well):
  - Visceral congestion
  - Cyanosis
  - Petechiae
  - Fluidity of blood

Types of Asphyxia

Compression of Neck

HANGING

- Compression of neck by noose, with compression of arterial and venous blood supply to and from brain
- Suspension may be complete or incomplete
- Hanging is almost always suicidal and very rarely accidental or homicidal
- Consciousness lost rapidly

Autopsy

- Fractures uncommon, but increased in elderly with calcification of cartilage
- "Hangman's fracture": fracture of odontoid process of C2 with fragments of bone driven into medulla oblongata
- Hangman's noose: classic hangman's noose with knot on left side to throw head backward to fracture neck
- Crease or groove in neck where ligature is located is called a "furrow"
- Soft material may leave no furrow
- In dependent areas of body with gravitational effect, get lividity, punctate hemorrhages, and Tardieu spots

STRANGULATION

Ligature Strangulation

- Most common in females
- Vascular occlusion with loss of consciousness in ~10–15 seconds
- Ligatures include electrical cords, telephone cords, sheets, and neckties

Autopsy

- Marked congestion about ligature; confluent scleral hemorrhages with conjunctival petechiae; furrow when present is usually horizontal and below the thyroid cartilage
- May get fracture of thyroid and hyoid cartilage

Manual Strangulation

- Compression of internal structures of neck by hands or forearms
- Compression of blood vessels with rapid loss of consciousness
- All manual strangulations are homicides

Autopsy

- Petechiae of sclerae, conjunctivae, and face, with cyanosis above level of compression
- Usually, hemorrhage is located in neck musculature and sometimes there are fractures of hyoid bone and thyroid cartilage (usually over the age of 30)
- Frequently see abrasions and fingernail marks on skin
- Victim is usually female
- Sexual assault should always be considered in manual strangulation
- Note: Petechiae is not confined to strangulation and may be seen in asphyxial deaths, heart failure, vomiting or coughing, and postmortem lividity in prone position

CHOKE HOLD (SHIME-WAZA)

- Also called bar arm control
- Forearm is placed against the front of the neck with force applied in a front to back direction, causing compression of the neck
- This is used to occlude the upper airway and carotid artery
- Excessive force can distort the larynx, leading to fractures of the larynx and, in some cases, the hyoid bone

- Carotid sinus stimulation may occur, leading to arrhythmia and death

Carotid Sleeper Hold (Carotid Take Down Hold)

- Symmetrical force is applied by the forearm and the upper arm to the side of the neck, such that the compression is on carotid arteries and jugular veins and not the larynx
- Consciousness is lost in 10–15 seconds
- Blood flow to the brain is decreased 85%
- May cause stimulation of carotid bradycardia and there may be increased catecholamines and arrhythmia that can lead to death if compression of arteries and veins is prolonged

Autoerotic Asphyxia

- Asphyxia by compression of the neck induced to enhance sexual enjoyment, usually during masturbation
- Almost always male
- Scene investigation: typically, the male is found nude or wearing female clothing, in a private area, and bound with a rope around the neck
- Virtually always has an escape mechanism in place
- Frequently, pornographic literature surrounds the scene
- Death typically occurs when there is a miscalculation of timing during the act of sexual gratification in which consciousness is lost and death occurs
- Investigation is important to ensure that these cases are not certified as suicide

Obstruction of Airway

Smothering

- A mechanical obstruction or occlusion of external airway (nose and mouth)
- Usually homicide or suicide
- Most common suicidal smothering is a plastic bag over the head

Autopsy

- Non-specific, often without petechiae
- Accidental smothering occurs when an infant is trapped between a small mattress and railing, with face against mattress
- Gags can cause smothering, obstructing airway and swelling by saliva, creating a greater obstruction (even though unintentional, this is homicide)
- Most homicidal smotherings occur in the very young, very old, debilitated, or incapacitated by disease or drugs

Entrapment (Environmental Suffocation)

- Smothering in which individual is located in a confined space and uses all of oxygen
  - Example: child in refrigerator
- May also occur when an individual enters an area with a deficiency of oxygen (example: excessive carbon dioxide in underground wells produced by plants that produce C02 and deplete oxygen)

Autopsy

- Non-specific

Obstruction of Airway by Foreign Material (Choking)

- Caused by obstruction of air passages
- Most are accidents that occur in children aspirating foreign bodies (e.g., balloons, buttons, pen tops, peanut butter, and hot dogs)
- May occur homicidally with gags in oral airway
- In adults, airway obstruction frequently involves food
- In neurologically impaired or acute intoxication (with alcohol or drugs), food lodges in larynx and the individual cannot breathe
- Cafe coronary: individual eating in restaurant suddenly stands up and collapses:
  - CPR performed with the idea that this is of cardiac origin
- Small amount of food in airway at autopsy is not indicative of choking; individuals aspirate food agonally in cardiac arrest (20–25%)
- Food must be bolus in larynx, or, if aspiration of food, must extend from larynx to main bronchi, with complete obstruction by food
- Aspiration of food seen in neurologically impaired, intoxicated, and schizophrenics

Swelling of Airway

- Occurs in acute inflammatory processes with subsequent swelling and obstruction of airway
- Acute epiglottitis
- Clinically have sore throat and hoarseness, with difficulty swallowing
- Can get rapid airway obstruction and need a tracheal tube or tracheostomy
- Haernophilus influenzae most common cause in both children and adults

Autopsy

- Large edematous epiglottis with soft tissue obstructing airway
- Neoplasms of larynx (polyps or cancer)
- Diphtheria
- Asthma (see previous description)

Mechanical Asphyxia

Traumatic Asphyxia

- Almost always accidental
- Occurs when a large weight falls or compresses the chest or upper abdomen, making respiration impossible

- Most common when a car jack slips on an individual repairing a car, causing the vehicle to fall on top of the victim

Autopsy

- Purple to blue-black congestion of head, neck, and upper chest, with numerous petechiae of sclerae, conjunctivae, and periorbital skin
- Retinal hemorrhages may occur
- Also seen with constricting snakes

POSITIONAL ASPHYXIA

- Associated with intoxication by alcohol or drugs
- Individual falls into a confined area and, due to intoxication, is unable to extricate him- or herself
- By virtue of body position, is unable to breathe and, therefore, dies

Autopsy

- Congestion
- Cyanosis
- Petechiae

CHEMICAL ASPHYXIA

- Death not due to toxicity of gas, but to displacement of or inability to use oxygen

Carbon Dioxide

- Non-toxic and odorless
- Located in sewers, mines, and underground wells
- Death due to hypoxic environment and lack of oxygen

Methane

- A component of natural gas
- Sewers and mines:
  - Toxicology is –
  - Rarely does autopsy reveal cyanosis
  - Environment must be analyzed to determine what gases are present

Hydrogen Cyanide

- Prevents utilization of oxygen at cellular level
- May be either potassium or sodium cyanide
- Rapid-acting poison
- Cyanide binds to the ferric ion atom of the intracellular cytochrome oxidase
- Cyanide deaths are usually suicide and usually by persons who have availability of cyanide at place of employment (chemists, photographers, engravers)
- Hydrogen cyanide used for execution in gas chamber

Autopsy

- If taken orally, the body and stomach contents may smell like bitter almonds
- Ability to smell cyanide is genetic, most persons cannot smell it
- Gastric mucosa and livor mortis are bright red due to excessive oxyhemoglobin
- If inhalation of hydrogen cyanide, the livor mortis and blood are bright red
- If cyanide is present, it will decrease postmortem
- In decomposition, cyanide can be produced by bacteria

Hydrogen Sulfide

- Produced by fermentation of organic matter
- Found in sewers, sewage plants, cesspools, and oil and chemical industries
- "Sewer gas": hydrogen sulfide, carbon dioxide, and methane
- Deaths from hydrogen sulfide are usually accidents
- Smell of rotten eggs

Autopsy

- May get formation of methemoglobin
- Dark colored blood
- Organs may have green to blue-green appearance

Carbon Monoxide

- Colorless, odorless, and tasteless
- Sources: fires, automobile exhaust, defective heaters, incomplete combustion of burning product
- Produced whenever materials are burned with inadequate oxygen to produce complete combustion
- Get tissue hypoxia and competes with oxygen for binding sites on oxygen carrying heme proteins (hemoglobin, myoglobin, cytochrome C oxidase, cytochrome P-450)
- Carbon monoxide has 250–300 times greater affinity for hemoglobin than oxygen
- Smokers have regular levels of carboxyhemoglobin of ~3–6%
- Number one source of carbon monoxide in fatalities is fire
- Number two source of carbon monoxide in fatalities is inhalation of exhaust fumes
- Symptoms of carbon monoxide poisoning:
  - 0–10%: generally no symptoms
  - 10–20%: headache and weakness
  - 30–40%: severe headache, dizziness, nausea, and vomiting
  - 40–50%: slurred speech, blurred vision, stupor, difficulty breathing
  - >50%: comatose, respiratory failure, and death in pre-existing disease or elderly; carbon monoxide as low as 20–30% may be fatal
  - House fire carbon monoxide averages 50–60%
  - Car exhaust fatalities average 70%

Autopsy

- Cherry red livor mortis
- Common lesion, if survival, is bilateral necrosis of globus pallidus (non-specific)
- Brain is sensitive to effects of carbon monoxide
- Half-life elimination of carbon monoxide with 100% oxygen is 90 minutes
- Flash fire: can see rapid combustion of fire, such as from gasoline in which motor vehicle explodes and incinerates
- Individuals may not have significantly elevated carbon monoxide levels

Drowning

- Submersion in liquid and irreversible cerebral hypoxia
- Volume of water inhaled can range from small to large

DRY DROWNING

- 10–15% of all drownings get:
  - Small volume of water inhaled
  - Laryngospasm prevents further water from entering airway
  - Non-demonstrable at autopsy
- Most cases get inhalation of large volume of water in process of drowning
- Type of water inhaled has little to do with drowning:
  - Fresh water alters or denatures surfactant
  - Salt water dilutes or washes surfactant away

NEAR DROWNING

- Submersion victim is transported to hospital and survives for ~24 hours
- Rare instances get prolonged survival in cold water, especially in children

Autopsy

- No specific findings
- Diagnosis of exclusion
- Submersion wrinkling (washerwoman's hands, 1–2 hours in water)
- Edema fluid in mouth and airways
- Heavy lungs with edema fluid and foam cone in trachea and bronchi
- May have hemorrhage in petrous temporal ridge or mastoid bone
- Occasionally have right ventricular dilation
- No drowning test exists

DROWNING IN BATHTUBS

- Seen in children
- Seizure disorders
- Cardiac arrythmia
- Drug overdose
- Must rule out natural death with subsequent submersion and body dumped into water after death

SCUBA DIVING

- Most common cause of death is drowning
- May get carbon monoxide in tanks that is mixed with air from gasoline-driven compressors
- With rapid ascent to surface, may develop air embolism, pneumothorax, or interstitial emphysema

Atmospheric Pressure Changes

- Gas volume increases with decreased barometric pressure
- Solubility of gas in liquid (e.g., blood) is proportional to partial pressure of gas in ambient atmosphere
- Injurious effects are dependent on three characteristics when atmospheric pressure is abnormal:
  - Direction and magnitude of change
  - Rate of change
  - Duration of change

Decreased Atmospheric Pressure

- Lowering of pressure by as little as 50% can result in significant systemic hypoxia leading to death
- Increase in atmospheric pressure is tolerated better than decrease
- Hypoxia from decreased pressure results in significant shifting of blood volume to pulmonary system from peripheral vasoconstriction
- Develop pulmonary arterial hypertension and damage to capillary endothelium and alveolar pneumocytes

Acute Mountain Sickness

- Majority occurs when there is ascension rapidly to elevations >2,500 meters (8,200 feet)
- Symptoms include headache, nausea, vomiting, and insomnia
- May become life-threatening when develop acute high-altitude pulmonary edema and cerebral edema
- Usually develops first 8–24 hours at high altitude
- In addition to lower oxygen tension, also have lower environmental temperatures, increased ultraviolet radiation, and decreased humidity and get hyperventilation, dehydration, and hypokalemic alkalosis
- Hypobaric dysbarism (Aviator's Bend's)

Autopsy

- Congested lungs and interstitium with prominent alveolar edema and hyaline membranes
- Retinal hemorrhage and cerebral edema may also occur
- May also develop sickle cell crisis in persons with hemoglobin SC and sickle thalassemia

- Symptoms have been seen in pilots, especially early on with the advent of flight to heights capable of creating hypobarism

Increased Atmospheric Pressure

- Injuries occur on return from elevated to normal barometric pressure
- Rate of change of atmospheric pressure important in injury production
- Unless pressure is lowered slowly to normal, decompression sickness (dysbarism, Caisson disease, the bends, staggers, or chokes) can occur
- With increase in atmospheric pressure, get net flow of nitrogen (4/5 of air) from alveoli through blood in which gas dissolves into tissue
- Upon return to normal pressure, rapid gas bubble formation develops in tissue and blood because nitrogen forms faster than can be transported to lungs for expiration
- Ocean surface under pressure of 1 atmosphere
- Every 33 feet descended adds 1 additional atmosphere of pressure

Acute Decompression Sickness

- Associated with Henry's law in which rapid ascension with inability to exhale rapidly leads to accumulation of gas bubbles with mediastinal interstitial emphysema, subcutaneous emphysema, pneumothorax, and, in some cases, air embolism
- May get arterial gas embolism from ruptured alveoli, which may lodge in cerebral vessels with symptoms ranging from focal neurologic deficits developing hours after dive to rapid collapse and unconsciousness immediately after surfacing
- Females and obese predisposed
- Fatalities most associated with pulmonary and central nervous system (CNS) involvement
- Chronic complications of decompression sickness characterized by demyelination of dorsal and lateral columns of thoracic spinal cord

Barotrauma

- Associated with Boyle's law and due to failure of a gas-filled space to equalize its internal pressure to that of the outside environment
- Effects are most severe in cavities within bone that cannot expand or contract
- Barotrauma of middle ear is most common disorder in divers; may lead to pain and conduction hearing loss due to rupture of the tympanic membrane
- Barotrauma of inner ear may lead to sensorineural hearing loss and tinnitus
- Barotrauma of paranasal sinus is the second most common disease of divers, especially in frontal sinus:
  - May be associated with chronic dysfunction of sinuses with either anatomic abnormalities or chronic allergies

Thermal Injuries Related to Temperature Changes

- General principles:
  - Narrow range of internal temperature must be maintained:
    - Increase in tissue temperature more likely to cause injury than decrease
    - Cellular injury or death occurs if tissue temperature is maintained at a level >5° Centigrade above or >15° Centigrade below that which is normal for blood
    - Skin is principal site of heat loss or heat gain
  - Heat load = heat generated from oxidation of metabolic products + heat acquired from environment:
    - Normal body temperature = 98.6° Fahrenheit (37° Centigrade) orally
    - 1° Fahrenheit (0.6° Centigrade) higher rectal
    - Temperature variations by age, time of day, physical exertion (exercise may increase temperature 3–4°)
  - Newborn and elderly have temperatures 1° centigrade higher
  - Heat loss occurs from four mechanisms:
    - Conduction
    - Radiation
    - Evaporation
    - Convection

Local Hypothermia

- Localized injury from cold classified as immersion foot or frostbite:
  - Immersion (or trench) foot occurs with prolonged exposure to wet and cold, non-freezing conditions:
    - Primary injury is neuromuscular, resulting from ischemic tissue injury
  - Frostbite: exposure to freezing conditions involving damage to the skin and vasculature:
    - Get vasomotor alterations, aggregation, and stasis of erythrocytes leading to vascular obstruction
    - Typically involves exposed body surfaces, most prominently those farthest away from central circulation (ears, nose, and extremities)
    - May be superficial, involving the skin, or may cause gangrene of deep tissues

Systemic Hypothermia

- Results when heat loss exceeds heat production and allows body temperature to fall below 95° Fahrenheit:

  - Heat loss expedited by decreased humidity, wetness or immersion, or wet clothing
- Three stages of hypothermia:
  - Sensation of cold and shivering: body approximately 90° Fahrenheit
  - Stage of depression with developing bradycardia, hypotension, and bradypnea: body temperature 75–90° Fahrenheit
  - Cessation of thermal regulatory control: body temperature <75° Fahrenheit
- Unconsciousness develops at ~86° Fahrenheit
- Cardiac dysrhythmias common with ventricular fibrillation developing at core temperature of 77–82° Fahrenheit

Immersion Hypothermia

- More rapid loss of heat in water than in air:
  - Water temperature 4–9° centigrade = death in 70–90 minutes
  - 0° Centigrade = fatalities in $^1/_2$ hour
  - In water temperatures >70° Fahrenheit, survival time depends solely on the fatigue factor of the individual
  - When individuals die within 10–15 minutes after entry into frigid water, death is, apparently, not related to reduced body temperature, but to shock of rapid entry into cold water

Wind Hypothermia

- Body will lose heat more rapidly with increasing wind velocity
- Infants are more susceptible to hypothermia than adults (greater surface area to body mass)

Paradoxical Undressing

- Term employed when individual is found undressed in cold environment, believed to be caused by hallucination of warmth due to paralysis of thermal regulatory system

Hide and Die Syndrome

- Seen in elderly, paradoxical undressing: hidden in closets, cupboards, etc.
- Most cases of hypothermia involve elderly or people under the influence of alcohol:
  - Other predisposing conditions: infancy, exhaustion, or debilitating disease or injury
  - May also be associated with disease processes such as myxedema and sepsis

Autopsy

- No pathognomic findings of hypothermia
- If rapid death, usually no findings except cherry-red discoloration from retained oxyhemoglobin
- If prolonged survival, then may develop thromboses; pancreatitis; ulceration and hemorrhage of stomach, ileum, and colon; and bronchopneumonia

Local Hyperthermia (Burns)

- Inverse relationship between intensity of thermal exposure and amount of time required to produce burn (e.g., higher the temperature, the shorter duration of exposure necessary to create injury)
- Earliest evidence of hyperthermal injury is capillary dilation with increased capillary permeability and eventual capillary leakage
- Cutaneous burns may be identified as first, second, or third degree or as partial thickness or full thickness:
  - First-degree burn (e.g., sunburn)
  - Second-degree burn involves vesication or blister
  - Third-degree burn: scar formation in repair
  - Fourth-degree burn: charring
  - Partial thickness: no permanent damage to dermis; includes both first- and second-degree burns; regeneration of epithelium (second-degree burn) from margins of burned area and underlying hair follicle
  - Full thickness burns: damage to dermis and adnexal structure including hair follicles (third degree); form scar
- Get secondary shock with extensive burns due to loss of plasma at injury site
- Get bacterial infection where tissue sloughed
- Other complications include phlebothromboses, ulcers of stomach and small intestine (Curling's ulcer), renal failure, and inhalation damage (when associated with fire)
- Estimation of total body surface area: "Rule of 9s":
  - Head: 9%
  - Upper extremities: 9% each
  - Front of torso: 18%
  - Back: 18%
  - Each lower extremity: 18% (front and back)
  - Neck: 1%
- Household fires rarely exceed 1600° Fahrenheit:
  - Cremation at 1800–2000° Fahrenheit for $1^1/_2$–$2^1/_2$ hours

Smoke Inhalation

- Get cherry red lividity
- Soot in nares and oral cavity and may coat larynx, trachea, and brochi
- Absence of soot does not preclude carbon monoxide inhalation
- Cyanide produced in burns from synthetic substances only rarely contributes to death

- In fourth-degree charring, may see "pugilistic attitude" with boxer appearance of arms secondary to contraction of muscles of upper extremity
- "Fire epidural hematoma": postmortem artifact with fairly large aggregate of chocolate-brown dried blood overlying frontal, parietal, and temporal areas

Systemic Hyperthermia

- Failure of thermal regulation and may occur if exposed to significant heat from environment or inability of body to eliminate heat from metabolic processes

Mechanism of Heat Loss

Radiation

- Heat loss via energy emission from skin surface (65% of body heat loss)

Convection

- Cooling by air current (12–15% body heat loss)

Conduction

- Direct contact with cooler surfaces (very little heat loss)

Evaporation (Perspiration)

- Only heat loss mechanism that works when ambient temperature exceeds 92° Fahrenheit
- Amount of sweat vaporized is limited by ambient humidity
- Transpiration heat loss through exhaled water vapor (dissipates 5% of body heat)
- Important mechanism of heat loss in animals
- Functionally elevated temperatures lead to generalized vasodilatation, rapid pulse, and stimulation of respiratory centers

Heat Stroke

- Uncontrolled overproduction of body heat or impairment of body's ability to lose heat
- Commonly occurs in spell of hot (>90° Fahrenheit) humid weather
- Predisposing conditions include old age; cardiovascular disease and other debilitating conditions; skin disorder; medications including neuroleptic, diuretic, and anticholinergic or anesthetic agent; alcoholism; disorders with impaired heat loss; and failure to curtail physical activity
- Also increased risk in healthy young people, especially military recruits, laborers, and athletes who overexert themselves in hot, humid weather:
  - Especially prominent in individuals with sickle cell trait
- Environmental factors contributing to heat stroke include poor ventilation, residence of upper floors of buildings, and closed automobiles in direct sunlight
- Individuals >65 have 10–12 times risk of heatstroke as compared to younger adults

Autopsy Findings

- Nonspecific
- If survive following hyperthermia, may get complications, including pneumonia, renal failure, hepatic failure, and sepsis

Malignant Hyperthermia

- Drug-induced syndrome occurring during and after administration of general anesthesia
- Characterized by increased oxygen consumption and rapid rise in temperature
- Genetic predisposition that allows release of calcium from smooth endoplasmic reticulum with overload of calcium in mitochondria
- Previously associated with haloliane and succinylcholine
- Symptoms include tachycardia, hyperthermia, rhabdomyolysis, and skeletal muscle rigidity

Neuroleptic Malignant Syndrome

- Seen in individuals on antipsychotic medication, most notoriously phenothiazine therapy
- Estimated between 0.5–1% of patients exposed to neuroleptic
- Young men predominate
- Predisposing factors include physical exhaustion, dehydration, organic brain disease, and long-acting deponeuroleptic drugs
- Clinical symptoms include hyperthermia, hypertonicity of skeletal muscles, and fluctuating consciousness with instability of autonomic nervous system
- Mortality ranges from 20–30%
- Causes of death include respiratory failure, cardiovascular collapse, renal failure, arrhythmias, and thromboembolism (if prolonged survival)
- Respiratory failure may result from aspiration pneumonia
- May see in Parkinson's patients with sudden discontinuation of medication

Electrical Injuries

General Concepts

- Degree of injury dependent on:
  - Voltage of current
  - Type of current
  - Resistance at point of contact
  - Location of current path, critical
  - Duration of current
  - Body must complete a circuit between two conductors
  - Death may be produced with low voltage from alternating current (46 and 60 volt)
  - Any voltage >25 should be considered potentially lethal

  - Alternating current is more dangerous than direct current
  - Voltages <220 tend to fibrillate heart without affecting respiratory center
  - Voltages >1000 tend to produce paralysis of respiratory center without affecting heart
- Amount of current: C = V/R:
  - C = Current in amperes
  - V = Potential in volts
  - R = Resistance in ohms (body's opposition to flow of current)
- Effective current dependent on resistance of tissues involved:
  - Callused, thick skin may reach resistances of 1 million ohms or more
  - Wet or moist skin may have resistance of 1000 ohms
- More prolonged contact, more serious effect
- $^2/_3$ of electrical injuries occur at work (usually linemen or construction workers in contact with high-voltage power line):
  - Remaining $^1/_3$ occur in residences with low-voltage current
- 5% of all admissions to burn hospitals are related to electrical injury

Electrical Injury

- Greatest resistance to flow of current is skin
- Electrothermal injury limited to skin
- Death occurs from primary fibrillation of the heart
- Failure of respiratory center from fibrillation with paralysis of respiratory center or prolonged fibrillation of respiratory muscle

Autopsy

- Small, circumscribed, indurated lesion, central necrosis, and "nuclear streaming" of dermal nuclei
- High-voltage burns: large area of contact with deep charring injuries, even amputation of extremities
- May get coagulative necrosis of muscle nerve and skin, with thrombosis of blood vessel and eventual renal failure
- Heart and central nervous system: arm to arm conduction involves heart; head to foot conduction involves nervous system and heart
- Small current through chest can be fatal; large current through extremity alone may have limited effect

Lightning

- Typical lightning discharge occurs during storms, but may occur with clear skies; most commonly occurs in afternoon
- Highest conductor of electricity preferentially stuck includes trees, poles, antennae, pylons, and unprotected buildings
- Geographic features predisposing to strikes include caves, fissures, faults, metallic oars, and natural radioactivity
- Humans most exposed live on mountain or work outdoors (e.g., farmers or herders)
- Lightning may strike directly (entering through head or arm) or indirectly:
  - Direct strikes also occur in the open when carrying something metallic, such as umbrella, golf clubs, jewelry, or hearing aids
  - Indirectly as victim is secondarily struck following primary strike of tree or another person
- Effects of lightning depend on nature of strike (direct or indirect), intensity of current, time spent through body, pathway taken, and activity of person at time of strike
- Lightning may depolarize the entire myocardium or cause fracture or rupture of blood vessels and viscera
- If survive strike, victims may develop complications, including cardiac arrhythmias, infarction, cataracts, and renal failure
- Skin may show arborescent cutaneous hyperemia known as ferning or lightning print

TOXICOLOGY

Alcohols and Acetones

Ethanol (Drinking Alcohol)

- Source:
  - Beer: 3–6% ethanol content
  - Wine: 6–12% ethanol content
  - Distilled liquor: 20–85% ethanol content
  - Trace endogenous production
  - Cough syrup, mouthwash, and solvents contain ethanol
- Metabolism:
  - Absorbed from stomach and small intestine
  - Metabolized in liver to acetaldehyde and acetic acid
  - Elimination of alcohol: .015 g/dL per hour–.02 g/dL per hour
- Toxic effects:
  - Central nervous system: respiratory depression (lethal concentration ~0.4 g/dL, some survivors have had levels above this), Wernicke Korsakoff syndrome, delirium tremens
  - Liver: steatosis, cirrhosis, and hepatitis
  - Heart: cardiac arrhythmia and cardiomyopathy

Methanol (Wood Alcohol)

- Source:
  - Solvents, fuel, antifreeze, trace endogenous production
- Metabolism:
  - Methanol metabolized to formaldehyde, which is metabolized to formic acid
- Toxic effects:
  - Central nervous system depressant, blindness, acidosis
- Lethal dose = 100–200 mL

Isopropyl (Rubbing Alcohol)

- Source:
  - Solvents, rubbing alcohol
- Metabolism:
  - May be absorbed through skin or orally ingested:
    - Isopropanol is metabolized to acetate and formate
    - Acetone may be present in blood and urine (glucose will not be elevated)

Acetone

- Source:
  - Fingernail polish remover, solvent, small amount of endogenous production
- Metabolism:
  - Ingested and absorbed, acetone metabolized to acetate, formate, and isopropanol
- Toxic effects:
  - Acidosis, endogenous level may also be associated with ketoacidosis

Ethylene Glycol

- Source:
  - Antifreeze
- Route:
  - Ingestion
- Metabolism:
  - Many compounds including oxalate
- Toxic effects:
  - Central nervous system depressant, acidosis, and renal failure
- Unique pathologic findings:
  - Calcium oxalate crystals (kidneys and central nervous system)
- Lethal dose = 100 mL

Cocaine and Cocaethylene

Cocaine

- Source:
  - Erythroxylon coca plant
- Route:
  - Injection, snorting, sniffing, and ingestion
- Metabolism:
  - Metabolizes to three different compounds:
    - Benzoylecgonine, norcocaine, and ecgonine methyl ester
      - Benzoylecgonine and ecgonine methyl ester will metabolize to ecgonine
      - When alcohol is present, cocaine combines with ethanol to form by-product cocaethylene
- Active metabolites:
  - Norcocaine and cocaethylene
- Half-life:
  - Cocaine: $^1/_2$–$1^1/_2$ hours
  - Benzoylecgonine: 5–10 hours
  - Cocaethylene: 1–2 hours
- Mechanism:
  - Blocks re-uptake of sympathomimetic neurotransmitters into nerve terminal
- Biological effects of cocaine:

  - Increased blood pressure, heart rate, body temperature, and respiration
  - Dilated pupils
  - Anxiety, talkativeness, agitation, hyperactivity, and mood swings
  - Central nervous stimulation followed by central nervous depression
  - Addiction, tolerance, and withdrawal
- Toxicity:
  - Cardiovascular: arrhythmia, hypertension, myocardial infarction
  - CNS: seizures, strokes, psychosis
- Autopsy:
  - Hypertrophic heart, scarred injection sites, intravenous "drug tracks"
- Microscopic:
  - Myocardial fibrosis, pulmonary hemorrhage, and giant cell reaction in skin
- Lethal dose: variable
- Blood should be placed in sodium fluoride tubes to inhibit plasma esterases

Cocaethylene

- Source:
  - Only metabolite formed from a combination of cocaine and ethanol
- Metabolism:
  - In vitro studies found that conversion occurs in liver by nonspecific carboxylesterase, which catalyzes the transesterification of cocaine to cocaethylene
- Effects:
  - Increase of blood pressure and pulse
  - Improvement in psychomotor performance
  - More pleasant euphoria
  - Increases in plasma norcocaine concentration
  - Longer half-life
- Toxicity:
  - Greater cardio-toxicity than cocaine

Opiates

- Source:
  - Oriental poppy (Papver Somniforum)
- Drug of abuse:
  - Heroin
- Prescription drugs:
  - Morphine, hydrocodone, methadone, and codeine
- Route:
  - Injection, ingestion, and smoking
- Metabolism:
  - Heroin metabolized rapidly to 6-monoacetylmorphine, which is metabolized to morphine
- Half-life:
  - Heroin: 5 minutes
  - 6-monoacetylmorphine: 15–45 minutes
  - Morphine: 1–7 hours
- Physiologic effects:
  - Analgesia, euphoria, drowsiness, respiratory depression, pinpoint pupils, antitussive, hypotension, and lower seizure threshold
- Toxicity:
  - Central nervous system depressant and respiratory depressant
- Autopsy:
  - Needle tracks, skin popping, foam cone in airway
- Microscopic:
  - Foreign body granulomata in both skin and lungs
- Lethal levels: variable
- Mechanism of action:
  - Bind to opiate receptors in thalamus, limbic system, substantia gelatinosa, periaqueductal gray, blocks nociceptive (pain) reflexes

Amphetamines

- Source:
  - Drugs of abuse including designer drugs, amphetamine, methamphetamine, MDA, and MDMA
- Route:
  - Ingestion, injection, and smoking
- Physiologic effects:
  - Stimulation, sympathomimetic, and anorectic
- Metabolism:
  - Methamphetamine metabolizes to amphetamine, which metabolizes to norephedrine
- Toxicity:
  - CNS and behavior changes
  - Cardiovascular system, arrhythmias, and hypertension
- Lethal level: variable
- Mechanism:
  - Sympathomimetic
- CNS effect through antiserotonin action

Barbiturates

- Source:
  - Abusive use of medication (e.g., phenobarbital, secobarbital, and amobarbital)
- Route:
  - Ingestion, injection, drug rarely abused nowadays

- Physiologic effects:
  - Sedative-hypnotic, anticonvulsant
- Metabolism:
  - P-hydroxylation and conjugation in liver
- Toxicity;
  - Central nervous system: hypersensitivity
- Autopsy;
  - Barbiturate "blisters" (6–9% of acute barbiturate intoxication)
  - Globus pallidus necrosis (nonspecific)
- Lethal level:
  - Long-acting, barbiturates 8 mg/dL
  - Short-acting, 3.5 mg/dL
- Mechanism of action:
  - CNS depressant

Psychoactive Drugs

Lysergic Acid Diethylamide (LSD)

- Source:
  - Drug of abuse
- Route:
  - Ingestion
- Physiologic effects:
  - Hallucination, flashbacks, recurrent episodes of acute intoxication after days or weeks of abstinence, psychosis, and hyperthermia
- Metabolism:
  - Biotransformation by N-demethylation, N-deethylation, and hydroxylation
- Toxicity:
  - CNS behavioral effects
- Mechanism of action:
  - CNS effect through antiserotonin action

Phencyclidine (PCP)

- Source:
  - Drug of abuse
- Route:
  - Ingestion, injection, smoking, and snorting
- Physiologic effects:
  - Hallucinations, lethargy, hypertension, and decreased respiratory rate
- Toxicity:
  - CNS behavioral effects, respiratory depression, sudden death
- Metabolism:
  - Oxidative metabolism to two inactive metabolites
- Mechanism of action:
  - Blocks dopamine uptake and release of stored catecholamines

Marihuana

- Source:
  - *Cannabis sativa* plant
- Route:
  - Smoking and ingestion
- Active component:
  - Tetrahydrocannabinol (THC), stored in adipose tissue
- Metabolism:
  - THC (active) is metabolized to 11-hydroxy-THC (active) and 8-hydroxy-THC (active)
    - 11-hydroxy-TH metabolized to 11-carboxy-THC (inactive)
    - 8-hydroxy-THC metabolized to 8,11-dihydroxy-THC (inactive)
- Physiologic effects:
  - Euphoria, lethargy, drowsiness, anxiety, paranoia, and psychosis
- Toxicity:
  - Rarely lethal, but may have hallucinations
- Analysis:
  - THC in blood indicates recent use (within 24–48 hours)
  - Carboxy-THC in urine indicates use in past 3–4 weeks

Gamma-hydroxybutyrate (GHB)

- Source:
  - Metabolite of gamma aminobutyric acid
- Route:
  - Ingestion and injection
- Physiologic effects:
  - None until combined with alcohol, then drowsiness, euphoria, amnesia, and loss of consciousness
- Toxicity:
  - Respiratory depression, seizures, coma, hypotension, and death

Antidepressants

Tricyclic Antidepressants

Amitriptyline

- Source:
  - Prescription medication
- Route:
  - Ingestion and injection
- Physiologic effects:

  - Mood elevation
- Toxicity:
  - Hyperthermia, cardiac arrhythmia, coma, and convulsions
- Mechanism:
  - Not well known, but inhibits pump mechanism responsible for uptake of epinephrine and seratonin in adrenergic and serotonergic neurons
- Metabolism:
  - Amitriptyline metabolizes to nortriptyline (active)

Fluoxetine (Prozac)

- Source:
  - Medication
- Route:
  - Oral
- Physiologic effects:
  - Antidepressant, can have side effects of insomnia, anxiety, manic behavior, and suicidal ideation
- Toxicity:
  - Hypertension, tachycardia, and lethargy
- Mechanism:
  - Blockade of serotonin re-uptake

Antipsychotics

Phenothiazine

- Source:
  - Prescription drug
- Route:
  - Ingestion and injection
- Physiologic effects:
  - Psychotropic and antiemetic
- Toxicity:
  - Central nervous system: behavioral effects
  - Cardiovascular effects: sudden death, tardive dyskinesia, neuroleptic malignant syndrome
- Mechanism:
  - Strong anti-adrenergic and weaker peripheral anticholinergic activity
- Metabolism:
  - Elimination, slow
  - Conversion to sulfoxide
  - Demethylation

Haloperidol (Haldol)

- Source:
  - Prescription medication
- Route:
  - Oral, injection
- Physiologic activity:
  - Antipsychotic
- Toxicity:
  - Tardive dyskinesia, neuroleptic malignant syndrome, extrapyramidal symptoms, tachycardia, muscular rigidity, hypotension, sudden death
- Metabolism:
  - Extensively biotransformed to inactive metabolites
- Mechanism of action:
  - Unknown

Analgesics

Acetaminophen

- Source:
  - Over-the-counter medication
- Route:
  - Oral ingestion
- Physiologic effects:
  - Analgesic and antipyretic
- Toxicity:
  - Hepatotoxicity (24–48 hours after overdose)
- Lethal dose;
  - 20 grams
- Toxic concentration:
  - >160 mg/L
- Autopsy:
  - Centrilobular hepatic necrosis
- Metabolism:
  - Conjugated with glucuronide (45%), sulfate (20%), and cysteine (15–55%)

Acetylsalicylic Acid (Aspirin)

- Source:
  - Over-the-counter medication
- Route:
  - Ingestion
- Physiologic effects:
  - Analgesic, antipyretic, anti-inflammatory, and anticlotting effects
- Metabolism:
  - Hydrolyzed by liver and blood esterases; to salicylic acid (analgesic that accounts for most pharmacological activity of parent drug)
- Toxicity:
  - Sudden death by hypersensitivity, Reye syndrome, respiratory alkalosis, metabolic acidosis, hemorrhage, or chronic interstitial nephritis
- Lethal dose:

- 2–5 grams

♦ Toxic concentration:
- 500 mg/L

Metals

Arsenic

♦ Source:
- Pesticides, ceramics, wood preservatives

♦ Route:
- Ingestion, inhalation

♦ Mechanism:
- Inhibition of enzymes by binding to sulfhydryl groups, including respiratory enzymes

♦ Predilection for vascular endothelium, increasing permeability

♦ Toxicity:
- Gastrointestinal: nausea and vomiting, abdominal pain, "rice water diarrhea"
- Cardiovascular: dysrhythmia
- CNS: peripheral motor and sensory neuropathy
- Cutaneous: Bowen's disease, "Mees lines," hyperkeratosis of palms and soles, garlic odor

♦ Autopsy:
- Multiple keratoses, generalized visceral hyperemia, cerebral edema, many have fatty metamorphosis of liver
- In chronic poisoning, may have hyperkeratosis of hands and soles of feet

♦ Microscopic:
- Hepatocellular necrosis, interstitial myocarditis, subendocardial hemorrhage, renal tubular degeneration, hemorrhagic arsenical encephalitis

♦ Lethal dose:
- 200–300 mg (normally present in tissues in low concentrations)

Lead

♦ Source:
- Paints, battery, glazing putty, moonshine whiskey

♦ Route;
- Ingestion and inhalation

♦ Toxicity:
- Convulsions, intestinal cramps, hemorrhage, vomiting, anemia, peripheral motor neuropathy, Fanconi's syndrome (aminoaciduria, glycosuria, hyperphosphaturia)

♦ Autopsy:
- Lead line in gums at base of teeth, cerebral edema, eosinophilic intranuclear inclusions in proximal convoluted tubules, perivascular PAS + droplets in CNS, basophilic stippling, and increased red blood cell fragility

♦ Mechanism:
- Inhibits aminolevulinic acid dehydrase, ferrochelatase, and nucleotidase, which leads to blocked synthesis of hemoglobin

Mercury

♦ Source:
- Paint industry, dentistry

♦ Route:
- Inhalation, ingestion, transdermal absorption

♦ Toxicity:
- CNS: emotional lability, depression, outbursts of anger, insomnia
- Kidney: acute renal failure

♦ Autopsy:
- Swollen kidney with dark pyramids, atrophy of cerebral cortex and cerebellum

♦ Microscopic:
- Neuronal loss and gliosis

♦ Mechanism:
- Precipitation of proteins and inhibition of multiple enzyme systems, such as oxidative mitochondrial phosphorylation, and cytochrome C oxidase

Cobalt

♦ Source:
- Industry, medication, beer, radioactive cancer therapy

♦ Route:
- Ingestion, inhalation, radiation

♦ Toxicity:
- Nausea, vomiting, paralysis, hypotension

♦ Autopsy:
- Hemorrhage in liver and adrenal glands, renal and pancreatic degeneration, pericardial effusions, cardiac dilatation and hypertrophy (beer drinker's heart disease)

♦ Microscopic:
- Sudanophilic droplets in myocardium

♦ Mechanism:
- Inhibition of enzymes, alpha-ketoglutarate dehydrogenase, and pyruvate dehydrogenase

Thallium

♦ Source:
- Medication, over-the-counter preparation, pesticides

♦ Route:
- Ingestion

- Toxicity:
  - Alopecia with sparing of axillary, facial hair, and inner 1/3 of eyebrows, abdominal pain, vomiting, and ataxia
- Autopsy:
  - Alopecia
- Microscopic:
  - Degenerative changes in the neurons and nerve fibers

Other Chemicals

Organophosphates

- Source;
  - Insecticides
- Route:
  - Inhalation, ingestion, and absorption
- Toxicity:
  - Muscular paralysis, respiratory failure, blurred vision, salivation, sweating, and convulsions
- Autopsy:
  - Non-specific
- Mechanism:
  - Cholinesterase inhibition with accumulation of acetylcholine (look for decreased cholinesterase in blood)

Strychnine

- Source:
  - Rodenticides
- Route:
  - Ingestion, injection, inhalation
- Toxicity:
  - Stimulant, seizures (sardonic rigor), muscular paralysis
- Autopsy:
  - No specific finding
- Mechanism:
  - Blockade of post synaptic neuronal inhibition
- Lethal dose:
  - 60–100 mg

Freons

- Source:
  - Air conditioners, refrigerators, aerosol cans
- Route:
  - Inhalation
- Toxicity:
  - Arrhythmias, central nervous depression, simple asphyxia
- Autopsy:
  - No specific findings

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Chapter 6

Cytopathology

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Part A

Gynecologic Cytology

OVERVIEW: THE 2001 BETHESDA SYSTEM

Specimen Adequacy

- Satisfactory for evaluation (describe presence or absence of endocervical/transformation zone component and any other quality limiting factors)
- Unsatisfactory for evaluation (specify reason):
  - Specimen rejected (specify reason)
  - Specimen processed and examined, but unsatisfactory for evaluation of epithelial abnormality because of (specify reason)

General Categorization (optional)

- Negative for Intraepithelial Lesion or Malignancy
- Epithelial Cell Abnormality: see interpretation/result (specify "squamous" or "glandular" as appropriate)
- Other: see interpretation/result (e.g. endometrial cells in a woman > 40 years of age)

Descriptive Interpretations/Results

Non-Neoplastic

- Negative for intraepithelial lesion or malignancy (when there is no cellular evidence of neoplasia, state this in the General Categorization above and/or in the Interpretation/Result section of the report, whether or not there are organisms or other non-neoplastic findings)

Organisms

- *Trichomonas vaginalis*
- Fungal organisms morphologically consistent with *Candida spp*
- Shift in vaginal flora suggestive of bacterial vaginosis
- Bacteria morphologically consistent with *Actinomyces spp.*
- Cellular changes associated with Herpes simplex virus

Other Non-Neoplastic Findings
(Optional to report; not inclusive)

- Reactive cellular changes associated with:
  - Inflammation (includes typical repair)
  - Radiation
  - Intrauterine contraceptive device (IUD)
- Benign-appearing glandular cells status post hysterectomy
- Atrophy
- Endometrial cells (in a woman > 40 years of age)

Epithelial Cell Abnormalities

Squamous Cell

- Atypical squamous cells:
  - Of undetermined significance (ASC-US)
  - Cannot exclude HSIL (ASC-H)
- Low grade squamous intraepithelial lesion (LSIL):
  - Encompassing: HPV/mild dysplasia/CIN1
- High grade squamous intraepithelial lesion (HSIL):
  - Encompassing: moderate and severe dysplasia, CIS/CIN2 and CIN3
  - With features suspicious for invasion (if invasion is suspected)
- Squamous cell carcinoma

Glandular Cell

- Atypical:
  - Endocervical cells (NOS or specify in comments)
  - Endometrial cells (NOS or specify in comments)
  - Glandular cells (NOS or specify in comments)
- Atypical glandular/endocervical cells, favor neoplastic
- Endocervical adenocarcinoma in situ
- Adenocarcinoma:
  - Endocervical
  - Endometrial
  - Extrauterine
  - Not otherwise specified (NOS)

Other Malignant Neoplasms: (specify)

SPECIMEN ADEQUACY TERMINOLOGY/REPORTING

- Describe presence or absence of endocervical/transformation component and any other quality factors immediately after Satisfactory and Unsatisfactory terms. Any specimen with abnormal cells is by definition satisfactory for evaluation

Unsatisfactory Specimen Reporting

- Clarify laboratory's role in processing/evaluation in report; include comments/recommendations as appropriate
- Suggested wording to clarify reports follows:

- Rejected Pap:
  - Specimen rejected (not processed) because—(specimen not labeled, slide broken, etc.)
- Fully evaluated unsatisfactory Pap:
  - Specimen processed and examined, but unsatisfactory for evaluation of epithelial abnormality because of—(obscuring blood, etc.)
- Additional comments/recommendations, as appropriate

Conventional Smear Squamous Cellularity

- An adequate conventional specimen has an estimated minimum of approximately 8,000–12,000 well-preserved and well-visualized squamous epithelial cells (This minimum cell range should be an estimate)

Liquid-Based Squamous Cellularity

- Set a minimum limit of 5,000 well-visualized/preserved squamous cells

Endocervical/Transformation Zone Component

- At least 10 well-preserved endocervical or squamous metaplastic cells should be observed to report that a transformation zone component is present. It's absence does not mean a patient requires early repeat. However, attention to regular screening is suggested

Obscuring Factors

- Specimens with >75% of cells obscured should be termed unsatisfactory (assuming no abnormal cells are present). When 50–75% of cells are obscured, a statement describing the specimen as partially obscured should follow the satisfactory term. The percentage of cells obscured, not the slide area obscured, should be evaluated, although minimal cellularity rules should also be applied

ORGANISMS AND CONTAMINANTS

- Chlamydia should not be listed as an infectious entity in the Bethesda System to be diagnosed routinely on Pap smear

Trichomonas vaginalis

- 25% of women are carriers
- Often coexist with leptothrix and other coccoid bacteria
- Small, pear-shaped, faintly stained organism with small, oval, eccentric hyperchromatic nuclei and eosinophilic granules
- Cannonball cell with agglomeration of neutrophils onto squamous cells
- Small, perinuclear halo, cytoplasmic vacuolization, and polychromasia "moth eaten" squamous cells
- Granular debris and inflammation in background

Candida albicans

- 10% of females are carriers
- Incidence increased with pregnancy, oral contraceptives use, and diabetes
- Yeast form and pseudohyphae in inflammatory background
- Torulopsis glabrata: lack pseudohyphae

Bacterial Vaginosis

- Occurs in 10% to 30% of general population
- Patients have exponentially more anaerobes per ml of vaginal fluid than normal
- Etiology includes *Gardnerella vaginalis*, anaerobic lactobacilli and *Bacteroid* and *Mobiluncus* species
- *Gardnerella vaginalis* (*haemophilus-corynebacterium-vaginalis*):
  - May be cultured in 30% to 50% of asymptomatic women
  - Absence of lactobacilli
  - Whiff test on KOH preparation is positive
  - Minute rod-shaped gram variable bacillus
  - Clue cell:
    - Epithelial cell covered by adherent, small, uniformly spaced bacilli
    - Neither specific nor sufficient for the diagnosis of bacterial vaginosis

Actinomyces

- Gram positive filamentous organisms
- Associated with the use of IUD and vaginal pessaries
- Isolated aggregates of basophilic filamentous structures with radiating pattern
- Dirty, necrotic, inflammatory background
- Sulfur granules

Herpes Simplex Virus (HSV)

- 80% develop infection following exposure; 60% recurrence rate
- Multinucleation (90%), ground glass nucleus (90%), and intranuclear inclusion (20%); multinucleation, nuclear molding, and chromatin margination
- Cannot cytologically distinguish between type I and type II (genital) herpes, or between primary or secondary infection

Other Organisms

Doderlein bacilli (Lactobacillus acidophilus)

- Heterogenous group of bacilli
- Function to maintain an acid vaginal pH (3.5-4.5)
- Only species capable of causing cytolysis of intermediate squamous cell by hydrolyzing intracytoplasmic glycogen
- Results in cytolysis of intermediate squamous cells

Leptothrix

- Filamentous rods with or without branching
- Often associated with the presence of another organism (trichomonas, candida)

Molluscum contagiosum (Pox Virus)

- Large cells with cosinophilic intracytoplasmic inclusions and pyknotic degenerative nuclei

Enterobias vermicularis (Pinworm)

- Ovoid-shaped eggs with double-walled shell and flattened on one side

Entamoeba histolytica

- Large trophozoites with large nuclei and dot-like central karyosome
- Vacuolated cytoplasm containing ingested RBC

Contaminants

- Alteneria:
  - Short yellow brown conidiospores and transversely and longitudinally septate conidia (snow shoe-like)
- Pollen
- Vegetable cells:
  - Dense cell walls and structureless nuclei
  - May be observed in patients with rectovaginal fistulas along with goblet cells, inflammation, and necrotic debris
- Graphite-pencil markings
- Lubricant jelly
  - Not recommended for gynecologic examination prior to Pap smear
- Cotton, cardboard, and tampon fibers
- Trichome: "Octopus-like" structure derived from leaves of arrowhead tree
- Cockleburs:
  - Associated with IUD, oral contraceptive use, and second half of pregnancy
  - Related to cellular degeneration
  - Composed of nonimmune glycoprotein, lipid, and calcium
  - Cytologic findings:
    - Golden refractile crystalline rays surrounded by histiocytes
- Hematoidin crystals:
  - Indicative of previous hemorrhage, but do not contain iron
  - Composed of bile-like pigment formed from hypoxic tissue
  - Cytologic findings:
    - Finer crystalline rays with different shape
- Talc particles
- Ferning:
  - Arborizing, palm leaves-like pattern of cervical mucus that occurs at ovulation

REACTIVE CHANGES

Repair

- Cells in cohesive sheets with rare or absence of isolated cells
- Streaming of cells and pseudopodia
- Nuclear enlargement with fine chromatin and smooth nuclear contour
- Prominent nucleoli, often multiple and regular
- Delicate, cyanophilic cytoplasm without differentiation; streaming cytoplasm
- No tumor diathesis

Differential Diagnosis

- Squamous cell carcinoma:
  - Discohesive abnormal cells
  - Irregular chromatin distribution
  - Multiple irregular nucleoli
  - Tumor diathesis
- Acantholytic cells in pemphigus vulgaris:
  - Usually observed in vaginal smear
  - Increased number of single isolated cells (tombstone cells - Tzank cells)
  - Correlate with clinical history

Radiation Effect

- Cellular enlargement (macrocytosis), nuclear enlargement, normal N/C ratio
- Nuclear and cytoplasmic vacuoles, large perinuclear halos
- Finely granular or degenerative "smudged" chromatin; karyorrhexis and karyopyknosis
- Binucleation and multinucleation; micro- and macronucleoli
- Large bizarre cells; polychromasia
- Peripheral cytoplasmic projections (pseudopodia) and cytophagocytosis

IUD-Associated Change

- Small clusters of hypersecretory endocervical cells
- Abundant cytoplasm with distinct cell borders
- Large cytoplasmic vacuoles (bubble-gum cytoplasm)
- Large, uniform nuclei that may contain prominent nucleoli
- Inflammatory/reparative squamous changes
- Clean or inflammatory background
- +/– actinomycotic colonies

Differential Diagnosis

- Adenocarcinoma of endometrium:
  - Occurs in older patients (postmenopausal)
  - Generally many abnormal cells present with tumor diathesis
  - Irregular chromatin pattern and prominent nucleoli

Other Reactive Changes

Hyperkeratosis (HK)

Etiology

- Non-specific chronic cervicitis
- Uterine prolapse
- Reaction to previous biopsy, cryosurgery, or instrumentation
- In utero diethylstilbestrol (DES) exposure
- Pessary use
- SIL (approximately 10%); HK may represent a reparative surface reaction overlying SIL, usually LSIL or a reaction to persistent disease in patients with prior biopsy/cytology-proven SIL
- The presence of anucleated squamous cells during pregnancy suggests ruptured fetal membrane

Cytologic Findings

- Cluster or group of anucleated and granular superficial polygonal squamous cells
- Rare, isolated anucleated cells probably represent contaminants

Parakeratosis (PK)

- PK represents a reactive surface process similar to HK
- Persistence of PK without a known etiology may warrant further investigation

Cytologic Findings

- Isolated or loose sheets of miniature round to oval superficial cells with dense orangeophilic cytoplasm
- Small uniform pyknotic nuclei

Chronic Follicular (Lymphocytic) Cervicitis

- Polymorphous population of mature lymphocytes, plasma cells, and histiocytes
- No clinical significance; reporting is optional

PREGNANCY-RELATED CHANGES

Folic Acid Deficiency

- Cytologic finding similar to those of early radiation effect
- Nuclear and cellular enlargement; nuclear enfolding; binucleation and multinucleation
- Hypochromatic nuclei with smooth nuclear contour
- Cytoplasmic vacuolization and cytoplasmic polychromasia

Navicular Cells

- Boat-like intermediate cells with ecto-endoplasmic differentiation and glycogen
- Seen in late menstrual cycle, pregnancy, and high progesterone medications
- Cytolysis may be prominent under same conditions

Decidual Cells

- Maybe seen in smears from pregnant women and women on birth control pills or progesterone agents. Clinical history is important

Cytologic Findings

- Loose sheets of large, polygonal or round cells
- Abundant, delicate, eosinophilic or amphophilic cytoplasm
- Slight to moderate nuclear enlargement, but N/C ratio remains low
- Round nuclei with smudged and degenerative changes
- Nucleoli may be prominent

Syncytiotrophoblasts

- Rarely seen in normal pregnancy
- May indicate threatened abortion in 6% of patients when observed in the first trimester
- Suspect partial premature separation of the placenta when observed in the third trimester
- Suspect retained placental tissue when observed 4 weeks, after termination of pregnancy

Cytologic Findings

- Cells with abundant cyanophilic cytoplasm, distinct cell border and peripheral condensation
- Round to oval nuclei with nuclear overlapping but without molding
- Finely granular, evenly distributed chromatin with inconspicuous nucleoli

SQUAMOUS CELL ABNORMALITIES

Atypical Squamous Cells (ASC)

Definition

- Cytologic changes suggestive of a squamous intraepithelial lesion that are quantitatively or qualitatively insufficient for a definitive interpretation

Quality Assurance Monitoring of ASC

- ASC should comprise 5% or less of reports with ASC: SIL ratios of 2:1 to 3:1 in general screening practices. ASC:SIL ratios maybe lower for thin-layer cytology compared to smears

Atypical Squamous Cells of Undetermined Significance (ASC-US)

Definition

- Cytologic changes that are suggestive of a squamous intraepithelial lesion, but lack criteria for a definitive interpretation. The category includes: 1) a minority of cases formally classified as ASCUS, Favor Reactive and 2) most cases formally classified as ASCUS, NOS or ASCUS, Favor SIL

Cytologic Findings in Possible Cytologic Variants

- ASC of intermediate or superficial squamous cell type (NOS):
  - Cells usually isolated and few cells in smear
  - Cells resemble mature superficial or intermediate squamous cells
  - Nuclear area 2-3x size of intermediate cell nucleus or 2x nucleus of immature squamous metaplastic cells
  - Nuclei are normochromatic or mildly hyperchromatic
  - Nuclei are round and usually have smooth nuclear contour
  - Even chromatin without granularity
  - Absence of human papillomavirus cytopathic effect
  - Should not include inflammatory, reparative, or reactive atypia
- ASC of squamous metaplastic type:
  - Similar enlarged nuclei to ASCUS (70–120 μm^2)
  - Finely granular, evenly distributed chromatin
  - Cytoplasm less abundant, more cynaophilic
  - Cells rounder than conventional ASCUS
  - N/C ratio higher than conventional ASCUS
- ASC in an atrophic smear:
  - Nuclear enlargement with concomitant hyperchromasia, blue blobs
  - Marked irregularities in nuclear contours or chromatin distribution
  - Marked pleomorphism in the form of tadpole and spindle cells
  - Possible recommendation:
    - Repeat Pap after short course of estrogen therapy
- Atypical parakeratosis:
  - Isolated or clustered small cells (2-3x diameter of neutrophil)
  - Orangeophilic with variable/irregular outlines
  - High N/C ratio with irregular nuclear contours
  - Dark, often irregularly distributed chromatin
- ASC with equivocal changes for HPV:
  - Partial koilocytosis/perinuclear halos
  - Bi- or multinucleation
  - Spindled nuclei
  - Mild hyperchromasia

Atypical Squamous Cells; Cannot exclude HSIL (ASC-H)

Definition

- Cytologic changes that are suggestive of HSIL, but lack criteria for definitive interpretation. The association with underlying CIN2 and CIN3 for ASC-H is lower than for HSIL, but sufficiently higher than for ASC-US to warrant consideration of different management recommendations

Cytologic Findings

- Atypical cells of immature squamous metaplastic type:
  - Smaller in size than conventional ASC-US
  - Nuclear size 1.5-2x that of normal squamous metaplastic cells or 3x that of normal intermediate cells
  - Round to oval cell with dense amphophilic cytoplasm
  - Ectoplasm and endoplasm may be distinctive
  - High N/C ratio with mildly hyperchromatic nuclei
  - Finely granular and evenly distributed chromatin
  - Significant hyperchromasia and nuclear membrane irregularities may represent HSIL
- Atypical Repair:
  - Large nuclei
  - Irregular chromatin
  - Large nucleoli, often multiple and irregular
- Thick tissue fragments:
  - Overlapping of cells
- Isolated atypical small cells:
  - High N/C ratio
  - Nuclear irregularities/grooves
  - Hyperchromasia

Squamous Intraepithelial Lesion (SIL)

Definition

- SIL encompasses a spectrum of non-invasive cervical epithelial abnormalities traditionally classified as flat condyloma, dysplasia/carcinoma in-situ, and CIN. Low-grade lesions include the cellular changes associated with HPV cytopathic effect (so-called koilocytotic atypia) and mild dysplasia/CIN1. High-grade lesions encompass moderate dysplasia, severe dysplasia, and carcinoma in situ/CIN2,3)

Low Grade Squamous Intraepithelial Lesion (LSIL)

Cytologic Findings

- Single or sheets of large polygonal cells
- Nuclear enlargement (>150 μm^2): 3–6x size (usually 4–5x) of normal intermediate cell nucleus (30 μm^2) or 2-4x size of normal immature squamous metaplastic cell nucleus
- Mild nuclear hyperchromasia and moderate variation in nuclear size
- Subtle nuclear envelope irregularities in some nuclei
- Chromatin pattern usually finely granular and uniformly distributed
- Nucleoli are absent
- Binucleation/multinucleation may be present
- Cytoplasmic maturation with distinct borders
- In liquid based cytology the findings are similar to those of conventional preparations. There may be however:
  - Decreased hyperchromasia
  - Increased nuclear detail
  - More apparent nuclear membrane irregularities

Human Papillomavirus-Induced Change

- Koilocyte with perinuclear halos surrounded by dense peripheral cytoplasm
- Enlarged and hyperchromatic nuclei with slight irregular contour
- Dyskeratosis, binucleation and multinucleation, nuclear pleomorphism

Typing

- Low-risk types: 6, 11, 42, 43, 44
- High risk-types 16, 18, 31, 35, 39, 45, 51, 58, 59, 68
- Estimated prevalence of high risk HPV types:
  - Normal ~10%
  - ASC-US ~50–60%
  - ASC-H ~70–85%
  - LSIL ~86

Differential Diagnosis of LSIL

- HSIL
  - Increase in N/C ratio
  - Hyperchromasia
  - Chromatin abnormalities and irregularities
  - Cell arrangement change from sheets to syncytial aggregates
- ASC-US:
  - Few cells (x2-3 intermediate cell nucleus)
  - Slight nuclear enlargement (x2-3 intermediate cell nucleus)
  - Stippled chromatin
  - Smooth nuclear membranes

High Grade Squamous Intraepithelial Lesion (HSIL)

Cytologic Findings – Compared to LSIL

- Increased frequency of cell aggregates and syncytial-like arrangements
- Immature cytoplasmic characteristics or pleomorphic keratinized configurations
- Increased nuclear hyperchromasia
- Increased chromatin clumping and coarsening of chromatin
- Increased irregularities of nuclear outline
- Increased N/C ratio (cell and nuclear size however smaller than LSIL)

- Round to oval cells with lacy, delicate or metaplastic cytoplasm
- No tumor diathesis
- In liquid based cytology:
  - Fewer numbers of abnormal cells may be present
  - Cells tend to be more isolated or present in small groups
  - The nuclear membrane irregularities are prominent.
  - Hyperchromasia is often observed as coarsening of chromatin material rather than darkening

Differential Diagnosis of HSIL

- Invasive SCC:
  - Cellular pleomorphism
  - Irregular chromatin pattern
  - Nucleoli
  - Tumor diathesis
- Endocervical adenocarcinoma *in situ*:
  - Picket fence arrangement of columnar cells with peripheral palisading ("feathering") and granular cytoplasm
  - Columnar configuration
  - Monotonous population of hyperchromatic oval nuclei
- Repair
  - Cohesive, flat monolayer sheets of polygonal cells with distinct cell borders
  - Single nucleolus in every cell. No tumor diathesis
- Atypical reserve cell:
  - Metaplastic cytoplasm
  - Loose aggregates of small cell with sheet-like or syncytial arrangements
  - Finely granular chromatin
  - No associated LSIL

Keratinizing Dysplasia

- Elderly patients, usually present at distal portion of transformation zone
- Refers to the pleomorphic appearance of cells rather than cytoplasmic staining
- Severity determined by degree of pleomorphism rather than cytological atypia but difficult to predict
- Maybe difficult to distinguish from keratinizing squamous cell carcinoma
- Usually considered as HSIL

Cytological Findings

- Cellular pleomorphism with marked anisonucleosis
- Caudate, spindle, elongated, tadpole, or bizarre forms
- Coarsely granular or smudged chromatin
- Dense orangeophilic cytoplasm with distinct borders

Differential Diagnosis

- Keratinizing squamous cell carcinoma:
  - More discohesive with increased number of isolated cells
  - Nuclear pleomorphism
  - Tumor diathesis (however may not always be observed in keratinizing SCC)
  - Degenerative pyknotic nuclei may be observed

Cervical Squamous Cell Carcinoma

Cytologic Findings

- Many discohesive abnormal cells, some in aggregates
- Loss of cellular and nuclear polarity
- Cell size: 1/5 or less of normal superficial or intermediate squamous cell
- Nuclear size: x2–4 nucleus of intermediate Squamous cell
- Chromatin: coarse and irregular distributed with parachromatic clearing
- N/C ratio: over 60% (30–90%)
- Tumor diathesis
- In liquid based cytology:
  - There may be a greater depth to focus of cell groups
  - The nuclei maintain features indicative of malignancy but are usually less hyperchromatic
  - More prominent nucleoli
  - A distinctive necrotic background pattern may be observed

Classification

- Keratinizing Squamous Cell Carcinoma:
  - Keratinizing cell with significant pleomorphism (Spindle, bizarre, adpole, and caudate cells)
  - Dense orangeophilic cytoplasm with distinct cell border
  - Hyperchromatic, coarsely clumped chromatin with inconspicuous nucleoli
  - Anucleated squames and atypical parakeratotic cells
- Large Cell Non-Keratinizing Squamous Cell Carcinoma (LCNK):
  - Less anisocytosis and anisonucleosis than keratinizing carcinoma
  - Numerous single cells and syncytial groups of cells with indistinct borders
  - High N/C ratio
  - Round to oval nuclei
  - Nuclear overlapping
  - Coarse granular chromatin with chromatin clearing
  - Macronucleoli
- Small Cell Type:
  - Most are neuroendocrine carcinomas

- Single cells and syncytial groups of small, cuboidal or round cells
- High N/C ratio with scant cyanophilic cytoplasm
- Large, round to oval nuclei with hyperchromatic, coarsely granular chromatin
- Nuclear molding and small nucleoli

Differential Diagnosis

- Endometrial cells:
  - Three-dimensional cluster of cells with kidney bean shaped nuclei, evenly distributed chromatin, smooth nuclear contours
  - Foamy cytoplasm without macronucleoli
  - Lack tumor diathesis
- HSIL:
  - Loose aggregates and syncytial-like arrangement
  - Round to oval cells with delicate cytoplasm
  - Lack nuclear molding
  - No chromatin clearing
  - No tumor diathesis
- Reserve cell hyperplasia and atypical reserve cells:
  - Few clusters of small round cells in a clean background (miniature biopsies)
  - Small nuclei with fine evenly distributed chromatin. No nuclear molding
  - Metaplastic-type cytoplasm

ENDOCERVICAL CYTOLOGY

Normal Endocervical Cells

Cytologic Findings

- Cells may occur singly or in strips, rosettes, or sheets
- They are usually elongated and columnar. When viewed on end, they are smaller, polygonal or cuboidal, and demonstrate the typical "honeycomb" arrangement
- The cytoplasm is usually described as granular, but it may show fine vacuolization. The nuclei are round to oval and are often indented or possess a nuclear nipple-protrusion of the nuclear contents at one end
- The nuclear chromatin is finely granular and evenly dispersed
- Multiple small chromocenters and one or more small eosinophilic nucleoli may be present
- Binucleation or multinucleation is not uncommon
- Variability observed in cells derived from various regions of the endocervical canal

Endocervical Cells, Reactive Changes

Cytologic Findings

- Cells occur in sheets and strips with minor degrees of nuclear overlap
- Nuclear enlargement, up to three to five times the area of normal endocervical nuclei, may be seen
- Mild variation in nuclear size and shape occurs
- Slight hyperchromasia frequently is evident
- Nucleoli often are present
- Abundant cytoplasm and distinct cell borders often are discernible

Endocervical Tubal Metaplasia

- Normal finding especially upper endocervical canal
- May be related to unopposed estrogen

Cytologic Findings

- Small crowded cellular strips, clusters, or flat honeycomb sheets
- Evenly spaced uniform, basally oriented round to oval nuclei
- Large stripped nuclei may be observed
- Finely granular, evenly distributed or washed- out chromatin
- Small inconspicuous nucleoli
- Terminal bars, cilia, and mucus depletion
- Ciliocytophthoria

Differential Diagnosis

- Endocervical adenocarcinoma in situ (AIS):
  - Lack terminal bars or cilia
  - Nuclear hyperchromasia and coarse chromatin pattern
  - Nuclear feathering and rosettes
  - Apoptosis

Microglandular Hyperplasia

- Related to progesterone effect (pregnancy, birth control pills and postmenopausal on estrogen)

Cytologic Findings

- May be indistinguishable from those of reactive hyperplasia and regeneration/repair
- Associated endocervical changes:
  - Large sheets of polygonal or columnar cells with minimal stratification
  - Pseudoparakeratosis: degenerative changes in endocervical cells
- Spindle and elongated metaplastic cells
- Terminal bars and cilia may be present

Arias-Stella Reaction

- Non-neoplastic, hormone-related phenomenon of pregnancy. Clinical correlation is essential for diagnosis

Cytologic Findings

- Single or small groups of atypical glandular cells
- Low N/C ratio with abundant clear or faintly eosinophilic cytoplasm
- Nuclear enlargement, hyperchromasia, pleomorphism and nuclear groove
- Granular, evenly distributed chromatin, often smudged with ground-glass appearance

Glandular Cell Abnormalities

Atypical Endocervical Cells, NOS

- Whenever possible, atypical glandular cells can and should be qualified as to endocervical or endometrial origin. When the distinction cannot be made, the cytology report of "atypical glandular cells - AGUS" indicates the uncertainty as to the cell of origin. Atypical glandular cells rates in the typical cytology laboratory should be less than 1%, with compiled data showing means between 0.3 and 0.5%

Cytologic Findings

- Changes beyond those encountered in reactive processes, but are insufficient for favoring neoplasia or an unqualified diagnosis of adenocarcinoma *in situ* (AIS)
- Mild cellular crowding without nuclear pseudostratification
- Nuclear enlargement, hyperchromasia, and anisocytosis

Atypical Endocervical Cells, Favor Neoplastic

Cytologic Findings

- The presence of some but not all the criteria as outlined for Adenocarcinoma In Situ (AIS) or other "atypical" presentation which should be individually and specifically categorized in a qualifying statement

Follow-up of Atypical Endocervical Cells

- Benign: up to 35% of all cases
- Endocervical neoplasia <7% of cases
- SIL in the majority of cases
  - This points to the difficulties inherent in interpretation of these lesions, especially SIL, which may envelope endocervical glands and mimic glandular cells

Endocervical Adenocarcinoma In Situ *(AIS)*

- These features are for the most common "endocervical" form of AIS
- "Low grade glandular intraepithelial lesion" and/or "endocervical glandular dysplasia" should not be utilized

Cytologic Findings in Conventional Smears

- Moderate to highly cellular smear composed of tight clusters and cohesive sheets of glandular cells
- Pseudostratification, rosette formation and feathering at the edge of sheets
- Uniform nuclear enlargement, hyperchromasia, nuclear irregularities, and crowding with elongate configuration
- Coarsely granular, evenly distributed chromatin
- Mitosis and apoptotic bodies may be present
- Micronucleoli may be observed
- Delicate, finely vacuolated cytoplasm with diminished mucin production
- Clean or inflammatory background
- About 50% of AIS are associated with SIL

Cytologic Findings in Liquid-Based Specimens (Differences from Conventional Smears)

- Hyperchromatic crowded groups become denser and more three dimensional with greater nuclear overlap, increased apparent hyperchromasia of nuclei, and with increased difficulty in visualization of individual nuclei in the groupings
- "Disordered honeycomb" arrangement may be the only feature present in some cases
- Key architectural features may be more subtle than in conventional smears
- Margins of the groups become smoother and sharper with lesser degrees of nuclear protrusion (feathering)
- Pseudostratified strips of cells are often the most prominent architectural arrangement

Differential Diagnosis

- Tubal metaplasia:
  - Terminal bars, cilia, flat sheets
  - More evenly spaced nuclei, resemble honeycomb pattern
  - Absence of mitosis, apoptosis, or nuclear hyperchromasia
- Lower uterine segment:
  - Mixture of glandular and stromal cells
  - Large cell aggregates with tubular branched glands
  - Cell polarity retained
  - Smaller nuclei with finely granular chromatin
- Repair/Reactive changes:
  - Flat sheet of polygonal cells in a honeycomb arrangement
  - Lack of single cells
  - Abundant cytoplasm and distinct cell borders often are discernable
  - Uniform cells with low N/C ratio
  - Minor degrees of nuclear overlap
  - Nuclear enlargement, up to three to five times the area of normal endocervical nuclei, may be seen
  - Mild variation in nuclear size and shape occurs

- Slight hyperchromasia may be seen
- Nucleoli often are present

HSIL with Endocervical Involvement

- Feathering may occur but often restricted to one end of crowded sheet
- Syncytial arrangement
- Hyperchromatic nuclei
- Dense cytoplasm
- No strips, rosettes or pseudostratified atypical columnar cells
- Individual cells with dysplasia in background
- Normal endocervical cells are numerous
- AIS is much less frequent than HSIL

Endocervical Adenocarcinoma

Cytologic Findings

- Features of AIS, highly cellular smear
- Isolated strips and single or discohesive sheets of columnar or cuboidal cells
- Three dimensional clusters
- Round to oval nuclei with coarse granular chromatin
- Marconucleoli
- Nuclear pleomorphism, multinucleation, and mitotic figures
- More abundant foamy or finely vacuolated cytoplasm than AIS
- Necrotic granular (tumor) diathesis

Variant

- Minimal deviation adenocarcinoma (adenoma malignum):
  - Can be a very difficult diagnosis, can be suspected in the proper clinical context
  - Hypercellular smear
  - Strips, honeycomb sheets, and three dimensional clusters of cell with distinct cell border, abundant lacy cytoplasm and occasional nucleoli
  - Round to oval nuclei (rather than elongated) nuclei with coarse granular chromatin

Differential Diagnosis (see Table 6-1)

Benign Glandular Cells in the Specimens from Post-Hysterectomy Women

- The likely origins of these benign cells include: prolapse of uterine tube, vaginal endometriosis, fistula, vaginal adenosis not associated with DES exposure, or glandular metaplasia associated with prior radiation or chemo-therapy. These findings are considered benign and do not warrant an interpretation/diagnosis of "atypical glandular cells". The general categorization of such cases should be "negative for intraepithelial lesion or malignancy"

Table 6-1. Endocervical Adenocarcinoma vs. Endometrial Adenocarcinoma

Endocervical Adenocarcinoma (Endocervical Type)*	*Endometrial Adenocarcinoma (Endometrioid Type)*
Younger patients	Elderly patients
Strips, rosette and feathering arrangement	Syncytial arrangement
Larger columnar cells	Smaller cell with indistinct cell border
Granular cytoplasm	Amphophilic cytoplasm
Solitary macronucleoli	Multiple small nucleoli
Necrotic dirty background	Watery diathesis

** Note: The cytologic findings of moderately and poorly differentiated endocervical adenocarcinoma often overlap with those of endometrial adenocarcinoma. Other histologic types are identical to their endometrial counterpart*

ENDOMETRIAL CYTOLOGY

Endometrial Cells

Cytologic Findings

- Epithelial cells:
  - Loose clusters and cell balls
  - Cells are small, cuboidal to round
  - Scant amphophilic and often finely vacuolated cytoplasm
  - Round or bean shaped nuclei, slightly eccentric
  - Nuclear size similar to that of intermediate cell nucleus
  - Uniform finely powdered chromatin pattern
- Superficial stromal cells:
  - Individually the cells resemble and may be indistinguishable from histiocytes
  - Identify as stromal cells when numerous and loosely clustered
  - Round oval or reniform nuclei
  - Nucleus is usually centrally located but may be eccentric
  - Chromatin finely granular
  - Micronucleoli may be observed
- Deep stromal cells:
  - Loose aggregates late in the menstrual flow
  - Spindle or oval cells
  - Ill defined cytoplasmic borders
  - Nuclei reniform or cigar shaped, often with nuclear infoldings (grooves)
  - Nuclear chromatin finely granular, sometimes hyperchromatic
  - Small chromocenters may be observed
- Exodus:
  - Occur on days 6–10 of menstrual cycle
  - Cells balls composed of stromal cells surrounded by peripheral larger epithelial cells
- The presence of endometrial cells is related to:
  - Site of origin of endometrium
  - Days of menstrual cycle
  - The environment into which they are shed and interval that has elapsed since the cells were shed
  - Collection method
  - Processing techniques
- The significance of endometrial cells is in part dependent on:
  - Age of the patient
  - Day of last menstrual cycle
  - Menopausal state
  - Hormonal usage
  - Intrauterine devices
  - Recent instrumentation
- Abnormal shedding of cytologically normal endometrial cells may be observed with the following:
  - IUD use
  - Hormonal effect
  - Immediate postpartum period
  - Impending or early abortion
  - Acute and chronic endometritis
  - Recent intrauterine instrumentation
  - Endometriosis
  - Submucosal leiomyoma
  - Endometrial polyp
- Note:
  - Presence of endometrial cell peak in day 4–5 and may persist till day 12–14 of a 28 day menstrual cycle
  - Presence of endometrial cells after day 12–14 or in menopausal women is associated with an age-dependent (endometrial pathology more likely to be detected after age 40) increased detection of endometrial pathology (endometrial polyp, hyperplasia or adenocarcinoma)
  - Because of the lack of clinical impact and the unreliable clinical data often supplied with the sample, cytologically normal endometrial cells may need not be reported in women less than 40 years

Bethesda 2001 Reporting of Endometrial Cells

- "Cervical/vaginal cytology is a screening tool for squamous cell carcinoma and its precursor lesions. It is an inaccurate test for detection of endometrial lesions and should not be used to evaluate suspected endometrial abnormalities"
- Report benign appearing endometrial cells in all women from the age of 40 onward, regardless of hormonal therapy using the following format:
- General Categorization
- Descriptive Interpretation:
  - "Endometrial cells present. -See "Comment"
  - "No evidence of squamous intraepithelial lesion." (Optional)
- An educational comment appropriate for the local laboratory practice, such as the following, may be used. For example, "Endometrial cells after age 40, particularly out of phase or after menopause, may be associated with benign endometrium, hormonal alterations and less commonly, endometrial/ uterine abnormalities. Clinical correlation is recommended"

Atypical Endometrial Cells, Not Otherwise Specified (NOS)

- No well defined criteria to separate reactive vs. preneoplastic endometrial cells
- Should not be subdivided into categories
- May be seen in:
  - Endometrial polyp
  - Endometritis, acute and chronic
  - Endometrial metaplasia
  - Endometrial hyperplasia
  - Well-differentiated adenocarcinoma (FIGO grade 1)

Cytologic Findings

- Cells occur in small groups, usually 5 to 10 cells per group
- Mild cellular crowding without nuclear pseudostratification
- Nuclei are slightly enlarged with mild hyperchromasia, and anisocytosis
- Small nucleoli may be present
- Cell borders are ill-defined
- Compared with endocervical cells, these cells have scant cytoplasm, which occasionally is vacuolated

Endometrial Adenocarcinoma

Cytologic Findings

- Shedding is sparse and irregular especially for low-grade tumors
- Small cells that may be difficult to detect. Cell size increases from low to high-grade tumors
- Scant cyanophilic cytoplasm with fine vacuolization
- Loss of cell polarity
- Nuclear enlargement (>70 μm^2) and high N/C ratio
- Nuclear crowding and overlapping (3-D cell ball)
- Chromatin is not usually hyperchromatic
- Powdered chromatin with parachromatin clearing
- Nucleolar enlargement proportional to grade of tumor
- Singly or loose clusters of foamy histiocytes and lipophages
- Watery granular tumor diathesis
- In liquid based cytology:
  - The groups may be more spherical or clustered
  - The nuclei present in groups may show less visual accessibility due to overlap and increased cytoplasmic thickening
  - The nuclear features are usually well preserved
  - Nucleoli are prominent
  - Distinction between endocervical adenocarcinoma maybe more difficult

Differential Diagnosis

- Normal endometrial cell:
  - Round nucleus similar in size to intermediate squamous cell nucleus
  - No cytological features of malignancy
- Atypical endometrial cells of undetermined significance:
  - Cytological changes may overlap with those of low-grade endometrial adenocarcinoma
  - Cell polarity maintained
  - Nuclear size less than that of adenocarcinoma
  - No tumor diathesis
- Endocervical adenocarcinoma (see Table 6-1)

Papillary Serous Adenocarcinoma

Cytologic Findings

- Cells usually shed in papillary aggregates and have all the features of a poorly differentiated carcinoma
- Small compact cell balls elongated groups with peripheral molding or irregular tight clusters of cells may be identified
- Occasionally, the central connective tissue core may be seen. Psammoma bodies can be observed
- The cytologic features of papillary serous carcinoma of the endocervix and of the endometrium are indistinguishable
- Poorly differentiated endometrioid carcinoma FIGO Grade III and with extrauterine papillary carcinoma cannot be distinguished cytologically

Extra-Uterine Metastatic Adenocarcinoma

- Important to consider clinical history
- Ovarian carcinoma most common primary site (papillary serous)
- Other sites include fallopian tubes, gastrointestinal tract, pancreas and breast
- Presence of ascites and patent fallopian tubes increases yield
- Most are poorly differentiated adenocarcinomas

Cytologic Findings

- Three-dimensional, tubular, spherical or papillary tissue fragments
- Large cells with high N/C ratio, nuclear hyperchromasia and macronucleoli
- Generally, no specific cytological features point to the primary site
- Exceptions include the presence of psammoma bodies (favor ovarian), columnar cells with brush borders (favor GI) , and cords of cells (favor breast)

- Absence of tumor diathesis, provided implantation has not occurred

Malignant Mixed Müllerian Tumor

Cytologic Findings

- Two distinct tumor cell populations: malignant poorly differentiated glandular component with or with squamous differentiation, and pleomorphic spindle or multinucleated sarcomatous component
- Heterologous elements are rare and are cytologically difficult to recognize
- The malignant epithelial component sheds as single cells or in aggregates, whereas the sarcomatous cells usually occur as single cells and, rarely, in aggregates
- Tumor diathesis is usually evident

Lymphoma/Leukemia Involving (also see Chapters 7 and 8)

Cytologic Findings

- Vary with the type of lymphoma
- Complete lack of intercellular cohesion among the tumor cells. Some of the cells may appear to cluster, but no true aggregates are present
- The tumor cell population is monomorphic
- The cells have high N/C ratios. In most lymphoma cells, the cytoplasm is barely visible; however, a minority have a plasmacytoid appearance with more abundant cytoplasm
- The nuclear membrane usually shows marked convolutions and may show a nipple-like protrusion
- The chromatin is coarse with regular clumps
- Nucleoli are not common, except in the immunoblastic lymphoma category
- The subtyping of lymphomasis not reliable

Part B

Non-Gynecologic Cytology

OVERVIEW

Evaluation of Cytologic Smear

- Cellularity
- Are the cells representative of a lesion?
- Type of cells (epithelial, mesenchymal or lymphopoietic)
- Architectural arrangement of tissue fragments
- Relationship of cells
- Cellular changes: Nuclear to cytoplasmic (N/C) ratio, cytoplasm, nuclear change (chromatin, nuclear membrane, and nucleoli)
- Background: bloody, granular, watery proteineous, inflammatory, granuloma, mucoid, diathesis, etc.

Key Cellular Features

Benign Cellular Features

- Centrally located, single or multiple, round to oval nuclei
- Chromatin finally granular and evenly distributed
- Nuclear membrane smooth
- Single or multiple, small, rounded nucleoli
- Normal N/C ratio
- Well defined cytoplasmic border
- Tissue fragments are one to two cell layers with good polarity or honeycomb pattern

Reactive Cellular Features Due to Inflammation

- Centrally located, single or multiple, round to oval nuclei
- Nuclei enlarged with slightly enlarged nucleoli
- N/C ratio normal or slightly increased
- Chromatin slightly more granular and may be hyperchromatic
- Nuclear membrane may be wavy but uniform in thickness
- Background with inflammation, granular and cellular debris

Degenerative Changes Due to Reversible Injury

- Nuclear enlargement due to swelling (karyolysis)
- Chromatin smudged or washed out
- Nuclear membrane may be uneven in thickness
- Nucleoli may be indistinct
- Cells may become more rounded due to swelling
- Cytoplasmic disintegration and fraying (moth-eaten appearance)
- Cell borders not well defined
- Normal N/C ratio
- Background may or may not be inflamed

Degenerative Features Due to Irreversible Injury

- Nucleus wrinkled and decreased in size
- Loss of chromatin detail
- Pyknotic and smudged chromatin
- Fragmentation and condensation of chromatin (karyorrhexis)
- Hyperchromasia
- Nucleolus invisible
- Cytoplasmic borders not well defined and disintegrated
- N/C ratio may be increased due to loss of cytoplasm or decreased due to nuclear shrinkage

Cellular Features of Repair

- Monolayer sheets of well organized cells and very few single cells
- Cells bear striking resemblance to each other
- Little or no cellular overlap
- Enlarged cells with centrally located round nuclei
- Enlarged nuclei
- Prominent nucleoli/cherry red single macronucleoli
- Marginated chromatin (swelling)
- Well defined, uniform, thick nuclear membrane
- Well defined cell borders
- Cytoplasm may be streaming in the same direction (school of fish)

Atypical Repair

- Areas of atypical repair usually merge or coexist with typical repair
- Anisonucleosis within the monolayer sheet
- Increased cellular overlap within the sheet
- Increased number of single cells
- Increase chromatin granularity
- Altered nuclear polarity
- Hyperchromasia
- Cell borders blurred

General Features of Malignancy

- Increase N/C ratio (with few exceptions)
- Nuclei are round to oval, single or multiple, and frequently irregular
- Marked variation in nuclear size and shape (anisonucleosis)
- Chromatin is crisp and may vary from finely granular and evenly distributed to coarsely granular and unevenly distributed
- Chromatin rim may be irregular in thickness
- Nuclear membrane may be smooth but frequently irregular with grooves and sharp notches
- Nucleoli may vary from inconspicuous to prominent. They may be angulated or irregular

- Cellular discohesion with many single cells
- Cells within aggregates lose their polarity and form pseudosyncytia (cells blend with each other and lose their well defined borders)
- Background may contain tumor diathesis which appears as granular material with cellular debris and old blood

Cellular Patterns

Mixture of Epithelial Cells/Lymphocytes

- Branchial cleft cyst
- Sialadenitis
- Lymphoepithelial lesion
- Warthin's tumor
- Hashimoto's thyroiditis
- Thymoma
- Seminoma
- Medullary carcinoma of the breast
- Nasopharyngeal lymphoepithelioma-like carcinoma

Mixture of Epithelial Cells/ Spindle Cells (biphasic)

- Pleomorphic adenoma
- Tumors with marked stromal fibrosis
- Neuroendocrine tumors (e.g. carcinoid)
- Synovial sarcoma
- Malignant schwannoma
- Mesothelioma (biphasic)
- Phyllodes tumor
- Brenner's tumor
- Malignant mixed mullerian tumor
- Leiomyoblastoma
- Wilms' tumor
- Hepatoblastoma
- Epithelioid sarcoma
- Epithelioid leiomyosarcoma
- Melanoma

Plasmacytoid Cells

- Multiple myeloma
- Lymphoma (lymphoplasmacytic and Waldenstrom's lymphoma)
- Carcinoid
- Medullary thyroid carcinoma
- Islet cell tumor
- Breast carcinoma, lobular and ductal
- Urothelial/carcinoma
- Melanoma

Tumor with Discohesive Pattern

- Lymphoma
- Melanoma
- Sarcoma
- Squamous cell carcinoma
- Signet ring carcinoma
- Lobular carcinoma of the breast
- Seminoma
- Neuroendocrine tumors
- Small blue cell tumors: Ewing's sarcoma, primitive neuroectodermal tumor (PNET), neuroblastoma, and rhabdomyosarcoma

Tumors with Acinar Pattern

- Prostate carcinoma
- Thyroid follicular tumor
- Carcinoid and neuroendocrine tumor

Tumor with Trabecular Pattern

- Hepatic tumor (hepatocellular carcinoma, hepatic adenoma)
- Thyroid follicular tumor
- Breast carcinoma
- Carcinoid
- Merkel cell carcinoma

Granuloma

- Infectious (e.g. fungal, mycobacterium etc.)
- Non-infectious (e.g. sarcoidosis, Wegener's granulomatosis etc.)
- Reaction to foreign body (e.g. keratin, amyloid, suture material)
- Tumors with granulomatous component:
  - Squamous cell carcinoma
  - Seminoma
  - Hodgkin lymphoma
  - T-cell lymphoma

Intranuclear Cytoplasmic Inclusions

- Papillary thyroid carcinoma
- Medulllary carcinoma of the thyroid
- Hurthle cell neoplasm
- Hyalinizing trabecular adenoma of the thyroid
- Parathyroid adenoma
- Bronchioalveolar carcinoma
- Hepatocellular carcinoma
- Melanoma
- Meningioma
- Sclerosing hemangioma
- Breast carcinoma
- Adrenal cortical carcinoma

Intracytoplasmic Inclusions/Hyaline Globules

- Papillary thyroid carcinoma (septate vacuoles)
- Bronchioalveolar carcinoma, clara cell type (sufactant)
- Squamous cell carcinoma (keratin)
- Adenocarcinoma (mucin droplets)
- Hepatocellular carcinoma (Mallory bodies or inspissated secretions)
- Melanoma
- Yolk sac tumor (alpha-fetoprotein or human chorionic gonadotropins)
- Pleomorphic liposarcoma (sarcoma bodies)
- Rhabdoid tumor (intermediate filaments)

Extracellular Hyaline Globules

- Corpora amylacea
- Collagenous spherules
- Liesegang rings
- Alveolar proteinosis
- Amyloid (irregular and thick)
- Mesothelial hyperplasia and mesothelioma (collagen balls)
- Clear cell carcinoma of the kidney or ovary
- Adenoid cystic carcinoma (smooth globules)
- Monomorphic adenoma (irregular globules)

Signet Ring Cells

- Goblet cells
- Mesothelial cells
- Gastrointestinal tract carcinoma
- Mucinous carcinoma of the breast, ovary
- Mucinous carcinoid

Mucinous/Myxoid Background

- Mucinous carcinoma
- Pleomorphic adenoma
- Chondroid hamartoma
- Chondroid tumors
- Myxoid tumors

Psammoma Bodies

- Papillary carcinoma of thyroid, breast, ovary
- Bronchoalveolar carcinoma
- Malacoplakia
- Meningioma
- Endosalpingiosis
- Mesothelial hyperplasia and mesothelioma

RESPIRATORY CYTOLOGY

Overview

Normal Cellular Components of Lung Cytology

- Squamous cells
- Alveolar macrophages
- Bronchial epithelial cells
- Terminal bronchiolar and alveolar lining cells (pneumocytes)
- Inflammatory cells
- Megakaryocytes and mesothelial cells

Types of Cellular Specimens

Exfoliate

- Sputum
- Bronchial Brushings (BB)
- Bronchoalveolar lavage (BAL)

Fine needle aspiration

- Fine needle aspiration (FNA)
- Transbronchial needle aspirate

Spectrum of Cytologic Changes in Various Preparations

Sputum

- Adequacy of sputum specimen: macrophages must be present (exception: acute pneumonia)
- When positive, often shows small number of single or small tight clusters of tumor cells with frequent degenerative changes
- Often obscured by inflammatory exudate or food contamination
- Tumor diathesis is indistinguishable from inflammatory exudate or pneumonia
- May contain large number of squamous cells from oral cavity

Bronchial Brushings

- Contain large number of cells and tissue fragments with few macrophages
- Large number of columnar ciliated bronchial epithelial cells with or without reactive change
- Profuse mucus, and tumor diathesis well demonstrated

Bronchial Washings and Bronchoalveolar Lavage (BAL)

- Small number of tumor cells
- Large number of macrophages (many pigmented and multinucleated)
- Degenerative/distorted bronchial epithelial cells in tight clusters/balls which may have lost their cilia and stain hyperchromatic

Fine Needle Aspiration (FNA)

- Excellent cellular preservation and good representation of lesion (if smear is cellular)
- Large number of cells seen singly or in fragments
- Few macrophages and bronchial epithelial cells and rare mucus
- Pneumocytes may be abundant with reactive changes
- Mesothelial cells may be seen
- Tumor diathesis is well demonstrated

Transbronchial FNA

- Performed to sample a bronchial mass for primary diagnosis or hilar lymph nodes for staging and/or primary diagnosis
- Contain many bronchial cells, histiocytes, and mucin in addition to the lesional cells
- Aspirates of hilar lymph nodes should contain lymphocytes to document adequate sampling of the node when the aspirate is negative

Benign Lesions

Pulmonary Infarct

- Maximum atypia is seen during 2nd–3rd post-infarction weeks
- Sheets and papillary grouping of reactive pneumocytes
- Granular or vacuolated cytoplasm
- Nuclear and nucleolar enlargement
- Degenerative changes and metaplastic squamous cells
- Hemosiderin-laden macrophages

Pneumonia

- Numerous polymorphous leukocytes
- Cell debris
- Degenerative changes of the epithelial cells
- Bacterial colonies are significant only in FNA
- Carefully screen FNA with purulent materials to exclude carcinoma associated with obstructive pneumonia
- Culture suspicious FNA

Creola Bodies

- Benign reactive columnar cell hyperplasia, often seen in asthma
- Papillary tissue fragments or three-dimensional cell balls
- Smaller, less differentiated peripheral palisading cells with terminal plates and cilia
- Goblet cells may be seen within the peripheral palisading cells

Cigarette and Habitual Marijuana Smoking

- The earliest change in squamous metaplasia is reserve cell hyperplasia
- Reserve cell hyperplasia consists of tight clusters of uniform small cells with hyperchromatic nuclei
- Single or monolayered sheets of metaplastic cells with dense cyanophilic cytoplasm
- Immature squamous metaplasia
- Numerous multinucleated histiocytes

Radiation and Chemotherapy-Induced Atypia

- Cytomegaly, nucleomegaly, multinucleation and normal N/C ratio
- Cytoplasmic vacuolization and cytoplasmic polychromasia
- Bizarre cells with amphophilic cytoplasm, indistinct cell border, and cytophagocytosis of neutrophils
- Nuclear degeneration (karyorrhexis and karyolysis), hyperchromasia, and prominent nucleoli
- Smudged chromatin and poor nuclear detail

Amiodarone (Antiarrhythmic Drug)-Induced Changes

- Foamy alveolar macrophages with uniform, ill-defined, and smaller vacuoles than the coarse vacuoles seen in lipoid pneumonia
- Negative oil-red O stain
- Atypical pneumocytes with increased N/C ratio, hyperchromasia, and nuclear pleomorphism
- Cells retain cohesiveness, smooth or flattened cell border, and regular nuclear membranes
- Background of increased lymphocytes, neutrophils, and eosinophils
- Electron microscopy: osminophilic lamellar cytoplasmic inclusions

Hemosiderin-Laden Macrophages

Pediatric Patients

- Idiopathic pulmonary hemosiderosis (isolated)
- Pulmonary hemosiderosis associated with sensitivity to cow's milk
- Glomerulonephritis
- Collagen vascular and pruritic disease
- Cardiac diseases, intravascular lesions or malformations

Adult Patients

- Diffuse interstitial pulmonary disease
- Sarcoidosis

- Hypersensitivity pneumonitis
- Fibrosis associated with rheumatoid arthritis
- Radiation or chemotherapy

Quantitation of Hemosiderin-Laden Macrophages

- Percentage of cells containing hemosiderin (Prussian blue or Perl stain):
  - Result of >20% has a sensitivity of 10% and specificity of 92% for detecting pulmonary hemorrhage and hemosiderosis
- Hemosiderin score:
  - Adding staining intensity score (0–3) for each 100 cells measured
  - A score of >50 has a high sensitivity and specificity in the proper clinical setting

Lipid-Laden Macrophages in Bronchial Lavage

- Associated with tracheal aspiration in children with gastroesophageal reflux (GER) or lobular consolidation distal to an obstructed bronchus
- Aspiration of mineral oil
- Quantitation may be of value for predicting recurrent aspiration

Corpora Amylacea

- Seen in:
  - Heart failure
  - Pulmonary infarction
  - Chronic bronchitis

Sarcoidosis

- May see loose clusters of epithelioid cells and giant cells intermingled with lymphocytes
- Schaumann's bodies may be noted in the giant cells
- Asteroid bodies are not specific

Ferruginous Bodies

- General term that implies a variety of mineral fibers that have been inhaled and sheathed with golden brown iron-protein complex
- Asbestos bodies (consist of a clear colorless central fiber of uniform thickness within a golden brown iron-protein complex):
  - Indicative of occupational asbestos exposure
- Non-asbestos bodies: have a black or yellowish center and is not uniform in thickness

Ciliocytophthoria

- Anucleated cytoplasmic fragments bearing cilia
- Suggestive of viral infection (e.g. respiratory syncytial virus)

Asthma

- Curschmann's spiral:
  - Coiled strands of inspissated mucus
- Charcot-Leydin crystals:
  - Elongated red crystalline structure derived from eosinophil (lyso)phospholipase B, involved in prostaglandin metabolism
- Eosinophils and goblet cell hyperplasia
- Creola bodies (see description above)

Infectious Processes

Cytologic Features of Viral Infection

- Intranuclear inclusion bodies
- Loss of nuclear chromatin patterns
- Multinucleation
- Cytoplasmic inclusions
- Ciliocytopthoria
- Necrosis and inflammation
- Bronchial and alveolar hyperplasia

Aspergillosis

- Thick, uniform, septate hyphae 3–6 μm in width
- Dichotomous branching at 45° angle
- Birefringent needle-like crystals (calcium oxalate) produced by A. niger and others
- Fruiting heads form in aerobic conditions
- Stained by Papanicolaou, Periodic acid-Schiff (PAS) and Grocott methods
- Potentially a contaminant but should always be reported

Cryptococcosis

- Seen extracellularly or intracellularly within macrophages
- Yeast cells 5–10 μm in size surrounded by thick mucoid capsule (clear zone)
- Single narrow-based budding with tear drop appearance
- Green cytoplasm with clear capsule on Papanicolaou staining
- PAS, alcian blue and mucicarmine stain the capsule
- Gomori's methenamine silver (GMS) stains the organism
- Background inflammation varies from mild to necrosis

Histoplasmosis

- Readily recognized on methenamine silver stain
- Oval, single budding, yeast like organism (2–5 μm) in macrophages and neutrophils

Phycomycosis/Zygomycetes (Mucor, Rhizopus etc.)

- Occur in severely immunocompromised, diabetics, renal failure and patients with severe burns
- Non-septae broad hyphae of variable width (5–20 μm), resembling ribbons

- Irregular branching at up to 90º angles
- Pale staining with most staining methods

Coccidiodomycosis

- Endemic in western and southern states
- Intact or collapsed large thick-walled spherules 20–60 μm in diameter (empty or contain endospores, resemble a bag of marbles)
- Round, non-budding, nucleated endospores 2–5 μm in size
- Eosinophilic staining in Papanicolaou preparations
- Strongly stained by Grocott's method

Blastomycosis

- Yeast cells 8–15 μm in diameter
- Refractile thick cell wall (double contour), poorly stained in Papanicolaou samples
- Strong staining with Grocott's method
- Single broad-based budding
- No hyphae
- Suppurative granulomatous inflammation in background

Candidiasis

- Candida species are part of the normal flora of the oropharynx
- Diagnosis requires histologic demonstration of pulmonary parenchymal invasion or identification of materials from FNA
- Small spherical to oval yeast like cell 2–6 μm in diameter
- Pseudohyphae and spores (sticks and stones)
- Should see both pseudohyphae and inflammatory response to diagnose as pathogenic

Tuberculosis

- A mixed inflammatory exudate
- Epithelioid histiocytes and giant cells
- Langerhan's giant cells (peripheral nuclei) are infrequently found
- Fragmented granuloma may be seen in FNA material
- Caseation ranges from absent to conspicuous
- Organisms may be demonstrated in FNA samples
- Requires acid fast staining, yield is higher when necrosis is present

Pneumocystitis carinii *(PCP)*

- Eosinophilic foamy alveolar exudate
- Cluster of organisms with round clear spaces within the eosinophilic material (overlapping ringlets)
- Tiny basophilic dots are frequently seen in the clear spaces
- Cysts are 4–8 mm, spherical or cup shaped
- Trophozoites are 8/cyst
- Capsule/cyst stain: GMS, PAS, and toluidine blue
- Romanovsky (includes Diff-Quik, Geimsa and Wright stains) results in empty spaces against a purple background
- Trophozoites stain: Gram, Romanovsky (tiny purple dots)

Neoplastic Lesions

Keratinizing Squamous Cell Carcinoma (SCC)

Cytologic Findings

- Discohesive squamous cells with abnormal keratinization, pearls, and intercellular bridges
- Abundant orangeophilic waxy cytoplasm (Papanicolaou stain), pure blue (Romanovsky stain)
- Marked nuclear and cellular pleomorphism with variable N/C ratio
- Bizarre cell shapes including caudate and tadpole cells
- Irregular pyknotic nuclei with marked nuclear hyperchromasia
- Tumor diathesis

Differential Diagnosis

- Atypical squamous metaplasia:
  - Lack cellular and nuclear pleomorphism
- Vegetable cell contaminants:
  - Rectangular cell, refractile cellulose cell wall, and amorphous nuclei
- Pulmonary infarct:
  - Reparative features
  - Reactive type II pneumocytes
  - Hemosiderin-laden macrophages
- Necrosis in other carcinomas and cells heavily blood stained may acquire orangiophilia and mimic keratinization (look for viable cells and evidence of other differentiation)

Non-Keratinizing Squamous Cell Carcinoma

Cytologic Findings

- Irregular cohesive sheets
- Prominent nucleoli
- Clues to squamous differentiation:
  - Perinuclear halos and condensation of peripheral cytoplasm
  - Dense cytoplasm and well defined cell borders
  - Nucleoli vary in size and number
  - Chromatin is coarse and varies in density among cells

Differential Diagnosis

- Other poorly differentiated carcinomas:
  - Lack clues to squamous differentiation

- Adenocarcinoma:
  - Most adenocarcinomas have vacuolated cytoplasm and syncytial appearance with ill-defined cell borders
  - Prominent nuclei that tend to be more monotonous
  - Chromatin more vesicular
- Large cell undifferentiated carcinoma:
  - Highly atypical and discohesive
  - Lack clues to squamous differentiation

Adenocarcinoma

Cytologic Findings

- Isolated cells in columnar configuration with altered polarity
- Sheets, rosettes, acinar, syncytial grouping, cell balls, and papillary structures with smooth community border
- Abundant pale or vacuolated cyanophilic cytoplasm
- Intracytoplasmic lumens in certain types
- Peripherally located round nuclei with coarse granular chromatin
- Chromatin more vesicular than SCC
- Single prominent maronucleoli
- Frequent nuclear pseudoinclusions in bronchoalveolar carcinoma
- Clean or mucinous background

Variants

- Bronchoalveolar carcinoma:
  - Cellular smear with monotonous cell population
  - Sheets of slightly atypical cells with no cilia
  - Arrangements in cell ball, sheets or papillae
  - Cell balls with flower-petal like knobby border
  - Mucinous variants often display vacuolated or abundant foamy cytoplasm
  - Round to oval eccentrically located nuclei with prominent nucleoli
  - Occasional nuclear folds and intranuclear cytoplasmic inclusions
  - Variable pleomorphism and atypia among cells
  - Psammoma bodies

Differential Diagnosis

- Mesothelioma:
  - Flat sheets of uniform population of cells with dense two-tone type cytoplasm
  - Scalloped borders, thick cell membrane and cytoplasmic blebs
  - Centrally placed nuclei
  - Lack hyaluronidase resistant alcian blue staining
  - See Table 6-2.
- Squamous cell carcinoma (see non-keratinizing SCC)

Table 6-2. Staining Characteristics of Mesothelioma and Adenocarcinoma

Stain	*Mesothelioma*	*Adenocarcinoma*
Routine stains	Two-tone appearance with Papanicolaou	Homogeneously distributed stain
	Peripheral blebs with Diff-Quik	No peripheral blebs noted
Special stains	PAS + digestible material (glycogen)	Glycogen content is small
	Coalesced vacuoles may appear sausage-shaped	PAS + material not digested
Immunostains	Extracellular alcian blue+ material removable by hyaluronidas	No hyaluronic acid present
CEA	Consistently negative	Consistently positive
EMA	Variably positive with frequently“thick” membrane	Frequently positive in cytoplasm and cell periphery
LMWK and HMWK	Positive for both	Positive only for LMWK
Leu M1	Invariably negative	Occasionally positive
HBME-1	Positive in many cases (cytoplasmic or membranous)	Occasionally positive
Calretinin	Positive in many cases	Usually negative

- Hyperplastic type II pneumocyte proliferations and reactive/reparative changes:
  - Smooth outlined spherical clusters and cohesive sheets of cells
  - Scalloped borders and intercellular windows (gap) typical of reactive type II pneumocytes
  - Spectrum of reactive changes and continuity with recognizable benign cells
  - Rectangular or columnar cells with cilia and shows terminal plates
  - Normal N/C ratio with abundant cytoplasm, uniform nuclei, and prominent nucleoli
  - Multinucleated cells and degenerative changes with smudged chromatin
  - Lack of necrosis and tumor diathesis
  - Sputum and BAL may contain numerous clusters
- Creola body:
  - Benign reactive columnar cell hyperplasia, often seen in asthma
  - Papillary tissue fragments or three-dimensional cell balls
  - Smaller, less differentiated peripheral palisading cells with terminal plates and cilia
- Pap cell:
  - Derived from squamous metaplasia/parakeratosis in pharynx or upper respiratory tract
  - Small angulated cells with degenerative nuclei (pseudokeratosis)
- Granular cell tumor:
  - Isolated or small clusters of cells with a finely granular cytoplasm
  - Uniform round to oval nuclei frequently eccentric
  - Small nucleoli
  - Some spindled cells
  - S-100 protein +

Large Cell Undifferentiated Carcinoma

Cytologic Findings

- Single or disorganized groups of large malignant cells with pleomorphic cell population
- High N/C ratio with variable cytoplasm and intracytoplasmic neutrophils
- Nuclear enlargement with multiple large prominent nucleoli
- Thickened irregular nuclear membrane and coarse clumped chromatin pattern
- Delicate cyanophilic cytoplasm without evidence of squamous or glandular differentiation
- May contain giant cells (<25% of total cells)
- Tumor diathesis

Differential Diagnosis

- Giant cell carcinoma:
  - Neutrophil infiltrate and emperipolesis
  - Pronounced nuclear pleomorphism with multiple nuclei and nucleoli
  - Multinucleated cells constitute more than 25% of total cell population
- Metastatic Melanoma:
  - Dusty cytoplasm
  - Intranuclear pseudoinclusions
  - Positive staining to S-100 protein, HMB-45, and Melan-A (Mart-1)

Pulmonary Neuroendocrine Tumors

- Typical carcinoid
- Atypical carcinoid
- Large cell neuroendocrine carcinoma
- Small cell carcinoma

Typical Carcinoid

- Highly cellular smears
- Monotonous population of small round to oval cells
- Cells may have plasmacytoid appearance
- Occasional intranuclear inclusions
- Cohesive clusters, loosely cohesive sheets and single cells
- Acinar structures, papillae, cords of cells, interconnecting trabeculae, and nuclear palisading
- Low nuclear to cytoplasmic ratio
- No chromatin smearing
- Prominent capillaries

Atypical Carcinoid

- Slight to moderate nuclear pleomorphism
- More prominent nucleoli
- Occasional mitotic activity
- Single cell necrosis

Spindle Cell Carcinoid

- Common in peripheral carcinoid
- Can be typical or atypical
- Monotonous population of fusiform cells forming arches and coma shapes
- Single cells or loose aggregates
- Moderate cytoplasm with elongated processes that may show interconnection
- Small nuclear indentation
- Single small nucleoli
- Prominent capillaries

Large Cell Neuroendocrine Carcinoma

- Large polygonal to oval cells
- Some discohesion
- Nuclei are more than three times the size of a resting lymphocyte
- Nuclei variable in size and shape:
  - Large vesicular nucleus and prominent nucleoli similar to adenocarcinoma
  - Coarse stippled nucleus and occasional nucleoli similar to small cell carcinoma
- Obvious mitotic figures
- Obvious necrosis
- Nuclear molding variable
- Capillaries present surrounded by palisading cells

Small Cell Carcinoma

Cytologic Findings

- Cellular smears
- Dimorphic population of large cohesive sheets in a background of small blue cells with discohesion
- Background of single cells, doublets and short cords
- High N/C ratio with scant cytoplasm and coarsely clumped, "salt and pepper" chromatin
- Bare nuclei and elongated cells with pointed and angulated nuclei
- Nuclear size is equal or less than three times the size of a resting lymphocyte
- Paranuclear cytoplasmic inclusion (blue body)
- Chromatin smearing
- Pleomorphic, hyperchromatic, stippled nuclei with no nucleoli
- Extensive cellular molding
- Very obvious mitotic activity
- Necrotic background

Differential Diagnosis

- Reserve cell hyperplasia:
  - More cohesive, uniform cuboidal cells with smooth nuclear contours
  - Peripheral cells may have columnar configuration with cilia or terminal bars
  - Round uniform nuclei sometimes with very tight molding or crushing
  - Lack of discohesion or single cells
  - Lack tumor diathesis
- Benign lymphocytes and follicular bronchitis:
  - Small lymphocytes without anisonucleosis
  - Sharp demarcation of the euchromatin from heterochromatin
- Lymphoma/Leukemia:
  - Loosely aggregated lymphoid cells with intact cytoplasm
  - Vesicular nuclei, and visible nucleoli, no molding
  - Subtyping possible in BAL and FNA materials

Metastatic Carcinoma

- Metastatic Colon Carcinoma:
  - Geographic sheets in a background of extensive necrosis
  - Columnar cells with elongated hyperchromatic nuclei in a picket-fence or rosette pattern
  - Cytoplasmic vacuoles and prominent nucleoli may be seen
  - Prominent tumor necrosis
- Renal Cell Carcinoma:
  - Discohesive sheets of monotonous cells with uniform nuclei
  - Clear or granular cytoplasm
  - Numerous bare nuclei (due to fragile cytoplasm)
- Prostatic Adenocarcinoma:
  - Acinar arrangement of uniform cells with prominent nucleoli
- Breast Carcinoma:
  - Isolated cells or cell balls with eccentric nuclei imparting plasmacytoid appearance
  - Occasional cytoplasmic vacuoles and signet ring cells

SALIVARY GLAND AND HEAD/NECK CYTOLOGY

Statistics

- Most common salivary gland tumor:
  - Pleomorphic adenoma
  - Warthin's tumor (2nd most common)
- Most common parotid cancer in adults:
  - Mucoepidermoid carcinoma
- Most common malignancy of salivary glands other than parotid location:
  - Adenoid cystic carcinoma
  - Polymorphous low grade adenocarcinoma (2nd most common)
- Most common salivary gland malignancy in child:
  - Mucoepidermoid carcinoma
  - Acinic cell carcinoma (2nd most common)
- Most common cystic lesions of salivary glands:
  - Warthin's tumor
  - Mucoepidermoid carcinoma (2nd most common)
- Most common bilateral tumors of salivary glands:
  - Warthin's tumor
  - Acinic cell carcinoma (2nd most common)
- Most common bilateral cancer of salivary glands:
  - Acinic cell carcinoma
- Most common radiation induced malignancy:
  - Mucoepidermoid carcinoma

Salivary Glands

Normal Findings

- Acinar cells (serous or mucinous):
  - Cohesive tissue fragments of spherical acini outlined by their basement membrane
  - Often held together by small amount of fibrovascular tissue
  - May be connected by small ductular structure
  - Serous glands:
    - Abundant finely vacuolated cytoplasm
    - Small round basal nuclei
    - May result in numerous bare nuclei (not to be confused with lymphocytes)
- Ductal cells:
  - Small cohesive flat sheets
  - Small cells with dense cytoplasm
  - Round to oval nuclei

Non-Neoplastic Lesions

Sialadenosis

- Often bilateral enlargement of the parotid glands
- Numerous acinar epithelial cells
- Cells may appear normal or enlarged

Sialadenitis

Cytologic Findings

- Infective sialadenitis:
  - Tender swollen glands
  - Purulent material comprised of neutrophils, foamy cells, and endothelial cells
- Chronic sialadenitis:
  - Key features are interstitial fibrosis and atrophy
  - Hypocellular smear of cohesive clusters of epithelial cells with reactive changes
  - Fibroblasts and admixtures of polymorphous inflammatory cells
  - Oncocytic or squamous metaplasia (may have some atypia)
- Necrotizing sialometaplasia:
  - Mainly affect the minor salivary glands
  - Squamous metaplasia with atypia

Differential Diagnosis

- Benign lymphoepithelial lesions:
  - Admixtures of polymorphous lymphoid cells and myoepithelial islands
  - Few oncocytes and multinucleated histiocytes
  - Absence of acute inflammatory cells
- Malignant lymphoma:
  - Monotonous population of isolated lymphoid cells
  - Absence of oncocytes and multinucleated histiocytes
- Intraparotid lymph node:
  - Hypercellular smear of heterogeneous elements of lymphoid tissue

Benign Neoplastic Lesions

Pleomorphic Adenoma (Benign Mixed Tumor)

Cytologic Findings

- Biphasic population of epithelial cells and spindle stromal cell components
- Trabeculae, acinar and solid branching arrangement of epithelial cells
- Many single cells
- Cells may be plasmacytoid or vacuolated (sometimes signet ring)
- Well defined cytoplasmic border
- Round nuclei with finely granular chromatin
- Fibrillar chondromyxoid metachromatic stroma with irregular feathery outline on Romanovsky
- Tyrosine-rich crystals and metaplastic goblet or squamous cells may be seen

Differential Diagnosis

- Malignant mixed tumor:
  - Malignant components (glandular, squamous, small cell or sarcomatous)
- Epithelial-myoepithelial carcinoma:
  - Biphasic population of dark and clear cells
  - Numerous bare nuclei or bipolar cells
  - Absence of mesenchymal stromal component
- Mucoepidermoid carcinoma:
  - Goblet cells, columnar cells and intermediate cells
- Well differentiated adenoid cystic carcinoma:
  - Small cells with high N/C ratio
  - Hyperchromatic nuclei
  - Scant cytoplasm
- Basal cell (monomorphic) adenoma:
  - Numerous epithelial clusters and few single cells
  - Finely granular chromatin and scant cytoplasm
  - Variable amount of stromal material
  - Membranous variant: clusters surrounded by hyaline material (opposite to what is seen in adenoid cystic carcinoma)

Warthin's Tumor (Papillary Cystadenoma Lymphomatosum)

Cytologic Findings

- Orderly cohesive flat sheets and clusters of oncocytes intermixed with many lymphocytes
- Occasional aspirates may be dominated by lymphocytes

Differential Diagnosis

- Brachial cleft cyst:
  - Anucleated squamous cells and cholesterol cleft
- Benign lymphoepithelial lesions:
  - Myoepithelial islands and less frequent oncocytes
- Acinic cell carcinoma:
  - More cellular, sheets and acinar glandular structures, lymphocytes inconspicuous
  - Numerous bare nuclei
  - PAS-positive and diastase resistant
- Oncocytoma:
  - More abundant eosinophilic cytoplasm, lymphocytes inconspicuous
- Mucoepidermoid carcinoma;
  - Coexistence of glandular and squamous components with intermediate cells

Malignant Neoplasms

Mucoepidermoid Carcinoma

Cytologic Findings

- Discohesive sheets and clusters of glandular and squamous cells
- Intermediate cell differentiation is pathognomonic
- Dirty background containing mucus and debris
- Low grade: predominantly glandular component
- High grade: squamous component often predominant

Differential Diagnosis

- Mucocele:
  - Hypocellular smear with necrotic debris, inflammatory cells and mucoid material
- Warthin's tumor:
  - Admixture of oncocytic cells and lymphocytes
- Chronic sialadenosis
- Necrotizing sialometaplasia
- Pleomorphic adenoma
- Metastatic squamous cell carcinoma:
  - Abundant keratinized cells and keratin pearls, lack intermediate cells

Adenoid Cystic Carcinoma

Cytologic Findings

- Cellular smear of tight three dimensional cell balls
- Small uniform basaloid hyperchromatic cells surrounding smooth rounded hyaline globules composed of homogenous basement membrane material
- No squamous differentiation

Differential Diagnosis

- Monomorphic adenoma (trabecular adenoma):
  - Irregular interface between tumor cells and collagenous stroma
  - Tubular and branching growth pattern and more abundant finely fibrillar stroma
  - Round to oval uniform nuclei with inconspicuous nucleoli
- Monomorphic adenoma (membranous):
  - Clusters outlined by membranous material

Acinic Cell Carcinoma

Cytologic Findings

- Highly cellular material in a clean background
- Sheets and cords of monotonous cells with nuclear enlargement and nuclear pseudoinclusions
- Cohesive clusters sometimes with fibrovascular cores
- Poorly formed acinar structures

- Moderate sized nuclei with variable pleomorphism
- Abundant vacuolated or oncocytic cells
- Vacuolated cytoplasm (PAS-positive, diastase resistant)
- Stripped nuclei and lymphocytes
- Lack of ductal sheets

Differential Diagnosis

- Benign salivary gland acini:
  - Less cellular
  - Ductal epithelial cells, and fat present

Polymorphous Low Grade Adenocarcinoma

- Poorly cohesive clusters
- Small cells with scant cytoplasm and oval nuclei
- Finely granular chromatin and inconspicuous nucleoli
- Small hyaline oval globules

Salivary Duct Carcinoma

- Cytologic findings resemble those of comedocarcinoma of the breast
- Sheets of obviously malignant cells with high N/C ratio and pleomorphic nuclei
- Necrotic background

Head and Neck

Non-Neoplastic Lesions

Thyroglossal Duct Cyst

- Midline location and movable in a cranial direction when swallowing
- Hypocellular smear with squamous and glandular cells admixed with lymphocytes
- Thyroid follicular epithelium and variable colloid may be seen
- Occasional ciliated columnar respiratory epithelium

Epidermal Inclusion Cyst

- Abundant anucleated squames, inconspicuous lymphocytes
- Superimposed infection with neutrophils and multinucleated histiocytes

Brachial Cleft Cyst

Cytologic Findings

- Aspirate results in a thick yellow fluid
- Admixtures of numerous anucleated squamous cells and squamous cells of variable maturity, cholesterol clefts, elements of reactive lymphoid tissue, foamy histiocytes and acellular debris
- Occasional ciliated columnar respiratory epithelium

Differential Diagnosis

- Metastatic squamous cell carcinoma with cystic degeneration (diagnosis rests on finding few highly atypical or bizarre cells with abnormal keratinization)
- Suppurative lymphadenitis
- Thyroglossal duct cyst (distinguished by anatomic site)
- Epidermal inclusion cyst

Neoplastic Lesions

Paraganglioma (Carotid Body and Glomus Jugulare Tumors)

Cytologic Findings

- Single or poorly cohesive cells with vague follicular pattern
- Abundant pale cytoplasm with fine red garanules on Romanovsky
- Round to oval nuclei with finely granular chromatin
- Intranuclear pseudoinclusions may be seen
- Aspirates are very bloody

Differential Diagnosis

- Medullary carcinoma of the thyroid:
  - Aspirates are usually more cellular and less bloody
  - Amyloid may be seen
  - Part of multiple neuroendocrine tumor syndrome

Neurilemmoma/Schwannoma

- Frequently occur in the head and neck (45%) particularly lateral aspect
- More often in women than men
- Should always be included in the differential of head and neck lesions

Meningioma

- Extracranial tumors appear in relation to the base of skull, the scalp, orbit, nasal cavity, paranasal sinuses, and middle ear
- Should always be included in the differential diagnosis of any head and neck lesion

Squamous Cell Carcinoma

- Most common carcinoma in the head and neck region
- Lymph node metastasis of well differentiated carcinoma have a tendency for cystic degeneration
- Few atypical cells in a dirty background may be all that is seen in a cystic or necrotic mass (look for abnormal dense keratin and bizarre shaped cells)
- Cytologic features are similar to those described in the respiratory section

Nasopharyngeal Carcinoma

Cytologic Features

- Undifferentiated malignant cells in small clusters and single cells
- High N/C ratio and scant eosinophilic cytoplasm
- Lymphoepitheliomatous type:
  - Large open nuclei and prominent nucleoli
  - Well defined eosinophilic cytoplasm
- Undifferentiated type:
  - Basaloid cells with hyperchromatic nuclei
- Numerous benign lymphocytes in the background

Differential Diagnosis

- Undifferentiated type from basal cell carcinoma
- Lymphoepitheliomatous type from Hodgkin's lymphoma or large cell lymphoma

Olfactory Neuroblastoma

- Occurs in the upper nasal cavity and may metastasize to cervical lymph nodes
- Small blue cells forming pseudorosettes
- Bland nuclei with finely granular chromatin
- Fibrillary material may be seen in the center of rosettes

THYROID

Overview

- Reporting Terminology (Diagn Cytopathol 15:84-9, 1996)
  - Unsatisfactory for interpretation (specify reasons)
  - Benign thyroid nodule/colloid nodule/nodular goiter
  - Cyst/cystic goiter, with or without hemorrhage
  - Thyroiditis, specify type
  - Cellular follicular lesion, favor nonneoplastic process
  - Follicular neoplasm
  - Hürthle cell neoplasm
  - Malignant, specify type if possible
  - Other

Benign Lesions

Thyroid Cysts

- Majority are benign
- Result in degenerative, necrosis, or hemorrhage within adenomatous nodule or neoplasm
- Benign cysts collapse after aspiration
- Variable number of histiocytes, +/– hemosiderin
- Multinucleated foreign body giant cells may be present
- Occasionally lined by squamous or columnar cells (thyroglossal duct cyst)
- Mainly lack epithelial cell component
- Beware of cystic papillary carcinoma

Thyroiditis

Acute Thyroiditis

Cytologic Findings

- Enlarged gland with multiple abscesses
- Abundant neutrophils, macrophages, cellular debris, and fibrin
- Scant follicular cells

Differential Diagnosis

- Infected thyroglossal duct cyst:
  - Columnar ciliated or squamous cells
- Carcinoma with necrosis

Subacute Thyroiditis

- Common in middle age woman
- Resolve spontaneously in most cases
- Initial stage: degenerated follicular cells, multinucleated giant cells, epithelioid histiocytes, lymphocytes and neutrophils; background dirty.
- Late stage: low cellularity with few inflammatory cells and active fibroblasts

Subacute Lymphocytic Thyroiditis

- Painless swelling that resolves spontaneously
- May develop in postpartum women
- Moderate lymphocytes and no Hurthle cells

Chronic Thyroiditis

- Chronic granulomatous thyroiditis e.g. tuberculous, mycotic, etc.
- Reidel's thyroiditis:
  - Chronic fibrosing multifocal inflammation
  - Probably autoimmune
  - Sudden painless enlargement of a long standing mass
  - Dysphagia or dyspnea
  - Aspirates are poorly cellular and frequently non-diagnostic
  - May contain few lymphocytes, degenerated follicular cells and fibroblasts

Hashimoto's Thyroiditis

Clinical

- Middle aged women present with hypothyroidism
- Moderate generalized enlargement, micronodules can develop in late lesions

Cytologic Findings

- Acute phase: mostly lymphocytes
- Hypertrophic phase: admixture of lymphocytes and Hurthle cells.
- Atrophic phase: admixture of cells but much lower in cellularity
- Microtissue fragments composed of Hurthle cells and hyperplastic follicular epithelium
- Admixture of inflammatory cells with germinal center (immature) lymphocytes, small lymphocytes, plasma cells and histiocytes
- Characteristically the lymphocytes infiltrate the Hurthle cells
- The Hurthle cells can occasionally be quite bizarre
- Inconspicuous colloid component

Differential Diagnosis

- Hürthle cell neoplasm:
  - Large sheets of Hurthle cells with syncytial arrangement and lack of lymphocytes
  - Numerous discohesive Hurthle cells
  - Prominent Hurthle cell nodules that do not have lymphocytes can be indistinguishable from Hurthle cell neoplasms
- Riedel's thyroiditis:
  - Fewer follicular center cells and absence of squamous metaplasia or Hurthle cells
  - More abundant neutrophils and eosinophils
- Subacute (Dequervain's) granulomatous thyroiditis:
  - Follicular center (immature) lymphocytes and Hurthle cells uncommon
  - Admixtures of follicular epithelium, small lymphocytes, epithelioid histiocytes, and foreign-body giant cells
  - Foreign body reaction "ingesting" colloid .
  - Fibroblast and inflammatory debris
- Graves' disease:
  - Hypercellular smear with hyperplastic follicular epithelium
  - Inconspicuous colloid and inflammatory components
  - Flame cells

Black Thyroid Nodule

- Due to administration of minocyclines and tetracyclin
- Intracytoplasmic deposits of brown pigment in follicular cells
- Pigment consists of neuromelanin and lipofuscin

Nodular Goiter and Colloid Nodule

Cytologic Findings (see Table 6-3)

- Abundant colloid and variable number of follicular cells
- The presence of a labrithin of a rouloux of red blood cells and empty spaces with scant follicular cells suggests washed-out colloid
- Microtissue fragments, small follicles, and honeycomb sheets of follicular epithelium
- Nuclei are round with smooth contours.
- Minor variation in nuclear size in the sheet may be observed.
- Degenerative changes common (histiocytes, +/– hemosiderin, giant cells, and fibroblasts
- Regenerative (reparative) changes
- Hurthle cell change, foam cells, and giant cells with foamy cytoplasm
- Stromal calcification

Toxic Diffuse Hyperplasia (Graves' disease)

- Highly cellular smears consisting of colloid and follicular/Hürthle cells
- Flame cells (key feature):
  - Follicular cells with metachromatic materials in apical cytoplasm
  - Secondary to hyperfunctioning of endoplasmic reticulum
  - May also be present in aspirates from active nodules
  - Paravacuolar granules

Table 6-3. Differential Diagnosis of Follicular Lesions

Colloid Nodule/Goiter	*Follicular Neoplasm*
Abundant colloid and scanty cellularity	Cellular specimen with scant colloid
Honeycomb sheets of follicular cells	Syncytial sheets and microfollicles
Regenerative and degenerative changes	

- Non-specific findings, composed of lysosome with hemosiderin or lipofuscin
- Seen best on Romanovsky stain

Differential Diagnosis of Hyperplastic lesions

- Follicular neoplasm (see Table 6-3)
- Follicular variant of papillary carcinoma:
  - Nuclear features of papillary carcinoma are preserved

Neoplastic Lesions

Follicular Neoplasm Favor Benign

Cytologic Findings (See Table 6-3)

- Hypercellular smear, microfollicles, and microfollicular complexes
- Uniform nuclei, and orderly cellular arrangement
- Syncytial tissue fragments with loss of honeycomb pattern
- Rarely markedly atypical or bizarre cells may be observed in atypical adenoma
- Scant colloid

Differential Diagnosis

- Parathyroid adenoma:
  - High cellularity with microfollicular pattern
  - Indistinguishable from follicular neoplasm
- Nodular goiter (see Table 6-3):
  - Admixture of colloid and follicular epithelial cells with small nuclei
  - Honeycomb sheets

Hürthle Cell Neoplasm

- Cellular smear of monomorphic discohesive cells
- Sheets and single isolated large oval or polygonal cells with abundant eosinophilic cytoplasm
- Uniform small round nuclei with fine granular chromatin and single prominent nucleoli
- Adenomas may not be reliably distinguished from well-differentiated carcinoma on FNA biopsies
- Carcinoma often more discohesive with numerous isolated smaller cells with high N/C ratio, nuclear pleomorphism, nuclear overlapping, coarsely granular chromatin and multiple nucleoli

Papillary Carcinoma

- Microtissue fragments of monolayer sheets, syncytium, and papillae with or without fibrovascular core
- Follicular structures observed especially in follicular variant
- Dispersed cell pattern may rarely be observed .
- Numerous oval nuclei with irregular nuclear membranes (nuclear grooves imparting a coffee bean appearance)
- Any intranuclear cytoplasmic inclusions (diagnostic of papillary carcinoma, but may be observed in medullary carcinoma)
- Nuclei with fine granular chromatin and multiple small nucleoli
- Nuclear molding and crowding
- Septated cytoplasmic vacuoles seen on Romanovsky stain
- Squamous differentiation with dense metaplastic cytoplasm
- Psammoma bodies: colorless and refractile on Romanovsky, but laminations can still be appreciated
- "Bubble gum" colloid: metachromatic on Romanovsky stain and stringy on papanicolau stain (sticky and stretch out)
- Lymphocytosis may be seen (uncommon in other thyroid tumors)
- Giant cells with epithelioid cytoplasm (giant cells with foamy cytoplasm may be observed in goiter)

Follicular Carcinoma

Cytologic Findings

- Well differentiated carcinoma may be indistinguishable from adenoma
- Cellular smear with syncytial microtissue fragments and small follicles
- Disordered cellular pattern with crowding and pilling.
- Nucleomegaly with coarse granular chromatin and prominent nucleoli
- Loss of polarity within the cell aggregates with cellular crowding
- Scant colloid

Medullary Carcinoma

Cytologic Findings

- Discohesive clusters and isolated spindle or plasmacytoid cells
- Pale delicate cytoplasm with red azurophilic cytoplasmic granules (calcitonin)
- Eccentric round to oval nuclei with salt and pepper chromatin
- Bi- or multinucleation, and intranuclear cytoplasmic inclusions
- Fluffy, granular or acellular amyloid stroma, positive for Congo red stain
- Fine red metachromatic (neurosecretory) granules on Romanovsky stain
- Large atypical cells and giant cells may be observed

Differential Diagnosis

- Malignant lymphoma:
  - Numerous isolated monotonous cells and lymphoglandular bodies on Romanovsky stain

- Lack germinal center cells and epithelial components
- Lack of salt and pepper chromatin

Anaplastic Carcinoma

- Isolated or discohesive clusters of cells
- Marked nuclear pleomorphism and large bizarre cells with prominent macronucleoli
- Tumor diathesis

Metastatic Carcinoma

- Consider this diagnosis when the cytologic features are not consistent with conventional thyroid neoplasms
- Metastatic renal carcinoma with granular cytoplasm may be difficult to differentiate from Hurthle cell neoplasms

BREAST

Overview

Stromal and Epithelial Cells

- Fibroadenoma
- Phyllodes tumor
- Periductal stromal sarcoma
- Carcinosarcoma
- Adenocarcinoma with marked stromal fibrosis

Squamous Cells

- Subareolar abscess
- Fibrocystic change (rare)
- Phyllodes tumor (rare)
- Gynecomastia
- Infarcted papilloma (rare)
- Cysts (epidermal inclusion cyst and fibrocystic change)
- Metaplastic carcinoma

Apocrine Cells

- Fibrocystic changes
- Fibroadenoma
- Benign phyllodes tumor
- Apocrine carcinoma

Giant Cells

- Duct ectasia
- Granulomatous mastitis
- Foreign body reaction (e.g. suture material, silicon)
- Fat necrosis
- Medullary carcinoma

Small Cells

- Ductal carcinoma
- Tubular carcinoma
- Lobular carcinoma
- Lymphoma
- Carcinoid

Reporting Terminology (Diagn Cytopathol 1997;16:295-311)

- Benign: no evidence of malignancy
- Atypical/indeterminate: cellular findings are not diagnostic, clinical and radiologic correlation is warranted
- Suspicious/probably malignant: Highly suggestive of malignancy, recommend tissue biopsy
- Malignant: findings diagnostic of malignancy. Qualify further with specific diagnosis
- Unsatisfactory (due to):
  - Scant cellularity
  - Airdrying or distortion artifact
  - Obscuring blood or inflammaation
  - Other

Benign Lesions

Fat Necrosis

- Foreign body reaction with foamy histiocytes and giant cells
- Isolated atypical fibroblast with enlarged nuclei and fine vesicular chromatin
- Atypical ductal cells with reparative changes and granulation tissue
- Hemosiderin-laden macrophages indicate old blood
- Disrupted fat and dystrophic calcifications

Subareolar Abscesses

- Thick material obtained by aspiration
- Suppurative granulomatous inflammation
- Anucleated squamous cells in granular, necrotic dirty inflammatory background
- May contain mature metaplastic or parakeratotic cells
- Reactive and reparative epithelial changes

Lactational Changes

Cytologic Findings

- Moderate cellularity with uniform cell population

- Numerous bare nuclei (fragile hypervacuolated cytoplasm)
- Discohesive cells with prominent nucleoli and foamy vacuolated cytoplasm in a granular proteinaceous background (milky)
- Intranuclear pseudoinclusion and minimal nuclear pleomorphism
- Naked bipolar myoepithelial cells with prominent nucleoli

Differential Diagnosis

- Lactating adenoma:
  - More cellular
  - Numerous strips of epithelial clusters with foamy vacuolated cytoplasm
- Lobular carcinoma and signet ring cell carcinoma:
  - Significant cytologic atypia, nuclear pleomorphism, necrosis and loss of polarity

Fibrocystic Changes

- Triad of epithelial hyperplasia, cyst formation, and stromal fibrosis

Cytologic findings

- Cohesive sheets of ductal epithelial cells with honey comb arrangement
- Polymorphous population of cells is a key feature
- Bipolar/myoepithelial cells within the sheets and in the background
- Apocrine metaplasia
- Foamy histiocytes (content of cyst)
- Occasional fibroblasts in the background depending on the extent of fibrosis

Differential diagnosis

- Fibroadenoma:
  - Branching complex sheets
  - More bare nuclei in the background
- Well differentiated ductal carcinoma:
  - More irregular sheets with frayed edges and pointed borders
  - More pronounced nuclear atypia
  - Striped fibroblasts may mimic bipolar cells

Fibroadenoma

- Triad of complex epithelial fragments, myoepithelial cells, and fibromyxoid stroma

Cytologic Findings

- Cellular smear with a clean background
- Tight branching cohesive sheets of polymorphous cells forming antler horn or mitten-like papillary fronds
- Large monolayer and folded sheets
- Numerous striped bipolar naked myoepithelial cells
- Fragments of fibromyxoid stroma
- Occasional multinucleated giant cells (stromal origin)
- Mild nuclear and nucleolar enlargement and rare mitotic figures
- Occasional nuclear overlapping and few isolated cells
- Apocrine metaplastic cells and foamy histiocytes not uncommon

Differential Diagnosis

- Phyllodes tumor:
  - Dimorphic population of epithelium and stroma
  - Highly cellular stroma, with or without squamous metaplasia
  - Epithelial fragments similar to fibroadenoma
  - Cytologic atypia in naked bipolar cells and stromal fragments
  - Stromal fragments tend to be more cellular than fibroadenoma
  - Blood vessels across the stromal fragments
- Well differentiated ductal carcinoma:
  - Epithelium with pointed edges and irregular borders
  - Cytologic atypia with nuclear overlapping and nuclear membrane irregularity
  - Lack of stripped bipolar nuclei
- Tubular carcinoma:
  - Low cellular smears
  - Three dimensional tubular structures with angulated appearance
  - Less frequent bipolar cells
- Fibromatosis, nodular fasciitis, and mammary fibrosis:
  - Often indistinguishable on FNA biopsy
  - Hypocellular smear of isolated spindle fibroblasts and syncytial stromal fragments
  - Lack epithelial components
  - Myxoid stroma in an inflammatory background more common in nodular fasciitis
  - Fragments of mature adipose tissue and stromal fragments common in mammary fibrosis
- Fibrocystic changes:
  - Apocrine metaplasia, foamy macrophages, and epithelial hyperplasia
  - Granular, proteinaceous secretion
  - Lack of characteristic epithelial fragments

Gynecomastia

- Findings similar to fibroadenoma, but less cellular
- Branching, cohesive sheets of hyperplastic polymorphous cells and naked bipolar cells
- Frequent discohesive isolated columnar cells
- Cytologic atypia may be striking

Intraductal Papilloma

Cytologic Findings

- Cellular smear composed of sheets of polymorphous cells and few singly scattered cells
- Papillae and columnar cells with eccentric nuclei
- Minimal nuclear pleomorphism and nuclear membrane irregularity
- Mixtures of apocrine metaplasia, foamy macrophages and sheets of hyperplastic ductal cells

Differential Diagnosis

- Intracystic papillary carcinoma:
  - Branching three-dimensional papillae with more complex architecture and monomorphic cell population
  - Numerous single papillae
  - Increased discohesiveness, nuclear pleomorphism, and mitotic figures
  - Some cases may have numerous columnar cells

Ductal Carcinoma *In Situ* and Invasive Carcinoma

- Carcinoma *in situ* cannot be reliably separated from invasive carcinoma by cytology. The following are characteristic features suggested by the literature.

Ductal Carcinoma In Situ *(DCIS)*

Cytologic Findings

- Monotonous discohesive isolated cells often >10% of the atypical cell population
- Three-dimensional clusters of cells with papillary, solid or cribriform configuration
- Rare bipolar cells or bare nuclei
- Cytologic atypia with nuclear pleomorphism, nuclear hyperchromasia, coarsely granular chromatin, prominent macronucleoli, and necrosis in comedo-type DCIS

Differential Diagnosis

- Ductal hyperplasia without atypia:
  - Clusters and crowded sheets of cells in a complex arrangement with cellular streaming, nuclear spindling, and irregular lumen formation
  - Bipolar bare nuclei
- Atypical ductal hyperplasia:
  - Often indistinguishable from low grade DCIS
  - Clusters and flat sheets of epithelial cells with regular lumen formation
  - Loss of polarity and cell cohesion with increased isolated monotonous cells
  - Nuclear enlargement, crowding, and overlapping
  - Admixture of benign stromal cells and apocrine metaplastic cells
- Low grade ductal carcinoma:
  - Increased discohesive isolated monotonous cells
  - Absence of benign cellular components
  - Dirty, inflammatory background

Lobular Carcinoma In Situ

Cytologic Findings

- Hypocellular smear of single isolated uniform small cells and three dimensional cell balls
- Indian filing and nuclear molding
- Eccentric nuclei and intracytoplasmic vacuoles (signet ring cells)
- Irregularly rounded and large bare nuclei, inconspicuous nucleoli

Differential Diagnosis

- Atypical lobular hyperplasia:
  - Often indistinguishable from LCIS
- Invasive lobular carcinoma:
  - More cellular, more discohesive, more cytologic atypia

Intracystic Papillary Carcinoma

Cytologic Findings

- Cellular smear of isolated monomorphic cells and branching papillae with smooth border
- Tall columnar cells with cytologic atypia and nuclear pleomorphism
- Increased mitotic figures and discohesiveness
- Numerous histiocytes, hemosiderin-laden macrophages and hemorrhagic background
- Arborized thin-walled blood vessels
- Irregularly rounded and large bare nuclei

Differential Diagnosis

- Intraductral papilloma:
  - More cohesive, lack cytologic atypia, round to oval nuclei
  - Apocrine metaplasia, foamy histiocytes and small bipolar bare nuclei
- Fibroadenoma:
  - Dimorphic populations of cells without cytologic atypia
  - Larger, more complex cellular fragment
  - Numerous stripped bipolar nuclei

Invasive Ductal Carcinoma

Cytologic Findings

- Cellular smear composed of discohesive single cells with plasmacytoid appearance
- Sheets and syncytial fragments of malignant cells with nuclear overlapping

- Monotonous population of atypical cells
- Irregular contours of nuclear membrane, coarsely clumped chromatin
- Nucleomegaly and prominent nucleoli, and anisonucleosis
- Lack of naked bipolar myoepithelial cells and loss of polarity
- Background of necrosis and tumor diathesis (nuclear and cytoplasmic debris, ghosts of cells, and old blood)

Differential Diagnosis

- Cellular fibroadenoma:
  - Dimorphic populations of bipolar naked cells and branching tight clusters and sheets of epithelial cells with fenestration
  - Preserved cellular polarity
  - Absence of prominent nucleoli and nuclear overlapping

Lobular Carcinoma

Cytologic Findings

- Low to moderately cellular smear of discohesive small cells
- Indian filing of cell arrangement and numerous isolated single cells
- High N/C ratio, nuclear membrane irregularity, nuclear hyperchromasia, small nucleoli
- Targetoid intracytoplasmic vacuoles with eccentric nuclei, imparting signet ring appearance

Differential Diagnosis

- Mucinous (colloid) carcinoma:
  - Cellular clusters and single mildly atypical cells
  - Mucoid background

Mucinous (Colloid) Carcinoma

Cytologic Findings

- Cellular smear of numerous isolated cell, discohesive sheets and cell balls
- Mucoid background (pink by Papanicolaou and blue by Romanovsky stain)
- Arborized thin-walled blood vessels within the mucus
- Intracytoplasmic vacuoles and eccentric uniform nuclei

Differential Diagnosis

- Mucocele:
  - Scant cellularity, few clusters and cohesive flat sheets of cells
  - Lack three-dimensional cell balls and arborized thin-walled blood vessels
  - No cytologic atypia
  - Abundant extracellular mucin and scattered histiocytes and fibroblasts
- Cystic hypersecretory duct carcinoma:
  - Scattered isolated, clusters and sheets of epithelial cells
  - Pink bubbling secretions with cracked artifact imparting mosaic plate appearance

Medullary Carcinoma

Cytologic Findings

- Cellular smear of isolated cells and discohesive clusters and syncytial fragments
- Large pleomorphic cells with nucleomegaly, anisonucleosis and prominent nucleoli (may be bizarre)
- Inflammatory background with lymphocytes and plasma cells

Tubular Carcinoma

Cytologic Findings

- Low to moderately cellular smear of discohesive isolated monotonous cells and angulated glands
- Three dimensional tubular structure with central lumens and loss of polarity
- Bipolar naked myoepithelial cells present in 25-50% of the cases
- Numerous uniform isolated small cells with small nucleoli and vacuolated cytoplasm

Differential Diagnosis

- Fibroadenoma:
  - Flat branching sheets with honeycomb pattern and staghorn configuration
  - Bipolar bare nuclei and fibrous stroma fragments

Apocrine Carcinoma

Cytologic Findings

- Cellular smear of isolated cells and discohesive clusters and syncytial fragments
- Apocrine differentiation with dense waxy eosinophilic cytoplasm and apocrine snouts
- Cytoplasm heavily granular (rich in mitochondria)
- Nucleomegaly, nuclear pleomorphism, and prominent nucleoli

Differential Diagnosis

- Fibrocystic change:
  - Less cellular, more cohesive, lack cytologic atypia or anisonucleosis
  - No significant nuclear pleomorphism and lack marconucleoli

Phyllodes Tumor

Cytologic Findings

- Cellular smear of two cell population (epithelial and stromal)
- Bipolar naked nuclei with cytologic atypia
- Branching tight clusters of epithelial cells

- Squamous metaplasia (rare)
- More abundant and cellular stroma
- Spindle cells embedded in metachromatic staining stroma
- Stromal overgrowth and/or stromal atypia with increased mitosis suggest malignancy

Differential Diagnosis

- Fibroadenoma:
  - Less cellular stromal fragments, clean background, lack cytologic atypia
- Juvenile cellular fibroadenoma:
  - Stromal elements may be abundant, no significant cytologic atypia
- Ductal carcinoma:
  - Lack bipolar cells and hypercellular stromal fragments

Metaplastic Carcinoma

Cytologic Findings

- Hypercellular smear of mixtures of poorly differentiated malignant cells and areas of squamous, sarcomatous, chondroid or osseous metaplasia
- Squamous metaplasia is the most common type of metaplasia
- Dense waxy eosinophilic cytoplasm and anucleated keratinous debris
- Multinucleated giant cells with intracytoplasmic vacuoles and phagocytic debris

Differential Diagnosis

- Fibromatosis and nodular fasciitis:
  - Less cellular smear, lack cytologic atypia

LYMPH NODE

Reactive Hyperplasia

- Polymorphous mixed cell population with predominant mature small lymphocytes admixed with tingible body macrophages, plasmacytoid lymphocytes, and immunoblasts
- Lymphoglandular bodies in background
- Lymphohistiocytic aggregate (follicular center fragment):
  - Consisting of dendritic cells associated with centroblasts and centrocytes.
  - Indicative of benign process or follicular lymphoma
  - Differential diagnosis: granuloma, carcinoma
- Russell body: intracytoplasmic inclusion bodies seen in reactive plasma cells
- Mott cell: plasma cells with large numbers of Russell bodies appearing as hyaline globules (immunoglobulin in the endoplasmic reticulum)

Acute Lymphadenitis

- Sheets of neutrophils and heterogeneous lymphoid cells in a necrotic background
- Varying degree of cell necrosis
- Bacteria and fungi may be identified

Necrotizing Granulomatous Lymphadenitis

- Etiology includes cat scratch disease, mycobacterial infection, Yersinia, tularemia, brucellosis and fungal infection
- Varying number of granuloma: loose or tightly clustered epithelioid histocytes
- Variable degree of background necrosis and neutrophils (the latter are less conspicuous in aspirates from mycobacterium infection)

Cat Scratch Disease

- Polymorphous cell populations of lymphocytes, plasma cells, and neutrophils
- Poorly formed granuloma with scattered epithelioid histiocytes
- Some of the granuloma may show a stellate configuration with central scattering of neutrophils
- Dirty necrotic background

Non-Necrotizing Granulomatous Lymphadenitis

- Etiology includes sarcoidosis, toxoplasmosis, infectious mononucleosis, tuberculosis, drug reactions, syphilis, berylliosis, foreign body reaction, lymphoma (especially Hodgkin lymphoma and T-cell lymphoma), and lymph node draining malignancies (especially squamous cell carcinoma and seminoma)
- Granuloma without background of necrosis
- Numerous multinucleated giant cells

Infectious Mononucleosis

- Predominantly immunoblasts with cellular elements of reactive hyperplasia
- Immunoblasts have pale or deep blue cytoplasm on Romanovsky
- Round nuclei with fine chromatin and regular prominent nucleoli
- Frequent tingible body macrophages and plasmacytoid lymphocytes
- Lymphograndular bodies may be seen

Malignant Lymphoma (see Chapter 7)

- Highly cellular smear
- Discohesive cells
- Usually relatively monomorphic population of abnormal lymphocytes
- Lymphoglandular bodies:
  - Fragments of lymphocyte cytoplasm
  - Seen in both benign and malignant lesions
  - Rare in T-cell lymphoma
  - Best appreciated on Romanovsky as light-blue or blue-gray globular or flakelike structure
- Dutcher body:
  - Intranuclear inclusion bodies (versus Russell bodies: intracytoplasmic inclusions, nonspecific)
  - Often seen in Waldenstrom's macroglobulinemia
  - May indicate neoplastic processes
- Flame cell: often seen in IgA producing myeloma

Common Variants of Lymphoma

Small Lymphocytic Lymphoma

- Monomorphic population of small round lymphocytes
- Uniform round nuclei with regular nuclear borders, and coarsely granular chromatin, and inconspicuous nucleoli
- Scant basophilic cytoplasm
- Lack tingible body macrophages and mitotic figures inconspicuous

Mantle Cell Lymphoma

- Monomorphic population of small lymphocytes that are larger than mature lymphocytes
- Nuclei with irregular nuclear contours and irregularly distributed chromatin
- Some nuclei have marked indentation/cleaves with deep fold ("coffee bean" nuclei)
- Lack tingible body macrophages

Burkitt's Lymphoma

- Cells 2–3x larger than mature lymphocytes
- Predominantly round nuclei
- Clumped chromatin pattern
- One or several prominent nucleoli
- Moderate amount of cytoplasm with frequent lipid vacuoles
- High mitotic figures
- Tingible body macrophages and necrosis common (indicate rapid turn over of cells)

Diffuse Large B-cell Lymphoma

- Cells 3x larger than mature lymphocytes, more variable in cell size
- Round or convoluted nuclei; nuclei may have projections (nipple)
- Variable chromatin pattern
- Nucleoli invariably present with variable number and size, usually prominent
- Moderate to abundant cytoplasm with inconspicuous vacuoles
- Mitotic figures variable
- Tingible body macrophages often seen

Adult T-cell Lymphoma

- Round nuclei, may be variably convoluted
- Cell 2x larger than mature lymphocytes
- Delicate chromatin pattern with inconspicuous nucleoli
- Scant cytoplasm, abundant or inconspicuous vacuoles
- Hand-mirror cells often seen in lymphoblastic lymphoma and Ki-1 lymphoma
- High mitotic figures
- Variable number of tingible body macrophages and necrosis

Anaplastic Large Cell Lymphoma

- Large pleomorphic cells with irregular nuclear contours, coarsely granular chromatin, and prominent nucleoli
- Bi- or multinucleation, wreath-like nuclei may be seen
- Moderate amounts of pale to basophilic cytoplasm with projections (hand-mirror cells)

Hodgkin Lymphoma

- Heterogeneous population of lymphoid cells with background eosinophils, plasma cells, similar to reactive process
- Reed-Sternberg cells with gray cytoplasm, mirror-image nuclei, irregular nuclear membrane, coarse chromatin, and prominent nucleoli
- Atypical mononuclear Reed-Sternberg cells
- Lacunar cells (large cells with hyperchromatic single or multinucleated and lobulated nuclei) often seen in nodular sclerosing variant
- Popcorn cells (pale multinucleated giant cell with lobulated nucleus and lack prominent nucleoli) often seen in lymphocyte-rich variant
- Epithelioid histiocytes and collage fragments may be observed

Skin (see Chapter 9)

Pilomatrixoma (Calcifying Epithelioma of Malherbe)

- Sheets of degenerated, anucleated squamous cells (ghost cells)
- Clusters of basaloid small cells
- Background of calcification, nuclear debris, inflammatory cells, and foreign body giant cells

Squamous Cell Carcinoma

- See previous discussion

Basal Cell Carcinoma

Cytologic Features

- Tight cell aggregates and some discohesive cells
- Palisading nuclei at periphery of aggregates
- Small cells with scant cyanophilic cytoplasm (Pap stain) and indistinct cell borders
- Small hyperchromatic nuclei with inconspicuous nucleoli
- No nuclear molding

Differential Diagnosis

- Basaloid squamous cell carcinoma:
  - Generally exhibit more discohesion, occasional dense cytoplasm, and more prominent nucleoli
- Merkel cell carcinoma:
  - Predominantly discohesive population of small cells
  - neuroendocrine features

Malignant Melanoma

- This tumor should be considered in the differential diagnosis of every tumor of unknown primary

Cytologic Features

- Smears are highly cellular
- Predominantly discohesive population and many single cells
- Occasionally tight clusters
- Plamacytoid appearance with eccentric nuclei
- Abundant dense or slightly vacuolated cytoplasm, frequently has a dusty quality
- Melanin pigment within the cytoplasm, loose, and in the background histiocytes (melanotic melanoma)
- Marked nuclear pleomorphism
- Binucleated and multinucleated cells
- Intranuclear cytoplasmic inclusions
- Prominent nucleoli
- Spindle cell variant present with numerous spindle cells, sometimes intermixed with few classic cells
- Myxoid stroma may be seen in occasional cases
- Small cell variant consist of relatively smaller cells than the epithelioid variant
- Positive for S-100, HMB-45, and Melan-A/Mart-1

Differential Diagnosis

- Spindle cell tumors
- Anaplastic large cell carcinoma
- Myxoid soft tissue tumors
- Small cell tumors

Merkel Cell Carcinoma

- Highly cellular smears
- Discohesive cell population of small abnormal cells
- Some nuclear molding, pseudorosettes, or acinar forms
- Scanty cyanophilic cytoplasm
- Round to oval nuclei
- Finely granular chromatin (neuroendocrine pattern)
- Intracytoplasmic red granules seen by Romanovsky
- Discrete intracytoplasmic dots (keratin buttons by electron microscopy)
- Cytokeratin 20 shows characteristic dot pattern corresponding to the keratin buttons

Soft Tissue (see Chapter 12)

Adipose Tissue Tumors

Lipoma

Cytologic Findings

- Microtissue fragments and tight clusters of adipocytes
- Round cells with single large clear cytoplasmic vacuoles and distinct cell borders
- Small round to oval nuclei, often eccentrically located
- Background of lipid droplets

Differential Diagnosis

- Normal subcutaneous tissue:
  - Indistinguishable from lipoma, clinical findings important
- Well-differentiated liposarcoma:
  - Atypical lipocytes (lipoblasts) with irregular and enlarged hyperchromatic nuclei
  - Prominent plexiform capillary network

Liposarcoma

Cytologic Findings

- Lipoblasts in a finely vascular stroma

- Lipoblasts often arranged around a delicate branching capillary network
- Lipoblasts may have variable cytologic appearance: spindle or stellate cells with small lipid droplets, single large cytoplasmic vacuoles (signet-ring type), or multivacuolated cytoplasm
- Nuclei may show indentation or scalloping
- Lipid droplets are usually sharply outlined and best appreciated on Romanovsky
- Myxoid liposarcoma contains a matrix rich in acid mucopolysaccharide that appears magenta to purple on Romanvsky and is alcian blue positive and mucin negative
- Round liposarcoma composed of densely packed small round cells with finely vacuolated cytoplasm and pleomorphic nuclei
- Pleomorphic liposarcoma often yield highly cellular smear composed of bizarre microvacuolated pleomorphic giant cells

Differential Diagnosis

- Lipid laden histiocytes (lipophages):
  - Foamy cytoplasm with fine vacuoles and indistinct vacuoles
  - Bean-shaped nuclei that are rounded rather than scalloped
  - Background of hemorrhage, necrosis, inflammation, lipids and giant cells
  - Lack characteristic features of lipoblast and plexiform capillary network
- Angiolipoma:
  - Monomorphic univacuolated adipocytes with uniform nuclei
  - Branching vascular pattern
  - Lack lipoblasts
- Pleomorphic lipoma:
  - Pleomorphic single and multinucleated giant cells
  - Peripheral circular arrangement of nuclei (floret cells)
  - Mature adipose tissue
  - No necrosis, mitotic figures and true lipoblasts
  - Complete excision for histologic examination is necessary due to sampling variation in order to avoid underdiagnosis
- Lipoblastomatosis:
  - Occurs in children < 3 years
  - Identical cytologic findings as myxoid liposarcoma
- Hibernoma:
  - Small round centrally located nuclei without scalloping
  - Multiple small uniform cytoplasmic vacuoles
- Signet ring cell carcinoma:
  - Mucin positive
  - Lack lipoblast and plexiform capillary network

Fibrous and Fibrohistiocytic Lesions

Nodular Fasciitis

- Hypocellular smear of spindle to ovoid cells in a mucoid or metachromatic stroma
- Discohesive large plump myofibroblasts
- Oval nuclei with evenly distributed granular chromatin and inconspicuous nucleoli
- Tissue fragments containing fibrin and metachromatic mucoid substances may be observed
- Inflammatory background (lymphocytes, mast cells, and lipophages)

Fibromatosis

- Low to moderate cellularity with isolated cells or in loose clusters
- Spindled to oval uniform nuclei with finely granular chromatin, smooth nuclear contours and inconspicuous nucleoli
- Pale, delicate cyanophilic cytoplasm with tapered ends
- Stripped nuclei can be numerous
- Fragments of collagenous metachromatic stroma with mucoid ground substance
- Atrophic skeletal muscle cells may be present
- Scattered lymphocytes and variable number of histiocytes may be observed

Dermatofibroma (Benign Fibrous Histiocytoma)

- Numerous oval to spindle cells arranged in a vague storiform pattern
- Lack significant cytologic atypia
- Occasional inflammatory cells (lymphocytes, lipophages, hemosiderin-laden macrophages)
- Foreign body type giant cells and Touton cells may be seen

Dermatofibrosarcoma Protuberans

- Individual or loose clusters of spindle cells with storiform pattern arrangement (best appreciated in tissue fragments)
- Uniform oval to elongated nuclei with smooth nuclear contour and finely granular chromatin
- Finely fibrillar metachromatic stroma, best appreciated on Romanovsky

Fibrosarcoma

- Single or loose clusters of oval to spindle cells
- Nuclear pleomorphism dependent on tumor grade, but generally, unlike MFH, bizarre giant cells are not observed

- Coarsely granular chromatin and indistinct nucleoli, variable mitotic figures
- Tapered scant cytoplasm
- Scant metachromatic collagenous stroma

Malignant Fibrous Histiocytoma (MFH)

Cytologic Findings

- Hypercellular smear of dimorphic population of histiocytes and spindle cells
- Storiform growth pattern in myxoid or inflammatory background
- Multinucleated giant cells with irregular nuclei and coarsely granular chromatin
- Bizarre pleomorphic cells often clustered around vessels
- Frequent atypical mitotic figures

Differential Diagnosis

- Liposarcoma:
  - Isolated or discohesive sheets of pleomorphic cells in a metachromatic background
  - Lipoblasts and fine vasculature
  - Well define (discrete) lipid vacuoles with nuclear scalloping

Neural Tumors

Neurofibroma

- Variable cellularity
- Cells isolated or in small aggregates in the background of abundant myxoid stroma
- Elongated spindle cells with wavy serpentine nuclei
- Finely granular chromatin, scant pale cytoplasm with indistinct cell borders
- Lack prominent nucleoli
- Naked nuclei with blunt or tapered ends are common

Schwannoma (Neurilemmoma)

- Cellular smear of uniform spindle cells with elongated wavy nuclei in a fibrillar (or metachromatic) background
- Ancient schwannoma may show cytologic atypia with large pleomorphic hyperchromatic or multilobulated nuclei displaying intranuclear cytoplasmic inclusions and smudgy chromatin
- Lack prominent nucleoli and mitotic figures
- Antoni A: Anastomosing and intervening fascicles of spindle cells with nuclear palisading
- Antoni B: Poorly cellular area with myxoid degeneration and scattered spindle cells with indistinct cell borders and vacuolated cytoplasm

Granular Cell Tumor

- Cellular smear composed of single and loose clusters of large polygonal, elongated, or rounded cell
- Dirty granular background
- Cells have abundant eosinophilic or granular cytoplasm and indistinct cell border
- Uniform small centrally located nuclei with prominent nucleoli
- S-100 protein positive

Malignant Peripheral Nerve Sheath Tumors

Cytologic Findings

- Cellular smear composed of single and loose clusters of cells with irregular contours
- Irregular nuclei are wavy, buckled or comma shaped
- Atypical mitotic figures
- Pale cytoplasm with indistinct cell borders and long cytoplasmic processes
- Metachromatic fibrillary matrix

Differential Diagnosis

- Fibrosarcoma or monophasic synovial sarcoma:
  - May be cytologically indistinguishable, consider clinical presentation and relation to major nerves
  - More regular cell contours with tapered nuclei rather than wavy nuclei
  - S-100 protein negative

Primitive Neuroectodermal Tumors (PNET)

- See discussion for Ewing's sarcoma

Neuroblastoma

- Cellular smear of discohesive cell clusters and isolated single cells
- Cells with high N/C ratio, finely granular chromatin, and inconspicuous nucleoli
- Nuclear molding may be seen
- Polygonal ganglion cells with clear cytoplasm may be noted
- Bi- or multinucleation, eccentric nuclei, and prominent nucleoli
- Neuropils (tangles of neuritic processes) and occasional Homer-Wright rosettes

Ganglioneuroma

- Large polygonal ganglion cells with abundant amphophilic cytoplasm and eccentric nuclei
- Spindle stromal cells with wavy nuclei in a fibrillary background

Miscellaneous

Giant Cell Tumor of Tendon Sheath

- Cellular smears composed of 2 cell populations with similar nuclear features
- Small round to oval or spindle mononuclear cells similar to synnovial lining cells or osteoblasts

- Large multinucleated osteoclastic-type giant cells
- Moderate amount of distinct cytoplasm with hemosiderin deposition
- Uniform eccentrically located nuclei with fine granular chromatin and inconspicuous nucleoli
- Background of hemosiderin-laden macrophages, xanthoma cells, and inflammatory cells

Synovial Sarcoma

- Hypercellular smear of single cells and cell clusters
- Uniform spindle cells predominate
- Scant cytoplasm with tapered ends and oval or elongate nuclei with inconspicuous nucleoli
- Difficult to differentiate monophasic synovial sarcoma from low-grade fibrosarcoma
- Biphasic population of epithelioid cells and spindle cells in a metachromatic stromal background
- Occasional glandular arrangement of cuboidal or columnar cells in biphasic synovial sarcoma
- Increased mitotic figures
- Focal immunoreactivity for cytokeratin in the epithelial elements

Leiomyosarcoma

- Cellular smear composed of uniform spindle cells arranged as tightly woven fascicles
- Centrally located cigar-shaped nuclei with blunted ends
- Cytoplasmic vacuoles may result in a blunt or concave nuclear contours
- Variable degree of nuclear pleomorphism and necrosis

Angiosarcoma

- Hemorrhagic cellular smear composed of branching papillary clusters of spindle, polygonal or rounded cells
- Concentrically arranged whorls (pseudoacini or rosette-like) of endothelial cells may be observed
- Moderate amount of pale cytoplasm and occasional nuclear groove
- Nuclear pleomorphism and prominent nucleoli
- CD31 and CD34 positive

Kaposi's Sarcoma

- Isolated single and loosely cohesive clusters of spindle cells with well defined borders
- Elongate nuclei with finely granular chromatin and inconspicuous nuclei
- Pale delicate cytoplasm that may contain hemosiderin pigments
- Cells may contain characteristic diastase-resistant PAS positive hyaline globules
- Inflammatory background

Rhabdomyosarcoma

- Cellular smear of isolated or loose aggregates of round or spindle cells
- Scant cytoplasm that taper from nucleus as a "tadpole-shape" or as a broad bands (strap cell)
- Cytoplasmic cross striation is rarely observed
- Oval to round eccentric nuclei with variable nuclear pleomorphism, frequently eccentric
- Concentrically arranged fibrillary materials around the nucleus
- Variable mitotic figures and tumor diathesis
- Desmin +, muscle-specific actin +, and MyoD1+

Bone and Cartilage

Chondroma

- FNA not generally indicated and not performed
- Cytology cannot differentiate chondroma from low grade chondrosarcoma
- Hypocellular smear composed of fragments of cartilage
- The presence of cartilage indicates that the lesion is cartilaginous (or has a cartilaginous component), and assists in determining if the lesion is benign or malignant
- Small uniform chondrocytes in lacunae
- Lack mitotic figures or significant nuclear pleomorphism
- Metachromatic fibrillary matrix, best appreciated on Romanovsky

Chondroblastoma

- Variable cellularity with single isolated and discohesive clusters of uniform round to polygonal cells
- Single or binucleated cells with dense glassy eosinophilic cytoplasm
- Evenly distributed fine granular chromatin and inconspicuous nucleoli
- Occasional nuclear groove and intranuclear cytoplasmic inclusions may be observed
- Multinucleated osteoclasts and vacuolated histiocytes
- Metachromatic amorphous chondroid stroma

Giant Cell Tumor

- Numerous large osteoclastic-type giant cells
- Mononuclear cells with eosinophilic cytoplasm and nuclei that are similar to those of giant cells
- Cells with abundant eosinophilic cytoplasm

Chondrosarcoma

- Not generally aspirated as diagnosis is made radiographically and aspirates may not be representative

- Aspirates of possible lytic areas may be performed to exclude dedifferentiated chondrosarcoma
- Cellular smear composed of single isolated cells and discohesive clusters
- Mononuclear or binuclear cells in lacunae embedded in metachromatic stromal matrix
- Oval to polygonal cells with distinct cell border and abundant vacuolated cytoplasm
- Variable degree of cytologic atypia and mitotic figures
- Bi- and multinucleation are common

Osteosarcoma

- Numerous discohesive cells with marked nuclear pleomorphism and bizarre cells
- Multinucleated tumor cells and occasional osteoclast-like cells are observed
- Nucleoli may be prominent
- Cells with moderate to abundant eosinophilic granular cytoplasm
- Increased mitotic figures and abnormal mitotic figures may be seen
- Eosinophilic metachromatic osteoid matrix are best seen on Romanovsky

Ewing's Sarcoma and PNET

Cytologic Findings

- Cellular smear with tight clusters and isolated single monotonous cells (2–3x size of mature lymphocytes)
- Uniform round to oval nuclei with finely granular chromatin and inconspicuous nucleoli
- Nuclear molding with crush artifact, bare nuclei common
- Variable cytoplasmic vacuoles containing glycogen (PAS positive)
- Frequent mitotic figures and occasional Homer-Wright rosettes
- "Tigroid" background (also seen in seminoma)
- Mic2 (HBA71) protein positive

Differential Diagnosis

- Metastatic neuroblastoma:
  - Background of fibrillary neuropil
  - Ganglion cell differentiation and frequent Homer-Wright rosettes

Langerhan's Cell Histiocytosis (Eosinophilic Granuloma)

- Cellular smear composed of numerous isolated large histiocytes admixed with eosinophils
- Nuclei of histiocytes are round or reniform
- Finely granular chromatin, nuclear grooves
- Granular, occasionally vacuolated cytoplasm
- Variable number of eosinophils
- Occasional multinucleated osteoclast-like cells
- Birbeck granules (tennis racket-like structure) on electron microscopy are diagnostic
- CD1a positive

ESOPHAGUS, STOMACH, COLON, LIVER, AND PANCREAS

Esophagus

Normal Components

- Superficial and intermediate squamous cells
- Parabasal cells may be seen in ulcer or vigorous brushing
- Gastric cells may be noted in samples from gastroesophageal junction

Infection

(Findings Similar to Those Described in Respiratory Tract)

- Candida esophagitis
- Herpes simplex virus

Reflux Esophagitis

- Sheets of loosely cohesive squamous cells with reactive/regenerative atypia
- Normal polarity and N/C ratio retained
- Regular nuclear membranes and uniformly distributed fine chromatin
- Abundant cyanophilic cytoplasm
- Rare isolated single cells and lack significant nuclear pleomorphism
- Inflammatory cells (lymphocytes, eosinophils, and histiocytes) may be observed

Radiation Change

- Cytomegaly with normal N/C ratio
- Nuclei enlarged, hypochromatic and have prominent nucleoli (may be irregular)
- Degenerative change with nuclear pyknosis, smudging and karyorrhexis
- Nuclear and cytoplasmic vacuoles, multinucleation

- Dense amphophilic cytoplasm
- Granulation tissue formation with spindle fibroblasts and endothelial cells

Barrett's Esophagus

- The brushing should be taken several centimeters above gastroesophageal junction
- Isolated single cells and small clusters of columnar mucin-producing cells
- Interspersed goblet cells
- Lack significant cytologic atypia
- Suspect dysplasia when cytologic atypia is observed

Dysplasia

- Loosely cohesive sheets of hyperplastic epithelial cells with cytologic atypia
- Enlarged nuclei with nuclear hyperchromasia, irregular nuclear contours
- Low-grade dysplasia may be indistinguishable from reactive atypia
- High-grade dysplasia displays:
  - Increased N/C ratio
  - Increased hyperchromasia
  - Increased nuclear membrane irregularity
  - Increased nuclear pleomorphism and prominent nucleoli
- Lack tumor diathesis or numerous isolated single cells

Squamous Cell Carcinoma

- Discohesive clusters, syncytial sheets and isolated cells with orangeophilic waxy cytoplasm
- Keratin pearls, intercellular bridges and distinctive cell border
- Marked variation in size and shape and bizarre cells
- Nuclear pyknosis, karyorrhexis, and apoptosis
- Nuclear pleomorphism, hyperchromasia, irregular nuclear membrane, and coarse clumped chromatin

Adenocarcinoma

- Discohesive sheets, acini, papillae and isolated single columnar cells
- Loss of polarity and cellular cohesion with single isolated cells
- Nuclear pleomorphism, nucleomegaly with open chromatin and prominent nucleoli
- Indistinct cell border, cytoplasmic vacuoles (mucin)

Stomach

Normal Cytology

- Columnar cells in sheets with honeycomb pattern
- Round to oval basal nuclei with finely granular and evenly distributed chromatin
- Granular or vacuolated mucus-filled cytoplasm
- Degenerative epithelial changes are frequently observed

Gastric Ulcer

- Fibrinous exudate with sheets and islands of regenerative epithelial cells
- Spectrum of reactive atypia in the epithelial fragments
- Granulation tissue formation with plump spindle fibroblasts and endothelial cells
- Knowledge of clinical findings is essential for proper interpretation
- For gastric adenocarcinoma diagnosis, require nondegenerated cells with malignant cytologic features to avoid overdiagnosis ulcer-related atypia/regeneration

Chronic Gastritis

- Cell polarity maintained with relative normal N/C ratios
- Even chromatin distribution, regular smooth nuclear contour
- Lack significant nuclear pleomorphism
- Inflammatory background and cellular debris
- Helicobactor pylori may be seen in Pap-stained smears of gastric blushings, especially in mucus and are better appreciated on Romanovsky stain

Hyperplastic or Regenerative Polyp

- No specific cytologic features
- Microtissue fragments of normal gastric epithelium
- Honeycomb sheets of mucous epithelial cells with fine chromatin

Adenocarcinoma

- Hypercellular smear of discohesive sheets, three-dimensional clusters and isolated single cells
- Loss of nuclear polarity
- Nuclear pleomorphism, chromatin clumping and clearing, and prominent nucleoli
- Granular and vacuolated cytoplasm
- Signet ring cells should be distinguished from vacuolated histiocytes (muciphages)

Lymphoma

- Highly cellular smear with a monotonous population of small or large cleaved or non-cleaved lymphocytes
- Relatively clean background
- Negative reaction to mucin and immunostaining for keratin and leukocyte common antigen are extremely helpful in the differential diagnosis from poorly differentiated adenocarcinoma

Colon

Normal Cytology

- Honeycomb or picket-fence arrangement
- Tall columnar cells with brush borders and goblet cells
- Elongated nuclei with regular outline and finely granular chromatin

Adenomatous Polyp

- Microtissue fragments and strips of columnar cells with peripheral feathering
- Nuclear polarity and cell cohesion retained
- Even chromatin distribution, regular smooth nuclear membrane, and micronucleoli
- Lack prominent nucleoli, significant nuclear pleomorphism, or tumor diathesis

Adenocarcinoma

- Hypercellular smear of discohesive geographic sheets, clusters and isolated single columnar cells
- Loss of nuclear polarity with nuclear pleomorphism, uneven chromatin distribution, and prominent nucleoli
- Granular and vacuolated cytoplasm
- Signet ring cells should be distinguished from vacuolated histiocytes (muciphages)
- Tumor diathesis

Liver

Normal Components

Normal Hepatocytes

- Polygonal cells arranged in sheets, clusters or as single cells
- Eosinophilic or basophilic cytoplasm that may show vacuoles or pigment (hemosiderin, lipofuscin or bile)
- Round nuclei, central or slightly eccentrically located
- Smooth nuclear contour and evenly distributed finely granular chromatin
- Anisonucleosis common as well as bi- or multinucleation
- Nucleoli usually present, and may be prominent

Bile Duct Cells

- Honeycomb sheets or tightly packed glandular clusters
- Low columnar or cuboidal cells with basophilic cytoplasm
- Round to oval nuclei, often eccentric, with evenly distributed finely granular chromatin and micronucleoli

Kupffer Cells

- Single, bare, comma shaped nuclei between hepatocytes

Benign Lesions

Cysts

- Congenital cyst:
  - Clear fluid
  - Few uniform cuboidal cells and some macrophages
- Ciliated hepatic foregut cyst:
  - Located beneath the falciform ligament
  - Clusters of ciliated columnar cells
  - Macrophages
- Hydatid cyst:
  - Thick turbid fluid
  - Fragments of laminated cyst wall
  - Scolices and/or hooklets demonstrated with Pap stain

Reactive/Regenerative Changes

- Cell cohesion and nuclear polarity retained
- Normal N/C ratio, lack significant nuclear pleomorphism
- Significant variation between cells usually indicate benignity
- Occasional binucleation, and prominent nucleoli
- Bile duct epithelium and lipofuscin, and hemosiderin

Steatosis

- Cytoplasmic (fat) vacuoles

Hepatocellular Adenoma

Cytologic findings

- Clearly defined focal mass
- Sheets and clusters of monotonous polygonal normal hepatocytes or hepatocytes with slight nuclear enlargement
- Lack nuclear pleomorphism
- Glycogen, hemosiderin, and fatty change may be observed
- Absence of glandular cells of bile duct origin

Differential Diagnosis

- Well differentiated hepatocellular carcinoma:
  - Very subtle difference
  - Less fragile cytoplasm in adenoma with more distinct cell border
  - Low N/C ratio in adenoma
  - Fewer bare nuclei in adenoma
- Regenerative nodule and cirrhosis:
  - Marked anisokaryosis
  - Scattered cells with nuclear pleomorphism and high N/C ratio

Focal Nodular Hyperplasia

- Admixtures of fragments of bile ducts, fibrous stromal tissue, and hepatocytes
- The cytologic findings are not specific
- The presence of admixture of hepatocytes and bile duct cells in the proper clinical setting support the diagnosis of focal nodular hyperplasia

Hemangioma

- Bloody background, fibrovascular tissue fragments, vascular walls, and occasional fibrin
- Few scattered endothelial cells with elongated normochromatic nuclei

Bile Duct Hamartoma

- Admixtures of benign bile ductal cells and strands of fibrous stroma

Malignant Lesions

Hepatocellular Carcinoma

Cytologic Findings

- Findings dependent on degree of differentiation
- Cellular smear with predominantly trabecular pattern (>3–4 cell layers in thickness), mostly seen in well-differentiated tumors
- Sinusoidal endothelial cell lining surrounding and/or traversing the trabeculae
- Numerous single discohesive polygonal cells with round central nuclei, high N/C ratio, binucleation, smooth nuclear membrane, and prominent nucleoli
- Intranuclear cytoplasmic inclusions and intracytoplasmic bile
- Abundant granular cytoplasm
- Cytoplasmic eosinophilic hyaline globule (alpha fetoprotein, AFP)
- Mallory hyaline may be observed
- Small nuclear fragments, satellite nuclei and atypical naked nuclei
- Absent bile duct epithelium
- Canalicular polyclonal CEA and CD10 staining pattern

Variants

- Fibrolamellar hepatocellular carcinoma:
  - Large polygonal cells with eosinophilic granular cytoplasm
  - Nuclear enlargement with single prominent nucleoli and intranuclear cytoplasmic inclusions
  - Pale body (fibrinogen) and PAS-positive hyaline globules
  - Rows of fibroblasts may be observed

Differential Diagnosis

- Metastatic adenocarcinoma and cholangiocarcinoma:
  - Often indistinguishable based on cytologic findings
  - Lack sinusoidal endothelial cell lining, AFP, alpha-1-antitrypsin, intracytoplasmic Mallory hyaline, and bile production
  - Trabecular growth pattern and intranuclear inclusion are uncommon
  - Mucin production and diffuse cytoplasmic CEA staining pattern

Hepatoblastoma

Cytologic Findings

- Hypercellular smear with trabeculae, cords, tubular, acinar and papillary arrangement of cells covered by sinusoidal lining cells
- Mixture of fetal/embryonal type primitive cells and mesenchymal elements similar to other small round cell tumors of childhood
- Nuclei usually smaller than normal hepatocytes
- High N/C ratio, round, central, normochromatic or slightly hyperchromatic chromatin
- Smooth nuclear membrane and inconspicuous nucleoli
- Scant to moderate finely granular cytoplasm
- Small cytoplasmic vacuoles maybe noted but bile is rare
- Positive for low molecular weight keratin, and negative for vimentin, high molecular weight cytokeratin, and epithelial membrane antigen
- Extramedullary hematopoiesis may be seen (very rare)
- Cartilaginous or osseous metaplasia may be observed

Differential diagnosis

- Hepatocellular carcinoma:
  - Larger cells with more pleomorphism
  - Broader trabeculae than those seen in hepatoblastoma
- Hepatocellular adenoma:
  - Less cellular than hepatocellular carcinoma or hepatoblastoma
  - Unremarkable appearing hepatocytes

Cholangiocarcinoma

Cytologic Findings

- Well differentiated ones present as sheets and clusters of atypical cells that resemble bile duct epithelium
- The findings in less differentiated ones are those of adenocarcinoma, not otherwise specified
- Hypercellular smear of discohesive sheets, three-dimensional clusters and isolated single glandular cells
- Loss of nuclear polarity with nuclear pleomorphism, irregular nuclear membrane, chromatin clumping and clearing, atypical mitotic figures, and prominent nucleoli
- Cellular borders usually indistinct
- Granular and vacuolated cytoplasm, may contain mucin
- Tumor diathesis

Differential Diagnosis

- Reactive/regenerative atypia:
  - Cohesive monolayer sheets of cells with normal N/C ratios
  - Regular nuclear membrane, and evenly distributed chromatin

  - Cell polarity maintained and lack significant nuclear pleomorphism
  - Inflammatory background and cellular debris
- Hepatocellular carcinoma:
  - Cell balls and trabeculae with peripheral endothelium

Metastatic Adenocarcinoma

- Findings in metastatic adenocarcinoma from lung, stomach or pancreas are indistinguishable from cholangiocarcinoma
- Metastatic colon adenocarcinoma typically shows tall columnar cells with luminal borders and elongate or spindled hyperchromatic stratified nuclei

Metastatic Carcinoid

- Cellular smear of loosely arranged round monotonous cells
- Occasional rosette formation
- Basophilic or slightly granular cytoplasm
- Nuclei 2–3x normal lymphocytes, round regular central or slightly eccentric (plasmacytoid)
- Evenly distributed finely or coarsely chromatin (salt and pepper)
- Inconspicuous nucleoli
- Immunohistochemical staining for neuroendocrine makers (chromogranin A, synaptophysin and neuron specific enolase) helpful

Pancreas

Normal Components

Acinar cells

- Small clusters of cells with dense granular cytoplasm
- Round small peripherally located regular nuclei
- Evenly distributed finely granular chromatin

Ductal Cells

- Columnar or cuboidal cells in sheets (honeycomb pattern)
- Pale cytoplasm and round to oval uniform nuclei with fine granular chromatin and small nucleoli

Islet cells

- Isolated and loose clusters of cells with round to oval nuclei
- Uniform nuclei with finely granular chromatin (salt and pepper)
- Usually few cells and may not be distinguishable from acinar cells

Acute Pancreatitis

- Hypocellular smear with admixtures of ductal/acinar cells, neutrophils, and histiocytes in a dirty necrotic background
- Degenerative/regenerative epithelial cells with reactive atypia (may mimic adenocarcinoma)
- Lipophages and amorphous basophilic materials associated with fat necrosis

Chronic Pancreatitis

- Hypocellular smear with cohesive honeycomb sheets of ductal cells with reactive/reparative changes
- Lack nuclear pleomorphism and presence of single cells
- Acinar components less conspicuous
- Stromal fragments with myofibroblasts and variable chronic inflammatory background
- Ductal and acinar cells may show degenerative change

Pseudocyst

- Hypocellular smear of lipid-laden histiocytes, neutrophils, plasma cells, and lymphocytes in a dirty background
- Occasional atypical mesenchymal cells and myofibroblasts
- Flecks of calcification
- Possibly necrotic fat cells
- No or rare epithelial elements
- Fluid content positive for amylase and negative for CEA
- Purulent fluid should be cultured

Tumors (also see Chapter 29)

Microcystic Adenoma

- Microcysts lined by bland, uniform cells
- Aspirates result in clear watery fluid
- Hypocellular smear with flat sheets of low columnar or cuboidal cells with honeycomb arrangement
- Amphophilic cytoplasm with fine vacuolization containing glycogen
- Small uniform round to oval nuclei and inconspicuous nucleoli
- Lack cytologic feature of malignancy
- Scattered foamy or hemosiderin-laden macrophages
- Positive staining for glycogen and negative for mucin

Mucinous Cystic Neoplasm

- Low cellularity
- Findings ranged from cohesive sheets and papillary clusters of cells resemble benign endocervical cells to cells clearly derived from mucinous adenocarcinoma
- Single cells may resemble goblet cells
- Intracellular mucin deposition and mucin in the background
- Scattered muciphages and chronic inflammation
- Even if cytologically benign, these neoplasms require total resection
- CEA elevated in the cyst fluid

Ductal Adenocarcinoma

Cytologic Findings

- Cellular smear of sheets and clusters of cells with abortive lumen formation
- Loosely cohesive ductal cells arranged in "drunken honey comb" pattern
- Nuclear pleomorphism (nuclear size variation >4:1)
- Nuclear enlargement with increased N/C ratio
- Nuclear overlapping and crowding, nuclear membrane irregularity, irregular chromatin distribution ("washed-out" nuclear chromatin with rimming of nuclear membrane)
- Prominent macronucleoli, increased mitotic figures, and loss of nuclear polarity
- Multinucleation and frequent mitotic figures
- Cytoplasmic vacuolization, sometimes acquires squamoid appearance
- Tumor diathesis
- Lack acinar or islet cells

Differential Diagnosis

- Chronic pancreatitis
  - Reactive ductal cells are uniform in size and shape

Acinar Cell Carcinoma

- Clusters and isolated monotonous acinar cells; predominantly cohesive
- Uniformly hyperchromatic, centrally placed enlarged nuclei with irregular nuclear membrane and prominent nucleoli
- Moderate amount of granular eosinophilic cytoplasm
- PAS+ cytoplasmic staining
- Absence of benign ductal components

Islet Cell Tumors

- Hypercellular smear of loose clusters, rosettes and isolated round uniform cells
- Eccentric nuclei imparting a plasmacytoid appearance
- Uniform nuclei with salt and pepper chromatin
- Small to inconspicuous nucleoli
- Pale delicate basophilic granular cytoplasm
- Positive staining for PAS and alpha-antitrypsin
- Positive immunostaining for neuroendocrine markers
- Neurosecretory granules observed on electron microscopy

Solid-Pseudopapillary Tumor (Solid and Papillary Epithelial Neoplasm)

- Loosely cohesive microtissue fragments and cells with acinar-like arrangement
- Branching papillae with delicate fibrovascular cores, myxoid stroma and one to several layers of cells
- Uniform oval nuclei with fine chromatin and characteristic nuclear grooves
- Inconspicuous small nucleoli
- Variable amount of pale amphophilic cytoplasm
- Metachromatic material in fibrovascular cores and hyaline globules in some acinar-like structures on Romanovsky stain

OVARY

Overview

Sampling Method

- Transvaginal sonographically guided aspiration (most common route)
- Transabdominal
- Transrectal
- Laproscopic visualization and aspiration

Parameters to be Considered in FNA of Ovary

- At least 2 of these parameters must be consistent to establish the correct diagnosis:
  - Ultrasound and laparoscopic findings
  - Cytologic examination
  - Estradiol level in the fluid

Contaminants that may be Observed in FNA of Ovaries

- Squamous cells from skin or vaginal mucosa
- Colonic epithelium:
  - May be seen in transrectal and transabdominal aspirates
  - Usually few cells
  - May not indicate perforation of bowels
- Mesothelial cells
- Mesenchymal cells:
  - Adipose tissue
  - Smooth and skeletal muscle
  - Collagen

Note: it is important to ascertain the route of the needle and which form of possible contaminants may be present

Selected Lesions

Follicular Cyst

- Isolated single cells and tight clusters of granulosa cells of variable size

- Round to oval nuclei with nuclear grooves and coarse granular chromatin
- Occasional large polygonal luteinized granulosa cells with abundant granular or vacuolated cytoplasm
- Eccentric nuclei with finely granular chromatin and prominent nucleoli
- Lack ciliated bodies
- Estradiol level in fluid >20 nmol/L in 90% of follicular cyst

Corpus Luteum Cyst

- Numerous luteinized granulosa cells
- Abundant granular cytoplasm with indistinct cell borders and large nuclei with nucleoli
- Blood, fibrin, hemosiderin laden macrophages and fibroblast
- Abundant fibroblasts and hematoidin-laden macrophages suggest a regressing corpus luteum
- "Atypia" that mimics carcinoma may be noted in aspirates performed in postpartum period

Endometriotic Cyst

- Bloody smear with numerous hemosiderin laden macrophages
- Rare isolated or clusters of endometrial cells
- Marked degenerative changes may be observed

Mature Cystic Teratoma

- Abundant anucleated squames, mesenchymal cells, and columnar cell
- Viscous amorphous debris representing sebaceous secretion

Cystic Granulosa Cell Tumor

- May be indistinguishable from follicular cyst
- Follicular or trabecular arrangement of uniform granulosa cells
- Call-Exner bodies may be seen

Serous Cystadenoma

- Mildly cellular
- Clusters and groups with sheet-like (honeycomb) and papillary configuration
- Uniform columnar epithelial cells
- Lacks cytologic atypia
- Cilliary bodies (tufts of cilia) may be observed

Mucinous Cystadenoma

- Mildly cellular
- Honeycomb sheets of columnar mucin producing cells
- Uniform nuclei with finely granular evenly distributed chromatin
- Mucin background best appreciated on Romanovsky stain

Papillary Serous Cystadenocarcinoma

Cytologic Findings

- Hypercellular smear composed of isolated cells and branching papillary group of columnar or cuboidal cells with eosinophilic cytoplasm
- Eccentric hyperchromatic nuclei with irregularly distributed chromatin
- Nuclear pleomorphism and prominent nucleoli
- Psammoma bodies
- Cytologic features of borderline tumors (low malignant potential) vary from completely bland cells to highly atypical and almost indistinguishable from those of carcinoma

Differential Diagnosis

- Serous cystadenoma:
  - Less cellular
  - Clusters and groups of uniform columnar epithelial cells
  - Lacks cytologic atypia
- Atypical luteinized cells
- Endometriosis

Mucinous Cystadenocarcinoma

Cytologic Findings

- Numerous clusters of columnar cells with picket-fence configuration and cell balls
- Cytoplasmic vacuoles and eccentrically located nuclei
- Mucinous background

Differential Diagnosis

- Colonic cell contaminants from transrectal aspirates
- Mucinous cystadenoma:
  - Less cellular
  - Honeycomb sheets of columnar mucin producing cells
  - Uniform nuclei with finely granular evenly distributed chromatin

Endometrioid Carcinoma

- Clusters, sheets and syncytial groups of cells with acinar configuration
- Cuboidal to polygonal cells with low N/C ratio
- Abundant granular eosinophilic cytoplasm, fine cytoplasmic vacuoles, prominent nucleoli
- May be indistinguishable from serous adenocarcinoma

Clear Cell Carcinoma

- Sheets and clusters of large cells with abundant pale cytoplasm

- Nuclear pleomorphism and irregularity with hobnailing
- Cherry red macronucleoli

Granulosa Cell Tumor

- Cellular smear with solid, follicular and trabecular arrangement of cells
- Uniform cells with indistinct cell border, nuclear grooves, evenly distributed chromatin, and small nucleoli
- Occasional Call-Exner bodies: acinar-like structure with central amorphous reddish material

Brenner's Tumor

- Biphasic populations of epithelial and mesenchymal cells
- Sheets of polygonal to cuboidal epithelial cells
- Oval nuclei, nuclear groove and cytoplasmic eosinophilic globules

Fibrothecoma

- Hypocellular smear of spindle cells
- Elongated nuclei with evenly distributed chromatin

Carcinoid

- Discohesive cells with eccentric nuclei and plasmacytoid appearance
- Granular "salt and pepper" chromatin
- Bilateral ovarian involvement represents metastasis to the ovaries

Dysgerminoma

- Discohesive isolated large cells with abundant amphophilic cytoplasm
- Nucleomegaly, coarse clumped chromatin and macronucleoli
- Numerous lymphocytes and occasional histiocytes and giant cells
- Tigroid Background seen on Romanovsky:
  - Composed of interwoven lacy, PAS+ materials
  - Related to extracellular glycogen
  - Also occur in rhabdomyosarcoma and glycogen-rich clear cell tumors

KIDNEY

Simple Cyst

- Hypocellular smear with scant epithelial cells
- Pyknotic degenerative nuclei
- Scattered macrophages with finely vacuolated cytoplasm ("foamy cells")
- Amorphous proteineous materials and inflammatory cells
- More than 50% of men over age 50 may have cysts and 1–5% of cysts may harbor cancer

Oncocytoma

- Sheets and isolated polygonal cells with abundant eosinophilic cytoplasm
- Cells have normal N/C ratio and resemble proximal tubular cells
- Single or multiple nuclei with fine granular chromatin and inconspicuous nucleoli
- Occasional degenerative bizarre nuclei, bi- and/or multinucleation

Angiomyolipoma

- Microtissue fragments with few single or isolated cells
- Triphasic tumors:
  - Smooth muscle cells: spindle cells with cigar-shaped nuclei (smooth muscle)
  - Adipocytes
  - Blood vessels
- Smooth muscle cells may have epithelioid appearance mimicking sarcoma
- Bloody background
- Immunostaining for HMB-45+ (in smooth muscle)

Clear Cell Renal Cell Carcinoma

Cytologic Findings

- Smears can either be highly cellular or very bloody/necrotic and hypocellular
- Isolated cells, floral grouping and three-dimensional clusters of large columnar cells
- Tumor cells are larger than adjacent proximal tubular cells
- Variable nuclear pleomorphism depending on the tumor grade
- Nuclei with irregular nuclear membrane and coarsely granular chromatin
- Intranuclear vacuoles common
- Abundant vacuolated cytoplasm positive for glycogen or hemosiderin
- Metachromatic basement membrane-like material on Romanovsky
- Negative mucin

Variants

- Multilocular cystic renal cell carcinoma:
  - Isolated cells and discohesive sheets, papillae and loose clusters
  - Low nuclear grade, irregular nuclear borders
  - Intranuclear cytoplasmic inclusions
  - Granular vacuolated cytoplasm with glycogen and hemosiderin
  - Necrotic debris, foamy histiocytes, degenerating blood and inflammatory background

Differential Diagnosis

- Benign hepatocytes:
  - Cohesive sheets of polygonal cells with central nuclei and low N/C ratio
  - Cytoplasmic lipofuscin and bile production
- Normal adrenal cortical cells:
  - Cells with uniform nuclei and abundant vacuolated cytoplasm
- Vacuolated macrophages:
  - Single isolated cells, no clustering or grouping
- Adrenocortical neoplasm:
  - Lack metachromatic basement membrane-like material
  - Nuclear pleomorphism
- Pheochromocytoma:
  - Isolated single cells and loose clusters of variable sized cells
  - Nuclear pleomorphism and salt-pepper chromatin
  - Abundant red granules on Romanovsky
- Retroperitoneal seminoma:
  - Discohesive cells admixed with lymphocytes
  - Tigroid background composed of irregular, lacy PAS+ material
  - Thick irregular nuclear membrane and prominent nucleoli

Papillary Renal Cell Carcinoma

- Cellular smear of papillae with true fibrovascular cores
- May present as spherules or tubules
- Cuboidal or columnar cells with high N/C ratio
- Delicate basophilic cytoplasm with intracytoplasmic hemosiderin
- Relatively uniform nuclei with evenly distributed fine granular chromatin in most cases
- Psammoma bodies, scattered foamy histiocytes, and hemosiderin-laden macrophages
- Distorted aspirated normal glomeruli may mimic papillary renal cell carcinoma

Chromophobe Renal Cell Carcinoma

- Cellular smear composed of isolated and tight clusters of large polygonal cells
- Cells have distinct cell border and pale granular or vacuolated cytoplasm (Hale's colloidal iron +)
- Nuclei are enlarged and irregular with coarsely granular chromatin and occasional nucleoli
- Bi- and/or multinucleation

Collecting Duct Carcinoma

- Isolated cells and tubulo- papillary groups of pleomorphic cells with mucin production
- Cells have high N/C ratio and granular cytoplasm
- Hyperchromatic nuclei with coarsely granular chromatin and prominent nucleoli
- Metachromatic stromal fragments and inflammatory background (neutrophils may be numerous)

Wilms' Tumor

Cytologic Findings

- Microtissue fragments with tightly packed tubular structure surrounded by small blastemal cells
- Triphasic tumor with blastema, epithelial cells and spindle stromal cells
- Blastemal cells are small with high N/C ratio and hyperchromatic nuclei
- Epithelial components may form glands, complex branching tubules and glomeruloid bodies intermixed with metachromatic materials
- Small cuboidal or columnar cells with scant cytoplasm
- Skeletal muscle, cartilage and fat may be seen

Differential Diagnosis

- Neuroblastoma:
  - Isolated cells, loose clusters, and frequent Homer-Wright rosettes
  - Neuropil and occasional polygonal ganglion cells
- Rhabdoid tumor:
  - Clusters and isolated round to oval cells with macronucleoli and abundant cytoplasm
  - Intracytoplasmic eosinophilic globular hyaline inclusions
- Clear cell sarcoma:
  - Clusters and isolated polygonal or spindle cells with uniform nuclei
  - Fine vasculature
- Rhabdomyosarcoma:
  - Rhabdomyoblasts and absence of triphasic composition
- Teratoma:
  - Lack blastemal cells

URINARY BLADDER

Overview

Types of Cellular Specimens

- Spontaneous voided urine
- Instrumentation (catheterization/cystoscopy)
- Bladder washing
- Ureteral and pelvic brushing and washing
- Urethral brushing
- Ileal conduit urine

Specimen Preparation

- Direct smear
- Membrane filtration
- Cytocentrifugation
- Monolayer thin preparation
- Paraffin cell block
  (rarely used mainly for tissue fragments)

Cellular Components of Urinary Cytology

- Urothelial cells:
  - Superficial umbrella cells, large and often multinucleated (more frequent in washings and catheterized urine)
  - Intermediate pyramidal cells
  - Cuboidal basal cells
- Squamous cells:
  - May be due to contamination
  - Normally found in women and would show cyclic changes
  - In males their presence indicate squamous metaplasia
- Renal epithelial cells (indicates renal disease or injury)
- Intestinal epithelial cells in ileal conduit specimens
- Endometrial cells (endometriosis)
- Prostatic or seminal vesicle epithelial elements, spermatozoa (particularly following prostatic massage)

  Red cells and inflammatory cell

Reporting Terminology

- Unsatisfactory for evaluation
- Negative for malignancy
- Reactive urothelial cells
- Atypical urothelial cells, favor reactive
- Atypical urothelial cells of undetermined significance (including dysplastic cells)
- Atypical urothelial cells, suspicious for malignancy
- Malignant cells are present:
  - Derived from low grade urothelial carcinoma
  - Derived from high grade urothelial carcinoma
  - Derived from carcinoma in-situ
  - Derived from adenocarcinoma
  - Others (e.g. small cell and squamous cell carcinoma)

Benign Lesions and Mimics of Malignancy

Reactive Urothelial Cells

- Nuclei are relatively uniform with smooth contours, finely granular chromatin
- Peripheral condensation of chromatin
- Cytoplasmic vacuolization and prominent nucleoli (not seen in low grade urothelial carcinoma)

Instrument Artifact and Lithiasis

- Increased cellularity
- Cohesive, ball-shaped and papillary tight clusters with cytoplasmic collar and smooth border
- Flattened urothelial cell at periphery of cell balls
- Cytoplasmic vacuolization usually occur in reactive urothelium or high grade carcinoma, but rarely occur in low grade carcinoma
- Numerous multinucleated superficial cells

Decoy Cells

- Indicative of polyoma virus (Papovavirus) infection
- Infection may be asymptomatic or associated with hematuria
- Some patients are immunocompromised e.g. AIDS, diabetes mellitus, cancer or post-transplantation
- Many patients have no known predisposing factor
- Spontaneously resolves
- May have aneuploid DNA pattern
- Discohesive isolated enlarged cells without clustering
- High N/C ratio with eccentric nuclei and peripheral ring of chromatin
- Single intranuclear dense dark ink-black large smudgy inclusion (decoy cell)
- Some may have a thin halo around the inclusion (not to be confused with the conspicuous halo of cytomegalovirus)
- Some have short cytoplasmic tails (comet cells)

Ileal Conduit

- Columnar (colonic) degenerative epithelial cells without atypia
- Mucoid dirty background
- Eosinophilic cytoplasmic inclusions may be seen

Treatment Effect

Radiation

- Cytomegaly and bizarre cells (may be spindled)

- Multinucleation
- N/C ratio normal and nuclear degeneration with a smudged chromatin pattern
- Macronucleoli
- Cytoplasmic polychromasia, vacuolization, and cytophagocytosis

Chemotherapeutic effect

- N/C ratio normal or high, degenerative intranuclear and cytoplasmic vacuoles
- Multinucleation

Cyclophosphamide (Cytoxan) and Busulphan (Myleran) therapy

- Produce highly atypical cells that mimic high-grade urothelial carcinoma
- Cytomegaly
- High nuclear to cytoplasmic ratio
- Markedly hyperchromatic chromatin (frequently smudged)
- One or two large irregular nucleoli

Thiotepa and Mitomycin C

- Cause increased cell turnover and exfoliation in the initial stage
- Associated with reactive-like changes

Cyclosporine A

- Nephrotoxic and causes shedding of tubular cells, sometimes as papillary tissue fragments
- Cytoplasmic inclusions (giant mitochondria)
- Cytoplasmic vacuolization
- Microcalcifications may occur

Intravesical Bacilli Calmette-Guerin (BCG) Effect

- Multinucleated giant cells and lymphohistiocytic aggregates
- Mixed inflammatory cells and reactive urothelial cell
- Neutrophils (first week), lymphocytes and macrophages (later)

Laser Effect

- Spindled cells occur singly or in groups
- Elongated nuclei with uniform dense chromatin

Urothelial Papilloma

- Often indistinguishable from low grade papillary urothelial carcinoma
- Less cellular, small cells with hyperchromatic nuclei

Malignant Lesions

General Features

- May detect urothelial carcinoma long before it is detected clinically or confirmed histologically
- False positive cytology is truly false positive after extensive workup of the patient
- Urine cytology is more predictive of carcinoma as the grade gets higher
- High false negative rate for low grade tumors
- Cannot distinguish between low grade intraepithelial lesions, papilloma, and low grade urothelial carcinoma
- Cannot distinguish between high grade intraepithelial lesions, carcinoma in situ and high grade urothelial carcinoma
- Papillary clusters in voided urine are highly suspicious for carcinoma in the absence of infection or stone

Urothelial Carcinoma In Situ *(CIS)*

- Often indistinguishable from high grade urothelial carcinoma
- Predominantly isolated highly atypical single cells with cytoplasmic vacuolization (usually have more monotony than invasive high grade carcinoma)
- Enlarged nuclei with irregular nuclear contour, coursely granular chromain and prominent nucleoli
- Lack tumor diathesis

Urothelial Carcinoma

- 1998 International Society of Urologic Pathology Classification of Papillary Bladder Neoplasms (also see Chapter 25):
  - Papilloma
  - Papillary neoplasm of low malignant potential (formerly WHO grade 1 urothelial carcinoma)
  - Urothelial carcinoma, low grade (formerly WHO grade 2 urothelial carcinoma)
  - Urothelial carcinoma, high grade (formerly WHO grade 3 carcinoma)

Cytologic Findings

- Classification and grading of urothelial carcinoma is difficult based on cytology
- WHO Grade 1:
  - May be indistinguishable from benign reactive urothelial cells or papilloma
  - Lack cytoplasmic vacuolization and prominent nucleoli
- WHO Grade 2:
  - Papillary and three-dimensional clusters with ragged border
  - True papillary frond with fibrovascular core are pathognomonic

  - Increased N/C ratio with slight irregular nuclear contours and finely granular chromatin
  - Cytoplasmic homogeneity
  - Lack prominent nucleoli and cytoplasmic vacuolization
  - Umbrella cells are still present
- WHO Grade 3:
  - High grade urothelial carcinoma and CIS are often indistinguishable cytologically
  - Discohesive clusters and isolated single cells
  - Cytoplasmic vacuolization, lack surface maturation
  - Increased nuclear overlapping and crowding
  - High N/C ratio, nuclear pleomorphism, irregular nuclear contours, chromatin clumping and clearing, prominent nucleoli
  - Dirty inflammatory background with necrotic debris

Differential Diagnosis

- Reactive urothelial cells:
  - Cytoplasmic vacuolization and prominent nucleoli may be seen (incompatible with low-grade urothelial carcinoma)
- Instrument artifact and lithiasis:
  - Increased cellularity, multinucleated superficial cells
  - Flattened urothelial cells at periphery of cell balls
  - Cytoplasmic vacuoles (cytoplasmic vacuolization usually occur in reactive urothelium or high grade carcinoma, but rarely occur in low grade carcinoma)
- Decoy cells:
  - Discohesive isolated enlarged cells with high N/C ratio
  - Peripheral condensation of chromatin, dense smudgy intranuclear inclusion, and occasionally a thin halo
- Treatment effect:
  - N/C ratio normal, cytoplasmic vacuoles, cytoplasmic polychromasia
  - Multinucleated giant cells and reactive urothelial cell
  - Smudged chromatin
- Seminal vesicles:
  - Lipofuscin pigment
- Malacoplakia:
  - Macrophages containing Michaelis-Gutmann bodies
- Reactive renal tubular epithelium:
  - Suspect renal parenchymal ischemic necrosis
  - Round oval cells with small eccentric nuclei and granular cytoplasm
- Renal collecting duct epithelium:
  - Microtissue fragments or isolated small polygonal cells with scant cytoplasm
  - Centrally placed small nuclei with dense chromatin
- Urothelial papilloma:
  - Often indistinguishable from low grade papillary urothelial carcinoma
  - Less cellular, small cells with hyperchromatic nuclei

Urothelial Adenocarcinoma

Cytologic Findings

- Three dimensional grouping with nuclear palisading
- High N/C ratio, eccentric nuclei, irregular nuclear contours, prominent nucleoli
- Intracellular and extracellular mucin production

Differential Diagnosis

- Prostatic adenocarcinoma:
  - Acini and syncytial groups of cells with nucleomegaly and prominent nucleoli
  - Lack mucin
- Herpes simplex virus-induced changes
- Decoy cells
- Glandularis cystitis:
  - Glandular cells with cytoplasmic vacuoles, lack cytologic atypia
- Renal cell carcinoma:
  - Frequently degenerated
  - Single cells or small groups of abnormal cells
  - Nuclei round to oval, eccentric, hyperchromatic, with prominent nucleoli
  - Cytoplasm appears more granular than expected due to degeneration
- Nephrogenic adenoma:
  - single or small groups of vacuolated cells
  - Polygonal to columnar in shape
  - Uniform nuclei
- Ileal conduit:
  - Columnar (colonic) degenerative epithelial cells without atypia
  - Mucoid dirty background
  - Eosinophilic cytoplasmic inclusions may be seen
- Renal rejection:
  - Numerous renal tubular cells and T-lymphocytes
  - Casts and renal red blood cells with thick outer border and clear center

PLEURAL AND PERITONEAL FLUID

Reactive Mesothelial Cells (see Tables 6-4 and 6-5)

- Loose aggregates of cells with demarcation lines or "windows" between cells
- Fluffy cytoplasmic border (cilia) and centrally placed nuclei
- Ill-defined, fine, small centrally placed vacuoles with signet-ring change and peripheral PAS staining (glycogen)
- Two-tone cytoplasm staining with a rim of lighter blue cytoplasm around nucleus
- Bi- and multinucleation with similar nuclear size
- Continuum or spectrum of changes ranging from normal to atypia
- Psammoma bodies and mitotic figures

Causes of mesothelial hyperplasia:

- Heart failure
- Infection (pneumonia, lung abscess)
- Infarction
- Liver disease (hepatitis, cirrhosis)
- Collagen disease
- Renal disease (uremia, dialysis)
- Pancreatic disease
- Radiation
- Chemotherapy (Bleomycin, Cytoxan)
- Traumatic irritation (hemodialysis, surgery)
- Chronic inflammation (pleuritis)
- Underlying neoplasm (fibroid, hamartoma)
- Foreign substance (talc, asbestos)

Rheumatoid Pleuritis/Pericarditis

- Pink necrotic granular debris (key feature)
- Elongated spindle epithelioid histiocytes with dense granular eosinophilic cytoplasm
- Multinucleated giant cells, neutrophils, lymphocytes and scattered reactive mesothelial cells

Tuberculosis

- Predominant lymphocytes without mesothelial cells in the pleural fluids
- Entrapment of mesothelial cells in the fibrinous exudate

Mesothelioma

- Grouping of cells:
  - Excessive number of malignant cells
  - No evidence of two-cell population
  - Cohesive, three dimensional clusters with thick cell membrane (cellular spheres)
  - High number of cells in the cellular spheres
  - Doublets and triplets still recognizable
- Individual cells:
  - Ecto-endoplasmic demarcation (two tone cytoplasmic staining with denser, more eosinophilic perinuclear staining)
  - Fuzzy border around entire perimeter
  - Clasp-like articulation between two cells
  - Protrusion from pinched member of the pair
  - Window-like spaces between the cells
  - Peripheral vacuolization and bleb formation
  - Bland nuclei resembling one another

Table 6-4. Comparison Between Transudate and Exudate

	Transduate	*Exudate*
Appearance	Clear	Turbid
Specific gravity	<1.015	>1.015
Protein	<3 gm/dl	>3 gm/dl
Fluid/serum protein ratio	<0.5	>0.5
Fluid/serum LOH ratio*	<0.6	>0.6

**LOH = lactate dehydrogenase*

Metastatic Adenocarcinoma (See Table 6-2)

Cytologic Findings

- Two-cell population
- Papillary acinar structures and cell balls with smooth community border
- Three dimensional tight clusters with nuclear overlapping and nuclear molding
- Large, well-defined, smooth edged and eccentrically placed vacuoles
- Some types present as single large abnormal cells
- Diffuse (instead of peripheral) PAS (+diastase) staining and mucin production and positive hyaluronidase resistant alcian blue
- Bizarre cells, multinucleation with atypia and variable nuclear size
- High N/C ratios, irregular nuclear contours, anisonucleosis, prominent nucleoli, and mitotic figures
- Intranuclear or intracytoplasmic inclusions

Table 6-4. Features of Quiescent and Reactive Mesothelial Cells

Cytologic feature	*Quiescent*	*Reactive/Hyperplastic*
Pattern	Sheets, closely apposed to one another Break off in small groups	Doublets or triplets with windows between them May form papillary groups Connections by clasp like articulation
Shape and size	Round to oval 15-20 mm	Round to oval 20-40 mm
Nucleus	Monotonous Oval to round Mononuclear or binuclear Evenly distributed chromatin	Variable Oval to round Multinucleation Variable
Nucleolus	Inconspicuous	Variable
Cytoplasm	Moderate amount Translucent Peripheral vacuoles containing glycogen	Abundant Endo-ectoplasmic demarcation Peripheral vacuoles containing glycogen
Cell border	Fuzzy border due to microvilli	Cytoplasmic protrusions distal to cellular connections

Differential Diagnosis

- Reactive mesothelial cells:
  - "Windows" between cells and cilia, two-tone cytoplasm staining
  - Negative mucin staining
- Malignant mesothelioma (see Table 6-2 and 17-3):
  - Hypercellular smear with one cell population
  - Three-dimensional cohesive clusters of cells two-tone cytoplasm staining
  - Lack hyaluronidase resistant alcian blue staining
- Collagen ball:
  - Collagen covered by mesothelial cells, may be detached from the serosal surface or the ovary
  - Appear as smoothly contoured green bodies, naked or covered by a layer of mesothelial cells
- Ciliocytophthoria (ascites):
  - Detached cilliary tufts
  - Derived from fallopian tube lining cells, often seen in later half of menstrual cycle or after surgical manipulation
- LE cells:
  - Seen in patients with systemic lupus erythematosis
  - A neutrophil or sometimes a macrophage ingesting a denatured nucleus of a injured cell
- Tart cells:
  - Seen in patients with systemic lupus erythematosis
  - A macrophage that ingested a nonhomogenized nucleus of a dead cell

CEREBROSPINAL FLUID (CSF) AND CENTRAL NERVOUS SYSTEM

Specimen Preparation of CSF

- Cytospin
- Monolayer preparation
- Filter preparation:
  - More cells retained, but less optimal preservation and staining

Normal Components of CSF

- Usually no more than 5 cells/mm3
- Few lymphocytes and histiocytes
- Occasional neutrophils and eosinophils may be present after operative procedure involving subarachnoid space
- Contaminants include: cutaneous squamous cells, adipose tissue, skeletal muscle, cartilage, and vessels
- Hematopoietic precursors from bone marrow contaminants
- Corpora amylacea
- Talc powder
- Ventricular lining cells

Ependymal Cells

- Cuboidal to columnar cells with indistinct cell border, cytoplasmic vacuoles, and microcilia
- Difficult to differentiate from choroid plexus cell (not important)
- Less cohesive than choroid plexus cell with amphophilic cytoplasm
- May be pleomorphic in reactive conditions
- Phosphotungstic acid hematoxylin (PTAH) stains basal bodies of cilia

Choroid-Plexus Cells

- Often have papillary or microacinar configuration with dense eosinophilic cytoplasm
- Cell outline sharper than ependymal cells
- Cytoplasm may contain yellow pigment

Pia-arachnoid (Leptomeningeal) Cells

- Small round to spindle cells with abundant foamy cytoplasm and less defined cell border, resemble mesothelial cell

Brain Parenchyma

- Often seen in patients with ventricular shunts, intracranial hemorrhage, and head injury

Primitive (Blast-like) Cells of Neonates

- Probably derived from the subependymal germinal matrix
- Often seen in CSF of neonates with hydrocephalus or intraventricular hemorrhage
- Cohesive clusters of cells with high N/C ratio
- Neuron specific enolase positive and leukocyte common antigen negative

Inflammatory Conditions

- Neutrophils followed by mononuclear inflammatory cells in acute meningitis
- Viral infection characteristically shows mild lymphocytosis and rarely viral inclusions
- Mixed inflammation with lymphocytes may be observed in tuberculosis

Mollaret Meningitis

- Recurrent self-limiting aseptic meningitis
- Mollaret cell (activated monocytes), pleocytosis with increased lymphocytes and neutrophils

Acute Lymphocytic Leukemia/Malignant Lymphoma

Cytologic Findings

- Monotonous population of singly malignant cells with high N/C ratio, irregular nuclear contours, open chromatin, and prominent nucleoli
- Ancillary studies may be essential for diagnosis

Differential Diagnosis

- Reactive lymphocytes (due to intrathecal chemotherapy, viral infection, etc)
- Plasmacytoid and immunoblastic lymphocytes
- Puncture of marrow space
- Hematopoietic precursors at different stage of development
- Nucleated red cells and megakaryocytes
- Ventricular lining cells
- Primitive cells of neonates
- Medulloblastoma:
  - Tight clusters or single isolated small blue cells with nuclear molding

Astrocytoma

Cytologic Findings

- Low grade:
  - Hypocellular smear composed of dispersed small cells in a fibrillar background
  - Round nuclei with finely granular chromatin
  - Pale cyanophilic cytoplasm with indistinct cell borders
  - Long or blunt cytoplasmic processes may be seen in cells on FNA

  - Fibrillary background with small blood vessels in close association with tumor cells seen on FNA
- High grade:
  - Hypercellular smear
  - Nuclear hyperchromasia and nuclear pleomorphism
  - Tumor giant cells, bizarre nuclei, and prominent nucleoli
  - Endothelial proliferation best appreciated on Romanovsky
  - Degenerative changes and necrosis prominent
  - Atypical mitotic figures

Differential Diagnosis

- Reactive gliosis:
  - May be indistinguishable from low grade astrocytoma
  - Less cellularity, polymorphous population of cells
  - Admixtures of lymphocytes, histiocytes, and gemistocytes
  - Lack atypical mitoses and endothelial proliferation

Ependymomas

Cytologic Findings

- Honeycomb sheets or cohesive three dimensional aggregates of columnar and polygonal cells
- Low N/C ratio, small polarized round nuclei with finely to coarsely granular chromatin
- Cells with distinct cell borders and abundant eosinophilic cytoplasm
- Flexner-Wintersteiner (true) rosette and perivascular pseudorosette

Differential Diagnosis

- Normal ependymal Cells:
  - Often occur as singly isolated cells without clustering

Choroid Plexus Papilloma

Cytologic Findings

- Papillary and cohesive aggregates of cuboidal cells with distinct cell border
- Cells with low N/C ratio, uniform nuclei, smooth nuclear contours and fine chromatin
- Small or inconspicuous nucleoli

Differential Diagnosis

- Primitive Neuroectodermal tumors (PNET):
  - Small blue cells with hyperchromatic angulated nuclei and nuclear molding
  - Nuclei with course granular chromatin and smooth nuclear membrane
- Metastatic adenocarcinoma

Craniopharyngioma

- Anucleated squamous cells, lipid-laden macrophages, keratin pearls, and cholesterol crystals

Germinoma

- Isolated single cells and loosely cohesive sheets of large tumor cells admixed with lymphocytes
- Large vesicular uniform nuclei with prominent nucleoli
- Scant to moderate, delicate, occasionally vacuolated cytoplasm with distinct cell borders
- Granulomatous inflammation and tigroid background in Romanovsky stain
- Positive for placental alkaline phosphatase (PLAP)

Meningioma

- Cohesive clusters and syncytial arrangement of uniform spindle cells
- Cells with abundant eosinophilic cytoplasm
- Small nuclei with smooth nuclear contour and fine granular chromatin
- Psammoma bodies, whorls and intranuclear cytoplasmic inclusions
- Positive for epithelial membrane antigen (EMA)

Retinoblastoma

- Tight clusters of small blue cells with irregular coarsely granular chromatin
- Occasional rosette formation
- Tumor diathesis and inflammatory background

Medulloblastoma

Cytologic Findings

- Cellular smear composed of uniform population of small blue cells
- Nuclear molding
- Cells are isolated or as tight clusters
- Round hyperchromatic nuclei, high N/C ratio,
- Coarse granular chromatin and inconspicuous nucleoli
- Pseudorosette and nuclear molding

Differential Diagnosis

- Normal cerebellum:
  - Uniform cells of granular layer with smooth nuclear contours

Metastatic Carcinoma

- Variable number of cells
- Clusters of malignant cells with features that may be reminiscent of primary cancer
- Immunohistochemical staining is often helpful

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www.Bethesda2001.cancer.gov

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Part II

Organ Systems

Chapter 7

Lymph Node and Spleen

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Table of Contents

HOW TO WORK UP A LYMPH NODE

- Receive lymph node fresh
- Ensure excellent fixation (B5 or zinc sulfate formalin preferred)
- Snap freeze a portion (for frozen immunoperoxidase stains and molecular genetics)
- Virtually all diagnostic problems involving hematolymphoid neoplasms can be resolved by a combination of paraffin section immunoperoxidase stains, frozen section immunoperoxidase stains, and/or molecular genetics studies
- Flow cytometry (selected cases)
- Phenotypic approach: Most cost effective approach should be driven by the morphologic differential diagnosis. Remember: reimbursement is not guaranteed if ancillary studies cannot be shown to be diagnostically justified

CLASSIFICATION OF DISEASES

Lymphoid Hyperplasias

Follicular Hyperplasias

- Reactive follicular hyperplasia
- Toxoplasmosis
- Cytomegalovirus
- Human immunodeficiency virus
- Rheumatoid arthritis
- Syphilis
- Progressive transformation of germinal centers
- Castleman's disease, hyaline vascular type
- Castleman's disease, plasma cell type

Sinus Hyperplasias

- Lymphangiogram effect
- Whipple's disease
- Hemophagocytic syndrome
- Vascular transformation of lymph node sinuses

Paracortical Hyperplasias

- Infectious mononucleosis
- Atypical immunoblastic reaction
- Dermatopathic lymphadenopathy

Necrotizing Granulomatous Lymphadenitis

- Cat scratch disease
- Lymphogranuloma venereum
- Tularemia
- Yersinia
- Tuberculosis
- Fungal infection

Necrotizing Nongranulomatous Lymphadenitis

- Kikuchi-Fujimoto disease
- Systemic lupus erythematosis

Malignant Lymphoma/Leukemia (WHO Classification)

Precursor B- and T-cell Neoplasms

- Precursor B-lymphoblastic leukemia/lymphoma
- Precursor T-lymphoblastic leukemia/lymphoma

Mature B-cell Neoplasms

- Chronic lymphocytic leukemia/small lymphocytic lymphoma
- B-cell prolymphocytic leukemia
- Lymphoplasmacytic lymphoma/Waldenström macroglobulinemia
- Splenic marginal zone lymphoma
- Hairy cell leukemia
- Plasma cell neoplasms
- Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)
- Nodal marginal zone B-cell lymphoma
- Follicular lymphoma
- Mantle cell lymphoma
- Diffuse large B-cell lymphoma
- Mediastinal (thymic) large B-cell lymphoma
- Burkitt lymphoma/leukemia

Mature T-Cell and NK-Cell Neoplasms

- T-cell prolymphocytic leukemia
- Large granular lymphocytic leukemia
- Aggressive NK-cell leukemia
- Adult T-cell leukemia/lymphoma
- Extranodal NK/T-cell lymphoma, nasal type
- Enteropathy-type T-cell lymphoma
- Hepatosplenic T-cell lymphoma

- ♦ Subcutaneous panniculitis-like T-cell lymphoma
- ♦ Blastic NK-cell lymphoma
- ♦ Mycosis fungoides/Sézary syndrome
- ♦ Angioimmunoblastic T-cell lymphoma
- ♦ Peripheral T-cell lymphoma, unspecified
- ♦ Anaplastic large cell lymphoma

Hodgkin's Lymphoma

- ♦ Nodular lymphocyte predominant Hodgkin's lymphoma
- ♦ Classical Hodgkin's lymphoma
  - – Nodular sclerosis Hodgkin's lymphoma
  - – Mixed cellularity Hodgkin's lymphoma
  - – Lymphocyte-rich classical Hodgkin's lymphoma
  - – Lymphocyte depleted Hodgkin's lymphoma

Histiocytic Lymph Node Tumors

- ♦ Langerhans' cell histiocytosis
- ♦ Sinus hyperplasia with massive lymphadenopathy
- ♦ Histiocytic sarcoma

Spindle Cell Lesions of Lymph Node

- ♦ Bacillary angiomatosis
- ♦ Kaposi's sarcoma
- ♦ Palisaded myofibroblastoma
- ♦ Inflammatory pseudotumor of lymph node
- ♦ Follicular dendritic cell sarcoma
- ♦ Interdigitating dendritic cell sarcoma

Spleen

Predominantly White Pulp-Based Processes

- ♦ Benign Conditions
  - – Follicular and marginal zone B-cell hyperplasia
  - – T-zone hyperplasia
- ♦ Malignant Conditions
  - – Follicular lymphoma
  - – Mantle cell lymphoma
  - – Splenic marginal zone lymphoma
  - – Diffuse large B-cell lymphoma
  - – Hodgkin's lymphoma

Predominantly Red Pulp-Based Processes

- ♦ Benign Conditions
  - – Congestion
  - – Hemolytic anemia
  - – Idiopathic thrombocytopenic purpura
  - – Sepsis
- ♦ Malignant Conditions
  - – Chronic lymphocytic leukemia/small lymphocytic lymphoma
  - – Hairy cell leukemia
  - – Large granular lymphocytic leukemia
  - – Acute leukemia
  - – Chronic myelogenous leukemia
  - – Chronic idiopathic myelofibrosis

Non-hematolymphoid Splenic Tumors

- ♦ Benign tumors
  - – Splenic hamartoma
  - – Littoral cell angioma
  - – Hemangioma
  - – Lymphangioma
  - – Hemangioendothelioma
- ♦ Malignant Tumors
  - – Angiosarcoma

Discussion of Individual Diseases

LYMPHOID HYPERPLASIAS

Follicular Hyperplasias

Reactive Follicular Hyperplasia

Differential Diagnosis

- ♦ Follicular lymphoma (see Table 7-1)

Toxoplasmosis

Clinical

- ♦ Mostly young females (if pregnant, may result in birth defects in developing fetus)
- ♦ Transmitted by exposure to oocysts in cat feces or by ingestion of poorly-cooked meat
- ♦ Symptoms: flu-like or asymptomatic
- ♦ Site of involvement: posterior cervical nodes most common

Microscopic

- ♦ Toxo Triad
  - – Florid follicular hyperplasia

Table 7–1. Follicular Hyperplasia vs Follicular Lymphoma

Follicular Hyperplasia	*Follicular Lymphoma*
Younger patients	Older patients
Normal follicle density	Increased follicle density (back to back)
Follicles vary in size and shape	Follicles homogeneous
Well-defined mantle zone	Thin or absent mantle zone
Cellular polarization present	Cellular polarization absent
Heterogeneous follicle cells	Homogeneous follicle cells
Tingible body macrophages present	Tingible body macrophages absent
Mitoses common	Mitoses uncommon
Follicles confined to node	Follicles may be seen in perinodal tissue
No atypical cells between follicles	Interfollicular regions may contain neoplastic cells
Follicle center cells (FCC) bcl-2 negative	Follicle center cells (FCC) bcl-2 positive (usually)
FCC not light chain restricted	FCC light chain restricted
Ig/bcl-2 genes not rearranged	Ig/bcl-2 genes rearranged (Southern blot or PCR)

  - Monocytoid B-cell hyperplasia expanding and surrounding sinuses
  - Paracortical epithelioid histiocyte clusters that encroach on germinal centers
    - No necrosis
- Confirm diagnosis with serologic studies

Cytomegalovirus (CMV)

Microscopic

- Florid follicular hyperplasia
- Monocytoid B-cell hyperplasia expanding sinuses (CMV inclusions may sometimes be identified here)
- +/- immunoblastic proliferation (may be atypical)
- Confirm diagnosis serologically, immunohistochemically, or by *in situ* hybridization techniques

Human Immunodeficiency Virus (HIV)

Microscopic

- Early stage
  - Florid reactive lymphoid hyperplasia with absent mantle zones and follicle lysis of germinal centers (germinal centers disrupted by hemorrhage, disrupted FDC [follicular dendritic cell] meshwork, and increased T-cells)
  - Monocytoid B-cell hyperplasia expanding sinuses
  - Epithelioid histiocyte clusters
  - Increased plasma cells and polykaryocytes (large multinucleated giant cells) in interfollicular zones
- Late stage
  - Regressively transformed germinal centers
  - Depletion of lymphocytes from paracortex

Differential Diagnosis

- Castleman's disease, hyaline vascular type: Expanded mantle zones, hyalinized vessels

Rheumatoid Arthritis

Microscopic

- Florid follicular hyperplasia
- Marked interfollicular plasmacytosis (plasma cells also present within follicles)
- Clusters of neutrophils in sinuses

Differential Diagnosis

- Other inflammatory disorders (e.g., Sjögren's syndrome, Felty's syndrome, Still's disease)
- HIV infection
- Syphilis
- Castleman's disease, plasma cell type (this is a clinicopathologic diagnosis)

Syphilis (Luetic lymphadenitis)

Microscopic

- Florid follicular hyperplasia
- Interfollicular plasmacytosis
- Epithelioid granulomas
- Thick, fibrotic capsule - perivascular plasma cells
- +/- arteritis/phlebitis
- Confirm diagnosis serologically

Progressive Transformation of Germinal Centers

- Rarely precedes, accompanies, or succeeds nodular lymphocyte predominant Hodgkin's lymphoma (NLPHL)

Microscopic

- Associated with reactive follicular hyperplasia in the same node
- Large follicles with indistinct germinal center/mantle zone borders due to infiltration of germinal centers by mantle zone lymphocytes
- Residual large germinal center cells (EMA –) may mimic L&H cells (usually EMA +) of NLPHL

Differential Diagnosis

- NLPHL
  - Neoplastic Hodgkin cells have nuclear lobulation, centroblasts usually do not.
  - Hodgkin cells usually EMA +
- Follicular lymphoma, floral variant
  - Neoplastic follicle center cells usually bcl-2 + and exhibit kappa or lambda light chain restriction
- Mantle cell lymphoma
  - Neoplastic cells surround atrophic follicles
  - Monoclonal B-cells CD5 +

Castleman's Disease, Hyaline Vascular Type

Clinical

- Usually solitary mediastinal mass, may involve other sites

Microscopic

- Atrophic germinal centers (regressively transformed) with expanded mantle zones composed of concentric layers of lymphocytes
- Multiple regressively transformed germinal centers in one "cloud" of mantle zone lymphocytes
- Hyalinized blood vessels penetrate into follicles; interfollicular vascularity increased
- Few interfollicular plasma cells or transformed lymphocytes

Differential Diagnosis

- HIV infection
  - Absent mantle zones
  - Increased interfollicular plasma cells and polykaryocytes

Castleman's Disease, Plasma Cell Variant

Clinical

- Patients may have POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin lesions) or a variety of other signs and symptoms
- Sites of involvement: abdominal cavity and mediastinum, peripheral lymph nodes, extranodal sites
- Clinicopathologic diagnosis

Microscopic

- Florid follicular hyperplasia with regressive transformation of germinal centers
- Marked interfollicular plasmacytosis that extends to the lymph node capsule

Differential Diagnosis

- Rheumatoid arthritis
- HIV infection
- Syphilis

Sinus Hyperplasias

Differential Diagnosis of All Sinus Hyperplasias

- Metastatic carcinoma
- Metastatic malignant melanoma
- Anaplastic large cell lymphoma (ALCL)

Lymphangiogram Effect

Clinical

- Sites of involvement: Abdominal lymph nodes

Microscopic

- Sinuses distended by lipid vacuoles surrounded by histiocytes and multinucleated giant cells

Whipple's Diease

Clinical

- Age: middle-aged adults
- Sex: M>F
- Etiology: infectious disease of small bowel (etiologic agent: Tropheryma whippelli)
- Site of involvement: small bowel, abdominal lymph nodes, +/– peripheral lymph nodes

Microscopic

- Sinuses distended by large lipid vacuoles surrounded by vacuolated histiocytes
- PAS+ bacilli present within histiocyte cytoplasm in sinuses and in germinal centers
- Confirm diagnosis by PCR or electron microscopy

Differential Diagnosis

- Mycobacterium avium intracellulare (MAI): organisms are acid-fast + as well as PAS +
- Lymphangiogram effect: histiocytes are PAS –, acid-fast –
- Lipogranuloma: diagnosis of exclusion
- Silicon

Hemophagocytic Syndrome

Synonym

- Virus-associated hemophagocytic syndrome

Clinical

- Immunocompromised host
- Usually due to viral infection, may result from bacterial, fungal, or parasitic infection
- May complicate certain lymphomas:
  - Subcutaneous panniculitis-like T-cell lymphoma
  - ALCL
  - Extranodal NK/T-cell lymphoma, nasal type
- Sites of involvement: lymph nodes, spleen, bone marrow

Microscopic

- Sinuses distended by benign-appearing histiocytes containing phagocytized erythrocytes or other hematopoietic elements

Vascular Transformation of Lymph Node Sinuses

Clinical

- Lymph node enlargement
- Sometimes associated with deep venous thrombosis in adjacent vein

Microscopic

- Sinuses distended by proliferating anastamosing vascular channels, often with fibrosis
- Capsule spared

Differential Diagnosis

- Kaposi's sarcoma:
  - Capsular/subcapsular involvement
  - Spindle cell proliferation without distinct vascular channels
  - PAS + hyaline globules

Paracortical Hyperplasias

Differential Diagnosis of all Paracortical Hyperplasias

- Peripheral T-cell lymphoma
- Interfollicular Hodgkin's lymphoma

Infectious Mononucleosis

Microscopic

- Paracortical expansion (EBV+ cells located in paracortex)
- Focal necrosis
- Sinuses distended by atypical lymphocytes, monocytoid B-cells, and/or immunoblasts
- +/– follicular hyperplasia
- Cytology: polymorphous population of transformed lymphocytes, immunoblasts, RS-like cells, plasma cells, and histiocytes
- Confirm diagnosis by serologic studies or blood findings (lymphocytosis with >50% lymphocytes, >10% atypical lymphocytes)

Differential Diagnosis

- Diffuse large B-cell lymphoma: monoclonal
- Classical Hodgkin's lymphoma: Hodgkin cells CD15+, CD30+, CD45–
- Viral infection (e.g. CMV)
- Drug reaction (especially hydantoin)

Atypical Immunoblastic Reaction

Microscopic

- Similar to infectious mononucleosis

Causes

- Drug reaction (especially hydantoin): eosinophils often numerous
- Herpes simplex: viral inclusions may be seen in and around necrotic areas
- CMV: accompanied by monocytoid B-cell hyperplasia, CMV inclusions
- Postvaccinial (smallpox vaccine): RARE

Dermatopathic Lymphadenopathy

Clinical

- Usually associated with skin lesions

Microscopic

- Subcapsular paracortical regions expanded (often focally) by small lymphocytes, some with convoluted nuclei resembling small Sézary cells, interdigitating reticulum cells, Langerhans' cells, and histiocytes containing melanin, lipid, and hemosiderin
- Residual node displaced centrally

Differential Diagnosis

- Mycosis fungoides:
  - more architectural effacement, large and medium-sized pleomorphic lymphocytes present
  - aberrant T-cell phenotype
  - may require molecular genetics

Necrotizing Granulomatous Lymphadenitis

Cat Scratch Disease

Clinical

- Sites of involvement: axillary and cervical lymph nodes
- Etiologic agent: Bartonella henselae

Microscopic

- Central stellate abscesses containing neutrophils, surrounded by palisaded histiocytes and fibroblasts; sparse to no multinucleated giant histiocytes

- +/– follicular hyperplasia
- +/– monocytoid B-cells distending sinuses
- Bacilli (found in necrotic areas) stain positively with Warthin-Starry stain

Differential Diagnosis

- Lymphogranuloma venereum, Tularemia, Yersinia – all – on Warthin-Starry stain
- Toxoplasmosis: No necrosis, Warthin-Starry –
- Hodgkin's lymphoma

Lymphogranuloma Venereum (LGV)

Clinical

- Sexually transmitted disease caused by chlamydia trachomatis
- Involves inguinal lymph nodes in males, pelvic lymph nodes in females

Microscopic

- Morphologically indistinguishable from cat scratch disease, tularemia, yersinia
- Confirm diagnosis serologically

Tularemia

- Often history of tick bite
- Involves axillary lymph nodes
- Morphologically indistinguishable from cat scratch disease, LGV, yersinia
- Confirm diagnosis by serology or cultures

Yersinia

- Clinical history of abdominal pain and diarrhea, signs suggesting appendicitis
- Involves mesenteric lymph nodes
- Morphologically indistinguishable from cat scratch disease, LGV, tularemia

Tuberculosis (TB)

Microscopic

- Necrotizing granulomas with central caseous necrosis without neutrophils
- AFB + bacilli present in necrotic areas (may be difficult to find); PCR may help

Fungal Infection

- Morphologically similar to TB, but granulomas more commonly contain neutrophils and karyorrhectic nuclear debris
- Organisms GMS +, PAS +

Necrotizing Nongranulomatous Lymphadenitis

Kikuchi-Fujimoto Disease

Synonym

- Histocytic necrotizing lymphadenitis

Clinical

- Young adult females
- Involves cervical lymph nodes

Microscopic

- Patchy cortical and paracortical necrosis with extensive karyorrhectic debris and histiocytes centrally
- Immunoblasts, histiocytes, and plasmacytoid monocytes peripherally
- No granulocytes, few plasma cells

Systemic Lupus Erythematosis (SLE)

Clinical

- Young adult females
- Cervical or generalized lymphadenopathy

Microscopic

- Follicular hyperplasia
- Interfollicular zones contain increased plasma cells and immunoblasts
- Areas of necrosis may contain neutrophils or plasma cells
- Hematoxylin bodies (composed of DNA aggregates, polysaccharides, and immunoglobulin) found within areas of necrosis as well as in walls of blood vessels

MALIGNANT LYMPHOMA/LEUKEMIA (WHO CLASSIFICATION)

Precursor B-and T-Cell Neoplasms

Precursor B-Lymphoblastic Leukemia (B-ALL)/ Lymphoblastic Lymphoma (B-LBL)

Synonyms

- Rappaport: lymphoblastic (formerly diffuse poorly differentiated lymphocytic [PDL])
- Kiel: lymphoblastic, B-cell type
- Lukes-Collins: undefined cell
- Working Formulation: lymphoblastic
- FAB: L1 and L2
- REAL: precursor B lymphoblastic leukemia/lymphoma

Clinical

- Age: children > adults
- Presentation:
  - Acute lymphoblastic leukemia (bone marrow and peripheral blood involvement) - more common. Pancytopenia, adenopathy, hepatosplenomegaly, bone pain
  - Lymphoblastic lymphoma (solid tumor [lymph node, skin, bone], +/– minimal bone marrow or peripheral blood involvement (≤ 25% lymphoblasts in bone marrow - arbitrary cut-off); mediastinum rarely involved in B-LBL) - less common
- Clinical course:
  - Highly aggressive
  - Often curable with chemotherapy
  - Better prognosis:
    - >50 chromosomes
    - t(12;21)(p13;q22)
  - Poorer prognosis:
    - t(1;19), t(9;22), t(4;11)(q21;q23), hypodiploidy
    - lack of CD10, CD34, or CD24 expression
    - CD13 or CD33 expression

Postulated Cell of Origin

- Precursor B-lymphoblasts

Microscopic

- Low power:
  - Architecture effaced
  - Invasion of perinodal fat common
  - Tumor involves paracortex, may spare reactive follicles
- High power:
  - Monotonous population of lymphoblasts: medium-sized cells with round or convoluted nuclei, fine chromatin, inconspicuous nucleoli, scant cytoplasm
  - Frequent mitoses
  - +/– starry sky pattern (tingible body macrophages)
  - T and B phenotypes morphologically indistinguishable

Immunophenotype

- CD19 +, CD79a +
- CD43 +
- TdT (terminal deoxynucleatidyl transferase) +
- CD34 usually +
- CD20, CD22 usually +
- CD10 usually +
- Surface immunoglobulin (sIg) –
- CD13 and/or CD33 may be present

Genetics

- Ig heavy chain genes rearranged
- Light chain genes may be rearranged (~50%)
- T-cell receptor gene may be rearranged in B-LBL

Differential Diagnosis (Table 7-2)

- More mature B-cell neoplasms (e.g. blastoid variant of mantle cell lymphoma):
  - TdT and CD34 –
  - sIg +
- Precursor T-lymphoblastic leukemia/lymphoma:
  - B-cell associated antigens –
  - CD3, CD7 +
  - CD34 –
- Myeloid sarcoma (extramedullary myeloid tumor, granulocytic sarcoma):
  - CD13, CD33, myeloperoxidase (MPO), CD68, lysozyme +
  - CD19, CD22, CD10, CD79a –
- Burkitt lymphoma
  - More prominent starry-sky pattern, coarser chromatin, multiple nucleoli, amphophilic, agranular cytoplasm
  - sIg +
  - CD34, TdT –

Table 7–2. Paraffin Section Immunophenotype of Blastic Hematolymphoid Malignancies

Disorder	*TdT*	*CD34*	*CD43*	*MPO/Lys*[1]	*CD3*	*CD79a*	*CD20*	*Cyclin D1*
Precursor T-lymphoblastic leukemia/lymphoma	+	–	+	–	+	–	–	?
Precursor B-lymphoblastic leukemia/lymphoma	+	+	+	–	–	+	+/–	?
Myeloid sarcoma	+/–	+	+	+	–	–	–	?
Burkitt lymphoma	–	–	+	–	–	+	+	–
Blastoid mantle cell lymphoma	–	–	+	–	–	+	+	+

[1]*MPO/Lys: myeloperoxidase/lysozyme*

Precursor T-Lymphoblastic Leukemia/Lymphoma (T-ALL/T-LBL)

Synonyms

- Rappaport: poorly differentiated lymphocytic, diffuse (modified to lymphoblastic)
- Kiel: T-lymphoblastic
- Lukes-Collins: convoluted T-lymphocytic
- Working Formulation: lymphoblastic, convoluted or nonconvoluted

Clinical

- Age: adolescents and young adults
- Sex: M>F
- Presentation: rapidly enlarging mediastinal (thymic) mass, +/– lymphadenopathy, SVC syndrome, pericardial and pleural effusions
- Bone marrow involvement >25% = precursor T-lymphoblastic leukemia
- Clinical course: highly aggressive but potentially curable

Microscopic

- Monotonous population of lymphoblasts (medium-sized cells with round nuclei, fine chromatin, inconspicuous nucleoli, and scant cytoplasm)
- Numerous mitoses, tingible body macrophages (starry sky)
- Morphologically indistinguishable from B-LBL

Immunophenotype

- Mirrors stages of intrathymic T-cell ontogeny
- CD7 +, CD3 + (cytoplasmic + even if surface –), CD2 +, CD5 +
- Subset of cases expresses CD1, CD4 and CD8
- TdT +
- Immunoglobulin –
- B-cell associated antigens –

Genetics

- T-cell receptor gene rearrangement variable
- Immunoglobulin heavy chain gene rearrangement may be present

Differential Diagnosis

- B-LBL
  - B-cell associated antigens +
  - T-cell associated antigens –
  - CD10 +
- Mature B-cell lymphoma
  - Lacks blastic cytology
  - B-cell associated antigens +
  - T-cell associated antigens –
  - TdT –
- Mature T-cell lymphoma
  - Heterogeneous cell population that lacks blastic cytology
  - TdT –
- Myeloid sarcoma (extramedullary myeloid tumor, granulocytic sarcoma)
  - Eosinophilic cytoplasm
  - Myeloperoxidase (MPO) +, lysozyme +, CD68 +
  - T-cell associated antigens –

Mature B-Cell Neoplasms

Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL)

Synonyms

- Rappaport: well-differentiated lymphocytic, diffuse
- Kiel: CLL
- Lukes-Collins: small lymphocytic B, CLL
- Working Formulation: small lymphocytic, consistent with CLL
- REAL: B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma

Clinical

- Age: older adults (median age 60-65 yrs)
- Sex: M>F (slight)
- History of waxing and waning adenopathy common
- SLL: Usually disseminated at presentation (involvement of bone marrow, multiple lymph nodes, spleen, and liver common)
- ~30% of patients with SLL progress to CLL
- CLL criteria: >5,000/mm^3 circulating lymphocytes (and >30% lymphocytes in bone marrow)
- CLL: lymph nodes (in addition to bone marrow and peripheral blood) usually involved
- SLL and CLL morphologically indistinguishable on lymph node biopsy
- Clinical course:
  - Indolent but not curable with available therapy
  - Median survival: 60-70 months
  - May transform to large cell lymphoma; risk increases over time
  - Poorer prognosis:
    - Extensive clinical disease
    - Increased number of large cells (prolymphocytes and paraimmunoblasts)
    - Trisomy 12, 17p deletion, 11q deletion

    - Germline variable region genes (consistent with naive B-cell derivation) - may correlate with CD38 expression
  - Better prognosis
    - 13q deletion
  - Postulated cell of origin:
    - 40-50% - naïve B-cell (germline variable region genes)
    - 50-60% - post-germinal center B-cell (variable region genes contain somatic mutations)

Microscopic

- Low power:
  - Effaced architecture (75% of cases)
  - Extensive involvement of perinodal fat in one third of cases
  - May be interfollicular
  - Pale zones (proliferation centers) alternating with darker zones
- High power:
  - Monotonous population of small lymphocytes (rounded nuclei, clumped chromatin, scant cytoplasm, inconspicuous to small nucleoli, and infrequent mitotic figures)
  - Most cases also contain larger lymphoid cells (prolymphocytes and paraimmunoblasts), frequently forming indistinct nodules known as pseudofollicles, proliferation centers or growth centers

Immunophenotype

- CD19, CD20, CD79a +
- CD23 +
- CD5 +, CD43 +
- sIg weakly + (M+/–D), immunoglobulin light chain restricted
- CD10 –
- cyclin D1 –

Genetics

- Ig heavy and light chain genes are rearranged
- Trisomy 12q
- 13q abnormalities (13q14)-most common-slightly better prognosis
- 11q deletion-poorer prognosis
- 17p deletion-poorer prognosis

Variant

- Interfollicular small lymphocytic lymphoma
  - Microscopic: numerous residual follicles (tumor will subsequently spread through lymph node to obliterate architecture)

Differential Diagnosis (See Table 7-3 and 7-4)

- Lymphoplasmacytic lymphoma:
  - Monoclonal plasmacytoid lymphocytes and plasma cells present; Dutcher bodies
- Mantle cell lymphoma (MCL):
  - Slightly larger lymphocytes with cleaved nuclei; no proliferation centers
  - CD23 –
  - Cyclin D1 +
  - t(11;14) usually present
- Follicular lymphoma (FL):
  - Follicular pattern (at least partially), centrocytes usually predominate, no proliferation centers
  - CD5 –, CD43 –, CD23 usually –
  - CD10 +
  - Cyclin D1 –
  - t(14;18) common
- Marginal zone B-cell lymphoma:
  - Cellular heterogeneity, reactive follicles usually present, no proliferation centers
  - CD5 usually –, CD23 –
- T-cell prolymphocytic leukemia:
  - T-cell associated antigens +
  - B-cell associated antigens –
- B-cell prolymphocytic leukemia (see below)

B-Cell Prolymphocytic Leukemia (B-PLL)

Clinical

- Often present with higher WBC count and splenomegaly

Microscopic

- > 50% of blood lymphocytes have clumped chromatin with prominent single nucleolus (defined on the basis of peripheral blood involvement; not tissue sections)

Immunophenotype

- Strong sIg +, CD5 may be –, CD23 usually absent

Prognosis

- More aggressive clinical course

Lymphoplasmacytic Lymphoma/Waldenström Macroglobulinemia

Synonyms

- Rappaport: well-differentiated lymphocytic, plasmacytoid, diffused mixed lymphocytic and histiocytic
- Kiel: immunocytoma, lymphoplasmacytic type
- Lukes-Collins: plasmacytic-lymphocytic

Table 7–3. Morphologic Differential Diagnosis of B-cell Lymphoproliferative Disorders in Lymph Node, Spleen and Bone Marrow Histologic Sections

	Lymph Node	*Spleen*	*Bone Marrow*	*Cytology*
Chronic lymphocytic leukemia/small lymphocytic lymphoma	Diffuse pattern, proliferation centers	Red pulp cords and sinusoids	Intertrabecular nodules and interstitial	Small lymphocytes, prolymphocytes, and paraimmunoblasts
Lymphoplasmacytic lymphoma	Diffuse pattern, +/- proliferation centers	Red pulp cords and sinusoids, encroaches on borders of white pulp	Intertrabecular nodules and interstitial, may be paratrabecular	Small lymphocytes, plasmacytoid lymphocytes, plasma cells, Dutcher bodies
Mantle cell lymphoma	Diffuse or nodular pattern with atrophic germinal centers	White pulp with atrophic germinal centers and obliterated marginal zone	Intertrabecular nodules and paratrabecular aggregates	Small lymphocytes with nuclear irregularity. No large cells
Nodal marginal zone lymphoma	Perisinusal or surrounding benign germinal centers and mantle zones	White pulp with small germinal centers and residual non-neoplastic mantle cells	Intertrabecular nodules and paratrabecular aggregates	Medium size cells with irregular nuclei, abun -dant pale cytoplasm. Occasional large transformed cells
Hairy cell leukemia	Rarely involved. Hilum, perinodal soft tissue involvement	Red pulp cords and sinusoids Blood lakes	Interstitial	Small to medium size lymphocytes with abundant pale cytoplasm
Follicular lymphoma	True follicular nodularity	White pulp germinal centers expanded with benign mantle and marginal zone cells	Intertrabecular nodules and paratrabecular aggregates	Small cleaved cells and large non-cleaved cells in varying proportions

Table 7–4. Immunophenotypic Features of Small B-Cell Lymphoproliferative Disorders

	SIg	*CD19*	*CD20*	*CD23*	*CD10*	*CD5*	*CD3*
Chronic lymphocytic leukemia/small lymphocytic lymphoma	Monoclonal (dim)	+	+ (dim)	+	–	+	–
Lymphoplasma-cytic lymphoma	Monoclonal cIg in plasma cells	+	+	–/+	–	–/+	–
Mantle cell lymphoma[1]	Monoclonal (bright)	+	+ (bright)	–	–	+	–
Marginal zone lymphoma	Monoclonal (bright)	+	+ (bright)	–	–	–/+	–
Hairy cell leukemia[2]	Monoclonal (bright)	+	+	–	–	–	–
Follicular lymphoma	Monoclonal (bright)	+	+ (bright)	–/+	+	–	–

[1]In addition, mantle cell lymphoma is the only lymphoma + for cyclin D1.
[2]The cells of hairy cell leukemia characteristically and brightly co-express CD22 and CD11c and are + for CD103.

- Working Formulation: small lymphocytic, plasmacytoid, diffuse mixed small and large cell
- REAL: lymphoplasmacytoid lymphoma/immunocytoma

Clinical

- Age: older adults (median 63 years)
- Sex: M>F (slight)
- Monoclonal immunoglobulin serum or urine (usually IgM, occasionally IgG or IgA) usually present
- Waldenström macroglobulinemia: monoclonal IgM serum paraprotein (≥3g/dL)
- Autoimmune hemolytic anemia, autoimmune thrombocytopenia, coagulation factor inhibitors, and cryoglobulinemia may be seen
- Sites of involvement:
  - Lymph nodes, bone marrow, spleen (usually stage III or IV at presentation)
  - Peripheral blood lymphocytosis may be present
- Clinical Course
  - similar to CLL/SLL
  - indolent but not curable with available therapy
  - may transform to diffuse large B-cell lymphoma (~10%) - poor prognosis

Microscopic

- Diffuse or parafollicular proliferation of small lymphocytes, plasmacytoid lymphocytes (lymphocytic-like nuclei, plasma cell-like cytoplasm), and plasma cells
- Abnormal immunoglobulin production manifest by:
  - Dutcher bodies (intranuclear immunoglobulin inclusions)
  - Russell bodies (extracellular hyaline immunoglobulin bodies)
  - Crystalline immunoglobulin deposits (intracytoplasmic or extracellular)
  - Amyloid deposits
  - Intercellular light chain deposits, mimicking amyloid
- Sinuses spared (may contain immunoglobulin)
- Mast cells frequently seen
- Iron-containing epithelioid histiocytes may be present

Immunophenotype

- sIg present (usually IgM; IgD absent), monoclonal cIg in plasma cells
- CD19, CD20, CD22, CD79a +
- CD23 usually –
- CD43 – or +
- CD5 usually –, occasionally +
- CD38, CD71 +
- CD10 usually –

Genetics

- Ig heavy and light chain genes are rearranged
- t(9;14)(p13;q32) and rearrangement of PAX-5 gene in <50% of cases

Differential Diagnosis

- CLL/SLL:
  - Monoclonal plasmacytoid lymphocytes and plasma cells absent
  - CD5 +, CD23 +, sIg weakly +

Splenic Marginal Zone Lymphoma

Synonyms

- Rappaport: (not specifically listed) WDL or WDL-plasmacytoid
- Kiel: not specifically listed
- Lukes-Collins: small lymphocyte B, lymphocytic-plasmacytic, small
- Lymphocyte B, monocytoid
- Working Formulation: (not specifically listed) SLL
- REAL: splenic marginal zone lymphoma, with or without villous lymphocytes

Clinical

- Age: older adults (median seventh decade)
- Sex: M>F
- Marked splenomegaly, often without adenopathy
- Bone marrow and peripheral blood usually involved
- May present as leukemia (+/– villous lymphocytes: lymphoid cells with abundant cytoplasm and small thin villi, often concentrated at one pole, as seen on peripheral blood smear)
- Clinical course: indolent
- Splenectomy may be treatment of choice (+/– chemotherapy)

Microscopic (Spleen)

- Low power:
  - Both mantle and marginal zones involved
  - Residual germinal centers atrophic or hyperplastic
  - Red pulp may be involved - sinusoidal involvement correlates with leukemic phase
- High power:
  - Mantle zone: Small neoplastic lymphoid cells with little cytoplasm
  - Marginal zone: Medium-sized neoplastic cells with moderate-abundant pale cytoplasm and scant large transformed lymphocytes with round nuclei, prominent nucleoli, dispersed chromatin and abundant cytoplasm
  - Plasmacytic differentiation may be present

Immunophenotype

- ♦ sIg + (M>G or A), cIg may be +; light chain restricted
- ♦ CD19, CD20, CD22, CD79a +
- ♦ CD5 and CD43 usually –, CD10 – (may be + on flow cytometry)
- ♦ May be weakly TRAP +
- ♦ CD23 –, cyclin D1 –
- ♦ CD11c usually +
- ♦ CD103 –

Genetic Features

- ♦ loss of 7q21-32 common

Differential Diagnosis

- ♦ Splenic marginal zone hyperplasia
  - – sIg - polyclonal
- ♦ Hairy cell leukemia (HCL)
  - – Red pulp process, blood lakes common, monotonous tumor cells
  - – CD103 +, TRAP +, DBA.44 +
- ♦ CLL/SLL
- – Red pulp process, architecture effaced, proliferation centers present, cells have scant cytoplasm
- – CD5 +, CD43 +, CD23 +
- ♦ MCL
- – Architecture effaced, monotonous cells with scant cytoplasm
- – CD5 +, CD43 +, cyclin D1 +
- ♦ FL
- – Follicular pattern, at least partially; germinal centers expanded
- – CD10 and bcl-6 usually +

Hairy Cell Leukemia (HCL)

Clinical

- ♦ Age: middle-aged to older adults
- ♦ Sex: M>F
- ♦ Presentation:
  - – Splenomegaly, pancytopenia, monocytopenia
  - – Hepatomegaly variable, although liver is usually involved
  - – Lymphadenopathy is uncommon
- ♦ Peripheral blood: always involved, but characteristic hairy cells (lymphoid cells with abundant pale cytoplasm with circumferential hairy projections) may be hard to find
- ♦ Bone marrow: always involved, may be inaspirable due to increased reticulin fibrosis
- ♦ Clinical course:
  - – Indolent, may remit spontaneously
  - – Infection - common complication
  - – Median survival: 4-5 years
- ♦ Treatment:
  - – Splenectomy +/– nonconventional lymphoma chemotherapy (interferon, 2-CDA, deoxycoformycin)

Microscopic

- ♦ Spleen:
  - – Low power:
    - • Involves red pulp cords and sinusoids, white pulp atrophic
    - • Blood lakes (variable size) lined by neoplastic cells common
  - – High power:
    - • Monotonous population of small-medium lymphoid cells with oval-reniform nuclei and abundant pale cytoplasm
    - • Cells appear widely spaced
- ♦ Lymph node (uncommonly involved):
  - – Diffuse involvement, prominent hilar and perinodal fat involvement, may spare follicles

Immunophenotype

- ♦ sIg +, light chain restricted
- ♦ CD19, CD20, CD22, CD79a +
- ♦ CD11c + (strong), CD25 + (strong)
- ♦ CD103 + (most specific marker)
- ♦ DBA.44 + (tissue sections)
- ♦ TRAP +
- ♦ CD5 –, CD10 –, CD23 –, cyclin D1 –

Genetics

- ♦ Ig heavy and light chains rearranged (proves B-cell lineage)

Electron Microscopy

- ♦ Long microvilli with broad base and ribosome-lamella complexes
- ♦ Characteristic but not pathognomonic

Differential Diagnosis

- ♦ Splenic marginal zone lymphoma
  - – Involves white pulp mantle and marginal zones, blood lakes absent
  - – CD103 –, TRAP weakly + in cell subset
- ♦ Mastocytosis
  - – Tryptase +, CD103 –, TRAP –
- ♦ CLL/SLL
  - – Architecture effaced, proliferation centers present, cells have scant cytoplasm
  - – CD5 +, CD43 +, CD23 +
  - – CD103 –, TRAP –

- MCL
  - White pulp process, architecture effaced, monotonous cells with scant cytoplasm
  - CD5 +, CD43 +, cyclin D1 +
- FL
  - Follicular pattern, at least partially; germinal centers expanded
  - Involves splenic white pulp
  - CD10, bcl-6 usually +
  - CD103 –, TRAP –

Plasma Cell Neoplasms

Clinical

- Plasma cell myeloma (multiple myeloma) - disseminated bone marrow tumor - common
- Plasmacytoma - uncommon
  - Solitary plasmacytoma of bone
    - Age: median sixth decade
    - Sex: M>F
    - Solitary bone lesion
    - 40-50% progress to multiple myeloma
  - Extraosseous plasmacytoma
    - Age: median seventh decade
    - Sex: M>F
    - Usually involves upper aerodigestive tract, can arise in any organ
    - Regional lymph nodes may be involved
    - Primary plasmacytoma of lymph node extremely rare
    - 10-20% progress to multiple myeloma

Microscopic

- Monotonous infiltrate of mature to immature plasma cells
- No admixed lymphoid cells
- Lymph node: partially or completely effaced

Immunophenotype

- sIg –, cIg + (G, A or light chain only; M, D or E rare), light chain restricted
- CD19, CD22 – (CD79a often +); CD20 may be +
- CD45 usually –
- CD38 +, CD138 +

Genetics

- Ig heavy and light chain genes rearranged or deleted

Differential Diagnosis

- Reactive plasmacytosis
  - Background of hyperplastic lymphoid follicles
  - Heterogeneous population of plasma cells
  - cIg not light chain restricted
- Lymphoplasmacytic lymphoma (and other low grade B-cell lymphomas)
  - Plasma cells admixed with small lymphocytes (not pure plasma cell population)
- Diffuse large B-cell lymphoma (immunoblastic/plasmacytoid type)
  - CD19, CD20 +
  - CD45 +
  - CD38 –, CD138 –
- Osteosclerotic myeloma (POEMS syndrome)
- Heavy chain disease (HCD)
  - Gamma HCD
  - Mu HCD
  - Alpha HCD

Extranodal Marginal Zone B-Cell Lymphoma of Mucosa-Associated Lymphoid Tissue (MALT Lymphoma)

Synonyms

- Rappaport: (not specifically listed) well differentiated lymphocytic (WDL) or WDL-plasmacytoid, IDL, ILL, PDL, mixed lymphocytic-histiocytic (nodular or diffuse)
- Kiel: monocytoid B-cell, immunocytoma (some cases previously classified as centroblastic/centrocytic or centrocytic)
- Lukes-Collins: small lymphocyte B, lymphocytic-plasmacytic, small lymphocyte B, monocytoid
- Working Formulation: (not specifically listed) SLL (some consistent with CLL, some plasmacytoid), small cleaved or mixed small and large cell (follicular or diffuse)
- REAL: extranodal marginal zone B-cell lymphoma

Clinical

- Age: adults (median age approximately 60 years)
- Sex: F>M (slight)
- May occur in patients with autoimmune disorder (e.g. Sjorgren's syndrome) or chronic antigenic stimulation (e.g. helicobacter gastritis)
- Sites of involvement:
  - stomach, salivary gland, lung, thyroid, skin, etc.
  - may secondarily involve regional lymph nodes
  - bone marrow involvement uncommon (15-20%); peripheral blood involvement rare
- Clinical course:
  - indolent; when disseminated, usually incurable with available therapy

- 5 year survival 75-80%
- may recur in other extranodal sites
- may transform to large B-cell lymphoma

Microscopic

- Low power: perisinusoidal, parafollicular, or marginal zone distribution; mantle zone preserved. Tumor gradually effaces architecture, circumscribing and infiltrating germinal centers (follicular colonization)
- High power: heterogeneous population of marginal zone cells (small-medium lymphoid cells with round-slightly indented nuclei, clumped chromatin, abundant pale cytoplasm, and well-defined cytoplasmic membranes), monocytoid B-cells, small lymphocytes, and plasma cells (plasma cells usually located in interfollicular zones). Occasional large transformed cells may be seen
- Lymphoepithelial lesions (marginal zone cells infiltrating epithelium) typically seen
- Plasma cells often located in subepithelium

Immunophenotype

- sIg + (M>G or A), cIg may be + (40%)
- CD19, CD20, CD22, CD79a +
- CD5, CD43 usually –
- CD10, CD23, cyclin D1 –
- CD11c may be weakly +, CD25 –

Genetics

- t(11;18)(q21;q21) - 20-50% of cases; t(1;14)
- Trisomy 3 (12-85%)
- Trisomy 18 (7-36%)

Differential Diagnosis

- Hairy cell leukemia (HCL)
  - Peripheral blood, bone marrow, spleen involved. Lymph node involvement uncommon
  - When lymph node is involved, HCL markedly infiltrates perinodal fat and nodal hilum. This feature is rare in MALT lymphoma.
  - CD11c + (strong), CD25 + (strong), CD103 + (most specific)
- TRAP usually present
- Mastocytosis
  - Tryptase +
- CLL/SLL
  - Architecture effaced, proliferation centers present, cells have scant cytoplasm
  - CD5 +, CD43 +, CD23 +
- MCL
  - Architecture effaced; monotonous cells with scant cytoplasm
  - CD5 +, cyclin D1 +
- FL
  - Follicular pattern, at least partially; centrocytes and centroblasts
  - CD10 and bcl-6 usually +
- Monocytoid B-cell hyperplasia
  - Germinal centers intact - not invaded by neoplastic monocytoid cells
  - sIg - polyclonal

Nodal Marginal Zone B-Cell Lymphoma

Synonyms

- Rappaport: (not specifically listed) well differentiated lymphocytic (WDL) or
- WDL-plasmacytoid, IDL, ILL, PDL, mixed lymphocytic-histiocytic (nodular or diffuse)
- Kiel: monocytoid B-cell, immunocytoma (some cases previously classified as centroblastic/centrocytic or centrocytic)
- Lukes-Collins: small lymphocyte B, lymphocytic-plasmacytic, small lymphocyte B, monocytoid
- Working Formulation: (not specifically listed) SLL (some consistent with CLL, some plasmacytoid), small cleaved or mixed small and large cell (follicular or diffuse)

Clinical

- Localized or generalized lymphadenopathy

Microscopic

- Low power:
  - Parafollicular or marginal zone distribution
- High power:
  - Marginal zone B-cells and/or monocytoid B-cells, +/- occasional large transformed cells

Immunophenotype

- sIg + (M>G or A), cIg may be + (40%)
- CD19, CD20, CD22, CD79a +
- CD5, CD43 usually –
- CD10, CD23, cyclin D1 –
- CD11c may be weakly +, CD25 –

Follicular Lymphoma (FL)

Synonyms

- Rappaport: nodular poorly differentiated lymphocytic (PDL), mixed lymphocytic-histiocytic, or histiocytic
- Kiel: centroblastic/centrocytic follicular, follicular centroblastic
- Lukes-Collins: small cleaved, large cleaved or large noncleaved follicular center cell (FCC), follicular
- Working Formulation: follicular, small cleaved mixed, or large cell
- REAL: follicular center lymphoma, follicular

Clinical

- Age: adults (median age 55-59 years)
- Sex: M=F
- Comprises 35-40% of non-Hodgkin lymphomas in U.S. (less common in other countries)
- Usually disseminated at presentation (>80% stage III/IV)
- Sites of involvement:
  - lymph nodes, spleen (25-55%), liver, bone marrow (40%), peripheral blood (uncommon)
  - Extranodal presentation without lymph node involvement uncommon (exception: primary follicular lymphoma of the skin)
- Clinical course:
  - Indolent but usually not curable with available therapy (grade 3: more aggressive but potentially curable with aggressive therapy)
  - Repeated relapses despite achievement of complete remission with or without therapy (23% remit spontaneously)
  - Transformation to large B-cell lymphoma common (up to 60-80% overall), regardless of treatment status
  - 5 year overall survival 72%; 5 year failure-free survival 40%
- Adverse prognostic indicators:
  - Increased number of centroblasts
  - Increased proportion of tumor with diffuse pattern (controversial)
  - Monocytoid B-cell differentiation

Terminology

- Subtype according to architectural pattern and follicular center cell composition:
  - Architecture: state approximate percent follicular pattern in report
    - follicular (>75% follicular pattern)
    - follicular and diffuse (25-75% follicular pattern)
    - focally follicular (<25% follicular pattern)
  - Follicular center cell composition:
    - Grade 1=predominantly small cleaved cells (centrocytes)
      - 0-5 noncleaved cells (centroblasts)/40x high power field (hpf) by counting method - must count cells in 10 follicles
      - <25% large noncleaved cells by estimation method
    - Grade 2=mixed small cleaved (centrocytic) and large cell (centroblastic)
      - 6-15 large noncleaved cells/hpf by counting method
      - 25-50% large noncleaved cells by estimation method
    - Grade 3=predominantly large cell
      - >15 large noncleaved cells/hpf by counting method
      - >50% large noncleaved cells by estimation method
      - Counting method cut-offs are based on hpf of 0.159 mm^2. Compensatory factor must be used for different oculars.

Microscopic

- Follicular pattern (at least partially); diffuse areas may be present
- Back to back arrangement of relatively uniform follicles (increased follicle density); intervening lymphoid stroma compressed
- Tumor may infiltrate nodal capsule, perinodal blood vessels, and perinodal fat
- Limited or absent mantle zone
- Follicles lack cellular polarization
- Follicles composed of centrocytes (small cleaved follicular center cells—usually predominate) and centroblasts (large noncleaved follicular center cells—usually in the minority)
- Follicles lack tingible body macrophages (may be present in grade 3 subtype)
- Low mitotic rate in follicles (may be high in grade 3 subtype)

Immunohistochemistry

- sIg + (usually IgM)
- Ig light chain restricted
- bcl-6 +, CD10 usually + (75%), interfollicular neoplastic cells also usually CD10 + (albeit more weakly)
- CD19, CD20, CD22, CD79a +
- CD5 –, CD43 –
- CD23 usually –
- Cyclin D1 –
- Intrafollicular lymphocytes bcl-2 + (83-100% of grade 1, 52-85% of grade 3)
- N.B.: bcl-2 is + in many other small B-cell lymphomas (as well as normal B and T-cells, normal hematopoietic precursors, and many other nonhematopoietic cells and tumors), therefore bcl-2 is:
  - useful in distinguishing FL from follicular hyperplasia
  - not useful in distinguishing FL from other small B-cell lymphomas

Genetics

- t(14;18)(q32;q21): bcl-2 gene (chromosome 18) juxtaposed to J-region of immunoglobulin heavy chain gene (chromosome 14) leading to increased bcl-2 protein expression.

- bcl-2 protein: prevents B-cell apoptosis (programmed cell death) leading to extended B-cell survival
- t(14;18) also present in 30% of diffuse large B-cell lymphomas
- Additional genomic defects (e.g. involving 3q27 or 17p, del 6q, trisomy 2,3,7,12,18, or 21, dup 2p) may be associated with grade 2 or 3 subtypes and more aggressive clinical course

Variants

- FL in children (rare)
  - Localized disease
  - Head and neck or inguinal region
  - Grade 2 or 3 subtypes common
  - Favorable outcome
- Sclerotic
  - Synonym: nodular sclerotic lymphosarcoma
  - Broad collagenous bands or fine sclerotic compartmentalization
  - No prognostic significance
- Follicular signet ring cell lymphoma
  - Lymphoid cells (usually centrocytes) contain cytoplasmic clear vacuoles (usually monoclonal IgG) or Russell body-like inclusions (usually monoclonal IgM)
- Multilobated nuclei
  - Most common in grade 3 subtype
- Plasmacytic differentiation
  - Large number of plasma cells
  - Plasma cells—polyclonal > monoclonal
  - Usually interfollicular, may be intrafollicular
  - May contain Russell bodies or Dutcher bodies
- Floral variant
  - Mimics progressive transformation of germinal centers (PTGC)
  - Floral/serrated appearance due to regular invasion of neoplastic follicles by small lymphocytes (B and T)
  - Usually grade 3
- FL with hyaline vascular follicles (rare)
  - Neoplastic follicles with concentrically arranged lymphoid cells and hyalinized venules
- Diffuse follicle center lymphoma
  - Synonyms:
    - Rappaport: diffuse poorly differentiated lymphocytic
    - Kiel: centroblastic/centrocytic, diffuse
    - Lukes-Collins: diffuse small cleaved FCC
    - Working Formulation: diffuse small cleaved cell
    - REAL: follicle center lymphoma, diffuse (predominantly small cell)
  - Microscopic:
    - Diffuse architecture
    - Majority of centrocytes with occasional centroblasts
    - Immunophenotype of follicle center cells (pan B-antigen +, sIg +, CD10 +, bcl-2 +, bcl-6 +)

Differential Diagnosis

- Follicular Hyperplasia (FH)
  - See Table 7-1
- Castleman's disease, hyaline vascular type
  - Reactive condition
  - Broad mantle zones with onionskin pattern
  - Small (regressively transformed) germinal centers containing hyalinized vessels
  - Intrafollicular lymphocytes bcl-2 –, polyclonal
  - Interfollicular lymphocytes CD10 –
- PTGC
  - Reactive condition, rarely associated with NLPHL
  - Expansile follicles in background of reactive follicles
  - No atypical cells in interfollicular zones or perinodal tissue
  - Intrafollicular lymphocytes bcl-2 –, polyclonal
  - Interfollicular lymphocytes CD10 –
- NLPHL
  - nodules larger than follicles of FL
  - centrocytes scant
  - L&H cells may resemble centroblasts, but have more pronounced nuclear lobulation, delicate chromatin, small nucleoli, wispy pale cytoplasm
  - L&H cells are usually EMA + and are often surrounded by CD57 + T-cells
  - nodular lymphocytes CD10 –
- MCL
  - diffuse or vaguely nodular pattern, cells homogeneous
  - CD5 +, CD43 +
  - CD10 –, bcl-6 –
  - cyclin D1 +
- MALT lymphoma
  - Lymphoepithelial lesions in extranodal sites
  - Perifollicular growth pattern
  - More abundant pale cytoplasm in centrocyte-like cells
  - Monoclonal plasma cells common
  - Neoplastic cells CD10 – (although residual normal follicle center cells may be CD10 +)
  - CD43 may be +

- CLL/SLL with prominent proliferation centers
  - Proliferation centers composed of prolymphocytes and paraimmunoblasts
  - CD5 +, CD43 +, CD23 +
  - CD10 –
- Lymphoblastic lymphoma with lobular pattern
  - blast-like cytology
  - TdT +, sIg –
  - both may be CD10 +

Mantle Cell Lymphoma (MCL)

Synonyms

- Rappaport: intermediately or poorly differentiated lymphocytic, diffuse or nodular (ILL/IDL/PDL)
- Kiel: centrocytic (mantle cell) lymphoma
- Lukes-Collins: small cleaved follicular center cell (FCC)
- Working Formulation: small cleaved cell, diffuse or nodular; rarely diffuse mixed xor large cleaved cell
- Other: mantle zone lymphoma

Clinical

- Age: older adults (median age 63 years)
- Sex: M>F
- Sites of involvement:
  - High stage at presentation: lymph nodes, spleen (~60%), peripheral blood (at least 25%)
  - Extranodal sites, especially GI tract (lymphomatous polyposis) and Waldeyer's ring
- Clinical course:
  - Moderately aggressive, incurable with available therapy
  - Median survival: 3-5 years
  - May progress to blastoid variant
- Adverse prognostic indicators:
  - Blastoid subtype
  - High mitotic rate
  - Peripheral blood involvement

Microscopic (lymph node)

- Low power:
  - Architecture effaced
  - Diffuse or vaguely nodular pattern
  - Tumor may involve or expand mantle zones of some reactive follicles (pure mantle zone pattern less common)
  - Hyalinized small capillaries in ~75%
  - Scattered epithelioid histiocytes without tingible bodies common (starry sky pattern on low power)
  - Monotonous population of small to medium-sized lymphoid cells without proliferation centers, paraimmunoblasts, or transformed cells
- High power:
  - Neoplastic cells: round to irregular nuclei (+/- clefts), clumped chromatin, scant cytoplasm
  - Few mitoses

Immunophenotype

- sIg + (M+/-D)
- Immunoglobulin light chain restricted (lambda>kappa)
- CD19, CD20, CD22, CD79a +
- Cyclin D1 + (specific for MCL)
- CD5 +, CD43 +
- CD23 –, CD10 –

Genetics

- t(11;14)(q13;32) demonstrable in up to 75% of cases by Southern blot analysis or conventional cytogenetics, and in nearly 100% of cases by fluorescence *in situ* hybridization
  - translocation of CCND1 (bcl-1) oncogene (chromosome 11) into Ig heavy chain locus (chromosome 14) results in overexpression of cyclin D1 (bcl-1 [PRAD-1]) gene product-required for progression from G1 to S phase in cell cycle; not normally overexpressed in lymphoid cells
- Variable region genes unmutated in most cases, consistent with pre-germinal center B-cell derivation

Variants

- Blastoid type (synonyms: lymphoblastoid, blastic, anaplastic, pleomorphic, centrocytoid-centroblastic)
  - Composed of lymphoblast-like cells with dispersed chromatin, small nucleoli, and high mitotic rate (+/- starry-sky pattern)
  - May indicate progression/transformation
- Monocytoid-like: abundant pale cytoplasm

Differential Diagnosis

- CLL/SLL:
  - Proliferation centers
  - Dim sIg expression, CD23 +
  - Cyclin D1 –
- Marginal zone B-cell lymphoma:
  - Parafollicular proliferation of monocytoid-like cells
  - CD5 usually –, may be CIg + (40%), CD43 usually –, CD23 may be + (<50%)
  - Cyclin D1 –
- Follicular lymphoma:
  - Follicular architecture, at least partially

- CD5 –, CD10 and bcl-6 usually +, CD23 may be + (<50%)
- Cyclin D1 –
- t(14;18) usually present

♦ Large B-cell lymphoma:
- Larger cells, prominent nucleoli, mitoses common
- CD5 –, CD43 –
- Cyclin D1 –

♦ Lymphoblastic lymphoma:
- Lymphoblastic cytology, numerous mitoses
- TdT +, sIg –
- CD34 usually +
- Cyclin D1 –
- T-cell antigen expression in most cases
- B-cell precursor phenotype in rare cases

Diffuse Large B-Cell Lymphoma

Synonyms

♦ Rappaport: diffuse histiocytic, occasionally diffuse mixed lymphocytic-histiocytic

♦ Kiel: centroblastic, B-immunoblastic, large cell anaplastic (B-cell)

♦ Lukes-Collins: large cleaved or large noncleaved FCC, B-immunoblastic

♦ Working Formulation: diffuse large cell cleaved, noncleaved or immunoblastic, occasionally diffuse mixed small and large cell

Clinical

♦30-40% of all adult non-Hodgkin lymphomas

♦ Age: median seventh decade (wide age range)

♦ Sex: M>F (slight)

♦ Most arise de novo

♦ Some result from transformation of lower grade lymphoma (e.g. FL, CLL/SLL, or Hodgkin's lymphoma [classical or lymphocyte predominant])

♦ May occur in patients with AIDS

♦ Presentation:
- Rapidly enlarging mass (up to 40% extranodal)
- 30% have B symptoms (fever, night sweats, or weight loss)
- Bone marrow involvement less frequent (10%) than in low grade lymphomas

♦ Clinical course:
- Aggressive but potentially curable

Microscopic (lymph node)

♦ Low power:
- Complete, partial, sinus, or interfollicular involvement
- Infiltration of perinodal tissue, sclerosis, necrosis (apoptosis or coagulative necrosis) common

♦ High power:
- Variable cytology
- Large cells with vesicular nuclei, prominent nucleoli, cytoplasm variable
- Bizarre cells may be present
- Mitoses common

Immunophenotype

♦ CD19, CD20, CD22, CD79a +

♦ CD45 usually +

♦ May express CD10 (25-50%) or CD5 (10%)

♦ Bcl-2 expressed in 30-50% - associated with adverse disease-free survival

Genetics

♦ Bcl-2 gene (18q21) rearranged in 20-30% (e.g. t(14;18))

♦ Bcl-6 gene (3q27) rearranged in a third; point mutation in 70%

Differential Diagnosis

♦ Carcinoma
- CD45 –, B-cell associated antigens –, keratin +

♦ Malignant melanoma
- CD45 –, B-cell associated antigens –, S100 +, HMB45 usually +

♦ Hodgkin's lymphoma (classical)
- Neoplastic (Hodgkin) cells larger with more prominent nucleoli
- CD45 –, B-cell associated antigens – or weakly + in Hodgkin cell subset
- CD15 usually +, CD30 usually +
- Inflammatory background present

♦ Kikuchi-Fujimoto disease
- Zonation phenomenon, with karyorrhectic debris and phagocytic histiocytes in center, and immunoblasts, lymphocytes and plasmacytoid monocytes at periphery

♦ Atypical immunoblastic reaction (infections, mononucleosis, other viral infection, drug reaction, etc.)
- Partial preservation of lymph node architecture
- Large cells admixed with small lymphocytes and plasma cells
- Immunohistochemically, large cells are predominantly T-cells or mixture of T and B-cells
- B-cell polyclonal

Variants

♦ WHO classification suggests that subclassifying large B-cell lymphoma is impractical (due to poor interobserver reproducibility) and irrelevant (as treatment is currently similar for all types)

♦ Centroblastic

- Composed of centroblasts (medium to large lymphoid cells with vesicular chromatin and multiple nucleoli)
- Monomorphous or polymorphous (may be multilobate)

♦ Immunoblastic
- >90% of cells are immunoblasts (single central nucleolus, ample basophilic cytoplasm)

♦ Anaplastic
- Large bizarre cells
- May grow in sheets and/or have sinusoidal growth pattern
- Unrelated to T-cell anaplastic large cell lymphoma

♦ T-cell/histiocyte rich
- Neoplastic large B-cells associated with prominent reactive T-cell component (>75% of cell population) +/– histiocytes

T-CELL/HISTIOCYTE RICH VARIANT

Clinical

♦ Age: older adults (mean age 56 years)
♦ Sex: M>F (slight)
♦ Presentation:
- Lymphadenopathy more common than extranodal involvement
- Usually high stage at presentation (spleen, bone marrow involvement common)

Microscopic

♦ Low power: diffuse architecture
♦ High power
- Predominantly small lymphoid cells (T>>B) +/– histiocytes interspersed by individual or small groups of large lymphoid B-cells with variable appearance (may resemble Reed-Sternberg cells)

Immunophenotype

♦ Small lymphocytes:
- Mostly T-cells (immunologically normal)

♦ Large lymphoid cells:
- React with B-cell markers, usually CD30 –, light chain restricted (golgi or perinuclear staining)

Differential Diagnosis

♦ NLPHL
- Macronodular architecture
- L&H cells may be surrounded by CD57 + T-cells
- Follicular dendritic cells (CD21 +) may be prominent

♦ Other mature B-cell neoplasms
♦ ALCL
♦ Classical Hodgkin's Lymphoma
♦ Carcinoma
♦ Melanoma

Mediastinal (Thymic) Large B-Cell Lymphoma

Synonyms

♦ Mediastinal large cell lymphoma with sclerosis
♦ Mediastinal clear cell lymphoma

Clinical

♦ Age: young adults (median age fourth decade, mean 32 years)
♦ Sex: F>M (2:1)
♦ Presentation:
- Locally invasive anterior mediastinal mass (derives from thymus)
- Superior vena cava (SVC) syndrome, cough, dyspnea, chest pain

♦ Relapses: extranodal (kidney, adrenal, liver, skin, brain, etc.)

Microscopic

♦ Thymus usually (if not always) involved
♦ Diffuse infiltrative growth into anterior mediastinal soft tissue
♦ Fine, compartmentalizing sclerosis common

Cytology

♦ Large cells with variable appearance
♦ Cells uniform to pleomorphic
♦ Nuclei round, elongate, folded, multilobated, or multinucleated
♦ Chromatin vesicular or granular, often with distinct nucleoli
♦ Moderate-abundant cytoplasm (formalin artifact)
♦ Associated small lymphocytes and histiocytes may be present

Immunophenotype

♦ sIg usually –
♦ CD19, CD20, CD22, CD79a +
♦ CD45 usually +
♦ CD30 usually – (may be weakly +)
♦ CD15 –, CD5 –, CD10 –

Genetics

♦ Ig heavy and light chains rearranged

Differential Diagnosis

♦ Thymic carcinoma
- More cohesive growth pattern, nuclei less irregular
- Keratin +, CD45 –

♦ Classical Hodgkin's Lymphoma (e.g. syncytial variant of nodular sclerosis classical Hodgkin's Lymphoma)

  - Larger neoplastic cells with prominent nucleoli
  - Inflammatory background (eosinophils, neutrophils, plasma cells)
  - CD15 +, CD30 +, CD45 –
- Anaplastic large cell lymphoma
  - Larger neoplastic cells with bizarre nuclei
  - CD30 +, p80/ALK-1 may be +, T-cell or null cell phenotype
- Seminoma
  - Male predominance
  - CD45 –, PLAP (placental alkaline phosphatase) +

Burkitt Lymphoma/Leukemia

Synonyms

- Rappaport: undifferentiated lymphoma, Burkitt's type
- Kiel: Burkitt's lymphoma
- Lukes-Collins: small noncleaved FCC
- Working Formulation: small noncleaved cell, Burkitt's type

Clinical

- Endemic (African):
  - Age: young children (mean age 4-7 years)
  - Sex: M>F (2-3:1)
  - Geography: equatorial Africa (may be associated with both malaria and EBV)
  - Majority (95%) are EBV-associated (clonally homogeneous EBV genomes present in tumor cells)
  - Sites of involvement: extranodal
    - Jaws and other facial bones
    - Ovary, testis, thyroid, salivary gland, kidney, CNS
    - Bone marrow involvement rare (<10%)
    - Lymph nodes and mediastinum spared
- Sporadic (nonendemic):
  - Age: older children
  - Sex: M>F
  - Minority (<20%) associated with EBV
  - Sites of involvement: extranodal
    - Abdominal cavity: intestine (especially terminal ileum, cecum, and mesentery), also stomach, peritoneum, and retroperitoneal tissue
    - Facial bones, ovary, testis, CNS, lymph nodes less common
    - Bone marrow involvement in 10-30%
    - Rarely presents as Burkitt leukemia
    - Mediastinal involvement infrequent
- Immunodeficiency associated (primarily associated with AIDS):
  - Age: middle age
  - Sex: M>F
  - EBV + in up to 50%
  - Sites of involvement: extranodal (CNS, GI tract)
  - Occurs early in course of AIDS
- Clinical course:
  - Aggressive but potentially curable
- Adverse prognostic indicators:
  - Large tumor bulk
  - CNS or bone marrow involvement
  - High pretreatment serum LDH

Microscopic

- Low power:
  - Diffuse, infiltrative growth pattern
  - Cells appear cohesive (jigsaw-puzzle-like appearance)
  - Starry sky pattern due to macrophages ingesting apoptotic tumor cells
- High power:
  - Monotonous population of medium-sized cells with round nuclei, multiple nucleoli, and basophilic cytoplasm
  - Numerous mitoses

Immunophenotype

- SIg + (usually IgM)
- CD10 and bcl-6 usually +
- TdT –, CD34 –, MPO –, cyclin D1 –
- CD5 –

Genetics

- 75-80%: t(8;14)(q24;q32) = translocation of c-myc (chr 8) to Ig heavy chain region (chr 14)
- 16%: t(8;22) = translocation of c-myc (chr 8) to Ig lambda light chain region (chr 22)
- 8%: t(2;8) = translocation of c-myc (chr 8) to Ig kappa light chain region (chr 2)
- Results in deregulation of myc gene leading to altered B-cell growth and differentiation

Differential Diagnosis

- Lymphoblastic lymphoma
  - Mediastinum - most common site
  - Blastic cytology (dispersed chromatin, inconspicuous nucleoli, scant cytoplasm)
  - TdT +, sIg –, usually T-cell lineage
- Large B-cell lymphoma
  - Uncommon in children
  - Larger, more heterogeneous cells
  - Fewer, more prominent nucleoli

- Myeloid sarcoma (extramedullary myeloblastic , granulocytic sarcoma)
  - Eosinophilic cytoplasm
  - Myeloperoxidase (MPO) +, lysozyme +, CD68 +
  - CD34 +, TdT may be +

Variant

- Atypical Burkitt/Burkitt-like

Mature T-Cell and NK-Cell Neoplasms

T-Cell Prolymphocytic Leukemia (T-PLL)

Synonyms

- Rappaport: WDL, PDL
- Kiel: T-cell prolymphocytic leukemia/T-cell lymphocytic leukemia
- Lukes-Collins: small lymphocyte T, prolymphocytic
- Working Formulation: small lymphocytic, consistent with CLL, diffuse small cleaved cell
- French-American-British (FAB): T-PLL
- REAL: T-cell chronic lymphocytic leukemia/ prolymphocytic leukemia

Clinical

- 1-2 % of all small lymphocytic leukemias
  - Age: older adults
  - Presentation: marked lymphocytosis (>100,000/mm^3)
  - Sites of involvement:
    - Skin and mucosa
    - Bone marrow, spleen, liver, lymph nodes
  - Clinical course:
    - Aggressive
    - Median survival <1 year

Microscopic (lymph nodes)

- Architecture:
  - Diffuse or paracortical involvement
  - Pseudofollicles absent
  - +/– numerous prominent small vessels
- Cytology
  - Morphologically similar to B-CLL, although nuclear contours usually more irregular and nucleoli often present
  - “small cell” variant - small cell size, nucleoli often not visible
  - “cerebriform” (Sézary cell-like) variant - very irregular nuclear contours

Immunophenotype

- CD2, CD3, CD5, CD7 +
- CD4 + (65%) or CD4 and CD8 + (20%) or CD8 + (15%)

Genetics

- T-cell receptor gene rearranged
- Inv 14(q11;q32) common

Differential Diagnosis
(all are + for B-cell associated antigens)

- CLL/B-PLL
- MCL
- FL
- Marginal zone B-cell lymphoma

Large Granular Lymphocytic (LGL) Leukemia

Synonyms

- Rappaport: SLL, CLL
- Kiel: T-CLL
- Lukes-Collins: small lymphocyte, T
- Working Formulation: small lymphocytic, consistent with CLL
- FAB: T-CLL, T-LGL

Clinical

- Presentation:
  - LGL lymphocytosis (>1000/mm^3)
  - Neutropenia +/– anemia
  - May be associated with rheumatoid arthritis or + rheumatoid factor
- Sites of Involvement:
  - Peripheral blood
  - +/- mild-moderate splenomegaly
  - Bone marrow relatively spared
  - No lymphadenopathy or hepatomegaly
- Clinical course:
  - Indolent

Microscopic

- Peripheral blood smear: lymphoid cells with round nuclei, rare nucleoli, and eccentric abundant pale blue cytoplasm with azurophilic granules
- Spleen: red pulp involvement, small lymphocytes, can be subtle

Immunophenotype

- T-cell lineage:
  - CD2 +, CD3 +, CD8 +, CD5 and CD7 often dim by flow cytometry
  - CD16 +, CD56 –, CD57 sometimes +
  - TIA-1 +, granzyme B +
- NK-cell lineage (may be more indolent):
  - CD2 +, CD7 +, CD3 –, CD5 –, CD8 –
  - CD16 +, CD56 usually +, CD57 usually –
  - TIA-1 +, granzyme B +

Genetics

- T-cell lineage: T-cell receptor genes rearranged
- NK-cell lineage: Germline T-cell receptor genes

Aggressive NK-Cell Leukemia

Clinical

- Rare overall (more common in Asia)
- Age: young adults
- Presentation: fever, hepatosplenomegaly +/– lymphadenopathy, leukemia blood picture +/– cytopenias
- Strongly associated with EBV
- Clinical course: aggressive/fulminant

Microscopic

- Peripheral blood:
  - Large granular lymphocytes with atypical features

Immunophenotype

- CD2 +, CD56 +
- CD3 –
- cytotoxic granule associated protein-+ (e.g. TIA-1, granzyme B)
- EBV usually +

Genetics

- T-cell receptor genes germline
- EBV commonly in clonal episomal form

Adult T-Cell Leukemia/Lymphoma (ATL/L)

Synonyms

- Rappaport: diffuse PDL, mixed lymphocytic-histiocytic, or histiocytic
- Kiel: pleomorphic small, medium, and large cell types (HTLV1+)
- Lukes-Collins: T-immunoblastic sarcoma
- Working Formulation: diffuse small cleaved cell, mixed small and large cell, diffuse large cell, large cell immunoblastic
- REAL: adult T-cell lymphoma/leukemia

Clinical

- Age: adults
- All are HTLV-1 +
- Geography: Japan, Caribbean, Brazil; sporadic in U.S.
- Acute variant (most common):
  - Presentation: marked lymphocytosis, hypercalcemia
  - Sites of involvement: liver, spleen, lymph nodes, skin, bone marrow, bone (lytic bone lesions), lung, peripheral blood
  - Clinical course: highly aggressive, rapidly fatal
- Lymphomatous variant:
  - Prominent lymphadenopathy, no leukemia phase
  - Aggressive course
- Chronic variant:
  - Presentation: mild lymphocytosis, skin rashes
  - Sites of involvement: lymph nodes, lung, skin, bone marrow, peripheral blood
  - Clinical course: less aggressive, but may transform to acute phase
- Smoldering variant:
  - Skin or lung involvement, normal white blood cell count
  - Less aggressive, but may transform to acute phase

Microscopic

- Peripheral blood: lymphoid cells with hyperlobated nuclei ("flower" cells)
- Lymph nodes:
  - Low power: diffuse involvement
  - High power: markedly pleomorphic small and large lymphoid cells

Immunophenotype

- CD2, CD3, CD5 +, CD7 usually –
- Most are CD4 +
- CD25 +

Genetics

- T-cell receptor genes rearranged
- HTLV-1 genomes present

Extranodal NK/T-Cell Lymphoma, Nasal Type

Clinical

- Age: adults > children
- Geography: Asia and Latin America >> US/Europe
- Virtually all cases associated with EBV
- Sites of involvement: Destructive nasal or midline facial tumor most common ("nasal NK/T-cell lymphoma"); may involve other extranodal sites (e.g. skin, soft tissue, testis, upper respiratory tract, gastrointestinal tract)
- May be complicated by hemophagocytic syndrome - adversely affects survival
- Treatment: radiotherapy and chemotherapy

Microscopic

- Low power: angiocentric/angioinvasive lymphoid infiltrate
- High power: broad cell spectrum: small, medium, and/or large atypical cells, any of which may predominate. A prominent inflammatory infiltrate may be present early in course of disease.

Immunophenotype

- CD2 and CD56 usually +
- Surface CD3 (detected by monoclonal anti-CD3 antibodies) usually – (cytoplasmic CD3ε, detected by polyclonal anti-CD3 antibodies, often +)
- Other T-cell associated antigens including CD5 and CD7 occasionally +
- CD16, CD57 usually –
- Cytotoxic granule associated proteins (TIA-1, granzyme B, perforin) usually +

Genetics

- EBV genome virtually always present, therefore *in situ* hybridization with probes to EBV-encoded small nuclear RNA may be helpful
- T-cell receptor and Ig genes usually germline

Enteropathy-Type T-Cell Lymphoma

Clinical

- Age: adults
- Most patients have history of gluten-sensitive enteropathy (celiac disease)
- Presentation: abdominal pain, jejunal perforation, peritonitis
- Clinical course: aggressive

Macroscopic

- Jejunal ulceration, often with perforation, +/– mass
- May be multifocal

Microscopic

- Ulcerated small bowel mucosa with underlying tumors composed of varying proportions of small, medium, and/or large/anaplastic atypical lymphoid cells
- +/– prominent inflammatory cells (histiocytes and eosinophils)
- +/– villous atrophy of adjacent small bowel mucosa

Immunophenotype

- CD3 +, CD7 +, CD103 +
- CD5 often –

Genetics

- T-cell receptor genes are clonally rearranged

Hepatosplenic T-Cell Lymphoma

Clinical: (γδ Type)

- Age: young adults
- Sex: M>F
- Presentation: fever, cytopenias
- Sites of involvement: spleen, liver, bone marrow, +/– peripheral blood; lymph nodes spared
- Clinical course: highly aggressive, usually incurable with available therapy

Microscopic

- Architecture: splenic, hepatic, and bone marrow sinusoids involved
- Cytology: monotonous population of medium-sized round or folded lymphoid cells with abundant pale cytoplasm
- Cell may appear cohesive

Immunophenotype

- CD2, CD3, and CD7 +, CD5 usually –
- CD4, CD8 usually –
- Most cases are γδ T-cell receptor +; minority of cases are αβ T-cell receptor +

Genetics

- Clonal rearrangement of T-cell receptor genes
- Iso (7q) common

Differential Diagnosis

- Hairy cell leukemia:
  - Older adults
  - B-cell associated antigens +, T-cell associated antigens –
  - CD103 +, TRAP +

Subcutaneous Panniculitis-Like T-Cell Lymphoma

Clinical

- Age: adults (median fifth decade, wide age range)
- Sex: F>M (slight)
- Presentation: Multiple red, painless, deep subcutaneous nodules, +/– ulceration
- Sites of involvement: Subcutaneous tissue (lower extremities > upper extremities > trunk)
- May be associated with systemic B symptoms
- May be complicated by hemophagocytic syndrome - frequently fatal
- Clinical course: aggressive
- Treatment: systemic chemotherapy

Microscopic

- Low power:
  - Lymphoid infiltrate involving subcutaneous fat septae and lobules (+/– fat necrosis), +/– extension into deep dermis. Neoplastic cells frequently rim individual fat cells
  - Epidermis and dermal appendages spared
- High power:
  - Neoplastic cells: Variable mixture of small, medium, and large lymphoid cells, often very atypical,

especially with progression of disease. Transmural vascular infiltrates may be present. Karyorrhexis common.
  - Background: Reactive histiocytes, +/– erythrophagocytosis (not necessarily indicative of clinical hemophagocytic syndrome)

Immunophenotype

- CD45 +
- CD2, CD3, CD43 +, +/– aberrant absence of CD5 or CD7
- Most are CD8 +
- Cytotoxic granule associated proteins (Tia-1, granzyme B, perforin) +
- Most are αβ +
- Minority are γδ + (may correlate with CD56-+, CD4, CD8 double – phenotype and more aggressive course)

Genetics

- T-cell antigen receptor genes usually rearranged

Differential Diagnosis

- Mycosis fungoides/Sezary syndrome
  - Involves dermal-epidermal junction—rarely extends to subcutaneous tissue
  - Histiocytic infiltrate absent
- Granulomatous slack skin syndrome (variant of cutaneous T-cell lymphoma)
  - Extensive dermal granulomas, few atypical lymphoid cells
  - Subcutaneous tissue spared
- FL
  - B-cell process
- Infectious panniculitis
  - Neutrophilic (bacterial/fungal) or granulomatous (mycobacterial) inflammation of fat septae and lobules; atypical lymphoid cells are rare/absent.
- Erythema nodosum
  - Involves fat septae, not lobules. Ulceration absent.
  - Mixed inflammatory infiltrate (lymphocytes, histiocytes, giant cells, neutrophils)
  - Heals spontaneously in 3-6 weeks
- Erythema induratum
  - Involves fat septae and lobules, and may cause medium and small-vessel vasculitis, but transmural vascular inflammation is mixed (neutrophils, histiocytes, giant cells); atypical lymphoid cells rare/absent.

Blastic NK-Cell Lymphoma

Clinical

- Rare overall
- Age: middle-aged to elderly
- Sites: skin, lymph node, soft tissue, peripheral blood/bone marrow
- Clinical course: aggressive

Microscopic

- Monotonous infiltrate of blast-like cells

Immunophenotype

- CD56 +, CD4 and CD43 usually +
- CD3 –, myeloperoxidase –, CD33 –
- EBV –
- TdT may be +
- Extensive phenotyping required to exclude AML and T-ALL/T-LBL

Genetics

- Germline T-cell receptor genes

Mycosis Fungoides/Sézary Syndrome (MF/SS)

Synonyms

- Rappaport: mycosis fungoides/Sezary syndrome
- Kiel: small cell, cerebriform
- Lukes-Collins: cerebriform T

Clinical

- Age: adults (median age 55 years)
- Sex: M>F (2:1)
- Sites of involvement:
  - MF: multifocal skin lesions (patch, plaque, and tumor stages), +/– subtle peripheral blood involvement
  - SS: diffuse skin involvement (erythroderma) with prominent peripheral blood involvement
  - Lymph node and visceral organ (lung, liver, spleen) involvement occurs late in course of disease
- Clinical course:
  - MF: prognosis correlates with clinical stage
  - SS: aggressive
  - May eventually transform to LCL (ALCL-like)

Microscopic

- Skin: band-like infiltrate at dermal-epidermal junction, epidermal infiltration (Pautrier's microabscesses)
- Lymph nodes: paracortical involvement initially, later becomes diffuse
- Cytology: predominantly small (and a minority of large) atypical lymphoid cells with convoluted, "cerebriform" nuclei associated with intermixed, non-neoplastic Langerhans' cells

Immunophenotype

- CD2, CD3, CD5 +, often CD7 – (other combinations of "aberrant" phenotypes may be seen)
- Usually CD4 +

Genetics

- T-cell receptor genes clonally rearranged

Differential Diagnosis

- Skin:
  - Inflammatory dermatoses with lichenoid pattern of skin involvement (e.g. drug eruption, autoimmune diseases, actinic reticuloid, etc.)
  - Lymphomatoid papulosis
  - Other malignant lymphomas
- Lymph nodes:
  - Dermatopathic lymphadenopathy - normal T-cell phenotype, polyclonal T-cell receptor genes
  - Other malignant lymphomas

Angioimmunoblastic T-Cell Lymphoma

Synonyms

- Rappaport: not listed (diffuse mixed lymphocytic-histiocytic, histiocytic)
- Kiel: T-cell, angioimmunoblastic (AILD)
- Lukes-Collins: immunoblastic lymphadenopathy-like T-cell lymphoma
- Working Formulation: not listed (diffuse mixed small and large cell, diffuse large cell, large cell immunoblastic)

Clinical

- Age: adults (middle-age to elderly)
- Sex: M=F
- Presentation: fever, weight loss, skin rash, polyclonal hypergammaglobulinemia
- Sites of involvement: lymph nodes (generalized lymphadenopathy)
- Clinical course:
  - Moderately aggressive, may respond to treatment
  - Prone to infectious complications

Microscopic

- Architecture: paracortical to diffuse involvement; loss of germinal centers; sinuses open; tumor may invade perinodal fat
- Cytology: tumor composed of lymphoid cells including medium-sized cells with round nuclei and abundant clear cytoplasm, in background of small lymphocytes and immunoblasts, +/– epithelioid histiocytes, eosinophils, and/or plasma cells
- Follicular dendritic cell clusters surrounding arborizing high endothelial venules often prominent

Immunophenotype

- T-cell associated antigens +
- CD4 usually +
- Follicular dendritic cells CD21 +

Genetics

- T-cell receptor genes usually rearranged
- Ig heavy chain genes occasionally rearranged (10-30%)
- EBV often present in scattered lymphocytes (usually B-cells)
- Trisomy 3, trisomy 5 may be present

Peripheral T-Cell Lymphoma, Unspecified

Synonyms

- Rappaport: diffuse PDL, diffuse mixed lymphocytic-histiocytic, histiocytic
- Kiel: T-zone lymphoma, lymphoepithelioid cell lymphoma, pleomorphic, small, medium, and large cell, T-immunoblastic
- Lukes-Collins: T-immunoblastic lymphoma
- Working Formulation: diffuse mixed small and large cell, large cell immunoblastic (polymorphous or clear cell)

Clinical

- Age: adults
- Presentation: +/– eosinophilia, pruritus, or hemophagocytic syndrome
- Sites of involvement: lymph nodes, skin, subcutis, liver, spleen
- Clinical course: aggressive, usually incurable

Microscopic (lymph nodes)

- Architecture: paracortical or diffuse involvement
- Cytology:
  - Cell spectrum characterizes PTCL: small, medium, and large lymphocytes
  - Nuclear irregularity and hyperchromasia in small and medium-sized cells
  - Prominent nucleoli, dispersed chromatin, abundant clear cytoplasm in large cells
  - Variable number of eosinophils and/or epithelioid histiocytes may be present
  - Vascular proliferation may be seen

Variants

- T-zone variant:
  - Interfollicular growth pattern
  - Small to medium-sized tumor cells with little pleomorphism, +/– clusters of clear cells
  - Prominent high endothelial venules
  - Abundant reactive cells (eosinophils, plasma cells, histiocytes)
- Lymphoepithelial cell variant (Lennert lymphoma):
  - Diffuse growth pattern
  - Small tumor cells with little pleomorphism
  - Prominent clusters of epithelioid histiocytes

Immunophenotype

- Aberrant T-cell phenotypes, defined by loss of a pan-T-cell antigen from a cell population, are frequent. Antigens absent: CD7 (75%), CD5 (50%), CD3 (10%), CD2 (10%)
- CD4 + more commonly than CD8
- B-cell associated antigens –

Genetic Features

- T-cell receptor genes usually clonally rearranged

Anaplastic Large Cell Lymphoma

Synonyms

- Rappaport: not listed (histiocytic, diffuse)
- Kiel: large cell anaplastic
- Lukes-Collins: T-immunoblastic sarcoma
- Working Formulation: not listed (diffuse large cell, immunoblastic)
- Other: malignant histiocytosis, sinusoidal large cell lymphoma, regressing atypical histiocytosis, Ki-1 lymphoma

Clinical

- Presentation: advanced stage disease, +/– B symptoms
- Sites of involvement: lymph nodes and extranodal sites (soft tissue, skin, bone, etc.)
- Age: bimodal
  - Children/young adults: usually ALK + (see genetic features below)
  - Older adults: usually ALK – (see genetic features below)
- Better prognosis: ALK + (median survival 14 years)
- Poorer prognosis: ALK – (median survival 3 years)
- Architecture
  - Diffuse involvement, often with infiltration of sinuses
  - Cohesive growth pattern common

Cytology

- Very large pleomorphic cells with embryoid nuclei, multiple prominent nucleoli, and abundant cytoplasm
- +/- background of granulocytes and macrophages

Immunophenotype

- CD30 + (cell membrane and Golgi staining)
- Tumor usually + for at least one T-cell antigen (CD2 and CD4 more often + than CD3, CD5, or CD7)
- CD45 usually +
- CD43, CD45RO often +
- EMA usually + in p80/ALK-1 + cases, EMA usually – in p80/ALK-1 – cases

Genetics

- ALK + cases: genetic alterations of ALK locus
  - t(2;5)(p23;q35) - most frequent translocation ⇒ juxtaposition of nucleophosmin (NPM) gene on chromosome 5 and anaplastic lymphoma kinase (ALK) gene on chromosome 2 ⇒ hybrid NPM-ALK gene expressed
  - ALK antibody: detects ALK gene product
    - Cytoplasmic and nuclear staining associated with t(2;5)
    - Cytoplasmic or membranous staining with variant translocations—e.g. t(1;2), t(2;3), t(2;17), inv(2)
  - ALK positivity associated with younger patients, EMA positivity, and better prognosis
  - EBV genome absent
- ALK – cases:
  - Genetic alterations of ALK locus absent
  - ALK negativity associated with older patients, EMA negativity, and poorer prognosis, or with primary cutaneous ALCL
  - T-cell receptor gene rearranged in ~90% of cases, regardless of expression of T-cell antigens

Morphologic Variants

- Lymphohistiocytic variant
  - Infrequent smaller neoplastic cells and rare cells with bilobed nuclei in histiocytic background. Histiocytes have a peculiar plasmacytoid cytology with eccentric round nuclei and abundant pink cytoplasm with perinuclear clearing
- Small cell variant
  - Small to medium-sized neoplastic cells, often surrounding blood vessels

Differential Diagnosis

- Carcinoma: keratin +, CD45 –
- Malignant melanoma: S-100 +, HMB45 usually +, CD45 –
- Sarcoma: Vimentin +, CD45 –
- Classical Hodgkin's Lymphoma: CD15 +, CD45 –, EMA –, ALK –

Table 7–5. Differential Diagnosis of Poorly Differentiated Large Cell Neoplasms

	CD30	*Keratin*	*HMB-45/S-100*	*CD15*	*CD68/Lysozyme*	*CD45*
Anaplastic large cell lymphoma (ALCL)	+	–	–	–	–	+/–
Carcinoma	–	+	–/+	+/–	–	–
Melanoma	–	–	+	–	–[1]	–
Histiocytic sarcoma	–	–	–	–/+	+	+/–

[1]*Most cases of melanoma are CD68 +, but they are lysozyme and CD45 –*

Hodgkin's Lymphoma (HL)

Nodular Lymphocyte Predominant Hodgkin's Lymphoma (NLPHL)

Synonyms

- Lukes et al: lymphocytic and/or histiocytic, nodular, lymphocytic and/or histiocytic, diffuse (some cases)
- Lennert and Mohri: paragranuloma, nodular or diffuse

Clinical

- Age: median mid 30's (wide age range)
- Sex: male > female (2.5:1)
- Presentation:
  - Localized involvement of peripheral lymph nodes (usually cervical, supraclavicular, axillary); mediastinum spared
  - 70-80% present at stage I or II
- Better prognosis: younger patients, presentation at low stage
- Poorer prognosis: older patients, presentation at high stage
- Occasionally preceded, accompanied, or succeeded by progressive transformation of germinal centers (PTGC)
- Clinical course:
  - Vast majority have complete response to therapy
  - May relapse or develop other lymphoma, especially large B-cell lymphoma

Microscopic

- Low power: macronodules (may be highlighted by immunostains, particularly CD21, which stains follicular dendritic cells), +/– diffuse areas, often with rim of uninvolved lymph node
- High power:
  - Neoplastic cells:
    - L & H cells (lymphocytic and /or histiocytic Reed-Sternberg [RS] cell variants; also called popcorn cells) may be numerous: large cells with multilobated vesicular nuclei, delicate chromatin, small nucleoli, and scant wispy cytoplasm
    - Classic RS cells rare or absent
  - Background cells:
    - Lymphocytes (polyclonal, mostly B-cells) and groups of epithelioid histiocytes
    - L & H cells may be surrounded by CD57+ T-cells
    - Follicular dendritic cells (CD21 +) often prominent
    - Rare plasma cells, eosinophils, or neutrophils

Immunohistochemistry

- L & H cells:
  - CD45 +
  - CD19, CD20, CD22, CD79a +
  - CD15 –, CD30 usually –
  - EMA usually +
  - Ig –

Genetics

- Whole tissue DNA: polyclonal
- DNA isolated from individually selected L&H cells: usually monoclonal Ig gene rearrangements

Differential Diagnosis

- Progressive transformation of germinal enters (PTGC)
  - L & H cells have nuclear lobulation, centroblasts usually do not
  - Centroblasts are EMA –
- Classical Hodgkin's Lymphoma, especially lymphocyte-rich type
  - Neoplastic cells are classic RS cells morphologically and immunohistochemically (CD15 +, CD30 +, CD45 –, B-cell associated antigens –)
- FL, especially floral variant
  - Lymph node architecture usually completely obliterated
  - Follicles/nodules composed predominantly of neoplastic B-cells (e.g. few normal lymphocytes or epithelioid histiocytes)
  - Intrafollicular lymphocytes are bcl-2 +, monoclonal sIg
- Large B-cell lymphoma, T-cell/histiocyte rich variant
  - Diffuse architecture
  - Tumor cells may be arranged in clusters, without being surrounded by rosettes of CD57+ T-cells
  - No intermixed CD21-+ FDC's
  - Tumor cells often show monoclonal sIg

Classical Hodgkin's Lymphoma

Nodular Sclerosis

Clinical

- Age: young adults
- Sex: F>M (slight)
- Sites of involvement: lower cervical, supraclavicular, and anterior mediastinal lymph nodes most common
- Poorer prognosis: higher stage, greater bulk of disease
- Clinical course: often curable (95% of patients presenting at stage I and II, 50-70% of patients present at stage III and IV)

Microscopic

- Low power:
  - Nodular pattern with fibrous band separating nodules, +/– diffuse areas, +/– necrosis
  - May be interfollicular
- High power:
  - Hodgkin and Reed-Sternberg (HRS)
    - Lacunar cells (RS cell variants) common: multilobated nuclei, small nucleoli, abundant pale cytoplasm that retracts with formalin fixation

    - Classic RS cells may be rare
  - Background cells:
    - Lymphocytes (mostly T-cells), eosinophils, histiocytes, plasma cells, neutrophils (associated with B symptoms), and fibroblasts
    - Broad range of appearances depending on relative contribution from different cell populations and degree of sclerosis. HL is classified as NS type whenever there are collagen bands and lacunar cells, regardless of all else.

Immunophenotype

- HRS cells:
  - CD30 +
  - Usually CD15 + (paranuclear, cytoplasmic, and/or membranous staining pattern), at least in a subset of HRS cells
  - CD45 –
  - B-cell associated antigens weakly + in a subset of RS cell variants in some cases
  - T-cell associated antigens usually – in RS cell variants
  - EMA –
  - p80/ALK-1 –
  - Fascin usually +

Genetics

- Whole tissue DNA: polyclonal
- DNA isolated from isolated single HRS cells: usually monoclonal Ig gene rearrangements

NSHL Grading, BNLI (British National Lymphoma Investigation) Criteria

- Grade II:
  - Sheets of RS cells in ≥ 25% of nodules (syncytial variant of NSHL)
- Grade I:
  - Scattered RS cells in mixed inflammatory background in > 75 % of nodules. Prognostic significance of grading NSHL is controversial

Mixed Cellularity Hodgkin's Lymphoma (MCHL)

Clinical

- Age: adults (wide age range)
- Sex: M>F
- Presentation: higher stage (lymph nodes, spleen, liver, bone marrow often involved)

Microscopic

- Architecture:
  - Diffuse or vaguely nodular
  - Lymph node capsule intact
  - No broad bands of fibrosis
  - May be interfollicular
- Cytology
  - HRS cells:
    - Classic RS cells common: large cells with large single or multiple nuclei that often have more than one lobe, a single prominent eosinophilic nucleolus per lobe, and abundant cytoplasm
  - L & H cells, lacunar cells absent
  - Background cells:
    - Lymphocytes, epithelioid histiocytes, eosinophils, neutrophils, and plasma cells

Immunophenotype

- HRS cells:
  - CD30 +
  - Usually CD15 + (paranuclear, cytoplasmic, and/or membranous staining pattern)
  - CD45 –
  - B-cell and T-cell associated antigens usually –
  - EMA –
  - p80/ALK-1 –

Differential Diagnosis

- Large B-cell lymphoma, T-cell/histiocyte-rich type
  - Immunophenotyping essential to make distinction

Lymphocyte-Rich Classical Hodgkin's Lymphoma (LRCHL)

Clinical

- Age: adults
- Sex: M>F
- Presentation: lymphadenopathy; usually lower stage (I or II)

Architecture

- Nodular or diffuse involvement
- Cytology:
  - Neoplastic cells: infrequent classic RS cells, +/– lacunar variants
  - Background cells: numerous lymphocytes with occasional histiocytes, eosinophils, or plasma cells

Immunophenotype

- HRS cells:
  - CD30 +
  - CD15 + (paranuclear, cytoplasmic, and/or membranous staining pattern)
  - CD45 –
  - B-cell and T-cell associated antigens usually –
  - EMA –, p80/ALK-1 –

Differential Diagnosis

- NLPHL:
  - Immunophenotyping essential to make distinction

Lymphocyte Depleted Hodgkin's Lymphoma (LDHL)

Clinical

- RARE
- Age: older adults
- Also seen in HIV+ patients and patients from developing countries
- Sites of involvement: abdominal lymph nodes, spleen, liver, bone marrow
- Extranodal sites involved in HIV+ individuals (usually EBV-+)
- Presentation: high stage

Architecture

- Diffusely effaced

Cytology

- Innumerable RS cells, bizarre multinucleated cells and RS cell variants of no special type

Immunophenotype

- HRS cells:
  - CD30 +
  - Usually CD15 + (paranuclear, cytoplasmic, and/or membranous staining pattern)
  - CD45 –
  - B-cell and T-cell associated antigens usually –
  - EMA –, p80/ALK-1 –

Differential Diagnosis

- Diffuse large B-cell lymphoma
  - CD45 +
  - B-cell associated antigens +
  - CD15, CD30 –
- Anaplastic large cell lymphoma
  - CD45 +, EMA +, ALK-1/p80 +
  - CD15 –
  - T-cell associated antigens often +

Table 7–6. Immunophenotypic Distinction Between Hodgkin's Lymphoma and Anaplastic Large Cell Lymphoma

Marker	*Anaplastic Large Cell Lymphoma*	*Hodgkin Lymphoma*
CD30	+ (strong, all cells)	+
CD45	+/–	–
CD15	–	+ (80%)
CD43	+ (70%)	–
CD45RO	+ (50%)	–
CD3 (paraffin)	+ (50%)	–
EMA	+/–	–
P80 or ALK-1	+ (50%)	–
CD20	–	–/+

HISTIOCYTIC LYMPH NODE TUMORS

Langerhans' Cell Histiocytosis

Synonyms

- Langerhans' cell granulomatosis
- Histocytosis X

Clinical

- Age: children
- Sex: M>F
- Presentation: unifocal disease (solitary eosinophilic granuloma), multifocal unisystem disease (previously called Hand-Schuller-Christian syndrome), or multifocal multisystem disease (previously known as Letterer-Sewe syndrome)
- Sites of involvement:
  - Lymph nodes or other organs (skin, bone, lungs, etc.)
- Prognosis: related to number of affected organs at presentation

Microscopic

- Sinuses distended by Langerhans' cells (mononuclear cells with fine chromatin, nuclear grooves, moderate eosinophilic cytoplasm)
- Background cells:
  - +/- eosinophils, which may form microabscesses
  - +/- mononuclear and multinuclear histiocytes
  - +/- neutrophils and lymphocytes

Immunophenotype

- Langerhans' cells:
  - S-100 protein +
  - CD1a +
  - PLAP (placental alkaline phosphatase) usually +

Electron Microscopy

- Langerhans' cells contain Birbeck granules (racket- or rod-shaped structures with osmiophilic core and double outer sheath)

Sinus Histiocytosis with Massive Lymphadenopathy (SHML)

Synonym

- Rosai-Dorfman disease

Clinical

- Age: mean age 20 years (wide age range)
- Sex: M>F (slight)
- Sites of involvement:
  - Bilateral cervical lymphadenopathy most common; may involve other lymph nodes or other sites (e.g. skin, upper respiratory tract, bone)
- Clinical course: most cases spontaneously regress

Microscopic

- Capsular fibrosis
- Sinuses distended by large histiocytes containing intact intracytoplasmic lymphocytes as well as intracytoplasmic plasma cells and erythrocytes ("emperipolesis")
- Medullary cords contain numerous plasma cells

Immunohistochemistry

- Histiocytes: S-100 +, CD68 +, CD1a –

Histiocytic Sarcoma

Clinical

- RARE
- Age: adults; wide age range
- Sites of involvement: lymph nodes, skin, extranodal sites
- Clinical course: aggressive

Microscopic

- Low power:
  - Diffuse proliferation of large atypical cells
- High power:
  - Large pleomorphic cells with ample eosinophilic cytoplasm, +/- reactive cells (small lymphocytes, eosinophils, benign histiocytes)

Immunophenotype

- + for histiocytic markers (CD68, lysozyme, CD11c, CD14)
- – for myeloid markers (myeloperoxidase, CD33, etc.), B-cell markers, and T-cell markers
- CD45 may be +

Differential Diagnosis

- Diffuse large B-cell lymphoma: CD20 +
- Carcinoma: keratin +
- Melanoma: S-100, HMB-45 +; may be CD68 +; CD45 and lysozyme –

SPINDLE CELL LESIONS OF LYMPH NODES

Bacillary Angiomatosis

Clinical

- Etiologic agent: *Bartonella henselae*
- Patients are immunosuppressed (especially AIDS)
- Sites of involvement: skin, lymph nodes, spleen
- Treatment: antibiotics

Microscopic

- Multiple nodules composed of proliferating vessels lined by plump, +/- pleomorphic endothelial cells with pale, vacuolated cytoplasm
- Interstitium contains distinctive eosinophilic granular material (=aggregates of bacilli), +/- neutrophils
- +/- foamy macrophages, granulomas, or peliotic spaces
- Bacilli + on Warthin-Starry stain and Giemsa stain (less sensitive)

Differential Diagnosis

- Epithelioid hemangioma/hemangioendothelioma
  - Cells have eosinophilic cytoplasm without vacuoles
  - No extracellular granular material made up of aggregates of bacilli, Warthin-Starry stain –
- Kaposi's sarcoma
  - Based in lymph node capsule
  - Fascicles of spindle cells present
  - Warthin-Starry stain – for bacilli

Kaposi's Sarcoma

Clinical

- Classic: most common presentation is lower extremity skin lesions in elderly Jewish or Mediterranean men. Indolent clinical course
- African (endemic): Equatorial Africa
  - Cutaneous: most common in young men; uncommon regional lymph node involvement
  - Lymphadenopathic: most common in children, M>F; localized or generalized lymphadenopathy. Aggressive clinical course
- Epidemic: Common in HIV+ patients, especially gay men. Involves lymph nodes, mucocutaneous sites, gastrointestinal tract, lung.

Etiologic Agent

- Human herpes virus 8 (HHV8)

Microscopic

- Low power:
  - Single or multiple nodules, or extensive replacement of lymph node
  - Capsular/subcapsular involvement
- High power:
  - Fascicles of spindle cells with vascular slits containing extravasated red blood cells
  - Mitoses common
  - +/- lymphocytes, plasma cells, histiocytes, and hemosiderin deposits
  - Eosinophils hyalin globules (PAS-D+) often seen within spindle cells or histiocytes

Immunophenotype

- CD31 +, CD34 +, Factor VIII +/-
- Actin –

Differential Diagnosis

- Vascular transformation of lymph node sinuses
  - Capsule spared, distinct vascular channels, no PAS+ hyaline globules
- Inflammatory pseudotumor of lymph node
  - No vascular slits, no PAS+ hyaline globules
  - Follicular hyperplasia and plasmacytosis are prominent
- Palisaded myofibroblastoma
  - No vascular slits, no PAS+ hyalin globules
  - Actin +, Factor VIII –
- Epithelioid hemangioma/hemangioendothelioma
- Bacillary angiomatosis
  - No spindle cell fascicles; bacilli Warthin-Starry +

Palisaded Myofibroblastoma

Synonym

- Hemorrhagic spindle cell tumor with amianthoid fibers

Clinical

- Age: wide age range
- Sex: M>F (slight)
- Location: inguinal lymph nodes most common; cervical, mediastinal nodes rare
- Clinical course: benign; no local recurrences or metastases

Microscopic

- Short fascicles of bland spindle cells (+/- perinuclear vacuoles), palisaded nuclei
- Intersitial hemorrhage and/or hemosiderin
- Stellate foci of collagen (amianthoid-like fibers)
- Periphery of tumor often hemorrhagic, with compressed rim of residual lymph node
- Mitoses rare

Immunophenotype

- Actin +, Vimentin +
- Desmin –, S-100 –, Factor VIII –

Differential Diagnosis

- Kaposi's sarcoma
  - Lymph node capsule based
  - Red cells within vascular slits; PAS+ hyaline globules common; CD31, CD34 +
- Intranodal schwannoma
  - Distinct Antoni A and B areas; S-100 +
- Vascular transformation of lymph node sinuses
- Inflammatory pseudotumor of lymph nodes
- Follicular dendritic cell sarcoma
  - Nests of plumper cells; no amianthoid-like fibers or hemorrhage; CD21, CD35 +

Inflammatory Pseudotumor of Lymph Node

Clinical

- Age: young adults
- Presentation: lymphadenopathy (superficial or deep), often with constitutional symptoms
- Treatment: excision of node is often curative

Macroscopic

- Enlarged lymph node(s), may be matted

Microscopic

- Proliferation of spindle cells (histiocytes and fibroblasts) and blood vessels, with acute and chronic inflammation and sclerosis
- Primarily involves hilum, trabeculae, and capsule

Differential Diagnosis

- Kaposi's sarcoma
  - Vascular slits and PAS+ hyaline globules present
  - Sclerosis less prominent
- Castleman's disease
- Hodgkin's Lymphoma

Follicular Dendritic Cell Sarcoma

Microscopic

- Partial to complete replacement of lymph node
- Fascicles and nests of oval to spindle shaped cells with bland vesicular nuclei, inconspicuous nucleoli, and pale cytoplasm
- Few mitoses
- Scattered small lymphocytes present

Immunophenotype

- CD21, CD35 usually +
- CD68 usually +
- S-100 usually –

Interdigitating Dendritic Cell Sarcoma

Microscopic

- Histologic spectrum from spindle cells to rounder, lymphoid-like cells

Immunophenotype

- S-100 +, CD68 usually +
- CD21 –, CD35 –

SPLEEN

Predominantly White Pulp-Based Processes

Benign Conditions

Follicular and Marginal Zone B-Cell Hyperplasia

Clinical

- Associated with blood cytopenias and hypersplenism (of various causes)

Microscopic

- Secondary germinal centers present
- Follicles vary in size and shape, containing mixed population of follicle center cells and tingible body macrophages
- +/– expansion of marginal zone by monocytoid B-cells
- Red pulp expanded by lymphocytes and plasma cells

Immunophenotype

- sIg - polyclonal

T-Zone Hyperplasia

Etiologies

- Infectious mononucleosis, drug reaction, herpes simplex virus, cytomegalovirus, etc.

Microscopic

- Paracortical expansion by polymorphous population of transformed lymphocytes, immunoblasts, plasma cells, and histiocytes
- +/– follicular hyperplasia

- Sinusoids and cords distended by atypical lymphocytes, monocytoid B-cells, and/or immunoblasts
- Capsular infiltration by immunoblasts may be present (may predispose to rupture)

Malignant Conditions

Follicular Lymphoma

- See description in lymph node section

Macroscopic

- Miliary pattern of splenic involvement

Microscopic

- White pulp germinal centers expanded by centrocytes and/or centroblasts without tingible body macrophages; nodules may be surrounded by residual mantle zone and marginal zone cells

Mantle Cell Lymphoma

- See description in lymph node section

Microscopic

- Predominantly which pulp involvement
- Initially involves follicular mantles, then obliterates both germinal centers and marginal zones, and infiltrates red pulp
- Sinusoidal involvement correlates with peripheral blood leukemia phase

Splenic Marginal Zone Lymphoma

- See description in lymph node section

Microscopic (Spleen)

- Low power:
  - Both mantle and marginal zones involved
  - Residual germinal centers atrophic or hyperplastic
  - Red pulp may be involved - sinusoidal involvement correlates with leukemic phase
- High power:
  - Mantle zone: small neoplastic lymphoid cells with little cytoplasm
  - Marginal zone: medium-sized neoplastic cells with moderate-abundant pale cytoplasm and scant large transformed lymphocytes with round nuclei, prominent nucleoli, dispersed chromatin and abundant cytoplasm
  - Plasmacytic differentiation may be present

Diffuse Large B-Cell Lymphoma

- See description in lymph node section

Macroscopic

- Solitary or multiple splenic tumor masses, or diffuse involvement of splenic parenchyma

Microscopic

- Tumor nodules composed of sheets of large lymphoma cells, +/– necrosis, hemorrhage, or sclerosis

Hodgkin's Lymphoma

- See description in lymph node section

Macroscopic

- Solitary or multiple splenic tumor masses; miliary pattern rare

Microscopic

- Arises in periarteriolar lymphoid sheath or marginal zone, later effaces follicles +/– red pulp involvement

Predominantly Red Pulp-Based Processes

Benign Conditions

Congestion

Etiology

- Secondary to portal hypertension (right-sided heart failure, cirrhosis, etc.)

Microscopic

- Proliferation of cord macrophages with subsequent cord thickening and fibrous connective tissue deposition
- Focal hemorrhages with hemosiderin deposition and Gamna-Gandy (siderotic nodule) formation

Hemolytic Anemia

Clinical

- Congential or acquired

Microscopic

- Cords congested with hemopoietic elements
- Erythrophagocytosis within cords may be seen
- Sinusoids appear empty, with prominent endothelial cells
- Minimal hemosiderosis (may be more prominent in acquired hemolytic anemia)
- White pulp may be expanded in acquired hemolytic anemia

Idiopathic Thrombocytopenic Purpura (ITP)

Clinical

- Age: adults (often women of childbearing age)
- Platelets destroyed by antiplatelet antibodies (IgG, +/– IgM)
- Target antigens: platelet glycoprotein complexes IIb/IIIa and Ib/IX
- Treatment: steroids +/– splenectomy
- Splenomegaly uncommon

Microscopic

- Red pulp cords expanded by foamy or ceroid-laden macrophages due to platelet phagocytosis
- Red pulp plasmacytosis
- +/– reactive follicular hyperplasia (?suppressed by steroid therapy)
- Findings may be subtle

Sepsis

Clinical

- Blood-borne infection

Microscopic

- Acute congestion of red pulp
- Mixed inflammatory infiltrate (neutrophils, plasma cell, +/– eosinophils) throughout red pulp

Malignant Conditions

CLL/SLL

- See description in lymph node section

Macroscopic

- Milliary pattern initially; diffuse involvement later

Microscopic

- White pulp initially expanded by neoplasm
- Red pulp cords and sinusoids subsequently diffusely involved by neoplasm, with obliteration of white pulp landmarks
- Cytology: monotonous small lymphocytes interspersed with prolymphocytes and paraimmunoblasts (similar to lymph node)

Hairy Cell Leukemia (HCL)

- See description in lymph node section

Microscopic

- Low power:
  - Involves red pulp cords and sinusoids, white pulp atrophic
  - Blood lakes (variable size) lined by neoplastic cells common
- High power:
  - Monotonous population of small-medium lymphoid cells with oval-reniform nuclei and abundant pale cytoplasm
  - Cells appear widely spaced

Large Granular Lymphocytic (LGL) Leukemia

- See description in lymph node section

Microscopic

- Red pulp infiltrated by neoplastic small lymphocytes (may be subtle)

Acute Leukemia

- Splenic involvement may be seen in AML; rare in ALL
- Mild-moderate splenomegaly
- Involves red pulp cords with secondary involvement of sinusoids (AML-M6 may primarily involve sinusoids)

Chronic Myelogenous Leukemia (CML)

Macroscopic

- Marked splenomegaly

Microscopic

- Low power
  - Neoplastic cells diffusely infiltrate red pulp cords and sinusoids, with obliteration of white pulp
- High power
  - polymorphous infiltrate of myeloid cells at all different stages of differentiation

Chronic Idiopathic Myelofibosis

Macroscopic

- Marked splenomegaly

Microscopic

- Trilinear extramedullary hematopoiesis in red pulp cords and sinusoids, with cord macrophage proliferation and variable fibrosis. Splenic infarcts common

Non-hematolymphoid Splenic Tumors

Benign Tumors

Splenic Hamartoma

Clinical

- Usually incidental finding

Macroscopic

- Spherical, well-circumscribed nodule that compresses adjacent splenic parenchyma

Microscopic

- Irregular, disorganized vascular channels lined by endothelial-type cells
- Vascular channels surrounded by loosely-arranged lymphocytes and macrophages, resembling cords
- +/– extramedullary hematopoiesis

Immunophenotype

- CD8 + splenic sinusoidal lining cells

Littoral Cell Angioma

Clinical

- Splenomegaly +/– fever

Macroscopic

- Single or multiple well-circumscribed hemorrhagic nodules

Microscopic

- Anastomosing vascular channels resembling splenic sinusoids
- +/– pseudopapillary pattern
- Vascular channels lined by plump bland endothelial cells that may contain PAS+ eosinophilic cytoplasmic globules
- Endothelial cells may be exfoliated into vascular channel lumens

Immunophenotype

- Endothelial cells: Factor VIII +, CD68 +, lysozyme +, CD8 –

Hemangioma

Lymphangioma

Hemangioendothelioma

Malignant Tumors

Angiosarcoma

Clinical

- Age: older adults (median age 53 years)
- Sex: M=F
- Presentation: abdominal pain or mass
- Clinical course: dismal prognosis (most patients dead of disease within one year). Hematogenous metastases (liver, lung, bone marrow, lymph nodes)

Macroscopic

- Splenomegaly with multiple ill-defined deep red nodules with hemorrhage and necrosis

Microscopic

- Anastomosing vascular channels lined by atypical budding endothelial cells
- Solid spindle cell areas, +/– vascular slits
- +/– papillary areas
- Hemorrhage and necrosis common

Immunophenotype

- Factor VIII +, CD34 +, CD31 +

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Chapter 8

Bone Marrow

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Table of Contents

NOTE:

In the interim between the writing of this chapter and it's publication, the World Health Organization Classification of Tumours of the Haematopoetic and Lymphoid Tissues was released. Most of the disorders described in this chapter remain essentially unchanged, however, some of the entities have been significantly altered in the new WHO classification.

Regarding myeloid neoplasms, the new WHO classification essentially represents a refinement of the entities outlined by the French-American-British (FAB) system. Perhaps the most important single change is the reduction of the percentage of blasts and/or promonocytes required for the diagnosis of AML from 30% to 20%. This change affects the diagnoses of myelodysplasia and acute leukemia. As a result, the diagnoses of refractory anemia with excess blasts in transformation and chronic myelomonocytic leukemia in transformation have essentially been defined out of existence. This change was made based on the observation that patients with a blast count of greater than 20% had clinical outcomes similar to patients that had been diagnosed with AML based on the 30% blast percentage threshold of the FAB system.

Additional changes have been made in the classification of myelodysplastic and myeloproliferative diseases. Changes in the classification of myelodysplasia include the addition of the category of refractory cytopenia with multilineage dysplasia. This category allows for a more concise diagnosis to be rendered in cases in which there is dysplasia in lineages other than, or in addition to, erythropoesis, and there are fewer than 5% blasts present. Disorders that can have mixed myeloproliferative and myelodysplastic features, such as chronic myelomonocytic leukemia and juvenile CML, are placed in a new group of myelodysplastic/myeloproliferative diseases. The myeloproliferative diseases remain essentially unchanged with the exception of the addition of the disease entity chronic neutrophilic leukemia, a rare disease manifested by persistent neutrophilic leukocytosis in the absence of detectable BCR/ABL fusion.

In the WHO classification the major categories of AML included in the FAB remain under the heading "Acute myeloid leukemia not otherwise categorized." The major changes in the diagnosis of AML introduced by the WHO classification include the reduction of the required blast percentage from 30% to 20% and the introduction of the disease category of "AML with recurrent genetic abnormalities." The latter was added in an attempt to emphasize the importance of these abnormalities in the diagnosis, treatment, and prognosis of cases of AML in which they are present. Most of the genetic abnormalities included are reciprocal translocations and they usually lead to leukemias with distinctive pathologic features. The prototypic entity in this category is acute promyelocytic leukemia (FAB-M3), which is universally associated with translocations involving the retinoic acid receptor alpha gene on chromosome 17q12. These translocations typically also involve the *PML* gene on chromosome 15q22, although other less common translocation partners such as the *PLZF* gene on chromosome 11q23 and the *NPM* gene on chromosome 5q32 have been described. Other types of *AML* in the WHO classification that are defined by the presence of specific chromosomal abnormalities include those associated with (8;21)(q22;q22) translocations involving the *AML* and *ETO* genes (FAB-M2), those associated with inversion of chromosome 16 or 16;16 translocations at bands p13 and q22 involving the *CBFβ* and *MYH11* genes (FAB-M4eo), and those with translocations involving the MLL gene on chromosome 11q23. These translocations can be detected by conventional metaphase analysis and by fluorescence *in situ* hybridization (FISH) studies, and the abnormal gene transcripts (RNA) can be detected by reverse transcriptase PCR (RT-PCR). Identification of these abnormalities is becoming of greater importance as highly sensitive RT-PCR based assays that detect abnormal gene transcripts are being

devised and implemented to detect minimal residual and recurrent disease. It is quite likely that the number of acute myeloid leukemias that are defined by specific genetic abnormalities will continue to expand.

The WHO has also attempted to incorporate morphologic and clinical features in AML that are of potential prognostic and theraputic importance that were not encompassed by the FAB system. It has been found that cases of AML with abnormal maturing erythroid, granulocytic, or megakaryocytic cells have an adverse prognosis when compared to cases in which such changes are not seen. As a result, AML with multilineage dysplasia has been added as a distinct diagnostic category. In order for this diagnosis to be rendered, at least two of the three myeloid lineages must show features of dysplastic maturation (ringed sideroblasts, hypogranular neutrophils, multinucleated megakaryocytes, etc.). Treatment with or exposure to ionizing radiation and cytotoxic drugs such as alkylating agents and topoisomerase II inhibitors is known to lead to an increased risk of the subsequent development of both myelodysplasia and AML. Given the poor prognosis of AML arising in this setting (particularly those secondary to radiation treatment and alkylating agents), the WHO classification provides a disease category of AML, therapy related.

These descriptions are only meant to acquaint the reader to some of the major changes in the classification of myeloid neoplasms introduced by the new WHO classification which is expected to become rapidly assimilated as the diagnostic standard for these diseases. The reader therefore is strongly recommended to refer to the WHO classification of tumours of haematopoetic and lymphoid tissues for a more complete description of the diagnostic entities included and explanation of the rationale used in generating the classification.

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CHRONIC MYELOPROLIFERATIVE DISORDERS (CMPDs)

- Bone marrow stem cell disorders characterized by autonomous proliferation of one or more hematopoetic cell lines
- Result in increased cells in peripheral blood
- Sometimes result in extramedullary hematopoeisis in liver and spleen

Chronic Myeloid Leukemia (CML)

Clinical

- Primarily a disease of adults; median age = 53 years; 36% older than 60 years
- Very uncommon in children
- Patients typically present with anemia, fever, malaise, and splenomegaly
- Leukostasis associated with a high white blood cell count, occurs in approximately 10%:
  - May be more common in patients <20 years
- Blast transformation typically occurs 3–4 years after diagnosis:
  - Represents aggressive phase of illness

Laboratory

- Leukocyte count >100 $x10^9$/L in at least 70% of patients; may exceed 350 $x10^9$ /L
- Circulating granulocyte precursors (promyelocytes, myelocytes) are present and usually represent >15% of nucleated cells
- Basophilia, anemia, and thrombocytosis often present
- Decreased neutrophil alkaline phosphatase level in 90% to 95% of all cases:
  - May be one of the earliest manifestations of the disease

Cytogenetics

- Translocation t(9;22)(q34;q11) with resulting Philadelphia (Ph) chromosome (abnormal chromosome 22) in >95% of cases
- Results in fusion gene BCR/abl that produces an abnormal tyrosine kinase
- Ph– CML cases: smaller gene translocation events resulting in BCR/abl gene formation; usually identified by molecular genetic techniques
- Blast transformation accompanied by cytogenetic evolution in 70% to 80% of all cases
- Common secondary abnormalities include second Ph chromosome, trisomy 8, isochromosome 17q, trisomy 19, or additional aneuploidy

Histopathology

- Marrow markedly hypercellular, with granulocytic hyperplasia with normal or left-shifted maturation; blasts typically <5%
- Megakaryocyte proliferation with micromegakaryocytes may be prominent
- Immature myeloid elements may be present in marrow sinusoids
- Reticulin fibrosis often present (>80%):
  - Usually begins focally around vessels; may progress to more diffuse fibrosis with disease progression
- Diffuse marrow fibrosis may be associated with a worse prognosis
- Blast transformation generally defined as >20% blasts in peripheral blood or bone marrow:
  - May be myeloblastic (75%) or lymphoblastic (25%)

Differential Diagnosis

- Leukemoid reaction: Basophilia, leukocyte count >$100x10^9$, low neutrophil alkaline phosphatase level, and t(9;22)(q34;q11) are features of CML distinct from neutrophilic leukemoid reaction
- Atypical CML
- Chronic myelomoncytic leukemia (CMML)
- Other CMPD

Treatment and Prognosis

- In first 3–4 years of disease (chronic phase), hydroxyurea and alpha-interferon can control blood cell counts in CML patients
- For younger patients (<55 years), bone marrow transplantation is the treatment of choice:
  - Can affect long-term disease-free survival in up to 75% to 80% of all patients
- In absence of bone marrow transplantation, most patients with CML develop blast crisis
- Blast crisis treated as acute leukemia, although response is generally poor, with clinical response seen in only 30% of all cases
- Median survival after blast crisis = 7 months

Atypical CML

Clinical

- Disease more common in adults
- Patients typically present with anemia, thrombocytopenia, and leukocytosis

Laboratory

- Peripheral blood shows leukocytosis
- Immature granulocyte precursors (promyelocytes and myelocytes) present and are >15% of nucleated cells (similar to CML)

- Monocytes usually >3% of nucleated cells in peripheral blood

Cytogenetics

- Ph chromosome or evidence of BCR/abl fusion gene is absent

Microscopic

- Hypercellular bone marrow with increased granulocyte precursors showing dysplastic maturation
- Basophilia typically not present

Differential Diagnosis

- Atypical CML is imprecisely defined and can be difficult to distinguish from myelodysplasia, especially CMML
- CML
- CMML

Treatment and Prognosis

- Prognosis appears to be less favorable than CML

Chronic Myelomonocytic Leukemia (CMML), Myeloproliferative

Clinical

- Primarily a disease of older individuals; more common in males
- Patients typically present with leukocytosis and anemia
- Splenomegaly may be present

Laboratory

- Peripheral blood shows leukocytosis with variable percentages of neutrophils and monocytes
- Granulocyte precursors may be present, but are <15% of nucleated cells
- Monocytes >3% and immature monocytes may be present
- Basophilia may be present
- Neutrophil alkaline phosphatase may be low or normal
- Promonocytes and blasts comprise <5% of bone marrow cells

Cytogenetics

- Ph chromosome or evidence of BCR/abl fusion gene is absent

Microscopic

- Bone marrow is hypercellular, with increased granulocyte precursors showing normal maturation
- Marrow monocytosis is variably present; abnormal monocytes can be highlighted with cytochemical stains for alpha-napthyl butyrate esterase

Treatment and Prognosis

- Disease typically progresses with increased granulocytic and monocytic immaturity, terminating in marrow failure and acute myelomonocytic leukemia

Juvenile Myelomonocytic Leukemia

Clinical

- Rare, aggressive form of leukemia
- Most patients < 2 years; 95% <4 years
- M:F = 2:1
- Median survival = 10 months to 1 year
- Patients typically present with hepatosplenomegaly, lymphadenopathy, and facial eczematoid rash
- Familial neurofibromatosis present in some cases

Laboratory

- Peripheral blood shows leukocytosis that usually is less pronounced than in adult CML
- Immature myeloid cells present in peripheral blood; percentage of lymphocytes, myeloblasts, and monocytes typically higher than that seen in adult CML
- Basophilia is usually absent
- Neutrophil alkaline phosphatase levels are normal, increased, or decreased
- Fetal hemoglobin is markedly increased, ranging from 40% to 55%, and anti-I antibody titers are high

Cytogenetics

- Ph chromosome or evidence of BCR/abl fusion gene is absent
- Monosomy 7 in subset

Microscopic

- Bone marrow is hypercellular due to increased myeloid precursors and monocytes; there may be increased blasts, but these are <20% of bone marrow cellularity
- Myelodysplasia is absent
- Megakaryocytes are usually decreased

Treatment and Prognosis

- Prognosis is poor, with a median survival of 10–12 months
- Patients usually have progressive marrow failure with increased blasts and progressive myelodysplasia
- Bone marrow transplantation may be beneficial

Polycythemia Vera (PV)

Clinical

- Rare disorder
- Median age at diagnosis = 60 years
- M:F = 12:1
- Increased incidence in people of Jewish ancestry

- Presenting symptoms include those related to increased red cell mass such as headache, weakness, dizziness, and pruritis
- Bleeding
- Thrombosis

Laboratory

- Polycythemia Vera Study Group (PVSG) established following diagnostic criteria for making a diagnosis of PV:
  - Either all of A criteria or A1 and A2 plus any of B criteria must be present to make a diagnosis of PV:
    - A criteria:
      - A1: Increased red blood cell mass; males >36 ml/kg, females >32 ml/kg
      - A2: Normal arterial oxygen saturation >92%
      - A3: Splenomegaly
    - B criteria:
      - B1: Thromobocytosis >400x10^9/L (present in 50% to 80%, platelet aggregation abnormal in 50%)
      - B2: Leukocytosis >12x10^9/L in absence of fever or infection (present in 80%; basophilia may be present)
      - B3: Increased neutrophil alkaline phosphatase in absence of fever or infection
      - B4: Increased serum vitamin B12 level or increased unsaturated vitamin B12-binding protein

Cytogenetics

- Chromosome abnormalities present in 40% to 50%
- Most common abnormalities are trisomy 8, trisomy 9, and deletion of 20q
- Patients with abnormal cytogenetics may have shorter survival

Microscopic

- Markedly hypercellular bone marrow with panhyperplasia most prominent in erythroid and megakaryocytic lineages
- Megakaryocytes may be clustered and are cytologically abnormal (usually large with dispersed chromatin)
- Approximately 10% to 20% of patients progress to a myeloid metaplasia phase with reticulin and collagen marrow fibrosis (post-polycythemia myeloid metaplasia)

Differential Diagnosis

- Reactive erythrocytosis
- Agnogenic myeloid metaplasia

Treatment and Prognosis

- Average survival = 1.5–3 years in untreated patients, 9–14 years in treated patients
- Most common cause of death is thromboembolic complications
- Periodic phlebotomy is the treatment of choice; alkalating agents avoided due to increased risk of leukemia
- Patients that progress to myeloid metaplasia are treated supportively
- PV patients are at increased risk of developing leukemia
- Approximately 7% of patients without progression to myeloid metaplasia develop acute leukemia
- Approximately 12% of patients with progression to myeloid metaplasia develop acute leukemia
- Development of acute leukemia is treatment-related: Patients treated with radioactive phosphorus or prolonged exposure to alkalating agents are most likely to develop acute leukemia

Essential Thrombocytosis

Clinical

- Uncommon disorder
- Median age at diagnosis = 61 years
- May occur in younger patients
- Younger patients appear to have a better prognosis
- M:F = 1:1
- Patients present with abnormal bleeding and evidence of peripheral vascular and/or central nervous system ischemia

Laboratory

- Thrombocytosis; peripheral blood smear may show platelets to be morphologically normal or large, hypogranular platelets may be present
- Criteria for diagnosis (established by PVSG) are as follows:
  - Platelet count > 600x10^9/L (platelet count typically 1000x10^9/L or higher)
  - Hemoglobin level <13g/dL or normal red cell mass
  - Stainable iron in marrow or no response to iron therapy
  - No Ph chromosome or genetic evidence of BCR/abl fusion gene
  - Collagen marrow fibrosis either absent or <$^1/_3$rd biopsy without both splenomegaly and leukoerythroblastic reaction
  - No demonstrable cause of thrombocytosis

Cytogenetics

- Ph chromosome or evidence of BCR/abl fusion gene is absent

Microscopic

- Bone marrow cellularity moderately to markedly increased in 70% of all cases; may be normocellular or slightly hypercellular
- Megakaryocytes increased, cytologically atypical forms (usually very large with dispersed chromatin), and megakaryocyte clusters are present
- Erythroid and granulocytic hyperplasia may be present, but are less pronounced than in other CMPDs
- Reticulin fibers are increased in 25% to 50% of all cases; less common in younger patients

Differential Diagnosis

- Reactive (secondary) thrombocytosis
- Other CMPD

Treatment and Prognosis

- Hydroxyurea or anagrelide are the treatments of choice
- Platelet aggregation antagonists such as aspirin may be used
- Younger patients (<40 years) have a low incidence of thromboembolic complications
- Mean survival = 5–8 years
- Patients may progress to myelofibrosis
- 2% to 5% of patients develop acute leukemia; development of leukemia may be associated with del(17p)

Agnogenic Myeloid Metaplasia (AMM)

Clinical

- Disease of adults; median age at diagnosis = ~65 years
- More common in males
- Patients present with weight loss, fatigue, and hepatosplenomegaly

Laboratory

- Hematologic findings are variable
- Approximately 50% of patients have anemia with a hemoglobin <10 g/dl
- Leukocytosis (approximately 40%) or leukopenia may be present
- Thrombocytopenia (37%) or thrombocytosis (13%) may be present
- Peripheral blood smears show red cell poikliocytosis with dacrocytes and nucleated RBCs; large, hypogranular platelets may be present
- Immature granulocytes and circulating megakaryocytic precursors may also be present
- Blasts may be present; usually do not exceed 10%
- Disease progression associated with increased leukocytosis and immature cells in peripheral blood
- Neutrophil alkaline phosphatase usually increased
- Radiologic evidence of osteosclerosis may be present

Cytogenetics

- Ph chromosome or evidence of BCR/abl fusion gene is absent

Microscopic

- Marrow is hypercellular with either diffuse hematopoetic hyperplasia or variable amounts of connective tissue and foci of hematopoetic elements
- Degree of fibrosis is variable; reticulin fibrosis may lead to a "streaming pattern" of hematopoetic precursors
- Marrow sinusoids are dilated and contain hematopoetic precursors
- Marked collagen fibrosis and osteosclerosis may be present
- Megakaryocytes are increased, with dysplastic forms and clusters present
- Spleen and liver show dilated sinusoids containing trilineage hematopoetic elements (extramedullary hematopoiesis [EMH])
- Lymph nodes can show hematopoiesis occurring in sinuses and perifollicular areas
- Fibrous hematopoetic tumors may be identified in extramedullary sites, including retroperitoneum, pelvis, mesentery, and pleura

Differential Diagnosis

- Other CMPD
- Acute myelofibrosis
- Marrow involvement by lymphoma and metastatic carcinoma

Treatment and Prognosis

- Supportive transfusion therapy
- Hydroxyurea to control leukocytosis, thrombocytosis, and splenic EMH
- Splenectomy for symptomatic splenomegaly
- Prolonged course; median survival = 5 years
- Favorable prognostic factors at diagnosis include hemoglobin >10 g/dl and platelet count >100x10^9/L

Systemic Mastocytosis

Clinical

- Rare disorder that occurs in a wide range of ages from young adults to elderly
- Males affected slightly more than females
- Patients may present with urticaria and osteoblastic and osteolytic bone lesions only, or they may present with signs and symptoms of systemic histamine release, including flushing, hypotension, tachycardia, syncope, generalized pruritis, urticaria, bronchospasm, and headache

- Pathologic bone fractures may occur
- Gastrointestinal symptoms (nausea, vomiting, abdominal pain, or diarrhea) present in 25% to 80% of all cases
- Gastric ulceration may occur
- Symptoms of histamine release may be episodic and triggered by a physical stimulus such as extremes of temperature
- Hepatosplenomegaly (20% to 70%) and lymphadenopathy (10% to 50%) may be present
- Hepatic fibrosis with resulting portal hypertension has rarely been reported

Laboratory

- There may be increased mast cell mediators (histamine, prostaglandin D_2, heparin, tryptase) present in the serum
- Testing of serum for tryptase levels is most specific serologic test for systemic mastocytosis, but elevated levels can be seen during allergic reactions as well
- Hematologic abnormalities are present in peripheral blood of majority of patients; common abnormalities include anemia, leukopenia, leukocytosis, eosinophilia, and thrombocytopenia
- Both osteoblastic and osteolytic lesions are seen on bone radiographs
- Circulating mast cells are uniformly present in mast cell leukemia and are rarely present in systemic mastocytosis

Cytochemistry and Immunohistochemistry

- Mast cell granules stain metachromatically with Geimsa or toliduene blue
- Mast cells react strongly with antibodies to tryptase in immunohistochemical reactions

Microscopic

- Bone marrow is the most common site of involvement other than the skin
- Up to 90% of patients with systemic mastocytosis will have bone marrow involvement
- Scattered mast cells may be present in bone marrow aspirate
- Typically appear as large cells with abundant cytoplasm containing densely packed granules and round to oval nuclei with inconspicuous nucleoli
- Numerous free granules may be present in aspirate background, although intact mast cells may be difficult to identify
- Pattern of marrow involvement may be focal (>80% of all cases) or diffuse (<20%)
- Focal lesions may be paratrabecular, perivascular, or interstitial
- All patterns may be present in an individual case
- Paratrabecular lesions may be associated with fibrosis and increased size and irregularity of adjacent bony trabeculae
- Perivascular lesions may lead to medial and adventitial hypertrophy of associated vessel
- In histologic sections, mast cells appear as medium-sized spindled or epithelioid cells with relatively abundant eosinophilic cytoplasm and round to oval nuclei with dispersed chromatin and inconspicuous nucleoli
- Mast cell lesions may be composed entirely of mast cells or may be associated with a polycellular background of lymphocytes (both B and T cells), eosinophils, and histiocytes
- When present, polycellular infiltrate often surrounds individual groups of mast cells
- In diffuse lesions, mast cells completely replace normal marrow elements and are usually admixed with a variably abundant polycellular background
- As is seen with focal trabecular lesions, bony trabeculae are irregular and increased in size
- In both focal and diffuse involvement, increased osteoclastic activity with thinning of bony trabeculae may be present
- A significant number of patients with systemic mastocytosis will have an associated hematopoetic stem cell disorder (myeloproliferative disease, myelodysplastic syndrome, or AML) either at diagnosis or during the course of the disease
- Findings consistent with one of these disorders may be present in the bone marrow specimen
- In cases not associated with a hematopoetic stem cell disorder, uninvolved marrow may be normocellular or hypercellular, with multilineage hyperplasia
- In rare cases, marrow is hypercellular and hematopoietic marrow is entirely replaced by immature, atypical mast cells

Differential Diagnosis

- Langerhan's cell histiocytosis
- Hairy cell leukemia
- AMM (idiopathic myelofibrosis)
- Marrow involvement by peripheral T-cell lymphoma

Prognosis and Treatment

- No curative therapeutic regimen; treatment is largely supportive
- Histamine antagonists are helpful in controlling symptoms of histamine release
- Splenectomy may be helpful in controlling cytopenias
- In majority of cases, disease is chronic, unremitting, and slowly progressive
- Clinical features associated with a poor prognosis

include older age, presence of constitutional symptoms, presence of liver function test abnormalities, and presence of an associated CMPD or MDS

- Male sex may be associated with a slightly poorer prognosis
- Approximately 40% of patients will progress to acute leukemia:
  - Most develop myelogenous leukemia
- Rare instances of mast cell leukemia may develop:
  - Development of mast cell leukemia is associated with a particularly dismal prognosis
  - Median survival = 5 months

Hypereosinophilic Syndrome

Clinical

- Very rare
- Occurs in all ages; 70% 20–50 years
- M:F = 9:1
- Patients can present with a variety of systemic disorders, most due to organ infiltration by eosinophils:
  - Constitutional (occurs in >50%): fatigue, weakness, anorexia, fever
  - Cardiovascular (occurs in >70%): heart failure, arrythmia, endocardial disease, cough, dyspnea, pulmonary infiltrates
  - Hematologic (occurs in >50%): thromboembolism, anemia, splenomegaly
  - Neurologic (occurs in >50%): altered mental status, peripheral neuropathy, focal cerebral lesions
  - Dermatologic (occurs in >50%): angioedema, rash, dermatographism
  - GI (occurs in >40%): diarrhea, nausea, abdominal cramps
  - Immunologic (occurs in >40%): increased IgE, circulating immune complexes

Laboratory

- Absolute eosinophilia present; eosinophilia may be extreme (>100x10^9/L)
- Other hematologic abnormalities may be present, usually mild
- Basophilia present in approximately 25%

Cytogenetics

- A number of cytogenetic abnormalities have been reported; no single cytogenetic abnormality is seen consistently

Microscopic

- Bone marrow is hypercellular, with increased eosinophils in all stages of development
- Macrophages with ingested Charcot-Leyden crystals may be present
- Granulocytic dysplasia may be present

Differential Diagnosis

- Reactive (secondary) hypereosinophilia (parasitic infection, hypersensitivity, malignancy)
- CML

ACUTE MYELOID LEUKEMIAS (AML)

AML

- Bone marrow based neoplasm of myeloid lineage hematopoietic precursors

Clinical

- Most common form of acute leukemia
- Most forms of AML are relatively uncommon in adolescence and childhood; most patients >35 years
- Patients generally present acutely ill with fever, anemia, thrombocytopenia, malaise, and leukocytosis (60%); normal to low white blood cell counts (40%) may be present
- Disease specific features (See Table 8-1)

Laboratory

- In general, diagnosis of acute leukemia can be made when blasts comprise >20% of bone marrow cellularity
- Peripheral blood leukocytosis with leukemic cells are present in approximately 70% of all cases
- French-American-British (FAB) modified classification of AMLs is widely used
- Accepted FAB classification is based on a variety of morphologic, cytochemical, phenotypic, and karyotypic features (See Table 8-2)

Immunophenotype

- See Table 8-3

Cytogenetics

- See Table 8-4
- Certain cytogenetic findings bear prognostic significance (See Table 8-5)

Microscopic

- Bone marrow is generally markedly hypercellular with

Table 8-1. Clinical Features of AML Subtypes

AML Subtype	*Clinical Features*
AML-M0	None
AML-M1	Hepatosplenomegaly (30%); median age = 46 years
AML-M2	Lymphadenopathy (25%) or hepatosplenomegaly (15%); 20% <25 years, 40% >60 years; cases with t(8;21) associated with involvement of extramedullary sites
AML-M3	Clinical and/or laboratory evidence of DIC (80% to 90%) with associated hemorrhagic complications; may occur in younger patients; median age = 38 years
AML-M4	Gingival hyperplasia, leukemic skin infiltrates may be present; lymphadenopathy (50%), hepatosplenomegaly (30%), soft tissue leukemic infiltrates (5% to 10%); median age = 50 years; M:F = 1.4:1; elevated serum lysozyme
AML-M5A	More common in younger patients; median age = 16 years; 75% <25years; extramedullary tumors common; occur in paraspinal tissues, skin, orbit, and testes; may be presenting symptom; hepatosplenomegaly (50%), lymphadenopathy (30%); elevated serum lysozyme
AML-M5B	More common in older patients; median age = 49years; M:F=1.8:1; hepatosplenomegaly and lymphadenopathy (50%); extramedullary lesions (30%) with gingiva and skin common sites; elevated serum lysozyme
AML-M6	Median age = 54 years; organomegaly uncommon
AML-M7	Hepatosplenomegaly, lymphadenopathy, lytic bone lesions (children); may be associated with mediastinal germ cell tumors

marrow composition varying with subtype of AML (See Table 8-6 for blast characteristics)

- Bone marrow is hypocellular (cellularity <30%) in 5% of all cases
- Hypocellular AML is more common in elderly patients; rare in children
- Marrow fibrosis is common in megakaryoblastic leukemia (AML-M7)

Differential Diagnosis

- AMLs must be distinguished from each other by criteria listed in tables
- Acute lymphoblastic leukemia (ALL)
- Myelodysplastic syndromes

Treatment and Prognosis

- Remission is induced in 50% to 85% of all cases
- Long-term disease-free survival in 20% to 40% of all cases; with bone marrow transplant, increases to 40% to 50%
- FAB classification has not proved useful to predict risk of failure
- AML arising in setting of previous myelodysplastic syndrome associated with a poorer prognosis:
  - Remission is induced in only 20% to 40% of these cases
- Factors associated with poor prognosis include increased age, obesity, leukocytosis, leukostasis, renal insufficiency or other complicating medical conditions, pre-existing myelodysplasia, and chemotherapy-induced AML

Other Types of AML Not Included in FAB Classification

Acute Basophilic Leukemia

Clinical

- No distinctive clinical symptoms
- Hyperhistaminemia may be present

Laboratory

- Leukocytosis (may exceed $100x10^9$), anemia, and thrombocytopenia
- Increased 24-hour urine histamine may be present

Cytogenetics

- Association with t(9;22)(q34;q11), trisomy 21, and deletion 7q reported

Microscopic

- Immature blasts or blasts with abundant basophilic cytoplasmic granules >30% of marrow cells
- Blast granules are metachromatic, with toluidine blue

Table 8-2. FAB Classification of AMLs

Subtype	*Bone marrow*	*% of cases*
AML, minimally differentiated (AML-M0)	>20% blasts; <3% blasts MPO; SBB +; blasts express myeloid lineage antigens (CD13, CD33)	5
AML, without maturation (AML-M1)	>20% blasts; >3% blasts MPO; SBB +; <10% maturing granulocytes	10–20
AML, with maturation (AML-M2)	>20% blasts; >3% blasts MPO; SBB +; >10% cells maturing granulocytes	30
Acute promyelocytic leukemia hypergranular (APL-M3)	>20% blasts and abnormal hypergranular promyelocytes with multiple Auer Rods; >85% cells strongly MPO; SBB +	12
Acute promyelocytic leukemia hypogranular (APL-M3V)	>20% blasts and abnormal hypogranular promyelocytes with rare hypergranular forms and Auer Rods; >85% cells strongly MPO; SBB +	4
AML, myelomonocytic (AML-M4)	>30% myeloblasts, monoblasts, and promonocytes; >20% monocytic cells (BE, NAE positive); > 20% maturing neutrophils (SBB, MPO +) monocytes in PB > $5x10^9$/L;	12
AML, myelomonocytic, with eosinophilia (AML-M4EO)	Same as AML-M4 with marrow eosinophilia; eosinophils may be abnormal with large basophilic granules	4
AML, monocytic, poorly differentiated (AML-M5A)	>80% monocytic cells (BE, NAE positive some cases weakly); >80% monocytic cells monoblasts; <20% cells SBB; MPO +	8
AML, monocytic, differentiated (AML-M5B)	>80% monocytic cells (BE, NAE +); <80% monocytic cells monoblasts; <20% cells SBB; MPO +	5
Erythroleukemia (AML-M6)	>50% erythroid precursors, often PAS +; dyserythropoiesis may be present; >30% non-erythroid cells myeloblasts	3
AML, megakaryocytic (AML-M7)	>20% blasts; >50% cells show megakaryocytic features by morphology, immunophenotype, or EM	<1

SBB = Sudan black B; MPO = myeloperoxidase; BE = alpha-napthyl butyrate esterase; NAE = alpha-napthyl acetate esterase, PAS = periodic acid-Schiff.

Table 8-3. AML Immunophenotype*

Surface antigen	*MO*	*M1/M2*	*M3*	*M4/M5*	*M6*	*M7*
HLA-DR	+	+	–	++	–	+
CD11	+	+	+	++	–	–
CD13	+	+	+	++	–	–
CD14	+	+	–	++	–	–
CD33	+	++	+	++	+	+
CD41, CD61	–	–	–	–	–	++
Glycophorin A	–	–	–	–	++ **	–

***Erythroid cells only.*
There is complexity and phenotypic overlap in patterns of antigen expression by AML blasts. Although phenotypes listed in this table are characteristic for different FAB-AML subtypes, other features (morphology, cytochemistry, and cytogenetics) are better definitional criteria than immunophenotype for AML subtypes.

Table 8-4. Cytogenetic Abnormalities in AML

Subtype AML	*Associated Cytogenetic Abnormalities*
AML-M1	+8, -7, -5 or del 5q, t(v;11)(v;q23), t(6;9)(p23;q34), t(9;22)(q34;q11), inv(3)(q21q26) or t(3;3)(q21;26), complex defects all variably present
AML-M2	t(8;21)(q22;q22) present in approximately 20% of cases; abnormalities listed for AML-M1 may also be present
AML-M3	t(15;17)(q22;q11-22) present in 95% to 100% of cases
AML-M4	+8, -7, -5 or del 5q, t(v;11)(v;q23), t(6;9)(p23;q34), complex defects
AML-M4EO	inv(16)p13q22) or t(16;16)(p13;q22) present in 100% of cases
AML-M5A and M5B	+8, t(v;11)(v;q23), or complex defects
AML-M6	+8, -7, -5 or del 5q, inv(3)(q21q26) or t(3;3)(q21;26), complex defects
AML-M7	-7, -5 or del 5q, complex defects

Table 8-5. Prognostic Significance of Cytogenetic Findings in AML

Cytogenetic finding	*Prognostic significance*
Inversion(16) or 16:16 translocation	Favorable
t(15;17), t(6;9), t(8;21), t(9;11), t(9;22), +8	Intermediate
Monosomy 7 or deletion 7q	Unfavorable
Normal, inversion 3, deletion 5q	Indeterminate

Table 8-6. Blast Features

Blast type	*Size*	*Cytoplasm*	*Nucleus*
Myeloblast type I	Medium to large, usually uniform	Moderate, basophilic, without granules	Fine chromatin, 2–4 distinct nucleoli
Myeloblast type II	Medium to large, usually uniform	Moderate, basophilic, with 1–20 azurophilic granules	Fine chromatin, 2–4 distinct nucleoli
Myeloblast type III	Medium to large, usually uniform	Moderate, basophilic, with numerous azurophilic granules	Fine chromatin, 2–4 distinct nucleoli
Monoblasts	Large, 40–50 microns	Abundant, variable basophilic, with fine to coarse azurophilic granules, variably vacuolated	Round to oval, with either a single prominent nucleolus or multiple nucleoli
Megakaryoblast	Variable in size	May be sparse or abundant with cytoplasmic blebs	Chromatin may be dense and compact or dispersed with distinct nucleoli

stains, – for MPO, SBB, alpha-napthyl butyrate esterase, and chloracetate esterase
- These granules have distinctive "scroll" structures by electron microscopy
- Blast nuclei may be indented or lobulated
- Reticulin marrow fibrosis may be present

Differential Diagnosis
- AML, other FAB subtypes
- ALL

Treatment and Prognosis
- Similar to other types of AML

Transient Myeloproliferative Disorder (TMPD) of Down's Syndrome and AML

Clinical
- Transient myeloproliferative disorder and acute myeloid leukemias both occur in neonates (<1 year) with Down's syndrome
- Transient myeloproliferative disorder and acute myeloid leukemias are morphologically indistinguishable
- TMPD undergoes spontaneous remission in 2–14 weeks; may recur with systemic illness
- Marked lymphadenopathy and hepatosplenomegaly may be present

Laboratory
- Leukocytosis (may be marked), thrombocytopenia (may be severe)

Cytogenetics
- Affects individuals with congenital trisomy 21
- Can rarely occur in phenotypically normal individuals' in these cases, hematopoetic cells may show trisomy 21

Bone Marrow
- Hypercellular, blasts >20% in both TMPD and AML
- Many cells and blasts show morphologic, cytochemical, and immunophenotypic evidence of megakaryocytic differentiation

Treatment and Prognosis
- As stated above, TMPD is by definition self-limited
- When AML develops behaves similar to other AML
- Diagnosis of AML in young children with Down's syndrome should be made with utmost caution

Acute Myelofibrosis

Clinical
- Very uncommon, occurs in adults and rarely in children
- Patients present with constitutional symptoms and cytopenias
- Splenomegaly not present
- Clinical course similar to AML

Laboratory
- Pancytopenia, frequently marked

Cytogenetics
- No associated cytogenetic abnormalities

Histopathology
- Markedly hypercellular with panhyperplasia and clusters of immature cells
- Marked reticulin fibrosis usually present

Differential Diagnosis
- AML
- Agnogenic myeloid metaplasia
- Metastatic malignancy
- Marrow involvement by lymphoma

Treatment and Prognosis
- Few cases; appears to behave similar to AML; may be identical to AML-M7

ACUTE LYMPHOBLASTIC LEUKEMIA (ALL)

ALL
- Bone-marrow-based neoplasm of B-cell and T-cell precursors

Clinical
- Most common leukemia in childhood
- Bimodal age distribution; most cases in children under 10 years, with a second smaller disease peak in elderly adults
- Patients present with constitutional symptoms and bleeding
- Organ infiltration is common, leading to hepatosplenomegaly, lymphadenopathy, altered mental status (meningeal infiltrates), and bone pain (periosteal infiltrates)
- In children under 15 years, ALL is approximately twice as common in whites as compared to blacks
- T-cell ALL has distinct clinical features, including

Table 8-7. ALL Immunophenotype

ALL subset	*TdT*	*HLA-DR*	*CD2*	*CD3*	*CD5*	*CD10*	*CD19*	*CD20*	*CD24*	*sIg*	*cIg*	*Frequency*
T-Cell	+	–	+	+	+	–	–	–	–	–	–	10 to 20%
Early Pre-B	+	+	–	–	–	+	+	–	+	–	–	60 to 70%
Pre-B	+	+	–	–	–	+	+	–	+	–	+	15 to 20%
B-Cell	–	+	–	–	–	–	+	+	+	+	–	1 to 3%

SIg = surface immunoglobulin; CIg = cytoplasmic immunoglobulin.

Table 8-8. Cytogenetic Findings in ALL

Type of ALL	*Cytogenetic findings*	*Frequency*
B-cell ALL (ALL-L3)	t(8;14)(q24;q32), less common t(2;8) or t(8;22)	>90%
Pre-B ALL	t(1;19)(q23;p13); t(9;22) in adults	25%
T-cell ALL	translocations of 14q11	25%
Mixed lineage ALL	translocations of 11q23 or14q32; t(9;22)(q34;q11)	Unknown

Table 8-9. Prognostic Significance of Cytogenetic Findings in ALL

Cytogenetic findings	*Prognostic significance*
Hypodiploidy; all translocations	Unfavorable
Hyperdiploidy: >50 chromosomes	Favorable
Hyperdiploidy: 47–50 chromosomes; normal	Intermediate

occurrence in slightly older children, male predominance, presence of mediastinal mass in 50% of all cases, and high leukocyte counts

- B-cell ALL has distinct clinical features, including occurrence in older children, high incidence of abdominal (ileocecal) mass (L3 subtype only), and high incidence of CNS disease (leukemic meningitis)

Laboratory

- Leukocytosis due to circulating lymphoblasts may be present; however, white count is frequently slightly elevated, normal, or decreased
- Anemia and thrombocytopenia are frequent
- ALL may be subdivided on the basis of immunophenotype (See Table 8-7)
- Early pre-B ALL most common; has similar laboratory and clinical features to pre-B ALL
- Cytoplasmic Ig in pre-B ALL is mu heavy chain
- Myeloid antigens are expressed in approximately 15% of childhood ALL cases and in 25% of adult ALL cases
- Malignant lymphocytes may express an aberrant combination of early and late antigens
- At relapse, ALL may show either a loss of a surface antigen (common) or a conversion to a myeloid immunophenotype (rare)

Cytogenetics

- Bear prognostic significance (See Tables 8-8 and 8-9)

Microscopic

- Bone marrow is typically markedly hypercellular at diagnosis, with extensive marrow infiltration and marrow replacement by lymphoblasts, comprising >20% of marrow cellularity
- FAB morphologic criteria for subclassification of ALL into three distinct subtypes (See Table 8-10)

Differential Diagnosis

- Increased marrow lymphocyte precursors (hematogones)
- AML
- Chronic lymphocytic leukemia (CLL)
- Prolymphocytic leukemia (PLL)
- Malignant lymphoma

Table 8-10. Morphologic Features of ALL Subtypes According to FAB Classification and Immunophenotypic Correlate

Feature	*ALL-L1*	*ALL-L2*	*ALL-L3*
Size	Small	Large	Large and homogeneous
Chromatin	Homogeneous	Variable	Finely stippled
Shape	Regular, occasional clefts	Irregular, frequent clefts	Oval to round
Nucleoli	Rare	Present	1–3, prominent
Cytoplasm	Scant	Moderate	Moderate
Basophilia	Variable, usually moderate	Variable, occasionally intense	Intense
Vacuolation	Variable	Variable	Prominent, oil red O +
Frequency*	71%	27%	2%
Immunophenotypic Correlate	T-cell, early pre-B, and pre-B ALL	T-cell, early pre-B, and pre-B ALL	B-cell ALL

**In childhood ALL only.*

Table 8-11. Prognostic Variables in ALL

Variable	*Favorable*	*Unfavorable*
Age	1 to 10 years	<1 and >10y
Race	White	Black
Sex	Female	Male
WBC	$<10x10^9$/L	$>50x10^9$/L
Response to induction chemotherapy	Bone marrow free of disease at day 14	Residual bone marrow disease at day 14
Relapse	No relapse	Relapse
Morphology	L1	L2 and L3
Cytogenetics	Hyperdiploid >50 chromosomes	Hypodiploid; any translocation particularly t(9;22) and t(4;11)
Immunophenotype	Early pre-B and pre-B	CD10-, T-cell, B-cell, and mixed phenotype

- Metastatic small cell tumors, including neuroblastoma, embryonal rhabdomyosarcoma, Ewing's sarcoma, and medulloblastoma:
  - Neuroblastoma: most common nonhematopoietic tumor to involve bone marrow in children:
    - Can be difficult to make this distinction morphologically

Treatment and Prognosis

- A number of important prognostic factors (see Table 8-11)
- Morphology and sex may not be important prognostic variables
- Treatment relatively effective, with cure rates up to 70% in good prognostic group cases and 40% to 50% in poorer prognostic group cases

MYELODYPLASTIC SYNDROMES (MDS)

Myelodysplastic Syndrome (MDS)

- Disorders of myeloid progenitor cells characterized by peripheral blood cytopenias, hypercellular bone marrow, and dysplastic maturation of one or more myeloid lines
- Myeloblasts may be increased, but are <20% of bone marrow cellularity

Clinical

- Most common in older adults (over 50 years); very rare in children
- Patients typically present with anemia that is refractory to hematinic therapy
- Patients may also present with bleeding complications secondary to thrombocytopenia and platelet dysfunction or infection secondary to neutropenia
- Treatment-related MDS occurs in patients exposed to chemotherapeutic agents or radiotherapy (discussed in greater detail below)

Laboratory

- Most patients present with cytopenias
- Abnormal red blood cells (oval macrocytes and tiny microcytes), platelets (large, hypogranular), neutrophils (nuclear hypolobulation, hypogranularity), or monocytes may be present in peripheral smears

Immunophenotype

- Immunophenotyping may be helpful in determining the percentage of blasts (CD34 +)
- Otherwise, does not play a role in the diagnostic evaluation of MDS

Cytogenetics

- Chromosome abnormalities present in 70% to 80% of patients with primary MDS
- Finding cytogenetic abnormalities can be used to support a diagnosis of MDS
- Certain cytogenetic findings bear prognostic significance (See Table 8-12)
- Certain cytogenetic abnormalities are associated with specific hematologic syndromes:
  - 5q-: associated with a syndrome that is slightly more common in women and is characterized by moderate to marked anemia and dysplastic neutrophils and megakaryocytes:
    - Shows indolent clinical behavior
  - Monosomy 7: associated with a male predominant syndrome in young children (median age = 10 months) characterized by recurrent infections, hepatosplenomegaly, monocytosis, and leukoerythroblastosis:

Table 8-12. Prognostic Significance of Cytogenetic Findings in MDS

Cytogenetic finding	*Prognostic significance*
20q-, 5q-, single defect	Favorable
+8	Intermediate
-7, 7q-, complex abnormalities	Unfavorable
9q-, t(1;3), t(2;11)	Indeterminate

Table 8-13. Types of Primary Myelodysplastic Syndromes

Type	*Criteria*
Refractory anemia (RA)	Anemia, abnormal RBCs, ringed sideroblasts (RS) <15%, blasts <1% in PB, blasts<5% in BM
Refractory anemia with ringed sideroblasts (RARS)	Anemia, RS >15% in BM, blasts <1% in PB, blasts < 5% in BM
Refractory anemia with excess blasts (RAEB)	Cytopenias (typically of 2–3 lines), dysmyelopoesis, blasts <5% in PB, blasts >5% and <20% in BM
Chronic myelomonocytic leukemia, myelodysplastic (CMML)	As in RAEB with persistent monocytosis in PB (monocytes >1x10^9/L)

- Dysplastic changes frequently present in erythroid, granulocytic, and monocytic lineages similar to JMML (see chronic myeloproliferative disorders)
- Clinically aggressive

– 20q-: associated with anemia, thrombocytopenia, and dysplastic changes in erythroid and megakaryocytic lineages that may be subtle

Microscopic

♦ Morphologic features of dysmyelopoesis:
– Dyserythropoesis:
- Features include nuclear irregularity, nuclear fragmentation, irregular staining or stippled cytoplasm, nuclear-cytoplasmic asynchrony, and ringed sideroblasts:
  - Ringed sideroblasts are erythroid precursors, with a ringing of the nucleus by sideroblastic iron revealed by an iron stain
  - Mature red blood cells show anisopoikilocytosis with microcytes, oval macrocytes, and dacrocytes

– Dysgranulopoiesis:
- Features include slowed nuclear maturation, nuclear hypolobulation (pseudo-Peleger-Huet anomaly), and abnormal (often markedly decreased) cytoplasmic granulation

– Dysmegakaryocytopoiesis:
- Features include micromegakaryocytes; large megakaryocytes with hyposegmented nuclei or multiple nuclei dispersed in cytoplasm; and large, hypogranular platelets

♦ Primary MDS may be subtyped by morphologic features:
– Some subtypes have been previously defined by FAB (see Authors note); additional categories have been added

Specific Features

♦ Refractory anemia (RA):
– Most cases show erythroid hyperplasia with quantitatively normal granulopoiesis and megakaryocytes
– Rare cases show erythroid hypoplasia with a hypocellular marrow
– Iron staining often shows increased storage iron
– Clinically, other causes of anemia must be excluded

♦ Refractory anemia with ringed sideroblasts (RARS):
– Most cases show erythroid hyperplasia with quantitatively normal granulopoiesis and megakaryocytes
– Some cases of RARS represent metabolic defects in heme metabolism, rather than a clonal disorder of abnormal hematopoetic precursors:
- Former cases show more subtle morphologic abnormalities of erythropoiesis than latter
- Difficult to distinguish these two entities by morphology

– Ancillary studies such as cytogenetics may be helpful in supporting a diagnosis of myelodysplasia in cases of RARS

♦ Refractory anemia with excess blasts (RAEB):
– Bone marrow is hypercellular with panmyeloid hyperplasia in the majority (80% to 90%) of cases:
- Remainder are normocellular or hypocellular

– Typically occurs in older patients
– Single lineage or multilineage dysplasia may be present
– Clusters of blasts may be seen in marrow interstitium not in their usual perivascular or paratrabecular location, a phenomenon referred to as abnormal localization of immature precursors (ALIP)

♦ Chronic myelomonocytic leukemia, myelodysplastic (CMML):
– Distinguished from myeloproliferative form of

Table 8-14. Prognosis in Myelodysplastic Syndromes

Syndrome	*Median survival (months)*	*Progression to AML (%)*
RA	50	12
RARS	51	8
RAEB	11	44
CMML	11	14

CMML primarily on basis of peripheral blood leukocyte count and presence (myeloproliferative) or absence (myelo-dysplastic) of splenomegaly
- – Bone marrow findings similar to RAEB, except increased monocytes present
- – Degree of monocytosis and maturity of monocyte population varies widely between patients
- – Myelofibrosis, ALIP, and extramedullary hematopoetic tumors may be seen
- – Up to 50% of patients develop a hypergammaglobulinemia that typically is polyclonal

♦ MDS-Unclassified:
- – Marrow typically hypercellular with single lineage or multilineage hyperplasia and dysplasia. Blasts <19% in PB and <5% in BM

Differential Diagnosis

♦ Congenital dyserythropoietic anemia
♦ Folate/B12 deficiency
♦ Heavy metal or drug toxicity
♦ Myeloproliferative disorder
♦ AML

Prognosis and Treatment

♦ Prognosis in cases of MDS worsens with increasing degrees of marrow dysplasia and immaturity
♦ Other poor prognostic indicators include old age, marked thrombocytopenia, and karyotypic abnormalities
♦ Survival data (See Table 8-14)
♦ Treatment consists of supportive transfusion therapy for more indolent disorders, or antileukemic chemotherapy or bone marrow transplantation for patients with more aggressive disorders

Treatment-Related Myelodysplastic Syndromes

Clinical

♦ Occur in patients treated with chemotherapeutics (particularly alkalating agents and epipodophyllotoxin) and radiotherapy
♦ Typically presents 4–6 years after chemotherapy or radiotherapy
♦ Occurs in 15% to 20% of patients treated with standard regimens for Hodgkin's disease and multiple myeloma and in up to 44% of patients treated with high-dose epipodophyllotoxin
♦ Risk factors include increased age, agent used, and increased cumulative dose (i.e., increased length of treatment and/or increased repetition of exposures)
♦ Patients often present with constitutional symptoms and cytopenias similar to other types of MDS patients
♦ May be diagnosed at an earlier (pre-clinical) stage

Laboratory

♦ Peripheral blood smear often shows multilineage dysplasia
♦ Nucleated RBCs and ringed sideroblasts may be present in peripheral blood

Cytogenetics

♦ Chromosome abnormalities occur with high frequency
♦ Multiple chromosomal abnormalities often present
♦ Approximately 80% of chromosomal abnormalities associated with alkalating agents and radiation involve deletions or loss of chromsomes 5 and 7 (-5, -7, -5q, -7q)
♦ Treatment with epipodophyllotoxin is associated with abnormalities of 11q23

Microscopic

♦ Bone marrow may be normocellular (50%), hypercellular (25%), or hypocellular (25%)
♦ Reticulin fibrosis may be present
♦ Trilineage dysplasia is present in majority of cases; dyserythropoiesis and ringed sideroblasts are almost universally present
♦ Degree of dysplasia varies from subtle to severe abnormalities
♦ Marked trilineage dysplasia may be present in marrows with <5% blasts, making classification difficult

Table 8-15. Factors Associated with Poor Prognosis in Treatment-Related MDS

Age >65 years
Hodgkin's disease, multiple myeloma, or ovarian carcinoma as primary malignancy
Treatment with nitrosureas, alkylating agent, or procarbizine
Platelet count <100x10^9/ml
Marrow blasts >5%
Cytogenetic abnormalities other than t(15:17) or t(8;21)

- Patients with a history of alkalating agent or radiation exposure that progress to AML most often have one of following subtypes:
  - AML-M2, AML-M4, AML-M6, or an AML that is unclassifiable (approximately 50% of cases unclassifiable due to involvement of multiple lineages)
- Patients with a history of epipodophyllotoxin exposure that progress to AML most frequently develop AML-M4 or AML-M5

Treatment and Prognosis

- Patients with treatment-related MDS and AML have a poorer prognosis with clinically more aggressive disease than patients with de novo disease
- Median survival time = 4–8 months for treatment-related MDS– Only slightly longer than that for patients with treatment-related AML
- Factors associated with poor prognosis
  - See Table 8-15

LOW-GRADE B-CELL LEUKEMIA

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL)

Clinical

- Mean age = 55 years; rare in patients <40 years old
- M:F = 2:1
- Patients frequently asymptomatic at presentation; constitutional symptoms may be present
- Patients often have lymphadenopathy and moderate hepatosplenomegaly

Laboratory

- Average lymphocyte count at diagnosis = 90x10^9/ml; counts may be as high as 400x10^9/ml
- Anemia may be present either due to bone marrow failure or autoimmune hemolytic anemia
- Hypogammaglobulinemia is present in 50% to 75% of all cases
- 15% to 35% of patients develop autoimmune hemolytic anemia or thrombocytopenia

Immunophenotype

- See Table 8-16
- Shows monoclonal immunoglobulin light chain restriction, although level of cell-surface immunoglobulin expression is much lower than in other low-grade B-cell lymphomas

Cytogenetics

- Clonal abnormalities demonstrated in approximately 50% of cases when sample is stimulated with B-cell mitogens
- Most common abnormalities are +12, and abnormalities of 13q, 14q, 6q, and chromosome 11

Microscopic

- See Table 8-17
- CLL may involve marrow in three patterns:
  - Focal pattern:
    - Randomly scattered, poorly circumscribed lymphoid aggregates are present
    - Hematopoetic marrow is relatively preserved
  - Diffuse pattern:
    - Lymphoid cells fill marrow, replacing both normal hematopoetic tissue and fat
  - Interstitial pattern:
    - Malignant lymphoid cells infiltrate marrow interstitium with preservation of normal marrow architecture and hematopoetic precursor cells

Differential Diagnosis

- Other low-grade lymphocytic leukemias
- Reactive (polyclonal) blood and bone marrow lymphocytosis
- Benign marrow lymphoid aggregates

Prognosis and Treatment

- Dependent on stage of disease
- Many staging systems (Rai and Binet are most fre-

quently used), all show that::

- – Patients with marrow lymphocytosis without cytopenias and without multi-organ involvement have a good prognosis (median survival >10 years)
- – Patients without cytopenias and with multi-organ (spleen, liver, lymph nodes) involvement have an intermediate prognosis (median survival = ~5 years)
- – Patients with anemia (hemoglobin <10g/dL) and/or thrombocytopenia (platelets <100x10^9/L) have a poor prognosis regardless of organ involvement (median survival = ~2.5 years)

♦ Patients with diffuse marrow involvement are usually advanced stage and have a poor prognosis

♦ Treatment is usually only partially effective in reducing lymphocyte burden and, therefore, is reserved for patients with symptomatic disease

♦ Hypogammaglobulinemia is not associated with a poor prognosis

♦ Autoimmune complications, such as autoimmune hemolytic anemia and autoimmune thrombocytopenia, can be treated with transfusions, corticosteroids, intravenous immunoglobulin, or splenectomy

Transformed CLL/SLL

Clinical

♦ CLL can undergo prolymphocytic transformation; transformation to a diffuse, large B-cell lymphoma (termed Richter's transformation); or Hodgkin's disease

♦ Transformation can occur at any point during course of disease, although typically there is a latency period of at least 1.5 years

♦ Clinical findings of transformation may include increasing lymphadenopathy or splenomegaly and worsening constitutional symptoms

Laboratory

♦ With prolymphocytic transformation, prolymphocytes comprise >10% of peripheral blood lymphocytes

Table 8-16. Immunophenotype of Low-Grade B-cell Leukemias and Lymphomas

	SIg	*CD20*	*CD5*	*CD10*	*CD11c*	*CD22*	*CD23*	*CD103a*
CLL	Weak +	Weak +	+	–	–/+	–/+	+	–
PLL	+	+	+/–	–/+	–	+	–/+	–
HCL	+	Strong +	–	–	Strong +	Strong +	–	+
MZL	+	+	–	–	+/–	+	+/–	–
MCL	+	+	+	–	–	+	–	–
FL	+	+	–	+	–	+	–/+	–

CLL = chronic lymphocytic leukemia; PLL = prolymphocytic leukemia; HCL = hairy cell leukemia; MZL = marginal zone lymphoma; MCL = mantle cell lymphoma; FL = follicular lymphoma.

Table 8-17. Morphologic Features of Chronic B-Cell Leukemias

	Size	*Nucleus*	*Cytoplasm*
CLL	Small, slightly larger than RBCs	Condensed, clumped chromatin, nucleoli absent	Sparse, faintly basophilic
PLL	Medium to large with	Regular, round to oval, dispersed chromatin with single nucleolus	Rim of clear cytoplasm
HCL	Small to medium	"Monocytoid," round to slightly lobulated, coarse chromatin (less clumped than CLL) with inconspicuous nucleoli	Variable amount of faintly basophilic cytoplasm with a shaggy (hairy) border

Immunophenotype

- In many instances, essentially unchanged from CLL, but loss of CD5 and/or CD23 for cells of prolymphocytic or Richter's transformation can occur

Microscopic

- In prolymphocytic transformation, large foci of prolymphocytes or admixed prolymphocytes and small lymphocytes may be seen
- Prolymphocytic transformation defined on basis of blood morphology (>10% prolymphocytes), not on bone marrow or extramedullary histopathologic findings
- In Richter's transformation, there is histologic transformation to diffuse large cell lymphoma
  - Marrow may not be involved

Differential Diagnosis

- Prolymphocytic leukemia
- Diffuse large cell lymphoma

Treatment and Prognosis

- Prolymphocytic and Richter's transformation are both associated with a worse prognosis than CLL

Prolymphocytic Leukemia

Clinical

- Affects older patients (median age = 64 years)
- M:F = 2:1
- Patients typically have marked splenomegaly, moderate to marked hepatomegaly, and little adenopathy

Laboratory

- Marked lymphocytosis usually present (average initial lymphocyte count = $350x10^9$/L)
- Prolymphocytes >55% of total blood lymphocytes
- Monocytosis may be present

Immunophenotype

- See Table 8-16

Microscopic

- See Table 8-17 for cytologic features
- Bone marrow typically shows a focal or diffuse pattern of involvement by malignant prolymphocytes
- Associated small lymphoid cells and larger lymphoid cells with prominent nucleoli (paraimmunoblasts) may be present
- Splenic red-pulp and white-pulp infiltrated by malignant lymphoid aggregates
- Mitotic rate typically low

Differential Diagnosis

- CLL with prolymphocytic transformation
- T-cell prolymphocytic leukemia
- Large cell lymphoma

Prognosis and Treatment

- Aggressive disease that is poorly responsive to therapy
- Average survival = 1 year

Hairy Cell Leukemia (HCL)

Clinical

- Primarily disease of adults in fifth and sixth decades of life; average age at diagnosis = 50 years
- M:F = 4:1
- Patients characteristically have splenomegaly and pancytopenia
- Hepatomegaly and adenopathy (usually abdominal) may also be present

Laboratory

- Normochromic, normocytic anemia, and monocytopenia are almost always present
- Lymphopenia and neutropenia are usually present

Immunophenotype, Cytochemistry, and Ultrastructure

- See Table 8-16 for immunophenotypic information
- Neoplastic lymphocytes are almost universally + for tartate-resistant acid phosphatase (TRAP) activity
- In some cases, only a minority of cells show cytochemical reactive
- Demonstration of TRAP activity is relatively sensitive and specific method for diagnosis of HCL
- Numerous filamentous cytoplasmic projections are demonstrable by electron microscopy

Cytogenetics

- Cytogenetic abnormalities are present in approximately 10% of cases, although no specific chromosomal abnormalities are seen

Microscopic

- See Table 8-17 for cytologic features of HCL
- Bone marrow hypercellular in >80% of cases
- Remaining cases show patchy or diffuse hypocellularity
- Hairy cell infiltrates are typically diffuse, although focal involvement may be seen
- Diffuse infiltrates are characteristically comprised of cells with abundant eosinophilic cytoplasm and regular, round to oval nuclei with small, indistinct nucleoli
- In some cases, cells may be spindled or nuclei may be lobulated
- Spleen and liver show massive sinusoidal infiltration by HCL cells

- Cells usually show strong immunoreactivity for CD20, DBA-44, and TRAP in paraffin-embedded sections

Differential Diagnosis

- Other low-grade B-cell leukemias
- Marginal zone lymphoma
- Systemic mastocytosis

Treatment and Prognosis

- Patients susceptible to secondary infections
- Primary therapeutic agents are interferon alpha, deoxycoformycin (pentostatin), and 2-chlorodeoxyadenosine:
  - Prior to introduction of these drugs, primary therapeutic options were splenectomy and observation
  - Introduction of these agents has improved clinical outcomes, average survival is now approximately 6 years

T-CELL LEUKEMIAS

T-Cell CLL (Small Variant of T-Prolymphocytic Leukemia by FAB Criteria)

Clinical

- Similar to B-cell CLL, with a predominance of disease in older males
- Splenomegaly may be more prominent than in B-cell CLL; however, lymphadenopathy may be less marked
- Skin infiltration may occur

Laboratory

- Similar to B-cell CLL

Immunophenotype

- Summarized in Table 8-18

Microscopic

- Similar to B-cell CLL, except may have more nuclear irregularity
- Histologic pattern of marrow involvement similar to B-cell CLL

Differential Diagnosis

- B-cell CLL
- Other low-grade lymphoproliferative disorders
- Reactive (polyclonal) T-cell lymphocytosis

Prognosis and Treatment

- More aggressive than B-cell CLL and more refractory to treatment

T-Cell Prolymphocytic Leukemia

Clinical

- Between 5% and 30% of all cases of prolymphocytic leukemia
- Disease of older adults (mean age = 69 years)
- Affects males slightly more than females
- Patients present with hepatosplenomegaly, lymphadenopathy, serous effusions, and skin lesions

Laboratory

- Patients usually have natked leukocytosis (>100×10^9/L)
- > 50 % have anemia (hemoglobin <10g/dL) and thrombocytopenia (platelets < 100×10^9/L)
- Human T-cell leukemia virus-1 (HTLV-1) –

Immunophenotype and Immunohistochemistry

- See Table 8-18 for immunophenotypic data
- Cells are TdT –
- Some cases may show TRAP activity

Cytogenetics

- > 75% of cases show abnormalities involving long arm of chromosome 14 at bads q11 and q32, most common being inv(14)(q11q32)
- >50% of cases with abnormalities of chromosome 14 also show +8

Microscopic

- Morphologic features similar to B-cell prolymphocytic leukemia
- In approximately 50% of cases, nuclear membrane is convoluted rather than regular and oval
- Cells showing nuclear convolutions are usually less irregular than Sezary cells
- In some cases, nuclear features can resemble Sezary cells
- Bone marrow involvement is variable and occurs in 30% to 50% of all cases
- Degree of marrow involvement does not always correlate with degree of peripheral blood lymphocytosis
- Like B-cell prolymphocytic leukemia, pattern of marrow involvement can be focal, diffuse, or interstitial

Differential Diagnosis

- B-cell prolymphocytic leukemia
- Other T-cell lymphoproliferative disorders

Table 8-18. Immunophenotype of Low-Grade T-Cell Leukemias

	CD2,3,5,7	*CD4*	*CD8*	*CD25*	*CD16*
CLL	+	+/–	+/–	–	–
PLL	+	+	–/+	–	–
Adult TCL	+	+	–	+	–
LGL	+/–	–	+	–	+
Sezary	+	+	–	–	–

PLL = prolymphocytic; TCL = T-cell leukemia; LGL = leukemia of large granular lymphocytes; Sezary = Sezary syndrome.

Treatment and Prognosis

- More aggressive disease than B-cell prolymphocytic leukemia; median survival time = 7.5 months
- Generally refractory to treatment

Adult T-Cell Leukemia-Lymphoma (ATCL)

Clinical

- Most common in Japan, the Caribbean, Western Africa, and southeastern United States:
  - Rare outside these areas
- Lymphadenopathy almost universally present; splenomegaly and hepatomegaly common; CNS involvement uncommon (10%)
- Skin involvement common (approximately 50%); usually presents as maculopapular rash and frequently precedes other clinical manifestations
- Both an acute, aggressive form and a clinically indolent form of the disease exist

Laboratory

- Patients almost universally show serologic evidence of HTLV-1 infection
- Hypercalcemia and lytic bone lesions common; may reflect parathyroid-related hormone production by tumoral cells
- Cytopenias typically mild
- In acute, aggressive cases, numerous atypical lymphoid cells showing marked cytologic variability and moderate to marked nuclear irregularity present in peripheral blood
- In chronic, indolent cases, lymphoid cells with convoluted nuclei but less cytologic variability are present in peripheral blood:
  - These cells may comprise <5% of peripheral blood lymphocytes

Immunophenotype

- See Table 8-18

Cytogenetics

- Chromosome abnormalities common and most frequently involve 14q11 or 14q32
- +3 or +7 may be associated with more aggressive disease

Microscopic

- Bone marrow involvement is variable, and may be minimal or absent
- Marrow involvement is usually sparse, diffuse infiltration or poorly circumscribed focal lesions
- Marrow may show increased osteoclastic activity independent of marrow involvement by leukemia

Differential Diagnosis

- T-cell prolymphocytic leukemia
- Sezary syndrome

Prognosis and Treatment

- Acute, aggressive form has poor prognosis, with a mean survival of 5 months
- Chronic form tends to continue in indolent form until acute, aggressive phase occurs
- Patient may continue in indolent form for years before acute phase occurs
- Factors associated with poor prognosis include increased peripheral blood leukocyte count, increased absolute number of leukemic cells in peripheral blood, combined leukemic and lymphomatous presentation, high serum calcium, age >40 years, and elevated lactic acid dehydrogenase
- Disease is refractory to treatment; few patients have a durable remission

Leukemia of Large Granular Lymphocytes

Clinical

- Affects older adults; average age = 55–65 years
- Slight male predominance
- Some patients present with infection secondary to neutropenia
- Splenomegaly and hepatomegaly variably present

Laboratory

- Lymphocytosis variably present and often mild
- Absolute increase in large granular lymphocytes (>500/L) in most cases
- Neutropenia present in 40% to 60% of all cases
- Anemia, thrombocytopenia variably present; rare cases present as pure red cell aplasia or cyclic neutropenia

Immunophenotype and Cytochemistry

- See Table 8-18
- A small number of cases lack expression of T-cell antigen receptor complex CD3 and are + for CD2, CD7, and CD16:
  - These cases have natural killer cell (NK cell) phenotype
- Clonal T-cell antigen receptor gene rearrangements will be present in cases with a cytotoxic/suppressor T-cell phenotype and absent in cases with an NK phenotype
- Cells focally cytochemically reactive for tartate-resistant acid phosphatase

Microscopic

- Malignant lymphoid cells: large granular lymphocytes with relatively abundant, lightly basophilic cytoplasm with coarse azurophilic granules and round to oval nuclei with coarse, condensed chromatin and inconspicuous to absent nucleoli
- Marrow may be hypercellular, normocellular, or hypocellular
- Degree of marrow involvement is variable and usually very subtle
- Leukemic cells involve marrow as interstitial infiltrates with small, scattered aggregates of lymphoid cells
- Infiltration of splenic and hepatic sinusoids can occur

Differential Diagnosis

- Viral infection
- Reactive lymphocytosis
- Myelodysplastic syndrome

Prognosis and Treatment

- Indolent disease
- Most disease morbidity and mortality related to malignancy-induced cytopenias

Sézary Syndrome

Clinical

- Leukemic phase of mycosis fungoides; patients have erythematous skin rash and Sezary cells in peripheral blood
- Males>Females
- Average age = ~60 years
- Lymphadenopathy present in approximately 50% of all cases; hepatosplenomegaly present in approximately 30%

Laboratory

- Peripheral blood lymphocytosis
- RBCs, neutrophils, and platelets usually normal
- Mild eosinophilia may be present

Immunophenotype

- See Table 8-18

Cytogenetics

- Tetraploidy (large cells) or normal to hyperdiploidy (small cells) may be present
- No structural abnormalities are consistently identified

Microscopic

- Characteristic Sezary cell is large (12–25μm diameter) with high N/C ratio and large, markedly convoluted (cerebriform) nucleus with variably dispersed chromatin lacking prominent nucleoli
- Small Sezary cell variant (8–11μm diameter) has convoluted nucleus with coarse, condensed chromatin:
  - Nuclear convolutions may be more difficult to identify due to condensed chromatin
- Cytoplasmic PAS + granules may be present, forming a perinuclear ring
- Bone marrow is typically normocellular, with a sparse interstitial infiltrate of Sezary cells
- Marrow involvement by Sezary syndrome is often more readily apparent in marrow smears than in biopsy sections

Differential Diagnosis

- T0-cell prolymphocytic leukemia

Prognosis and Treatment

- Multiple modes of therapy including ultraviolet phototherapy, radiotherapy, and chemotherapy are available
- Treatment generally effective; long-term remissions can be achieved

LYMPHOMATOUS INVOLVEMENT OF BONE MARROW

- Will focus on morphologic features of bone marrow involvement by non-Hodgkin's and Hodgkin's lymphoma
- For a detailed discussion of clinical and immunophenotypic features of these disorders, please see Chapter 7
- Can be difficult to distinguish leukemia from lymphoma

Non-Neoplastic Lymphoid Aggregates

Clinical

- Non-neoplastic bone marrow lymphoid aggregates can be associated with numerous conditions, including older age (present in 30% to 40% of elderly patients), collagen vascular diseases, drug therapy, and viral infections

Immunophenotype

- Immunophenotypic studies demonstrate a polyclonal population of B cells and T cells

Microscopic

- Typically round, well-circumscribed, aggregates of small lymphocytes with scattered admixed histiocytes, plasma cells, and mast cells
- Benign lymphoid aggregates typically located in marrow interstitium and, although they may abut bony trabeculae, do not follow true paratrabecular pattern
- Well-formed germinal centers uncommon and usually associated with autoimmune diseases, severe infections, or drug reactions

Follicular Lymphoma and Diffuse, Large B-Cell Lymphoma

Clinical

- Frequency of marrow involvement varies with histologic subtype, with involvement common in follicular grade 1 and grade 2 lymphoma
- Involvement relatively uncommon in follicular grade 3 and diffuse large B-cell lymphoma
- Subtypes of large B-cell lymphoma included with diffuse, large B-cell lymphoma include T-cell rich B-cell lymphoma and histiocyte rich B-cell lymphoma

Immunophenotype

- + for surface Ig, CD19, CD20, and CD22; variably + for CD10 and CD23

Microscopic

- Follicular (small cleaved, and mixed) grade 1 and grade 2 lymphomas characteristically involve marrow by forming paratrabecular infiltrates
- Diffuse large B-cell lymphoma can infiltrate marrow in a paratrabecular or interstitial pattern; involvement can be minimal or marked
- Morphologic discordance with marrow involvement by a low-grade follicular lymphoma that has transformed to a more aggressive large cell lymphoma in a non-marrow site occurs in 20% to 40% of all patients

Differential Diagnosis

- Benign lymphoid aggregates
- Other lymphomas

Mantle Cell Lymphoma

Clinical

- Marrow involvement is relatively common; marrow involved in approximately 70% of all cases
- Some patients develop a leukemic peripheral blood involvement

Immunophenotype

- Strong surface Ig, CD19, CD20, CD22, and CD5; cyclin D1 +
- Variable expression of CD43
- Lack expression of CD10 and CD23

Microscopic

- Bone marrow involvement may be focal, paratrabecular, or interstitial; may be diffuse and replace normal marrow
- Diffuse, interstitial involvement is associated with leukemic peripheral blood picture

Differential Diagnosis

- Benign lymphoid aggregates
- Other lymphomas

Monocytoid B-Cell Lymphoma/Marginal Zone Lymphoma

Clinical

- Marrow involvement is generally thought to be rare (<5% of cases)
- Bone marrow involvement may be associated with more aggressive disease

Immunophenotype

- Strong surface Ig, CD19, and CD20
- Variable expression of CD11c, CD22, and CD23
- Lack expression CD5, CD10, CD25, and cyclin D1

Table 8-19. Frequency of Marrow Involvement by Subtypes of Hodgkin Lymphoma

Subtype	*Frequency (%)*
Lymphocyte predominant	<5
Nodular sclerosis	<10
Mixed cellularity	<20
Lymphocyte depleted	50–70
Overall	5–20

Microscopic

- Infiltrate usually composed of mixture of lymphoid cells including small cells, plasmacytoid cells, and cells with abundant, clear cytoplasm
- Paratrabecular or interstitial involvement may be identified
- Degree of involvement is variable

Differential Diagnosis

- Benign lymphoid aggregates
- Other lymphomas, particularly splenic lymphoma with villous lymphocytes
- Hairy cell leukemia

Peripheral T-Cell Lymphoma (PTCL) and CD30+ Anaplastic Large Cell Lymphoma (ALCL)

Clinical

- Bone marrow involvement relatively common for all subtypes of PTCL, occurring in approximately 60% to 75% of patients, but less common in ALCL

Immunophenotype

- PTCLs almost uniformly express CD3
- ALCLs variably express CD3 and typically show uniform strong membrane expression of CD30
- See Chapter 7 for immunophenotypic information

Microscopic

- Pattern of involvement may be diffuse, focal, or interstitial (particularly in ALCL)
- Interstitial marrow infiltrates may blend with normal hematopoetic precursors, making a morphologic diagnosis of marrow involvement by lymphoma difficult:
  - In these cases, aspirate smear cytology and immunohistochemistry are helpful in accurately determining the degree of marrow involvement
- Marrow fibrosis commonly occurs with involvement by PTCL
- Discordance between lymphoma morphology in marrow as compared to a non-marrow site rarely occurs

Differential Diagnosis

- Reactive lymphoid infiltrates
- Hodgkin's disease
- Large B-cell lymphoma
- CMPD (in cases with marked marrow fibrosis)
- Systemic mastocytosis

Prognosis and Treatment

- Bone marrow involvement by PTCL associated with poor prognosis

Hodgkin's Lymphoma

Clinical

- Frequency of marrow involvement varies with histologic subtype (see Table 8-19)

Immunophenotype

- See Chapter 7

Microscopic

- Pattern of involvement may be focal, diffuse, or fibrotic
- Lesions typically composed of mixture of Reed-Sternberg cells and Reed-Sternberg variants, small lymphocytes, plasma cells, and eosinophils
- Histopathologic criteria for diagnosis of marrow involvement in patient with proven HD have been established and consist of three primary features:
  - Presence of Reed-Sternberg cells or variants in typical mixed background of Hodgkin's disease
  - Presence of atypical histiocytes in either cellular background of HD or in areas of fibrosis in patient with proven HD
  - Marrow fibrosis or necrosis in patient with proven HD
- Serial sections and immunohistochemistry can confirm involvement in the above situations

Differential Diagnosis

- Granulomas
- Peripheral T-cell lymphoma
- Anaplastic large cell lymphoma
- Large B-cell lymphoma

Prognosis and Treatment

- Bone marrow involvement is typically seen in patients with advanced stage disease and, therefore, often associated with poorer prognosis

PLASMA CELL DISORDERS AND RELATED CONDITIONS

Multiple Myeloma

Clinical

- Disease of adults; mean age at diagnosis = 62 years; <5% of cases occur before age 40 years
- Approximately twice as common in blacks than whites
- May be slight disease predominance in men
- Common presenting symptoms include pallor, bone pain, pathologic fractures (axial skeleton > appendicular skeleton), neurologic symptoms secondary to nerve root or spinal cord compression, fatigue secondary to anemia, renal failure, and hepatomegaly
- POEMS syndrome (Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal protein, Skin change) may be associated with osteosclerotic myeloma

Laboratory

- Tumor effects:
  - Lytic bone lesions due to plasma cell tumors (axial skeleton > appendicular skeleton) detected by plain radiographic films, but not by bone scans
  - Bone marrow infiltration and replacement can cause cytopenias
- Immunoglobulin effects:
  - >95% have abnormal immunoglobulin in serum (90%) or urine (75%)
  - Detectable by protein electrophoresis, immunoelectrophoresis, or immunofixation
  - Immunoglobulin isotype varies, frequencies are: IgG, 55%; IgA, 22%; light chain only, 18%; IgD, 2%; IgE, <1%; IgM, <1%
  - Paraprotein precipitation in renal tubules damages tubular epithelium, leading to a foreign body giant cell reaction, interstitial fibrosis, and, ultimately, progressive renal failure (myeloma kidney)
- Cytokine effects:
  - Osteoclastic activity is stimulated by release of tumor necrosis factor (TNF) and interleukin 1 (IL-1), leading to bone resorption and generalized osteopenia
  - Increased B_2-microglobulin, hypercalcemia (20% to 25% of cases)

Diagnosis

- Minimal criteria for diagnosis (after Salmon and Durie:)
  - >10% plasma cells in bone marrow or presence of plasmacytoma
  - And one of following three: M protein in serum >3g/dL, M-protein in urine, or Lytic bone lesions
- Number of plasma cells actively synthesizing DNA at time of biopsy may be assessed by measuring incorporation of thymidine analogues into nuclear DNA
- Degree of plasma cell proliferative activity is then assessed and reported as plasma cell labeling index
- Cases in which monoclonal plasma cells are >10% of total marrow cellularity and serum M-protein is present at level >3g/dL, but lack all other clinical signs of multiple myeloma are designated smoldering myeloma
- Neoplastic plasma cells are present in peripheral blood in approximately 15% of cases, usually in very low numbers
- Cases in which abnormal plasma cells comprise >20% of total peripheral blood leukocytes or exceed 2 x 10^9/L are referred to as plasma cell leukemia

Cytogenetics

- Cytogenetic abnormalities are present in 25% to 50% of multiple myeloma cases and 90% to 100% of plasma cell leukemia cases
- Most common abnormalities are complex rearrangements and hyperdiploidy; both numeric and structural abnormalities are present in most cases
- Defects of chromosome 1 and chromosome 14 at band q32 are most common structural abnormalities

Microscopic

- Multiple myeloma is multifocal disease and therefore degree of bone marrow involvement varies:
  - Usually parallels clinical severity
- In some instances, relatively minimal bone marrow involvement will be seen in clinically advanced disease or apparent advanced bone marrow involvement will be seen in clinically low stage disease

- Neoplastic plasma cells generally larger than normal plasma cells and have more dispersed nuclear chromatin; may have eosinophilic, intranuclear inclusions (Dutcher bodies)
- Cytoplasmic changes include ragged cytoplasmic borders, cytoplasmic blebs, vacuolization, and hyaline or crystalline inclusions (Russell bodies)
- Plasmablasts, immature plasma cells with high nuclear/cytoplasmic ratio and open nuclei with prominent nucleoli, may be present
- Cases in which plasmablasts predominate may be referred to as plasmablastic multiple myeloma
- Myeloma cells may involve marrow in diffuse, interstitial, or nodular pattern
- Histologic findings that strongly correlate with marrow involvement by multiple myeloma include:
  - Nodules of monoclonal (by immunoglobulin light chain immunohistochemistry) plasma cells that occupy at least $^1/_2$ of a high power field
  - Monoclonal plasma cells occupying an entire interfatty marrow space and excluding normal hematopoetic elements
  - Monoclonal plasma cells comprising 50% or more of total marrow cellularity

Differential Diagnosis

- Reactive plasmacytosis
- Solitary plasmacytoma of bone
- Extramedullary plasmacytoma
- Smoldering myeloma
- Monoclonal gammopathy of undetermined significance
- Amyloidosis
- Heavy chain disease

Prognosis and Treatment

- Often unrelenting disease that only partially responds to therapy; average survival = 30 to 36 months
- Factors associated with poorer prognosis:
  - Advanced age
  - Hypercalcemia
  - Elevated B_2-microglobulin
  - Renal failure
  - Plasma cell labeling index >1.0
  - Plasma cell leukemia
  - Anemia
- Patients usually treated with melphalan, prednisone, or cyclophosphamide as single therapy or combined therapy agents
- Average of 50% to 60% of patients respond to therapy, but complete clinical remissions rare
- Both allogeneic and autologous bone marrow transplants have been used and possibly allow for longer periods of remission, but have not been shown to improve long-term survival

Solitary Plasmacytoma of Bone and Extramedullary Plasmacytoma

Clinical

- Age distribution similar to multiple myeloma
- Solitary plasmacytoma of bone typically presents as isolated bone mass
- Extramedullary plasmacytoma typically presents in upper respiratory tract (80%)

Laboratory

- Both of these disorders present as isolated monoclonal plasma cell proliferation without any clinical or laboratory evidence of multiple myeloma
- A very small amount of monoclonal protein may be present in serum or urine of some patients with solitary plasmacytoma of bone

Microscopic

- Both disorders are characterized by tumors composed of monoclonal plasma cells with cytologic features similar to those described in multiple myeloma

Differential Diagnosis

- Multiple myeloma
- Smoldering myeloma
- Inflammatory pseudotumor

Prognosis and Treatment

- Approximately 55% of patients with solitary plasmacytoma of bone will develop overt clinical myeloma, usually within 3 to 4 years
- Approximately 10% of patients will develop recurrent or new bone lesions
- Approximately 25% of patients with extramedullary plasmacytoma will develop local recurrence; progression to overt multiple myeloma is rare
- Both disorders are treated with local radiation and close clinical follow-up

Reactive Plasmacytosis

Clinical

- Can occur in a number of clinical settings, including connective tissue diseases, chronic infections, HIV infection, myelodysplastic syndromes, and malignancy

Laboratory

- Patients with reactive plasmacytosis typically will have polyclonal gammopathy, a low plasma cell labeling index, and no detectable M-protein in serum or urine

Microscopic

- Plasma cells show polyclonal light chain expression by immunohistochemistry
- Typically dispersed in marrow in interstitial pattern; small aggregates may be present
- May have a perivascular distribution
- Minimal cytoplasmic and nuclear irregularities, binucleate forms, and Russell bodies may be present

Differential Diagnosis

- Multiple myeloma
- Monoclonal gammopathy of uncertain significance
- Amyloidosis
- Waldenstrom's macroglobulinemia

Prognosis and Treatment

- Depends on underlying condition responsible for reactive plasmacytosis

Monoclonal Gammopathy of Uncertain Significance (MGUS)

Clinical

- Patients are typically asymptomatic and disorder is discovered during medical evaluation
- Occurs in approximately 1% of persons >50 years and 3% of those >70 years

Laboratory

- Patients by definition have serum M-protein, typically <3g/dL, and no clinical or laboratory evidence of multiple myeloma, amyloidosis, macroglobulinemia, or other plasma cell diseases

Microscopic

- Bone marrow typically normocellular, with plasma cells distributed in interstitial pattern
- Plasma cells typically comprise <10% of total marrow cellularity

Prognosis and Treatment

- Approximately 25% of patients with MGUS will develop overt lymphoproliferative disease (approximately 20% at 10 years and 30% at 20 years)
- Multiple myeloma most common disease to arise in MGUS, although may develop primary systemic amyloidosis, Waldenstrom's macroglobulinemia, or other lymphoproliferative disorders

Amyloidosis

Clinical

- Disease of older adults; rare before age 40 years
- Five types of amyloidosis (see Table 8-20)
- Considerable clinical overlap between primary amyloidosis and multiple myeloma; in some cases, may be difficult to distinguish these entities

Laboratory

- Nephrotic renal failure with proteinuria (>1g/24h) and elevated serum creatinine
- Abnormal electrocardiogram (low voltages and heart block) and abnormal echocardiography
- Monoclonal protein present in serum or urine in >90% of patients with primary amyloidosis
- Stainable amyloid in subcutaneous fat aspirate
- Immunohistochemical studies may be useful in identifying type of amyloid protein

Microscopic

- Amyloid appears as homogeneous, glassy eosinophilic substance in H+E sections
- In paraffin, amyloid stains metachromatically with crystal violet or methyl violet; fluorescent when stained with thioflavin T; stains red and demonstrates apple-green birefringence in polarized light with Congo red
- Amyloid characteristically causes thickening of vessels by depositing in vessel wall
- Mild plasmacytosis and stainable amyloid in wall of small vessels and in periosteal fibrous tissue most common bone marrow findings
- Less commonly, amyloid is identified in marrow interstitium and may even displace normal hematopoetic tissues

Differential Diagnosis

- Multiple myeloma
- Heavy chain disease

Prognosis and Treatment

- Prognosis is worst for primary amyloidosis (median survival = 13 months), slightly better for secondary amyloidosis (median survival = 2 years), and best for familial amyloidosis (median survival = 6 years)
- Treatment for primary amyloidosis consists primarily of chemotheraputics and cardiac transplantation
  - Cardiac transplantation is not curative
- Secondary amyloidosis treated by treating underlying disorder
- Renal tranplantation may be necessary to treat renal failure
- Liver transplantation may be curative for familial amyloidosis
- Renal transplantation can halt and even reverse dialysis-associated amyloidosis

Heavy Chain Disease

- Group of exceedingly rare disorders characterized by overproduction of monoclonal immunoglobulin heavy

Table 8-20. Types of Amyloidosis

Type (% of cases)	*Clinical Associations*	*Primary Symptoms*	*Amyloid Forming Protein*
Primary (70%)	Idiopathic	Weakness, fatigue, weight loss, periorbital purpura, macroglossia, congestive heart failure, nephrotic syndrome, peripheral neuropathy, syncope, voice change	Variable portions of a monclonal kappa or lambda light chain (also referred to as AL)
Localized (19%)	Long-term hemodialysis	Carpal tunnel syndrome, joint pain, radiolucent bone lesions	Beta-2 microglobulin
Senile (4%)	Older patients	Congestive heart failure, atrial fibrillation	Transthyretin (prealbumin) without identifiable mutations
Familial (4%)	Inherited disease	Peripheral neuropathy, nephrotic syndrome, congestive heart failure	Transthyretin (prealbumin) with point mutation(s)
Secondary (3%)	Collagen vascular disease, inflammatory bowel disease	Nephrotic syndrome, malabsorption, heart and peripheral nerves rarely involved	Protein A (also referred to as AA), derived from serum amyloid A protein

chain (complete or incomplete)

- Clinical and laboratory aspects (see Table 8-21)

Microscopic

- Patients with alpha chain characteristically have dense lymphoplasmacytic infiltrate with numerous plasma cells involving lamina propria of small bowel and mesenteric lymph nodes:
  - Bone marrow typically normal
- Patients with gamma chain disease often have lymphoplasmacytic B-cell lymphoma similar to Waldenstrom's macroglobulinemia:
  - May also be associated with CLL or large cell lymphoma
- Patients with mu chain disease typically have long history of CLL:
  - May also be associated with amyloidosis or myeloma
- Up to 66% of patients may have increased plasma cells with vacuolated cytoplasm in their bone marrows

Differential Diagnosis

- Waldenstrom's macroglobulinemia
- Multiple myeloma
- Amyloidosis

Prognosis and Treatment

- Little information regarding prognosis and treatment available for these rare disorders
- Appears prognosis is related to underlying lymphoproliferative disorder

Waldenström's Macroglobulinemia

Clinical

- Relatively uncommon disorder; approximately 1,300 new cases in United States per year
- Disease of older adults; median age = 63 years; rare before age 40 years
- Approximately 60% of patients are male
- Increased risk disease incidence in first degree relatives and monozygotic twins
- Weakness, fatigue, oronasal bleeding, blurred vision, dizziness, hearing loss, and headache are common presenting symptoms due to blood hyperviscosity
- Congestive heart failure may be present
- Hepatomegaly occurs in approximately 25%; splenomegaly, and lymphadenopathy less common
- Flame-shaped retinal hemorrhages and vascular congestion on fundoscopic exam

Laboratory

- Serum viscosity increased in 90% of patients
- Normochromic normocytic anemia with increased plasma volume common
- Monoclonal protein (often a large amount) almost universally present in serum; may be IgM (60% of cases), IgG (30%), IgA, biclonal, or isolated heavy chain
- In 75% of cases, associated light chain is kappa; in 25%, associated light chain is lambda
- Other serum immunoglobulins may be decreased (50%

Table 8-21. Clinical and Laboratory Features of Heavy Chain Diseases

Disease (type of heavy chain)	*Age*	*Clinical and Laboratory Features*
Alpha chain disease (Ig alpha)	Young adults, peak age = 20–30	Severe malabsorption, chronic diarrhea, abdominal pain, and mesenteric adenopathy
Gamma chain disease (Ig gamma)	Older adults, median age = 64	Weakness, fatigue, fever, lymphadenopathy, hepatosplenomegaly, anemia, leukopenia, thrombocytopenia, and hypogammaglobulinemia
Mu chain disease (Ig mu)	Median age = 48 years	Long history of chronic lymphocytic leukemia, myeloma, or amyloidosis

of cases)

- Monoclonal protein present in urine in approximately 80% of cases
- Bleeding time and platelet function often abnormal
- Rouleaux typically present in peripheral blood smear
- Lymphocytosis with circulating neoplastic lymphocytes with features consistent with CLL or lymphoplasmacytic lymphoma present in approximately 30% of all cases

Immunohistochemistry and Flow Cytometry

- Cases associated with lymphoplasmacytic lymphoma demonstrate monoclonal cytoplasmic expression of kappa or lambda light chain in paraffin
- Neoplastic lymphoid cells of lymphoplasmacytic lymphoma typically express HLA-DR, CD19, CD20, CD22, and react with plasma cell antibodies PCA-1 and PC-1 CD9 and CD24 expression may be found in some cases

Microscopic

- Bone marrow involved by neoplastic proliferation of lymphoid cells in 85% of cases
- Most common underlying lymphoproliferative disorders are lymphoplasmacytic B-cell lymphoma or small lymphocytic lymphoma/CLL (B-cell type)
- Lymphoplasmacytic B-cell lymphoma characterized by neoplastic proliferation of small B-cells with variety of morphologies ranging from small lymphocytes to well-developed plasmacytoid lymphocytes that may contain intranuclear immunoglobulin inclusions
- Pattern of marrow involvement typically interstitial
- Degree of marrow involvement ranges from focal involvement to diffuse bone marrow replacement
- Rare cases are associated with other lymphoproliferative disorders such as follicular lymphoma and multiple myeloma

Differential Diagnosis

- Multiple myeloma
- Smoldering myeloma

Prognosis and Treatment

- Frequently chronic, slowly progressive disease; median survival = 5 years
- Cause of death frequently related to hyperviscosity (hemorrhage, infection, neurologic dysfunction)
- Primary treatment related to controlling underlying lymphoproliferative disorder
- Plasma exchange may be helpful for controlling hyperviscosity

HISTIOCYTIC DISORDERS

Langerhans' Cell Histiocytosis (Histiocytosis X)

Clinical

- Three clinical types of Langerhan's cell histiocytosis (LCH) are recognized:
  - Unifocal LCH:
    - Typically presents as solitary lytic bone lesion in child or young adult
    - Patients generally asymptomatic, usually present with bone pain or pathologic fracture or as incidental radiologic finding
    - Males affected more than females
  - Multifocal LCH (Hand-Schuller-Christian Disease or

Polyostotic Histiocytosis X):
  - Patients present with fever, rash, diabetes insipidus, exopthalmos, and recurrent otitis media
  - Approximately 50% have posterior pituitary or hypothalamic involvement causing diabetes insipidus
  - Approximately 30% have retro-orbital involvement causing exopthalmos
- Progressive Disseminated LCH (Letterer-Siwe Disease):
  - Presents in children <3 years old; may be present at birth
  - Patients present with diffuse maculopapular rash, splenomegaly, hepatomegaly, and multiple lytic bone lesions
  - Pulmonary involvement may be present

Laboratory

- Primary laboratory feature is multiple lytic bone lesions
- Cytopenias may develop secondary to splenomegaly or bone marrow infiltration in aggressive form of disease

Immunopheotype and Ultrastructure

- Langerhan's cells thought to be derived from antigen-presenting histiocytes
- Express S100 and CD1a (Leu-6) and weakly express CD45 (LCA) in paraffin sections
- CD4 expression may be demonstrated in frozen tissue
- Presence of intracytoplasmic Birbeck granule, a pentilaminar, rod-like structure that may be attached to cell membrane, is diagnostic ultrastructural feature

Microscopic

- Langerhan's cells appear as mature histiocytes
- They have eosinophilic cytoplasm and central grooved or indented nucleus (coffee bean nucleus) with dispersed chromatin and singe inconspicuous nucleolus
- Multinucleated forms may be present
- Langerhan's cells are usually admixed with polymorphous background cell population consisting of eosinophils, neutrophils, plasma cells, lymphocytes, and histiocytes with foamy cytoplasm
- Bone marrow lesions may be focal or large confluent lesions that replace normal marrow elements
- Lesions contain variable numbers of background cells; in rare instances, lesion may be composed entirely of Langerhan's cells
- Bone marrow involvement can also take form of subtle interstitial single cell infiltrate; immunohistochemistry facilitates recognition of this pattern of involvement

Differential Diagnosis

- Granulomas
- Hodgkin's disease
- Systemic mastocytosis

Prognosis and Treatment

- Prognosis for unifocal LCH is excellent:
  - Lesions either regress spontaneously or with low dose radiation therapy
- Prognosis for multifocal LCH is good:
  - Approximately 50% will have spontaneous remission; remainder typically show excellent response to chemotherapy
- Patients with progressive disseminated LCH have dismal prognosis if <6 months old:
  - Older patients may respond to aggressive chemotherapy, but significant number of patients have progressive disease that is refractory to chemotherapy

Storage Disorders

Gaucher's Disease

- Represents group of autosomal recessive disorders characterized by deficiency in glucocerobrosidase
- Three types of Gaucher's disease:
  - Type I (adult, nonneuropathic) is most common (80% of cases) and typically presents in young adulthood with hepatosplenomegaly and lytic bone lesions
  - Type II (acute neuropathic) and Type III (subacute neuropathic) present in early childhood with profound neurologic disorders

Laboratory

- Most patients with Type I present with peripheral blood cytopenias

Cytochemistry and Ultrastructure

- Typically show intense periodic acid-Schiff (PAS) and tartrate-resistant phosphatase positivity
- Cytoplasmic storage material comprised of membrane-bound structures containing hollow tubules evident by electron microscopy

Microscopic

- Large histiocytes with abundant pale-gray to blue fibrillar cytoplasm with "wrinkled tissue paper" appearance and small, centrally located nuclei
- May form focal marrow lesions or may diffusely replace normal marrow elements
- Foci of cells may show reticulin fibrosis or bone necrosis (latter particularly in spine and long bones)
- Preserved hematopoetic marrow may be hypercellular, with multilineage hyperplasia

Differential Diagnosis

- Langerhan's cell histiocytosis
- Hairy cell leukemia
- Marrow involvement by granulomatous disease
- Hemophagocytic syndrome

Prognosis and Treatment

- Type I disease is slowly progressive
- Type II and Type III disease are progressive diseases with severe neurologic impairment culminating in death during childhood
- Splenectomy may be required to treat hypersplenism
- Enzyme replacement therapy and, in selected cases, allogeneic bone marrow transplantation may be helpful in treating disease

Neimann-Pick Disease

- Several disease variants exist, all characterized by a deficiency in sphingomyelinase activity
- Typically presents early in childhood with severe psychomotor deficits and hepatosplenomegaly

Laboratory

- Cytopenias secondary to hypersplenism may be present

Electron Microscopy

- Membranous cytoplasmic structures resembling lamellated myelin (zebra bodies) may be evident in electron microscopy

Microscopic

- Characterized by large histiocytes with small central or eccentric nuclei and abundant "sea blue" finely vacuolated cytoplasm
- Cytoplasm may have a foamy appearance
- Marrow diffusely replaced by abnormal histiocytes; focal histiocytic lesions may also be present

Differential Diagnosis

- Hyperlipidemia
- Other storage disorders

Prognosis and Treatment

- Uniformly progressive disease that results in death early in childhood

Mucopolysaccaridoses

- Group of autosomal recessive diseases characterized by deficiency in enzyme required for degradation of glycosaminoglycans
- Cause varying degrees of mental retardation

Ultrastructure

- Lysosomes filled with lamellated inclusions (zebra bodies) may be detected by electron microscopy

Microscopic

- Large histiocytes with variably sized basophilic inclusions evident in marrow aspirate
- Biopsy sections show histiocytes dispersed as individual cells and small aggregates in marrow interstitium

Differential Diagnosis

- Systemic mastocytosis
- Other storage disorders

Prognosis and Treatment

- Prognosis depends on particular disease present; some, such as Hurler's disease, may be fatal
- Treatment generally supportive
- Enzyme replacement therapy by fibroblast transplantation may be helpful in some diseases

Hemophagocytic Syndrome (HPS)

Clinical

- Systemic disease caused by proliferation of activated benign histiocytes engaged in hemophagocytosis; usually associated with viral infection
- Patients present with acute onset of fever, malaise, hepatosplenomegaly, lymphadenopathy, rash, pulmonary infiltrates, and pancytopenia
- History of antecedent viral, or less commonly bacterial, infection often present
- May also occur as complication of lymphoma (most commonly panniculitic T-cell lymphoma and CD30+ ALCL)
- Rare familial form (familial erythrophagocytic lymphohistiocytosis) exists:
  - Patients typically present with similar symptoms in early childhood, related to perforin gene mutations

Laboratory

- Peripheral blood shows anemia and thrombocytopenia; neutropenia variably present
- Serologic evidence of liver dysfunction and disseminated intravascular coagulation is often present
- Serologic evidence of recent Epstein-Barr virus or cytomegalovirus infection is frequently present in spontaneous form of disease
- Hypertriglyceridemia is universally present in familial disease; may also be present in infection-associated disease
- Atypical lymphocytes may be present in peripheral blood

Microscopic

- Histiocytes with ingested red blood cells, platelets, and nucleated hematopoetic precursors may be present in bone marrow aspirate
- Bone marrow often hypocellular, with diffuse, interspersed histiocytes as both single cells and small aggregates
- Early in disease, marrow may be hypercellular, with trilineage hyperplasia and histiocytes may not be evident; stains for CD68 (PGM-1) may facilitate recognition in paraffin sections

- In severe cases, marked histiocytic infiltration with destruction of normal marrow elements may be present
- Granulomatous lesions and lymphoid aggregates may be present
- Histiocytic proliferation with erythrophagocytosis may also be noted in lymph node sinuses and hepatic and splenic sinusoids

Differential Diagnosis

- Infections associated with diffuse histiocytic infiltrates (histoplasmosis, leishmaniasis)
- Hodgkin's disease
- Storage disorders
- Langerhan's cell histiocytosis
- Marrow involvement by granulomatous disease

Prognosis and Treatment

- Infection-associated hemophagocytic syndrome is a rapidly progressive disease with a mortality rate of 30% to 40%
- Patients that survive typically recover in 1–8 weeks
- Familial form of disease is aggressive and usually rapidly fatal
- Chemotheraputic agents may be helpful in treating the infection-associated disease
- Bone marrow transplantation can cure the familial form of the disease

Pathogens Associated With Diffuse Histiocytic Marrow Infiltrates

Clinical

- Intracellular pathogens that infect histiocytes may be associated with diffuse histiocytic marrow infiltrates
- In endemic areas of the United States (Mississippi River valley and its tributaries), disseminated histoplasmosis is frequently associated with diffuse histiocytic marrow infiltrates
- Visceral leishmaniasis is a frequent cause of diffuse histiocytic marrow infiltrates in areas of the world where it is endemic (southern Europe, North Africa, Asia, and Asia Minor)
- In immunocompromised host, mycobacterium avium-intracellulare (MAI) may cause diffuse histiocytic marrow infiltrates

Laboratory

- Culture can be helpful in establishing a diagnosis of histoplasmosis, leishmaniasis, or MAI

Microscopic

- Bone marrow may be normocellular or hypercellular marrow histiocytic infiltrate is diffuse and interstitial
- Poorly formed granulomas may be present with both histoplasmosis and MAI
- MAI organisms will react strongly with stains for acid-fast bacilli (Zeihl-Neilsen, auramine-rhodamine)
- Differentiating amastigotes of leishmania from histoplasma in tissue sections may be difficult:
  - Histoplasma is Gomori-methamine silver + and amastigotes of leishmania are GMS and PAS –
  - Giemsa stains highlight nuclei and kinetoplasts of leishmania

Differential Diagnosis

- Hemophagocytic syndrome
- Storage disorders
- AIDS
- Granulomatous infections (see below)

Prognosis and Treatment

- Most (85%) of non-immunocompromised patients with disseminated histoplasmosis respond to therapy with agents such as flucytosine and amphotericin B
- Antimony compounds and pentamadine are agents of choice for the treatment of leishmaniasis
- Transfusion therapy may be required for anemia
- Bacterial superinfection may occur
- Antituberculous drugs may be helpful in reducing symptoms of disseminated MAI infection; however, this organism is generally resistant to treatment and disseminated infection carries a poor prognosis

Granulomatous Bone Marrow Infiltrates

Clinical

- Bone marrow granulomas may be seen in up to 7% of bone marrow biopsies performed for lymphoma staging that lack evidence of marrow involvement by lymphoma
- Bone marrow granulomas may be seen in marrows involved by lymphoma and may represent a host-immune response to tumor
- In most instances, bone marrow granulomas do not have demonstrable infectious pathogen
- A number of pathogens may cause bone marrow granulomas
- See Table 8-22
- Marrow granulomas may be seen in sarcoidosis

Laboratory

- There are varied laboratory methods used in the diagnosis of these disorders that are beyond the scope of this chapter
- Certain methods that can be performed on paraffin-embedded sections (cytochemistry, in situ hybridization) may be helpful in establishing pathogen in cases of infectious granulomatosis

Microscopic

Table 8-22. Pathogens Causing Bone Marrow Granulomas

Viral	EBV, HIV, CMV, viral hepatitis
Bacterial	Mycobacteria sp., brucellosis, tularemia
Fungal	Coccidiomycosis, histoplasmosis, cryptococcus
Protozoal	Toxoplasmosis
Other	Rickettsial infections (Rocky Mountain spotted fever, Q fever), mycoplasmosa

EBV = Epstein-Barr virus; HIV = human immunodeficiency virus-1; CMV = cytomegalovirus.

- Usually dispersed in marrow interstitium
- Granulomas of sarcoidosis are typically well-formed non-caseating granulomas with little associated chronic inflammation ("naked" granulomas)
- Granulomas of infectious disease may be caseating, but this is not always the case
- Granulomas consisting of epithelioid histiocytes surrounding a lipid droplet (fibrin-ring granuloma) are associated with Q fever, but may be seen in other conditions (brucellosis, EBV, CMV)

Differential Diagnosis

- Infections associated with disseminated histiocytic infiltrates
- Hodgkin's disease

Prognosis and Treatment

- Dependent on underlying disease process
- Detailed discussion regarding these for entities listed above are beyond the scope of this text

MISCELLANEOUS CONDITIONS

Bone Marrow Involvement by Metastatic Malignancy

Clinical

- In adult women, breast carcinoma is a malignancy that most commonly involves the bone marrow; up to 20% of patients with breast cancer will develop bone marrow metastases
- In men, prostatic carcinoma and lung carcinoma most commonly involve marrow
- Bone marrow metastases are found in approximately 15% to 20% of patients with prostatic carcinoma, marrow involvement is more frequent in patients with poorly differentiated carcinoma
- Of lung carcinomas, small cell carcinoma has the highest rate of marrow involvement, at approximately 20%
- Non-small cell carcinoma (adenocarcinoma and squamous cell carcinoma) involves marrow in approximately 5% to 15% of all cases
- In adults, gastrointestinal carcinomas also show a relatively frequent rate of bone marrow metastasis
- In children, neuroblastoma has the highest frequency of marrow involvement; approximately 70% of patients will develop bone marrow metastasis during the course of their disease:
  - Marrow involvement is commonly present at diagnosis
- Other childhood tumors that frequently involve bone marrow include Ewing's sarcoma, rhabdomyosarcoma, retinoblastoma, and medulloblastoma
- Most common symptoms related to bone marrow involvement are bone pain, palpable bony lesion, and pathologic fracture

Laboratory

- Peripheral blood may show leukoerythroblastic reaction characterized by presence of immature erythroid and granulocytic cells in peripheral blood
- Patients with (or without) carcinomatous marrow involvement (particularly with mucinous adenocarcinoma) may develop microangiopathic hemolytic anemia characterized by fragmented red blood cells, polychromatic red blood cells, and thrombocytopenia in peripheral blood:
  - Associated with consumption of serum coagulants leading to abnormally prolonged prothrombin and activated partial thromboplastin times (PT and

Table 8-23. Bone Marrow Findings in AIDS Patients

Histologic finding	*Comments*
Serous fat atrophy	Seen in 5% to 50%; more prominent in advanced disease; also seen in severely malnourished patients
Naked, pyknotic megakaryocyte nuclei	When numerous, suggestive of HIV infection; also seen in some myelodysplastic syndromes
Plasmacytosis	Seen in 30% to 80%; usually interstitial and polyclonal
Lymphoid aggregates	Seen in 10% to 50%; usually interstitial, large, poorly circumscribed, and contain atypical cells; may be difficult to distinguish from neoplastic infiltrate
Histiocytosis	Granulomas may be present due to secondary infection; mycobacterial infection may be associated with diffuse histiocytic infiltrate; diffuse histiocytic infiltrates may also be seen in absence of secondary infection
Megaloblastic differentiation	Seen frequently; exacerbated by zidovudine therapy; clonal hematopoetic stem cell disorders are typically not present
Red cell hypoplasia or aplasia	May be due either to infection with parvovirus B19 or to zidovudine therapy
Megakaryocytic hyperplasia	Usually reactive secondary to either immune-mediated thrombocytopenia or hypersplenism
Increased storage iron	Anemia of chronic disease (increased storage iron and anemia due to ineffective iron utilization) present in up to 85%
Neoplastic infiltrate	Most frequently B-cell lymphoma, Hodgkin's disease, acute leukemia, and rarely Kaposi's sarcoma may also be present

APTT), decreased fibrinogen, and elevated fibrin split products (FSPs)

- Presence of both leukoerythroblastic reaction and findings of microangiopathic hemolytic anemia are highly suggestive of bone marrow involvement
- Rarely, neoplastic cells may be present in peripheral blood; most common in children with neuroblastoma
- Hypercalcemia and elevated lactate dehydrogenase (LDH) may be present
- Radiographic studies are helpful in identifying bone marrow metastases

Microscopic

- In adults, neoplastic cells are rarely present in bone marrow aspirate due to encasement of tumor by desmoplastic fibrotic reaction
- Tumors of childhood are frequently present in both marrow aspirate and biopsy specimen
- Pattern of marrow involvement is highly variable and may be focal, diffuse, or both
- Malignant cells of metastatic carcinoma (excluding small cell carcinoma) are significantly larger than hematopoetic precursor cells and more readily identifiable
- Neoplastic cells of small cell carcinoma and blastic childhood neoplasms are similar in size to non-neoplastic immature myeloid precursors and may be difficult to distinguish from acute leukemic blasts in marrow specimens
- Myelofibrosis is a common secondary response to marrow involvement by metastatic malignancy; fibrosis may be focal or diffuse
- Bony trabeculae may be increased in size and bone density or there may be increased osteoclastic activity with resulting loss of bony trabeculae

Differential Diagnosis

- Marrow involvement by malignant lymphoma
- Agnogenic myeloid metaplasia
- AML
- ALL

Prognosis and Treatment

- Directly related to nature of primary disease process

Bone Marrow Findings in Patients With AIDS

Clinical

- Most patients with AIDS have hematologic manifestations attributable to their illness and its treatment
- HIV virus appears to have a primary role in causing hematologic abnormalities
- Secondary infectious pathogens and toxic effects of drugs (most notably zidovudine) also can cause hematologic abnormalities
- Hematologic abnormalities may be more severe in advanced disease
- A complete discussion of clinical features of HIV is beyond the scope of this text

Laboratory

- Number of peripheral blood abnormalities may be present; most common are lymphopenia (>90%), anemia (70% to 95%), thrombocytopenia (10% to 40%), and neutropenia (20% to 50%)
- Hypersplenism may be present, as may immune-mediated thrombocytopenia
- Clinical and laboratory features of disseminated intravascular coagulation may be present
- Immune-mediated mechanisms (autoantibodies to hematopoetic cells) may contribute to cytopenias

Histopathology

- Diverse bone marrow abnormalities are seen in AIDS patients (See Table 8-23)
- Bone marrow may be either hypercellular or hypocellular
- Hypocellularity is frequently attributable to the myelosuppressive effects of zidovudine (AZT)
- Megaloblastoid and myelodysplastic changes may be seen with HIV infection; however, they appear to be exacerbated by AZT

Differential Diagnosis

- Although none of the histologic features are specific for HIV infection, any combination of the above features, particularly when seen with serous fat atrophy and/or denuded, pyknotic megakarocyte nuclei, are highly suggestive of HIV infection

Prognosis and Treatment

- Cytopenias may be treated with either supportive transfusions or cytokine therapy
- Treatment of secondary malignancies is complicated by increased sensitivity of the marrow to chemotheraputic agents
- Overall prognosis is related to a combination of clinical and laboratory features

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Chapter 9

Dermatopathology

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Table of Contents

CUTANEOUS NEOPLASMS AND DEVELOPMENTAL ANOMALIES

Epithelial Neoplasms and Developmental Anomalies

Cystic Lesions: Neoplastic or Developmental

Epidermoid Cyst (Infundibular Cyst)

Clinical

- Dome-shaped lesions with central punctum; multiple lesions may be associated with Gardner's syndrome

Microscopic

- Dermal cyst with/without an epidermal connection lined by stratified squamous epithelium with a granular layer; cyst contains laminated keratin debris

Comedonal Cyst

Microscopic

- Similar to the epidermoid cyst but characterized by follicular plugging and hyperkeratosis; may be more superficial and typically has a larger epidermal ostia or punctum

Milia

Clinical

- Small white-yellow papules which may occur sporadically or in association with blistering diseases (epidermolysis bullosa, porphyria cutanea tarda, pemphigoid, etc.) which disrupt or occlude the eccrine ducts or hair follicles

Microscopic

- A small epidermoid-like cyst located in the superficial dermis

Steatocystoma

Clinical

- May occur in a solitary form (simplex) or as multiple lesions inherited in a autosomal dominant fashion (multiplex)

Microscopic

- An irregular, collapsed, intradermal cyst lined by a stratified squamous epithelium with an irregular, corrugated internal cuticle. Sebaceous glands are usually evident in the duct walls, and the cyst contains proteinaceous debris but no keratin

Dermoid Cyst

Clinical

- An embryonic closure defect which typically involves the skin lateral to the eye, the scalp, neck or near the mastoid process. Usually detected early in life

Microscopic

- A unilocular dermal or subcutaneous cyst lined by stratified squamous epithelium and having hair follicles, glands and, sometimes, smooth muscle in the cyst wall

Cysts Associated with Branchial Cleft Deformities

Clinical

- Cystic lesions may be formed in and around the ear in association with branchial cleft deformities. These differ from the branchial cleft cyst of the neck by their location and their microscopic

Microscopic

- May be similar to an epidermoid cyst except for their tendency to collapse and assume a multiloculated appearance. Other forms, in addition to the above, have adnexal structures and even cartilage within their walls

Branchial Cleft Cyst

Clinical

- A developmental anomaly presenting as a cyst in the lateral aspect of the neck

Microscopic

- A lymphoepithelial cyst characterized by a stratified squamous or a pseudostratified ciliated lining with a dense lymphocytic infiltrate with germinal centers in the wall

Eruptive Vellus Hair Cyst

Clinical

- Small flesh-colored papules in children and young adults

Microscopic

- An epidermoid-like cyst that contains numerous, small vellus hairs

Pigmented Terminal Hair Cyst

Microscopic

- An epidermoid-like cyst containing numerous pigmented, terminal hairs

Trichilemmal (Pilar) Cyst

Clinical

- Dome shaped papules/nodules found predominantly on the scalp; may be single or multiple

Microscopic

- A dermal or subcutaneous cyst lined by an eosinophilic stratified squamous epithelium that lacks a granular layer. The cyst contents are composed of solid, nonlaminated keratin

Proliferating Trichilemmal Cyst/Tumor

Clinical

- Multinodular scalp lesion more common in females

Microscopic

- Well-defined, multilobular tumor with trichilemmal keratinization; dense fibrous tissue surrounds the individual lobules; cystic areas may be inconspicuous
- Malignant forms occur but are rare
- More marked infiltration, cytologic atypia and mitotic activity characterize the malignant variants

Bronchogenic Cyst

Clinical

- A developmental cyst usually found near the precordium early in life

Microscopic

- This cystic lesion attempts to recapitulate the bronchi with a cyst lined by respiratory epithelium and a cyst wall with smooth muscle, glands and/or cartilage

Thryoglossal Duct Cyst

Clinical

- A developmental cyst found in the midline of the neck, near the hyoid bone

Microscopic

- The cyst may be lined by cuboidal, columnar or stratified squamous epithelium
- The cyst wall contains thyroid follicles with or without skin appendages and lymphocytic inflammation
- Smooth muscle and cartilage are absent

Cutaneous Ciliated Cyst

Clinical

- Usually found on the lower extremities or buttocks of reproductive aged women

Microscopic

- Ciliated, cuboidal to columnar lined, multiloculated cyst surrounded by fibrous tissue
- No endometrial or fallopian tube type stroma is evident within the cyst walls

Endometriosis and Endosalpingiosis

Clinical

- Blue-red cysts/nodules most commonly seen in the vulvar or periumbilical regions of reproductive aged females

Microscopic

- Similar to the cutaneous ciliated cyst except that the cyst wall contains endometrial/fallopian tube type stroma with or without hemosiderin deposition

Hidrocystoma

Microscopic

- Unilocular or multilocular cysts lined by either apocrine or eccrine epithelium
- Apocrine: decapitation secretion (apical snouts) and a myoepithelial layer; may have papillary projections
- Eccrine: a two-layered cuboidal epithelium with no myoepithelial layer or decapitation secretion

Hybrid Cyst

Microscopic

- A cystic lesion combining the histologic features of more than one cyst type, usually trichilemmal and epidermoid cysts

Digital Mucous Cyst

Clinical

- A fluctuant, sometimes tender, translucent nodule of the digits

Microscopic

- Dermal mucin deposited into a cyst-like space that may or may not also contain fibroblasts and collagen
- There is no true epidermal lining, and the cystic spaces may be multiloculated

Oral Mucocele

Clinical

- A translucent, blue nodule usually found on the lower lip

Microscopic

- A cystic space containing varying degrees of central mucin and lined by chronic inflammatory cells with numerous foamy histiocytes
- There is no true epithelial lining

Epidermal Tumors and Proliferations

Actinic Keratosis (Senile, Solar)

Clinical

- White-yellow, erythematous and scaly patches or plaques on sun damaged skin; some may be pigmented

Microscopic

- While a variety of histologic types exist, all have in common epidermal dysplasia, which may also involve the hair follicles
- Hyperplastic, atrophic, acantholytic, epidermolytic, lichenoid, pigmented, bowenoid and clear cell catego-

ries exist and reflect additional alterations to the dysplastic epidermis (e.g. lichenoid variant= actinic keratosis with a band-like lymphocytic inflammatory infiltrate; bowenoid variant= actinic keratosis with full thickness dysplasia= carcinoma in-situ)

Benign Lichenoid Keratosis (Lichen Planus-Like Keratosis)

Clinical

- Solitary papule or plaque found primarily on the trunk or upper extremities

Microscopic

- Very similar to lichen planus with a dense band-like lymphocytic infiltrate at the dermal-epidermal interface with basilar vacuolar degeneration and cytoid bodies
- In contrast to lichen planus, eosinophils and parakeratosis may be seen
- In contrast to a lichenoid actinic keratosis, there is no keratinocyte dysplasia

Seborrheic Keratosis

Clinical

- Brown, elevated and sharply demarcated lesions which occur most commonly on the face, trunk and upper extremities
- These benign tumors often have a "stuck on" appearance and are more common in middle aged and older adults
- The sudden appearance of numerous seborrheic keratosis in association with visceral malignancy is referred to as the Leser-Trelat sign

Microscopic

- An epidermal proliferation of bland basaloid and polygonal keratinocytes associated with prominent keratin cyst formation
- The lesion is sharply delineated at its base and appears to grow up from the epidermis
- Irritated forms demonstrate more endophytic growth and form numerous squamous eddies
- Acanthotic, adenoid, clonal, pigmented and hyperkeratotic variants exist

Inverted Follicular Keratosis

Microscopic

- An endophytic epidermal growth with numerous squamous eddies which, like seborrheic keratosis, is sharply delineated but is centered on the hair follicles
- Note: this entity is considered a variant of seborrheic keratosis by some experts and a viral induced lesion by others

Warty Dyskeratoma

Clinical

- A benign, solitary, umbilicated nodule or papule on sun-exposed skin

Microscopic

- A hair follicle centered, endophytic squamous proliferation which is sharply delineated
- The base of the lesion typically reveals elongated trabeculae with varying degrees of dyskeratosis that underlies broad areas of acantholytic dyskeratosis located immediately below a keratin-filled, central crater

Linear Epidermal Nevus

Clinical

- Localized and systemic forms exist and are characterized by a linear arrangement of closely set papillomatous papules
- The systemic form may be associated with other defects, including skeletal and central nervous system abnormalities

Microscopic

- Both variants demonstrate epidermal papillomatosis, acanthosis and hyperkeratosis
- Many histologic variants exist, but, importantly, the presence of epidermolytic hyperkeratosis may be associated with systemic involvement

Nevus Comedonicus

Clinical

- Comedo-like papules with a central keratin plug usually in a linear arrangement on the palms, soles or other sites

Microscopic

- Deep epidermal invaginations with laminated keratin similar to a comedo
- Epidermolytic hyperkeratosis may be evident

White Sponge Nevus

Clinical

- Extensive, white patches and plaques involving mucosal sites (chiefly oral but also vaginal, rectal and esophageal) which are evident early in life and are inherited in an autosomal dominant pattern

Microscopic

- There is acanthosis and pallor of the mucosal lining due to prominent cytoplasmic clearing (intracellular edema) of the suprabasilar keratinocytes
- Similar changes are seen in leukoedema and pachyonychia congenita

Leukoedema

Clinical

- Patchy white plaques and patches of the oral mucosa with an adult onset
- These lesions remit and recur and are not inherited

Microscopic

- Similar to white sponge nevus from which it differs by clinical grounds

Geographic Tongue (Lingua Geographica)

Clinical

- Irregular, erythematous patches with white borders on the tongue

Microscopic

- The erythematous areas show loss of the normal granular and horny layers while the white areas demonstrate acanthosis with neutrophilic inflammation

Clear Cell Acanthoma

Clinical

- Solitary, slowly growing nodules or plaques with an oozing surface
- These lesions are most common on the lower extremities

Microscopic

- A plate-like epidermal thickening by a proliferation of clear, heavily glycogenated keratinocytes
- The tumors are sharply demarcated from the adjacent epidermis (eyeliner sign) and, characteristically, have neutrophils scattered throughout the proliferation, an important feature in separating this entity from other tumors with a plate-like growth pattern

Large Cell Acanthoma

Clinical

- Erythematous patches on sun-exposed skin

Microscopic

- A sharply defined epidermal proliferation of enlarged, pale keratinocytes with mild dysplasia
- Comment: these lesions are aneuploid and are best considered to be a variant of actinic keratosis

Squamous Cell Carcinoma *In-Situ* (Bowen's Disease)

Clinical

- Erythematous, irregular, scaly patches and plaques that may involve any skin surface as well as the mucous membranes
- Bowen's disease of the penis is often referred to as erythroplasia of Queyrat
- Sun-exposure, arsenic and other chemicals are associated with and increased risk of development of Bowen's disease
- Approximately 5% of these lesions develop an invasive component

Microscopic

- Epidermal acanthosis associated with full thickness epidermal dysplasia, which may involve the adnexa
- A dense lichenoid inflammatory infiltrate may also be present
- Intraepidermal spread (Borst-Jadassohn phenomena) may be prominent and should be differentiated from melanoma and Paget's disease

Bowenoid Papulosis

Clinical

- Red-brown papules or plaques on the external genitalia and perineum of young adults
- Lesions are frequently multiple, and there is a strong association with Human Papilloma Virus (HPV) types 16 and 18 with other types occurring less frequently
- Unlike Bowen's disease, these lesions may regress and are less likely to give rise to an invasive carcinoma

Microscopic

- Fairly discrete areas of epidermal acanthosis associated with varying degrees of epidermal dysplasia, koilocytosis, hypergranulosis and parakeratosis
- In-situ carcinoma may be present

Squamous Cell Carcinoma

Clinical

- Indurated, hyperkeratotic nodules which may show ulceration or verruciform changes
- Currently, squamous cell carcinoma is the second most common cutaneous malignancy
- The incidence is increasing
- While most are related to sun exposure, other risk factors include fair complexion, chronic inflammation, immunosuppression, burns, HPV infection and chemical exposure (e.g. arsenic)
- The overall rate of metastases is approximately 5% but is >10% at mucosal sites and the ear

Microscopic

- Atypical nests of epidermoid cells invasive into the dermis and, usually, with overlying epidermal dysplasia
- Differentiation varies from poorly differentiated (minimal keratin production, marked nuclear pleomorphism, high mitotic rate) to well differentiated (abundant keratin pearl formation, minimal cytologic atypia and few mitoses)

- The presence of keratin production, intercellular desmosomes ("spines") and overlying epidermal dysplasia are useful features in separating this tumor from other entities
- Variants include clear cell, spindle cell, acantholytic and verrucous tumors

Verrucous Carcinoma

Clinical

- A variant of squamous cell carcinoma that typically appears as a large hyperkeratotic nodule
- All cutaneous surfaces may be involved but plantar, oral (oral florid papillomatosis) and anogenital lesions are particularly common
- These tumors frequently recur but have little metastatic potential

Microscopic

- An endophytic and exophytic growth of well-differentiated squamous epithelium with extensive keratinization
- The deep component shows a broad, pushing front at its advancing edge
- If any significant nuclear dysplasia is present, a diagnosis of squamous cell carcinoma should be made

Keratoacanthoma

Clinical

- A rapidly growing, umbilicated nodule with a central keratin plug
- Multiple lesions may be present
- Typically, these tumors regress over the course of a few months, but they may recur
- These tumors are considered to be a variant of squamous cell carcinoma by some experts

Microscopic

- A well-defined, sharply demarcated, craterform squamous proliferation with a central keratin plug
- The squamous epithelium frequently has a glassy appearance and lacks significant cytologic atypia
- A lichenoid inflammatory infiltrate may be present
- The presence of cytologic atypia, infiltrative borders or atypical mitoses warrants a diagnosis of a squamous cell carcinoma

Pilar and Pilosebaceous-Derived Tumors

Dilated Pore of Winer

Clinical

- Flesh colored papule or cyst with a central keratotic plug found chiefly on the head and neck

Microscopic

- A cone-shaped dilatation of the follicular infundibulum with a central keratin plug
- The wall of the pore is proliferative with finger-like projections extending into the adjacent dermis
- No secondary hair follicles are evident within the cyst wall

Pilar Sheath Acanthoma

Clinical

- Small nodule with a central keratin filled pore on the upper lip

Microscopic

- Similar in architecture to the dilated pore but with a more proliferative wall
- The epithelium of the wall is paler than that of the dilated pore and may have some degree of peripheral palisading suggesting abortive hair follicle development
- No well-developed secondary hair follicles with hair formation are evident

Trichofolliculoma

Clinical

- Solitary, flesh-colored nodules with a central pore from which numerous white hairs emerge

Microscopic

- Similar to the dilated pore, a central, elongated and dilated infundibulum is present
- Numerous secondary hair follicles radiate peripherally from the central cavity that is filled with laminated keratin and numerous hairs
- If sebaceous glands are evident within the secondary follicles, than a diagnosis of a sebaceous trichofolliculoma is appropriate

Tumor of the Follicular Infundibulum

Clinical

- Small, hyperkeratotic papules or plaques on the head and neck

Microscopic

- A plate-like expansion of the epidermis by interanastomosing and interweaving trabeculae of glycogenated squamous epithelium within the superficial dermis
- The trabeculae show multiple attachments to the epidermis and to the hair follicles
- The trabeculae may show some peripheral palisading but lack mucin deposition or stromal retraction
- Elastic fibers are often condensed at the base of the lesion

Differential Diagnosis

- Fibroepithelioma of Pinkus and eccrine syringofibroadenoma

- Fibroepithelioma of Pinkus has narrower trabeculae with more pronounced basaloid differentiation while eccrine syringofibroadenoma shows scattered eccrine ducts within its trabeculae

Basaloid Follicular Hamartoma

Clinical

- Small, flesh-colored papules or plaques on the head and neck
- Solitary, multifocal and inherited variants have been described

Microscopic

- Small, starfish or octopus-like proliferations of basaloid cells within the dermis arranged as anastamosing trabeculae with peripheral palisading and surrounding fibrosis

Trichilemmoma

Clinical

- Verrucous, hyperkeratotic papules usually found on the face
- Multiple trichilemmomas occur in the autosomal dominant disorder, Cowden's disease

Microscopic

- A single lobule or, occasionally, a multilobular proliferation of round, clear (glycogen rich) squamous cells giving a plate-like thickening to the epidermis
- There is usually a follicular accentuation to the proliferation with the pale cells growing down pre-existing follicular structures
- The lobules are surrounded by a PASD positive basement membrane
- A desmoplastic variant exists which, in addition to typical trichilemmoma areas, has central trabeculae surrounded by a dense, hypocellular stroma

Trichoadenoma

Clinical

- Yellow to flesh-colored papule on the face

Microscopic

- Numerous keratin filled cysts lined by a stratified squamous epithelium are evident within the dermis
- A granular layer is present (epidermoid keratinization), and the cysts have a surrounding fibrous stroma
- Solid trabeculae are rare

Trichoepithelioma

Clinical

- Small flesh-colored papules on the face of young to middle aged adults
- Solitary, desmoplastic and multiple (autosomal dominant inheritance) variants exist

Microscopic

- An admixture of keratin filled cysts and trabeculae of basaloid cells with peripheral palisading and a surrounding fibrous stroma
- Stromal retraction is not evident, and true hair bulb formation is rarely seen

Differential Diagnosis

- Keratotic basal cell carcinoma is different from trichoepithelioma by having stromal retraction, mucin deposition, individual cell necrosis and numerous mitoses
- Microcystic adnexal carcinoma differs from desmoplastic trichoepithelioma by the presence of deeper infiltration with eccrine ducts lined by an eosinophilic cuticle. A layered appearance with cysts predominating superficially and trabeculae predominating at the deep aspect of the tumor are characteristic

Trichoblastoma

Clinical

- A controversial entity having histologic and clinical overlap with trichoepithelioma and basal cell carcinoma

Microscopic

- A proliferation of germinative basaloid cells arranged in nests, sheets or trabeculae
- Conspicuous hair bulb differentiation is seen at the edge of the nests or sheets but also as single, primitive hair follicle- like structures surrounded by a dense fibrous sheath
- Stromal clefting and extensive mucin deposition are typically absent

Differential Diagnosis

- Basal cell carcinoma shows stromal clefting, mucin deposition, single cell necrosis and lacks primitive hair bulb structures
- Trichoepithelioma has admixed keratin-filled cysts and has few to no primitive hair bulbs

Trichodiscoma

Clinical

- A hamartomatous proliferation of the hair disc which presents as multiple flesh-colored papules on the face and also elsewhere on the body

Microscopic

- A nodular mesenchymal proliferation surrounded by an epidermal collarette

- Centrally there are stellate fibroblasts embedded in collagen, reticulin and elastic fibers with abundant mucin deposition
- Thin walled vessels with prominent basement membranes are seen within the proliferation

Perifollicular Fibroma and Fibrofolliculoma

Clinical

- Both occur as solitary and, more often, multiple flesh-colored papules on the face or neck

Microscopic

- Perifollicular fibromas show a loose, concentric proliferation of fibrous tissue around normal hair follicles while fibrofolliculomas show both a fibrous and a follicular proliferation centered on a dilated follicle
- The epithelial component of the latter consists of epithelial trabeculae that arise from the infundibulum and are surrounded by fibrous tissue

Pilomatricoma (Calcifying Epithelioma of Malherbe)

Clinical

- Deep-seated, frequently calcified nodules on the head, neck and upper extremities of children and young adults
- These lesions may be solitary or multiple (autosomal dominant inheritance) or may be a marker of a systemic disease (Gardner's syndrome)

Microscopic

- A cystic or multinodular tumor with a biphasic epithelial growth pattern consisting of eosinophilic, ghosts or shadow cells centrally and basophilic, basaloid cells peripherally
- Granulomatous inflammation and calcification are frequent and may obscure the characteristic growth pattern

Basal Cell Carcinoma

Clinical

- Well-delineated, pearly, translucent, pink-tan papules or nodules with telangiectasia
- Superficial, nodular/ulcerative, pigmented, diffuse, morpheaform and fibroepitheliomatous variants exist
- Most are found on sun-exposed skin of the elderly, but occasional cases are evident on non-sun-exposed skin
- Basal cell carcinoma is currently the most common cutaneous malignancy, and the incidence is increasing
- Risk of developing basal cell carcinomas is related to sun-exposure and skin type
- Multiple tumors are seen in Basex syndrome and basal cell carcinoma- nevus syndrome (Gorlin's syndrome), an autosomal dominant inherited disease also having odontogenic keratocysts, palmar-plantar pits, ectopic calcification and skeletal abnormalities
- Basal cell carcinoma has little tendency to metastasize

Microscopic

- A proliferation of atypical basaloid cells in nests, trabeculae and/or cysts within the dermis but often demonstrating multifocal epidermal attachment
- Peripheral palisading, stromal retraction, mucin deposition, single cell necrosis and mitoses are characteristic and are useful in separating this tumor from other entities
- Nodulocystic, metatypical (keratotic), pigmented, adenoidal, infiltrating, superficial and morpheaform histologic variants exist with the latter two having an increased risk of recurrence

Fibroepithelioma of Pinkus

Clinical

- Polypoid or plaque-like lesions on the thigh or trunk
- Considered a premalignant lesion by many experts

Microscopic

- Interanastomosing epithelial strands with multiple points of attachment to the epidermis and surrounded by a fibrous stroma
- The trabeculae are thinner than tumor of the follicular infundibulum, being 2-3 epithelial cells in thickness

Malignant Pilomatricoma

Clinical

- A rare tumor occurring as tumors or nodules on the face

Microscopic

- Similar to a benign pilomatricoma but showing areas with infiltration, mitoses and nuclear pleomorphism

Nevus Sebaceous

Clinical

- Single or multiple, yellow papules to plaques with or without verruciform features on the head and neck of infants, adolescents and young adults
- A linear form exists
- Nevus sebaceous with cerebral abnormalities is referred to as the nevus sebaceous syndrome
- Basal cell carcinoma is the most common malignancy associated with nevus sebaceous while syringocystadenoma papilliferum is the most common benign proliferation associated with this condition

Microscopic

- The epidermis frequently demonstrates papillomatosis or verruciform change
- Numerous immature or abortive hair follicles are situated within the superficial dermis with a reduction in the number of mature terminal hairs
- The sebaceous glands appear haphazardly distributed within the dermis and may appear atrophic, hyperplastic or relatively normal in size
- Apocrine glands are a frequent finding in the deep dermis

Sebaceous Hyperplasia

Clinical

- Small yellow papules on the face and forehead of older adults

Microscopic

- Enlarged, hyperplastic sebaceous glands emptying into a central hair follicle often situated in the superficial dermis

Sebaceous Adenoma

Clinical

- Pink to yellow papules on the face and neck of older adults
- Multiple lesions are often associated with visceral malignancy (Muir-Torre syndrome)

Microscopic

- A multilobulated tumor often showing attachment to or emptying through the overlying epidermis
- The lobules are composed of basaloid cells peripherally and multivacuolated cells centrally
- By definition, the basaloid cells comprise less than 50% of cells of the individual lobules
- Infiltration, necrosis and frequent mitoses are absent

Sebaceous Epithelioma

Clinical

- Similar to sebaceous adenoma

Microscopic

- A faintly lobular tumor similar to the sebaceous adenoma
- Basaloid cells comprise more than 50% of the cells in the individual lobules
- While occasional mitotic figures may be seen, abundant mitotic activity, infiltration, nuclear pleomorphism or necrosis should lead to a consideration of sebaceous carcinoma or basal cell carcinoma with sebaceous differentiation

Sebaceous Carcinoma

Clinical

- Ulcerated or non-ulcerated nodules on the head and neck region of older adults
- The periocular region is a particularly common site where derivation from the meibomian gland occurs
- These tumors are associated with a high metastatic potential and increased mortality (~25%)

Microscopic

- These tumors may show irregular lobules or a diffuse infiltrating pattern
- Attachment to the overlying epidermis may be present, and pagetoid spread is common in the periocular variants
- These tumors show a spectrum of sebaceous differentiation varying from tumors composed predominantly of basaloid cells to tumors with numerous multivacuolated sebaceous cells
- Infiltration, necrosis, nuclear pleomorphism, nucleoli and mitoses are usually readily evident
- Perineural and capillary-lymphatic space invasion may be seen

Immunophenotype

- Cytokeratin and EMA+; S100 and CEA-

Eccrine-Derived Tumors and Proliferations

Syringoma-Like Proliferations Associated with Alopecia

Clinical

- No specific clinical findings are associated with this lesion which presents simply as alopecia of any etiology

Microscopic

- This is a relatively rare, apparently, non-neoplastic proliferation of the eccrine ducts in response to alopecia
- The microscopic is that of the particular form of alopecia affecting the patient with the addition of a diffuse, haphazard proliferation of the eccrine ducts limited to the mid and upper dermis
- Ducts, trabeculae, comma and tadpole-shaped forms may all be seen
- No nuclear pleomorphism or perineural invasion is evident, but mitotic figures may be seen
- This proliferation may be seen throughout the scalp in cases of severe alopecia

Differential Diagnosis

- Syringoma is usually a more localized and circumscribed eccrine proliferation and lacks the haphazard appearance of the above

- Microcystic adnexal carcinoma and eccrine syringoid carcinoma are more infiltrative lesions that typically involve the lower dermis and the subcutis and show frequent perineural invasion

Eccrine Syringofibroadenoma

Clinical

- Single or multiple papules or nodules with a wide age range and distribution
- The extremities are most commonly involved

Microscopic

- Interanastomosing cords and trabeculae of epithelial cells extending into the dermis with multiple points of attachment to the epidermis
- The cords are thin and surrounded by a fibrous stroma
- Scattered throughout the epithelial cords are areas of eccrine duct differentiation with prominent eosinophilic cuticles

Differential Diagnosis

- Tumor of the follicular infundibulum and fibroepithelioma of Pinkus lack eccrine differentiation

Syringoma

Clinical

- Multiple flesh-colored or faintly yellow papules on the eyelids or upper face
- Other sites may also be involved, and linear and eruptive variants occur
- Clear cell variants may be associated with diabetes

Microscopic

- A fairly well circumscribed but unencapsulated neoplasm involving the mid to upper dermis composed of eccrine derived cords and ducts
- The cords may show characteristic tadpole shaped forms
- Two or more cell layers with an internal eosinophilic cuticle and varying degrees of clear cell change line the ducts
- In general, the tumor does not infiltrate the deep dermis or subcutaneous fat, lacks mitotic activity and necrosis and has no significant pleomorphism

Immunophenotype

- Eccrine-derived tumors typically stain positively for the cytokeratins, EMA and CEA, which highlights the luminal aspect of the eccrine ducts

Differential Diagnosis

- Desmoplastic trichoepithelioma has numerous keratotic cysts, frequent calcification and lacks eccrine duct formation
- Microcystic adnexal carcinoma is much more infiltrative and typically involves the deep dermis and subcutaneous fat

Chondroid Syringoma (Benign Mixed Tumor)

Clinical

- A benign, slowly growing, typically solitary tumor nodule on the head and neck; other sites may be involved

Microscopic

- A well-circumscribed, biphasic tumor nodule located within the dermis and/or the subcutaneous fat
- Epithelial cords, trabeculae and ducts are embedded in an abundant myxoid, fibromyxoid or cartilaginous matrix
- The epithelial component lacks nuclear pleomorphism, infiltration, necrosis and mitotic activity
- The ducts may show eccrine and/or apocrine differentiation

Differential Diagnosis

- Pleomorphic adenoma (benign mixed tumor of the salivary glands) should be differentiated from chondroid syringoma because of its tendency to recurrence and, possibly, malignant transformation
- As these tumors are similar histologically, location and the presence of adjacent normal salivary glands are the most reliable features used to separate these entities

Malignant Chondroid Syringoma

Clinical

- A rare, highly malignant tumor with a predilection for the distal extremities
- These tumors frequently recur and metastasize and are associated with increased mortality

Microscopic

- Malignant appearing, infiltrating epithelial cords, ducts and sheets that overgrow the benign mesenchymal matrix
- Necrosis, mitoses and nuclear pleomorphism are present
- An adjacent benign mixed tumor is not typically seen

Differential Diagnosis

- Carcinosarcoma shows a malignant mesenchymal component in addition to an epithelial malignancy

Papillary Eccrine Adenoma

Clinical

- A firm, pink to tan nodule on the distal extremities of adolescents and young adults with a female predominance
- Blacks are more commonly affected than whites

Microscopic

- A fairly well circumscribed but unencapsulated proliferation of eccrine ducts and duct-like structures within the dermis
- The ducts are lined by a multilayered cuboidal epithelium without apical snouts
- Micropapillary projections and transluminal bridging may be seen
- The tumor stroma is fibrotic and frequently hyalinized. Cribiform structures, necrosis, mitotic activity and nuclear pleomorphism are absent

Differential Diagnosis

- Aggressive digital papillary adenoma/adenocarcinoma (see below)

Aggressive Digital Papillary Adenoma/Adenocarcinoma

Clinical

- Asymptomatic flesh-colored nodule on the digits of middle aged adults
- The recurrence rate is approximately 50% for these tumors, and the overtly malignant lesions have a metastatic rate of approximately 25-40%

Microscopic

- Generally, an unencapsulated and poorly circumscribed proliferation of eccrine ducts, tubules, cysts and nests within the dermis and/or subcutaneous fat
- The ducts and cystic structures are lined by a multilayered epithelium with abundant micro- and macropapillae
- Cribiform structures are frequently identified
- Varying degrees of nuclear pleomorphism, mitotic activity and necrosis may be seen
- Tumor grade correlates with metastatic potential, but all forms may metastasize
- Note: all of these lesions are best classified as adenocarcinomas due to their propensity for recurrence
- A histologic grade should be given as a prognostic indicator for the risk of metastases

Differential Diagnosis

- Papillary eccrine adenoma does not show the infiltration, nuclear atypia, mitotic activity or the cribiforming of the aggressive digital papillary adenocarcinoma

Nodular Hidradenoma (Clear Cell Hidradenoma, Solid-Cystic Hidradenoma and Eccrine Acrospiroma)

Clinical

- Solid or cystic, intradermal nodule 0.5-2.0cm in diameter
- These tumors are usually solitary but may be multiple
- The head, neck and extremities are most commonly involved
- Predominates in young adults with a slight female predominance

Microscopic

- A well-circumscribed and often pseudoencapsulated tumor composed of a single lobule or, more often, multiple lobules of eosinophilic to clear cells in the dermis
- Cystic change may be prominent
- Tubular structures lined by cuboidal to columnar cells with an eosinophilic cuticle are evident in most tumors and are important in proper classification
- Foci of squamous and/or mucinous differentiation may be seen
- While this tumor is predominantly intradermal, occasional attachments may be seen to the overlying epidermis
- Necrosis, mitotic activity and nuclear pleomorphism are absent or minimal in extent

Hidradenocarcinoma (Malignant Nodular Hidradenoma)

Clinical

- Similar distribution to their benign counterparts but occur in older individuals (>50 years of age)
- Recurrence and metastatic rate is approximately 50%

Microscopic

- Like the hidradenoma, this tumor is composed of eosinophilic and/or clear cells forming lobules within the dermis
- The malignant variants, however, are asymmetrical, infiltrating, mitotically active and demonstrate nuclear pleomorphism and/or necrosis

Differential Diagnosis

- Clear cell squamous cell carcinoma, clear cell renal cell carcinoma, clear cell melanoma and trichilemmal carcinoma
- Look for tubular structures with an eosinophilic cuticle to confirm eccrine differentiation; CEA may be useful in that it highlights the luminal border of eccrine-derived structures

Hidroacanthoma Simplex (Intraepidermal Poroma)

Clinical

- A rare, benign variant of poroma typically involving the extremities of older individuals

Microscopic

- An intraepidermal proliferation (Borst-Jadassohn phenomenon) of round to faintly spindled cells with eosinophilic to faintly clear cytoplasm

- Intracytoplasmic glycogen is evident on PAS staining
- Rare eccrine ducts/tubules may be seen
- The individual cells are remarkably uniform and lack nuclear atypia
- The tumor cells are sharply demarcated from the squamous cells of the adjacent epidermis

Eccrine Poroma

Clinical

- A red to flesh-colored tumor found most frequently on the sole of the foot or hand, but other sites may be involved
- These tumors may reach many centimeters in diameter and may be pedunculated
- While the majority of these tumors are solitary, multiple lesions may be seen (eccrine poromatosis)

Microscopic

- This tumor is composed of numerous cords or trabeculae of small rounded tumor cells which rain down form the epidermis into the dermis in a fairly circumscribed manner
- The epidermal component is similar to hidroacanthoma simplex while the dermal component often shows numerous well-formed lobules with frequently conspicuous duct formation
- Cystic change is typically less than that seen in hidradenoma while the degree of epidermal involvement is significantly greater
- The tumor cells show intercellular bridges and should not be confused with squamous cells that are larger and more polygonal
- Poromatous lesions that are entirely limited to the dermis are often call dermal duct tumors

Porocarcinoma (Malignant Eccrine Poroma)

Clinical

- The malignant counterpart to the eccrine poroma affects similar sites but tends to occur in older individuals with a long history of progressive tumor growth
- The recurrence and metastatic rate approaches 25%
- Multiple cutaneous metastases are not uncommon

Microscopic

- Like their benign counterparts, epidermal, dermal and mixed epidermal-dermal variants are seen
- The epidermal variants and the cutaneous metastases typically show frank pagetoidosis with scattered foci of ductal differentiation
- The mixed variants are by far the most common and have a similar architecture to their benign counterpart; however, these tumors are infiltrative, mitotically active and demonstrate nuclear pleomorphism and occasionally perineural and capillary-lymphatic invasion

Cylindroma and Malignant Cylindroma

Clinical

- Solitary or multiple, red to purple nodules on the head, neck or scalp
- Multiple tumors (turban tumors) are inherited in a autosomal dominant fashion and may be associated with multiple trichoepitheliomas

Microscopic

- Multiple, dermal based lobules are found in the dermis and have an interlocking or "jigsaw puzzle" appearance
- The individual lobules are surrounded by an eosinophilic basement membrane
- Two cell types are evident within the lobules: a lymphocyte-like population of cells with hyperchromatic nuclei which predominate at the periphery of the lobules and a population of larger cells with oval, vesicular nuclei which predominate centrally
- Hylanizing basement membrane-like material is also frequently evident within the lobules
- Malignant variants demonstrate nuclear pleomorphism, mitotic activity, loss of the surrounding basement membrane and infiltration of adjacent tissue
- Malignant variants are rare and may arise in the background of multiple benign cylindromas

Eccrine Spiradenoma and Malignant Eccrine Spiradenoma

Clinical

- Usually solitary, blue to flesh-colored, intradermal nodules on the ventral aspect of the body
- These tumors are frequently painful. Rarely, multiple tumors may be seen in a linear or zosteriform distribution

Microscopic

- One or more, basophilic tumor lobules are evident in the dermis and are usually encapsulated
- The lobules are composed of two cell types similar to the cylindroma: a small, lymphocyte-like population and a larger cell type with oval, vesicular nuclei
- Ductal differentiation may be conspicuous within the lobules, and pseudovascular spaces may give a hemangiomatous quality to the lesion
- The intervening stroma often demonstrates lymphangiectasia
- The rare malignant variants require an adjacent benign focus of typical microscopy for confident diagnosis
- The malignant variants are characterized by infiltration, mitoses, nuclear pleomorphism, necrosis and lymphatic invasion

Eccrine Duct Carcinoma

Clinical

- A nodular and often ulcerated lesion of long standing duration found most commonly on the head, neck and extremities of older adults
- Approximately 50% metastasize to lymph nodes or visceral sites

Microscopic

- An infiltrating dermal tumor composed of strands, trabeculae and tubules with varying degrees of lumen formation
- The histologic pattern is very similar to ductal carcinoma of the breast, which should always be excluded clinically
- There is at least some degree of nuclear pleomorphism, and nucleoli are frequently prominent
- Mitotic figures and necrosis may also be identified

Syringoid Eccrine Carcinoma (Eccrine Epithelioma)

Clinical

- Typically, a plaque or an ulcerated tumor of the scalp of middle-aged adults
- This tumor is locally aggressive with frequent recurrences, but metastases are rare

Microscopic

- A dermal-centered tumor showing extensive infiltration with involvement of the subcutaneous fat
- This tumor is composed of infiltrating cords and trabeculae with faint lumen formation and a dense, hyalinizing stroma
- Unlike microcystic adnexal carcinoma, keratocysts are rarely present
- The individual cells often have basaloid features but lack peripheral retraction
- Nuclear pleomorphism is mild, and mitotic figures are scarce
- Perineural invasion is frequent

Microcystic Adnexal Carcinoma

Clinical

- A flesh-colored to yellow, slowly growing firm plaque or nodule involving the head, neck or face of older adults
- Like syringoid eccrine carcinoma, this is a locally aggressive tumor with frequent recurrences but with no tendency to metastasize

Microscopic

- A dermal-centered tumor showing extensive infiltration of the deep dermis and subcutaneous tissues
- Keratocysts, trabeculae and ductules are evident throughout the lesion, but keratocysts tend to predominate superficially while trabeculae predominate at the deeper aspect of the tumor
- The middle of the tumor shows an admixture of all forms giving this tumor a triphasic or trilayered look from superficial to deep
- The individual epithelial units are frequently invested by a dense fibrous stroma giving this tumor a sclerotic appearance
- Perineural invasion is common while nuclear pleomorphism and mitotic activity are rare

Mucinous Eccrine Carcinoma

Clinical

- A flesh-colored to blue nodule on the head and neck region (particularly the eyelid) of older adults with a male predominance

Microscopic

- A dermal based tumor showing islands of relatively bland epithelial cells floating in pools of mucin similar to colloid carcinoma of the breast

Adenoid Cystic Carcinoma

General

- A rare, primary cutaneous neoplasm showing a similar microscopic to its counterparts elsewhere but having a less aggressive course

Mucoepidermoid Carcinoma

General

- A rare primary tumor of skin showing similar histologic features to its salivary gland counterpart

Apocrine-Derived Tumors and Proliferations

Apocrine Nevus

Clinical

- A rare lesion typically presenting as a papule in the axilla or on the scalp

Microscopic

- An increase in the number or size of mature appearing apocrine glands

Syringocystadenoma Papilliferum

Clinical

- Typically a solitary, verrucous to papillary lesion on the scalp, face or neck, but other sites may be involved
- In children, this tumor frequently arises within a nevus sebaceous

Microscopic

- A partially cystic, dermal centered tumor showing overlying epidermal invagination

- The cystic space contains abundant papillary structures lined by a bilayered epithelium with apical snouts, consistent with apocrine differentiation
- The fibrovascular cores contain abundant plasma cells

Hidradenoma Papilliferum

Clinical

- Typically a solitary, asymptomatic nodule presenting in the genital region of females
- Similar lesions have been described within the ear, nipple and eyelid

Microscopic

- A well demarcated, dermal-based neoplasm showing no involvement of the overlying epidermis
- This tumor is also frequently cystic in areas and is characterized by numerous trabeculae, epithelial fronds and papillary structures lined by a bilayered epithelium showing apocrine differentiation (apical snouts)
- The stroma is fibrovascular and lacks the plasma cells of syringocystadenoma papilliferum
- Occasional cases show a more pronounced fibrous stroma with a lobular architecture akin to fibroadenoma of the breast
- Rare cases show malignant transformation with high-grade nuclear features, frequent mitoses, necrosis and infiltration

Tubular Apocrine Adenoma

Clinical

- A well-defined nodule occurring most commonly on the scalp of adults

Microscopic

- An unencapsulated, but well-demarcated proliferation of numerous ducts/glands lined by a bilayered to multilayered epithelium showing apocrine differentiation
- Small papillary structures and occasional cribiforming may be seen and resemble proliferative lesions in the breast
- These lesions may show some degree of nuclear atypia and mitotic activity but generally are not considered carcinomas unless obvious infiltration of surrounding tissues is seen

Apocrine Carcinoma

Clinical

- A rare primary tumor of skin that typically presents as an erythematous nodule with or without ulceration in older adults
- A variety of sites may be affected including the scalp, eye, ear and anogenital regions amongst others
- Recurrences and metastases may occur

Microscopic

- A variety of histologic appearances may be present including cystic, papillary, sheet-like and ductal variants
- Infiltration of adjacent tissues is seen, and pagetoidosis may be evident
- Nuclear pleomorphism may be mild to marked, and varying degrees of mitotic activity and necrosis may be evident
  - By definition, areas of apocrine differentiation should be identified, at least focally

Differential Diagnosis

- Apocrine carcinoma of the breast has similar histologic and immunophenotypic characteristics and should be excluded clinically

Neuroendocrine-Derived Tumors

Merkel Cell Carcinoma

Clinical

- An aggressive neoplasm typically presenting as a slowly growing nodule on the sun exposed skin (head and neck region) of older adults
- The recurrence and metastatic rate is approximately 40-50%

Microscopic

- A variety of histologic forms may be seen and include sheet-like, ribboned, nested, trabecular and organoid variants
- Pseudorosettes may be prominent
- These tumors are typically dermal based but frequently involve the subcutis and may show an intraepidermal growth pattern
- Focal areas of squamous, eccrine or sebaceous differentiation may be seen, and these tumors may arise in conjunction with another, histologically distinct neoplasm
- The cytologic and immunophenotypic appearance is characteristic and common to all variants
- Cytologically, the tumor cells have very high nuclear/cytoplasmic ratios, indistinct cell borders, hyperchromatic, and finely granular nuclei with inconspicuous nucleoli and thin nuclear membranes
- Nuclear molding and mitoses are abundant
- Immunophenotypically, the tumor cells express low molecular weight cytokeratin (CAM 5.2) in a perinuclear dot-like pattern which may also be seen with neurofilament staining
- Cytokeratin 20 staining is generally positive, and these tumors express a variety of neuroendocrine markers including neuron-specific enolase, chromogranin, synaptophysin and neurofilament, but are generally negative for S100 and vimentin

Differential Diagnosis

- Merkel cell carcinomas must be differentiated from a variety of other neuroendocrine tumors of either metastatic or primary origin
- Small cell neuroendocrine carcinomas from visceral sites metastatic to skin have an essentially identical histologic appearance but have recently been reported to be cytokeratin 20 negative
- Cutaneous neuroblastoma generally shows a filamentous background and/or focal ganglion cell differentiation and is typically cytokeratin negative (except for the olfactory variant)
- Primitive neuroectodermal tumors/extraosseous Ewing's sarcomas are usually cytokeratin negative and typically express MIC-2

Soft Tissue Neoplasms and Developmental Anomalies

Adipocyte-Derived Tumors and Proliferations

Lipoma

Clinical

- A sporadic or multifocal tumor of the middle aged to elderly typically involving the trunk and/or extremities

Microscopic

- A thinly encapsulated proliferation of mature adipose tissue
- The adipose tissue may be accompanied by a wide variety of other types of mesenchymal-derived tissue: fibrous (fibrolipoma), bone (osteolipoma), cartilage (chondroid lipoma), bone marrow (myelolipoma), mucoid substances (myxoid lipoma), smooth muscle (myolipoma) and smooth muscle and vessels (angiomyolipoma)

Angiolipoma

Clinical

- A painful, subcutaneous nodule(s) involving the upper extremities of young adults

Microscopic

- Thinly encapsulated proliferations of mature adipocytes and variably sized, thin walled vessels
  Microthrombi are readily identified within the vessel lumina
- A cellular variant showing numerous small vessels with few adipocytes exists and must be differentiated from other vascular tumors that lack the proliferation of mature adipocytes

Spindle Cell Lipoma

Clinical

- A solitary, painless, subcutaneous nodule with a predilection for the base of the neck of middle aged to older adults

Microscopic

- An encapsulated proliferation of mature adipocytes and bland, bipolar spindle cells embedded in a myxoid matrix with collagen fibers
- The spindle cells may predominate and typically show bland, uniform features
- Lipoblasts and the plexiform capillary network of myxoid liposarcoma are absent
- Occasional cases show bizarre, multinucleated cells and merge with pleomorphic lipoma

Pleomorphic Lipoma

Clinical

- Similar to spindle cell lipoma

Microscopic

- Similar to spindle cell lipoma with the addition of numerous, multinucleated (floret cells) cells with hyperchromatic, peripherally situated nuclei

Lipoblastoma and Lipoblastomatosis

Clinical

- These are tumors of infants and young children and typically present as painless masses on the extremities in a localized (lipoblastoma) or diffuse (lipoblastomatosis) fashion
- The latter may recur with incomplete excision

Microscopic

- Multilobular proliferations of immature and mature adipocytes embedded in a myxoid matrix and separated by thin fibrous septae
- The adipocytes may show a wide spectrum of differentiation from spindle cells to multivacuolated lipoblasts to mature, univacuolated adipocytes
- These lesions tend to mature histologically with time

Lipofibromatous Hamartoma of Nerve

Clinical

- A tumor-like condition that presents as a mass of the wrist and/or forearm
- Typically, these patients are young children, but adult presentations also occur
- Sensory defects, parathesias, pain and macrodactyly may be prominent
- Due to the intimate association of this proliferation with nerves, surgical excision is contraindicated and may lead to permanent sensorimotor impairment

Microscopic

- A proliferation of benign fibroadipose tissue is evident in and around nerve fibers which show secondary degeneration, atrophy and fibrosis

Lipomatosis

Clinical

- Multiple clinical forms exist including a diffuse variant typically involving the extremities or trunk of young children, a symmetrical variant (Madelung's disease) involving the neck region of middle-aged adult males as well as visceral and pelvic variants

Microscopic

- All are unencapsulated proliferations of mature adipose tissue involving the subcutis, skeletal muscle and, occasionally, other structures

Nevus Lipomatosus Superficialis

Clinical

- A hamartomatous proliferation typically presenting as multiple, polypoid papules or plaques on the buttocks, posterior trunk or thigh of children to young adults

Microscopic

- Small lobules of mature adipocytes are evident in the superficial and mid dermis and may be associated with keratin plugs and loss of adnexal structures

Hibernoma

Clinical

- A slow-growing, asymptomatic mass of the chest or upper back of young to middle-aged adults
- Other sites may also be affected

Microscopic

- An encapsulated, multilobular tumor composed of an admixture of multivacuolated and univacuolated adipocytes and large cells with eosinophilic cytoplasm and distinct cell membranes

Liposarcoma

Clinical

- These are rare tumors of skin that generally present as slowly growing subcutaneous masses in older adults

Microscopic

- The myriad of histologic types of liposarcoma are addressed in detail elsewhere
- Generally, the liposarcomas involving skin are of the well-differentiated (atypical lipoma) or myxoid types
- The former has lipoma-like, sclerosing and spindle cell variants which may recur but typically do not metastasize

Neural-Derived Tumors and Proliferations

Neurofibroma

Clinical

- Solitary and multiple forms exist
- The solitary variant is typically a soft, polypoid, flesh-colored tumor occurring in adults
- The multiple or diffuse variant has a strong association with neurofibromatosis type 1 and may show extensive, cosmetically deforming lesions with a bag of worms appearance and feel
- The diffuse variant is seen more frequently in childhood and adolescence
- The diffuse variant has definite malignant potential while the sporadic variant lacks this characteristic

Microscopic

- A variety of histologic subtypes exist, but all are characterized by a proliferation of wavy, pointed spindle cells embedded in a variably collagenous to myxoid matrix
- These tumors are unencapsulated but are generally well circumscribed
- They not infrequently incorporate dermal adnexal structures, but direct adnexal invasion is rare
- Plexiform, diffuse, myxoid and pacinian variants exist
- The plexiform variant is thought to be diagnostic of neurofibromatosis while the diffuse variant may also be associated with this disease at an increased rate

Special Studies

- Neurofibromas are derived from nerve and, as such, demonstrate positive staining for axonal markers such as neurofilament and silver impregnation techniques
- Similar to other neural-derived tumors, these lesions are also positive for S100, CD57 and neuron-specific enolase

Schwannoma (Neurilemmoma)

Clinical

- A peripheral nerve sheath derived tumor that generally presents as a solitary nodule/mass on the head, neck or extremities of adults
- Rarely, multiple tumors may be evident (schwannomatosis), and at least some of these cases are associated with neurofibromatosis type 2
- In general, schwannomas have little, if any, malignant potential

Microscopic

- A well-circumscribed, encapsulated tumor within the subcutis or deeper tissues
- Occasionally, dermal involvement may be evident
- The tumor is composed of spindle cells with wavy, pointed nuclei embedded in a collagenous and highly vascular stroma
- Classically, cellular, Antoni A areas with palisading, Verocay bodies are admixed with paucicellular, myxoid, Antoni B areas

- Degenerative changes are frequent findings and include hyalinization, vascular thrombosis, dystrophic mineralization and hemorrhage
- The ancient variants typically show some degree of nuclear pleomorphism and enlargement with a smudgy chromatin pattern
- Plexiform variants exist and typically present in childhood or adolescence
- These tumors are composed of multiple, cellular, Antoni A-like, encapsulated nodules that must be differentiated from plexiform neurofibroma and plexiform fibrohistiocytic tumor
- Cellular variants are moderately to markedly cellular and may have mitotic activity. Nuclear pleomorphism and necrosis, however, are absent. Melanotic variants also exist and must be differentiated from malignant melanoma

Special Studies

- Schwannomas are derived from the peripheral nerve sheath and, therefore, lack axonal differentiation; that is, they are neurofilament and silver staining negative
- Schwann cells are S100 positive and are generally surrounded by type IV collagen-rich basement membrane
- Epithelial membrane antigen typically stains the capsule of schwannomas

Traumatic Neuroma

Clinical

- Reactive, nonneoplastic proliferations of nerve in response to injury
- Typically present as small, often painful, nodules at sites of previous injury

Microscopic

- A well-localized but unencapsulated, haphazard proliferation of nerve fibers associated with dermal fibrosis (scar)

Palisaded and Encapsulated Neuroma (Solitary Circumscribed Neuroma)

Clinical

- Solitary, flesh-colored papule on the face of middle-aged to older adults

Microscopic

- A nodular to multinodular, often dumbbell-shaped proliferation of spindle cells embedded in a collagenous matrix
- These lesions are well circumscribed but only partially encapsulated
- The superficial component generally lacks a true capsule and tends to resemble a neurofibroma while the deep component is encapsulated and resembles a schwannoma
- The spindle cells demonstrate wavy, pointed nuclei and lack mitotic activity
- Contrary to its name, true nuclear palisading is rare in this lesion
- A nerve may be evident entering the base of the lesion

Special Studies

- Like neurofibroma, this lesion contains both axons and schwann cells and, hence, is S100 and neurofilament positive

Granular Cell Tumor

Clinical

- Slowly growing, sometimes painful, flesh-colored nodules with a predilection for the tongue, trunk and extremities of adults
- While usually solitary, multiple and familial variants exist

Microscopic

- Irregular fascicles and/or sheets of large, round to polygonal cells with eosinophilic, granular cytoplasm
- Cell borders are indistinct giving this tumor a syncytial appearance
- Nuclei are generally round to ovoid, central and monomorphic
- Nuclear pleomorphism, mitotic activity, necrosis and large tumor size may be associated with the rare malignant variants
- Prominent pseudoepitheliomatous hyperplasia of the epidermis is often seen overlying this tumor and must not be mistaken for squamous cell carcinoma

Special Studies

- While the cell of origin remains to be clarified, most authorities support a schwann cell derivation for these tumors
- Accordingly, these tumors are usually, but not always, S100 and neuron specific enolase positive

Differential Diagnosis

- Secondary granular cell change is not an uncommon finding in other tumor types (dermatofibroma, neurofibroma, etc.) which should be excluded prior to making the diagnosis of granular cell tumor
- This tumor should also be differentiated from congenital epulis discussed below

Congenital Epulis

Clinical

- A polypoid gingival lesion in newborns that may spontaneously regress

Microscopic

- Similar to granular cell tumor, but these lesions are S100 negative

Nerve Sheath Myxoma (NSM) and Cellular Neurothekeoma

Clinical

- Soft, mobile, flesh-colored papules on the face or upper extremities of young adults
- These tumors may recur with incomplete excision

Microscopic

- NSM is a fascicular to lobular dermal tumor composed of spindle and stellate cells embedded in myxoid lobules which in turn are separated by fibrous septae
- Cellular neurothekeoma is composed of more uniform, epithelioid cells in nests and fascicles with minimal myxoid background material
- Mitotic activity and mild nuclear pleomorphism may be seen in both lesions

Special Studies

- NSM is typically S100+ and is likely derived from the peripheral nerve sheath
- Cellular neurothekeoma is S100- and its cell of origin is unclear
- The lack of S100 positivity in the cellular variants allows these lesions to be readily distinguished from most melanocytic neoplasms

Perineurioma

Clinical

- A benign tumor of perineural origin that typically presents as a subcutaneous mass on the trunk and limbs of adults

Microscopic

- A well-circumscribed proliferation of bland spindle cells in fascicles with whorled and storiform areas

Special Studies

- Like perineural cells, this tumor is S100- and EMA+

Malignant Peripheral Nerve Sheath Tumor

General

- A rare, primary cutaneous malignancy frequently associated with neurofibromatosis type 1 when primary in the skin
- These lesions are discussed in detail in the soft tissue pathology chapter

Cutaneous Meningothelial Heterotopias/Meningiomas

Clinical

- Classic meningocele is typically a transilluminating mass along the lower spine and represents a congenital defect
- Rudimentary meningocele is thought to be a herniation of the meninges into the superficial tissues of the scalp with a subsequent loss of its intracranial attachment
- Cutaneous meningioma comes in three forms: type I is congenital lesion involving the head and paravertebral regions of children and is secondary to misplaced arachnoid cells during embryogenesis; type II occurs on the head and neck region of adults and is thought to be secondary to a proliferation of arachnoid cells through a cranial foramina; type III represents a metastasis or direct extension of tumor into skin form an intracranial primary

Microscopic

- Meningoceles are typically cyst-like structures lined by arachnoid cells and having surrounding dense fibrous tissue with occasional collections of meningothelial cells in whorl-like structures
- Meningiomas are usually well-circumscribed deep dermal to subcutaneous proliferations composed of spindle cells arranged in fascicles and whorls with or without psammoma body formation
- Nuclear pleomorphism and mitotic activity may be seen, particularly in the type III variants
- Special studies
- Meningothelial proliferations are usually vimentin and EMA+
- Cytokeratin and S100 may also be expressed by these tumors

Heterotopic Glial Tissue (Nasal Glioma)

Clinical

- Flesh-colored mass on the nasal bridge of infants to young adults Intranasal involvement may also be present
- Radiographic studies should be performed to exclude an intracranial attachment

Microscopic

- Nodules of benign eosinophilic, fibrillar, glial tissue within the deep dermis and subcutis
- Rarely, neuronal cells may also be seen

Smooth Muscle-Derived Tumors and Proliferations

Smooth Muscle Hamartoma

Clinical

- A congenital, sometimes pigmented, indurated plaque on the trunk which typically presents in infancy

Microscopic

- A haphazard proliferation of smooth muscle fascicles in the dermis with or without basilar epidermal hyperpigmentation

Becker's Nevus

Clinical

- An acquired, organoid, hyperpigmented plaque with hypertrichosis on the back of young adults and as adolescents
- This lesion may be associated with other congenital abnormalities

Microscopic

- Epidermal acanthosis and basilar hyperpigmentation occasionally associated with a mild haphazard proliferation of smooth muscle fascicles within the dermis

Piloleiomyoma (Pilar leiomyoma)

Clinical

- Multiple, somewhat painful papules or nodules on the trunk or extremities of young adults
- May be inherited in an autosomal dominant fashion

Microscopic

- A fairly well circumscribed yet irregular proliferation of smooth muscle fascicles within the dermis
- The individual cells have elongated eosinophilic cytoplasm and cigar-shaped nuclei
- No nuclear pleomorphism, mitotic activity or necrosis is evident

Angioleiomyoma

Clinical

- A solitary, sometimes painful nodule on the extremities of adults

Microscopic

- A nodular, well-circumscribed proliferation of smooth muscle in fascicles admixed with numerous, variably sized vessels
- Degenerative changes are frequent

Leiomyosarcoma

Clinical

- Two clinical variants exist: a superficial or cutaneous variant and a deep or subcutaneous variant
- The former predominates on the limbs of young adults and is likely derived from the arrector pili muscle
- This variant may locally recur but generally does not metastasize
- The subcutaneous variant predominates on the limbs of the elderly and has both local recurrence and metastatic potential

Microscopic

- The cutaneous variant demonstrates an irregular, infiltrating and haphazard proliferation of smooth muscle bundles reminiscent of piloleiomyoma
- However, unlike piloleiomyoma, this tumor has low-grade nuclear pleomorphism, mitotic activity and, rarely, necrosis
- The deep or subcutaneous variant is akin to leiomyosarcomas arising elsewhere and consists of a nodular, at least focally infiltrating, proliferation of smooth muscle fibers in well-formed to ill-defined bundles with varying degrees of nuclear pleomorphism, mitotic activity and necrosis

Fibrohistiocytic, Histiocytic, and Langerhans' Cell-Derived Proliferations

Fibrous Histiocytoma (Dermatofibroma)

Clinical

- Usually single, occasionally multiple, slightly elevated, smooth, flesh-colored to hyperpigmented nodules on the extremities or trunk of adults

Microscopic

- Numerous subtypes have been described but all are generally made up of a proliferation of histiocytes, fibroblasts and collagenous tissue in varying proportions
- The prototypical lesion (dermatofibroma) consists of a fairly well circumscribed, unencapsulated, mid-dermal proliferation with feathery edges, an overlying Grenz zone and epidermal hyperplasia with basilar hyperpigmentation
- The cellular component consists of spindled, fibroblast-like cells admixed with plump histiocytic cells in an irregular fashion
- Storiform areas may be evident, and there may be focal extension into the subcutis
- Chronic inflammatory cells, multinucleated giant cells, xanthomatized histiocytes, and hemosiderin-laden histiocytes are also frequently identified within these lesions
- Important variants include atypical dermatofibroma (dermatofibroma with monster cells), aneurysmal fibrous histiocytoma and epithelioid cell histiocytoma, all of which may be mistaken for other more aggressive entities
- Atypical dermatofibroma is a lesion showing large, hyperchromatic, multinucleated giant cells in addition to typical dermatofibroma features and should be distinguished from atypical fibroxanthoma and malignant fibrous histiocytoma
- Aneurysmal fibrous histiocytoma is a fibrous histiocytoma with prominent intralesional hemorrhage and cystic, pseudovascular spaces
- This lesion should be distinguished from angiomatoid fibrous histiocytoma, a lesion of intermediate grade malignancy occurring in the pediatric population

- Epithelioid cell histiocytoma is composed of a polypoid well-circumscribed proliferation of angulated, epithelioid, histiocytic-appearing cells surrounded by an epidermal collarette
- This lesion should be distinguished from melanocytic tumors, both Spitz's nevus and melanoma

Special Studies

- Most fibrous histiocytomas express FXIIIa but are negative for CD34
- Dermatofibroma sarcoma protuberans tends to have the opposite staining pattern, but overlap and divergent staining patterns occasionally occur

Angiomatoid Fibrous Histiocytoma

Clinical

- A fairly deep-seated, usually subcutaneous, nodule or mass within the extremities of children and adolescents
- This lesion is considered to be of borderline or intermediate malignancy and may recur and, rarely, metastasize

Microscopic

- A circumscribed, partially cystic and lobular mass usually centered on subcutaneous tissue
- This tumor is composed of an admixture of cystic, blood-filled pseudovascular spaces, myxoid lobules of histiocytic appearing cells and peripheral lymphocytic inflammation and fibrosis
- The neoplastic cells are somewhat spindled to plump, epithelioid cells with eosinophilic to amphophilic cytoplasm and mildly pleomorphic nuclei
- Mitotic figures may be evident

Special Studies

- The histiocytic-appearing cells often show expression of smooth muscle actin, desmin and CD34, suggesting to some a myofibroblastic derivation to this tumor

Plexiform Fibrohistiocytic Tumor

Clinical

- A slowly growing deep dermal to subcutaneous mass on the extremities of children to young adults
- This is a tumor of intermediate malignancy that may recur and rarely metastasizes

Microscopic

- An unencapsulated, irregular biphasic tumor consisting of short fibromatosis-like fascicles of plump spindle cells admixed with nodules of histiocytic and osteoclast-like giant cells with minimal nuclear pleomorphism
- The admixture of nodules and fascicles gives this tumor a plexiform appearance at low power

Juvenile Xanthogranuloma

Clinical

- Solitary to multiple, yellow to red papules on the head and neck region of infants is the most common presentation
- However, adolescents and adults may also be affected, and other body sites may be involved
- Visceral involvement may be evident with the eye being the most common extracutaneous site of involvement
- Typically, the cutaneous lesions regress over time

Microscopic

- Fairly well circumscribed collection of histiocytes within the dermis admixed with Touton giant cells, xanthomatized histiocytes and chronic inflammatory cells
- The epidermis is spared, but periadnexal involvement is common
- Spindle cell and inflammatory cell rich variants exist

Reticulohistiocytoma and Multicentric Reticulohistiocytosis

Clinical

- Solitary and multicentric variants exist
- The former is usually a yellow to brown nodule on the upper body of adults while the latter shows multiple lesions associated with a destructive arthritis and constitutional symptoms, also in adults
- Occasionally, the multicentric variant is associated with visceral neoplasia

Microscopic

- Both variants are characterized by fairly well circumscribed proliferations of large, eosinophilic histiocytes with "glassy" cytoplasm
- The individual cells may contain more than a single nucleus but Touton giant cells are usually absent, and xanthomatized histiocytes are not generally present
- Mild nuclear pleomorphism and admixed inflammation with eosinophils and lymphocytes may be evident

Atypical Fibroxanthoma

Clinical

- Typically a solitary, often ulcerated polypoid nodule on the sun-exposed skin (head and neck) of the elderly
- A less common variant occurs on the trunk and extremities of young adults
- These tumors, when limited to superficial tissues, may locally recur but have minimal metastatic potential

Microscopic

- A nodular, often well circumscribed, proliferation of very pleomorphic epithelioid to spindle cells with frequent mitoses, often atypical

- These tumors are usually centered on the dermis and frequently abut the dermal-epidermal junction where they stop abruptly
- Epidermal ulceration is common, but true epidermal involvement with pagetoid spread should raise concerns about malignant melanoma or squamous cell carcinoma
- Rarely, the tumor is composed of spindle cells in poorly defined fascicles and may be mistaken for leiomyosarcoma
- While occasional tumors may show superficial involvement of the subcutaneous tissues, extensive subcutaneous involvement and/or prominent vascular invasion and necrosis should lead to an alternate diagnosis (e.g. malignant fibrous histiocytoma)

Special Studies

- This tumor is a diagnosis of exclusion; therefore, S100, cytokeratin and desmin should be negative by immunoperoxidase technique to exclude malignant melanoma, carcinoma and leiomyosarcoma, respectively
- Smooth muscle actin may be expressed by a subset of these tumors and is not indicative of smooth muscle differentiation (leiomyosarcoma) in the absence of desmin positivity

Malignant Fibrous Histiocytoma

General

- These tumors are rarely primary cutaneous lesions and have overlapping histologic features with atypical fibroxanthoma
- The latter tumor is often considered to be a superficial variant of malignant fibrous histiocytoma with minimal metastatic potential
- The term malignant fibrous histiocytoma should be used for those tumors that demonstrate deep tissue involvement, vascular invasion or extensive necrosis as detailed above
- The histologic subtypes and clinical distribution of this tumor are detailed in the soft tissue tumor chapter

Xanthomas and Xanthelasma

Clinical

- Numerous clinical and histologic subtypes exist, many of which are related to systemic lipid abnormalities and represent storage disorders
- Eruptive
  - Yellow papules on the buttocks and other sites associated with type I hyperlipoproteinemia
- Tuberous
  - Yellow papules and nodules on the extensor surfaces associated with hyperlipoproteinemia types II-IV
- Tendinous
  - Nodules or masses on the tendons of the extremities associated most frequently with type II hyperlipoproteinemia
- Planar
  - Yellow papules and plaques that may involve intertriginous sites, palmar creases or more multiple sites in a diffuse fashion
  - The intertriginous variant is associated with type II hyperlipoproteinemia, the palmar variant with type III hyperlipoproteinemia, and the diffuse variant is often associated with hematopoeitic disorders
- Xanthelasma
  - Yellow plaques on the eyelids, which are associated with lipid abnormalities in only approximately 50% of patients (type III hyperlipoproteinemia)
- Xanthoma disseminatum
  - Not a true storage disorder but, rather, a non-X histiocytosis that presents as yellow-red papules and plaques on the flexural surfaces and mucosal membranes of young adults
  - There is no association with lipid abnormalities with this disorder
- Verruciform xanthoma
  - Usually a solitary, yellow-red, papillomatous lesion of the mouth, this localized process may be seen at a number of cutaneous sites as a primary lesion or as a secondary phenomena in other disorders (e.g. squamous cell carcinoma, epidermal nevi, lupus erythematosus)

Microscopic

- All of the above lesions show an admixture of xanthomatized histiocytes, non-xanthomatized histiocytes and chronic inflammatory cells in varying proportions depending on the age and evolution of the lesion
- These lesions are typically dermal limited but, occasionally, show more extensive cutaneous involvement
- Epidermal involvement is not evident
- Occasional cases will have numerous multinucleated giant cells and/or Touton giants cells and, hence, show overlap with juvenile xanthogranuloma
- This is particularly true of xanthoma disseminatum, which should be distinguished by clinical criteria
- Verruciform xanthoma is a special histologic variant characterized by epidermal acanthosis, papillomatosis, parakeratosis, intraepidermal neutrophils and a subepidermal proliferation of markedly xanthomatized histiocytes

Special Studies

- Xanthomas and the non-X histiocytoses are S100-, CD1a-, macrophage markers+ (CD68) and Birbeck granule

Langerhans' Cell Histiocytosis (LCH, Histiocytosis X)

Clinical

- Three clinical variants of this disease have historically been described
- Letterer-Siwe disease is an acute disseminated form characterized by numerous brown papules on the scalp or face of infants with visceral involvement
- Hand-Christian-Schuller disease is a chronic, multifocal variant with osseous and localized visceral involvement that affects older children and adults and only occasionally involves the skin
- Eosinophilic granuloma is a chronic, focal variant that typically involves osseous sites in adults but may involve skin
- Many cases of LCH do not fit into the above categories and can show a wide spectrum of manifestations

Microscopic

- Nodular or loose aggregates of Langerhans cells within the dermis variably admixed with multinucleated cells, eosinophils, neutrophils and chronic inflammatory cells
- Epidermal involvement is common and aids in distinguishing this lesion from the non-X histiocytoses and urticaria pigmentosa
- Proper diagnosis rests on identifying the Langerhans' cell that is a histiocyte-like cell with abundant, eosinophilic to amphophilic cytoplasm and a reniform, sometimes twisted nucleus with occasional longitudinal grooves

Immunoperoxidase

- Langerhans' cells are S100+ and CD1a+

Electron Microscopy

- Birbeck granules are considered diagnostic of Langerhans' cell differentiation

Congenital Self-Healing Reticulohistiocytosis

Clinical

- Single or multiple, sometimes ulcerated, papules or nodules on the face, trunk and extremities of newborns
- Lesions are usually present at birth but occasionally will develop during the perinatal period
- Lesions typically regress within 2 to 4 months

Microscopic

- The histologic appearance of this lesion is similar to that of LCH, from which it cannot be reliably be separated on histologic grounds alone
- In general, this entity has larger, more eosinophilic cells with "glassy" cytoplasm than LCH
- PASD positive intracytoplasmic inclusions may be seen in this tumor but are apparently not present in LCH
- Epidermal involvement may rarely be present

Immunoperoxidase

- S100+, CD1a+

Electron Microscopy

- In addition to Birbeck granules, dense, myelin-like bodies with lamination are evident in this entity and may allow distinction from LCH

Differential Diagnosis

- This entity is best separated from LCH using clinical criteria; the electron microscopic findings may aid in this process

Indeterminate Cell Histiocytosis

General

- Occasional histiocyte-like proliferations demonstrate S100+ and CD1a+ on immunoperoxidase studies but no Birbeck granules on electron microscopy
- These proliferations have no distinct clinical or histologic characteristics at present

Benign Cephalic Histiocytosis

Clinical

- A non-X histiocytosis usually presenting as multiple yellow to red papules on the face of young children which completely regress with time

Microscopic

- A cellular, somewhat cohesive infiltrate of plump histiocytes often with admixed eosinophils is evident within the dermis
- The overlying epidermis may be attenuated or ulcerated, but epidermotropism is not evident
- Mild nuclear pleomorphism may be seen

Eruptive Histiocytoma

Clinical

- A non-X histiocytosis characterized by numerous, flesh-colored to red papules occurring in crops on the trunk, proximal extremities, and, occasionally, the mucosal membranes of adults
- Lesions may regress, persist and/or recur

Microscopic

- A bland infiltrate of histiocytes with or without coinfiltration of other inflammatory cells within the dermis

Fibrous Proliferations and Tumors

Hypertrophic Scar and Keloid

Clinical

- Hypertrophic scars are slightly raised, red, smooth and firm lesions at sites of previous injury which have no tendency for recurrence and no racial predilection

- Keloids are raised to polypoid, red to flesh-colored lesions usually, but not always, occurring at sites of injury and growing beyond the limits of the injured site
- These lesions may recur and are more common in blacks

Microscopic

- A fairly cellular, often nodular proliferation of dermal fibroblasts in a variably collagenized stroma with only minimal hyalinization characterizes the hypertrophic scar
- Keloids show more extensive, and often, less cellular nodular fibroblastic proliferations with extensive hyalinization of collagen

Nodular Fasciitis/Proliferative Fasciitis/Proliferative Myositis

Clinical

- Reactive, non-neoplastic proliferations presenting as rapidly growing, deep nodules or masses on the trunk or extremities of adults
- Virtually any site may be affected

Microscopic

- All are proliferations of bland, reparative, bipolar spindle cells embedded in a variably myxoid to collagenized stroma
- Most lesions are centered on the fascia/subcutaneous tissue interface, but dermal, vascular, and skeletal muscle variants are not uncommon
- The spindle cells have bland nuclear features, scattered normal mitotic figures and wispy, pointed cytoplasm giving these lesions a "tissue culture" appearance
- Extravasated erythrocytes and admixed chronic inflammatory cells are additional features
- The proliferative variants have, in addition to the above, a population of large, ganglion-like cells admixed within the spindle cells

Fibroma of Tendon Sheath

Clinical

- Slowly growing, benign fibrous nodule firmly attached to the tendon sheath on the distal extremities of adults

Microscopic

- A well-circumscribed, lobulated proliferation composed of densely hyalinized, paucicellular collagen centrally and more cellular fibroblastic proliferations peripherally
- The individual lobules often have peripheral stromal clefting but lack nuclear pleomorphism, mitotic activity or necrosis

Giant Cell Tumor of Tendon Sheath

Clinical

- Similar to fibroma of tendon sheath (see above)

Microscopic

- A well-circumscribed, nodular to multilobular tumor composed of a proliferation of plump histiocyte-like cells admixed with multinucleated giant cells, spindle cells, foam cells and hemosiderin-laden cells in a variably collagenized matrix
- Mitotic figures may be evident, but no cytologic atypia or necrosis is evident
- The latter aid in distinguishing this lesion from epithelioid sarcoma

Acrochordons (Soft Fibroma, Skin Tags, Fibroepithelial Polyps)

Clinical

- Polypoid, filiform or pedunculated flesh-colored lesions typically involving the groin, axilla and neck region of adults

Microscopic

- A polypoid lesion with epidermal acanthosis overlying a variably hyalinized fibrovascular core
- Adipocytes may be abundant in the central aspect of the lesion

Pleomorphic Fibroma

Clinical

- A benign polypoid to dome-shaped, flesh-colored lesion on the trunk or extremities of adults

Microscopic

- A paucicellular, polypoid proliferation of large, pleomorphic cells with hyperchromatic nuclei, small nucleoli and scant cytoplasm embedded in a fibrous stroma
- Rare mitotic figures may be seen in these lesions and do not imply an aggressive course

Sclerotic Fibroma

Clinical

- Usually a solitary, flesh-colored nodule in adult patients
- Multiple lesions may be associated with Cowden's disease

Microscopic

- A well-circumscribed, nodular proliferation of hyalinized, paucicellular fibrous tissue with laminated, cleft-like stromal spaces

Angiofibroma (Fibrous Papule, Oral Fibroma, Acquired Digital Fibrokeratoma, Pearly Penile Papules)

Clinical

- Papular to polypoid, flesh-colored lesions usually in adults

Microscopic

- A faintly polypoid, well-circumscribed proliferation of fibrovascular tissue with scattered hyperchromatic, occasionally multinucleated, stellate cells within the upper dermis
- In the digital variant there is overlying epidermal acanthosis and hyperkeratosis with the dermal collagen fibers oriented parallel to the long axis of the lesion

Elastofibroma

Clinical

- Typically a deep-seated, subscapular mass in older adults
- Occasionally other sites are involved

Microscopic

- An irregular, unencapsulated proliferation of paucicellular collagen admixed with enlarged and often globular elastic fibers best visualized with elastic stains

Dermatomyofibroma

Clinical

- A benign, solitary, flesh-colored to hyperpigmented plaque on the shoulder region of young adults

Microscopic

- A well-circumscribed proliferation of spindled, bland myofibroblastic cells in thin fascicles within the dermis
- The fascicles are oriented parallel to the epidermis except near adnexal structures where they assume a perpendicular growth pattern relative to the epidermis
- No nuclear pleomorphism, necrosis or significant mitotic activity is evident

Myofibroma/Myofibromatosis

Clinical

- Solitary and multifocal variants exist
- The solitary variants may be seen in infants, young children and adults and typically present as a dermal or subcutaneous nodule on the head, neck, trunk or extremities
- The multifocal variants are seen in infancy or as congenital lesions
- Multiple soft tissue lesions may be seen, and, if visceral involvement is present, there is increased morbidity and mortality
- The solitary variants in children, however, have a tendency to regress

Microscopic

- An unencapsulated, well-circumscribed, biphasic dermal and/or subcutaneous tumor composed of an admixture of peripheral smooth muscle-like fascicles admixed with more centrally located immature, mesenchymal-like spindle cells embedded in a myxoid background
- The latter component often has a hemangiopericytoma-like proliferation of blood vessels
- Mitotic figures and necrosis may be seen and usually do not herald an aggressive course

Infantile Digital Fibroma/Fibromatosis

Clinical

- A benign, rapidly growing nodule on the fingers or toes of infants and young children
- Lesions may be multiple and typically regress over time

Microscopic

- A moderately cellular, usually well circumscribed proliferation of spindled myofibroblasts embedded in a collagenous stroma
- The spindle cells have characteristic actin-positive intracytoplasmic eosinophilic inclusions

Fibrous Hamartoma of Infancy

Clinical

- A hamartomatous lesion typically presenting as a deep dermal to subcutaneous nodule or plaque on the trunk of young children (usually less than 3 years of age)

Microscopic

- A deep dermal to subcutaneous, irregular, triphasic proliferation that merges with adjacent tissue
- The proliferation is composed of an admixture of densely collagenized, fibromatosis-like fascicles of bland spindle cells, myxoid, myofibroblastic lobules and adipocytes showing a range of differentiation from lipoblast-like to mature univacuolated cells
- The collagenized fascicles frequently appear to arise from the deep dermis and "rain down" into the subcutaneous tissue

Fibromatosis

General

- A variety of fibromatoses may present as cutaneous masses, and these are discussed within the soft tissue pathology chapter

Giant Cell Fibroblastoma

Clinical

- A tumor of intermediate grade malignancy occurring almost exclusively in children as a nodule or plaque on the torso or extremities
- This tumor shows a tendency to local recurrence but has minimal to no metastatic potential
- Giant cell fibroblastoma is frequently associated with dermatofibroma sarcoma protuberans (see below) and may precede, follow or occur with this related lesion

Microscopic

- An infiltrative, dermal and often subcutaneous tumor composed of mildly pleomorphic spindle cells embedded in a variably myxoid stroma
- The hallmark of this tumor is the presence of pseudovascular spaces lined by pleomorphic, hyperchromatic and multinucleated-appearing cells that are not truly of endothelial origin

Special Studies

- Similar to DFSP, these tumors may express CD34

Dermatofibroma Sarcoma Protuberans (DFSP)

Clinical

- An indurated, red to blue, plaque-like or multinodular lesion on the trunk or extremities of young to middle aged adults
- Childhood variants also exist and may have coinfiltrating giant cell fibroblastoma
- This tumor has a significant local recurrence rate but rarely metastasizes
- When a fibrosarcoma component is present, the risk of metastases increases significantly

Microscopic

- An infiltrative, dermal and subcutaneous proliferation of monotonous spindle cells in distinctly storiform pattern
- Unlike dermatofibroma, there typically is no epidermal hyperplasia, but basilar hyperpigmentation may be seen
- Tumor cells infiltrate the subcutaneous fat in a characteristic lace-like fashion
- The tumor cells are remarkably bland-appearing and monomorphic
- The mitotic rate is usually low
- Occasional tumors have a prominent myxoid background while others show transition to higher-grade fibrosarcoma
- DFSP usually lacks the coinfiltration of inflammatory cells, giant cells and xanthoma cells typically present in dermatofibroma
- A pigmented variant of DFSP, the Bednar tumor, exists and has in addition to the above, variable numbers of melanin-laden, dendritic appearing cells

Special Studies

- DFSP is typically CD34+, S100- and FXIIIa-

Fibrosarcoma

Clinical

- Two clinical variants exist: an infantile (congenital) form and an adult form
- The former typically presents as a large mass on the extremities of infants and has a relatively good prognosis compared to its adult counterpart
- The adult variant also typically involves the extremities but has a high recurrence and metastatic rate with subsequent increased mortality

Microscopic

- Both variants are characterized by a proliferation of mildly pleomorphic spindled cells embedded in a variably collagenized matrix
- The spindle cells are arranged in fascicles with a herringbone pattern that is more cellular than the fascicles of the fibromatoses
- Mitotic activity is always present but varies in quantity
- The infantile variant may have more immature rounded cells with a less prominent herringbone pattern
- Chronic inflammatory cells are frequently admixed within this variant

Special Studies

- Vimentin+, some are actin+
- This tumor is a diagnosis of exclusion, and other sarcomas and the fibromatoses should be considered prior to diagnosis

Epithelioid Sarcoma

Clinical

- A malignant tumor of uncertain origin typically presenting as firm, often ulcerated nodules on the hand, wrist or forearm of adolescents and young adults
- This tumor frequently shows multiple recurrences as well as metastases

Microscopic

- Usually a multinodular tumor involving the dermis and/or subcutaneous tissue
- The nodules frequently are well demarcated and have central necrosis, simulating necrotizing epithelioid granulomas
- The lesional cells are plump, round, histiocyte-like cells with abundant eosinophilic cytoplasm and relatively uniform ovoid nuclei
- An admixed spindle cell component may be evident
- There is usually a faint, collagenized stroma surrounding the individual cells
- Multinucleated giant cells are not typically seen in this tumor, a feature that aids in distinguishing this lesion from giant cell tumor of tendon sheath

Special Studies

- The lesional cells have a relatively unique immunophenotype being EMA+, vimentin+ and cytokeratin+

Synovial Sarcoma

General

- Synovial sarcoma may rarely present as a cutaneous mass and is discussed in detail in the soft tissue pathology chapter

Vascular Proliferations, Malformations, and Tumors

Reactive, Nonneoplastic Vascular Proliferations and Telangiectasias

Nevus Flammeus

Clinical

- A congenital vascular telangiectasia/malformation with many clinical forms including the salmon patch and the port-wine stain
- The former is a pink-red, macule/patch on the glabella that regresses during childhood
- The latter is a large, unilateral, red facial plaque that persists and may be associated with Sturge-Weber, Klippel-Trenaunay or other vascular syndromes

Microscopic

- Dilated (telangiectatic), thin-walled vessels are present within the papillary and superficial reticular dermis

Phakomatosis Pigmentovascularis

General

- A group of hamartomatous lesions consisting of nevus flammeus in combination with a variety of pigmented lesions (mongolian spot, nevus spilus, and nevus pigmentosus)

Eccrine Angiomatous Hamartoma

Clinical

- An angiomatous, sometimes painful, nodular lesion on the acral regions of children

Microscopic

- A hamartomatous proliferation of mature eccrine glands and thin-walled vessels in the deep dermis or subcutaneous fat
- Occasionally, other mesenchymal elements, particularly adipocytes, may also be admixed with the above

Nevus Anemicus

Clinical

- A solitary, circumscribed, pale, macule or patch on the torso thought to be secondary to vascular hyperreactivity to catecholamines

Microscopic

- No histologic abnormalities are evident within this clinical lesion

Lymphangioma Circumscriptum

Clinical

- Grouped, vesicle-like lesions arranged in a plaque-like form on any cutaneous surface and appearing at birth or early in life

Microscopic

- Dilated, thin-walled lymphatic structures lined by flattened, bland endothelial cells are evident within the superficial dermis and are intimately associated with an acanthotic, surrounding epidermis
- Occasional cases have a deeper dermal component, and these variants may recur if superficially excised

Cavernous Lymphangioma

Clinical

- A congenital or infantile, doughy mass involving the head, neck or extremities which may recur if incompletely excised

Microscopic

- Numerous, variably sized lymphatic spaces are evident within the dermis and subcutaneous tissues
- The lymphatic spaces are lined by flattened, bland endothelium and are variably filled with eosinophilic proteinaceous material
- Chronic inflammatory cells may be seen within the vessel walls or the stroma of this proliferation

Cystic Hygroma

Clinical

- A large, cystic mass of the posterior neck of infants that is usually congenital and may be associated with Turner's syndrome

Microscopic

- Numerous, large and cystically dilated lymphatic spaces within the dermis and subcutaneous tissues are evident in this lesion
- Lymphoid aggregates are frequently present in the walls of these structures and aid in differentiating this lesion from other hemangiomatous processes

Lymphangiomatosis

Clinical

- A rare, often fatal, congenital disease which typically presents as sponge-like masses involving the skin of the extremities along with bone and visceral involvement
- Rare cases are limited to the extremities and a have a better prognosis than their systemic counterparts

Microscopic

- Infiltrating, interanastomosing and variably dilated lymphatic structures are evident in the dermis and underlying soft tissues in this entity

Spider Angioma (Nevus Araneus)

Clinical

- A red papule with "spidery" red legs on any cutaneous surface in both children and adults
- These lesions occur with an increased incidence in pregnancy, liver disease and thyrotoxicosis

Microscopic

- A central, dilated dermal arteriole is present and is interconnected to a superficial network of dilated capillaries

Venous Lake

Clinical

- A dark blue papule on the sun-damaged skin of older adults, especially the ears, lips and face

Microscopic

- A superficial, dilated venous structure is evident within the dermis

Hereditary Hemorrhagic Telangiectasia (Osler-Weber-Rendu Syndrome)

Clinical

- An autosomal dominant inherited disorder characterized by cutaneous and visceral telangiectasias beginning in childhood

Microscopic

- Telangiectatic superficial vessels are present in the dermis

Angiokeratoma

Clinical

- Four clinical variants exist:
- Fordyce
  - Multiple, dark papules on the scrotum or vulva of the elderly
- Mibelli
  - An autosomal dominant inherited disease characterized by warty papules on the extremities of children
- Angiokeratoma corporis diffusum
  - Widespread cutaneous lesions with a bathing-trunk distribution and an association with Fabry's disease (x-linked, a-galactosidase deficiency)
- Solitary

Microscopic

- The microscopy of all these variants is similar consisting of superficial, thin-walled, ectatic vessels closely associated with an acanthotic epidermis
- The Fabry's-associated variant may show vacuolization of endothelial and smooth muscle cells which corresponds to glycolipid lamellar deposits on electron microscopy

Angiolymphoid Hyperplasia with Eosinophils (ALH, Epithelioid Hemangioma)

Clinical

- Red-blue, papules and nodules on the head of adults of uncertain etiology
- Occasional patients will have peripheral blood eosinophilia

Microscopic

- Well-circumscribed nodule or nodules are evident within the dermis and/or subcutaneous tissue and are composed of an admixture of variably sized vessels, a polymorphous lymphoid infiltrate and a variable number of eosinophils
- Enlarged, often vacuolated and hobnailed, endothelial cells line the vessels
- The lymphoid infiltrate is composed of an admixture of T and B-lymphocytes on immunoperoxidase studies and, rarely, forms germinal centers

Differential Diagnosis

- ALH should be distinguished from Kimura's disease, which it vaguely resembles clinically and histologically
- The latter is more common in adolescents and young adults of Asian descent and is characterized by cutaneous nodules with a wider cutaneous distribution associated with lymphadenopathy and peripheral eosinophilia
- Histologically, Kimura's disease lacks the vascular proliferation of ALH and has more prominent lymphoid follicles with germinal center formation

Pyogenic Granuloma (Lobular Capillary Hemangioma)

Clinical

- A hyperplastic, possibly neoplastic, lesion typically presenting as a solitary (occasionally multiple), polypoid, glistening red mass which may locally recur

Microscopic

- A polypoid, intradermal lesion frequently surrounded by an epidermal collarette and characterized by a lobular proliferation of bland capillaries and venules in a myxoid background
- Overlying ulceration and prominent inflammation are frequently present

Bacillary Angiomatosis

Clinical

- An infectious disease mimicking a vascular neoplasm, this lesion is most commonly seen as an angiomatous lesion in immunosuppressed patients but may also

affect the immunocompetent. Bartonella quintana and henselae are the responsible organisms

Microscopic

- A pyogenic granuloma-like vascular proliferation with the additional features of numerous neutrophils, leukocytoclasia and granular, basophilic, intracytoplasmic masses within the endothelial cells lining the vascular proliferation
- The masses prove to be clumps of bacteria that stain nicely by the Warthin-Starry technique

Differential Diagnosis

- Verruga peruana is a related disease that is endemic in Peru and caused by Bartonella bacilliformis

Intravascular Papillary Endothelial Hyperplasia (Masson's Hemangioma)

Clinical

- A proliferative/reorganizing thrombus that may involve any cutaneous or mucosal surface but is frequently seen in rectal tissue

Microscopic

- Typically a localized process involving a single vessel or occasionally multiple adjacent vessels and characterized by numerous, intraluminal, endothelial-lined papillary structures with hylanized connective tissue cores
- The endothelial cells lack nuclear atypia or significant mitotic activity and, generally, do not "pile up" or stratify

Pseudo-Kaposi's Sarcoma

Clinical

- A group of pseudoneoplastic lesions including acroangiodermatitis and Stewart-Bluefarb syndrome
- The former is a variant of severe stasis dermatitis that typically involves the lower extremities of older adults
- The latter is an arteriovenous malformation unilaterally involving a lower extremity in a young adult

Microscopic

- Acroangiodermatitis is characterized by a relatively superficial proliferation of small, bland vascular structures which are often thick-walled and may be arranged in a lobular architecture
- There is associated chronic inflammation, dermal hemosiderin deposition, erythrocyte extravasation and overlying epidermal acanthosis and hyperkeratosis
- The Stewart-Bluefarb syndrome shows a transdermal proliferation of similar vessels and, occasionally, an arteriovenous malformation may identified in the deeper tissues

Differential Diagnosis

- These reactive proliferations should be distinguished from Kaposi's sarcoma which is characterized by a more infiltrative vascular proliferation which surrounds adnexa, dissects dermal collagen and shows a vessel around vessel growth pattern (the promontory sign)

Benign Vascular Neoplasms

Angioma Serpiginosum

Clinical

- Multiple, gyrate papules on the extremities of children and young adults

Microscopic

- A clustered proliferation of thick-walled capillaries is evident within the papillae of the superficial dermis

Hemangiomas (Infantile, Cavernous, Capillary, Superficial, and Deep)

Clinical and General

- A variety of confusing terms have been utilized for hemangiomas rapidly developing in infancy, shortly after birth
- Traditionally, pathologists have classified these lesions as capillary or cavernous hemangiomas, with the thought that the former regress while the latter do not
- It is now clear that this division is erroneous and that, instead of representing distinct histologic entities, capillary and cavernous histologic changes are merely the histologic findings along points of time in the evolution of all infantile hemangiomas
- Dermatologists instead classify infantile hemangiomas as superficial or deep depending on whether the overlying skin surface is bright red or largely normal
- Further, almost all infantile hemangiomas experience some regression after their initial period of rapid growth, regardless of the histologic type

Microscopic

- Early lesions ("cellular hemangioma") show a highly cellular, often lobular proliferation of endothelial cells with indistinct lumina and scattered mitosis
- These lesions may be dermal limited or extend into the underlying soft tissue
- As the lesions age, vascular lumina become more apparent being composed of small capillary-sized vessels ("capillary hemangioma") which than progress to larger cavernous sized vessels ("cavernous hemangioma")

Cherry Angiomas

Clinical

- Acquired, small, red papules on the trunk of adults

Microscopic

- Dilated, mildly thickened capillary blood vessels in the papillary dermis

Acral A-V Tumor (Arteriovenous Hemangioma, Cirsoid Aneurysm)

Clinical

- Small, red-blue, papules on the head, neck or extremities of adults

Microscopic

- Localized, mid to upper dermal proliferation of variably sized, thick-walled vessels having features of both arteries and veins

Tufted Angioma (Tufted Angioblastoma)

Clinical

- Angiomatous appearing, red to brown, macules or plaques on the neck, torso and shoulders of children and young adults

Microscopic

- Multiple, cellular lobules of endothelial cells with peripheral, slit-like spaces are evident within the dermis and superficial subcutaneous tissue giving this lesion a "cannonball"-like pattern

Microvenular Hemangioma

Clinical

- An acquired, slowly growing red-blue papule on the extremities of young adults

Microscopic

- A poorly circumscribed, dermal proliferation of monomorphic, thin-walled, branching venules lined by bland endothelium
- The venules dissect through the collagen raising some concern for Kaposi's sarcoma or low-grade angiosarcoma, but the atypia associated with these two lesions is absent

Targetoid Hemosiderotic Hemangioma

Clinical

- A red papule surrounded by clear and ecchymotic halos in succession on the trunk or extremities of adults

Microscopic

- Thin-walled, somewhat dilated vascular structures with intraluminal papillae and hobnailed endothelium characterize this lesion centrally
- The peripheral and deep aspects of this tumor show interanastomosing vascular spaces that dissect the dermal collagen in association with hemosiderin deposition and chronic inflammatory cells

Glomeruloid Hemangioma

Clinical

- An unusual vascular proliferation that occurs in the setting of POEMS syndrome, these lesions are typically red, dome-shaped to flat, papules and macules on the trunk and extremities of adults

Microscopic

- A glomerulus-like proliferation of tightly entwined capillary-sized blood vessels is present in the upper dermis
- The endothelial cells have characteristic, intracytoplasmic, eosinophilic, PAS+ inclusions that represent absorbed immunoglobulin

Kaposiform Hemangioendothelioma

Clinical

- A childhood neoplasm with a predilection for the retroperitoneum that rarely involves skin

Microscopic

- A multinodular, cellular neoplasm involving the dermis and underlying soft tissue
- The nodules are composed of fascicles of bland spindle cells, small congested capillaries, slit-like vascular spaces and epithelioid endothelial cells with hemosiderin, hyaline globules and primitive cytoplasmic lumina
- No significant mitotic activity is evident
- The multinodularity, the lack of plasma cells and the lack of atypia all aid in distinguishing this lesion from the histologically similar Kaposi's sarcoma

Spindle Cell Hemangioendothelioma

Clinical

- Single or multiple, red-blue, often painful nodules on the extremities of children and young adults

Microscopic

- A fairly well-circumscribed, dermal and/or subcutaneous, nodular tumor composed of an admixture of large, cavernous vascular spaces admixed with a spindle cell to faintly epithelioid, cellular component
- The large vascular spaces frequently have thrombosis with intravascular papillary projections
- The spindle cells often have vacuole-like, intracytoplasmic lumina

Acquired Progressive Lymphangioma (Benign Lymphangioendothelioma)

Clinical

- An acquired, slowly enlarging, bruise-like plaque on the extremities or trunk of young adults

Microscopic

- Thin-walled, anastomosing, irregular vascular channels are evident within the dermis and predominate superficially where they are oriented horizontally to the epidermis

- The deeper dermis also has scattered irregular lumina that are oriented haphazardly or perpendicularly to the overlying epidermis
- The vascular lumina are lined by bland, flattened endothelium and lack any significant intraluminal contents

Angiomatosis

Clinical

- A rare, benign, vascular proliferation of childhood characterized by an angiomatous growth involving a large area of the trunk and/or extremity with or without hypertrophy of the affected segment

Microscopic

- An irregular and haphazard proliferation of variably sized vessels and adipocytes is evident within the dermis and underlying soft tissues
- A characteristic finding is the presence of small vascular structures clustered near or within the wall of a large, thick-walled vein

Vascular Tumors of Low-Grade Malignancy

Epithelioid Hemangioendothelioma

Clinical

- Solitary or multiple, cutaneous and/or visceral masses with a wide age range and geographic distribution
- These lesions may recur and occasionally metastasize

Microscopic

- A proliferation of epithelioid to spindled endothelial cells as cords and nests in a myxoid to hylanized stroma
- Intracytoplasmic lumina with erythrocytes are evident within the epithelioid cells, but well-formed vascular structures are rarely identified
- The tumor often seems to arise from a large vessel wall, often preserving its vascular architecture

Retiform Hemangioendothelioma

Clinical

- A plaque-like or nodular tumor on the extremities of young adults characterized by frequent recurrences and low metastatic potential

Microscopic

- An irregular proliferation of branching, angulated blood vessels lined by hobnailed endothelial cells is present within the dermis and has been likened to similar appearing structures within the rete testis
- A deeper, more solid component with spindled and epithelioid cells and papillary structures may also be evident

Dabska's Tumor (Malignant Endovascular Papillary Angioendothelioma)

Clinical

- A rare, tumor typically presenting as a mass on the head, neck or extremities of children and adolescents

Microscopic

- An irregular, dermal proliferation of vascular structures lined by hobnailed endothelium and having numerous papillary, intraluminal projections lined by atypical, hyperchromatic endothelial cells with occasional mitoses
- Admixed lymphocytes are also frequently present

Kaposi's Sarcoma

Clinical

- Five different clinical subtypes exist:
- Classic
  - Red-blue plaques on the lower extremities of elderly men of Mediterranean descent
- African, endemic variants
  - A nodular, indolent variant affecting the limbs of young to middle-aged men
  - A lymphoadenopathic, aggressive variant affecting young children
- Immunosuppression-associated variant
  - Usually related to transplantation with a potentially aggressive course
- AIDS-related variant
  - An aggressive variant that may involve any anatomic site
- Kaposi's sarcoma has been recently linked to human herpes virus type 8 which may play an important role in its pathogenesis

Microscopic

- The microscopic is similar in all of the above variants
- In the patch stage, a few, irregular and infiltrating small vessels are present predominantly within the superficial dermis
- The vessels infiltrate adnexa and frequently grow in a vessel-around-vessel pattern, the "promontory sign"
- Scattered lymphocytes, plasma cells and extravasated erythrocytes are evident within the dermis, and hemosiderin deposition is also frequently present
- The plaque stage shows, in addition to the above, a transdermal infiltrate with spindle cell areas arranged in irregular fascicles
- The spindle cell component has characteristic sieve-like spaces with extravasated erythrocytes, mild nuclear pleomorphism, occasional mitotic figures and eosinophilic hyaline globules

- The nodular variant is composed almost exclusively of a fairly well circumscribed, nodular, dermal and/or subcutaneous proliferation of spindle cells in fascicles with similar features to the plaque stage

Malignant Vascular Tumors

Angiosarcoma

Clinical

- Three clinical variants exist
- Idiopathic angiosarcoma of the face and scalp of the elderly
  - This variant presents as multiple bruise-like, infiltrating plaques and nodules
- Post-irradiation angiosarcoma
  - Infiltrating, plaques, ulcers or nodules occurring years after radiation to the involved site
- Lymphedema associated angiosarcoma (Stewart-Treves syndrome)
  - Angiosarcomas arising in the setting of prolonged lymphedema, usually post-mastectomy patients
- The overall survival for patients with cutaneous angiosarcoma is poor with frequent recurrences and early lymph node and visceral metastases characterizing their clinical course

Microscopic

- All three clinical variants of angiosarcoma show the same spectrum of histologic findings
- Well-formed, small, often slit-like, vessels that interanastomose and dissect the dermal collagen in an infiltrative fashion characterize the low-grade variants
- The endothelial cell lining may be flattened and nondescript, but areas with nuclear hyperchromasia, mitotic activity and stratification are usually evident
- A papillary network lined by atypical endothelial cells may be prominent
- High-grade lesions are typically more cellular and are composed of sheets or fascicles of polygonal, epithelioid or spindle cells with nuclear pleomorphism, mitoses and often prominent nucleoli
- Well-formed vascular structures may be scant, but intracytoplasmic lumina are often identified and aid in the differential diagnosis

Special Studies

- CD31, CD34, FVIII and Ulex europaeus I lectin stain, to a variable degree, endothelial-derived tumors
- CD31 is probably the most specific and sensitive endothelial cell marker amongst this group

Tumors of Perivascular Cells

Glomus Tumor

Clinical

- These tumors of specialized arteriovenous anastomoses (Sucquet-Hoyer canal) most often present as painful, red-blue nodules on the fingers, but any cutaneous site may be involved
- A multicentric variant with autosomal dominant inheritance exists

Microscopic

- These tumors are characterized by a well-circumscribed, deep dermal proliferation of small vessels and a variable number of round to polygonal cells with eosinophilic cytoplasm and uniform, round to ovoid nuclei
- Rarely, mild, degenerative nuclear pleomorphism may be present
- The glomangioma, a common variant, has, in addition to the above, a component of large, cavernous vascular structures
- Tumors that also have a proliferation of smooth muscle, usually perivascular, have been called glomangiomyoma
- Rare malignant glomus tumors have also been described

Special Studies

- The glomus cells are smooth muscle actin+, vimentin+ and may stain for desmin

Hemangiopericytoma

General

- A controversial neoplasm that rarely involves the skin, this tumor is a diagnosis of exclusion as its histologic pattern may be mimicked by a wide variety of neoplasms
- This tumor is discussed in more detail in the soft tissue pathology chapter

Melanocytic Proliferations and Pigmentary Disorders

Pigmentary Disorders of the Skin

Melasma

Clinical

- An, acquired, symmetrical, brown hypermelanosis of the face that is more common in women

Microscopic

- An increase in melanin deposition within the basal epidermis and/or within dermal melanophages

Freckle (Ephelid)

Clinical

- Small, well-demarcated red-brown macules on sun-exposed areas. The lesions darken with sun exposure

Microscopic

- Basal keratinocyte hyperpigmentation without elongation of the rete ridges

Postinflammatory Hyperpigmentation

Clinical

- An acquired excess of melanin pigmentation in areas of preceding inflammation

Microscopic

- Increased melanophages within the superficial dermis with/without basilar keratinocyte hyperpigmentation

Dowling-Degos Disease

Clinical

- An autosomal dominant disorder characterized by reticulated, pigmented macules of the flexural areas in combination with pitted, perioral, acneiform scars and comedone-like lesions on the neck and back

Microscopic

- Filiform to antler-like epidermal downgrowths in association with basilar keratinocyte hyperpigmentation, dermal melanosis and mild dermal lymphohistiocytic inflammation

Kitamura's Reticulate Hyperpigmentation

Clinical

- An autosomal dominant disorder characterized by reticulated, depressed pigmented macules on the dorsal hands and feet with pits and breaks on the palms and soles

Microscopic

- Basilar hyperpigmentation with elongation of the rete ridges and epidermal atrophy

Vitiligo

Clinical

- Acquired, depigmented, white patches surrounded by a normal or hyperpigmented border

Microscopic

- Absence of melanocytes within the depigmented areas

Albinism

Clinical

- An inherited disorder of the tyrosinase gene characterized by the lack of ocular pigment (ocular albinism; X-linked recessive) or the lack of ocular, follicular and cutaneous pigment (oculocutaneous albinism; autosomal recessive)

Microscopic

- Normal appearing epidermis containing a normal complement of melanocytes but a complete or markedly reduced amount of melanin production

Piebaldism

Clinical

- An autosomal dominant disorder with onset at birth characterized by a stationary hypomelanosis of the skin and hair involving the lateral trunk, arms, legs and forehead (white forelock)

Microscopic

- Absence of melanocytes and melanin within affected regions

Nevus Depigmentosus

Clinical

- A congenital, stable hypopigmented macule or patch on the trunk or extremities

Microscopic

- Normal number of melanocytes but reduced melanin production within the lesional areas

Idiopathic Guttate Hypomelanosis

Clinical

- Numerous, small hypopigmented macules on the sun-exposed surface of the extremities

Microscopic

- Marked reduction of melanin granules within lesional skin in association with epidermal atrophy and flattening of the rete ridges

Café-au-Lait Spot

Clinical

- Light brown, pigmented macule that may be found on any cutaneous surface and, if numerous, may be associated with neurofibromatosis

Microscopic

- Increased melanocytes and increased melanin production within the basal epidermis

Electron Microscopy

- Macromelanosomes

Becker's Nevus (Becker's Melanosis)

Clinical

- A hamartomatous lesion characterized by a hyperpigmented patch with hypertrichosis over the shoulder region or back

Microscopic

- Slight epidermal acanthosis/papillomatosis with basal keratinocyte hyperpigmentation and dermal melanosis
- A dermal, smooth muscle hamartomatous component may also be present

Mucosal Melanotic Macules

Clinical

- A pigmented macule/patch on the mucosa of the oral or genital region

Microscopic

- Basilar keratinocyte pigmentation with or without dermal melanosis

Benign Melanocytic Proliferations

Mongolian Spot

Clinical

- A slate-blue patch on the lower back of newborns and infants, often of Asian or African descent
- The lesions typically regress over time

Microscopic

- Long, wavy, variably pigmented, individual melanocytes are present within the deep dermis and are oriented parallel to the overlying epidermis

Nevus of Ito and Ota

Clinical

- Both of these lesions present as a slate-blue to mottled macule or patch which may be congenital or develop in adolescence
- The nevus of Ito typically involves the skin of the scapular, deltoid or supraclavicular regions while the nevus of Ota involves the skin of the face, usually in a unilateral fashion
- The nevus of Ota may be associated with ipsilateral scleral, conjunctival, corneal or retinal pigmentation
- The pigmentation persists
- These lesions may be present individually or in combination with one another or with the mongolian spot

Microscopic

- Both of these entities are characterized by the presence of pigmented, spindled and dendritic, individual melanocytes within the mid and upper dermis

Blue Nevi

Clinical

- Two subtypes exist
- A small, well-circumscribed blue to blue-black papule on the hands or feet characterizes the common blue nevus
- A 1-3cm or larger blue to blue-gray plaque on the sacrum or buttocks typifies the cellular blue nevus

Microscopic

- Common blue nevus: a symmetrical and fairly well circumscribed proliferation of spindled to dendritic nevomelanocytes within the dermis
- The dermis frequently is sclerotic within the lesional area
- Cellular blue nevus
- Typically a large, dermal and/or subcutaneous, symmetrical nodule composed of an admixture of spindled, dendritic, and rounded nevomelanocytes
- The spindled and dendritic component predominates at the periphery of the lesion while nests of more rounded nevomelanocytes with melanophages are more common centrally
- Atypical variants may show nuclear pleomorphism, mitotic activity, an infiltrating architecture and even necrosis

Solar Lentigo

Clinical

- A uniformly pigmented macule/patch on areas chronically exposed to sunlight
- Solar lentigines are frequently multiple and are markers of increased risk of melanoma development

Microscopic

- Elongation of the rete ridges with basilar keratinocyte hyperpigmentation and a mild to marked proliferation of basilar melanocytes in a lentiginous (single cell, non-nested) fashion

Lentigo Simplex

Clinical

- A congenital or acquired, sharply demarcated, round to oval, macular area of hyperpigmentation, usually less than 5mm in diameter
- Most lesions develop in childhood, but new lesions may form in adulthood
- Multiple lesions may be associated with the LEOPARD, NAME or Peutz-Jeghers syndromes
- The speckled lentiginous nevus (nevus spilus) is a variant characterized by a light brown patch with superimposed, darkly pigmented macules

Microscopic

- Mild to moderate elongation of the rete ridges in association with basilar and, often, suprabasilar keratinocyte hyperpigmentation and a lentiginous proliferation of bland nevomelanocytes
- Some lentigines show focal junctional nesting and, hence, overlapping features with a junctional nevus
- The term “jentigo” has, at times, been used for such lesions

Common Melanocytic Nevi

Clinical

- Benign, melanocytic proliferations that typically develop in childhood and adolescence
- The appearances of common melanocytic nevi vary from pigmented macules/papules to flesh-colored nodules to papillomatous lesions depending on the relative degree of junctional versus dermal activity and the site of origin
- These nevi are typically small (<1cm), evenly pigmented, symmetrical and sharply bordered
- The presence of large numbers of nevi on a single individual is a marker of increased risk of melanoma

Microscopic

- Common melanocytic nevi are characterized by symmetrical and well circumscribed proliferations of bland, round nevomelanocytes as nests along the dermal-epidermal junction and/or within the dermis
- The dermal component, if present, shows maturation and lacks significant mitotic activity or cytologic atypia
- The junctional component may show nevomelanocytic nests with or without an accompanying lentiginous melanocytic proliferation
- The nests within the junctional component are uniform in size and spacing and are typically limited to the basal epidermis

Dysplastic Nevus (Clark's Nevus, Atypical Nevus, B-K Mole)

Clinical

- A tan-brown to black, irregularly and asymmetrically pigmented macule/papule, usually >5mm in diameter
- Multiple lesions may be inherited as the B-K mole (dysplastic nevus) syndrome or the familial atypical mole syndrome
- This syndrome(s) is associated with a markedly increased risk of melanoma development. Most lesions are sporadic and are associated with a lesser risk of melanoma development

Microscopic

- Typically a compound nevomelanocytic proliferation showing a spectrum of architectural and cytologic features which include
- Junctional shouldering
- Lamellar dermal fibrosis
- Bridging of the rete ridges by melanocytic nests
- Melanocytic nuclear pleomorphism with nucleoli
- Early upward migration of melanocytes within the epidermis
- Perivascular chronic inflammation at the base of the lesion

Spitz Nevus (Spindle and Epithelioid Cell Nevus)

Clinical

- Smooth-surfaced, round, sharply circumscribed, pink to red papule most commonly involving the face and/or the extremities of children to young adults

Microscopic

- Spitz nevi are generally well circumscribed and symmetrical proliferations which may be junctional, compound or dermal
- The nuclear pleomorphism that is present within these lesions may be mistaken for malignant melanoma
- The prototypical Spitz nevus has the following histologic features
- Epidermal hyperplasia
- Hypergranulosis
- Kamino bodies (cytoid bodies)
- Large junctional nests of epithelioid to spindled melanocytes
- Clefting between the junctional nests and the epidermis
- Deep dermal maturation
- Nuclear pleomorphism with nucleoli
- Additional features that may be present and may mimic melanoma include
- Brisk mitotic activity
- Upward epidermal migration of melanocytes
- Adnexal involvement

Congenital Nevus

Clinical

- A variant of the melanocytic nevus which is present at birth
- Congenital nevi are often divided into three groups based on their size: small (<1.5 cm), medium (1.5-20 cm) and large (>20cm).
- These nevi are typically brown to black and frequently show an irregular surface with hypertrichosis
- Congenital nevi are associated with an increased risk of melanoma development; the risk is greatest for the large congenital nevi, which may show malignant transformation in up to 20% of cases

Microscopic

- Congenital nevi are similar to the common melanocytic nevi in that they are symmetrical, well-circumscribed proliferations with deep maturation
- They differ from common melanocytic nevi by having involvement of the deep reticular dermis/subcutis and by showing frequent involvement of adnexal structures

Deep Penetrating Nevus

Clinical

- A darkly pigmented, uniform papule/nodule most often presenting on the trunk or extremities of young adults

Microscopic

- A distinctly, wedge-shaped proliferation of uniformly atypical melanocytes within the dermis and, occasionally, along the dermal-epidermal junction
- The nevomelanocytes are arranged into poorly formed nests and irregular fascicles which extend into the deep reticular dermis and/or subcutis without deep maturation
- These nevomelanocytes have nuclear pleomorphism and nucleoli, but mitotic figures are absent to scarce
- Dense melanin pigmentation is present throughout the lesion within the melanocytes and adjacent melanophages

Halo Nevus

Clinical

- A typical melanocytic nevus with a surrounding zone of depigmentation

Microscopic

- A chronically inflamed nevus of any type
- The lymphocytes are densely arranged within the dermal component of the nevus and may completely obscure the underlying melanocytic lesion
- The remaining melanocytes may show some degree of atypia and disorganization, but the typical features of a regressing melanoma are absent

Malignant Melanoma

Clinical

- The majority of melanomas show a variegated, asymmetrical distribution of dark brown to black pigment within a lesion of greater than 0.5 cm in diameter
- However, amelanotic melanomas do exist and may mimic other neoplasms
- Melanomas are divided clinicopathologically into four basic subtypes
- Superficial spreading malignant melanoma
  - Accounts for approximately 60% of melanomas
  - Related to sun exposure
  - Shows both a macular and a nodular appearance clinically
  - May affect all age groups but predominates in adults
- Lentigo maligna melanoma
  - Accounts for approximately 10-15% of melanomas
  - Related to sun exposure
  - Largely a disease of the elderly
  - Grows initially as dark macule or patch (lentigo maligna) and develops a papular or nodular component when invasive (lentigo maligna melanoma)
  - Head and neck region most commonly affected
- Nodular malignant melanoma
  - Accounts for approximately 10-20% of all melanomas
  - Nodular, often symmetrical appearance clinically
  - May be amelanotic
- Acral-lentiginous melanoma
  - Accounts for 5-10% of all melanomas
  - Tumors of the palms, soles, nails, and genitalia
  - Most common melanomas of dark-skinned races

Prognostic Factors

- Tumor thickness is the most important prognostic factor at present, as measured by Clark level or Breslow depth
- Ulceration
- Lymphatic invasion
- Location of the primary melanoma
- Signs of regression
- Sex
- Age

Microscopic

- Almost all melanomas begin as epidermal proliferations which, if left unchecked, may invade into the dermis and underlying tissues
- Melanomas have a constellation of atypical cytologic and architectural features that may be present in varying portions within a given lesion including
- Architectural asymmetry
- Poor circumscription
- Upward epidermal migration of melanocytes, nested or single
- Melanocytic nests vary in size, shape and distribution
- No deep maturation of melanocytes
- Cytologic atypia in the form of nuclear pleomorphism, prominent nucleoli and mitotic figures
- Invasion of lymphatic spaces and nerves
- Adnexal involvement
- The lentiginous variants of melanoma show a predominant single, non-nested proliferation of melanocytes within the epidermis with or without upward epidermal migration
- The invasive component may be nested or may show a distinct spindled appearance with or without neurotropism (desmoplastic melanoma)
- The superficial spreading variant of melanoma shows a nested epidermal component with prominent upward

epidermal migration, and the invasive component is typically nested but may be spindled

- The nodular melanoma is largely a dermal tumor with a minor, overlying epidermal component

Staging (See TNM Classifications)

- Stage I
  - Tumor thickness 1.5 mm or less
- Stage II
  - Tumor thickness 1.51-4.00 mm
- Stage III
  - Tumor thickness greater than 4 mm or nodal and/or satellite metastases
- Stage IV
  - Tumor metastatic to distant sites

Lymphoproliferative Disorders and Leukemias (also see Chapter 7)

Classification of Cutaneous Lymphomas

- A variety of cutaneous lymphomas exist, many of which differ significantly from their systemic counterparts in terms of histologic features, behavior and/or treatment
- In 1997, the European Organization for Research and Treatment of Cancer (EORTC) proposed a new, cutaneous lymphoma classification based on clinical, histologic and immunophenotypic criteria with an emphasis on disease entities rather than histologic subgroups
- While this is a significant departure from the REAL and WHO classifications of lymphoma, the EORTC classification is a significant advance in our understanding of cutaneous lymphomas and sets the groundwork for future lymphoma classification
- The following lymphoma discussion will focus on the EORTC classification of lymphoma, and the reader is urged to refer to the systemic lymphoma chapter for comparison (Chapter 7)

EORTC Classification

- Primary Cutaneous T-Cell Lymphoma (CTCL)
  - Indolent
    - Mycosis fungoides (MF)
    - MF + follicular mucinosis
    - Pagetoid reticulosis
    - Large cell CTCL, CD30+
      - Anaplastic
      - Immunoblastic
      - Pleomorphic
    - Lymphomatoid papulosis
  - Aggressive
    - Sézary syndrome
    - Large cell CTCL, CD30-
      - Immunoblastic
      - Pleomorphic
  - Provisional
    - Granulomatous slack skin
    - CTCL, pleomorphic small/medium-sized
    - Subcutaneous panniculitis-like T-cell lymphoma
- Primary Cutaneous B-Cell Lymphoma
  - Indolent
    - Follicular center cell lymphoma
    - Immunocytoma (marginal zone lymphoma)
  - Intermediate
    - Large B-cell lymphoma of the leg
  - Provisional
    - Intravascular B-cell lymphoma
    - Plasmacytoma

Primary Cutaneous Follicular Center Cell Lymphoma

Clinical

- Solitary or grouped papules, nodules or plaques
- Head and neck region most commonly involved
- May be associated with annular erythemas
- Rarely disseminate but frequently recur

Microscopic

- A tumor composed of follicular center cells either in the form of centrocytes (cleaved cells) or centroblasts
- Tumor cells are arranged into ill-defined nodules or diffuse sheets
- Germinal center formation may or may not be present

Immunophenotype

- CD20+, CD79a+, usually surface immunoglobulin (Sig)+
- CD5-, CD10-, bcl-2-

Differential Diagnosis

- Marginal zone lymphoma
- Lymphoid hyperplasia
- Systemic follicular lymphoma (bcl-2+)

Immunocytoma (Marginal Zone Lymphoma)

Clinical

- Solitary or multiple tumors/nodules
- Extremities most often involved
- Excellent long term survival ~ 100%

Microscopic

- Nodular or diffuse, often bottom-heavy infiltrates
- Benign germinal centers usually present
- Malignant small lymphocytes, plasmacytoid lymphocytes, plasma cells and centrocyte-like cells infiltrate diffusely outside of the germinal centers and may encroach upon the germinal centers
- Reactive T-cells, eosinophils and histiocytes are frequently admixed throughout the neoplasm

Immunophenotype

- CD20+, CD79a+, CD43+/–, Sig+, cytoplasmic immunoglobulin (Cig)+
- CD5–, CD23–, cyclinD1–

Differential Diagnosis

- Lymphoid hyperplasia
- Follicular lymphoma

Large B-Cell Lymphoma of the Leg

Clinical

- Red to blue nodules/plaques involving one or both legs
- Typically affects older patients, >70 y/o
- Frequently disseminates
- ~50% five year survival

Microscopic

- Diffuse, sheet-like proliferation of large atypical lymphocytes
- Epidermotropism is generally absent
- The large lymphocytes may have centrocytic, centroblastic or immunoblastic features

Immunophenotype

- CD20+, CD79a+, bcl2+, Sig+/–

Genotype

- No t(14,18) translocation

Intravascular Large B-Cell Lymphoma

Clinical

- Violaceous, indurated plaques or patches
- Lower extremities most often involved
- Central nervous system involvement may also be present
- Poor prognosis

Microscopic

- Large atypical lymphocytes are present within dilated vessels of the dermis and/or subcutis
- Rarely, atypical lymphocytes may be present adjacent to the vessels

Immunophenotype

- CD20+, CD79a+, Sig+

Plasmacytoma

Clinical

- Solitary or multiple nodules involving any cutaneous surface
- Excellent prognosis
- No evidence of myeloma

Microscopic

- Diffuse sheets of mature or atypical plasma cells

Immunophenotype

- CD79a+, CD20–, Cig+

Mycosis Fungoides

Clinical

- Persistent, erythematous patches and/or plaques which may progress to tumors over the course of many years
- Annular and serpiginous plaques may be present
- Trunk and extremities most commonly involved
- Generally an indolent disease with tumor formation and systemic spread occurring only after many years to decades

Microscopic

- A band-like, epidermotropic proliferation of variably sized lymphocytes is present in the superficial dermis
- The epidermotropic lymphocytes frequently populate the basal layer of the epidermis and are generally unassociated with spongiosis
- The epidermotropic lymphocytes may aggregate into intraepidermal microabscesses (Pautrier's microabscesses)
- The epidermotropic lymphocytes are frequently larger than those within the dermis and display varying degrees of nuclear convolution and cerebriform change
- The tumor stage shows a more diffuse, often sheet-like, proliferation of atypical, often large, lymphocytes with or without epidermotropism

Immunophenotype

- CD3+, CD4+, CD7+/–, CD8–, CD30–
- Rare CD8+ variants exist

Mycosis Fungoides with Follicular Mucinosis

Clinical

- Erythematous papules or plaques typically affecting the head and neck region
- Hair loss within the affected regions
- Typically affects adult patients

Microscopic

- Marked folliculotropism of atypical lymphocytes
- Mucinous degeneration of follicular epithelium
- Lymphocytes usually have the atypical nuclear features of mycosis fungoides, and epidermotropism may be evident

- Eosinophils are often present

Immunophenotype

- Similar to mycosis fungoides

Differential Diagnosis

- Primary (idiopathic) variants of follicular mucinosis affect younger individuals and appear unrelated to mycosis fungoides
- Other systemic diseases may show secondary follicular mucinosis (e.g. lupus erythematosus)

Pagetoid Reticulosis

Clinical

- Hyperkeratotic patches or plaques limited to a distal extremity (Woringer-Kolopp type)
- No systemic involvement present
- Excellent prognosis
- The systemic or disseminated form (Ketron-Goodman type) is best considered to be mycosis fungoides

Microscopic

- A distinctly epidermotropic proliferation of large atypical lymphocytes with irregular, often cerebriform, nuclei
- Minimal to no dermal component

Immunophenotype

- Similar to mycosis fungoides

CD30+ Lymphoproliferative Disorders Including Lymphomatoid Papulosis and CD30+ Large, T-Cell Lymphoma

General

- Lymphomatoid papulosis (LyP) and CD30+, large, T-cell lymphoma are part of a spectrum of related clinicopathologic entities having in common a good prognosis and numerous CD30+ large lymphocytes histologically (see Table 9-1)

Sezary Syndrome

Clinical

- Generalized erythroderma in association with generalized lymphadenopathy and leukemic infiltration of the blood by malignant T-cells
- Alopecia, palmoplantar keratoderma and leonine facies are common findings
- Poor prognosis with a 5 year survival of less than 50%

Microscopic

- Similar to mycosis fungoides but epidermotropism may be absent

Immunophenotype

- Similar to mycosis fungoides

Large Cell Cutaneous T-Cell Lymphoma, CD30-

Clinical

- Solitary, localized or generalized plaques, nodules or tumors
- Rapid development of generalized skin involvement is common
- No preceding mycosis fungoides
- Aggressive clinical course with a ~ 15% five year survival

Microscopic

- Diffuse to nodular infiltrates of medium to large-sized atypical lymphocytes
- Large cells comprise >30% of all cells
- Angiocentricity is common
- Epidermotropism may be present but is not marked

Table 9-1: Comparison of Lymphomatoid Papulosis (LyP) and CD30+ Cutaneous T-Cell Lymphoma (CTCL)

	LyP	*CD30+CTCL*
Clinical		
• Lesion type	Multiple	Single or grouped
• Size of lesion(s)	<1cm	>1cm
• Distribution	Extremities /trunk	Extremities/ head/neck
• Remit	100%	25-50%
• Systemic spread	None	25%
• 5yr survival	100%	90%
• Age	Any age	Older adults
Microscopic		
• Pattern	Wedge-shaped	Diffuse sheets
• Subcutis	Spared	Involved
• Inflammation	Marked	Sparse
• Necrosis	Rare	Common
• Epidermotropism	Common	Tare
Immunophenotype and Molecular Genetics		
• CD30+ pattern	CD30+ Clusters	CD30+ Sheets
• Immunophenotype	CD3+, CD4+	CD3+/-, CD4+/-
• TCR clonality	10-20%	Usually +
• t(2,5) translocation	±	±

Immunophenotype

- CD3+, CD30-, CD4+/-

Granulomatous Slack Skin

Clinical

- Pendulous plaques involving the axilla and groin regions
- Probably a rare variant of mycosis fungoides
- Males are affected more often than females

Microscopic

- Dense, dermal, atypical lymphocytic infiltrate admixed with numerous multinucleated histiocytes
- Multinucleated cells often have a wreath-like arrangement of nuclei
- Elastolysis is frequently present
- Dermal lymphocytes are generally small and have cerebriform nuclear features

Immunophenotype

- Similar to mycosis fungoides

Pleomorphic Small/Medium-Sized Cutaneous T-Cell Lymphoma

Clinical

- One or more nodules/tumors without preceding mycosis fungoides
- Affects middle-aged to older adults

Microscopic

- Dense, diffuse or nodular infiltrate of small to medium-sized, atypical lymphocytes with or without subcutaneous involvement
- <30% large cells
- Epidermotropism may or may not be present

Immunophenotype

- CD3+, CD4+, CD30-

Subcutaneous, Panniculitis-Like T-Cell Lymphoma

Clinical

- Subcutaneous nodules or plaques typically involving the lower extremities
- Frequent, severe constitutional symptoms
- Hepatosplenomegaly may be present
- Hemophagocytic syndromes are common
- Systemic dissemination is uncommon
- ~50% five year survival

Microscopic

- A variably dense, polymorphous, panniculitis-like infiltrate is present with no or minimal dermal involvement
- The pleomorphic lymphocytes may be small, medium or large T-cells which characteristically "ring" around the adipocytes
- Lipophages, plasma cells, eosinophils, neutrophils and, occasionally, lymphoid follicles may be present
- Necrosis, karyorrhexis, hemophagocytosis and angiodestruction are common

Immunophenotype

- CD3+, CD8+, Tia-1+, porin+, CD56-

Genotype

- Clonal T-cell receptor, alpha/beta genotype most common
- EBV negative

Leukemia Cutis

General

- All forms of leukemia may involve the skin during the course of their evolution
- Most often, this occurs in patients with a known diagnosis of leukemia
- However, cutaneous disease may be the first manifestation of a leukemic process in evolution

Clinical

- Macules, papules, nodules, tumors, plaques and ulcers may all be manifestations of leukemia cutis
- Any cutaneous surface may be involved
- Gingival involvement is particularly characteristic of acute myelogenous leukemia of the monocytic type (AML, M5)

Microscopic

- The most common pattern of leukemic infiltration of skin is the diffuse dermal, reticular or splaying pattern where the neoplastic cells splay apart the dermal collagen fibers in a discohesive fashion
- Perivascular to angiocentric infiltrates are also seen frequently in chronic lymphocytic leukemia (CLL) and in AML
- Nodular patterns of infiltration are also common
- The cytologic features of a particular leukemic infiltrate reflect their systemic cell of origin
- *CLL: small, monotonous lymphocytes
- *AML: myeloblasts with or without eosinophilic myelocytes, differentiated monocytes, etc.
- *CML (chronic myelogenous leukemia): a spectrum of granulocytic cells and myeloblasts
- *ALL (acute lymphoblastic leukemia): medium-sized, fairly monotonous lymphoblasts

Immunophenotype

- CLL: CD20+, CD23+, CD5+, CD43+/-, CD3-
- AML: CD3-, CD20-, CD43+, MPO+/-, CD68+/-
- CML: CD3-, CD20-, CD43+, MPO+
- ALL: CD3 or CD20+, TdT+/-, MPO-

IMMUNODERMATOLOGY

Methods, Terminology and Techniques

Direct Immunofluorescence (DIF)

- A skin biopsy that has been snap frozen or placed in transport media (such as Michel's media) is incubated with fluorescein conjugated antibodies against immunoglobulin and complement
- Standard panel of conjugates includes IgG, IgA, IgM, C3 and fibrinogen

Indirect Immunofluorescence (IIF)

- The patient's serum is incubated with normal human skin that has been split at the level of the lamina lucida using 1.0M NaCl (salt-split skin).
- Fluorescein conjugated antibodies to IgG are then added
- If circulating antibody to basement membrane zone is present, the conjugate will localize to the epidermal side, the dermal side or to both
- This pattern reflects the location of the immune deposits (for example hemidesmosome or sublamina densa) and allows distinction between certain immunobullous diseases
- The titer of the circulating antibody is determined by incubating the patient's serum with fluorescein conjugated antibodies to IgG on an epithelial substrate, usually monkey esophagus
- Other substrates may be used in specific conditions, such as rat bladder epithelium for paraneoplastic pemphigus or guinea pig esophagus for pemphigus foliaceus
- Progressively more dilute samples of patient serum are used (1:5, 1:10, 1:20, 1:40, 1:80, 1:160, 1:320, 1:640, 1:1280 and so on)
- The dilution at which fluorescence can no longer be subjectively identified is the antibody titer
- Indirect immunofluorescence can also be performed using fluorescein conjugated antibodies to IgA
- This is helpful for diseases involving IgA, such as linear IgA bullous dermatosis and dermatitis herpetiformis

Western Immunoblotting

- A more specific technique to identify the antigens that the patient's antibodies are directed against

ELISA

- Enzyme linked immunosorbant assays have recently been developed for a number of immunobullous diseases
- These allow rapid, sensitive and specific identification of antibodies

Immunobullous Diseases

Patterns of Antibody Deposition

- A. Linear deposition along the basement membrane zone
- B. Deposition in intercellular spaces
- C. Granular deposition along the basement membrane zone
- D. Granular deposition in the dermal papillae
- E. Cytoid bodies and shaggy deposition along the basement membrane zone
- F. Thick linear deposition along the basement membrane zone and perivascular deposition
- G. Deposition on eosinophils and diffuse deposition on connective tissue
- H. Deposition in blood vessels

Linear Deposition Along the Basement Membrane Zone

Bullous Pemphigoid (BP)

Clinical

- Most commonly occurs in the elderly but has been reported in children and neonates
- Clinical presentation characteristic for pruritic tense bullae (negative Nikolsky sign) that heal without scarring
- The primary lesion is often urticarial
- Brunsting-Perry pemphigoid is a clinical subtype with scarring
- Distribution is mainly flexural, lower extremities and trunk
- Mucous membrane lesions occur in 10%- 30%

Microscopic

- Typically shows subepidermal separation with inflammatory infiltrate of eosinophils and lymphocytes
- Eosinophilic spongiosis may be present
- Neutrophils may also be seen, but are not prominent
- Basal layer spongiosis without frank separation may be seen in early or perilesional biopsies

Electron Microscopy

- Separation occurs within the lamina lucida

Immunopathology

- DIF on a perilesional skin biopsy specimen shows linear deposition of antibody (IgG > IgA) and complement at the basement membrane zone

- Eosinophils are often prominent
- IIF using salt-split human skin demonstrates localization of the antibody to the epidermal side of the split
- A combined pattern (epidermal and dermal) is occasionally seen
- Indirect immunofluorescence detects circulating IgG basement membrane zone antibodies in 50 to 70% of patients
- The antibody titer is not predictably correlated with disease activity or prognosis
- Implicated antigens
  - Most commonly detected antigen is a 230-Kd hemidesmosomal cytoplasmic protein (BP antigen I)
  - The second most commonly detected is a 180-Kd hemidesmosomal transmembrane protein (BP antigen II)

Cicatricial Pemphigoid

Clinical

- Characterized by inflammation and scarring of the mucosal membranes, most commonly conunctiva
- May also involve oral and genital mucosa
- Primary oral lesion is often desquamative gingivitis
- Skin lesions are less common, but can occur
- Ocular scarring may lead to synblepharon, decreased tear production, entropion and blindness

Microscopic

- May see subepithelial separation but usually see nonspecific mucositis with inflammatory infiltrate of eosinophils, plasma cells and lymphocytes
- Neutrophils may also be present, but are not prominent

Electron Microscopy

- Separation occurs at the level of the lamina lucida

Immunopathology

- DIF pattern is identical to that seen in bullous pemphigoid
- There is linear deposition of IgG, IgA and C3 along the basement membrane zone
- Eosinophils are often present in the lamina propria
- IIF usually does not detect circulating antibodies
- When antibodies are present, IIF using salt-split skin localizes the antibodies to the epidermal side in some cases, and to the dermal side in others

Implicated Antigens

- Most commonly implicated antigens are the same as for bullous pemphigoid (230-Kd and 180-Kd hemidesmosomal proteins), corresponding to the epidermal pattern of binding on salt-split skin
- Some patients have antibodies to epiligrin (laminin 5), a component of the anchoring filaments
- This subset of patients has been associated with the dermal pattern of binding on salt-split skin

Herpes Gestationis (Pemphigoid Gestationis)

Clinical

- Occurs exclusively in women
- Characterized by pruritic tense bullae (negative Nikolsky sign) that heal without scarring
- Primary lesion is often urticarial
- May begin around the umbilicus
- Usually most prominent on abdomen and flexural skin
- Mucosal lesions are very rare
- Most commonly occurs during the second or third trimester of pregnancy and resolves after delivery
- Post-partum flares can occur
- In subsequent pregnancies, the eruption occurs earlier and is more severe
- May also occur with hormonal medication or menses in susceptible women
- Has been reported with molar pregnancy and gestational malignancy

Epidemiology

- Increased frequency of HLA-B8, DR3 and DR4

Microscopic

- Usually identical to bullous pemphigoid
- Typically see subepidermal separation with inflammatory infiltrate of eosinophils, lymphocytes and occasionally neutrophils
- Early or perilesional biopsies may not show frank separation
- Basal cell necrosis may be more prominent than in bullous pemphigoid
- Might see eosinophilic spongiosis and/or an inverted tear-drop pattern of epidermal edema

Electron Microscopy

- Separation occurs within the lamina lucida

Immunopathology

- DIF shows linear deposition of complement along the basement membrane zone
- Linear deposition of IgG may also be present, but is less prominent than complement
- This pattern reflects the nature of the circulating antibody, referred to as “herpes gestationis factor” (HG factor)
- HG factor is an IgG antibody (usually IgG1) that avidly fixes complement
- It is often present in such low titers that DIF and IIF fail to identify it, but the complement it fixes can be detected
- IIF is usually negative

- Low titers of circulating IgG antibodies to basement membrane zone are identified in less than 20% of patients
- When present, salt-split skin localizes these antibodies to the epidermal side of the separation

Implicated Antigens

- The majority of patients have antibodies that are directed against the minor bullous pemphigoid antigen, BP antigen II (180-Kd transmembrane hemidesmosomal protein)
- A smaller group of patients have antibodies directed against the major bullous pemphigoid antigen, BP antigen I (230-Kd cytoplasmic hemidesmosomal protein)

Epidermolysis Bullosa Acquisita (EBA)

Clinical

- Adults are affected more commonly than children
- Racial differences are seen, with blacks affected more frequently
- Three different clinical patterns are observed:
- A mechanobullous eruption with non-inflammatory blisters and increased skin fragility in an acral distribution, that heals with scarring and milia. This is the most frequent presentation
- An inflammatory ("bullous pemphigoid-like") vesicobullous eruption that heals without scarring or milia
- Mucosal erosions with scarring ("cicatricial pemphigoid-like")
- All three types of lesions may be present; considerable overlap exists
- Associated diseases include systemic lupus erythematosus, other diseases of autoimmunity (inflammatory bowel disease, Goodpasture's syndrome, glomerulonephritis, rheumatoid arthritis, thyroiditis, diabetes) and malignancy (multiple myeloma, chronic lymphocytic leukemia)
- Prognosis is generally poor

Epidemiology

- Increased incidence of HLA-DR2

Microscopic

- If a non-inflamed mechanobullous lesion is biopsied, microscopic will show a subepidermal separation with minimal inflammation
- If clinical lesion is inflamed, biopsy will have subepidermal separation with neutrophils, eosinophils and lymphocytes along the basement membrane and in the upper dermis
- Neutrophils tend to predominate over eosinophils
- Basal layer spongiosis without frank separation may be seen in early or perilesional biopsies

Electron Microscopy

- Separation usually occurs at the level of the lamina densa/sublamina densa
- Occasionally occurs in the lamina lucida

Immunopathology

- DIF has a pattern identical to bullous pemphigoid, with linear deposition of IgG and complement along the basement membrane zone
- IgA, IgM and fibrinogen are less commonly present. Indirect immunofluorescence is necessary to distinguish EBA from pemphigoid
- IIF on salt-split skin shows a dermal pattern of binding
- Circulating IgG antibody to basement membrane zone is commonly present

Implicated Antigens

- The majority of patients have antibodies that are directed against the 290-Kd non-collagenous domain (NC-1) on the alpha chain of collagen type VII (anchoring fibrils)
- Rarely, antibodies to a 145-Kd non-collagenous globular domain on the alpha chain of collagen type VII have been identified

Bullous Systemic Lupus Erythematosus (BSLE)

Clinical

- Patients with systemic lupus erythematosus may also develop autoimmunity to basement membrane zone
- These patients present with a blistering eruption, especially on sun-exposed skin
- They will also have other signs and symptoms of systemic lupus
- They do not usually have other cutaneous manifestations of lupus
- Patients with systemic lupus can also have blistering for other reasons, such as concurrent primary bullous disease or severe medication or photosensitivity reaction

Epidemiology

- Increased incidence of HLA-DR2

Microscopic

- Typically shows subepidermal separation with inflammatory infiltrate of neutrophils and lymphocytes in the dermal papillae (as in dermatitis herpetiformis) and along the basement membrane zone
- Neutrophils predominate

Immunoelectron Microscopy

- IgG and complement are deposited in the sublamina densa
- Separation occurs at the level of the sublamina densa

Immunopathology

- DIF shows either linear or granular to fibrillar deposition of IgG and complement along the basement membrane zone
- IgM and IgA are occasionally present
- IIF using salt-split skin demonstrates immune deposits on the dermal side of the separation
- Circulating IgG to basement membrane zone is present in some but not all patients
- Antinuclear antibodies are often seen

Implicated Antigens

- As in EBA, the majority of patients have antibodies that are directed against the 290-Kd non-collagenous domain (NC-1) on the alpha chain of collagen type VII (anchoring fibrils)
- Rarely, antibodies to a 145-Kd non-collagenous globular domain on the alpha chain of collagen type VII have been identified
- Antibody specificity is the same as that seen in epidermolysis bullosa acquisita
- In some cases, antibodies to type VII collagen cannot be detected
- Some authors propose two subtypes, BSLE 1 and BSLE 2, based on the presence (BSLE 1) or absence (BSLE 2) of antibodies to type VII collagen

Linear IgA Bullous Dermatosis (Chronic Bullous Disease of Childhood)

Clinical

- Occurs in adults and children, probably more common in children and in women
- Clinically heterogeneous
- Clinical exam shows a vesiculobullous eruption on normal or erythematous skin
- May have a "cluster-of-jewels" appearance
- Commonly occurs on trunk and flexures in adults and on lower abdomen, groin and periorificial in children
- Oral lesions occur in about 70%
- Other mucosal surfaces, including conjunctivae, may be involved
- Disease associations include:
  - Medications (captopril, vancomycin, lithium), gastrointestinal diseases (inflammatory bowel disease, gluten sensitive enteropathy) malignancy (hematogenous, carcinoma, melanoma) various infections, other diseases of autoimmunity
- Prognosis is generally good

Microscopic

- Usually shows subepidermal separation with inflammatory infiltrate of neutrophils, eosinophils and lymphocytes
- Neutrophils predominate over eosinophils, especially in early lesions
- Basal layer spongiosis without frank separation may be seen in early or perilesional biopsies
- May see neutrophilic microabscesses in dermal papillae, similar to dermatitis herpetiformis

Immunoelectron Microscopy

- Mixed findings occur
- In some cases, there is IgA deposition in the lamina lucida (beneath the hemidesmosomes)
- In others cases, IgA is found in the sublamina densa, in association with anchoring fibrils
- IgA may also be found deposited in both locations

Immunopathology

- DIF shows linear deposition of IgA along the basement membrane zone
- IgG, IgM, C3, and fibrinogen may be present but are of lower intensity than IgA
- IIF on salt-split skin may show an epidermal pattern (most common), a dermal pattern or both
- Circulating IgA antibodies (usually IgA1) to basement membrane zone can be identified in 60-70%

Implicated Antigens

- Several different antigens have been identified
- Most common is a 97-Kd component of the anchoring filaments termed LAD-1
- Immune deposition here corresponds to an epidermal pattern of binding on salt-split skin
- Antibodies to a 290-Kd component of collagen type VII have also been identified
- Epitope is different than that of EBA
- Immune deposition here corresponds to a dermal pattern of binding on salt-split skin
- Other antibodies have also been identified
- LABD is likely a heterogeneous group of diseases, with a variety of autoantibodies

Deposition in Intercellular Spaces

Pemphigus

- A group of diseases all characterized by: clinically: cutaneous and/or mucosal blistering or erosions histologically: acantholysis
- Immunopathologically
  - Autoantibodies to epithelial cell surfaces giving an intercellular space pattern of antibody deposition (ICS pattern)

Pemphigus Variants

- Pemphigus vulgaris
- Pemphigus vegetans

- Drug-induced pemphigus
- Pemphigus foliaceus
- Pemphigus erythematosus
- IgA pemphigus
- Paraneoplastic pemphigus

Pemphigus Vulgaris

Clinical

- Most commonly occurs in adults (mean age 50-60) but has been reported in children
- Increased incidence with Ashkenazi jewish or Mediterranean heritage, but no race is exempt
- Oral lesions (erosions) usually develop first
- Disease may be confined to the oral cavity
- Skin lesions are typically flaccid bullae that rupture easily leaving erosions and crusts
- Gentle pressure on the blister roof will cause extension of the bulla (positive Nikolsky's sign) due to the fragility of the surrounding skin
- Any stratified squamous epithelial surface may be involved, including other mucosal surfaces
- Pemphigus vegetans is a clinical subtype characterized by chronic lesions that develop into hyperkeratotic plaques, often in intertriginous sites
- Most commonly implicated medications in drug-induced pemphigus are penicillamine and captopril

Microscopic

- Characteristic for suprabasilar separation with acantholysis
- Basal layer remains attached, with separation at the lateral and apical margins ("tombstoning")
- Acantholysis extending down hair follicles helps to distinguish pemphigus from other causes of acantholysis such as Hailey-Hailey and Darier's disease
- Eosinophilic spongiosis may be present
- There is a mixed inflammatory infiltrate in the dermis
- Pemphigus vegetans has more acanthosis and eosinophilic spongiosis with relatively subtle suprabasilar separation and acantholysis

Electron Microscopy

- First sign is loss of attachment of cell membrane between adjacent keratinocytes, at the level of the desmosome
- Widening of intercellular spaces follows, as desmosomes pull apart
- Intracellular keratin filaments begin to show perinuclear clustering and the acantholytic cells then "round up" and float free

Immunopathology

- DIF shows IgG and C3 bound to the keratinocyte cell surface in an ICS pattern; also referred to as intercellular substance
- May be seen throughout the thickness of the epidermis or only in the deeper levels
- In active disease, IIF is nearly always positive for circulating IgG antibodies to ICS
- False negatives are more likely in drug induced and early disease
- Antibody titer correlates fairly well with disease activity
- False positive "pemphigus-like" antibodies are not uncommon and can be seen with medications (penicillin), infections (dermatophytes), and full thickness epidermal disruption (burns)
- The titer of false positive antibody is usually low (less than 1:80)

Implicated Antigen

- Autoantibodies (IgG4 > IgG1 and IgG3) are directed against desmoglein 3, a 130-kd transmembrane glycoprotein located in desmosomes
- It exists in a molecular complex with plakoglobin, an 85-kd intracellular protein

Pemphigus Foliaceus

Clinical

- Characterized by superficial erosions and crusts flaccid vesicles or bullae may be present
- Usually begins on head/neck (seborrheic distribution) and spreads acrally
- Mucosal lesions are rare
- May be exacerbated by sunlight
- Clinical variants include a sporadic form, a drug-induced form, and an endemic form (Fogo selvagem)
- Fogo selvagem is seen in agricultural and poverty-stricken regions of Brazil and South America
- Familial cases are frequently seen
- Peak incidence in the second and third decade
- The black fly (Simulian pruinosum) has been epidemiologically implicated as a vector
- Sporadic form occurs in elderly patients with no family history
- No environmental factors have been implicated
- Drug-induced form most commonly linked to "thiol" drugs (penicillamine and captopril) but has also been seen with "masked thiols" (penicillins and cephalosporins) and non-thiols (enalapril)
- Other associations include myasthenia gravis and thymoma (benign and malignant)

Microscopic

- As in pemphigus vulgaris, but more superficially located
- Acantholysis occurs in a subcorneal or intraepidermal location

Electron Microscopy

- Acantholysis affects ALL layers, including the basal layer

Immunopathology

- DIF and IIF have findings similar or identical to those seen in pemphigus vulgaris
- DIF cannot reliably distinguish P. vulgaris from P. foliaceus
- In active disease, IIF is nearly always positive for circulating IgG antibodies to ICS
- Antibody titer correlates fairly well with disease activity
- Guinea pig esophagus appears to be better than monkey esophagus as a substrate for detection of antibodies

Implicated Antigen

- Autoantibodies are directed against desmoglein 1, a 160-kd transmembrane glycoprotein located in desmosomes
- Like desmoglein 3 (antigen in P. vulgaris), desmoglein 1 exists in a molecular complex with plakoglobin

Pemphigus Erythematosus

Clinical

- A rare disease characterized by facial lesions with features of both lupus erythematosus and pemphigus foliaceus (or seborrheic dermatitis) and lesions on the trunk more suggestive of pemphigus (flaccid bullae, erosions and crusts)
- Usually photodistributed
- Mucosal lesions are rare
- May occur in any age; mean onset 40-60 years
- Clinical signs of lupus may be present, but usually are not
- When present, lupus is usually mild or localized only
- Antinuclear antibodies are present in 30-60%
- Most commonly associated medications are penicillamine and captopril
- Various autoimmune diseases (myasthenia gravis) and malignancies (bronchogenic carcinoma) have also been associated

Microscopic

- Superficial acantholysis (similar to P. foliaceus) is the main feature
- A subcorneal separation or pustule may be present
- Lichenoid dermatitis may be seen, but changes characteristic of lupus are NOT usually found

Electron Microscopy

- Demonstrates findings similar to early pemphigus
- Most marked changes occur at the level of the stratum granulosum and upper stratum spinosum

Immunopathology

- DIF characterized by the combination of a typical ICS pattern with IgG and/or C3, as well as granular to linear deposition of IgM along the basement membrane zone
- A lupus band is usually NOT present
- As in P. vulgaris and P. foliaceus, IIF is usually positive for circulating antibodies against ICS

Implicated Antigen

- Unknown

IgA Pemphigus (Numerous Synonyms: Intraepidermal Neutrophilic IgA Dermatosis, Atypical Neutrophilic Dermatosis, Intercellular IgA Vesico-pustular Dermatosis and IgA Pemphigus Foliaceus)

Clinical

- A rare disease, only reported in caucasians
- Has been reported in children
- Clinical lesions include flaccid vesicles and pustules, sometimes in an annular or circinate pattern
- Distribution is often central
- Mucosal lesions do not occur
- The clinical course is fairly mild
- Two subtypes are IgA pemphigus of the subcorneal pustular dermatosis type (SPD) and IgA pemphigus of the intraepidermal neutrophilic type (IEN)

Microscopic

- SPD-type has subcorneal separation with neutrophils
- IEN-type has an intraepidermal cleft with neutrophils (slightly deeper than the SPD-type)
- Suprabasilar separation may be seen
- In both types, acantholysis is sparse
- Neutrophilic microabscesses, as seen in dermatitis herpetiformis, have been reported

Immunopathology

- DIF is characterized by deposition of IgA in an ICS pattern
- In general, deposition of C3 and other immunoglobulins does not occur
- Circulating IgA against ICS present in less than half of reported cases

- Circulating anti-ICS IgG (lower titer than anti-ICS IgA) has been rarely reported

Implicated Antigen(s)

- Most likely a heterogeneous group of diseases with antibodies directed against several different antigens
- Most strongly implicated antigen is desmocollin 1, a 115-kd protein found on the extracellular surface of the desmosome, which has been linked to the SPD-type
- A 120-kd protein has been linked to the IEN-type
- Other antigens, including some linked to P. vulgaris, have also been associated

Paraneoplastic Pemphgius

Clinical

- Association between pemphigus and malignancy has long been recognized
- Described as a distinct entity in 1990
- Over 50 cases reported since then
- More common in older adults, but has been reported in children
- Malignancy usually presents first
- Prognosis is very poor; both malignancy and pemphigus are usually treatment resistant
- Hematopoeitic malignancies (CLL, Castleman's tumor, Waldenstrom's macroglobulinemia and non-Hodgkin's lymphoma) have been most commonly associated, but poorly differentiated sarcomas, adenocarcinoma, and even benign thymoma have been linked
- Clinically characterized by severe painful and recalcitrant erosions of mucosal surfaces
- Oral mucosa most commonly involved
- May also affect conjunctivae, genital mucosa and respiratory epithelium
- Cutaneous eruption is polymorphous
- Initially may have a pruritic papulosquamous eruption
- Blisters may later develop, including on palms and soles (reminiscent of erythema multiforme)
- Chronic lichenoid changes have also been described

Microscopic

- In about half of the cases, a combination of histologic features is seen, including:
- suprabasilar separation and acantholysis
- lichenoid changes (vacuolar degeneration, a band-like infiltrate and exocytosis of inflammatory cells)
- dyskeratotic and necrotic keratinocytes (as seen in erythema multiforme)
- Many cases will not have all of these features
- Eosinophilic infiltration is not typically seen
- Atypia of infiltrating cells also not seen

Immunoelectron Microscopy

- Immune complexes present in a variety of locations, including the hemidesmosomes, desmosomal plaques, keratinocyte plasma membrane and extracellular regions of desmosomes

Immunopathology

- DIF has the characteristic combination of an ICS pattern with IgG +/- C3, and linear to granular deposition of C3 +/- IgG along the basement membrane zone
- Other lichenoid features, such as cytoids (dyskeratotic keratinocytes) and shaggy deposition of fibrinogen are variably present
- Circulating IgG against epithelial cell surfaces has been detected on many substrates, including stratified squamous (as in other forms of pemphigus) as well as transitional and columnar epithelium
- Best sensitivity/specificity profile in urinary bladder epithelium (rat and mouse)

Implicated Antigens

- Autoantibodies are directed against a complex of four antigens
- Most strongly and consistently detected are antibodies against a:
- 190-kd protein (identity unknown)
- 210-kd protein (desmoplakin 2)
- Also detected are antibodies against a:
- 230-kd hemidesmosomal protein (bullous pemphgoid antigen 1)
- 250-kd protein (desmoplakin 1)

Granular Deposition Along the Basement Membrane Zone: Lupus Erythematosus

Lupus Variants

- Discoid lupus erythematosus
- Localized
- Disseminated
- Subacute cutaneous lupus erythematosus
- Systemic lupus erythematosus
- Bullous systemic lupus erythematosus

Discoid Lupus Erythematosus (DLE)

Clinical

- DLE is a cutaneous disease, usually not accompanied by systemic signs of lupus
- It is photodistributed and thus typically affects the face, head and neck, chest and upper back
- Disease may be localized or widespread (disseminated)
- More common in young women
- Increased incidence in blacks

- Clinical lesions are patches, papules and plaques
- Characteristic features include telangiectasia, atrophy, scarring and follicular plugging
- Scalp involvement results in scarring alopecia
- Response to treatment (photoprotection, topical steroids and systemic antimalarials) is variable, but tends to be good

Microscopic

- Epidermal atrophy, hyperkeratosis, and thickening of the basement membrane accompany basal liquifactive degeneration, pigment incontinence and a variable degree of lichenoid inflammation
- Periadnexal and perivascular infiltrate is present in the upper and mid dermis
- Follicular infundibular plugging is often seen
- Dermal mucinosis often present

Immunopathology

- On involved or sun-exposed skin, DIF shows granular deposition along the basement membrane zone with IgM, sometimes referred to as a lupus band
- The strict definition of a lupus band reserves the use of the term for the presence of granular IgM along the basement membrane zone in uninvolved and nonsun-exposed skin, as seen in systemic LE
- Granular deposition with other conjugates, including C3, IgA and IgG, is usually present, which helps to confirm the diagnosis
- Fibrinogen often forms a shaggy band along the basement membrane zone, typical for a lichenoid reaction
- DIF may be negative (or only have minimal granular IgM deposition) in a biopsy from an old "burned-out" lesion or from the atrophic center of a lesion, making site selection for biopsy critical for the diagnosis
- DIF is negative in uninvolved and nonsun-exposed skin
- May also see epidermal antinuclear antibodies, most commonly with IgG
- Indirect immunofluorescence is negative

Subacute Cutaneous Lupus Erythematosus (SCLE)

Clinical

- SCLE is a photodistributed, symmetric and often widespread eruption, most commonly seen in females
- Mean age of presentation is around 40, which is slightly older than other types of LE
- There is a strong association with the presence of anti-Ro (SS-A) antibodies and Sjögren's syndrome
- Systemic lupus erythematosus is present in 50%
- ANA is positive in about half; other antibodies including anti-La (SS-B), anti-thyroid and anti-cardiolipin are variably present
- Lesions are nonscarring and nonindurated
- May see annular/polycyclic plaques with central clearing or papulosquamous lesions (scaly pink-red papules)
- Lesions LACK atrophy, scarring, and follicular plugging
- Clinical course is usually relatively benign, but a subset of patients may go on to develop severe systemic disease

Epidemiology

- Increased incidence of HLA-DR3 and HLA-DR2 as well as inherited homozygous C2 and C4 deficiency

Microscopic

- Many features are similar to changes seen in discoid LE, but histologic distinction between the two can sometimes be made
- In general, SCLE has LESS:
  - Hyperkeratosis
  - Basement membrane thickening
  - Follicular involvement
  - Follicular plugging
- Dermal infiltrate, and it is more superficially located
- SCLE tends to have MORE:
  - Epidermal atrophy
  - Liquifactive degeneration
  - Cytoid bodies
  - Pigment incontinence
  - Satellite cell necrosis
  - Lymphocyte exocytosis
- Exceptions to these rules are frequent, and in many cases, SCLE cannot be histologically distinguished from other types of LE

Immunopathology

- DIF has findings that are distinct from other types of LE
- There is a discrete "particulate" or speckled pattern of epidermal deposition with IgG that occurs predominantly in the basal layer, and is associated with the presence of anti-Ro (SS-A) antibodies
- Particulate dermal-epidermal deposition can be seen in other types of lupus and is NOT suggestive of SCLE
- Other DIF changes typical for LE (granular deposition along the basement membrane zone with IgM and other conjugates) may be present, but often are not
- May also see epidermal antinuclear antibodies, most commonly with IgG
- Circulating antinuclear antibodies are detected in 50%
- Indirect immunofluorescence is usually otherwise negative

Bullous Systemic Lupus Erythematosus

- DIF is characterized by linear OR granular deposition along the basement membrane zone
- See description under *Linear deposition along the basement membrane zone*

Systemic Lupus Erythematosus

Clinical

- SLE is an autoimmune disease with a wide variety of possible systemic manifestations
- Over 75% of patients will have some form of cutaneous involvement, including malar erythema, photosensitivity, oral involvement (cheilitis, ulcers, petechiae and gingivitis), or discoid lesions
- Non-specific lesions may be seen in SLE, but may also be seen in a variety of other conditions or in normal patients
- These include vasculitis and vasculopathy, Raynaud's phenomenon, livedo reticularis, perniosis, urticaria and urticarial vasculitis, nonscarring alopecia, and rheumatoid nodules
- Most common in women of childbearing age (F:M 9:1) and dark skinned patients (black, hispanic and so on)
- Increased incidence of complement deficiency, both due to excessive consumption by immune complexes and an increased incidence of inherited deficiencies of complement components (most commonly homozygous C2 deficiency)
- Mean age of onset is in the thirties
- May be induced by medication
- Clinical course is variable; may be mild and controlled with medication or severe and recalcitrant
- Most commonly affected systems include joints (90%), kidneys (50%), lungs (40%), and the central nervous system (30%), but a wide variety of other organs may also be affected
- Constitutional signs are frequent and include fatigue, fever, weight loss and malaise
- Most common cause of mortality is due to renal involvement

Microscopic

- Microscopic depends on the type of lesion biopsied
- No changes diagnostic for systemic LE exist
- Discoid lesions show changes as described for discoid LE
- Vasculitic lesions clinically associated with lupus anticoagulant syndrome show thrombotic microangiopathy, indistinguishable from other types of thrombotic microangiopathy (such as cryoglobulin associated microangiopathy)
- Biopsy of malar erythema is non-specific, with telangiectasia and rarely liquifactive degeneration or interface dermatitis

Immunopathology

- As discussed above, the strict definition of a positive lupus band test is the presence of granular deposition of IgM (and other conjugates) along the basement membrane zone in a biopsy from nonsun-exposed and uninvolved skin
- The presence of a lupus band is correlated with a higher incidence of systemic disease
- Granular deposition with other conjugates (IgG, IgA and C3) is usually seen
- Circulating antinuclear antibodies may be detected on indirect immunofluorescence, but IIF is otherwise negative

Granular Deposition in the Dermal Papillae

Dermatitis Herpetiformis (DH)

Clinical

- DH is a chronic, intensely pruritic eruption with usual onset in the second to fourth decade, though it may occur at any age
- Primary lesions are pruritic urticarial papules that develop into small tense vesicles
- Due to the intense pruritus of the lesion, an excoriation is usually all that remains at the time of exam
- Most commonly affects extensor surfaces, particularly on pressure points, including the extensor surfaces of the forearms (elbows), knees, back, buttocks and sacrum
- Associated with gluten-sensitive enteropathy which is clinically significant in 10% or less, but histologically detectable (by villous atrophy and increased lymphocytic infiltrate) in 60% to 70% of patients
- Cutaneous disease and small bowel disease both respond to gluten-free diet
- Also clinically characterized by a rapid (within 24 to 48 hours) response to dapsone
- DH is also associated with an increased incidence of GI lymphoma and other malignancies
- Other organs with associated conditions include the thyroid (hyper and hypothyroidism, thyroid nodules and malignancy) and stomach (atrophy and hypochlorhydria)
- A variety of other autoimmune diseases have also been associated (Sjögren's syndrome, insulin dependent diabetes, rheumatoid arthritis, myasthenia gravis, and SLE, among others)

Epidemiology

- Increased frequency of HLA haplotypes B8, A1, DR3 and DQw2

Microscopic

- Early lesions show neutrophils along the basement membrane zone and in the dermal papillae, accompanied by fibrin deposition, leukocytoclasis and rare eosinophils
- Clefts appear at the sites of neutrophil accumulation, termed papillary microabscesses
- Perivascular lymphohistiocytic infiltrate is often present in the upper and middle dermis

- As vesicles or bullae develop, findings become nonspecific (subepidermal separation with neutrophils and eosinophils)

Immunopathology

- DIF characteristically has granular deposition of IgA in the dermal papillae and along the basement membrane zone
- Granularity is most pronounced in the dermal papillae
- Granular deposition with other conjugates (C3, IgG and IgM) is rarely present, but has been reported
- These changes are found in perilesional (within 3-5 mm) normal-appearing skin
- Several antibodies can be produced by patients with dermatitis herpetiformis and/or gluten sensitive enteropathy, including IgG and/or IgA anti-endomysial antibodies, anti-gliadin and anti-reticulin antibodies
- The patient's titer of IgA anti-endomysial antibody, detected using monkey esophagus substrate, correlates with disease activity as well as patient's compliance with the gluten-free diet

Implicated Antigen

- Unknown

Clumped Cytoid Bodies and Shaggy Deposition of Fibrinogen Along the Basement Membrane Zone

Lichenoid Tissue Reaction

- Cytoid bodies are round, homogeneously fluorescent cells that appear scattered as single cells or clumped in groups along the basement membrane zone
- They can also be seen in the epidermis (erythema multiforme) or upper dermis
- They are thought to represent necrotic keratinocytes and/or fragments of basement membrane
- Scattered cytoids can be seen nonspecifically in many conditions
- Shaggy deposition of fibrinogen along the basement membrane zone gives a pattern that has been likened to "dripping paint"
- While neither of these two findings is specific, the combination of clumped cytoids and shaggy deposition of fibrinogen is seen in lichenoid tissue reactions
- The diagnosis in each of these entities is dependent on the appropriate histopathology being present

Variants

- Lichen planus
- Lupus erythematosus
- Dermatomyositis
- Erythema multiforme
- Paraneoplastic pemphigus
- Lichenoid dermatitis
- Lichenoid drug reaction
- Graft versus host disease
- Other dermatoses

Lichen Planus

Immunopathology

- The "classic" lichenoid tissue reaction is often seen, with clumped cytoid bodies along the basement membrane zone and shaggy deposition of fibrinogen along the basement membrane zone
- Mucosal lesions are less likely to have cytoid bodies; shaggy fibrinogen may be the only finding present
- Yeast (candida) can sometimes be found in mucosal lesions
- Although clumped cytoids are quite characteristic of LP, LP cannot be diagnosed on immunopathology alone. Microscopic consistent with LP must also be present to make the diagnosis

Lupus Erythematosus

- See section above

Immunopathology

- The typical features seen in lupus erythematosus are listed above. In addition, lupus may also demonstrate lichenoid features on immunopathology, often in combination with typical granularity along the basement membrane zone
- Immunofluorescence of aged or "burned out" lesions may only have lichenoid changes

Dermatomyositis

Immunopathology

- Although granularity along the basement membrane zone similar to that seen in lupus erythematosus (the lupus band) has been reported, immunofluorescence usually does NOT demonstrate these changes
- A lichenoid tissue reaction and nonspecific discontinuous granularity along the basement membrane zone are more commonly seen
- Subepidermal fibrin deposition may also be seen

Erythema Multiforme

Immunopathology

- Erythema multiforme is characterized by epidermal cytoid bodies and weak perivascular deposition of IgM in the superficial dermis
- Shaggy deposition of fibrinogen and cytoids in the dermis and at the dermal-epidermal junction may also be seen
- Granular deposition of IgM, C3 and fibrinogen along the dermoepidermal junction are occasionally present

Paraneoplastic Pemphigus

- See section B5 above

Immunopathology

- In addition to the characteristic features described above, clumped cytoids and shaggy deposition of fibrinogen along the basement membrane zone can also be seen

Lichenoid Dermatitis

Immunopathology

- Dermatitis due to any number of causes may also demonstrate a lichenoid tissue reaction
- This pattern is more likely to be seen in chronic dermatitis

Lichenoid Drug Reaction

Immunopathology

- In addition to lichenoid changes, drug reactions will also have eosinophils in the superficial and middle dermis

Graft Versus Host Disease

Immunopathology

- Lichenoid features can occasionally be seen in chronic graft-versus-host disease
- Epidermal cytoids may also be observed
- Granular deposition of IgM along the basement membrane zone is observed in about 40% of patients with acute disease and around 85% of patients with chronic disease
- In addition, IgM and C3 can sometimes be found within dermal vessel walls

Weak Thick Linear Deposition Along the Basement Membrane Zone and Perivascular Deposition

Porphyrias

- The porphyrias are a group of inherited or acquired diseases that result from deficiency in the activities of enzymes of the heme biosynthetic pathway
- The characteristic clinical appearance of each of the subtypes results from accumulation of intermediaries or their byproducts
- While the clinical appearance, course and prognosis of the porphyrias with cutaneous manifestations varies from type to type, the microscopic and immunofluorescence are the same or very similar. The variants tend to vary by degree

Variants

- Aminolevulinic acid dehydratase porphyria (ALA)
- Acute intermittent porphyria (AIP)
- Congenital erythropoietic porphyria (CEP)
- Porphyria cutanea tarda (PCT)
- Hepatoerythropoietic porphyria (HEP)
- Hereditary coproporphyria (HCP)
- Variegate porphyria (VP)
- Erythropoietic protoporphyria (EPP)
- Pseudoporphyria (drug-induced) (PP)

Clinical

- The following discussion pertains to the porphyrias with cutaneous manifestations
- Cutaneous changes can either be immediate or delayed
- An immediate reaction, as seen in EPP, includes erythema, pain, edema and purpura
- The other types of cutaneous porphyria show delayed phototoxicity, presenting as fragility, blistering, scarring and hypertrichosis
- Other reported clinical findings include sclerodermoid changes, alopecia and hyperpigmentation
- In inherited homozygous PCT, abnormal enzyme levels are seen in the liver and the red blood cells
- In heterozygous PCT, where abnormal enzyme levels are expressed in the liver, disease expression usually requires a "second hit" to the liver such as concomitant infection (hepatitis or HIV), alcohol ingestion, estrogen therapy or pregnancy
- Diagnosis and subtyping of porphyria is based in part on the clinical presentation, microscopic and immunofluorescence. However, the porphyrin levels in the urine, stool and red blood cells are the gold standard of diagnosis

Microscopic

- The subtypes demonstrate similar findings to varying degrees
- They are characterized by a pauci-inflammatory subepidermal separation with upward protrusion of the dermal papillae ("festooning")
- There is homogeneous thickening of the blood vessels in the dermal papillae
- There is PAS positive deposition of material in and around the upper dermal blood vessels as well as along the basement membrane zone
- Actinic elastosis is usually present
- Thickening of the basement membrane zone, hyperkeratosis, acanthosis and hypergranulosis are variably present
- Occasionally, PAS positive globules arranged in a linear fashion may be seen in the blister roof ("caterpillar bodies")

Electron Microscopy

- EM shows extensive reduplication of the basal lamina of the upper dermal blood vessels and basement membrane zone

- There are widened perivascular spaces containing fibrillar material and small collagen fibrils
- In some cases there are irregular clumps of amorphous material embedded in the perivascular material
- The site of separation is the lamina lucida

Immunopathology

- Again, the subtypes demonstrate similar findings to varying degrees
- There is marked deposition of immunoglobulin and complement (IgG, IgM, C3, IgA and fibrinogen) in and adjacent to the upper dermal blood vessels
- In addition, there is weak thick deposition of immunoglobulin and complement along the basement membrane zone
- In general, these changes are more pronounced in involved sun-exposed skin, and in active lesions
- EPP demonstrates changes more marked than PCT, VP or PP

Deposition on Eosinophils and Diffuse Deposition on Connective Tissue

Urticaria

Clinical

- Referred to as hives or wheals, they are characterized by pruritic, erythematous or white, nonpitting edematous papules or plaques that change in size and shape over hours
- They vary in size from small papules to large plaques
- The depth of involvement varies from superficial to deep
- Episodes of urticaria are arbitrarily defined as either acute or chronic
- Chronic includes episodes persisting for longer than six weeks
- While the cause of acute urticaria is often established (usually food, drug or contact), the cause of chronic urticaria is usually not identified
- There are many implicated etiologic factors and associations, including foods and food additives, medications and hormonal perturbations, inhaled allergens, various internal diseases and malignancies, contactants (via both immunologic and nonimmunologic mechanisms), primary skin diseases (immunobullous diseases for example) and genetic diseases
- Urticaria may be separated into a variety of subtypes based on the etiology

Clinical Subtypes

- Physical urticarias
- Dermatographism
- Pressure urticaria
- Cholinergic urticaria
- Exercise-induced urticaria
- Solar urticaria
- Cold urticaria
- Heat, water and vibrational urticaria
- Aquagenic pruritus
- Angioedema
- Acquired angioedema
- Hereditary angioedema
- Contact urticaria
- Urticaria secondary to an ingested substance (food, medication or other)
- Pruritic and urticarial papules and plaques of pregnancy
- Urticarial vasculitis

Microscopic

- All of the subtypes of urticaria demonstrate similar histopathologic features
- Acute urticaria shows dermal interstitial edema, dilated venules with endothelial swelling and a minimal degree of inflammation, including intravascular neutrophils and perivascular lymphocytes and eosinophils
- In chronic urticaria, there is interstitial edema with a perivascular and interstitial polymorphous infiltrate of neutrophils, eosinophils and lymphocytes, as well as intravascular neutrophils
- The deeper the clinical form of urticaria, the deeper the extension of the histopathologic findings
- Angioedema extends into the subcutaneous tissue
- Hereditary angioedema demonstrates deep dermal and subcutaneous edema with minimal accompanying inflammation

Immunopathology

- DIF demonstrates deposition on eosinophils with IgA, and to a lesser degree with IgG, and IgM
- Fibrinogen shows diffuse deposition on the connective tissue throughout the dermis
- This pattern is nonspecific but consistent with the clinical diagnosis of urticaria

Deposition in Blood Vessels

Vasculitis

Immunopathology

- In general, vasculitis is characterized by intravascular deposition of immunoglobulins and complement
- IgM is usually the predominant immunoglobulin deposited, but IgG and IgA are also seen
- Fibrinogen is often deposited in a perivascular pattern, with diffusion into the surrounding interstitial tissue

- The diagnosis of vasculitis should be reserved for specimens that show intravascular deposition with multiple immunoreactants
- Further, because vascular fluorescence can be seen nonspecifically in various inflammatory conditions, as well as in dependent locations (such as lower extremity), histopathology that is typical for vasculitis must also be present to justify the diagnosis
- Some of the clinical subtypes of vasculitis have more distinctive immunopathologic findings
- For example, Henoch-Schönlein purpura has a granular deposition of IgA in the superficial vessels that predominates over the deposition of other immunoglobulins
- Urticarial vasculitis has findings typical for urticaria in addition to immunoglobulin deposition in blood vessels
- Further, a subset of patients with urticarial vasculitis have systemic lupus erythematosus (either overt or in evolution) and demonstrate (in addition to features of urticarial vasculitis) granular deposition of IgM and other immune reactants along the basement membrane zone, typical for lupus erythematosus

TNM CLASSIFICATION OF MALIGNANT MELANOMA OF THE SKIN (1997 REVISION)

- T: Primary Tumor
  - T0: No evidence of primary tumor
  - Tis: Melanoma in situ (Clark's Level I)
  - T1: Tumor ("Breslow") thickness* ≤0.75 mm and invades the papillary dermis (Clark's Level II)
  - T2: Tumor thickness >0.75 mm, but ≤1.5 mm, and/or invades to papillary/reticular dermal interface (Clark's Level III)
  - T3: Tumor thickness >1.5 mm, but ≤4 mm, and/or invades the reticular dermis (Clark's Level IV)
  - T3a: Tumor thickness > 1.75 mm, but ≤ 3 mm
  - T3b: Tumor thickness > 3 mm, but < 4 mm
  - T4: Tumor thickness >4 mm, and/or invades the subcutaneous tissue (Clark's Level V) and/or satellite nodules (s) within 2 cm of the primary tumor (T4b)
- N: Regional Lymph Nodes
  - N1: Metastasis ≤3 cm in greatest dimension
  - N2: Metastasis >3 cm in greatest dimension in any regional nodes or in-transit metastasis**
- M: Distant Metastasis
  - M1a: Metastasis in skin or subcutaneous tissue or lymph nodes beyond regional lymph nodes
  - M1b: Visceral metastasis

* The tumor thickness is measured from the superficial aspect of the granular cell layer of the epidermis (or the base of the lesion if the tumor is ulcerated) to the deepest point of tumor invasion

** In transit metastasis involves skin or subcutaneous tissue more than 2 cm from the primary tumor but not beyond regional lymph nodes

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Chapter 10

Neuropathology

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Table of Contents

GENERAL REACTIONS TO INJURY

Macrophage/Microglial Reactions

Gitter Cells

- Central nervous System (CNS) macrophages recruited from native microglia or systemic circulation
- Large accumulations in infarcts and demyelinating disease
- Wide range of morphology with accompanying subacute gliosis and occasional mitoses; commonly leads to misdiagnosis of glioma

Microglial Activation (Rod Cells, Microglial Nodules)

- Microglia are specialized antigen-presenting mononuclear cells of the CNS that: a) become elongated when activated (rod cells); b) surround dying neurons, a process known as neuronophagia; and c) cluster to form microglial nodules, a characteristic response in viral and paraneoplastic (autoimmune) encephalitis

Gliosis (Reactive Astrocytosis)

- Accompanies all forms of brain injury

Subacute

- Astrocytic hypertrophy with prominent radially oriented, stellate processes and often plump eccentric cytoplasm (gemistocytes, gemistos = full in Greek); cells are evenly distributed (as opposed to astrocytoma) and have no mitoses, highlighted by glial fibrillary acidic protein (GFAP) immunostain

Chronic

- Difficult to discern individual processes, dense fibrillary background, other signs of chronic injury (neuronal loss, rarefaction, hemosiderin, etc.); grossly firm, rubbery, atrophic, and/or dark, associated T2 MRI changes

Pilocytic

- Chronic gliosis with Rosenthal fibers
- Common adjacent to cysts and slow-growing neoplasms, especially craniopharyngioma, pineal cyst, ependymoma, hemangioblastoma, and syrinx
- Potential confusion with pilocytic astrocytoma on small suprasellar, posterior fossa, or spinal cord biopsies, but less cellular and lacks microcystic component and granular bodies

Cerebral Edema

- Component of most forms of brain injury; two types (often mixed)

Vasogenic Edema

- Most common type, predominantly extracellular, results from breakdown of blood-brain barrier (BBB)

Cytotoxic Edema

- Intracellular, generally ischemic or toxic etiology (osmotic imbalance, ionic pump failure, etc.)

Hydrocephalus

Acute

- Often due to intraventricular hemorrhage or meningitis; life-threatening

Chronic

- Most caused by obstruction to flow; increased cerebral spinal fluid (CSF) production also a factor in choroid plexus papilloma

Obstructive

- Obstruction within ventricular system (including foramina)

Non-obstructive

- Extraventricular obstruction (e.g., arachnoid granulations)

Hydrocephalus Without Increased Intracranial Pressure

- Ex vacuo: secondary to parenchymal loss (e.g., Alzheimer's disease)
- Normal pressure hydrocephalus: clinical triad of dementia, gait disturbance, and urinary incontinence; etiology unclear; some evidence of intermittently raised CSF pressure

Herniation Syndromes

- Secondary to mass effect from edema, hemorrhage, tumor, abscess, etc.; high mortality
- Result of unyielding surrounding structures (skull, dural folds), therefore more common after closure of sutures

Cingulate (Subfalcine)

- Inferomedial herniation of cingulate gyrus (above corpus callosum) under falx cerebri; occasional superimposed anterior cerebral artery infarct from arterial compression

Uncal (Transtentorial)

- Inferomedial herniation of uncus (posteromesial temporal structure) under tentorium cerebelli
- Compression of adjacent optic tract results in "blown pupil" because parasympathetic fibers run along the periphery of the nerve
- Compression of adjacent vessel leads to posterior cerebral artery infarct

- Displacement of opposite cerebral peduncle (corticospinal tract) into tentorium results in Kernohan's notch, with false lateralizing hemiplegia on same side as herniation

Tonsillar

- Downward herniation of cerebellar tonsils into foramen magnum
- Resulting compression of medulla can lead to respiratory arrest
- Tonsils may fragment and fall into spinal subarachnoid space

Duret (Secondary Brainstem) Hemorrhage

- Downward herniation of brainstem results in kinking of penetrating arteries (perpendicular branches off basilar artery) with acute hemorrhagic infarctions in pons, (characteristically narrow and medial in antero-posterior plane)
- In contrast, primary hypertensive brainstem hemorrhages are often globular and internal contusions (diffuse axonal injury) are typically posterolateral

GLIOMAS

Key Features in Differential Diagnosis of CNS Tumors

Location

- Intra-axial (parenchymal) vs. extra-axial (dural)
- Superficial (cortical) vs. deep
- Intraventricular vs. paraventricular
- Supratentorial vs. infratentorial
- Sellar, suprasellar, hypothalamic
- Pineal region
- Cerebellar vs. cerebellopontine angle vs. brainstem (ventral or dorsal)
- Spinal cord: extradural vs. intradural; extramedullary vs. intramedullary

Age/Sex

Imaging Appearance = "Equivalent to Gross Examination" for Biopsy Specimens

- Site of origin/epicenter
- Mass effect, associated edema, etc.
- Infiltrative vs. discrete
- Enhancing: uniform vs. irregular; focal mural nodule vs. ring; nonenhancing
- Cystic vs. solid
- Single vs. multiple
- Calcified vs. noncalcified
- Seeding (meningeal or nerve root enhancement) vs. nonseeding
- Other: melanin, lipid, hemorrhage (MRI), calcium (CT)

Histology

Immunohistochemistry

- See Table 10-1

Diffuse Astrocytomas

Variants

Fibrillary

- Most common cell type; inconspicuous cytoplasm; elongated, irregular hyperchromatic nuclei; highly infiltrative; hypocellular examples difficult to distinguish from gliosis; often GFAP –

Gemistocytic

- Abundant, eccentric, eosinophilic, GFAP-rich cytoplasm; short, polar cytoplasmic processes; round, variably hyperchromatic nuclei; irregular distribution of tumor cells (unlike reactive gemistocytes); associated perivascular inflammation; rare mitoses, but high-grade examples frequently associated with proliferating small cell astrocytes; high rate of anaplastic transformation

Giant Cell

- Multinucleate astrocytes with abundant cytoplasm and bizarre nuclei; GFAP +; often deceptively circumscribed grossly; usually Grade IV

Small Cell

- Small cells with minimal cytoplasm and often oval hyperchromatic nuclei may superficially resemble oligodendroglioma; high mitotic index, usually Grade IV, differential diagnosis = other small cell malignancies, often GFAP –, but S-100 +

Gliomatosis Cerebri

- A clinicopathologic diagnosis requiring extensive involvement of multiple lobes or brain compartments (sometimes the whole neuraxis); nuclei are typically elongated, twisted, and bland; frequent secondary structures (subpial or subependymal condensation, perivascular aggregates, perineuronal satellitosis); brainstem involvement common; may be associated with multiple foci of dedifferentiation to glioblastoma multi forme

Table 10-1. Typical Immunoprofiles of CNS Neoplasms

Tumor	*+*	*±*	*–*
Astrocytoma	S-100, GFAP		CK[1], LCA, SYN, HMB-45
Oligodendroglioma	S-100	GFAP[2]	CK[1], LCA, SYN
Ependymoma	S-100, GFAP	EMA(lumens), CK	LCA, SYN
Choroid plexus tumors	S-100, CK, VIM, Transthyretin[3]	GFAP	EMA, CEA
Metastatic carcinoma	EMA and CK, CK7 (lung), CK20 (colon)	CEA, S-100, SYN	GFAP, LCA, HMB-45
Melanoma	S-100, HMB-45		GFAP, CK, LCA
Lymphoma	LCA, CD20 (L26)	EMA[4]	CK, GFAP, HMB-45, SYN
Meningioma	EMA, VIM	S-100, CD34, CK[5]	GFAP, HMB-45
Hemangiopericytoma	VIM, Factor XIIIa[6]	CD34	EMA, CK, GFAP, S-100
Medulloblastoma	SYN	S-100, GFAP	CK, LCA, EMA
Atypical teratoid/rhabdoid tumor	EMA, CK, actin	SYN, GFAP, desmin, AFP	PLAP, β-hCG, LCA
Ganglioglioma	SYN, NF, CG, GFAP		CK, EMA, PLAP
Central neurocytoma	SYN	GFAP, S-100	NF, CG, CK, LCA
Schwannoma	S-100[7], CD34, Coll 4	GFAP, HMB-45[8]	EMA, NF, CK
Paraganglioma	SYN, CG, S-100[9]	NF	GFAP, CK, HMB-45
Hemangioblastoma	S-100, NSE	GFAP	CK, EMA
Germinoma	PLAP	β-hCG[10], CK	AFP, EMA, HMB-45, LCA
Yolk sac tumor	AFP, CK	PLAP, EMA	β-hCG, GFAP
Choriocarcinoma	β-hCG, CK, EMA	PLAP	AFP, GFAP, HMB-45, LCA
Embryonal carcinoma	CK, PLAP		β-hCG, AFP, EMA, LCA
Teratoma	CK, PLAP, EMA	AFP	β-hCG

[1]CAM 5.2 recommended because AE1/AE3 frequently stains gliomas; [2]Strongly positive in microgemistocytes; [3]Not specific for choroid plexus; [4]Positive in myeloma; [5]Positive in secretory variant; [6]Characteristic pattern of scattered, individual immunoreactive cells; [7]Diffuse, strong expression; [8]Positive in melanocytic variant; [9]Positive in sustentacular cells; [10]Positive in syncitiotrophoblasts.
Note: GFAP = glial fibrillary acidic protein, CK = cytokeratin, LCA = leukocyte common antigen, SYN = synaptophysin, EMA = epithelial membrane antigen, VIM = vimetin, CEA = carcinoembryonic antigen, PLAP = placental alkaline phosphatase, AFP = α-fetoprotein, β–hCG = β–human chorionic gonadotrophin, CG = chromogranin, Coll 4 = collagen type IV, NSE = neuron specific enolase

Gliosarcoma (Feigin Tumor)

- A Grade 4 tumor with astrocytic and sarcomatous elements
- A metaplastic process analogous to carcinosarcoma
- Sarcoma usually fibrosarcoma or malignant fibrous histiocytoma, but may include bone, cartilage, muscle, and even epithelium
- Often superficial and deceptively circumscribed

Note: All gliomas are S-100 protein immunoreactive.

Prognostic Variables

- Patient age: strongest predictor in many series; survival time decreases with advancing age
- Histologic grade
- Histologic cell type: Oligo better than Oligoastro better than Astro
- Preoperative performance status
- Extent of resection: variable conclusions among series, but gross total resection may be beneficial

Grading Schemes

- See Table 10-2

Grade II Astrocytoma (Astrocytoma)

Clinical

- Age peak = 30–40 years old
- Insidious onset
- Seizures > functional deficits
- Survival 5–8 years
- High rate of anaplastic transformation in adult, especially gemistocytic variant
- Death due to infiltration of vital structures or herniation

Imaging/Gross

- Ill-defined low-density lesion on CT or T1 MRI; nonenhancing
- Bright T-2 on MRI
- No gross circumscription; often rubbery
- Epicenter in white matter; variable obliteration of grey-white matter junction

Smear

- Minimal to mild hypercellularity
- Nuclear hyperchromasia/atypia
- Variable cytology: inconspicuous cytoplasm to variable process formation; plump cell body with eccentric nuclei and processes (gemistocytic)

Microscopic

- Same features as above plus:
  - Uneven distribution/clustering of cells
  - Occasional microcysts
  - Predominantly white matter involvement but cortical infiltration common

Table 10-2. Grading Schemes for Astrocytoma

Three-tiered	**Four-tiered**
Ringertz	Kernohan
Modified Ringertz (Burger)	St. Anne-Mayo (see below)
WHO (see below)	

St. Anne-Mayo (functionally 3-tiered) (AMEN)

Criteria	*Scoring*
Atypia (nuclear)	Grade 1 = 0 criteria (very rare)
Mitoses (1 is enough)	Grade 2 = 1 criterion (nearly always atypia)
Endothelial proliferation	Grade 3 = 2 criteria (usually addition of mitoses)
Necrosis	Grade 4 = 3 or 4 criteria
Equivalents in terms of WHO grade:	Grade 1 has no WHO equivalent
	Grade 2 = (Differentiated) *Astrocytoma*
	Grade 3 = *Anaplastic astrocytoma*
	Grade 4 = *Glioblastoma multiforme (GBM)*

WHO (1993 Revision)

Adopted the morphologic parameters of the St. Anne-Mayo scheme but doesn't score and uses Roman numerals (II, III, IV) instead

Gr. II defined by atypia only

Gr. III defined by mitotic activity (number not specified)

Gr. IV defined by necrosis *or* endothelial proliferation, typically in association with atypia and mitoses (Note: Kernohan, Ringertz, and modified Ringertz schemes require necrosis for GBM)

Note: WHO Grade I corresponds to pilocytic astrocytoma.

Grade III Astrocytoma (Anaplastic Astrocytoma)

Clinical

- Age peak = 40–50 years old
- Often more rapid onset than Grade II
- Seizures less common; deficits more frequent
- High rate of transformation to GBM
- Survival 2–3 years

Imaging/Gross

- Similar to Grade II astros; may have focal enhancement on CT/MRI but not ring enhancing

Smear

- Increased cellularity
- Like Grade II but often with greater atypia, more visible cytoplasm, as well as process formation

Microscopic

- Same features as above plus:
  - Mitotic activity
  - Microcysts rare
  - No endothelial proliferation or necrosis
  - May have lower grade component

Grade IV Astrocytoma (Glioblastoma Multiforme)

Clinical

- Age peak = 50–60 years old
- Rapid onset with functional deficits
- Survival is age dependent, but often short (<1 year) in elderly

Imaging/Gross

- Deceivingly circumscribed
- Ring enhancing
- Variegated due to hemorrhage/necrosis
- May cross corpus callosum (butterfly lesion)

Smear

- Marked pleomorphism frequent but not invariable; may be monomorphous
- Variable process formation and cytoplasm
- Endothelial proliferation and/or necrosis

Microscopic

- Same as above plus:
  - Endothelial proliferation = multiple layers; not simply glomeruloid capillaries with lots of lumens as seen commonly in pilocytic astrocytomas
  - Necrosis usually but not invariably associated with palisading
  - Infiltrative margin (relative circumscription in "primary/de novo GBM")
  - Frequent presence of lower grade component ("secondary GBM")

Differential Diagnosis

- See Table 10-3

Table 10-3. Common Differential Diagnoses of Astrocytomas

Common diagnosis	*Useful stains*
Astrocytoma vs. Reactive gliosis	GFAP shows equally spaced astrocytes with radiating processes, MIB-1 = low
Astrocytoma vs. Demyelinating disease	LFB-PAS shows myelin loss; Bielschowsky or Neurofilament IPs show axonal sparing; KP-1 shows numerous macrophages
Diffuse vs. Circumscribed astrocytoma	PAS with diastase highlights EGBs; Neurofilament IPs = relatively solid growth (i.e., rare axons within the tumor)
Recurrent tumor vs. Radiation Necrosis	H&E shows coagulative necrosis without pseudopalisading; dystrophic Ca^{2+}; vascular hyalinization/telangiectasias; MIB-1 = low
GBM vs. Metastasis vs. Lymphoma vs. Small cell carcinoma	CAM 5.2 (epithelial), EMA (epithelial, meningothelial), S-100 (melanocytic, glial), HMB-45 (melanocytic), GFAP (glial), LCA (lym phoid), CD20 (B-cell), Cytokeratin (CK) 7 (lung or breast primary), CK 20 (GI, especially colon primary), Synaptophysin (SYN) (PNET, Neuroendocrine-ex. small cell carcinoma)

Note: Some keratins (e.g., AE1/AE3) stain neoplastic and nonneoplastic glial cells.

Circumscribed Astrocytomas

Pilocytic Astrocytoma (WHO Grade I)

Clinical

- Children/young adults
- Cerebellum, hypothalamus: third ventricle, optic nerve, cerebral hemisphere, spinal cord
- Slowly progressive symptoms
- Excellent prognosis (80% 20-year survival)
- Malignant transformation exceedingly rare

Imaging/Gross

- Demarcation
- Enhancement
- Bright T-1 MRI signal due to mucinous/proteinaceous fluid in cystic element
- Often partially cystic with mural nodule

Smear

- Bipolar cells with bland, oval to elongated nuclei and long piloid (hair-like) processes
- Note: cytology similar to fibrillary astrocytoma in many cases
- Rosenthal fibers (RFs)
- Eosinophilic granular bodies (EGBs)
- Bizarre or multinucleated cells ("pennies on a plate" arrangement of nuclei)
- Glomeruloid vessels without multilayering of endothelial cells

Microscopic

- Variable: same as above plus:
  - Often biphasic compact (piloid) and loose (microcystic) pattern; either pattern may predominate
  - Diffuse variant may simulate Grade II fibrillary astro
  - Oligodendroglioma-like regions common

Differential Diagnosis

- Pilocytic gliosis (other underlying lesion; no microcysts; generally no EGBs)
- Ganglioglioma (dysmorphic neurons)
- Pleomorphic xanthoastrocytoma (more pleomorphic, partly reticulin-rich)
- Fibrillary astrocytoma (non-enhancing, generally noncystic, no RFs or EGBs)
- Oligodendroglioma (lacks piloid component, RFs and EGBs; rarely in cerebellum or spinal cord)

Pleomorphic Xanthoastrocytoma (PXA) (WHO Grade II–III)

Clinical

- Children/young adults
- Chronic seizures
- Good prognosis in most cases
- Worse prognosis with anaplastic transformation (15%) but far more favorable than GBM

Imaging/Gross

- Cyst with enhancing mural nodule
- Superficial; often with leptomeningeal component
- Temporal lobe (less often parietal)

Smear

- Cellular pleomorphism; bizarre nuclei, cytoplasmic pseudoinclusions
- Glial appearance
- Eosinophilic granular bodies

Microscopic

- Same as above plus:
  - Xanthomatous cells variable, often few
  - Perivascular lymphocytic cuffing
  - Scant mitoses
  - No endothelial proliferation or necrosis
  - Anaplastic transformation (15%) = frequent mitoses, monomorphic smaller, often epithelioid cells, necrosis, and occasionally endothelial proliferation

Differential Diagnosis

- Ganglioglioma (dysmorphic neurons)
- Pilocytic astrocytoma (less pleomorphic, reticulin poor)
- GBM (No EGBs, mitoses, deep epicenter)
- Dural-based sarcoma, e.g., MFH (GFAP –, mitoses)

Subependymal Giant Cell Astrocytoma (SEGA) (WHO Grade I)

Clinical

- Children/young adults
- Obstructive hydrocephalus
- Tuberous sclerosis (may be first manifestation); rarely syndrome-unassociated
- Excellent prognosis (possibly hamartomatous in nature)

Imaging/Gross

- Intraventricular (anterior near foramen of Monro)
- Large, sharply demarcated; solid and often calcified
- "Candle guttering"-associated

Smear

- Large spindle to epithelioid cells with primarily glial, but occasionally neuron-like features

Microscopic

- Same as above plus:
  - True giant cells uncommon

- Perivascular pseudorosettes
- Non-infiltrative of surrounding tissue (NF stain)
- Scattered mast cells
- Variable GFAP staining; ± minor NF

Differential Diagnosis

- Gemistocytic astrocytoma (infiltrative, more uniformly GFAP +, white matter epicenter)
- Giant cell astrocytoma (infiltrative, more uniformly GFAP +, white matter epicenter)
- Ependymoma (no syndrome association; more GFAP +, periventricular)

Oligodendroglioma

Clinical

- 30–40 years old
- History of seizures > neurologic deficits
- Survival:
  - Grade II: ~10 years,
  - Grade III 2–4 years
- Treated with radiation ± chemotherapy (PCV)
- Anaplastic transformation less frequent and slower than in diffuse astrocytoma

Imaging/Gross

- Cerebral hemisphere, especially frontal lobes
- Extensive cortical involvement
- Demarcated relative to deeper white matter
- ± calcification

Smear

- Uniform round nuclei in loose background of axons
- Bland chromatin/inconspicuous nucleoli
- Small skirt of cytoplasm; occasional "minigemistocytes"
- Few cytoplasmic processes
- ± calcification

Microscopic

- Same as above plus:
  - Perinuclear halo artifact (lacking in frozen sections and promptly fixed specimens)
  - "Chicken-wire" capillary pattern
  - Microgemistocytes (GFAP +; smaller and rounder than the astrocytic version)
  - Gliofibrillary oligodendrocytes (small GFAP +, torch-shaped process)
  - Extensive cortical infiltration with secondary structures:
    - Perineuronal satellitosis
    - Subpial condensation
    - Hypercellular nodules (occasional)

Grading

- No general consensus but similar to ependymoma (see below)
- Smith (AFIP) grade = A–D, Mayo = 1–4, WHO = oligo (II) vs. anaplastic oligo (III-IV)
- Gr 1: rare (rule out DNT—see below)
- Gr 2: conventional oligodendroglioma
- Gr 3: anaplastic oligo: hypercellular, pleomorphic, mitotically active, endothelial proliferation or necrosis
- Gr 4: anaplastic oligo: rare, GBM-like but arose from oligodendrogioma and should not be termed GBM

Differential Diagnosis

- Demyelinating disease/infarct (Many KP-1 + macrophages; axonal sparing in demyelination, axonal loss in infarct)
- Pilocytic astrocytoma (RFs, EGBs, different location and imaging)
- Central neurocytoma (intraventricular, rosettes)
- Clear cell ependymoma (pseudorosettes, sharp demarcation)
- Dysembryoplastic neuroepithelial tumor (intracortical only, patterned nodules, floating neurons)
- Mixed glioma (oligo and astro elements)
- Metastatic carcinoma (sharp demarcation, enhancing, CAM 5.2/EMA +)
- Lymphoma (deep, homogeneously enhancing, angiocentricity, CD20 +)

Mixed Oligoastrocytoma

- Controversial entity with varying definitions and philosophies among experts
- Three possibilities:
  - Diffuse glioma with distinct oligodendroglial and astrocytic components
  - Both elements intermixed
  - Single cell type with features intermediate between oligodendroglioma and astrocytoma
- Similar presentation, imaging, behavior, and therapy as pure oligodendroglioma; graded the same way as pure oligodendrogliomas
- Generally behave better than astrocytoma; difficult to predict on histology
- There is no convincing evidence for the existence of other types of mixed gliomas, such as "oligoependymoma" or "astroependymoma"

Ependymoma

Clinical

- Children/young adults
- Paraventricular with ventricular indentation

- Supratentorial, fourth ventricle, spinal cord
- Obstructive hydrocephalus
- Difficult to predict; age >2 years and gross total removal afford better prognosis
- Spinal ependymomas: better prognosis, esp. myxo-papillary
- CSF dissemination in <5%

Imaging/Gross

- Sharp demarcation
- Calcification (intracranial)
- Cyst formation (supratentorial)
- Enhancement on CT/MRI

Smear

- Uniform round nuclei in fibrillary background
- Distinct nucleolus
- Perivascular pseudorosettes

Microscopic

- Same as above plus:
  - Ependymal true rosettes (infrequent)/canals (rare)
  - Sharp demarcation (like metastasis)

Grading

- No consensus; less correlation with clinical behavior than in astrocytoma and oligodendroglioma
- Mayo = 1–4, WHO = ependymoma (II) vs. anaplastic ependymoma(III)
- Gr 1: ependymoma: no mitoses
- Gr 2: ependymoma: few mitoses
- Gr 3: anaplastic ependymoma: mitoses, ± endothelial proliferation (necrosis not important, unless associated with palisading)
- Gr 4: anaplastic ependymoma: GBM-like (rare)

Variants

- Clear Cell Ependymoma:
  - Mimics oligodendroglioma; look for pseudorosettes and demarcation
- Papillary Ependymoma:
  - Perivascular pseudorosettes rather than true fibrovascular cores
- Myxopapillary Ependymoma:
  - WHO Grade I variant, filum terminale, myxoid perivascular stroma, thin capsule; excellent prognosis if resected intact; may seed spontaneously or if ruptured intraoperatively; rare primary pre- or postsacral soft tissue examples show tendency to lung metastases
- Tanycytic Ependymoma:
  - Long, thin processes with vague pseudorosettes

Differential Diagnosis

- Medulloblastoma/PNET (synaptophysin +)
- Oligodendroglioma (lacks sharp circumscription and pseudorosettes)
- Central neurocytoma (origin in septum pellucidum, synaptophysin +)
- Choroid plexus papilloma (origin in choroid plexus, connective tissue stroma; strong uniform cytokeratin staining)
- Papillary meningioma (falls apart to form pseudopapillae, EMA +, GFAP –)
- Pilocytic astro (some infiltration on NF stain; biphasic pattern, RFs and EGBs)
- Schwannoma of cauda equina region (nerve origin; reticulin-rich, collagen IV +, may be GFAP +)
- Paraganglioma of cauda equina region (origin in filum or nerve root; Zellballen or carcinoid-like pattern; chromogranin +)

Subependymoma (WHO Grade I)

Clinical

- Usually older
- Often incidental; otherwise hydrocephalus-associated
- Benign despite occasional mitoses
- Rare intratumoral hemorrhage may be life-threatening

Imaging/Gross

- Intraventricular: lateral > 4th > 3rd; rare in spinal cord
- Sessile or pedunculated
- Often calcified

Smear/Histology

- Ependymoma-like nuclear features
- Lobulated/demarcated
- Immediately subependymal
- Paucicellular with prominent clustering of cells
- Process-rich, highly fibrillar, anucleate background
- Degenerative features: nuclear atypia, abundant microcysts, hyalinized vessels, calcium, hemosiderin deposits
- May have minor component of ependymoma with pseudorosettes ("mixed subependymoma-ependymoma" if more than minor: WHO Grade II)

Differential Diagnosis

- Ependymoma: more cellular, occasional true rosettes
- Fibrillary astrocytoma: intraparenchymal, infiltrative, lacks distinct clustering

Choroid Plexus Neoplasms

Choroid Plexus Papilloma (WHO Grade I)

Clinical

- Hydrocephalus (mechanisms: obstructive and increased CSF production)

- Lateral ventricle in congenital/childhood cases
- Fourth ventricle in adults
- Benign/surgically curable

Radiology/Gross

- Intraventricular
- Polypoid/papillary ("cauliflower" appearance)
- Discrete
- Enhancing
- Often calcified

Smear/Histology

- True papillae (fibrovascular cores)
- Simple cuboidal to columnar epithelium lacking "cobblestone" cell surfaces of normal choroid plexus
- Subepithelial basement membrane
- Clear cytoplasmic vacuoles in some
- Limited architectural complexity/solid growth
- Low mitotic rate
- Occasionally necrosis (no prognostic significance)
- Focal ependymal differentiation common (GFAP + tapered processes)
- IHC = S-100 +, CAM 5.2 +, Transthyretin (Prealbumin) +, GFAP ±, EMA –, CEA –

Differential Diagnosis

- Normal choroid plexus (smaller cells, "cobblestone" epithelial lining)
- Papillary ependymoma (falls apart to form pseudopapillae, fibrillary processes, GFAP +, CAM 5.2 –, lacks PAS +, Collagen IV +, basement membrane)
- Choroid plexus carcinoma (more solid, complex, infiltrative, mitoses)

Choroid Plexus Carcinoma (WHO Grade III)

Clinical

- Rare
- Age <3 years in majority; sometimes congenital
- Highly aggressive/nearly uniformly fatal
- High rate of metastasis, mainly CSF
- Rare long-term survivors with complete excision

Radiology/Gross

- Intraventricular
- Enhancing
- Infiltrative
- CSF seeding in some

Smear/Histology

- More solid and complex than papillomas
- High mitotic rate
- High grade cytology
- May have small cell-like appearance mimicking embryonal tumors (e.g., PNET)
- Infantile examples may be markedly pleomorphic with eosinophilic globules
- IHC = S-100 +, CAM 5.2 +, Transthyretin (prealbumin) +, GFAP ±, EMA –, CEA –

Differential Diagnosis

- Anaplastic ependymoma (GFAP +, nonuniform CK +)
- GBM (GFAP +, CK –)
- Medulloblastoma/PNET (synaptophysin +, CK –)
- Atypical teratoid/rhabdoid tumor (paranuclear inclusions, EMA +, actin +)
- Metastatic carcinoma (adult, EMA +, CEA ±, S-100 ±)

NEURONAL/GLIONEURONAL NEOPLASMS

Derivations/Definitions Used in Neuronal Tumors

- Ganglio = ganglion cell
- Neurocyte = small mature neuron (e.g., cerebellar internal granular layer, dentate fascia)
- Neuroblast = primitive small cells with "neuropil" or Homer Wright rosette formation
- Medulloblast = theoretical cerebellar precursor cell (?external granular layer)
- Paraganglio = specialized autonomic neuroendocrine cell
- Medullo (neuro) epithelium = primitive epithelial tubules/canals resembling the embryonic neural tube
- Pineo, Esthesio, Retino = derived from or differentiating toward specialized neuronal receptor cells
- Cytoma = mature; blastoma = primitive
- Examples: ganglioglioma, ganglioneuroblastoma, gangliocytic paraganglioma, esthesioneuroblastoma

Ganglion Cell Tumors (Ganglioglioma/ Gangliocytoma) (WHO Grade I)

Clinical

- Children/young adults
- Chronic seizures
- Benign/surgically curable

- Hamartoma vs. tumor: nature of lesion unsettled
- Rare malignant transformation (usually astrocytic component): WHO Grade III

Imaging/Gross

- Superficial
- Temporal lobe favored
- Demarcated
- Cystic with enhancing mural nodule or solid, variably enhancing

Smear/Histology

- Lobular/nodular
- Spongy/microcystic
- Dysmorphic/binucleate ganglion cells (SYN/NF/CG +)
- Perivascular chronic inflammation
- Eosinopilic granular bodies/Rosenthal fibers
- Collagen containing stroma in some (reticulin, trichrome +)
- Glial component: fibrillary or pilocytic; oligodendroglial elements rare

Special Variants

- Desmoplastic infantile ganglioglioma (DIG):
  - Age <2, supratentorial, hemispheric, firm, massive, cystic, dura-attached, spindle, and plump ganglion-like cells; superficially resembles sarcoma
- Dysplastic cerebellar gangliocytoma (Lhermitte-Duclos disease):
  - Unilateral expanded folia with replacement of internal granular layer by dysmorphic ganglion cells; associated with Cowdens syndrome (PTEN gene)

Differential Diagnosis

- Diffuse astrocytoma with cortical infiltration (neurons normal in cytology and distribution)
- Pilocytic astrocytoma (no ganglionic component)
- Pleomorphic xanthoastrocytoma (bizarre, multinucleate astrocytic cells)
- Dysembryoplastic neuroepithelial tumor (mucinous intracortical nodules, internodular "specific component" featuring "floating neurons")

Central Neurocytoma (WHO Grade I to II)

Clinical

- Young/middle-age adults
- Signs/symptoms of obstructive hydrocephalus
- Some are surgically curable
- Rare atypia/anaplasia

Imaging/Gross

- Lateral ventricle near foramen of Monroe; origin in septum pellucidum
- Rarely intraparenchymal (e.g., hemispheric)
- Often large and globular
- Calcified

Smear/Histology

- Uniform, round nuclei; speckled chromatin (oligo-like)
- Streaming and vague perivascular pseudorosettes
- Fine fibrillary background
- Exaggerated Homer Wright-like rosettes (similar to pineocytoma)
- Salt and pepper chromatin
- Calcification
- Synaptophysin +, neurofilament ±

Differential Diagnosis

- Oligodendroglioma (superficial, synaptophysin –)
- Cellular or clear cell ependymoma (paraventricular, GFAP +)

Pineal Parenchymal Tumors

Pineocytoma

Clinical

- Middle to late adulthood
- Pineal region symptoms (Parinaud's syndrome paralysis of upward gaze, etc.)
- "Favorable prognosis" only in comparison to pineoblastoma

Imaging/Gross

- Globular, discrete
- Contrast enhancing, ± calcification

Smear/Histology

- Round salt and pepper nuclei
- Loss of lobularity
- Pineocytic rosettes (large, exaggerated Homer Wright rosettes)
- Solid sheets
- Argyrophilic, club-shaped neuritic processes (Bodian, Bielschowsky)
- Synaptophysin +

Differential Diagnosis

- Normal pineal (no rosettes, often difficult diagnosis on small biopsy)
- Pineoblastoma (increased proliferation, PNET-like, CSF seeding)
- Pineal parenchymal tumor, intermediate type (lacks pineocytomatous rosettes, occasional mitoses, occasional seeding)
- Ependymoma (GFAP +, synaptophysin –)

Pineoblastoma

Clinical

- Childhood
- Rapid recurrence
- CSF seeding

Imaging/Gross

- Enhancing
- Infiltrative, CSF seeding, drop metastases

Smear/Histology

- Small "blue cell tumor"
- No pineocytomatous rosettes
- Occasional Homer Wright rosettes
- Occasional photoreceptor differentiation (trilateral retinoblastoma)
- Rare glial or mesenchymal differentiation

Differential Diagnosis

- Pineocytoma (low proliferation, pineocytomatous rosettes)
- Cellular ependymoma (low proliferation, GFAP+)
- Seeding from medulloblastoma (clinicopathologic correlation)
- Malignant germ cell tumor (PLAP, AFP, β-hCG, CK, etc.)

Dysembryoplastic Neuroepithelial Tumor (DNT/DNET) (WHO Grade I)

Clinical

- Age of onset <20 years
- Longstanding chronic seizures (partial complex type)
- Slow or no growth
- Benign/surgically curable
- Hamartoma vs. tumor; nature of tumor unsettled

Imaging/Gross

- Supratentorial; temporal lobe, infrequent other sites
- Intracortical
- Multinodular
- May be "cystic appearing" due to high mucin content, occasional calcification

Microscopic

- Patterned mucin-rich intracortical nodules
- "Specific glioneuronal element" (internodular) with
  - Floating neurons
  - Oligo-like cells
- Minimal perineuronal satellitosis
- ± Cortical dysplasia

Differential Diagnosis

- Oligodendroglioma (white matter involvement, occasional nonpatterned nodules, perineuronal satellitosis, no floating neurons)
- Oligoastrocytoma (same as above)
- Ganglioglioma (cyst-mural nodule, lymphocytic infiltrate, no floating neurons)

Paraganglioma (WHO Grade I)

Clinical

- Adults
- Back pain, radiculopathy, or incontinence
- Almost always benign/surgically curable

Imaging/Gross

- Filum terminale or nerve root (rarely skull base or sella)
- Enhancing/discrete
- Large feeder vessels

Smear/Histology

- Zellballen and carcinoid-like pattern
- Neuroendocrine cells with salt and pepper chromatin
- Ganglion cells in 50%
- Synaptophysin/chromogranin +; neurofilament ±
- S-100 + sustentacular cells

Differential Diagnosis

- Myxopapillary ependymoma (GFAP +, synaptophysin–, Chromogranin –)

Embryonal Tumors

Types

- Medulloepithelioma (age <5, epithelial canals)
- Medulloblastoma and variants:
  - Classic (vermis, infiltrative, PNET cytology)
  - Desmoplastic medullo (adults, lateral hemisphere, reticulin-rich nodules)
  - Large cell medullo (large nucleoli, aggressive)
  - Medullomyoblastoma (rhabdomyoblastic differentiation)
  - Melanotic medullo (pigmented, aggressive)
- PNET (primitive neuroectodermal tumor)
- Ependymoblastoma (ependymal true rosettes)
- Atypical teratoid/rhabdoid tumor (carcinoma-like)
- Pineoblastoma (pineal region, neuroblastic/retinal differentiation)
- Neuroblastoma/ganglioneuroblastoma (maturation)
- Olfactory neuroblastoma (esthesioneuroblastoma, paraganglioma-like)

- Retinoblastoma (eye, Flexner-Winterstein rosettes, fleurettes)
- PNET = medulloblastoma-like tumor outside the cerebellum

Medulloblastoma/PNET (WHO Grade IV)

Clinical

- Children/young adults
- Rapid, aggressive clinical course
- Rapidly fatal without therapy (Rx)
- 5-year survival with Rx = 60% to 70% in medulloblastoma; less with PNET
- Rx = surgery, craniospinal radiation, multidrug chemotherapy

Imaging/Gross

- Solid (as opposed to pilocytic astrocytoma)
- Noncalcified (as opposed to ependymoma)
- Homogeneously enhancing
- CSF spread ('icing')/drop metastases

Smear/Histology

- Small round or "carrot-shaped" nuclei, inapparent nucleoli, scant cytoplasm
- Classic pattern: reticulin-free sheets
- Desmoplastic variant: reticulin-rich, "germinal center-like" nodules, "Indian filing"
- Undifferentiated or with lines of differentiation
- Neuroblastic differentiation (fibrillarity, Homer Wright rosettes)
- Glial, mesenchymal, or melanocytic differentiation less common
- Subarachnoid invasion
- Synaptophysin +, GFAP ±

Differential Diagnosis

- Small blue cell tumors (primary or metastatic)
- Cellular ependymoma (low proliferation, GFAP +, SYN –)
- Atypical teratoid/rhabdoid tumor (rhabdoid, epithelioid, spindle cells; EMA +, CK +, actin +, desmin ±)

Atypical Teratoid/Rhabdoid Tumor

Clinical

- Infants <2 years old
- Rapid, highly aggressive clinical course
- CSF seeding seen at presentation in 35%
- Almost uniformly fatal within 1 year, despite therapy

Imaging/Gross

- Similar to medulloblastoma/PNET
- All sites, cerebellum most common

Smear/Histology

- Larger, epithelioid component resembling carcinoma or malignant rhabdoid tumor of kidney
- Spindled cells or even chondroid foci may be seen
- PNET component in 65%
- EMA +, CK +, actin + in majority of cases
- Synaptophysin +, GFAP + in some cases
- β-HCG –, PLAP – (i.e., not a germ cell tumor); occasional AFP +

Differential Diagnosis

- Small blue cell tumors (primary or metastatic)
- Cellular ependymoma (low proliferation, EMA –, CK –, actin –, synaptophysin –)
- Medulloblastoma/PNET (more uniformly small cells, EMA –, CK –, actin –)

Olfactory Neuroblastoma (WHO Grade III)

Clinical

- Bimodal peaks, adolescence and elderly
- Epistaxis, nasal obstruction
- Favorable prognosis in most, especially with gross total resection
- Subset are aggressive, difficult to predict
- Metastasis, high MIB-1, or neuroblastic predominence equate with lower survival

Imaging/Gross

- Cribriform plate
- Intranasal and/or intracranial
- Polypoid

Smear/Histology

- Mixed patterns of paraganglioma and neuroblastoma
- Nests/lobules/sheets
- "Neuroendocrine nuclei"
- Delicate fibrillary background
- Rare rosettes (Homer Wright or Flexner types)
- Synaptophysin/neurofilament/chromogranin +
- Usually CK –
- S-100 + sustentacular cells in paraganglioma like pattern

Differential Diagnosis

- Sinonasal undifferentiated carcinoma (CK +, synaptophysin –, S-100 –)
- Neuroendocrine carcinoma (CK +, S-100 –)
- Small cell melanoma (HMB-45 +)

Retinoblastoma

Clinical

- Age <3

- Leukocoria ("cat's eyes"), strabismus
- Sporadic/familial; Rb gene on 13q14
- Favorable prognosis in developed countries due to early stage at detection and effective adjuvant therapy
- Familial cases at risk for other neoplasms, especially osteosarcoma

Macroscopic

- Gray-white
- Fleshy
- Necrotic with dystrophic calcification
- Obtain optic nerve margin

Smear/Histology

- Small blue cell tumor
- Retinal; often bilateral and multifocal in familial
- Flexner-Wintersteiner rosettes
- Homer Wright rosettes (rare)
- Fleurettes (extremely rare)

Spread

- Optic nerve
- Leptomeningeal/CSF
- Extraocular
- Lymphatic and/or hematogenous

Differential Diagnosis

- Lymphoma (LCA +, synaptophysin –)

MENINGEAL NEOPLASMS

Meningioma (WHO Grade I)

Clinical

- Adults
- F:M ratio = 1.5 intracranial, 10:1 spinal (possibly progesterone receptor-related)
- NF2 gene (chromosome 22) implicated in most familial and half of sporadic cases
- Insidious/asymptomatic onset
- Occasionally radiation-induced
- Slow growth (unless atypical or malignant)
- Recurrence:
  - 5% to 10% in gross totally resected, benign (WHO I) meningiomas
  - 40% to 60% in subtotal resection or atypical/malignant grade
- Decreased survival in atypical and malignant meningioma

Imaging/Gross

- Extra-axial location
- "Dural tail" sign (enhancement beyond tumor; tumor vs. granulation tissue)
- Hyperostosis of adjacent skull (related to osteoblast-stimulating factors; usually reflects bone invasion)

Smear

- Cellular smears with 3D clusters; fibrous tumors smear poorly
- Epithelioid to spindle cells
- Nuclear pseudoinclusions

Microscopic

- Highly variable
- Polygonal epithelioid to elongated cells
- Stroma scant, collagenous, or mucinous
- Whorls
- Psammoma bodies
- Nuclear pseudoinclusions
- Hyalinized vessels

Immunohistochemistry

- See Table 10-4

Variants

- Meningothelial
- Fibrous
- Transitional
- Psammomatous
- Microcystic
- Secretory
- Lymphoplasmacytoid
- Angiomatous
- Metaplastic
- Chordoid (WHO II)
- Clear cell (WHO II)
- Rhabdoid (WHO III)
- Papillary (WHO III)

Differential Diagnosis

- Metastatic carcinoma (strong, uniform CK +)
- Melanoma (HMB-45 +)
- Hemangiopericytoma/other sarcoma (reticulin rich, EMA –)
- Solitary fibrous tumor (strong and diffuse CD34 +, EMA –)
- Schwannoma (strong and diffuse S-100 +, collagen IV – rich; EMA –)
- Inflammatory pseudotumor (entrapped microscopic meningothelial nests only)
- Glioma with dural invasion (GFAP +, EMA –)

Atypical Meningioma (WHO Grade II)

- High risk of recurrence even after gross total resection
- Definition has been debated, but generally as follows:
  - Necrosis (usually micronecrosis) significant in some studies, but not others
  - Frequent mitoses most important! sufficient by itself
- Note: Nuclear hyperchromasia/pleomorphism not important!
- New WHO definition:
  - Brain invasion or
  - High mitotic index, e.g. ≥4/10 HPF (may be focal) or
  - At least three of four features
    - Sheeting (pattern-less growth with loss of whorls and fascicles)
    - Small cells (lymphocyte-like nests with high N/C ratio)
    - Hypercellularity
    - Macronucleoli

Malignant (Anaplastic) Meningioma (WHO Grade III)

- Extracranial metastasis: clinical definition; occasionally these appear histologically benign or
- Anaplasia: difficult to define
  - Carcinoma, sarcoma, or melanoma-like appearance, focally or diffusely (requires IHC or EM demonstration of meningothelial features)
- Excessive mitotic index (e.g., > 20/10 HPF)
- Median survival <1.5 years

Table 10-4. Immunohistochemistry of Meningiomas

Positive	*Negative*
EMA (weak; membrane pattern)	Estrogen Receptor
CK (secretory variant; otherwise rare)	GFAP
Progesterone Receptor	CD34 (±)
Vimentin	
S-100 (20%; 80% fibrous variant)	
CEA (secretory variant)	

Hemangiopericytoma (Once Termed "Angioblastic Meningioma") (WHO Grade II or III)

Clinical

- Adults
- F:M = 1
- No chromosome 22 abnormality
- Considered a meningeal sarcoma
- Recurrence rate = 60%
- Metastases = 25%
- Mean survival = 7 years

Imaging/Gross

- Extra-axial, densely contrast-enhancing on CT/MRI
- Highly vascular on angiogram
- Frequently invades overlying bone
- No associated hyperostosis of skull

Smear

- Cellular without molding/whorling of meningioma

Microscopic

- Staghorn vessels
- Pale zones
- Variable collagen deposition
- Variable mitotic rate
- Reticulin rich
- Factor XIIIa + in scattered individual cells (most cases)
- EMA –, S-100 –

Differential Diagnosis

- Meningioma (tight whorls, psammoma bodies, reticulin poor, EMA +)
- Other sarcomas (e.g., fibrosarcoma, mesenchymal chondrosarcoma, MPNST)
- Solitary fibrous tumor (strong, diffuse CD34 +; malignant examples may be difficult to differentiate from hemangiopericytoma)

Other Primary Mesenchymal Neoplasms

Benign

- Generally rare; includes most soft tissue neoplasms (e.g., chondroma, fibrous histiocytoma, hemangioma, solitary fibrous tumor, etc.)

Sarcomas

- Typically high-grade malignant; includes fibrosarcoma, MFH, osteosarcoma, chondrosarcoma (especially mesenchymal chondrosarcoma), etc.

- Some are thought to be radiation-induced
- Poor prognosis

Secondary Dural Neoplasms

- Invade dura and clinically mimic meningioma

Metastases

- Lung or breast carcinoma, melanoma, leukemia/lymphoma most common

Extension from Bone

- Multiple myeloma, metastatic carcinoma, etc.

Extension from Brain

- Gliosarcoma, GBM, desmoplastic infantile astrocytoma (DIA), or ganglioglioma (DIG)

Inflammatory Pseudotumors

- Unknown etiology
- Dura-based masses; diagnosis includes rheumatoid arthritis, Rosai-Dorfman disease, Erdheim-Chester disease, and a variety of granulomatous disorders
- Clinically and radiologically mimic meningioma
- Often plasma cell-rich fibroinflammatory background

OTHER NON-GLIAL NEOPLASMS

Hemangioblastoma (WHO Grade I)

Clinical

- Adults (30–65)
- Polycythemia (10%)
- Sporadic or von Hippel-Lindau (VHL) associated (~20%, chromosome 3p)
- Single or multiple (VHL)
- Benign

Imaging/Gross

- Intra-axial
- Cerebellum, less often brainstem or cord
- Rare supratentorial or peripheral nerve involvement
- Cyst with enhancing mural nodule

Smear

- Deceptively fibrillary
- Variable nuclear pleomorphism
- Lipidized stromal cells (may be difficult to find)

Microscopic

- Highly vascular
- Lipid-laden stromal cells
- Reticulin rich (reticular variant) or poor (cellular variant)
- May incite marked intra- and peritumoral pilocytic gliosis
- NSE +, S-100 +, GFAP ±, EMA –

Differential Diagnosis

- Pilocytic astrocytoma (reticulin –; lacks lipidized cells)
- Metastatic renal cell carcinoma (EMA and/or CK +)

Craniopharyngioma

Adamantinomatous Craniopharyngioma (WHO Grade I)

Clinical

- Children/young adults
- Frequently recurs
- Significant morbidity and long-term mortality, despite benign histology

Imaging/Gross

- Suprasellar
- Cystic
- "Motor oil" contents
- Calcified

Smear

- 3D clusters
- Squamous cells with intercellular bridges
- Wet keratin (diagnostic; resembles ghost cells of pilomatrixoma)
- Cholesterol crystals

Microscopic

- Resembles adamantinoma of bone and ameloblastoma of jaw
- Infiltrative growth
- Keratinizing squamous esp. with basal palisading
- Stellate reticulin (spidery processes within intercellular edema)
- Wet keratin (pilomatrixoma-like)
- Xanthogranulomatous, cholesterol-rich debris
- May incite marked pilocytic gliosis

Differential Diagnosis

- Papillary craniopharyngioma (nonkeratinizing squamous epithelium)
- Rathkes cleft cyst (respiratory type epithelium ± squamous metaplasia; mucin content > xanthogranulomatous debris)
- Pilocytic astrocytoma (biphasic, including loose component)

Papillary Craniopharyngioma (WHO Grade I)

Clinical

- Adult
- More resectable than adamantinomatous; less recurrence
- Better prognosis than adamantinomatous

Imaging/Gross

- Third ventricle, suprasellar
- Solid/cystic
- Noncalcified

Histology

- Demarcated
- Solid and papillary
- Nonkeratinizing squamous epithelium
- No granular layer
- Mucin (±) goblet cells

Differential Diagnosis

- Adamantinomatous craniopharyngioma (complex, infiltrative epithelium, wet keratin, calcified)
- Rathkes cleft cyst (squamous metaplasia beneath respiratory epithelium)

Germ Cell Tumors

Clinical

- Child/young adult
- Parinaud's syndrome (paralysis of upward gaze) in pineal examples
- Precocious puberty (even in nonsuprasellar/third ventricular examples)
- Male predilection of pineal region lesions
- Germinoma radioresponsive
- Mature teratoma resectable
- Nongerminomatous germ cell tumors variably chemosensitive

Imaging/Gross

- Pineal and/or suprasellar
- Solid or cystic
- Calcification common in teratoma

Smear/Histology

- As in testis
- Germinoma (= seminoma)
- Immature teratoma = primitive (fetal-like) elements, often neural
- Malignant teratoma = carcinoma/sarcoma elements

Prognosis

- Good: pure germinoma, mature teratoma
- Intermediate: germinoma with syncitiotrophoblasts, immature teratoma, malignant teratoma, mixed germ cell tumor (predominantly germinoma or teratoma)
- Poor: choriocarcinoma, yolk sac tumor, embryonal carcinoma, mixed germ cell tumor (predominantly nongerminomatous malignancies)

Lymphoma/Leukemia

Primary CNS Lymphoma

Clinical

- Elderly
- Immunosuppressed
- Steroid responsive
- Death within 2 years

Imaging/Gross

- Single or multiple
- Periventricular
- Supra- and/or infratentorial
- Brainstem and spinal cord uncommon
- Homogeneously enhancing
- Disappearance with steroid therapy

Smear/Histology

- Infiltrative
- Angiotropic, but permeates parenchyma
- >90% large B-cell type
- Component of small, reactive CD3 + T cells
- Necrosis and EBV-immunopositivity in AIDS/immunosuppression

Differential Diagnosis

- Oligodendroglioma (superficial, S-100 +, LCA –, CD20 –)
- Inflammatory/demyelinating process (numerous KP-1 + macrophages)
- Small cell carcinoma (CAM5.2 +, SYN +, CD20 –)
- Small cell GBM (GFAP +, S-100 +, CD20 –)
- Medulloblastoma/PNET (SYN +, CD20 –)
- Melanoma (HMB-45 +, S-100 +, CD20 –)

Secondary (Systemic) Lymphoma/Leukemia

- Dural/epidural/leptomeningeal
- Cranial or spinal nerve roots involvement common
- Parenchymal involvement is secondary
- Intravascular lymphoma: infarcts due to plugging of vessels (see Vascular Disorders)

Metastases

Clinical

- Hematogenous (parenchymal: lung primary; meningeal:- breast/GI/prostate primary)
- Perineural (from head and neck primary)
- Direct extension from bone
- Poor prognosis, except germ cell tumors
- Improved survival after resection of solitary metastases (e.g., renal cell carcinoma, melanoma)

Imaging/Gross

- Single or multiple
- Gray-white junction
- Meningeal carcinomatosis
- Contrast enhancing

Smear/Histology

- Discrete margin
- Limited parenchymal spread in small cell carcinoma and melanoma
- Adenocarcinomas most common; other carcinomas less so
- Melanoma relatively common
- Sarcomas rare

Patterns

- Hemorrhagic:
  - Melanoma
  - Renal cell carcinoma
  - Choriocarcinoma
- Young patient:
  - Germ cell tumors
  - Alveolar soft parts sarcoma
- Unknown primary:
  - Adenocarcinoma (lung or breast are CK7 +, GI are CK20 +, see Table 25-2)
  - Melanoma (skin; primary may have regressed)

TRAUMA (see Chapter 5)

Closed Head Injury

- Most common form
- Dura intact may be associated with serious brain injury despite minor or no external injuries

Open Head Injury

- Dura breached and brain exposed to environment; increased risk of infection in survivors

Blunt Head Injury

- Common cause of traumatic death
- Generally multilevel, involving external to internal structures (e.g., scalp laceration, skull fracture, subdural hematoma, cortical contusion, internal contusion)

Skull Fractures

- Need to strip dura for adequate examination
- Linear: follows direction of force and spreads along paths of least resistance
- Depressed: impact over small surface (e.g., hammer)
- Comminuted: impact over larger surface (e.g., brick)
- Compound: associated with scalp laceration
- Basilar: often complex, patterns include hinge and ring fractures (e.g., MVA, landing on feet from high fall, or forceful hyperextension)
- "Raccoon eyes": hemorrhage into eyelids due to orbital roof fracture
- "Battle sign": hemorrhage overlying mastoid region due to petrous temporal fracture

Epidural Hematoma

- Relatively uncommon: usually result of skull fracture with laceration of middle meningeal artery
- Lens-shaped with depression of convexity

Subdural Hematoma

- Common, often fatal, usually traumatic; skull fracture in 50%
- Caused by tearing of bridging veins
- Direct impact not necessary (e.g., shaken infant); common in child abuse
- Organized examples have thin inner membrane and a thick outer membrane attached to dura may coexist with diffuse axonal injury (DAI)

Subarachnoid Hemorrhage

- Trauma most common cause; may accompany contusion, laceration, or subdural hematoma
- Nontraumatic form associated with ruptured aneurysms and other vascular malformations
- Extend into sulci and Virchow-Robin spaces

Cortical Contusion

- Maximum damage over gyral crests with sparing of sulci (opposite of infarct):
  - Coup: adjacent to point of impact; most prominent with mobile object striking stationary head (e.g., hammer)
  - Contacoup: opposite point of impact; prominent when mobile head hits stationary object (e.g., frontal lobe injury when hitting back of head during fall):
    - Common sites include fronto-orbital and temporal poles where they contact irregular bony surfaces of the skull base

Pontomedullary Transection (Brainstem Avulsion)

- Results from extremely forceful hyperextension
- Partial or complete; instantly fatal in most cases

Gunshot Wounds (see Chapter 5)

- An unfortunately common component of urban American life (+ death), damage generally described in terms of direction of missile trajectory (e.g., entrance wound, bullet tract, exit wound)

Penetrating Wound

- Bullet enters, but doesn't exit

Perforating Wound

- Bullet enters and exits

Entrance Wound

- Abrasion ring:
  - Close or contact: soot deposits and burns
  - Intermediate: "powder tattoo"
  - Distant: no deposits
  - Skull surface bevels in at entrance (wider inner table defect)

Exit Wound

- Skull defect bevels out (wider outer table defect)

Bullet Track: Low Velocity Missiles

- Associated with contusion-lined cavity; high-velocity missles: extensive damage (avulsion, "burst lobe")

Secondary Track

- Caused by ricochet of bullet off inner table of skull

Spinal Cord Trauma

- Motor vehicle accident and falls most common cause

Upper Cervical Injuries

- Usually instantly fatal and associated with brain injury

C4-C8 Injuries

- Most common site of nonfatal trauma; region susceptible to hyperextension, hyperflexion, etc.

Cervical Spondylosis

- May predispose to hyperextension injuries

Central Cord Necrosis

- Common in nonpenetrating injury; generally fusiform and extending over multiple segments

Post-Traumatic Syringomyelia

- Late complication of central cord necrosis; may extend rostrally over time, causing neurologic deterioration in paraplegics

ISCHEMIC/ANOXIC/VASCULAR DISORDERS

Cerebral Infarct [Cerebrovascular Accident (CVA) "Stroke"]

- Obstruction of major arterial (ACA, MCA, PCA, basilar, vertebral) or smaller branch (e.g., PICA, cortical/leptomeningeal)
- Cerebral atherosclerosis, thromboembolic disease, or combination; individual susceptibility due to variations in anatomy of circle of Willis anatomy and its collaterals
- Embolic disease from heart or neck vessels (e.g., carotid bifurcation); MCA territory most common (straight shot); often multiple and hemorrhagic
- Time course of infarct (see Table 10-5)

Anoxic Encephalopathy (Global Ischemic Injury)

- Systemic circulatory failure/hypotension (e.g., resuscitation after cardiac arrest)
- "Selective Vulnerability" = regional (e.g., hippocampus CA1 > CA2) and cellular (e.g., neuronal > glial) variations in susceptibility to ischemia

Hippocampal Necrosis

- Affects pyramidal neurons of Sommer's sector (CA1) and sometimes endplate (CA4) with relative sparing of CA2 and CA3

Purkinje Cell Necrosis (Cerebellar Cortex)

Watershed (Borderzone) Infarct

- Typically linear and hemorrhagic, between two or all three of the major arterial zones of vascular supply (e.g., ACA and MCA territories)
- Reflect susceptibility of endarterial vessels (i.e., vessels farthest from source)

Individual Neuronal Necrosis

- Scattered necrotic neurons in cortex (especially depths of sulci) and/or deep gray matter with preservation of intervening cells

Laminar/Pseudolaminar Necrosis

- Extensive, typically bilateral linear intracortical infarcts involving entire cortex (laminar) or middle laminae (pseudolaminar; see hypoglycemic brain injury below)

Brain Death Syndrome ("Respirator Brain")

- Extensive global insult
- Marked edema results in increased intracranial pressure (ICP) > systemic pressure, thus preventing brain perfusion
- If "life" maintained by respirator (too philosophical to discuss here, but legally brain death = patient death), brain autolysis occurs in vivo. Note: respirator does not cause the injury, thus the objection to the term "respirator brain"
- Gross and microscopic appearance is identical to postmortem autolysis (i.e., without reactive changes)

Multi-infarct Dementia

- Overdiagnosed clinically, many have Alzheimer's Disease with one or more incidental infarcts at autopsy; requires extensive damage with stepwise clinical course
- Rare cases due to extensive cortical microinfarcts secondary to small vessel leptomeningeal disease with gross appearance of "granular atrophy"

Table 10-5. Gross and Micro Features of Cerebral Infarct

	Gross features	*Micro features*
Acute (hrs-days)	Soft, edematous Anemic = non-reperfused Hemorrhagic = reperfused	Coagulative necrosis, "red dead" neurons, spongy neuropil, mild neutrophil response
Subacute (days-wks)	Partially liquefied	Liquefactive necrosis, neuronal and glial dropout, marked macrophage (Gitter cell) response, reactive capillaries and gliosis at periphery
Chronic (mos-yrs)	Cystic cavity with collapse of surrounding tissue	Cyst lined by "gliotic scar" (no collagen), parenchymal loss in vascular distribution, subpial sparing (as opposed to old contusion); ± hemosiderin, ± scattered macrophages

Venous Infarcts

- Thrombosis of dural sinuses or cerebral veins; may complicate infection or hypercoagulable state
- Typically hemorrhagic, bilateral, and affects white > grey matter

Small Vessel Disease/Deep Infarcts

- Arteriolar disease with deep grey and white matter infarcts, myelin rarefaction, and/or frank demyelination

Arteriolosclerosis

- Associated with hypertension, diabetes, and age

Binswanger's Disease

- Rare complication of hypertension with diffuse cerebral white matter disease and clinical dementia

CADASIL (Cerebral Autosomal Dominant Arteriopathy With Subcortical Infarcts and Leukoencephalopathy)

- Recently described familial neurodegenerative disorder associated with missense mutations in the Notch 3 gene on chromosome 19q
- Mid-late adult onset dementia and/or pseudobulbar palsy; infrequent hemorrhage
- Identical distribution to Binswanger's except no hypertension
- Pathognomonic PAS +; granular, electron dense deposits in media of small and perforating arterioles

"Leukoaraiosis"

- Radiologic term for white matter changes often incidentally found in elderly; thought to represent small vessel ischemic changes

Related Disorders (Patterns of Selective Vulnerability)

Hypoglycemic Brain Injury

- Rare in pure form
- Resembles ischemia except no gross infarcts; sparing of Purkinje cells
- Pseudolaminar necrosis affects superficial laminae (rather than middle laminae as in hypotension, above)

Carbon Monoxide Poisoning

- CO outcompetes O_2 for hemoglobin binding
- Resembles hypoxia except shows selective vulnerability for globus pallidus and white matter
- Acute death: cherry red discoloration, body and brain
- Delayed death: pallidal necrosis, white matter necrosis/demyelination, and/or cortical, hippocampal, and cerebellar ischemic damage

Methanol Poisoning

- Metabolized by liver to formaldehyde and formic acid, which cause most of the damage
- Selective vulnerability (necrosis): retinal ganglion and photoreceptor cells (blindness); basal ganglia (putamen and claustrum)

Intracranial Hemorrhage (also see Trauma)

Berry (Saccular) Aneurysm/Subarachnoid Hemorrhage (SAH)

- Saccular outpouchings (as opposed to fusiform atherosclerotic aneurysms of posterior circulation) at bifurcations in circle of Willis, especially anterior circulation
- Rupture risk proportional to size and associated with high mortality/morbidity
- Higher incidence in polycystic kidney disease, Ehlers-Danlos syndrome, Marfan syndrome and neurofibromatosis type 1

Hypertensive Intracerebral Hemorrhage

- Deep, especially basal ganglia, thalamus, cerebellum, and pons
- Displaces, rather than destroys, tissue (unlike hemorrhagic infarct); thus, once resolved/resorbed, leaves a slit-like (rather than round) space

Cerebral Amyloid Angiopathy (CAA): Superficial Lobar Hemorrhage

- Affects the elderly
- βA4 amyloid (CNS form identical to that in neuritic plaques) deposited in leptomeningeal and superficial cortical vessels
- Most Alzheimer's patients have CAA, but those presenting with lobar hemorrhage not always demented
- Clinical diagnosis includes intratumoral hemorrhage, so may be seen as surgical specimen

Vascular Malformations

Berry (Saccular) Aneurysm (See Above)

Arteriovenous Malformation (AVM)

- Mostly intracerebral, occasionally spinal
- Present with hemorrhage in more than half; seizures and headaches also common
- Consist of tortuous arterial, venous, and arteriovenous vessels, often with chronic degenerative changes (hyalinization, Ca^{2+}, thrombosis, hemosiderin, gliosis)
- Extensive intervening brain parenchyma; arterial component is elastic +

Cavernous Angioma ("Cavernoma")

- Large, thin-walled, elastic stain and actin immuno-negative vessels, and often minimal intervening brain parenchyma
- Grossly spongy, chronic degenerative changes (see above)
- Incidental finding or associated with hemorrhage and/or seizures; 1% chance of bleed/year

Others

- Venous angiomas and capillary telangiectasias consist of thin-walled vessels with intervening brain parenchyma devoid of degenerative changes
- Typically cerebral white matter or pons; often incidental

Other Vascular Disorders

Vasculitis

- Often secondary to meningitis or other inflammatory/infectious process
- Primary CNS vasculitis is commonly granulomatous; probably autoimmune; inflammation confined to vessel wall and causes secondary infarcts in young to middle age:
  - Poor prognosis unless treated aggressively with immunosuppressives
  - May be missed on biopsy due to patchy distribution; angiography helpful

Intravascular Lymphoma

- Previously termed "angioendotheliomatosis," this is not an endothelial tumor
- Rather it is a highly aggressive, systemic lymphoma largely confined to intravascular spaces of various organs
- Most present with confusing CNS manifestations due to vascular occlusion with multiple infarcts
- Antemortem diagnosis often missed
- Usually large cell morphology, B-cell phenotype

NEURODEGENERATIVE DISORDERS

Summary Table (Table 10-6)

- Neurodegenerative disorders are progressive, fatal, usually idiopathic with regional atrophy, neuronal loss, and gliosis

Alzheimer's Disease (AD)

- Most common neurodegenerative disorder
- Incidence increases with age
- Varying criteria, but diagnosis based on neocortical (not hippocampal) burden of neuritic plaques (NP) and/or neurofibrillary tangles (NFT), highlighted by silver stains (Bielschowsky, Bodian, Gallyas, etc.) or immunos for Tau (microtubule associated protein)
- Coexistent cerebral amyloid angiopathy (CAA) in most
- βA4 amyloid (CNS form of amyloid) in NPs and CAA
- NFTs in neuronal perikarya and neuritic processes = paired helical filaments
- Majority are sporadic with higher risk for apoE4 and lower risk for apoE2 alleles
- ~10% familial forms (aut. dom. in most) with younger age of onset; AD1 (APP or amyloid precursor protein) gene on chr. 21, AD2 on chr. 19, AD3 on chr.14, AD4 on chr. 1
- Down syndrome patients get early onset AD, probably due to overexpression of AD1 gene

Frontal (Frontotemporal) Lobe Dementia (Without Specific Pathology)

- Second most common cause of dementia in some series
- Frontal lobe symptoms include personality changes, disinhibition, etc.
- Nonspecific pathology (neuronal loss and gliosis) without NFTs, NPs, Lewy bodies, Pick bodies, swollen neurons, etc. (i.e., diagnosis of exclusion)
- Generally sporadic and idiopathic
- Considered by some to be a form of Pick's disease without Pick bodies (analogous to solid variants of cysts in surgical pathology)
- Occasionally associated with MND (ALS/frontal lobe dementia)

Multi-infarct Dementia

- Overdiagnosed clinically; many have AD changes with one or more incidental infarcts at autopsy
- Requires extensive damage with stepwise clinical course
- Rare cases grossly associated with "granular atrophy" due to extensive cortical microinfarcts secondary to small vessel leptomeningeal disease

Idiopathic Parkinson's Disease (IPD)

- Most common cause of parkinsonism
- Other forms usually associated with additional symptoms not L-Dopa responsive ("Parkinson's Plus") and

Table 10-6. Neurodegenerative Disorders, The Minimalist's Approach

Disorder	*Clinical*	*Regions of pathology*	*Histology*	*Genetic/other associations*
Alzheimer's Ds. (AD)	Dementia	Cortex, Mesial temperal lobe, Nucleus basalis	Neurofibrillary tangles, plaques, amyloid angiopathy	Apo E4 allele, Ad1 (APP) gene-chr. 21 (Down syn.), AD2-AD4 genes
Frontal lobe dementia	Dementia, frontal lobe sx's	Frontotemporal cortex	Neuronal loss and gliosis only (Dx of exclusion)	ALS/dementia complex (Rare)
Pick's Ds.	Dementia, frontal lobe sx's	Frontotemporal cortex	Pick bodies, swollen neurons (Pick cells)	Rare familial associations
Parkinson's Ds. (IPD)	Parkinsonism, ± Dementia	Subst. Nigra, Locus ceruleus	Lewy bodies (LB)	Combined AD/IPD, DLBD, LB variant of AD
Huntington's Ds. (HD)	Chorea, Dementia	Caudate, Putamen	Neuronal loss and gliosis only	Huntington gene (chr 4p), aut. dom., triple repeat expansion
Creutzfeldt-Jakob Ds. (CJD)	Dementia, myoclonus, EEG findings	Gray matter (cerebral/cerebellar cortex, deep gray)	Spongiform change, amyloid (Kura) plaques	PrP gene/protein (all forms), Bovine SE and nvCJD, GH extracts, grafts, etc. Also iatrogenic CJD, cannibalism and Kuru
Progressive Supranuclear Palsy (PSP)	Parkinsonism, upward gaze palsy, ± dementia	Subcortical, esp. brainstem nuclei, globus pallidus, and dentate	Neurofibrillary tangles, (globose type), glial inclusions, neuropil threads	
Corticobasal Degen. (CBD)	Dementia, "alien limb" syndrome, parkinsonism	Frontotemporal cortex, subst. nigra, other subcortical nuclei	Swollen neurons, neurofibrillary tangles, glial inclusions, nueropil threads	
Multisystem atrophy (MSA)	Striatonigral degeneration (parkinsonism) ± olivoponto-cerebellar atrophy (ataxia), ± Shy-Drager syn (autonomic dysfunction)	Putamen, subst. nigra, locus ceruleus, basis pontis, Purkinje cells	Glial inclusions, neuropil threads	
Amyotrophic Lateral Sclerosis (ALS)/MND	Upper and lower motor neuron disease (weakness, hyperreflexia, fasciculations)	Ant. horns and roots, lat. columns, XII cr. n.	Myelin pallor, neuronal loss, Bunina bodies, LB-like inclusions	5-10% familial; minority with superoxide dismutase (SOD) gene mutations
Spinal muscular atrophies (SMA)	Type 1 infantile (Werdnig-Hoffman)-floppy infant, LMN only	Ant. horns + roots, skeletal muscle atrophy	Myelin pallor, neuronal loss, characteristic muscle histology in infantile form	Aut. rec., gene(s) on chr. 5q
Friedrich's ataxia	Ataxia, cardiac dz, neuropathy	Post. columns + roots, periph. n., lat. columns, dentate, sup. cerebellar ped.	Myelin pallor, neuronal loss	Aut. rec., frataxin gene (chr. 9q), triple repeat expansion
Spino-cerebellar ataxias (SCA)	Ataxia, variable sx's depending on variant, some overlap with MSA	Variable, Purkinje cells, OPCA, spino-cerebellar tracts, MND (type 3)	Myelin pallor, neuronal loss	Aut. dom. in most, caused by triple repeat expansion
Neuroaxonal dystrophies	Infantile and adult forms, Hallervorden-Spatz Dz (HSD)	Widespread in infantile, Globus pallidus in HSD	Axonal spheroids (swellings) + iron deposition in HSD	Aut. rec. in most, genes not yet identified
Lafora's dz (Myoclonic epilepsy)	Seizures, myoclonus, dementia, visual sx's	Cortex, globus pallidus, nigra, thalamus, PNS, cerebellum	Lafora body	Aut. rec., gene on chr. 6q

include PSP, CBD, MSA, postencephalitic parkinsonism, ALS/dementia/Parkinsonism of Guam, dementia pugilistica, drug-induced (MPTP) parkinsonism, etc.

- Typically affects lateral substantia nigra more severely (Lateral = Least pigment, Medial = Most pigment)
- Lewy body (LB) = diagnostic hallmark
- Dementia not uncommon; some due to coexistent AD (AD/IPD) or cortical Lewy bodies, others likely subcortical in nature
- If cortical LBs also found, diagnosis = diffuse Lewy body disease (DLBD) and is often associated with psychiatric symptoms; if AD changes as well, diagnosis = Lewy body variant of AD

Huntington's Disease (HD) (see Chapter 2)

- Autosomal dominant; onset fourth to sixth decade (i.e., after procreation, thus allowing for gene survival)
- Slowly progressive, uniformly fatal
- Chorea usually precedes dementia
- Atrophy, neuronal loss, and gliosis of neostriatum (caudate and putamen); some cortical atrophy in late stage disease
- Huntington gene on chr 4q with CAG triple repeat expansion (<37 copies = normal; >37 copies = disease)
- Genetic anticipation = younger onset and increased severity with each generation due to continued expansion of triple repeat
- Repeat expansion most likely to occur in paternal transmissions (i.e., during spermatogenesis)
- Lateral ventricles have "bat wing" configuration due to atrophy of caudate head

Pick's Disease (Lobar Atrophy)

- Rare form of dementia; usually sporadic, <20% familial
- Earlier onset than AD (45–65 years)
- Frontotemporal disease with sx's similar to frontal lobe dementia (see above)
- Sparing of precentral gyrus and posterior 2/3 of superior temporal gyrus
- Striking cortical atrophy described as "knife edge" or "walnut brain;" typically asymmetric
- Pick bodies = round, silver stain and Tau immunopositive neuronal inclusions in cortex and mesial temporal structures (hippocampus, amygdala, entorrhinal cortex)
- Pick cells = swollen (achromatic or chromatolytic); cortical neurons appear large, pink; neurofilament (NF) + and devoid of Nissl substance (thus resemble reactive neurons of central chromatolysis)

Creutzfeldt-Jakob Disease (CJD)/ Spongiform Encephalopathies (SE)

- Rapidly fatal form of dementia
- Uniform, worldwide incidence of 1/1,000,000 per year
- Majority are sporadic (i.e., no evidence of infectious or genetic cause)
- 10% familial (PrP gene mutations)
- Rare cases are iatrogenic (infectious) due to inadvertent inoculation of contaminated tissue such as dural graft, corneal transplant, EEG electrodes, or human growth hormone extracts
- Transmissible agent is protease-resistant prion protein (PrP)
- Disease occurs with conformational change of PrP structure into β-pleated sheet (amyloidogenic)
  - Some gene mutations increase likelihood of this conversion (familial)
  - Single pathogenic PrP can induce further protein conversions of wild type protein, thus creating a chain reaction
- Etiology of sporadic CJD poorly understood, but most likely represents somatic age-related gene mutation or spontaneous protein conversion; homozygosity for Met or Val at codon 129 increases risk of sporadic CJD
- Classic cases have triad of rapid dementia, myoclonus, and periodic short wave activity on EEG
- Classic histology shows triad of neuronal loss, gliosis, and spongiform change (often patchy) defined by small, "sharply defined, punched out" vacuoles in gray matter (cortex and/or deep nuclei)
- Differential Diagnosis includes
  - Status spongiosus: superficial cortical vacuolation commonly seen in end-stage AD; in comparison, CJD typically affects deep cortex or entire cortex
  - Edema or ischemia: vacuoles larger and ill-defined
  - Artifacts: vacuoles larger and ill-defined; also affect white matter
- Cerebellar amyloid plaques in ~5%

Other Spongiform Encephalopathies (SE)

New Variant CJD (nvCJD)

- Cluster of cases reported from England with epidemiologic link to bovine spongiform encephalopathy (BSE)
- Unusually young age of onset (<40 years)
- Prolonged clinical course
- Dementia less prominent; behavioral changes
- Numerous cerebral cortical and cerebellar amyloid plaques (unique histology among the SEs)
- Patients homozygous for Met at codon 129
- Link to BSE puzzling because bovine skeletal muscle contains little to no pathogenic PrP (as compared to brain)

Gerstmann-Sträussler-Scheinker Disease (GSS)

- Rare familial SE with cerebellar ataxia and amyloid plaques in cerebellar molecular layer ("GSS plaques"); various PrP gene mutations

Fatal Familial Insomnia (FFI)

- Autosomal dominant SE with rapid course, sleep disturbances, hallucinations, motor and autonomic symptoms, prominent thalamic, and inferior olive disease; PrP gene mutations

Kuru

- Literally "trembling disease" in the Fore language of New Guinea
- Largely of historic interest; it established the "transmissible agent" from diseased brains
- Linked to cannibalistic ritual involving brains of deceased; now discontinued, the disease is disappearing
- Predominantly a cerebellar disease with "spiked-ball" amyloid ('Kuru") plaques

Progressive Supranuclear Palsy (PSP; Steele-Richardson-Olszewski Disease)

- Supranuclear (upward) gaze palsy due to involvement of oculomotor (CN III) nucleus (similar to Parinaud's syndrome, see pineal tumors)
- Parkinsonism and/or dementia (subcortical), clinical syn-drome nonspecific: overlaps with IPD, CBD, MSA, etc.
- Subcortical NFTs with globose configuration
- Tau immunopositive glial cytoplasmic inclusions (GCI) and neuropil threads (overlap with CBD and MSA)

Corticobasal (Ganglionic) Degeneration (CBD)

- Relative newcomer to neurodegenerative world; mostly sporadic
- Cortical and subcortical (basal ganglia, substantia nigra) pathology
- Overlap with Pick's disease; = asymmetrical frontal lobe dementia with swollen neurons
- Overlap with PSP; subcortical NFTs, neuropil threads, and GCIs with parkinsonism
- "Alien limb" syndrome typical, but not always present

Multisystem Atrophy (MSA)

- Three clinical syndromes, often coexist; mostly sporadic:
  - Striatonigral degeneration (SND): putamen and nigra = parkinsonism
  - Olivopontocerebellar atrophy (OPCA): inf. olives, basis pontis, Purkinje cells = ataxia
  - Shy-Drager: intermediolateral spinal columns (thoracic cord) = autonomic
- Gross atrophy with subcortical Gallyas and Tau positive GCIs and neuropil threads
- Some overlap with inherited SCAs, PSP, and CBD

Amyotrophic Lateral Sclerosis (ALS)/Motor Neuron Disease (MND)

- Combined upper (UMN) and lower motor neuron (LMN) disorder, but occasionally only one level is involved
- Weakness, wasting, fasciculations, hyperreflexia, Babinski, EMG signs of denervation, etc.
- 5% to 10% familial, of which a minority have mutation in superoxide dismutase (SOD) gene (i.e., most cases are sporadic/idiopathic)
- Clinical mimics may include polio, HIV, HTLV-1, lead poisoning, autoimmune disease, etc. ("Secondary MND")
- Grossly, atrophy of anterior spinal roots most prominent pathologic feature
- Histology shows myelin pallor (LFB-PAS or other myelin stain) of lateral columns and anterior roots, loss of anterior horn neurons, Bunina bodies (small eosinophilic cytoplasmic inclusions), Lewy body-like inclusions, and neurogenic pattern of muscle fiber atrophy
- Rare cases are associated with frontal lobe dementia

Spinal Muscular Atrophy (SMA)

- Group of autosomal recessive MNDs (LMN only), one or more genes on chr. 5q (also see Chapter 2)
- Histology shows loss of anterior horn neurons, atrophy of anterior nerve roots, and neurogenic muscle fiber atrophy
- Variants:
  - Type 1 = infantile (Werdnig-Hoffman disease): most common SMA, "floppy baby," die within a couple of months from respiratory failure; characteristic skeletal muscle histology with large group neurogenic atrophy (small and round, not angulated) and scattered round hypertrophic fibers
  - Type 2 = chronic infantile: intermediate severity with survival into teens
  - Type 3 = chronic, proximal (Kugelberg-Welander syndrome); clinical presentation similar to muscular dystrophy

Friedreich's Ataxia (see Chapter 2)

- Most common form of inherited ataxia; aut. rec. inheritance
- GAA triple repeat expansion (see HD) in frataxin gene, chr 9q
- Onset in childhood or teens with variable survival (rarely past 30s)

- Cardiomyopathy typical (unlike SCA, see below)
- Ataxia due to combined peripheral neuropathy, atrophy of spinocerebellar tracts (cerebellar afferents), and degeneration of superior cerebellar peduncle (efferents)
- Myelin pallor in posterior columns, dorsal nerve roots, lateral columns, spinocerebellar tracts, superior cerebellar peduncles, and peripheral nerve
- Neuronal loss in dentate nucleus and others

Spinocerebellar Ataxia (SCA)

- Group of inherited, mostly aut. dom. forms of ataxia
- Number of variants growing (see Chapter 2)
- CAG triple repeat expansions
- Genetic anticipation (see HD)
- Some overlap with MSA, but no GCIs or neuropil threads
- Machado-Joseph disease = form of SCA 3 with parkinsonism, bulging eyes, and anterior horn cell loss (MND) that may mimic ALS

Neuroaxonal Dystrophy

- Group of neurodegenerative disorders characterized by axonal spheroids (swellings)
- Infantile form = autosomal recessive; widespread CNS and PNS disease; death in early childhood; diagnosis can be made on skin, nerve, conjunctival or rectal biopsy
- Hallervorden-Spatz disease = autosomal recessive in most. early and late onset variants; movement disorder and dementia; characteristic "eye of tiger" sign on MRI; spheroids and iron accumulation in globus pallidus

Lafora's Disease (Myoclonic Epilepsy)

- Rare neurodegenerative disorder of carbohydrate metabolism
- Autosomal recessive, gene on chromosome 6q
- Onset in childhood or teens; death in early adulthood
- Myoclonic seizures, cerebellar symptoms, dementia
- Widespread CNS and PNS disease
- PAS+ Lafora body (similar to corpora amylacea, polyglucosan bodies, brain sand, "blue balls") that normally accumulates in brain with age, except it is intracytoplasmic (neuronal processes, glia, Schwann cells, endothelium, skeletal and cardiac muscle, hepatocytes, sweat ducts) and surrounded by a halo
- Diagnosis can be made on skin, liver, or nerve bx

INFLAMMATORY/INFECTIOUS DISEASES

Acquired Demyelinating Disorders

Multiple Sclerosis (MS)

- Prototypic CNS demyelinating disorder
- Idiopathic, probably multifactorial with genetic and environmental components
- Young adults, multifocal, remitting-relapsing disease, but many exceptions
- Periventricular, subcortical, optic pathway, brainstem, spinal cord lesions
- Gross = sharply demarcated gray, translucent plaques (i.e., white matter without myelin resembles gray matter)
- Histo = triad of numerous macrophages, perivascular lymphocytes, and gliosis
- LFB-PAS and Biels or NF immunostain useful to show loss of myelin with relative sparing of axons (in contrast to infarcts); PAS + myelin debris in macrophages
- Activity of plaques relates to degree of inflammation.
- "Shadow plaques" represent partial remyelination.

Variants

- Marburg's variant = acute fulminant MS; severe, rapid course, often fatal: some overlap with ADEM (see below); occasional solitary lesion mimics tumor
- Devic's variant = optic pathway and spinal cord affected
- Schilder's variant = giant, bilateral plaques, usually in children; some cases have turned out to represent adrenoleukodystrophy (see metabolic disorders)
- Balo's concentric sclerosis = rare pattern with alternating rings of myelin loss and preservation/remyelination

Acute Disseminated Encephalomyelitis (ADEM)/ Perivenous Encephalomyelitis

- Spectrum of disorders including postinfectious/post-vaccinial encephalomyelitis and acute hemorrhagic encephalomyelitis (AHEM):
  - Research model = experimental allergic encephalomyelitis (EAE)
- Often, but not invariably associated with inciting viral infection or vaccination
- Acute, fulminant course with high mortality
- Probably autoimmune attack against CNS myelin or related antigen (analogous to GBS and PNS myelin) due to cross reactivity with viral antigen
- Widespread, perivenous demyelination, inflammation, and/or hemorrhage

- Brainstem and spinal cord involvement is common and may predominate.

Guillain-Barré Syndrome (GBS)/Acute Inflammatory Demyelinating Polyneuropathy (AIDP)

- Rapid, progressive radiculopathy/polyneuropathy with paralysis
- Analogous to ADEM except PNS
- Inciting events include viral infection, vaccination, surgery, trauma, and neoplastic disease
- Research model = experimental allergic neuritis (EAN)
- CIDP = chronic form

Demyelinating Viral Infections

- HIV, HTLV-1, JC virus (PML), Measles virus (SSPE)

Paraneoplastic Encephalomyelitis

- Rare complication of neoplasia, especially lung (small cell), ovarian, and breast carcinomas
- Associated with serologically detectable antibodies in most; e.g., anti-neuronal antibody (ANNA-1 or anti-Hu)
- Probably cross reactivity of neuronal and tumor antigens; therefore, primary tumor is often small, low stage, and associated with inflammation
- Affects any level of CNS, PNS, and/or muscle; combinations common
- Histology is identical to viral encephalitis
- Clinical disease patterns include limbic, cerebellar, or brainstem encephalitis; opsoclonus/myoclonus; myasthenic syndromes; gastric paresis; etc.
- Lambert-Eaton myasthenic syndrome due to effects of presynaptic calcium channel antibodies
- Patients often die of paraneoplastic disease rather than of tumor.

Neurosarcoidosis

- CNS disease in ~5%, though systemic disease may not be obvious
- Predilection for basal meninges, thus affecting cranial nerves, optic pathway, and hypothalamus
- Parenchymal (brainstem, spinal cord, or cerebral) disease may also occur.
- Granulomas tend to spread into deeper brain along Virchow-Robin spaces.
- Variable clinical course; some fatal despite therapy

Bacterial Infections

Meningitis

- Purulent and/or secondary vasculitis with infarcts
- Typically due to hematogenous source, access to CSF via choroid plexus where there is no BBB, therefore frequently coexisting ependymitis/plexitis
- Neonates = group B strep; E. coli, other Gram negative rods
- Children = H. influenza, N. meningitidis
- Adults = strep pneumonia, N. meningitidis
- Complications = venous infarcts, hydrocephalus, deafness, cranial palsies, postmeningitic epilepsy, developmental delays, and cognitive deficits

Abscess

- Usually hematogenous (e.g., septic emboli); occasionally due to contiguous spread
- Predisposing factors = endocarditis, heart valve disease, congestive heart disease with L to R shunt, IV drug abuse, periodontal disease, dental work, sinus infection, and mastoiditis
- Tend to lodge at microvascular branch points near cortical gray-white junction, especially in MCA territory
- Early cerebritis (presuppurative) progresses to microabscess progresses to walled-off abscess
- Neuroimaging may mimic primary or metastatic neoplasm.

Tuberculosis (TB)

- Basal meninges and cranial nerves
- Parenchymal disease = tuberculoma; cerebellum and pons commonly affected
- May develop secondary vasculitis with multiple infarcts
- High mortality without early treatment

Neurosyphilis

- Typically presents in late tertiary stage
- Meningeal and/or parenchymal involvement; spinal cord and/or brain
- Hallmark = microglial activation and endarteritis obliterans with secondary infarcts
- Paretic dementia (general paresis of insane) = meningeal fibrosis, hydrocephalus, and cortical atrophy with perivascular lymphoplasma cellular inflammation, and microglial activation (i.e., encephalitis); organisms demonstrable
- Tabes dorsalis = atrophy of posterior nerve roots, DRGs, and posterior spinal columns, especially lumbosacral and/or cervical; no organisms, no inflammation, so etiology is uncertain

Whipple's Disease

- CNS disease rare, but may occur without obvious systemic findings

- Cortical subpial, basal ganglia, hypothalamus, brainstem, and cerebellum
- Inflammatory nodules
- Hallmark = perivascular macrophages stuffed with PAS + bacilli (Tropheryma whippelii); free organisms may also be found
- EM or PCR may be helpful.

Fungal Infections

Meningitis

- Cryptococcus most common; especially frequent in AIDS patients:
  - Yeast with thick polysaccharide-rich capsule results in grossly mucoid exudate.
  - Process extends deep within Virchow-Robin spaces to form microabscesses.
  - Minimal inflammatory response
  - High mortality

Granuloma/Abscess

- Candida, coccidiodomycosis, and histoplasmosis are most common.
- Organism load and inflammatory response varies with immunocompetence.

Angioinvasive Forms

- Aspergillus and mucor (zygomycetes)
- Hemorrhagic and necrotizing due to vascular involvement
- Mucor likes low pH and high glucose, therefore increased incidence in diabetics with ketoacidosis: frontal lobe disease results from spread of primary sinus infection

Viral Infections

- Characterized by microglial nodules, microglial activation, perivascular lymphs, and/or viral inclusions

Encephalitis

- Herpes most common cause of sporadic cases (see below):
- Arboviruses most common cause of epidemic cases
  - Transmitted to humans from animal reservoirs (e.g., horse) via arthropods (e.g., mosquito)
  - No inclusions, specific diagnosis depends on serology
  - Variable mortality rates

Herpes Simplex (HSV)

- Mostly Type 1; Type 2 occurs in infants exposed during vaginal delivery
- Temporal lobes almost always involved; bilateral, asymmetric
- Hemorrhagic and necrotizing
- Cowdry A and B nuclear inclusions, may be difficult to find in bx; immunostains helpful
- Most cases fatal unless treated early (acyclovir)

HIV Encephalitis/AIDS Dementia Complex

- Common complication of AIDS with cognitive, behavioral, and motor deficits
- Mild cerebral atrophy grossly
- Abnormalities in white matter, thalamus, and basal ganglia (subcortical dementia)
- Hallmark = macrophage-derived multinucleated giant cells (HIV +)
- Also perivascular lymphs and macrophages, microglial nodules (i.e., encephalitis), myelin rarefaction, or frank white matter necrosis

Vacuolar Myelopathy of AIDS

- Less common, but also felt to represent direct consequence of HIV infection
- Vacuolation of myelin in posterior and lateral columns, mainly thoracic cord, with minimal to no inflammation; resembles vitamin B12 deficiency
- Paraparesis, ataxia, and incontinence
- Most patients have coexisting HIV encephalitis.

Cytomegalovirus (CMV)

- Common opportunistic infection, especially in AIDS patients and in neonates
- Represents "reactivation disease" in most adult cases
- Ventriculitis, choroid plexitis, and encephalitis (especially periventricular regions)
- Nuclear and cytoplasmic inclusions in glial, neuronal, choroid plexus, endothelial, and histiocytic cells
- Represents the "C" in TORCH; results in microcephaly, chorioretinitis, hydrocephalus, periventricular calcifications, and CNS malformations

JC Virus/Progressive Multifocal Leukoencephalopathy (PML)

- Papovavirus named after patient's initials (JC) (see neurodegenerative disorders)
- Virtually uniformly fatal infection of immuno-compromised, especially AIDS
- Is a "reactivation disease"; most of population is seropositive
- Hallmark = demyelinating (or frankly necrotizing) plaques featuring enlarged, nuclear-inclusion bearing oligodendrocytes
- Also typical are large, bizarre astrocytes that may mimic astrocytoma on bx

- Minimal inflammation
- EM and/or in situ hybridization diagnostically useful

Subacute Sclerosing Panencephalitis (SSPE)

- Rare reactivation disease of children who had measles years earlier
- Generally fatal with gray and white matter involvement
- Encephalitis histology with intranuclear oligodendroglial and neuronal inclusions; neuronophagia common
- Patients typically have high measles antibody titres
- EM and PCR also diagnostically useful

Rabies

- Single stranded RNA virus
- Enters CNS via axonal transport from peripheral nerves; therefore incubation period relates to site of inoculation
- Typically, but not invariably, transmitted through bite of rabid animal
- Histology = encephalomyelitis pattern and/or neuronophagia
- Hallmark = Negri body (one or more eosinophilic, bullet-shaped cytoplasmic inclusions) in hippocampal, neocortical, or Purkinje cell neurons

Poliomyelitis

- CNS disease develops in <10% of patients with enteric infection
- Rare in USA because of widespread vaccination
- Same syndrome may occur with a variety of enteroviruses.
- Hemorrhagic, necrotizing myelitis involving predominantly lower motor neurons of anterior horns; microglial nodules, neuronophagia
- Brain involvement in some fatal cases

Parasites

Cysticercosis

- Most common CNS parasitic infection
- Most common cause of epilepsy in Mexico
- Encysted larval form of the pig tapeworm Taenia solium
- Becomes symptomatic when organism dies and elicits a host inflammatory response
- Multiloculate cysts often at base of brain or in subarachnoid space/fourth ventricle = racemose form
- Single or multiple; parenchymal or intraventricular, and/or hydrocephalus
- Gross = cyst with larval nodule
- Micro = larva with diagnostic scolex

Toxoplasmosis

- Common opportunistic infection of AIDS patient and of neonates ("T" in TORCH)
- Is a "reactivation disease" in adults
- One of only treatable CNS disorders in AIDS; therefore, often treated empirically prior to resorting to bx
- Multiple, enhancing deep and cortical lesions; main differential diagnosis = lymphoma
- Necrotizing encephalitis with microglial nodules, macrophages, secondary vasculitis, and/or abscess formation
- Chorioretinitis also common
- Encysted and free organisms seen at periphery necrosis on H&E stain
- Immunostains useful for confirmation
- Healed lesions show abundant lipid-laden macrophages and dystrophic calcification.

Amebic Meningoencephalitis

- Rare disorder usually due to Naegleria fowleri
- Lethal, hemorrhagic meningoencephalitis at base of brain (frontotemporal)
- Children/young adults swimming in warm fresh water
- Gains access through nose to region of cribriform plate
- Acanthameba species is a rare cause of granulomatous encephalitis in the immunocompromised or of keratitis in contact lens users.

Cerebral Malaria

- Most serious complication of malaria; associated with high mortality
- P. falciparum most common; lesions due to high parasite load creating sticky red cells that occlude microcirculation
- Ring hemorrhages are typical

PEDIATRIC AND SEIZURE NEUROPATHOLOGY

Malformations

Neural Tube Defects

Anencephaly

- Most common brain malformation
- Frog-like facies; sphenoid wing deformity resembles "bat with folded wings"
- Area cerebrovasculosa = ectatic vessels and brain remnants
- Underdeveloped hypothalamus/pituitary leads to adrenocortical hypoplasia
- Interaction of environmental/genetic factors poorly understood
- Associated with high amniotic fluid AFP

Craniorachischesis

- Anencephaly and lack of spinal closure, flattened, malformed spinal cord or area medullovasculosa (tissue similar to area cerebrovasculosa)

Encephalocele

- Herniation of brain through skull defect
- Usually occipital; occasionally anterior (frontal) at bridge of nose
- Typically asymmetric and/or overlying skin ulceration
- Neurologic deficit depends on extent of herniation and other malformations

Myelomeningocele

- Herniation of malformed spinal cord and meninges through a vertebral defect and/or overlying skin ulceration
- Usually associated with Arnold-Chiari malformation and hydrocephalus
- Neurologic deficit depends on level of defect and associated rostral spinal malformations; lumbosacral level is most common

Spina Bifida Occulta

- Minor lumbosacral defect with intact overlying skin

Holoprosencephaly

- Failure of cerebral hemispheres to separate: "face predicts brain"; cyclopia, proboscis, agnathia, cleft lip/palate, etc.
- Most cases are sporadic
- Common associations = maternal diabetes, TORCH infections, fetal alcohol syndrome, and trisomy 13
- Variations:
  - Alobar = small, monoventricular brain, no interhemispheric fissure, olfactory aplasia, fused basal ganglia and thalami, thin membrane over posterior ventricle (posterior cyst)
  - Semilobar = shallow interhemispheric fissure, minimal gyration
  - Lobar = normal interhemispheric fissure, well-developed gyration, fusion of midline structures
  - Arrhinencephaly = olfactory aplasia with lack of bulbs, tracts, and gyrus rectus (i.e., no olfactory sulcus)

Congenital Hydrocephalus

Arnold-Chiari (Chiari II) Malformation

- Elongated, S-shaped brainstem with herniation of medulla and cerebellar vermis below foramen magnum
- "Beaking" of quadrigeminal plate with fusion of inferior colliculi
- Compressed fourth ventricle with obstructive hydrocephalus
- Associated myelomeningocele in most
- Associated migrational/gyral defects in some

Dandy Walker Malformation

- Agenesis of cerebellar vermis with dilated fourth ventricle cyst covered by thin membrane (easily torn)
- Large posterior fossa
- Etiology of hydrocephalus uncertain; aqueductal stenosis in some
- Associated malformations common (e.g., polymicrogyria, agenesis of corpus callosum, etc.)

Aqueductal Stenosis

- Rare cause of hydrocephalus
- Histologically associated with atresia, forking, etc.
- Ependymal granulations and gliosis suggest prior infection (TORCH)

Migrational/Gyral Defects

- Often associated with seizures, mental/psychomotor retardation, learning disorders, etc.
- Timing of insult (ischemic, infectious, genetic, etc.) determines abnormality
- Normally, neuroblasts migrate from periventricular germinal matrix to cortex and other sites; excess neurons removed by apoptosis, remaining neurons mature

Polymicrogyria

- Most common gyral abnormality
- Small gyri with shallow sulci and "fused" molecular layers

- Cortical dysplasia (architectural distortion) with simplified 2- to 4-layer neocortex
- Underlying neuronal heterotopias common ("migrational arrest")
- Commonly seen at edge of porencephalic cyst

Lissencephaly/Pachygyria

- Small brain (microcephaly) with broad or no gyri
- Thick cortex extending almost to ventricles (minimal white matter)
- Other coexisting malformations common
- Sporadic or familial
- Miller-Diecker syndrome associated with LIS-1 gene on 17p

Gray Matter Heterotopia

- Defect of neuroblast migration (get stuck before reaching cortex)
- Diffuse neuronal heterotopia = numerous neurons scattered throughout white matter
- Nodular heterotopia = subcortical or subependymal nodules, most common form
- Laminar heterotopia = band of gray matter between cortex and ventricle ("double cortex")

Cortical Dysplasia

- Umbrella term for all forms of disordered neuronal architecture; synonyms = microdysgenesis and hamartia

Destructive Malformations

- Intrauterine ischemia, infections (TORCH), etc.

Sclerotic Ulegyria

- Mushroom-shaped gyri ("ulegyria")
- Cortical microinfarcts of sulcal depths (narrow) with sparing of gyral crests (wide)
- Associated neuronal loss and gliosis ("sclerotic")

Porencephaly

- Large area of damage, often MCA territory
- Result of liquefactive necrosis
- Large cyst, often extending from meninges to ventricle
- Polymicrogyria common at edge of cyst

Hydranencephaly

- "Basket brain"
- Severe, bilateral cerebral damage
- Most of cortex and white matter lost resulting in large, bilateral thin cysts
- Thalamus usually preserved

Agenesis of Corpus Callosum

- Complete vs. partial (posterior portion only)
- No overlying cingulate gyrus (helpful in distinguishing postmortem artifacts)
- "Bat's wing"-shaped lateral ventricles
- Probst bundles = callosal remnants in lateral roof of ventricle
- May be associated with callosal lipoma

Syringomyelia/Syringobulbia

- Cystic cavity in spinal cord or brainstem
- Variants:
  - Hydromyelia = distension of central canal (ependymal lining may slough, so often lumped with syringomyelia or syrinx)
  - Idiopathic or primary type usually associated with Chiari Type I malformation (chronic cerebellar tonsillar herniation and/or hydrocephalus) with cerebellar ataxia and dissociated sensory loss from cervical syrinx; young adult, often progressive
  - Secondary types associated with tumor, trauma, infarcts, etc.

Fetal/Perinatal Insults

Intraventricular Hemorrhage

- Premies <32 weeks estimated gestational age most commonly affected
- Usually arise from dissection of germinal matrix hemorrhage (poorly developed capillaries presumably undergoing involution)
- Associated with perinatal ischemia/respiratory distress syndrome
- Choroid plexus hemorrhage is more common source in term infants
- High mortality unless it is a small, contained hemorrhage

Gray Matter Ischemia

- Produces ulegyria, porencephaly, and migrational defects (see above)
- Status marmoratus (marbled state):
  - Ischemic damage to basal ganglia and/or thalamus prior to myelination
  - Abnormal myelination occurs over gliotic fibers resulting in marbled appearance
  - Common in cerebral palsy
- Pontosubicular necrosis: reflects perinatal selective vulnerability with pontine nuclei and subiculum being more sensitive than CA1 of hippocampus

White Matter Ischemia/Periventricular Leukomalacia (PVL)

- White matter is a site of selective vulnerability in premies

- Sharply demarcated infarcts
- Become cystic upon resolution
- Often coexists with other ischemic lesions

Kernicterus

- Necrosis of globus pallidus and hippocampus in premies
- Unconjugated bilirubin (immature liver) crosses BBB to produce bright yellow gross appearance
- Rare today due to "bili lights" and other preventive therapies

Chromosomal Syndromes (see Chapter 2)

Down Syndrome (Trisomy 21)

- Gross changes not always obvious
- Brain short and blunted in AP direction
- Narrow superior temporal gyrus
- Small cerebellum and brainstem
- Premature Alzheimers (see Neurodegenerative section)

Edward Syndrome (Trisomy 18)

- Microcephaly, gyral defects

Patau Syndrome (Trisomy 13)

- Holoprosencephaly in most

Fragile X

- Most common form of familial mental retardation
- M > F (i.e., X-linked)
- Associated with triple repeat expansion of FMR-1 gene on Xq
- Microcephaly, neuronal heterotopias

Seizure-Associated Pathology

- Increasingly seen in surgical specimens (refer to individual lesions in previous sections for details)

Malformations

- Any of ones previously discussed; most common are polymicrogyria and neuronal heterotopias

Tuberous Sclerosis

- Triad of seizures, resultant mental retardation, facial angiofibromas
- Tubers = cortical dysplasia with balloon cells, mono- and multinucleated dysmorphic glioneuronal cells, associated gliosis and/or calcification firm, "potato-like" cortical lesion with subcortical degenerative change
- Gray matter heterotopias = similar histology (balloon cells) to tubers, but deeper and often perivascular
- Subependymal giant cell astrocytoma (SEGA) = malformative intraventricular tumor near foramen of Monro composed of spindle, epithelioid, and occasional giant cells forming sweeping fascicles and perivascular pseudorosettes; neuron-like cells less common; calcification; noninfiltrative growth pattern
- Candle gutterings = identical to SEGA, but smaller, waxy subependymal nodules throughout lateral ventricles (precursors to SEGA)
- Continuous, radial abnormalities from cortex to ventricle suggest migrational disturbance
- Non-CNS lesions = cutaneous angiofibroma, renal angiomyolipoma, pulmonary lymphangioleiomyomatosis (LAM), and cardiac rhabdomyoma
- Two genes identified: TSC1 on 9q, TSC2 on 16p

Tumors

- Dysembryoplastic neuroepithelial tumor (DNET): quasihamartomatous intracortical lesion featuring nodules and "floating neurons":
  - Often misdiagnosed as oligodendroglioma or oligoastro; common in epilepsy specimens (7%)
  - Excellent prognosis
- Low-grade diffuse gliomas: oligodendroglioma, oligoastrocytoma, astrocytoma
- Pilocytic astrocytoma
- Ganglioglioma
- Pleomorphic Xanthoastrocytoma (PXA)

Inflammatory/Infectious

Cysticercosis

- Most common cause of epilepsy in Mexico

Rasmussen's Encephalitis

- Progressive, unilateral process often associated with intractable seizures in young patients
- Hemispherectomy may be necessary for seizure control
- Histology identical to viral encephalitis
- Autoimmune vs. infectious; associated with autoantibodies to glutamate receptor in some patients

Vascular Malformations

- Most commonly cavernous angioma or AVM

TOXIC/METABOLIC DISORDERS

Alcohol- (and/or Malnutrition-) Related Pathology

- Not restricted to alcoholics

Trauma

- Alcoholics fall a lot

Wernicke-Korsakoff Syndrome

- Due to thiamine (vitamin B_1) deficiency
- Wernicke's encephalopathy = nystagmus, ataxia, confusion, and stupor
- Korsakoff's psychosis = anterograde and retrograde amnesia, confabulation (e.g., "Yes, I see the invisible pink thread you're holding.")
- Mamillary bodies/periventricular thalamus and brainstem affected
- Acute-subacute = petechial hemorrhages, capillary proliferation, gliosis, and/or necrosis with neuronal sparing
- Chronic = atrophy, hemosiderin, axonal/myelin loss, and vascular prominence

Cerebellar Degeneration

- Due to thiamine (vitamin B_1) deficiency
- Atrophy of anterior superior cerebellar vermis with Purkinje cell loss and Bergmann layer gliosis
- Truncal ataxia

Peripheral Neuropathy

- "Glove and stocking" distal (dying back) neuropathy with axonal degeneration
- Etiology poorly understood; may be multifactorial
- Yet another source of ataxia
- Associated tract degeneration of posterior spinal columns

Central Pontine Myelinolysis (CPM)

- Associated with too rapid correction of hyponatremia (an iatrogenic process)
- Symmetric, triangle-shaped zone of demyelination in central basis pons
- Relatively high mortality
- Extrapontine lesions noted in 10%

Hepatic Encephalopathy

- Liver failure with hyperammonemia
- Dementia/delirium/stupor/coma
- Gross = brain normal to edematous; bilirubin staining (jaundice) of dura, meninges, and choroid plexus (i.e., sites lacking BBB)
- Micro = Alzheimer Type 2 astrocytes (enlarged nuclei with pale, open chromatin and little cytoplasm) in gray matter, especially deep cortex, globus pallidus, and dentate nucleus

Subacute Combined Degeneration of Spinal Cord

- Due to vitamin B_{12} deficiency
- Vacuolation/myelin pallor of posterior and lateral columns; thoracic levels emphasized in books, but cervical levels also involved frequently (identical to vacuolar myelopathy in AIDS)
- Combined sensory and upper motor neuron deficits
- Similar, but reversible symptoms can be seen with folate deficiency

Fetal Alcohol Syndrome

- Complex etiology related to timing and volume consumed during pregnancy, genetic influences, etc.
- Common cause of mental retardation
- Facial abnormalities
- Growth retardation

Other Toxic Injuries

Carbon Monoxide

- See "Patterns of selective vulnerability" (p. 10–24)

Methanol

- See "Patterns of selective vulnerability" (p. 10–24)

Arsenic Poisoning

- GI symptoms, sensory neuropathy, weakness
- No morphologic CNS changes
- Peripheral neuropathy with segmental demyelination, axonal degeneration, and occasionally onion bulb formation (repeated exposures)

Lead Poisoning

- Usually children ingesting lead-based paint from old houses
- Cerebral edema and petechial hemorrhages → lead encephalopathy
- Peripheral neuropathy with segmental demyelination and/or axonal degeneration
- Anemia, renal and GI symptoms, lead lines in bone on X-ray

Methotrexate Toxicity

- Follows intrathecal or IV therapy for leukemias, etc.
- May cause a necrotizing leukoencephalopathy, especially when combined with radiation therapy

Table 10-7. Metabolic Disorders

Disease	*Clinical*	*Genetics*	*Enzyme*	*Accumulations*	*Pathology*
Wilson's disease	Liver failure, movement disorder	AR Chr. 13	Cu transporting ATPase (not ceruloplasmin)	Copper (↓ serum cerulo-plasmin)	Cystic deg. of putamen, Alz. Type 2 astros, perivascular copper + iron deposits
Tay-Sachs disease	Ashkenazi jews; death < age 5, cherry-red macula	AR Chr. 15	Hexosaminidase A	GM2-ganglioside	Foamy CNS, PNS, + retinal neurons; LFB +, PAS + granules. EM-MCBs
GM1-ganglio-sidosis	Like Tay-Sachs plus dysmorphism and visceromegaly	AR Chr. 3	β-galactosidase	GM1-ganglioside	Like Tay-Sachs + foamy hepatocytes, macroph-ages and endothelial cells
Ceroid lipofuscinosis	Various subtypes, ages, and severity	AR Multiple	Various enzyme defects	"Lipofuscin"	Cerebral atrophy, thick dura, N. loss, PAS +, EM-fingerprint + curvilinear bodies
Niemann-Pick Disease (Type A)	Visceromegaly, cherry-red macula, death < age 5	AR Chr. 11	Sphingo-myelinase	Sphingomyelin	Foamy neurons, endothelial cells and macrophages (NP cells)
Gaucher's Disease (Type 2)	Neuronopathic, CNS + visceral, death < age 2	AR Chr. 1	Glucocerebro-sidase	Glucocerebroside	Perivasc. PAS + Gaucher cells (macrophages) with "crumpled tissue paper"; neuronal loss
Mucopoly-saccharidoses	Hurlers (I) + Hunters (II-males), MR, dysmorphic	AR, except II = XL	Various enzyme defects	Glycosamino-glycans (GAG) high in urine	Thick skull and dura, perivasc. "pits" = GAG deposits. EM = "zebra bodies"
Fabry's disease	Males, kid./heart failure, p. neuropathy, death ~age 40	XL Chr. Xq	a-galactosidase A	Ceramides	Vascular dz. with cerebral infarcts, PAS + deposits in meninges, vessel walls, and other cells
Glycogen storage ds (II-Pompes)	Limb-girdle + resp. weakness, death < age 2	AR Chr. 17	Acid maltase	Glycogen	Vacuolar myopathy. In infantile form: heart, liver, neurons, and astrocytes affected
Zellwegers Syndrome	Dysmorphic, floppy, FTT, liver dz, death < age 1	AR	Peroxisomes absent (along with enzymes)	Numerous biochemical abnormalities	Migrational defects (patchy/ polymicrogyria, heterotopia), myelin loss, cirrhosis
Adrenoleuko-dystrophy	Boys ("Lorenzo's oil"), rapid course, CNS + adrenal disease	XL Chr. Xq	Peroxisomal membrane protein	Very long chain fatty acids	Diffuse myelin loss and inflam.; mimics MS. Adrenal atrophy with "balloon cells"
Metachromatic leukodystrophy	Usually infants/ kids, early bone marrow Tx helpful	AR Chr. 22	Arylsulfatase A	Sulfatides	Diffuse myelin loss; metachromasia on frozen sections. EM-prismatic inclusions
Krabbes leuko-dystrophy	Death < age 2, cherry-red macula	AR Chr. 14	Galactocerebro-sidase	Galactocerebro-side + psychosine	Diffuse myelin loss, "Globoid cells" = clusters of macrophages with eccentric nuclei

AR = autosomal recessive, XL = X-linked, TX = transplant, FTT = failure to thrive, Alz = Alzheimer's, N = neuron, MCB =membranous cytoplasmic bodies, MS = multiple sclerosis, MR = mental retardation

Metabolic Disorders

- Generally due to enzyme defect with accumulation of toxic byproducts
- Almost always autosomal recessive
- Diagnosed by biochemical analyses, biopsy of skin, conjunctiva, rectum, etc.
- Almost all exist as variants wherein youngest age = most severe, oldest age = least severe
- Table 10-7 presents most common, most severe, or CNS form
- Lipid accumulations may be seen in frozen sections, but are often lost in processing of paraffin sections
- Variable gross appearance: encephalomegaly from storage vs. microcephaly from atrophy

Lysosomal (Enzyme) Storage Disorders (see Table 10-7)

- Involve CNS and/or other organs
- Enlarged lysosomes often result in the formation of PAS + granules
- EM shows membranous cytoplasmic bodies (MCBs) often morphologically nonspecific, but supportive of a storage disorder

Mucopolysaccharidoses

- Include many subtypes: Gargoyle-like dysmorphism, Hurler (Type I) = most severe, Hunter (Type II) = X-linked: "Hunters are men"

Peroxisomal Disorders (see Table 10-7))

- Due to absence or decreased numbers of peroxisomes vs. abnormality of peroxisomal protein

Leukodystrophies (see Table 10-7))

- Metabolic disorder of myelin synthesis/breakdown
- Dysmyelination (abnormal formation) instead of demyelination (loss of normally formed myelin as in MS)
- Diffuse, symmetric, bilateral, with sparing of subcortical U-fibers

Adrenoleukodystrophy (ALD)

- X-linked, peroxisomal disorder/leukodystrophy with inflammation that can mimic MS (e.g., many cases of "Shilder's variant of MS" have turned out to be ALD)

SELLAR/SUPRASELLAR PATHOLOGY

Pituitary Adenomas

General Features

- Most common sellar neoplasm by far
- Hormonally functional tumors often present at microadenoma (<1 cm) stage, especially patients with Cushing's disease
- Non-functional tumors present as macroadenoma (>1 cm) due to mass effects, including visual deficits and/or hypopituitarism
- "Stalk effect" = mild to moderate prolactin (PRL) elevation from compression of stalk (blocks transport of dopamine, the normal PRL-inhibiting-factor, from hypothalamus)
- "Invasive adenoma" = gross intraoperative or radiologic descriptor; affects management and likelihood of recurrence, whereas microscopic invasion of dura alone is unimportant
- Differential Diagnosis may include ependymoma (perivascular rosettes), olfactory neuroblastoma (involves cribriform plate), small cell carcinoma (simulated by crush artifact of normal or adenoma tissues), etc.
- Loss of acinar architecture and the presence of prominent nucleoli are helpful to distinguish from normal pituitary
- Reticulin stain helpful to highlight architecture, especially in crushed specimens or with freezing artifacts; adenomas are reticulin-poor compared to normal

Histology Clues (Often True)

- Calcium = prolactinoma
- Amyloid bodies (rare) = prolactinoma
- High N/C ratio and fibrosis = medically treated prolactinoma
- Perivascular rosettes = gonadotrophic or null cell adenoma
- Crooke's hyaline change = hypercortisolism of any cause (seen in non-tumoral pituitary)
- Strong PAS + = corticotroph adenoma
- Weak PAS + = glycoprotein adenoma (FSH, LH, TSH)
- CK +, paranuclear "fibrous bodies" = GH-producing adenoma
- Immunostaining for hormones most useful in confirming prolactinoma (a medically treatable tumor) or in establishing the pituitary origin of tumor outside the sella
- EM most useful in cases where immunostains are nonconfirmatory or equivocal, as well as in establish-

ing the diagnosis of rare aggressive forms such as acidophil stem cell adenoma (ASCA)

Prolactinoma (Lactotrophic Adenoma)

- F > M; women present with amenorrhea and/or galactorrhea
- Often asymptomatic until large in men; decreased libido
- Medically treatable with bromocriptine: induces cellular arrest/atrophy with high N/C ratio; prolactin + and low proliferative index (unlike small cell carcinoma, a mimic)

Corticotrophic (ACTH) Adenomas

Cushing's Syndrome

- Clinical manifestations of hypercortisolism of any cause

Cushing's Disease

- Cushing's syndrome due to ACTH-producing pituitary adenoma

Nelson's Syndrome

- Bilateral adrenalectomy in setting of Cushing's disease (undetected microadenoma) results in uncontrolled tumoral growth due to loss of end-organ feedback
- Most are aggressive and difficult to manage
- Undergo progression to pituitary carcinoma in some patients

Microadenoma

- Most common presentation; may be difficult to find (deeper sections); occasionally "sucked away" before surgeon can get a specimen

Crooke's Hyaline Change

- Ring-like, CK accumulations in nonneoplastic corticotrophic cells
- Result of negative feedback from hypercortisolism of any cause
- Negative image on ACTH immunostains

Silent Corticotroph

- ACTH + adenoma but without clinical and/or biochemical Cushing's syndrome; often invasive macroadenomas

Growth Hormone (GH, Somatotrophic) and/or PRL-Producing Adenomas

- Acromegaly in adults, Gigantism in kids
- Mostly plurihormonal macroadenomas, immunopositive for GH, PRL, and TSH or alpha subunit
- Sparsely granulated (EM) tumors often minimally GH +, but show paranuclear CK + whorls known as "fibrous bodies"
- Mammosomatotroph adenoma = GH and PRL produced by same cells
- Acidophil stem cell adenoma (ASCA) = rare variant with serum PRL > GH level, often lack of acromegaly, giant mitochondria (EM) occasionally forming vacuoles on H&E:
  - Misdiagnosed as prolactinoma, but aggressive/relatively nonresponsive to bromocriptine

Gonadotrophic (FSH/LH) and Null Cell (IP-) Adenomas

- Elderly, M > F
- Clinically nonfunctional macroadenomas
- Mostly indolent and noninvasive

Thyrotrophic Adenoma/Hyperplasias

- Rarest of the adenomas in pure form
- Many arise due to the loss of feedback in primary hypothyroidism
- Adenomas causing secondary hyperthyroidism are distinctly uncommon

Atypical Pituitary Adenoma

- New diagnostic category
- High proliferative activity (mitoses, MIB-1); often p53 immunoreactive
- Increased risk of recurrence and aggressive behavior
- Usually PRL +, GH +, ACTH + (functioning adenomas)

Pituitary Carcinoma

- Rare; high morbidity/mortality
- Brain invasion (exceptional finding during life) or intracranial (CSF) and/or extracranial metastases
- PRL +, GH + or ACTH + (in association with Nelson's syndrome)
- Usually p53 + and high MIB-1 index

Pituitary Hyperplasia

- Diffuse (difficult to document) or
- Nodular (expanded acini filled by disproportionate number of one cell type; reticulin stain useful):
  - PRL: pregnancy, estrogen therapy
  - GH: hypothalamic or ectopic (neuroendocrine tumor) source of growth-hormone-releasing hormone
  - ACTH: hypothalamic or ectopic (neuroendocrine tumor) source of corticotropin-releasing hormone
  - FSH/LH: Klinefelter's and Turner's syndrome
  - TSH: hypothyroidism; associated with PRL hyperplasia due to a thyrotropin-releasing hormone

Apoplexy

- Spontaneous infarction of pituitary adenoma; usually large, nonfunctioning
- Reticulin and IPs helpful in partially preserved regions

Craniopharyngioma

- See "Other Nonglial Neoplasms" section, p. 10-20

Rathke's Cleft Cyst

- Developmental lesion; often incidental cyst between anterior and posterior pituitary lobes
- Symptomatic lesions generally >1 cm; cause hyperprolactinemia and/or visual disturbance
- Slow growing, surgically curable
- Clear: mucoid cyst contents
- Cuboidal to columnar, ciliated and nonciliated epithelium, and/or goblet cells:
  - Same histology as colloid cyst of third ventricle and enterogenous cyst of spinal cord
- Squamous metaplasia in some; differential diagnosis = craniopharyngioma, epidermoid cyst

Granular Cell Tumor

- Benign posterior pituitary or stalk tumor of probable "pituicyte" (posterior lobe glial stroma) origin
- Small, incidental examples common at autopsy; symptomatic lesions rare
- Identical morphology to granular cell tumors elsewhere
- Packed with PAS + lysosomes, S-100 protein +
- Diagnosis: pituitary adenoma with oncocytic change; no secretory granules or hormones

Histiocytosis X (Langerhans' Cell Histiocytosis)

- Most represent secondary CNS involvement from skull base
- Predilection for hypothalamus/infundibulum
- ± Diabetes Insipidus
- May appear xanthomatous; differential diagnosis = Rosai-Dorfman disease; Erdheim Chester disease

Hypothalamic Hamartoma

- Rare, often incidental, surgically curable malformation/tumor
- Some present with precocious puberty or gelastic seizures; rare pituitary hyperfunction (releasing hormone production)
- Sessile or pedunculated attachment to floor third ventricle; some separate
- Resembles normal hypothalamus, but less organized

Other Tumors

- Covered elsewhere; include pilocytic astrocytoma, meningioma, hemangioma, sarcoma (often post-irradiation), and metastases

Lymphocytic Hypophysitis

- Autoimmune disorder associated with hypopituitarism
- Almost exclusively in postpartum women
- Other minor coexistent autoimmune disorders in some
- Lymphoplasmacytic infiltrate without granulomas
- Treated with surgery and hormone replacement; fatal if untreated

Empty Sella Syndrome

Primary

- Congenital defect in diaphragma sella permits downward herniation of leptomeninges ("arachnoidocele") and marked compression of pituitary

Secondary

- "ex vacuo," (i.e,. parenchymal loss):
  - Sheehan's syndrome = infarction due to postpartum shock
  - Apoplexy
  - Postsurgical
  - Post-irradiation

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Chapter 11

Endocrine Pathology

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Table of Contents

THYROID GLAND

Non-Neoplastic Conditions

Heterotopic Thyroid

Clinical

- Normal thyroid tissue found along course of thyroglossal duct (from foramen cecum in posterior tongue down along anterior midline to below cricoid cartilage); may rarely be seen in mediastinum
- Seen in up to 10% of population, although usually subclinical due to small size
- Presents as nodule in midline neck or base of tongue (most common location)
- Patients with heterotopic thyroid (especially those with lingual thyroid) may lack a normal thyroid gland.
- Heterotopic tissue can give rise to thyroid malignancies (usually papillary carcinoma)

Macroscopic

- May be encapsulated
- Resembles normal thyroid tissue

Microscopic

- Normal thyroid architecture that may manifest all pathologic processes that affect normally located thyroid gland (hyperplasia, neoplasia, inflammation, etc.)
- Individual follicles may proliferate between adjacent structures (such as muscle), a phenomenon that may simulate invasion

Differential Diagnosis

- Metastatic thyroid carcinoma:
  - Follicular carcinoma or follicular variant of papillary carcinoma may resemble normal thyroid
  - Careful examination may reveal solid areas, necrosis, mitoses, anaplasia, or true invasion

Thyroglossal Duct Cyst

Clinical

- Cystic dilation of remnant of thyroglossal duct, found along normal course of thyroglossal duct (from posterior tongue, down along anterior midline to below cricoid cartilage)
- Duct may run anterior to, within, or posterior to hyoid bone
- Patients present during childhood with a midline nodule that may be tender and can be associated with the sinus tract.
- Heterotopic thyroid tissue associated with the cyst may give rise to thyroid malignancies (usually papillary carcinoma)

Macroscopic

- Mucin-filled cyst, up to 3 cm in diameter
- Normal thyroid tissue may be seen in the wall of the cyst

Microscopic

- Cyst is usually lined by pseudostratified ciliated or squamous epithelium
- If inflammation is prominent, lining may not be present.
- Surrounding stroma shows thyroid follicles and secondary inflammation

Differential Diagnosis

- Heterotopic thyroid:
  - Only thyroid tissue visible
  - No cyst or duct lining seen
- Branchial cleft cyst:
  - Location classically antero-lateral neck, not midline
  - Lined by mixed squamous and respiratory epithelium
  - Many lymphoid follicles
  - No thyroid follicles seen
- Thyroid neoplasm with cystic degeneration;
  - Adenoma, adenomatous goiter, or carcinoma may show cystic degeneration
  - Careful examination of the cyst wall and surrounding tissue is important

Acute Thyroiditis

Clinical

- Acute inflammation usually due to infectious disease
- May be due to regional infection, general sepsis, or local trauma
- Usually due to gram + bacteria, but gram – organisms or fungi may also be responsible

Macroscopic

- Thyroid may be enlarged, with areas of necrosis and abscess formation.

Microscopic

- Acute inflammatory infiltrates with associated necrosis

Differential Diagnosis

- Other types of thyroiditis (granulomatous or lymphocytic):
  - In other types, predominant inflammatory cells are either histiocytes or lymphocytes (neutrophils, if present, usually represent minority)
  - Not associated with other acute infections or trauma

Granulomatous (de Quervain's) Thyroiditis

Clinical

- Granulomatous inflammation of thyroid of uncertain etiology; thought to be related to viral infection
- Seen in middle-aged women
- Patients present with fever and malaise, sore throat, and thyroid enlargement and tenderness
- Early phase may show increased serum T3/T4 and decreased I^{131} uptake
- Usually resolves completely, but in some cases may result in some residual hypothyroidism

Macroscopic

- Thyroid enlargement (usually asymmetrical) up to twice normal size
- Cut surface section shows areas of irregular firm tan tissue among more normal-appearing thyroid tissue

Microscopic

- Mixed inflammation, predominantly lymphocytic and histiocytic
- Microabcesses are common
- Vague, non-caseating granulomata with foreign body-type giant cells centered on and destroying follicles and engulfing free colloid
- Patchy areas of fibrosis and regenerating follicles may be seen later in the disease

Differential Diagnosis

- Autoimmune thyroiditis:
  - Significantly less inflammation; predominantly lymphocytic with germinal centers
  - No gland destruction; rather, follicles show atrophy with Hürthle cell change
- Acute thyroiditis:
  - Inflammation predominantly neutrophilic rather than granulomatous
  - Usually associated with other infections (bacterial or fungal) or local trauma
- Tuberculosis or mycosis:
  - Rare, usually seen only in disseminated disease
  - Necrotizing granulomata
- Sarcoidosis:
  - Usually in patients with systemic disease
  - Granulomata are interstitial and do not result in follicular destruction
- Palpation thyroiditis:
  - Incidental finding as a result of vigorous palpation or minor trauma
  - Patchy, multifocal mixed lymphocytic and histiocytic inflammation involving isolated and widely distant follicles, in an otherwise histologically normal gland

Fibrous Thyroiditis (Riedel's Thyroiditis)

Clinical

- Rare, idiopathic process manifested by extensive fibrosis of the thyroid gland, extending beyond the gland into the surrounding tissue and usually involving the cervical musculature
- Thought to be related to fibrosing mediastinitis and retroperitoneal fibrosis (idiopathic fibrosclerosis)
- Patients tend to be adult or elderly (average age = 50 years), with slight female predilection
- Presents as poorly defined, rock-hard thyroid enlargement

Macroscopic

- Gland enlarged with firm white tissue replacing parenchyma and extending into surrounding tissue, obliterating normal anatomic boundaries
- Fibrotic process pervades adjacent muscles, nerves, and vessels, making excision very difficult or impossible

Microscopic

- Extensive fibrosis, infiltrating beyond the thyroid into the muscle and other tissue, with keloid-like hyalinized collagen
- Areas of more normal uninvolved thyroid are seen
- Patchy lymphoid and plasmacytic inflammation
- Involved vessels may show mural inflammation

Differential Diagnosis

- Fibrosing Hashimoto's thyroiditis:
  - Thyroid gland involved by fibrosis, but capsule intact and may be separated from adjacent structures
  - Microscopically, fibrosis appears more typical, rather than keloid-like

Lymphocytic Thyroiditis (Painless Thyroiditis)

Clinical

- Autoimmune thyroiditis caused by autoantibodies directed against thyroglobulin and other follicular cell antigens
- Usually seen in children and more common in women (F:M = 2:1)
- Patients present with asymptomatic goiter
- May be associated with transient hyperthyroidism
- Usually resolves within 1 year

Macroscopic

- Mild to moderate diffuse enlargement with slightly nodular appearance

Microscopic

- Scattered interstitial lymphoid follicles with germinal centers

- Follicles typically show minimal reaction to inflammation, but there may be some mild atrophy or Hürthle cell change

Differential Diagnosis

- Hashimoto's thyroiditis:
  - Larger, more numerous lymphoid follicles and scattered plasma cells and histiocytes
  - Significant follicular changes with extensive atrophy and Hürthle cell change
- Grave's disease:
  - Associated with hyperthyroidism
  - Follicles are hyperplastic

Hashimoto's Thyroiditis

Clinical

- Autoimmune thyroiditis caused by autoantibodies directed against thyroglobulin, thyroid stimulating hormone receptors, and other follicular cell antigens, resulting in follicular damage
- Classically occurs in young to middle-aged females (30–50 years old; F:M = 10:1)
- Patients present with diffuse firm goiter, tenderness, and hyperthyroidism
- As the disease progresses, thyroid function decreases, eventually resulting in hypothyroidism
- A milieu of lymphocytic inflammation and regenerative hyperplasia results in increased risk of lymphoma, leukemia, and thyroid carcinoma
- May be associated with autoimmune disease of adrenals (Addison's disease), pancreas (diabetes), or stomach (pernicious anemia)

Macroscopic

- Diffuse firm enlargement
- Cut surface is soft and rubbery, vaguely nodular, with tan-gray appearance of hyperplastic lymphoid tissue

Microscopic

- Marked interstitial lymphocytic inflammation with prominent lymphoid follicles with germinal centers
- Small, atrophic thyroid follicles lined by oxyphilic epithelium (Hürthle cells)
- Scattered plasma cells (polyclonal) and histiocytes can be seen
- Interstitial fibrosis may accentuate lobular architecture.
- Regenerative hyperplasia and squamous metaplasia may be seen

Variants

- Fibrosing Hashimoto's thyroiditis:
  - Represents ~10% of cases
  - Usually seen in elderly patients
  - Marked thyroid enlargement with some adhesion of gland to surrounding tissue (although surgical planes are readily identified)
  - Histologically shows extensive fibrosis, severe follicular atrophy with Hürthle cell change, and squamous metaplasia
  - Inflammatory cells are a mixture of lymphocytes and plasma cells
  - May be confused with Riedel's thyroiditis

Differential Diagnosis

- Lymphocytic thyroiditis:
  - Milder inflammation, with scattered lymphoid follicles
  - Little or no reactive changes in thyroid follicles
- Grave's disease
  - Follicles appear hyperplastic, rather than atrophic

Graves' Disease

Clinical

- Autoimmune thyroiditis caused by autoantibodies directed against thyroid stimulating hormone receptors, resulting in chronic follicular stimulation and hyperthyroidism (diffuse toxic goiter)
- Seen in young females (20–40 years old; F:M = 4:1)
- Patients present with diffuse goiter and hyperthyroidism
- Thyroid studies show increased serum T3/T4 and decreased I^{131} uptake, with markedly depressed thyroid stimulating hormone

Macroscopic

- Mild to moderate diffuse enlargement with soft consistency and pink tan color

Microscopic

- Markedly hyperplastic follicles lined by active tall columnar cells showing clear, sometimes vacuolated, cytoplasm
- Colloid appears pale and depleted, with scalloped edges at the epithelial border
- Epithelial hyperplasia results in papillary infolding of the follicles, resembling papillary carcinoma
- Interstitial lymphoid aggregates with germinal centers may be present
- Classic appearance is usually altered by preoperative medication:
  - Iodine therapy can greatly diminish hyperplasia, resulting in an almost normal-appearing gland
  - Propylthiouracil therapy increases hyperplasia

Differential Diagnosis

- Papillary thyroid carcinoma:
  - Presents as an expansile mass, rather than a diffuse process

  - Shows typical cytologic features (ground glass nuclei, nuclear grooves and nuclear pseudo inclusions)
- Lymphocytic thyroiditis:
  - Young patients, usually euthyroid
  - Thyroid follicles appear normal or show only mild atrophy
- Hashimoto's thyroiditis:
  - Thyroid follicles show atrophy and Hürthle cell change, not hyperplasia

Nodular Hyperplasia

Clinical

- Hyperplastic process due to low dietary iodine (endemic goiter) or unknown causes (sporadic goiter)
- Synonyms: multinodular goiter, adenomatoid goiter, and adenomatous hyperplasia
- Endemic goiter:
  - Seen in regions with low environmental iodine, usually affecting entire population
  - Low iodine prevents adequate T3/T4 synthesis, leading to increased thyroid stimulating hormone secretion
  - Increased circulating thyroid stimulating hormone (TSH) results in thyroid hyperplasia
- Sporadic goiter:
  - Seen commonly in United States; ~5% incidence
  - Exact etiology unknown, but pathogenesis probably similar to endemic form (inadequate T3/T4 secretion)
  - May be due to more subtle abnormality in thyroid hormone synthesis, iodine metabolism, or other hormonal factors
- Majority of patients are euthyroid, presenting with symptoms of multinodular thyroid enlargement, which may be generalized or have dominant nodule
- Degenerative changes within nodules may result in pain and tenderness
- Nodules associated with hyperplasia tend to show increased I^{131} uptake
- Does not appear to be associated with increased risk of carcinoma

Macroscopic

- Gland enlarged and its normal smooth symmetrical appearance distorted by multiple nodules of varying size
- Larger nodules typically show degenerative changes typified by cysts, hemorrhage, and calcification

Microscopic

- Many nodules of different sizes, some encapsulated
- May be quite varied in composition:
  - Highly cellular, with numerous small follicles
  - Huge cystic follicles containing abundant colloid and lined by flattened epithelium
  - Large cystic structures showing hyperplastic areas of follicles or papillary structures (foci of secondary proliferation)
- Hyperplasia may show varying degrees of Hürthle cell change
- Granulomatous inflammation may result from ruptured follicles
- Degenerative changes, with hemorrhage, fibrosis, and calcification, are seen in most cases

Differential Diagnosis

- Follicular adenoma:
  - Usually single and completely encapsulated
  - Microscopically, the nodule is composed of small, fairly uniform follicles that differ in appearance from the surrounding thyroid tissue.
  - Compresses surrounding tissue
- Follicular or papillary thyroid carcinoma:
  - Tends to be solitary lesion, rather than multicentric process
  - Microscopically, will show evidence of capsular or vascular invasion (follicular carcinoma) or diagnostic nuclear features (papillary carcinoma)

C-Cell Hyperplasia

Clinical

- Hyperplasia of C cells seen in association with (and thought to be precursor of) medullary thyroid carcinoma
- Commonly associated with multiple endocrine neoplasia (MEN) Types 2A and 2B and familial medullary thyroid carcinoma

Macroscopic

- Not grossly evident

Microscopic

- Usually located at junction of upper and middle one-thirds of central portion of lateral lobes
- Interfollicular or intrafollicular clusters of C cells, numbering more than six cells per follicle
- More rigid criteria require presence of expansile nodules of C cells
- No host fibrotic reaction

Immunohistochemistry

- Immunophenotype essentially same as for normal C cells:
  - Immunoreactive for calcitonin, low-molecular-weight cytokeratin (LMWK), synaptophysin, chromogranin, and carcinoembryonic antigen
- Hyperplastic C cells tend to show greater carcinoembryonic antigen immunoreactivity than normal C cells

Differential Diagnosis

- Reactive C-cell hyperplasia:
  - May be found in lymphocytic thyroiditis, secondary hyperparathyroidism, or adjacent to thyroid neoplasms (in these cases, significance of lesions in patients without family history or any other evidence of familial endocrine neoplasia is unknown)

Neoplasms

Benign Tumors

Follicular Adenoma

Clinical

- Neoplasm composed of benign thyroid follicles
- General incidence 5% to 10% of population
- More common in women
- Patients present with palpable nodule or asymmetrical thyroid enlargement.
- Patients are typically euthyroid, although some cases are associated with hyperthyroidism ("toxic adenomas").
- Tumor usually shows little or no I^{131} uptake.

Macroscopic

- Single encapsulated nodule, 1–3 cm in size
- Appearance of cut surface varies from gray-tan to pink and fleshy, depending on cellularity and colloid content
- Larger examples commonly show hemorrhage, cyst formation, fibrosis, and calcification

Microscopic

- Demonstrates complete capsule and compression of surrounding thyroid tissue
- A variety of growth patterns may be seen within the nodule (either as single pattern or mixture):
  - Follicles, ranging from tiny (microfollicular) to large and cystic (macrofollicular)
  - Areas of trabecular or solid growth
  - Focal hyperplasia with papillary or pseudopapillary architecture
- Growth pattern of cells within nodule classically stand in sharp contrast to appearance of normal thyroid parenchyma outside capsule
- Rare examples may have clusters of cells with large hyperchromatic nuclei

Immunohistochemistry

- Similar to that of normal thyroid follicular cells; immunoreactive for thyroglobulin and LMWK (see Table 11-1)

Variants

- Hürthle cell adenoma:
  - Composed largely of Hürthle cells
- Hyperplastic (papillary) adenoma:
  - Prominent secondary hyperplastic changes result in predominantly papillary pattern of growth
- Hyalinizing trabecular adenoma:
  - Features trabecular growth pattern with prominent intratrabecular hyaline material

Table 11-1. Immunohistochemical Profiles of Thyroid Tumors

	Follicular adenoma	*Papillary carcinoma*	*Follicular carcinoma*	*Insular carcinoma*	*Anaplastic carcinoma*	*Hürthle cell tumor*	*Medullary carcinoma*
LMWK	+	+	+	+	+/–	+/–	+
HMWK	–	–/+	–	–	–/+*	–	–
Thyro-globulin	+	+	+	+	–	+/–	–
EMA	+	+	+	–	–/+*	–	–
CEA	–	–/+	–	–	–/+*	–/+	+
CG	–	–	–	–	–	–	+
SYN	–	–	–	–	–	–	+
Calcitonin	–	–	–	–	–	–	+
S-100	–	–/+	–	–	–	–/+	–

Note: LMWK = low-molecular-weight cytokeratin; HMWK = high-molecular-weight cytokeratin; EMA = epithelial membrane antigen; CEA = carcinoembryonic antigen; CG = chromogranin; SYN = synaptophysin.

**Reactivity seen in areas of squamoid or other epithelial differentiation.*

- Nuclei are similar to those of papillary carcinoma and occasional psamomma bodies may be seen
- Low power view may resemble neuroendocrine neoplasm (paraganglioma or medullary thyroid carcinoma)
- Immunoreactive for thyroglobulin and occasionally for chromogranin; no immunoreactivity for calcitonin

Differential Diagnosis

- Papillary or follicular thyroid carcinoma:
  - Evidence of capsular or vascular invasion or both
  - May also have increased mitoses and nuclear pleomorphism
  - Papillary carcinoma infrequently has a trabecular pattern
  - Does not feature formation of hyalin among tumor cells and usually invasive
- Nodular hyperplasia:
  - Although this may demonstrate a dominant nodule, it is usually incompletely encapsulated
  - Surrounding thyroid shows hyperplastic changes similar to those seen within the nodule

Hürthle Cell Adenoma

Clinical

- Benign thyroid neoplasm composed of large follicular cells with granular oxyphilic cytoplasm
- Females affected more commonly than males
- Average age = 45 for adenoma and 55 for carcinoma
- Tumor usually shows little or no I^{131} uptake

Macroscopic

- Usually solid tumors with the typical brown cut surface seen in other oncocytic tumors
- Areas of hemorrhage, cyst formation, or calcification may be seen in larger tumors

Microscopic

- At least 75% of neoplasm composed of Hürthle cells
- Usually shows follicular growth pattern, although solid or papillary patterns also seen
- Characteristic polygonal cells with round regular nuclei with inconspicuous nucleoli and granular eosinophilic cytoplasm
- Some areas may show atypical nuclear features with occasional bizarre nuclei

Immunohistochemistry

- Immunoreactive for thyroglobulin, although staining not as strong as other thyroid follicular neoplasms
- Staining for carcinoembryonic antigen, S-100 protein, and HMB-45 protein also reported

Differential Diagnosis

- Follicular adenoma:
  - May show focal Hürthle cell features
- Follicular carcinoma:
  - May show Hürthle cell features
- Papillary carcinoma:
  - May show focal Hürthle cell features
  - Typical nuclear features (nuclear grooves, nuclear cytoplasmic inclusions, etc.)
- Hashimoto's thyroiditis:
  - May show focal Hürthle cell features, but nearly always in background of lymphoplasmacytic inflammation (with lymphoid follicles), fibrosis, and atrophy

Malignant Tumors

Papillary Carcinoma

Clinical

- Low-grade carcinoma representing most common thyroid malignancy in both adults and children
- Average age = 40 years
- Females affected more commonly than males
- Tumor usually shows little or no I^{131} uptake
- Associated with radiation exposure and Hashimoto's thyroiditis
- Tends to spread by lymphatic route; at diagnosis, 33% have lymph node metastases
- Prognosis generally very good, but related to:
  - Age: most deaths are in patients over 40
  - Stage: extrathyroidal extension has worse prognosis, distant metastases are worse still
  - Sex: males have slightly worse prognosis
  - Tumor size: larger tumor, worse prognosis
  - Encapsulated tumors have better prognosis
  - Anaplastic or squamous foci have much worse prognosis
  - Variant: see below

Macroscopic

- Variably sized, from microscopic to >10 cm, usually 2–3 cm
- Appears as solid, white, infiltrating masses, often with granular cut surface
- Capsule, if present, is usually incomplete
- May undergo significant cystic degenerative changes

Microscopic

- Composed of large masses of complex papillae with single layer or stratified epithelial cells supported by branching fibrovascular cores

- Features of high-grade malignancy (increased mitoses, necrosis, vascular invasion) typically absent
- General papillary architecture may blend with variable component of follicular or solid growth
- Diagnostic nuclear features include
  - Ground glass nuclei (large optically clear nuclei that tend to overlap)
  - Nuclear grooves (due to folded nuclear membrane)
  - Nuclear pseudoinclusions (due to intranuclear cytoplasmic invagination)
- Psammoma bodies (laminated basophilic bodies) occur in 50% of cases.
- Significant number of cases (25% to 75% depending on sampling) show multiple tumor foci

Immunohistochemistry

- Similar to that of normal thyroid follicular cells
- Immunoreactive for thyroglobulin, thyroid transcription factor (TTF-1) and LMWK (see Table 11-1)
- May show areas of high-molecular-weight cytokeratin (HMWK) expression

Variants

- Encapsulated variant:
  - Tumor completely surrounded by capsule
  - Although regional nodal metastasis is seen, widespread metastases and death are very rare
  - May be confused with adenoma or hyperplastic nodule
  - Immunohistochemical profile differs from typical papillary carcinoma (negative for S-100 protein and HMWK)
- Papillary microcarcinoma:
  - Papillary carcinoma measuring <1 cm
  - May appear similar to typical papillary carcinoma or have features of sclerosing variant
  - Prognosis similar to that of encapsulated variant
- Follicular variant:
  - Growth pattern follicular rather than papillary
  - Differentiation from follicular carcinoma depends on finding diagnostic nuclear features and areas of papillary growth.
  - Metastatic tumor resembles classic papillary carcinoma
  - Prognosis similar to classic papillary carcinoma
- Diffuse sclerosing variant
  - Marked fibrosis with lymphocytic infiltrate, extensively involving much of thyroid
  - Thyroid diffusely abnormal, with no dominant tumor evident
  - Numerous psammoma bodies
  - Areas of squamous metaplasia
  - Nodal and distant metastases common
  - Worse prognosis than classic papillary carcinoma
  - May be mistaken for Hashimoto's thyroiditis

Differential Diagnosis

- Follicular carcinoma
  - May resemble follicular variant of papillary carcinoma
  - Does not show focal papillary architecture or specific nuclear features (nuclear grooves, intranuclear cytoplasmic inclusions)
- Follicular adenoma:
  - Areas of reactive hyperplasia within cysts may show papillary features
  - Papillary growth focal and lacks typical nuclear features
- Grave's disease:
  - Areas of reactive hyperplasia within cysts may show papillary features
  - Papillary growth focal and lacks typical nuclear features
- Hashimoto's thyroiditis:
  - May resemble diffuse sclerosing variant due to fibrosis, inflammation, and squamous metaplasia
  - Carcinoma will show other features of malignancy, such as invasion or nuclear changes

Follicular Carcinoma

Clinical

- Malignant thyroid neoplasm with follicular differentiation, but without features of other follicular-derived thyroid malignancies (e.g., papillary carcinoma or Hürthle cell neoplasm)
- Usually presents as single palpable neck mass; patients may present with metastases
- Higher incidence in iodine-deficient regions
- Average age = 50 years
- Females affected more commonly than males
- Tumor usually shows little or no I^{131} uptake

Macroscopic

- Variable tumor appearance, ranging from encapsulated nodule (similar to adenoma) to poorly circumscribed mass with gross invasion of blood vessels and surrounding thyroid tissue
- Cut surface usually appears similar to follicular adenoma (gray-tan to pink and fleshy), with possible areas of hemorrhage or cyst formation.

Microscopic

- Can be very difficult to distinguish encapsulated forms from follicular adenoma

- Malignancy determined by:
  - Vascular invasion (clusters of malignant cells covered with endothelium within and attached to wall of venules located in and outside tumor, usually near capsule)
  - Capsular invasion (penetration of full thickness of capsular wall)
- Increased mitotic activity (including atypical mitoses), widespread nuclear pleomorphism, and necrosis are also helpful features
- Growth pattern varies from well-differentiated follicular to solid or trabecular pattern; cribriform areas may also be seen
- Psamomma bodies, squamous metaplasia, and nuclear features of papillary carcinoma are not seen

Immunohistochemistry

- Similar to that of normal thyroid follicular cells
- Immunoreactive for thyroglobulin, thyroid transcription factor (TTF-1) and LMWK (see Table 11-1)

Variants

- Minimally invasive follicular carcinoma:
  - Grossly encapsulated
  - Usually shows microfollicular or trabecular growth pattern
  - Malignant features usually limited to foci of capsular and/or vascular invasion
  - Metastases occur in <5% and <1% of cases with vascular invasion and capsular invasion only, respectively
- Widely invasive follicular carcinoma:
  - Grossly non-encapsulated and infiltrative
  - Microscopically, shows extensive invasion of blood vessels and surrounding thyroid
  - Metastases occur commonly, usually to bones and lungs

Differential Diagnosis

- Follicular adenoma:
  - Shows similar encapsulation and growth patterns but no invasion
  - Capsules of adenomas, on average, tend to be thinner than those of carcinomas.
  - The effects of fine-needle aspiration on an adenoma may mimic capsular invasion, but areas of hemorrhage and stromal repair should be evident.
- Papillary carcinoma, follicular variant:
  - Usually shows foci with some papillary differentiation
  - Typical nuclear features (nuclear grooves, nuclear cytoplasmic inclusions, etc.)

Insular Carcinoma

Clinical

- Poorly differentiated thyroid carcinoma
- Average age = 55 years
- Patients usually present with palpable neck mass.
- Tumor usually shows good I^{131} uptake.
- Relatively poor prognosis with lymph node and distant metastases common

Macroscopic

- Usually large (>5 cm) non-encapsulated tumor with infiltrative margins
- Cut surface usually pale gray-white, with areas of necrosis and calcification

Microscopic

- Distinctive nesting (insular) pattern of growth, reminiscent of carcinoid and medullary carcinoma
- Nests composed of sheets of cells with some microfollicles
- Small uniform cells with mild to moderate nuclear pleomorphism
- Additional features may include increased mitotic rate and necrosis
- Growth may be in characteristic "peritheliomatous" pattern with extensive necrosis with preservation of viable cells around vessels

Immunohistochemical

- Similar to that of normal thyroid (immunoreactive for thyroglobulin and LWMK) (see Table 11-1)

Differential Diagnosis

- Medullary thyroid carcinoma:
  - Cells tend to be more varied in morphology, with mixtures of round, polygonal, or spindled cells
  - Atypical nuclear features, mitoses, and necrosis less prominent features
  - Immunostaining shows expression of calcitonin and neuroendocrine markers, thyroglobulin –
- Follicular carcinoma (with solid or trabecular growth):
  - Atypical nuclear features, mitoses, and necrosis less prominent features
  - More typical areas of follicular growth normally seen

Anaplastic Carcinoma (Sarcomatoid Carcinoma)

Clinical

- Poorly differentiated thyroid carcinoma
- Seen in elderly patients
- Presents as rapidly expanding mass with symptoms of regional invasion (dysphagia, dyspnea, or dysphonia)

- Tumor usually fails to show I^{131} uptake
- Very poor prognosis; mean survival = 6 months

Macroscopic

- Grossly invasive mass replacing thyroid and extensively involving regional neck structures
- Areas of hemorrhage and/or necrosis common

Microscopic

- Variable patterns, sometimes seen in combination:
  - Squamoid: atypical epithelioid cells that may show areas of keratinization
  - Giant cell (pleomorphic): large cells with bizarre nuclei
  - Spindle cell: atypical spindle cells growing in fascicular or storifom patterns, similar to sarcoma
- Tumors may show areas of cartilaginous or osseous metaplasia, myxoid stroma, or multinucleated giant cells, or may have prominent vascular patterns
- Areas of typical papillary or follicular carcinoma may be seen; in cases where anaplastic pattern represents minority of tumor, prognosis is somewhat better

Immunohistochemistry

- Most cases show immunoreactivity for LMWK and vimentin in spindle cells
- Areas of squamoid differentiation may show variable immunoreactivity for HMWK, epithelial membrane antigen, and carcinoembryonic antigen
- Negative for thyroglobulin; focal immunoreactivity result of entrapped normal follicles

Differential Diagnosis

- Sarcoma:
  - Most cases of sarcomatous-appearing tumors of thyroid are, in fact, anaplastic carcinomas
  - May resemble malignant fibrous histiocytoma, angiosarcoma, hemangiopericytoma, or fibrosarcoma
  - Tumor should be extensively sampled to search for areas of epithelial differentiation
  - Cytokeratin immunoreactivity is very helpful in confirming a diagnosis of carcinoma

Hürthle Cell Carcinoma

Clinical

- Malignant thyroid neoplasm composed of large follicular cells with granular oxyphilic cytoplasm
- Females affected more commonly than males
- Average age 55
- Tumor usually shows little or no I^{131} uptake
- Has a relatively poor prognosis (5-year survival = 20–40%)

Macroscopic

- Usually solid tumors with typical brown cut surface seen in other oncocytic tumors
- Areas of hemorrhage, cyst formation, or calcification may be seen in larger tumors

Microscopic

- At least 75% of neoplasm composed of Hürthle cells
- Usually shows follicular growth pattern, although solid or papillary patterns may be seen
- Characteristic large polygonal cells with round nuclei with inconspicuous nucleoli and granular eosinophilic cytoplasm
- Areas may show atypical nuclear features with occasional bizarre nuclei
- Diagnosis of malignancy requires the same histologic findings as follicular carcinoma (vascular or capsular invasion)

Immunohistochemistry

- Immunoreactive for thyroglobulin, although staining not as strong as other thyroid follicular neoplasms (see Table 11-1)
- Staining for carcinoembryonic antigen, S-100 protein, and HMB-45 protein have also been reported

Differential Diagnosis

- Follicular adenoma:
  - May show Hürthle cell features
- Follicular carcinoma:
  - May show Hürthle cell features
- Papillary carcinoma:
  - May show Hürthle cell features
  - Typical nuclear features (nuclear grooves, nuclear cytoplasmic inclusions, etc.)
- Hashimoto's thyroiditis:
  - Shows focal Hürthle cell features, but nearly always in a background of lymphoplasmacytic inflammation (with lymphoid follicles), fibrosis and atrophy

Medullary Carcinoma

Clinical

- Neuroendocrine carcinoma composed of malignant C cells (parafollicular cells)
- Commonly associated with multiple endocrine neoplasia Types 2A and 2B, as well as familial medullary thyroid carcinoma
- Most tumors (80%) sporadic, usually presenting as solitary mass in patients in their fifth decade
- Tumor shows no I^{131} uptake
- Familial cases usually present earlier (mean age = 35), often as bilateral and multiple tumors

- An increasing number of cases are being detected as micro-tumors in closely monitored patients with family histories of multiple endocrine neoplasia
- May be associated with various ectopic hormone secretion syndromes (adrenocorticotrophic hormone, histamine, insulin, serotonin, etc.)

Macroscopic

- Non-encapsulated, firm gray mass

Microscopic

- Typically composed of round cells with granular amphophilic cytoplasm and round regular nuclei with coarse chromatin, growing in nests ("zellballen") separated by vascular septa and hyalinized collagen
- Tumor may show remarkable variety of growth patterns (trabecular, glandular, pseudo-papillary) and cell types (spindled, plasmacytoid, oncocytic, or squamoid)
- Amyloid (amorphous eosinophilic hyaline material) classically seen in stroma, although some tumors do not have any visible amyloid
- Calcification, sometimes coarsely laminated, may be present

Immunohistochemistry

- Immunoreactive for calcitonin, synaptophysin, chromogranin, cytokeratin, and carcinoembryonic antigen
- Usually – for thyroglobulin
- Amyloid stains appropriately with various reagents (cresyl violet, sulfated alcian blue) and demonstrates typical apple green birefringence with congo red under polarized light

Variants

- Variety of histologic architectures may be seen, including follicular, papillary, small cell, clear cell, giant cell, oncocytic, squamous, and melanotic.

Differential Diagnosis

- Other thyroid carcinomas:
  - The wide spectrum of growth patterns seen in medullary carcinoma may lead to confusion with more common thyroid tumors (papillary, follicular, insular)
  - Unusual cell morphology or nuclear features may suggest the possibility of an unusual pattern of medullary carcinoma
  - Careful sampling of the entire tumor for more typical morphology and immunostaining is important in diagnosis
  - Typical thyroid carcinomas are immunoreactive for thyroglobulin and negative for calcitonin
- Hyalinizing trabecular adenoma:
  - Intratrabecular hyaline material and nested growth pattern may resemble medullary carcinoma.
  - Hyaline material – for amyloid
  - Tumor cells calcitonin – and immunoreactive for thyroglobulin

PARATHYROID GLAND

Non-Neoplastic Conditions

Parathyroid Cyst

Clinical

- Benign glandular cyst
- Presents with palpable nodule or local tenderness
- No symptoms of hormone abnormality seen

Macroscopic

- Solitary fluid-filled cyst, 1–6 cm in diameter
- Thin-walled
- Usually seen in inferior glands

Microscopic

- Benign cyst lined by cuboidal epithelium with clear cytoplasm
- Associated adjacent normal parathyroid tissue

Differential Diagnosis

- Parathyroid adenoma:
  - Larger adenomas may undergo cystic degeneration
  - Clinical evidence of hyperparathyroidism usually seen
  - Surrounding tissue may show residual adenoma
- Thyroglossal duct cyst:
  - Seen in midline neck, usually at or above level of thyroid
  - Cyst wall usually demonstrates identifiable thyroid tissue
- Branchial cleft cyst:
  - Location classically antero-lateral neck
  - Lined by mixed squamous and respiratory epithelium

Chief Cell Hyperplasia

Clinical

- Diffuse parathyroid enlargement of all four glands due to autonomous hyperplasia (primary chief cell hyperplasia) or in response to chronically low serum calcium (secondary chief cell hyperplasia)

- Primary chief cell hyperplasia is commonly associated with multiple endocrine neoplasia Type I and IIA
- Secondary chief cell hyperplasia can be associated with kidney failure (renal loss of calcium) or calcium malabsorption

Macroscopic

- Primary chief cell hyperplasia shows pronounced enlargement of all glands (up to 10g each)
- Depending on degree of hypocalcemia, secondary chief cell hyperplasia is more variable in appearance, with glands ranging from normal size to moderately enlarged (up to 6g each)

Microscopic

- Hyperplasia principally of chief cells, although other cells types (oxyphil or water-clear) may be involved
- Cells are typically growing in large hyperplastic nodules scattered throughout gland (nodular chief cell hyperplasia), giving it an irregular, asymmetrical appearance
- Diffuse growth pattern may be seen, especially in younger patients
- Other microscopic findings may include areas of fibrosis, acinar structures, or scattered atypical nuclear features (as in adenoma)
- Distinction between primary and secondary chief cell hyperplasia cannot be made on morphologic grounds and is largely based on clinical findings.

Variants

- Water-clear cell hyperplasia:
  - Rare sporadic variant of hyperplasia with marked parathyroid enlargement (combined weights may be >100 g) and associated primary hyperparathyroidism
  - Enlargement usually asymmetric, with upper glands considerably larger than lower pair
  - Cells are very large and ballooned, with finely vacuolated water-clear showing marked size variation and growing in alveolar pattern with delicate intervening stroma

Differential Diagnosis

- Parathyroid adenoma:
  - Enlargement involves only a single gland, with other glands usually appearing atrophic
  - Microscopically, shows an encapsulated expansive cellular nodule compressing normal, sometimes atrophic, parathyroid tissue

Tumors

Parathyroid Adenoma

Clinical

- Benign chief-cell neoplasm
- More common in women (F:M = 3:1)
- Usually too small and too soft to be found on physical exam
- Majority of tumors hormonally active; most patients present with symptoms of primary hyperparathyroidism (elevated serum calcium, bone loss)

Macroscopic

- Small, slightly lobulated nodules, with delicate capsules, weighing 0.5–5 g
- Smooth, shining exterior, without adjacent tissues attached
- Gray-brown in color, with soft, flabby consistency
- Other parathyroid glands should appear normal or atrophic

Microscopic

- Encapsulated nodule of highly cellular parathyroid tissue
- Growth pattern is usually solid, but follicles or papillary structures can be seen
- Predominantly chief cells, but other cell types can be seen
- Areas with nuclear pleomorphism can be seen.
- Rare mitoses may be visible
- Remaining parathyroid tissue is compressed by the adenoma and may appear atrophic

Immunohistochemistry

- Identical to that of normal parathyroid chief cells

Variants

- Oxyphil adenoma
  - Composed nearly entirely of oxyphil cells
  - Usually non-functional
- Lipoadenoma:
  - Encapsulated nodular growth composed of islands or cords of chief cells separated by abundant mature-appearing adipose tissue

Differential Diagnosis

- Parathyroid hyperplasia:
  - Involves all parathyroid glands
  - Microscopically, gland appears diffusely enlarged, with an even distribution of cellularity and adipose tissue
- Parathyroid carcinoma:
  - Can be very difficult to distinguish from adenoma
  - Clinical evidence of malignancy very important (palpable mass, vocal cord paralysis, adherence of gland to local structures, post-surgical recurrence)
  - Microscopic features of malignancy include fibrous bands, mitotic figures, and capsular or vascular invasion

Parathyroid Carcinoma

Clinical

- Malignant epithelial tumor composed of parathyroid chief cells
- Similar to adenoma; majority of tumors hormonally active with patients usually presenting with symptoms of primary hyperparathyroidism (elevated serum calcium, bone loss)
- Additional clinical findings increase suspicion of malignancy:
  - Markedly elevated serum calcium
  - Palpable mass
  - Evidence of invasion (e.g., vocal cord paralysis)
- Prognosis generally good, although local recurrences common
- Death is usually a result of hypercalcemia rather than metastases

Macroscopic

- Gross appearance usually that of mass, firmly adherent to regional structures
- Tumor size ranges from 1–6 cm (mean = 3 cm) and weighs 1.5–30 g (mean 6.7 g)

Microscopic

- Often difficult to distinguish from adenoma because histologic features of malignancy may be focal and subtle
- Findings suspicious for malignancy include:
  - Solid or trabecular growth pattern
  - Dense fibrous bands
  - Increased mitotic activity
  - Capsular invasion
  - Vascular invasion
- It is important to note that some adenomas may show these features (fibrosis, rare mitoses, and solid growth); therefore, diagnosis of carcinoma must rely on both histologic and clinical features

Immunohistochemistry

- Identical to that of normal parathyroid chief cells

Differential Diagnosis

- Parathyroid adenoma:
  - May be very difficult to distinguish
  - Absence of suspicious clinical features (adherence to adjacent structures) and histologic features (mitoses, fibrosis, invasion) helpful in establishing benign diagnosis
- Parathyroid hyperplasia:
  - Involves all parathyroid glands
  - Microscopically, gland appears diffusely enlarged, with an even distribution of normal-appearing chief cells and adipose tissue

ADRENAL GLAND

Non-Neoplastic Conditions

Adrenal Heterotopia

Clinical

- Benign congenital anomaly with normal adrenal tissue appearing in abnormal locations
- Relatively common, seen in up to 30% of autopsy cases
- Usually located in retroperitoneal space near adrenals and kidneys, in pelvis, or in inguinal area
- May undergo hyperplasia in response to increased ACTH levels and rarely may give rise to cortical neoplasms

Macroscopic

- Small (<1 cm) nodules of yellow tissue resembling normal adrenal cortex

Microscopic

- Most consist of adrenal cortical tissue only, but some may also contain medulla.

Focal "Adrenalitis"

Clinical

- Cortical and medullary lymphoplasmacytic aggregates of uncertain etiology
- Seen in up to 50% of autopsy patients and particularly common in elderly

Microscopic

- Perivascular aggregates of lymphocytes and plasma cells

Differential Diagnosis

- Autoimmune adrenalitis:
  - Inflammatory response more diffuse
  - Marked cortical atrophy

Adrenal Aplasia

Clinical

- Unilateral or bilateral absence of adrenal gland, usually in setting of multiple congenital anomalies

- Seen in association with acardia, anencephaly, and renal agenesis

Adrenal Cysts

Clinical

- Benign pathologic finding
- Usually an incidental finding on CT or MRI
- Seen in adults in fourth to sixth decades
- May be simple developmental cysts or may arise from lymphangioendothelial cysts that undergo hemorrhage and fibrosis

Macroscopic

- Fluid-filled cysts ranging in size from 2–10 cm
- Walls may be focally calcified.

Microscopic

- Cyst walls composed of fibrous tissue with hemosiderin and elastic tissue occasionally identified
- Epithelial, endothelial, or no specific lining tissue

Differential Diagnosis

- Tumors such as adenoma, carcinoma, or pheochromocytoma may undergo cystic degenerative changes that may grossly mimic cyst

Adrenal Cytomegaly

Clinical

- An incidental histologic finding in up to 3% of newborns and 6.5% of stillborn fetuses
- Particularly prominent in infants with Beckwith-Wiedemann syndrome

Microscopic

- Markedly enlarged cells (up to 120 μm) with marked nuclear enlargement, hyperchromasia, and pleomorphism
- Nuclear cytoplasmic inclusions can occasionally be seen

Cytogenetics

- Cells may be polyploid/aneuploid, but are not considered neoplastic

Beckwith-Wiedemann Syndrome

Clinical

- Congenital disorder, sometimes familial, manifested by craniofacial abnormalities, abdominal wall defects, gigantism, macroglossia, and adrenal hyperplasia
- Estimated frequency = 1 in 13,000 births
- 7.5% of affected children develop a malignant neoplasm (usually nephroblastoma or adrenal cortical carcinoma)

Macroscopic

- Enlarged adrenals (up to 16 g) with cerebriform appearance

Microscopic

- Marked cytomegaly affecting nearly all cells of cortex
- Cortical microcysts may be seen
- Medullary hyperplasia

Adrenal Leukodystrophy

Clinical

- X-linked metabolic disorder characterized by:
  - Sensory and motor neuropathy
  - Spastic paraplegia
  - Adrenal insufficiency, culminating in Addison's disease

Macroscopic

- Cortical atrophy

Microscopic

- Attenuated cortex consisting of ballooned cells with abundant granular or hyaline eosinophilic cytoplasm
- Some cells may have cleared cytoplasm with intracytoplasmic striations

Electron Microscopy

- Cortical cells contain linear lamellar inclusions

Congenital Adrenal Hyperplasia (Adrenogenital Syndrome)

Clinical

- Pathologic manifestation of group of autosomal recessive disorders characterized by enzymatic defects in cortisol synthesis
- Insufficient cortisol results in increased ACTH secretion and subsequent bilateral adrenal hyperplasia
- Biosynthesis pathway blockages result in shunting of steroids into other pathways, usually those for sex steroids
- Usually presents in first few years of life with findings related to abnormal hormone levels: sexual development abnormalities, hypertension, adrenal insufficiency, sodium imbalances
- Most common enzymatic defect is 21-hydroxylase deficiency (seen in >90% of cases)
- Patients affected with longstanding disease may develop steroid-type neoplasms (adrenal cortical and testicular) due to stimulatory effects of chronically increased adrenocorticotrophic hormone (ACTH) levels

Macroscopic

- Marked diffuse enlargement with tan-brown coloration and cerebriform appearance
- Glands usually weigh 10–15 g each

Microscopic

- Marked hyperplasia of zona fasciculata

- Compact cells with eosinophilic cytoplasm (lipid-depleted) replace normal vacuolated (lipid-laden) fasciculata cells

Differential Diagnosis

- Adrenal cortical hyperplasia:
  - Usually older patients
  - Hormonal syndromes usually associated with glucocorticoid or mineralocorticoid excess, rather than sex steroid excess
  - Commonly nodular or mixed diffuse and nodular
- Beckwith-Wiedemann syndrome:
  - Associated with multiple anatomic anomalies
  - Marked cortical cytomegaly

Primary Adrenal Insufficiency (Idiopathic Addison's Disease)

Clinical

- Adult autoimmune disease where antibodies directed against adrenal antigens result in cortical cell destruction and subsequent adrenal insufficiency
- More common in females (F:M = 2:1)
- Patients typically manifest signs and symptoms of deficiencies in glucocorticoids and mineralocorticoids, including fatigue, weight loss, hypotension, poor stress tolerance, and increased pigmentation (due to increased ACTH)
- Sometimes associated with autoimmune disease of thyroid (Hashimoto's thyroiditis resulting in hypothyroidism), stomach (chronic atrophic gastritis resulting in pernicious anemia), or pancreas (inflammation of islets causing diabetes mellitus)

Macroscopic

- Marked cortical atrophy

Microscopic

- Marked cortical atrophy with remaining cortical tissue showing lymphocytic infiltrate
- Residual cortical cells are hypertrophied and have compact eosinophilic cytoplasm and enlarged nuclei (ACTH stimulation effect)
- Medulla uninvolved

Differential Diagnosis

- Other causes of adrenal cortical insufficiency:
  - Infectious agents such as mycobacteria, fungi, or viruses
  - Amyloid deposition
  - Adrenal hemorrhage (Waterhouse-Friderichsen syndrome)
  - Metastatic tumor
  - Pituitary lesions (tumor, necrosis, hemorrhage)

Secondary Adrenal Insufficiency

Clinical

- Adrenal insufficiency and atrophy due to lack of ACTH stimulation
- Usually due to primary pituitary disease:
  - Pituitary neoplasm
  - Post-partum necrosis (Sheehan's syndrome)
- Patients present with hypocortisolism: anorexia, weight loss, hypotension, poor stress tolerance, and hyperpigmentation (due to increased ACTH)

Macroscopic

- Cortical atrophy
- Cortex appears bright yellow due to accumulation of lipid
- Brown zona reticularis (normally seen internal to yellow zona fasciculata) is not present
- Normal-appearing medulla

Microscopic

- Atrophy of zona fasciculata and reticularis with relative sparing of zona glomerulosa

Differential Diagnosis

- Primary adrenal insufficiency
- Exogenous steroid administration

Adrenal Cortical Hyperplasia

Clinical

- Enlargement of adrenal cortex with increased serum cortisol, usually due to above normal stimulation by ACTH, either from pituitary or ectopic sources
- Patients may present with extra-adrenal tumor (ectopic ACTH secretion) or with symptoms of hypercortisolism.
- Most common sources of ACTH include:
  - Pituitary adenoma (Cushing's disease)
  - Small cell lung carcinoma
  - Carcinoid tumor (lung, gastrointestinal tract, thymus, or pancreas)
  - Islet cell carcinoma
  - Medullary thyroid carcinoma

Macroscopic

- Enlargement of cortex may be diffuse, nodular, or combination of both
- Diffuse hyperplasia results in moderate enlargement (12–24 g each) with uniform widening of cortex, which appears tan to brown
- Nodular hyperplasia shows varying numbers of individual nodules in the cortex
- Nodules may measure up to 3 cm and adrenals may weigh up to 50 g

- Diffuse and nodular hyperplasia may co-exist in the same patient

Microscopic

- Diffuse hyperplasia:
  - Expanded zona fasciculata with compact, lipid-depleted cells; zona glomerulosa cells appear vacuolated
- Nodular hyperplasia:
  - Nodules composed of clear cells, compact cells, or mixture of both

Differential Diagnosis

- Cortical adenoma
  - Usually single dominant nodule, rather than multiple nodules
  - Uninvolved cortex and contralateral adrenal are normal or show atrophy

Cortical Hyperplasia Associated with Hyperaldosteronism

Clinical

- Pathologic condition seen in ~40% of cases of primary hyperaldosteronism
- Patients exhibit typical manifestations of hyperaldosteronism: hypertension, weakness, hypokalemia, and hypernatremia

Macroscopic

- Cortex may be diffusely widened or have nodular appearance

Microscopic

- Cortical expansion due primarily to hyperplasia of zona glomerulosa with tongues of glomerulosa cells extending down into adjacent zona fasciculata
- In patients treated with diuretic spironolactone (Aldactone), cells may contain laminated eosinophilic inclusions ("spironolactone bodies")

Differential Diagnosis

- Typical adrenal cortical hyperplasia:
  - Associated with increased glucocorticoid levels
  - Hyperplastic cortex made up mostly of fasciculata cells, rather than glomerulosa cells

Cortical Macronodular Hyperplasia

Clinical

- Rare type of primary adrenal hyperplasia with tumor-like enlargement of both glands
- Average age = 50 years
- Patients usually present with symptoms of hypercortisolism.

Macroscopic

- Markedly enlarged adrenal glands (combined weight of 60–180 g), grossly distorted by multiple nodules ranging in size up to 3.5 cm
- On cross section, nodules are non-encapsulated and bright yellow in color

Microscopic

- Cortical cells are varied in appearance, predominantly large and vacuolated (lipid-laden) with some scattered, eosinophilic, compact (lipid-depleted) cells and rare balloon cells
- Pseudoglandular formations are occasionally present
- Focal lipomatous or myelolipomatous metaplasia can be seen

Differential Diagnosis

- Cortical carcinoma:
  - Unilateral
  - Typically >100 g
  - Cellular atypia, mitoses, necrosis, fibrous bands
  - Vascular or capsular invasion
- Typical adrenal hyperplasia:
  - Combined weight of adrenals usually <50 g
  - May have nodular appearance, but individual nodules are small (<0.5 cm)

Microadenomatous Hyperplasia (Primary Pigmented Nodular Adrenocortical Disease)

Clinical

- A type of primary adrenal hyperplasia with characteristic macroscopic findings
- More common in young women
- Patients show typical signs and symptoms of hypercortisolism: truncal obesity, muscle weakness, hypertension, abdominal striae, menstrual abnormalities/impotence
- Osteoporosis often prominent feature
- Familial forms are associated with:
  - Myxomas (cardiac, cutaneous, and mammary)
  - Spotty cutaneous pigmentation (ephelides, lentigines, and blue nevi)
  - Endocrine overactivity (acromegaly due to pituitary adenoma and sexual precocity due to large-cell calcifying Sertoli cell tumor of testes)
  - Schwannomas (psammomatous melanotic type)

Macroscopic

- Multiple pigmented cortical nodules (1–3 mm in size) situated in an atrophic cortex
- Glands are usually normal size, but may be smaller or larger than normal

Microscopic

- Small nodules composed of large granular eosinophilic cells, some with large hyperchromatic nuclei and prominent nucleoli
- Cells contain lipofuscin pigment.

Differential Diagnosis

- Pigmented cortical adenoma:
  - Larger, single nodule, usually 3–6 cm in size
- Cortical carcinoma:
  - Single, dominant mass, rather than multiple nodules
  - Marked cellular atypia, mitoses, necrosis, fibrous bands
  - Vascular or capsular invasion

Ovarian Thecal Metaplasia

Clinical

- Benign cortical proliferation resembling ovarian stroma
- Seen in <5% of females, usually postmenopausal, may also occur rarely in males
- No known significance

Macroscopic

- Small (<2 mm) firm fibrous nodule, usually wedge-shaped, attached to adrenal capsule
- Occasionally, multiple foci may be present

Microscopic

- Subcapsular proliferation of spindle cells that resemble normal ovarian stroma
- Scattered cortical cells may be entrapped within proliferation
- Fibrosis common; may be calcified

Adrenal Medullary Hyperplasia

Clinical

- Uncommon hyperplastic expansion of medulla
- Usually found incidentally
- Typically only associated with multiple endocrine neoplasia Types 2A and 2B
- May rarely be sporadic
- Thought to be precursor lesion to pheochromocytoma, especially in multiple endocrine neoplasia patients

Macroscopic

- Increased adrenal medullary volume with pearly gray color
- Enlargement may be uniform or have a somewhat nodular appearance
- Medullary tissue may extend beyond its normal location (restricted to head and body of adrenal) and be found within alar and tail regions

Microscopic

- Increased numbers of cells, either in sheets or nodules, expanding medulla
- There may be significant cellular pleomorphism and some nuclear pleomorphism as well

Differential Diagnosis

- Adrenal cortical atrophy:
  - May mimic medullary hyperplasia grossly by making medulla appear relatively large compared to thin, attenuated cortex
- Pheochromocytoma:
  - Nodular hyperplasia may look similar to early pheochromocytoma and, indeed, is thought to be a possible precursor of pheochromocytoma

Neoplasms

Benign Tumors

Cortical Adenoma

Clinical

- A benign cortical neoplasm, often associated with hormonal secretion
- Signs and symptoms related to specific hormones elaborated by adenoma:
  - Hypercortisolism (Cushing's syndrome), hyperaldosteronism (Conn's syndrome), or increased androgenic or estrogenic steroids (adrenogenital syndrome)
  - Some adenomas secrete multiple hormones and others are non-functional
- Identified incidentally on MRI or CT ("incidentalomas")
- Autopsy series show 10% to 20% incidence

Macroscopic

- Well-circumscribed, encapsulated masses, well-demarcated from surrounding cortex
- Size varies from several grams up to 500 g in rare cases
- Cortical tumors >100 g should be carefully evaluated for presence of malignancy and, even if benign-appearing histologically, should be regarded as having an indeterminate biological potential
- Necrosis rare, but cystic degeneration commonly occurs in larger tumors
- In cases of cortisol-secreting tumors, the adjacent cortex and contralateral adrenal gland are atrophic due to suppression of pituitary ACTH secretion by the tumor's hormone secretion

Microscopic

- Well-circumscribed, usually encapsulated, tumors composed of nests and cords of cells resembling those normally found in glomerulosa, fasciculata, or reticularis

- Adenomas may be a mixture of cell types
- Some tumors may contain significant nuclear pleomorphism, thought to be degenerative
- In pediatric patients, benign adenomas may demonstrate increased mitotic rate, fibrosis, necrosis, and nuclear pleomorphism

Variants

- Adenomas associated with Conn's syndrome:
  - Small (<2 cm), bright yellow, often poorly demarcated from surrounding cortex
  - Tumor cells resemble those of glomerulosa or fasciculata (clear cells) or a combination of the two
  - In patients treated with diuretic spironolactone (Aldactone), tumor cells (and sometimes extratumoral zona glomerulosa cells) may contain eosinophilic inclusions ("spironolactone bodies")
  - Zona glomerulosa of nearby cortex may be hyperplastic
- Adenomas associated with Cushing's syndrome:
  - Usually measure 3–4 cm in diameter and weigh 10–50 g
  - Usually appear as mixture of colors (yellow to brown) and may occasionally be darkly pigmented ("black adenoma")
  - Cells resemble zona reticularis and fasciculata with lipid-depleted (dark) and lipid-rich (pale) cytoplasm.
  - Fatty or myeloid metaplasia common
  - Cells of "black adenoma" contain abundant lipofuscin
  - Adjacent cortex (and that of contralateral adrenal) typically appears atrophic, with absence of normal zona reticularis
- Adenomas associated with adrenogenital syndromes:
  - Tend to be larger and may have red-brown appearance
  - Are relatively uncommon and must be carefully distinguished from cortical carcinoma
  - Not associated with atrophy of normal cortical tissue
- Non-functional adenomas and cortical nodules:
  - Small (>3 cm), yellow to brown in color, and may be multicentric
  - Not associated with atrophy of normal cortical tissue

Differential Diagnosis

- Nodular or macronodular hyperplasia:
  - Usually multiple nodules rather than single dominant nodule
  - Adjacent cortex and contralateral adrenal gland will commonly appear hypertrophic, not atrophic
- Cortical carcinoma:
  - Typically >100 g
  - Nuclear atypia, mitoses, necrosis, fibrous bands
  - Vascular or capsular invasion
- Pheochromocytoma:
  - Arising from adrenal medulla with normal adrenal cortex stretched out over its surface
  - Red-brown in color with areas of hemorrhage or cystic degeneration if large
  - Organoid growth pattern with nests of cells ("zellballen") and delicate vascular septa
  - Immunohistochemistry: immunoreactive for neurofilament, chromogranin, synaptophysin and S-100 (in sustentacular cell pattern); – for vimentin

Myelolipoma

Clinical

- Benign mixed stromal tumor composed of mature adipose and myeloid elements
- Usually incidental finding at autopsy or adrenalectomy
- Small foci of myelolipomatous transformation are commonly seen within adenomas or cortical hyperplasia.

Macroscopic

- Small, non-encapsulated spongy lesion, bright yellow with scattered small red-brown foci

Microscopic

- Mature adipose tissue with scattered normal-appearing hematopoietic islands

Oncocytoma (Oncocytic Adenoma)

Clinical

- Benign epithelial adrenal cortical neoplasm
- Usually asymptomatic, but may be associated with hormonal syndrome

Macroscopic

- Variably sized (60–850 g), well-circumscribed, often encapsulated
- Typical tan-brown color
- Central scarring common, but also may see hemorrhage or cystic change

Microscopic

- Composed of sheets of large regular polygonal cells with abundant granular eosinophilic cytoplasm
- Some nuclear pleomorphism common

Electron Microscopy

- Granular cytoplasm features many mitochondria that demonstrate both lamellar and tubular cristae
- May contain small electron-dense inclusions

Differential Diagnosis

- Adrenal cortical carcinoma:
  - Often associated with hormonal syndrome (but not always)

  - Gross invasion or necrosis
  - Increased mitoses, areas of necrosis, marked nuclear pleomorphism, invasion
- Pheochromocytoma
  - Cells can sometimes appear oncocytic, with abundant granular cytoplasm
  - Immunohistochemistry: immunoreactive for S-100 in sustentacular cell pattern

Pheochromocytoma

Clinical

- Benign tumor composed of adrenal medullary chromaffin cells
- Highest incidence in fourth and fifth decades, although 10% occur in children
- Patients present with signs and symptoms of catecholamine secretion (hypertension, cardiac dysrhythmias, and diaphoresis)
- Ectopic hormones may be produced as well (ACTH, somatostatin, or calcitonin)
- Usually within adrenal glands, but 10% to 20% of cases elsewhere in retroperitoneum, mediastinum, neck, or bladder (at these extra-adrenal sites, referred to as paragangliomas)
- 10% to 20% of cases associated with familial syndromes: MEN Type 2A and 2B (roughly half of patients affected, usually multicentric and bilateral), von Hippel-Lindau disease, von Recklinghausen's disease, and Sturge-Weber syndrome (1% to 5% of patients)

Macroscopic

- Encapsulated mass usually 3–5 cm, weighing <100 g
- Gray-pink to tan-brown in color
- Soft consistency
- Areas of hemorrhage and cyst formation can be seen with larger tumors

Microscopic

- Tumor grows in cords or nests (zellballen = "cell balls"), with delicate fibrovascular septa
- Variably sized cells with generally basophilic granular cytoplasm that may be vacuolated in some cases
- Occasional spindled cells
- PAS + cytoplasmic hyaline globules in up to 60% of cases
- Round to oval, slightly irregular nuclei with coarsely clumped chromatin (salt and pepper chromatin) and single, ordinarily inconspicuous nucleoli
- Moderate nuclear pleomorphism may be present
- Mitoses possible, but rare

Immunohistochemistry

- Tumor cells immunoreactive for chromogranin, synaptophysin, and neurofilament
- S-100 staining of thin, spindled sustentacular cells (not tumor cells) in characteristic pattern (see Table 11-2)
- Negative for cytokeratin and vimentin

Electron Microscopy

- Cytoplasm contains membrane-bound dense-core secretory granules that contain epinephrine or norepinephrine

Variants

- Malignant pheochromocytoma:
  - Estimated 5% to 10% of pheochromocytomas are malignant
  - Females more often than males
  - No reliable gross or histologic criteria exist for malignancy.
  - Suspicious features include extra-adrenal location, large tumor weight, confluent areas of necrosis, and vascular invasion or extensive local invasion
  - 5-year survival = 50%

Differential Diagnosis

- Adrenal cortical adenoma:
  - Small (3–6 cm) with bright yellow to tan-brown color
  - Uninvolved adrenal cortical tissue usually appears atrophic
  - Immunohistochemistry: immunoreactive for vimentin and possibly synaptophysin; no reactivity with S-100 or chromogranin
- Adrenal cortical carcinoma:
  - High-grade nuclear pleomorphism, necrosis, invasion
  - Increased mitoses
  - Immunohistochemistry: immunoreactive for vimentin and possibly S-100 protein (no sustentacular staining pattern), neurofilament, or synaptophysin
- Metastatic carcinoma:
  - Common primary sites include lung, breast, gastrointestinal tract, thyroid, and kidney
  - Growth pattern usually solid rather than nested
  - Immunohistochemistry: immunoreactive for cytokeratin, epithelial membrane antigen, and/or carcinoembryonic antigen
- Melanoma:
  - May be primary, or more commonly metastasis from an occult primary
  - Melanin pigment
  - Immunohistochemistry: tumor cells immunoreactive for S-100 protein and HMB-45

Table 11-2. Immunohistochemical Profiles of Adrenal Tumors

	Cortical carcinoma	*Neuro-blastoma*	*Ganglio-neuroma*	*Pheochromo-cytoma*	*Metastatic carcinoma*	*Malignant melanoma*	*Lipo-sarcoma*
LMWK	–	–	–	–	+	–	–
VIM	+		+	–	±	+	+
NF	±	+	+ (ganglion cells)	+	–	–	–
S-100	±	+ (stroma)	+ (stroma)	+ (sustentacular cells)	–	+	+
EMA	–		–	–	±	–	–
CG	–	+	+ (ganglion cells)	+	–	–	–
SYN	±	–	+ (ganglion cells)	+	–	–	–
CEA	–		–	–	±	–	–

LMWK = low-molecular-weight cytokeratin; VIM = vimentin; NF = neurofilament; EMA = epithelial membrane antigen; CG = chromogranin; SYN = synaptophysin; CEA = carcinoembryonic antigen.

Ganglioneuroma

Clinical

- Benign neurogenic tumor arising in adrenal medulla and sympathetic ganglia
- Older children (>7 years) and young adults
- Varied presentation; may present as mass or be seen as an incidental finding on CT or MRI or at autopsy
- May be associated with clinical syndromes such as hypertension, diarrhea, and/or hypokalemia (95% of patients have detectable elevations in catecholamine metabolites in urine)
- May be solitary or associated with other neurogenic tumors
- <30% of cases located in adrenal glands
- Most found in posterior mediastinum or in retroperitoneum, particularly presacral region

Macroscopic

- Large (average size = 8 cm), sharply circumscribed firm masses
- Homogenous gray-white appearance
- May contain small hemorrhagic or necrotic areas that may represent less differentiated foci

Microscopic

- Stroma closely resembles neurofibroma, with thin wavy spindled cells (Schwann cells) in collagenous matrix
- Scattered mildly atypical to normal ganglion cells with abundant cytoplasm and multiple nuclei
- May contain lymphocytic infiltrates that may be confused with neuroblasts

Immunohistochemistry

- Stroma immunoreactive with S-100 protein (see Table 11-2)
- Ganglion cells: immunoreactive with neurofilament, chromogranin, and neuron-specific enolase

Electron Microscopy

- Ganglion cells closely resemble those found in normal sympathetic ganglia

Differential Diagnosis

- Neurofibroma:
  - Stroma appears identical, however, no ganglion cells seen
- Ganglioneuroblastoma:
  - Contains less differentiated foci of neuroblasts (with typical microscopic and immunohistochemical features)

Malignant Tumors

Adrenal Cortical Carcinoma

Clinical

- Malignant epithelial neoplasm, commonly associated with hormone secretion
- Typically presents in fourth to fifth decade; F:M = 2:1
- Patients usually present with syndromes associated

with hormone excess (usually Cushing's syndrome or sex steroid overproduction), intra-abdominal mass, or metastases (lungs, retroperitoneal nodes, and liver most common)

- Median survival = 14 months; 5-year survival = 24%

Macroscopic

- Large cortical masses (usually >100 g in adults and >500 g in children); usually >6 cm and only rarely <3 cm
- Cut section pink to tan to yellow, depending on lipid content of tumor cells
- Commonly lobulated with areas of fibrosis, necrosis, hemorrhage, or calcification
- Invasion of adjacent structures

Microscopic

- Varied cellular appearance depending on lipid content: small cells with eosinophilic cytoplasm (lipid-depleted) to large and vacuolated (lipid-laden) ones
- Growth patterns may be alveolar, trabecular, or diffuse.
- Features strongly suggesting malignancy include:
  - High-grade nuclear pleomorphism
  - Frequent mitoses (>5 per 50 HPF), especially atypical forms
  - Broad fibrous bands
  - Necrosis (>2 HPF in diameter)
  - Diffuse growth pattern (comprising >30% of tumor)
  - Capsular or venous invasion
  - Predominantly lipid-depleted (non-clear) cells (<25% clear cells)
- Benign cortical adenomas in pediatric patients more commonly demonstrate high mitotic rate, necrosis, fibrous bands, and nuclear pleomorphism than their adult counterparts

Immunohistochemistry

- Immunoreactive for vimentin, but – for LMWK (see Table 11-2)
- May occasionally show immunoreactivity for neurofilament, S-100, synaptophysin, and neuron-specific enolase

Differential Diagnosis

- Cortical adenoma:
  - Smaller in size (usually 3–6 cm in adults)
  - Well-circumscribed, often encapsulated
  - May show some nuclear pleomorphism
  - No necrosis, increased mitoses, or invasion of capsule or vessels
- Metastatic carcinoma:
  - Common primary sites include lung, breast, gastrointestinal tract, thyroid, and kidney
  - Growth pattern usually solid rather than alveolar or trabecular
  - Immunohistochemistry: immunoreactive for cytokeratin, epithelial membrane antigen, and/or carcinoembryonic antigen
- Melanoma:
  - Exceptionally primary, more commonly metastasis from an occult primary
  - Melanin pigment
  - Immunohistochemistry: immunoreactive for S-100 protein and HMB-45
- Pheochromocytoma:
  - Arising from adrenal medulla with normal adrenal cortex stretched out over its surface
  - Red-brown in color with areas of hemorrhage or cystic degeneration if large
  - Organoid growth pattern with nests of cells ("zellballen") and delicate vascular septa
  - Immunohistochemistry: immunoreactive for neurofilament, chromogranin, synaptophysin, and S-100 (in sustentacular cell staining pattern); – for vimentin
- Liposarcoma
  - Gross appearance white to yellow, poorly circumscribed, with infiltrating edges
  - Malignant cells with spindled to epithelioid appearance
  - Lipoblasts
  - Immunohistochemistry: immunoreactive for vimentin and S-100

Neuroblastoma (Stroma-Poor Neuroblastoma)

Clinical

- Malignant neurogenic tumor composed of immature neuroblasts
- 1 in 7,000–10,000 live births
- 50% of patients are <2 years old, 90% <8 years old; median age = 21 months
- Patients usually present with intraabdominal mass; may rarely be associated with hormonal (catecholamines, vasoactive intestinal peptide) or other paraneoplastic syndromes
- Infants at increased risk include those with fetal alcohol syndrome or fetal hydantoin syndrome
- Prognosis related to number of factors:
  - Good prognostic signs: low stage (I–II), young age (<1 year), favorable histology, aneuploid tumors, <3 N-myc copies per cell, extra-adrenal location
  - Poor prognostic signs: higher stage (III–IV), older age, unfavorable histology, diploid tumor, >10 N-myc copies per cell, adrenal location
- 70% occur in retroperitoneum, usually adrenal gland

- Other sites include mediastinum, head and neck region, and pelvic region
- Common cytogenetic abnormalities include 1p deletions and amplification of N-myc oncogene (associated with poorer prognosis); tumor ploidy affects prognosis
- Associated with Beckman-Wiedemann syndrome and neurofibromatosis

Macroscopic

- Solitary, soft gray, well-circumscribed masses
- Areas of hemorrhage, necrosis, calcification, or cystic degeneration often seen in large tumors

Microscopic

- Cells small and uniform, with little cytoplasm and round, hyperchromatic nuclei with small nucleoli
- Individual cells separated by fine fibrillar eosinophilic matrix
- Cells arranged in sheets, which form vague lobules divided by thin fibrovascular septa
- Homer-Wright pseudorosettes (rings of neuroblasts, 1–2 layers thick, surrounding central area filled with eosinophilic fibrillary material) in 30% of cases
- Necrosis, hemorrhage, and calcifications common findings
- Tumors may show varying degrees of differentiation toward ganglioneuroma, with cellular and nuclear enlargement, prominent nucleoli, and stroma resembling neurofibroma

Immunohistochemistry

- Tumor cells immunoreactive for neuron-specific enolase, chromogranin, synaptophysin, microtubule-associated proteins, neurofilaments, alpha-internexin, secretogranin II, and vasoactive intestinal peptide (see Table 11-2)
- Stromal cells immunoreactive for S-100 protein, glial fibrillary acidic protein, and myelin basic protein

Electron Microscopy

- Neurosecretory granules (50–200 μm)
- Cell processes with microtubules
- Cytoplasmic filaments (100 μm)
- Synapse-like cell junctions

Variants

- Undifferentiated:
  - Contain <5% differentiating cells
  - 5-year survival = 36%
- Differentiating:
  - Contain >5% differentiating cells
  - 5-year survival = 72%
- Neuroblastoma, stroma-rich (see ganglioneuroblastoma)

Differential Diagnosis

- Ewings sarcoma (extraskeletal):
  - Usually older patients (>5 years)
  - Histology very similar to neuroblastoma (may even have pseudorosettes rarely)
  - Immunohistochemistry: cytoplasmic staining with periodic acid-Schiff reaction
  - Electron microscopy: glycogen deposits, no neurosecretory granules
  - Cytogenetics: characteristic t(11;22) translocation
- Nephroblastoma (Wilm's tumor):
  - Microscopically composed of three elements: undifferentiated blastema, mesenchyme, and epithelium
  - Tumors composed largely of blastema may resemble neuroblastoma; need to look carefully for other elements
  - Immunohistochemistry: blastema stains only for vimentin, no reactivity with neuroendocrine markers
- Rhabdomyosarcoma:
  - Areas of hypo- and hypercellularity, characteristic "strap cells"
  - Immunohistochemistry: immunoreactive for actin and desmin
  - Electron microscopy: actin and myosin filaments, no neurosecretory granules or cytoplasmic processes
- Lymphoma
  - Sheets of poorly cohesive cells with lymphocytic to epithelioid appearance; irregular nuclear borders
  - Immunohistochemisty: immunoreactive for T- and B-cell markers (CD3, CD20, leukocyte common antigen); - for neuroendocrine markers (synaptophysin, chromogranin, etc.)
  - Electron microscopy: no cytoplasmic filaments or cell junctions

Ganglioneuroblastoma (Stroma-Rich Neuroblastoma)

Clinical

- Combination tumor representing maturational intermediate between neuroblastoma and ganglioneuroma
- Usually seen in children <10 years, can occur in adults
- Presents as intraabdominal or intrathoracic mass; rarely seen with hormonal syndromes similar to neuroblastoma
- May occur in adrenal gland; more common in extra-adrenal retroperitoneum and mediastinum
- Cytogenetic findings similar to neuroblastoma

Macroscopic

- Varied, depending on relative proportion of fully differentiated and undifferentiated (or differentiating) elements:

- Differentiated variants tend to resemble typical ganglioneuromas (circumscribed firm white-gray masses)
- Undifferentiated variants show large nodular areas grossly resembling neuroblastoma (soft white-gray with areas of necrosis and hemorrhage.

Microscopic

- Differentiated and undifferentiated areas with morphologic features of ganglioneuroma and neuroblastoma, respectively
  - Differentiated: collagenous stroma with scattered atypical ganglion cells
  - Undifferentiated: sheets or nodules of small regular cells with hyperchromatic nuclei

Immunohistochemistry

- Typical for respective elements (see neuroblastoma and ganglioneuroma)

Electron Microscopy

- Typical for respective elements (see neuroblastoma and ganglioneuroma)

Variants

- Nodular (stroma-rich neuroblastoma, nodular):
  - Ganglioneuroma with one or more nodular masses of neuroblastoma
  - Poor prognosis (5-year survival = 18%)
- Intermixed (stroma-rich neuroblastoma, intermixed):
  - Ganglioneuroma with microscopic nests of neuroblasts
  - Good prognosis (5-year survival = 92%)
- Borderline (stroma-rich neuroblastoma, well differentiated):
  - Ganglioneuroma with scattered individual neuroblasts
  - Excellent prognosis (5-year survival = 100%)

Differential Diagnosis

- Neuroblastoma
  - Similar to ganglioneuroblastoma, but neuroblastomatous component usually composes >50% of tumor mass
- Ganglioneuroma
  - No undifferentiated elements seen
  - Lymphocytes within stroma may mimic nueroblasts

TNM CLASSIFICATION OF THYROID CARCINOMAS (1997 REVISION)

- Primary tumor (T)
  - Each category may be subdivided into solitary tumor or multifocal tumor
  - TX: primary tumor cannot be assessed
  - T0: no evidence of primary tumor
  - T1: tumor ≤1 cm in greatest dimension limited to thyroid
  - T2: tumor >1 cm but <4 cm in greatest dimension limited to thyroid
  - T3: tumor >4 cm in greatest dimension limited to thyroid
  - T4: tumor of any size extending beyond capsule
- Regional lymph nodes (N)
  - Regional lymph nodes are cervical and upper mediastinal lymph nodes
  - NX: regional lymph nodes cannot be assessed
  - N0: no regional lymph node metastases
  - N1: regional lymph node metastases
  - N1a: metastasis in ipsilateral cervical lymph node(s)
  - N1b: metastasis in bilateral, midline, or contralateral cervical or mediastinal lymph nodes
- Distant metastasis (M)
  - MX: distant metastasis cannot be assessed
  - M0: no distant metastasis
  - M1: distant metastasis

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Chapter 12

Bone and Joints

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Table of Contents

SKELETAL TRAUMA AND OTHER COMMON CONDITIONS

Heterotopic Ossification

Definition

- Bone formation within soft tissues
- No history of trauma, no known underlying metabolic condition

Clinical

- The most common clinical situation is post-operative ossification in the hip following arthroplasty
- Prevalence: 2–90%, depending on the population studied and the criteria used
- Two types:
  - Central
    - Around the neck of the femur
    - Individual-specific and is unrelated to prosthesis type, cement, or the mobilization regime
    - Strong genetic predisposition in certain populations
    - Radiation and anti-inflammatory drugs have been used to reduce the incidence
  - Lateral
    - Around the trochanter
    - Follows surgery using the lateral (McFarland) approach
    - A misnomer; represents a form of traumatic ossification (myositis ossificans)

Differential Diagnosis

- Metastatic calcification in hyperparathyroidism
- Traumatic ossification (myositis ossificans)

Myositis Ossificans

Definition

- Reaction to trauma; seen most often in soft tissues, but also in a subperiosteal location (subperiosteal hematoma)
- This is a time-honored term, and is considered acceptable despite being neither a muscle nor an inflammatory disorder

Clinical

- Most often represents a localized tissue disruption followed by a hematoma
- The hematoma is organized in a fashion similar to a healing fracture
- Clinically, may present as a painful mass or soft tissue tumor

Microscopic

- The central fibroblastic repair reaction can be alarming
- Zonation with maturation at peripheral
- Ossification commences from the outside to within; the entire mass may be ossified

Differential Diagnosis

- Fibrodysplasia progressiva (previously called myositis ossificans progressiva):
  - An entirely different, genetically related and progressive condition
- Bone forming tumors:
  - Recognition of the nature of the woven bone formed and the overall organization will help establish the correct diagnosis
  - Woven bone is lined by plump osteoblasts without cytologic atypia
  - No sheets of atypical osteoblasts
  - Evidence of maturation toward the periphery

Reflex Sympathetic Dystrophy (Algodystrophy)

Definition

- A condition of severe regional, patchy osteopenia and often pain, following trauma

Clinical

- Associated with trophic skin changes, edema of the extremity, and psychological disturbances
- Must be differentiated from other forms of osteopenia such as bone marrow edema, transient osteoporosis, migratory osteolysis, and idiopathic regional osteoporosis

Microscopic

- Proliferation of fibroblasts within the marrow space
- Bone necrosis and new bone formation may be seen

Osteonecrosis (Avascular, Aseptic, Ischemic Necrosis)

Definition

- The in situ death of bone, presumably from one or more vascular insults

Clinical

- Two main forms:
  - Medullary infarction (marrow cavity and trabecular bone):
    - Usually silent
  - Cortico-medullary infarction (cortex also involved):
    - May be painful and progressive
- Conditions predisposing to osteonecrosis:
  - Trauma, infection, fatigue fractures

- Alcohol abuse
- Dysbarism
- Gaucher's disease
- Connective tissue disorders
- Vasculitis
- Hemoglobinopathies, coagulopathies
- Radiation injury
- Corticosteroid therapy
- Pregnancy
- Aging
- Gout
- Pancreatitis
- Childhood osteochondritides such as Perthe's, Keinbock's, Sever's, Kohler's, Larsen's, Blount's, or Panner's disease

♦ The pathogenesis remains uncertain
♦ The condition is suspected on the basis of clinical history, physical findings, X-rays, and scanning techniques
♦ MRI is especially sensitive for detection
♦ Diagnosis is confirmed by biopsy

Microscopic

♦ Reactive hyperemia in the early course
♦ Fibrovascular proliferation adjacent to the bone
♦ The necrotic bone is walled off, in a fashion similar to sequestrum formation in osteomyelitis
♦ Revascularization of dead bone occurs in a few weeks
♦ Cutting cones carrying blood vessels enter the dead bone, removing it by osteoclastic resorption
♦ At the same time, osteoblasts lay down bone on top of this necrotic fragment
♦ The next stage is unpredictable, depending on the site and extent of damage:
  - May culminate in restitution (complete healing)
  - May lead to the relentless continuation of the repair process that damages the integrity of bone
  - This second course leads to fatigue fractures, collapse of the subchondral bone, cartilage disintegration, and joint deformity

Osteochondritis "Juvenilis"

♦ Refers to the earlier set of eponymic names for avascular necrosis occurring in certain bones
♦ Includes conditions such as Perthe's, Keinbock's, Sever's, Kohler's, Larsen's, Blount's, or Panner's diseases
♦ With the exception of Perthe's disease (which may be associated with constitutional skeletal abnormalities), these conditions are similar to the osteonecrosis occurring in the noneponymic locations

BONE INFECTIONS

Pyogenic Osteomyelitis

Acute Osteomyelitis

Clinical

♦ Infections can reach the bone by:
  - Hematogenous route:
    - Most common
    - An antecedent focus of infection may be present elsewhere
    - Most cases of hematogenous osteomyelitis are confined to the long tubular bones and to children
    - Most frequently seen in a metaphyseal location
  - Direct extension:
    - Has no predisposition in children or in adults

♦ Commonly encountered organisms:
  - Staphylococcus aureus (most common)
  - Escherichia coli, Klebsiella and Pseudomonas species
  - Salmonella (in patients with sickle cell anemia):
    - Results in a cortically based osteomyelitis
  - Treponema, gram – rods, streptococci, hemophilus influenzae and listeria species (occur in neonates)
  - Pseudomonas infections (addicts abusing intravenous street drugs)

Macroscopic

♦ Region is often intensely hyperemic
♦ The pressure exerted by the pus may compress smaller vessels, which may result in additional ischemic damage to the bone
♦ The exudate follows the path of least resistance and exits through the Volkmann canals into the subperiosteal space
♦ In the neonatal age group, the Sharpey's fibers are less well-developed; thus, considerable subperiosteal spread may occur
♦ Medullary spread may cause additional damage
♦ In severe cases, the combination of subperiosteal and

intramedullary spread can cause the entire diaphysis to become necrotic, forming a "ring sequestrum"

Microscopic

- Bone destruction, polymorphonuclear leukocytes, and cell debris

Chronic Osteomyelitis

Clinical

- Although de novo cases also occur, the majority are a result of unresolved acute osteomyelitis
- A protracted course, interspersed with acute exacerbations
- Because of the low levels of causative organisms, cultures are often negative
- Common organisms include:
  - *Staphylococcus aureus*
  - *Streptococci* (group A is more frequent)
  - *Klebsiella* (may cause extensive bone damage)
  - *Aerobacter*, *Proteus, Brucella*, *Staphylococcus epidermidis*, and *Bacteroides*

Microscopic

- Necrotic bone in an inflammatory background
- When the necrotic fragment separates from the adjacent tissue, it is known as a sequestrum:
  - The sequestrum is surrounded by infective granulation tissue
  - Separation of the sequestrum generally takes months to complete
  - The bone is often of cortical origin
- The bone surrounding a focus of chronic osteomyelitis is often dense, and is referred to as the "involucrum":
  - The involucrum is often of periosteal origin
  - The involucrum frequently has several openings of "cloacae" through which exudate, bone debris, and sequestra exit and pass through sinus tracts to the surface
  - Constant destruction of the neighboring soft tissues leads to scarring and squamous metaplasia of the sinus tract
- The microscopic diagnosis of chronic osteomyelitis can be difficult
- The inflammatory infiltrate is often sparse and may mimic the normal elements of the marrow space
- Microscopic recognition of the sequestrum is helpful for the diagnosis of infection:
  - The sequestrum is recognized by virtue of its anucleate nature; often the edges are jagged (because of the action of proteolytic enzymes and osteoclastic action)
  - Overdecalcification of bone during processing can cause the bone to become artificially "anucleate," making the recognition of dead bone particularly difficult

Differential Diagnosis

- Normal marrow:
  - Preservation of normal fat pattern of marrow
  - Lack of fibrous background

Sclerosing Osteitis (Sclerosing Osteomyelitis)

Definition

- The condition of gradual, usually unilateral bony sclerosis, often associated with pain

Clinical

- Constitutional symptoms are infrequent
- Usually affects children
- Most frequent sites include the tibia, jaw, and clavicle

Microscopic

- Non-specific
- Biopsy fails to show inflammation
- Culture results often negative

Chronic Multifocal Recurrent Osteomyelitis

Clinical

- Recurrent episodes of bone pain, erythema, and swelling
- X-rays and bone scans are consistent with osteomyelitis
- Antimicrobial therapy is not helpful
- Usually resolves with time

Microscopic

- Bone biopsies confirm the suspicion of osteomyelitis
- Organisms are usually not isolated
- May be related to the sero-negative spondyloarthropathies

Tubercular Osteomyelitis

Clinical

- Occurs frequently in children
- Occurs in vertebrae, or in long tubular bones in a metaphyseal location
- In adults, vertebrae or epiphyses of the long bones may be involved

Pathology

- May affect the bone, the joints, or (frequently) both
- Often occurs by hematogenous spread

- Usually represents a reactivation of a preexisting primary focus in the lung
- The emergence of multi-drug-resistant tuberculosis and the AIDS epidemic have reemphasized the importance of mycobacterial infections

Microscopic

- Granulomatous inflammation, often with Langerhans'-type giant cells
- Special stains reveal acid-fast organisms
- The disease has traditionally been divided into the "granular" and the "exudative" types

Fungal Osteomyelitis

- Fungal infection of bone is uncommon
- More common infections include:
  - *Blastomycosis*
  - *Coccidiodomycosis*
  - *Actinomycosis*
  - *Maduramycosis*
  - *Sporotrichosis*
- These infections often involve the hands, feet, or craniofacial skeleton

ARTHRITIDES

Osteoarthritis (OA)

- Also termed degenerative joint disease
- Represents failure of the diarthrodial (movable, synovial lined) joint
- Two forms:
  - Idiopathic (primary) OA:
    - Most common
    - No predisposing factor
  - Secondary OA:
    - Attributed to an underlying cause (developmental disorders, metabolic or endocrine conditions, crystal deposition, trauma, infection, avascular necrosis, neuropathic disease, etc.)
    - Pathologically indistinguishable from idiopathic form

Microscopic

- The most striking changes are seen in load-bearing areas of the articular cartilage
- In the early stage, the cartilage is thicker than normal
- The joint surface thins and the cartilage softens with progression
- The integrity of the surface is breached and vertical clefts develop with fibrillation
- Areas of fibrocartilaginous repair may develop
- The articular cartilage is metabolically active and the chondrocytes replicate, forming clusters (termed "cloning")
- Later, the cartilage becomes hypocellular
- Remodeling and hypertrophy of bone are also major features:
  - Appositional bone growth occurs in the subchondral region
  - The abraded bone under a cartilage ulcer may resemble ivory wood (termed "eburnation")
- Growth of cartilage and bone at the joint margin leads to osteophytes (spurs)
- Osteophytes alter the contour of the joint, restricting movement
- Thickening of the joint capsule along with chronic synovitis further restricts joint movement
- Periarticular muscle wasting follows

Neuropathic Arthropathy (Charcot's Joints)

Clinical

- Extremely destructive joint disorder in patients with neurosyphilis
- A consequence of damage to sensory innervation to the joint
- With the decline of tertiary syphilis, other causes of neuropathic joints have now become more important, such as:
  - Diabetes
  - Syringomyelia
  - Amyloid
  - Alcoholic neuropathy
  - Leprosy

Microscopic

- Fragmentation of the joint surface with extensive detritic synovitis resulting from particles of bone and cartilage embedded in the synovium

Crystal Arthropathies

Pathogenesis

- Crystal arthropathy can be caused by endoenous (monosodium urate [MSU], calcium pyrophosphate [hydroxyapatite]) and exogenous (corticosteroid ester

crystals, talc, polyethylene, methylmethacrylate) crystal deposition producing disease by triggering a cascade that results in cytokine-mediated cartilage destruction

Gout and Gouty Arthritis

Clinical

- Gout is the common end point of a group of disorders that produce hyperuricemia
- Marked by transient attacks of acute arthritis initiated by the crystallization of urates within and around joints
- Deposition of masses of urates in joints and other sites, creating tophi
- Factors that may result in the conversion of hyperuricemia into primary gout:
  - Age (gout rarely appears before age 20–30)
  - Duration of the hyperuricemia
  - Genetic predisposition:
    - X-linked abnormalities of hypoxanthine-guanine phosphoribosyl transferase (HGPRT)
    - Multifactorial inheritance
  - Heavy alcohol consumption
  - Obesity
  - Thiazide diuretics
- Gout can result in:
  - Acute arthritis
  - Chronic tophaceous arthritis
  - Gouty nephropathy
  - Tophi in various sites

Microscopic

- Characteristic needle-like crystals that are negatively birefregent under polarized light

Calcium Pyrophosphate Crystal Deposition Disease (Pseudogout, Chondrocalcinosis)

- Three types:
  - Sporadic
  - Hereditary
  - Secondary types linked to:
    - Hyperparathyroidism
    - Hemochromatosis
    - Hypomagnesemia
    - Hypothyroidism
    - Ochronosis
    - Diabetes
- More common at age 50 or older
- Joint involvement may mimic OA or rheumatoid arthritis (RA)
- Pathogenesis is uncertain:
  - Altered activity of the cartilage matrix enzyme produces and degrades pyrophosphate, resulting in its accumulation and eventual crystallization
  - The crystals first develop in the articular matrix, menisci, and intervertebral discs

Rheumatoid Arthritis (RA)

Clinical

- A systemic disease that manifests in the joints as a synovial lesion
- The inflammatory process can be initiated by:
  - Hypersensitivity initiates
  - Antigen-antibody reaction:
    - The antibody coats the cell membrane of lymphocytes and plasma cells, which travel to the synovium and react with the antigen, causing acute inflammatory reaction

Microscopic

- Nonsuppurative chronic inflammation in the capsule of the joint:
  - Hypertrophy and hyperplasia of the synovial cells resulting grossly in a papillary pattern on the surface of the synovium
  - Later, a pannus forms:
    - Combination of proliferating mesenchymal cells and granulation tissue starting at the periphery of a joint and subsequently destroying articular cartilage

METABOLIC BONE DISEASES

Osteoporosis

Definition

- A condition characterized by a reduced amount of normally mineralized bone

Classification

- Postmenopausal (type I)
- Age related (type II)
- Secondary (accounts for ~5% of cases):
  - Can be seen in a variety of conditions:
    - Osteogenesis imperfecta
    - Turner syndrome

- RA
- Systemic mastocytosis
- Hyperthyroidism
- Adrenal disease
- Steroid or heparin therapy
- Chronic alcoholism
- Space travel

Clinical

- ♦ Higher incidence associated with:
  - – Race (Caucasians > African Americans)
  - – Sex (F > M)
  - – Physical inactivity
  - – Slender body build
  - – Smoking
  - – Nulliparity
  - – Early menopause
- ♦ The major clinical symptoms are those of fractures
- ♦ Common sites include:
  - – Spinal vertebral crush fractures
  - – Hip fractures
  - – Colle's or other fractures of the distal radius
- ♦ The pattern of fractures varies slightly in the different osteoporotic groups:
  - – Type I:
    - Vertebra
    - Distal radius
    - Intertrochanteric femoral fractures
  - – Type II:
    - Vertebra
    - Femoral neck fractures
- ♦ Laboratory investigations include the exclusion of other metabolic diseases by assessing:
  - – Serum calcium
  - – Serum phosphate
  - – Alkaline phosphatase
  - – 25-hydroxy and 1,25-dihydroxy-vitamin D
  - – Urinary calcium
- ♦ Biologic markers that are useful for assessing bone turnover:
  - – Bone-specific alkaline phosphatase
  - – Serum osteocalcin
  - – Serum Type I collagen extension peptides
  - – Plasma tartrate resistant acid phosphatase
  - – Urinary levels of hydroxyproline
  - – Urinary pyridinoline crosslinks of type I collagen
- ♦ Pathogenesis:
  - – Postmenopausal osteoporosis:
    - Associated with increased osteoclastic activity
    - May be initiated or maintained by a variety of bone cytokines, perhaps initiated by RANK and RANK-ligand interaction
    - May be genetically predetermined by the polymorphisms of the Vitamin D receptor gene
  - – Age-related osteoporosis:
    - Inefficiency of bone formation in a normal remodeling cycle
    - Less bone is formed than is resorbed with each remodeling cycle throughout life

Microscopic

- ♦ Cortex:
  - – Enlarged Haversian and Volkmann's canals tunneled by osteoclasts
  - – The cortex is thinned:
    - Caused by resorption of the subperiosteal and endosteal surfaces
    - Endosteal resorption results in a blurring of the cortical-cancellous border, referred to as "trabeculization" of the cortex
- ♦ Trabecular bone:
  - – Thinning and perforation of the trabeculae:
    - Perforation is an irreversible process, which occurs when an osteoclast resorbs bone all the way through a trabeculum or when two osteoclasts fortuitously located at opposite ends of the trabeculum meet midway
  - – These thin trabeculae seem to "float" in the marrow space
  - – Increased osteoclastic activity may be seen in "high turnover" (postmenopausal) osteoporosis

Rickets and Osteomalacia

Definition

- ♦ Syndromes (rather than specific disease entities) characterized by a failure of normal mineralization of bone and epiphyseal cartilage
- ♦ Clinically characterized by bone deformities
- ♦ In Rickets (which occurs in children), bone and epiphyseal cartilage is involved

Causes of Rickets and Osteomalacia

- ♦ Deficiency states:
  - – Diet
  - – Lack of sunlight
- ♦ Gastrointestinal causes:
  - – Gastric resections
  - – Biliary and enteric causes

- Renal tubular causes:
  - Hypophosphatemic states
  - Fanconi syndromes
  - End organ defect
  - Renal tubular acidosis
- Unusual causes:
  - Phosphaturic tumors
  - Anticonvulsant therapy
- Renal osteodystrophy:
  - Renal failure

Pathology

- Rickets:
  - A disease of the growing skeleton
  - Affects the epiphyseal plate and bones of children
- Osteomalacia:
  - Occurs in adults, after the growth cartilage has fused and the epiphysis is obliterated
- In both instances, there is insufficient ionized calcium or inorganic phosphate (or both) to mineralize the skeleton, leading to less mineralized bone per unit volume of bone
- There may be less bone overall, but more strikingly, the bone that is present fails to mineralize properly
- Trabeculae are surrounded by unmineralized osteoid, called "osteoid seams":
  - Osteoid seams >12.5 μm are virtually diagnostic
  - Bone histomorphometry has shown that the mineralization lag time is >100 days in rickets/osteomalacia (normal = 80–90 days)
- All rachitic syndromes have similar histology and the individual diagnosis cannot be made on the basis of a bone biopsy
- Stains for aluminium may be considered in renal osteodystrophy
- In rickets, pressure effects cause deformity at the epiphysis-metaphysis junction, resulting in metaphyseal flaring and a disordered physis

Primary Hyperparathyroidism

- This entity was defined in part by von Recklinghausen under the term osteitis fibrosa cystica generalisata
- Most often results from a hyperplasia or adenoma (and rarely a carcinoma) of the parathyroid glands:
  - The diseased gland does not recognize the signal of high serum calcium concentration
  - There is increased production of 1,25-dihydroxy-vitamin D and parathyroid hormone, increasing absorption of calcium from the gut and bone and preventing its excretion in the kidney
  - Simultaneously, there is hyperphosphaturia
  - Serum levels of alkaline phosphatase are frequently high

Microscopic

- The bones are characterized by:
  - Fibrosis of the marrow
  - Osteoclastic resorption
  - Osteoblastic rimming on new and often incompletely mineralized lamellar bone trabeculae (narrow osteoid seams)
  - "Brown tumors":
    - These represent granulation tissue, inflammatory cells, and macrophages containing hemosiderin and giant cell formation
    - There is virtually no bone present in these areas
- Occasionally, cystic change may supervene
- Increased osteoclastic activity is seen in subperiosteal, intracortical, endosteal, subchondral, and trabecular surfaces:
  - Intracortical resorption is characterized by groups of osteoclasts (known as cutting cones) that tunnel through the cortex, enlarging the Haversian and Volkmann's canals:
    - These channels are often expanded to 1 mm or more in some cases, and may be seen radiographically as lucent lines within the cortex
  - Endosteal resorption is also visible radiographically as "scalloping" of the cortex at its marrow interface
  - Subchondral resorption is best seen histologically (and radiographically) at the sacroiliac joint

Paget's Disease (Osteitis Deformans)

Clinical

- Patients above the 4th decade
- Slight male predominance
- Common among the white population of England, France, Austria, Germany, Australia, New Zealand, and the United States
- Rare in Scandinavia, China, Japan, and Africa
- May be uni- or multi-focal
- Most frequent involvement in the axial and the proximal appendicular skeleton
- Less frequent involvement in the ribs, fibulae, and bones of the hands and feet
- Presenting symptoms:
  - Pain
  - Increased width of bone
  - Weight-bearing bones may be bowed or deformed
  - May be asymptomatic and discovered incidentally
  - Hyperdynamic circulation may lead to high output cardiac failure

  - The most common secondary malignancy is osteosarcoma
- Radiographically, three phases can be discerned: lytic, mixed, and blastic:
  - Eventually, the disease "burns itself out" in that particular site
- Laboratory investigations reflect this increased bone turnover through increased levels of serum alkaline phosphatase and urinary hydroxyproline

Etiology

- Possibly related to an infection by a paramyxovirus, similar to measles or respiratory syncitial virus:
  - In situ hybridization studies have localized canine distemper virus (a paramyxovirus) in Pagetic osteoblasts, osteoclasts, and osteocytes
  - The target of the virus is probably the osteoblast; however, the cell-associated virus particles have only been found in the osteoclasts
  - Retroviruses can induce the secretion of IL-6 from fibroblasts and macrophages
  - IL-6 is thought to be important in the pathogenesis of Paget's disease and is implicated in the recruitment and activation of osteoclasts

Microscopic

- Paget's disease is a focal process
- The histologic hallmark is mosaic lamellar bone:
  - Produced by haphazard cement lines (jigsaw-like pattern)
- Lytic phase:
  - Waves of osteoclastic activity
  - Numerous resorptive pits
- Mixed phase:
  - The osteoclasts are admixed with osteoblasts, which line the bone surfaces
  - The marrow adjacent to the bone becomes replaced by loose, vascularized, connective tissue
  - The newly formed bone is initially woven bone, and is later remodeled into lamellar bone
  - As the mosaic pattern becomes prominent, cell activity ceases
  - The fibrovascular tissue is replaced by normal marrow (burnt out phase)
  - Eventually, the bone becomes larger, with thick, irregular trabeculae and porous corticies
- Blastic phase:
  - Characterized by reactive and lamellar bone

Osteopetrosis (Albers-Schönberg Marble Bone Disease)

Definition

- A group of hereditary diseases characterized by osteoclast dysfunction resulting in diffuse, symmetric, stone-like, skeletal sclerosis and abnormally brittle bone

Clinical

- Traditionally, four clinical variants are distinguished; the two most common are autosomal recessive (malignant) type and autosomal dominant (benign) type
- Several variants are known:
  - Some are associated with a deficiency of osteoclast carbonic anhydrase II. Others are associated with a variety of genetic mutations, including mutations of c-src, macrophage colony stimulating factor, etc.
- Patients have a high postnatal mortality
- Survivors have anemia, fractures, and hydrocephalus
- Later in life, patients are prone to cranial nerve problems and recurrent infections
- Extramedullary hematopoisis results in hepatosplenomegaly

Microscopic

- Bones lack a medullary cavity
- The ends of the bones are bulbous (Erlenmeyer flask deformity)
- Neural foramina are small, compressing the exiting nerves
- Primary spongiosa consisting of ossifying cartilage persists
- Medullary cavity contains little or no hematopoietic elements due to overgrowth and accumulation of the primary spongiosa
- Bone is mainly woven and lacks remodeling
- The numbers of osteoclasts may be normal, increased, or decreased

Osteogenesis Imperfecta (OI)

Definition

- A heterogeneous group of conditions characterized by bone fragility and defects in genes encoding collagen type I

Classification

- Type I:
  - Autosomal dominant
  - Associated with defects in pro–α1 or pro-α2 collagen chains
- Type II:
  - Autosomal dominant or recessive
  - Associated with defects in pro-α1 or pro-α2 collagen chains or an unstable triple helix

- Type III:
  - Autosomal dominant or recessive
  - Associated with defects in pro-α2 chains or impaired formation of the triple helix
- Type IV:
  - Autosomal dominant
  - Associated with pro-α2 shortening and unstable triple helix

Microscopic

- Amount of osseous tissue is decreased
- There may be fibromembranous tissue with foci of bone, especially in the severe forms (this finding is more common in the skull)
- In the long bones, the cortices are thin, except at the site of a fracture
- Sparse trabeculae in the medullary cavity
- The inner (cambium) layer of the periosteum may be prominent
- The osteoblasts lining the bone trabeculae tend to be less plump, and more spindled than is normal
- Osteoclasts are sparse
- The growth plates are normal and ossification is not delayed
- The ossification centers may be smaller than normal
- The chondrocytes and cartilage matrix appear normal by light microscopy
- The teeth are abnormal:
  - The mesodermal component is severely affected and may be deficient
  - The ectodermal component is usually normal

Mucopolysacharidoses

Definition

- A heterogeneous group of lysosomal storage disorders, associated with glycosaminoglycan excretion in the urine and accumulation in the tissues
- Deficiencies in enzymes (acid hydrolases) that degrade the glycosaminoglycans
- Cartilage tends to be severely affected

Classification

- Type I (Hurler syndrome):
  - Associated with defects in α-L-iduronidase
  - Results in accumulation of dermatan sulfate
- Type II (Hunter syndrome):
  - Associated with defects in L-iduronosulfate sulfatase
  - Results in accumulation of heparan sulfate

Gaucher's Disease

Definition

- A group of conditions resulting from different allelic mutations in the structural gene of the enzyme glucocerobrosidase

Biochemical Basis

- The gene of glucocerebrosidase is located on chromosome 1q21
- The enzyme cleaves glucose from ceramide

Clinical

- Glucocerobroside accumulates in the phagocytic cells and in the cells of the central nervous system
- Skeletal manifestations include the Erlenmeyer flask deformity of the femur, osteonecrosis of the femoral head, bone infarcts, and pathologic fractures

Other Inherited Conditions

- See Tables 12-1 and 12-2

MUSCULOSKELETAL NEOPLASMS

Bone Cysts

Simple (Unicameral) Bone Cyst (UBC)

Clinical

- Most patients are within the first two decades of life, with male predominance
- Sudden onset of pain from pathologic fracture
- ~80% of cases are seen in either the humerus or femur
- May occur in the ilium and calcaneus in older patients
- Hemodynamic data may help the differential diagnosis from aneurysmal bone cysts and giant cell tumor

X-rays and Imaging Findings

- Geographic, lytic, and cystic lesions, often metaphyseal
- May encroach the epiphysis in skeletally immature individuals
- As the bone lengthens at the physeal end, the cyst may appear to "move" into a diaphyseal location

Microscopic

- An intramedullary cystic cavity, often unilocular, and filled with clear or straw-colored fluid
- Cyst lined by a thin, fibrovascular membrane

Table 12-1. Selected Inherited Conditions of the Skeleton

Condition	*Description*
Fibrodysplasia (Myositis) Ossificans Progressiva	An inherited skeletal disorder characterized by pain and fever in the aponeuroses, fasciae, and tendons leading to fibrosis and ossification in the muscles and fibrous tissues; misinterpretation of biopsy material as aggressive fibromatosis (desmoid) or osteosarcoma should be avoided
Chondrodystrophy and Osteochondrodysplasias	Includes a variety of conditions: Achondrogenesis, Fibrochondrogenesis, Thanatropic dwarfism, Metatropic dwarfism, Kniest syndrome, Achondroplasia, Hypochondropasia, Diastrophic dwarfism (dysplasia), Chondrodysplasia (punctata), Metaphyseal chondrod-dysplasia, Spondylo-epiphyseal dysplasia, and Multiple epiphyseal dysplasia (Dysplasia Epiphysealis multiples)
Melerheostosis	A condition characterized by dense bone formation around the diaphyseal cortex of a tubular bone; the bone formed resembles the dripping of a candle
Osteopoikilosis	A condition characterized by the development of multiple dense spots in many bones; the spots are particularly numerous in the diaphyses and metaphyses of the long tubular bones
Engelman's disease (Progressive diaphyseal hyperostosis)	A condition characterized by symmetrical fusiform enlargement and sclerosis of the shafts of major long bones; one or several bones may be involved; associated with hyperostosis of the skull
Congenital Deficiencies	A variety of focal deficiencies and supernumerary defects in the skeleton

- Irregular fragments of membranous, fibrovascular tissue
- Hemosiderin, granulation tissue or mild focal chronic inflammatory cells
- Pink, cementum-like, rounded material may be seen:
  - These may be examples of the Liesegang phenomenon, forming from diffusion and precipitation of supersaturated solutions

Intraosseous Ganglion

Definition

- An intramedullary, mucin-filled, fibrous-lined lesion

Clinical

- Wide age range, often with pain; incidental finding
- The distal and proximal tibia, femur, ulna, and the hands and feet are commonly involved

X-rays and Imaging Findings

- Geographic lesions that are epiphyseally located and show Lodwick IA margins
- The joint articular surface is usually normal (as opposed to subchondral cysts)

Microscopic

- Mainly myxoid tissue mixed with fibroblasts
- Fibrous tissue may be haphazardly interspersed or be arranged in the form of septa
- The outer layer is often heavily collagenized

Differential Diagnosis

- Extragnathic fibromyxoma
- Chondromyxoid fibromas
- Subchondral cysts of degeneration joint disease

Aneurysmal Bone Cyst (ABC)

Clinical

- Wide age range, but mostly occurs between ages 5–25 years
- Pain of a few weeks duration is most common
- Most primary ABCs of long bones are metaphyseal in location
- Secondary ABCs follow the site of predilection of their primary lesions
- May represent a change secondary to an arterio-venous malformation or to a variety of different bone neoplasms, including:
  - Giant cell tumor
  - Non-ossifying fibroma
  - Giant cell reparative granuloma
  - Fibrous dysplasia
  - Chondromyxoid fibroma
  - Chondroblastoma
  - Osteoblastoma
  - UBC

Table 12-2. Common Locations of Bone Lesions

Epiphyseal Lesions	*Metaphyseal Lesions*	*Diaphyseal lesions*
Chondroblastoma	Chondromyxoid fibroma	Adamantinoma
Giant cell tumor	Chondrosarcoma	Campanacci's disease
(Langerhans' cell histiocytosis)	Fibrosarcoma	
	Osteomyelitis	Ewing's tumor
	Osteosarcoma	Osteoid osteoma
	Malignant fibrous histiocytoma	Osteoblastoma
	Non-ossifying fibroma	(Metastatic disease)
	(Metastatic diseases)	(Lymphoma/myeloma)
	(Lymphoma/myeloma)	(Langerhan's cell histiocytosis)
	(Langerhan's cell histiocytosis)	(Pagets disease)
	(Pagets disease)	(Unicameral bone cyst)
	(Unicameral bone cyst)	(Hemangioma)
	(Hemangioma)	(Enchondroma)
	(Enchondroma)	(Fibrous dysplasia)
	(Fibrous dysplasia)	

Note: Although no entity is entirely specific to a particular location, those in parenthesis have a greater tendency to be particularly promiscuous in their location.

  - Hemangioma
  - Osteosarcoma
- The diagnosis of ABC is essentially that of exclusion
- Some of these lesions spontaneously regress

X-rays and Imaging Findings

- A benign (and probably non-neoplastic) lesion that is often multicystic, rapidly expansile, and locally destructive
- The ABCs of long bones may be eccentric, parosteal (an uncommon location), and central
- In the initial (or incipient) phase, there is a small lytic lesion that does not expand the bone
- In the stable phase, the X-rays have a characteristic picture with expanded bone and a "shell" around the lesion, along with trabeculations coursing within it
- In the healing phase, progressive ossification results in a coarsely trabeculated bony mass
- Fluid/fluid levels on CT scan or MRI are characteristic

Macroscopic

- Grossly (if intact), the lesions have a thin osseous bony shell surrounding a honeycombed mass with cavernous vascular spaces that "ooze" blood like a veritable sponge
- Older cysts may contain sero-sanguinous fluid rather than blood
- A careful search should be made for solid areas that may represent the precursor lesion

Microscopic

- Cavernous spaces that are filled with blood
- Lack the smooth muscle wall and endothelial cells of blood vessels
- Fibrous walls that contain varying proportions of osteoid, chondroid, giant cells, and inflammation
- The mineralizing component may have a chondroid aura, unusual in any other lesion
- The chondroid usually has a fibrillary or chondro-myxoid quality and may be focally calcified
- Mitotic figures may be numerous, particularly in the areas of osteoid formation
- The stromal cells lack anaplasia
- A solid variant of ABC has been described that may be related (if not identical) to a reparative giant cell granuloma

Differential Diagnosis

- Telangiectatic osteosarcoma:
  - The radiographic appearance can occasionally be misleading
  - Presence of cellular anaplasia and atypical mitotic figures
  - Irregular lace-like deposition of osteoid
- Ossifying hematoma and pseudotumor of hemophilia:
  - Subperiosteal hematomas
  - Radiographically, may mimic a parosteal ABC
  - Hemosiderin, zonation, and organized appearance of bone
- Giant cell tumor with ABC component:
  - Older patients
  - Sheets of giant cells
  - No marked osteoblastic change

Bone-Forming Lesions

Osteoid Osteoma

Clinical

- Majority found within the 1st 3 decades
- Presentation:
  - Severe, unremitting pain
  - Relief of pain by aspirin is seen in the majority of patients

X-rays and Imaging Findings

- Classic location: long bones
- The lesion has sclerotic borders on X-rays
- The nidus is lucent or may have a small central radiodense spot of calcification
- Demonstration of the nidus may require tomograms or CT scans
- Osteoid osteomas of the joints can be difficult to detect by plain films
- Technetium pyrophosphate bone scans: "hot" lesion

Macroscopic

- The nidus is red, spherical, and gritty
- Usually can be "shelled" out from the surrounding bone

Microscopic

- A benign neoplasm consisting of a nidus and surrounding reactive, sclerotic bone
- The nidus is a highly vascular, sharply defined osteoblastic proliferation usually <1.5 cm
- Sharp demarcation of the nidus from the surrounding sclerotic bone
- Nidus may be poorly ossified with a richly vascularized stroma
- Nidus may be ossified, with calcific or lacy osteoid composed of osteoid rimmed with plump osteoblasts
- Lack atypical mitotic figures
- The woven bone shows prominent osteoblastic rimming
- 0.1–0.2 cm zone of less trabeculated fibrovascular tissue around the nidus
- Sclerotic compact or spongy lamellar bone surrounds the fibrovascular tissue

Differential Diagnosis

- Clinical and radiologic mimics:
  - Intracortical abscess (such as salmonella infection)
  - Sclerosing osteomyelitis (of Garre)
  - Enostosis
  - Aseptic necrosis
  - Stress fracture
  - Langerhans' cell histiocytosis
  - Metastasis
- Histologic mimics:
  - Osteoblastoma:
    - Osteoid osteomas are always <2 cm
    - The previously termed "giant" osteoid osteomas (>2cm) were probably examples of osteoblastomas
    - Lack zonation and uniformity of maturation
  - Osteosarcoma:
    - Lack osteoblastic rimming
    - Infiltrative permeative margin with entrapped cortical bones
    - Cytologic atypia or atypical mitotic figures
    - Cartilage may be present

Osteoblastoma

Clinical

- Most seen in patients <30 years old, with male predilection
- Pain, but often less intense than that of osteoid osteoma; not relieved by aspirin
- Predilection for the axial skeleton, with the majority of cases affecting the posterior elements of the spine
- Metaphyseal or diaphyseal location

X-rays and Imaging Findings

- Most lesions measure between 4–6 cm
- Uniform, geographic, expansile lucent lesions
- Most lesions are cortical; ~1/3 may be intramedullary
- There may be a stippled calcification in the matrix of the lesion

Macroscopic

- Circumscribed, 2–10 cm
- A secondary cystic change (aneurysmal bone cyst) may supervene

Microscopic

- Benign or sometimes locally aggressive osseous lesions, with microscopic similarity to the osteoid osteomas
- Anastomosing bony trabeculae in a fibrovascular stroma; well-circumscribed
- The edges of the lesion merge into the adjacent bone, imparting an appearance of maturation
- The bony trabeculae are variably calcified:
  - Some lesions are heavily mineralized, whereas others may be made of just osteoid
  - Considerable intralesional variations in trabeculum size exist
    - In the majority of cases, the trabeculae are thick
    - Plump, mitotically active osteoblasts line these trabeculae
- Early lesions may be rich in giant cells
- Chondroid differentiation can occur, but is unusual in the absence of fracture
- Bizarre pleomorphic nuclei (thought to represent a secondary degenerative change) may be present
- Secondary aneurysmal bone cyst-like change occurs in 10% of cases

Variant

- "Aggressive" osteoblastomas:
  - Larger lesions occur in a wider age range
  - A subgroup also termed "malignant" osteoblastomas or "low-grade osteosarcomas" by some authors
  - In a variety of bones
  - Tend to recur
  - Wider and more irregular forms of trabecular pattern of osteoid
    - Occasional areas of non-trabecular (lace-like) osteoid
    - The osteoblasts are large (almost twice the size of normal osteoblasts) with an epithelioid quality
    - The nuclei may have a vesicular "histiocyte-like" appearance

Differential Diagnosis

- Osteoid osteomas
- Low-grade osteosarcoma:
  - The relationship between these two lesions is still unclear
  - The distinction between osteoblastoma and osteosarcoma may be impossible in limited material
  - Lacks sharp circumscription and osteoblastic rimming of the trabeculae
  - Permeation and inflitrative margin
  - Cellular anaplasia and atypical mitotic figures

Osteosarcoma and Its Variants

Clinical

- Osteosarcomas may arise:
  - De-novo (see below)
  - Secondarily on other lesions:
    - Paget's disease
    - Osteogenesis imperfecta
    - Bone infarct
    - Chronic osteomyelitis
    - Fibrous dysplasia
    - Giant cell tumor
    - Osteoblastoma
  - Traditionally, osteosarcomas that arise on an underlying low-grade chondrosarcoma have been termed dedifferentiated chondrosarcoma
  - Secondary osteosarcoma has much higher incidence of flat bone and diaphyseal involvement
- Associated with:
  - Prior radiation therapy
  - Possibly metallic or other orthopedic implants
  - The relationship with trauma is poorly documented and understood
- Some cases of osteosarcoma may be familial:
  - Children with bilateral retinoblastomas
  - Li Fraumini Syndrome (see Chapter 2)

De-novo Osteosarcoma

Clinical

- >85% of patients are <30 years of age
- The long tubular bones, in the active growth phase (2nd decade) (~3/4 of all tumors)
- The metaphyseal region is the site of >85% of these tumors; the diaphysis is the primary site in ~10%
- Epiphyseal location is rare
- Very low incidence of osteosarcoma (in fact of all malignant bone tumors) in the distal appendicular skeleton, such as the hands and feet
- Clinical presentations:
  - Pain is the most frequent presenting symptom, followed by swelling
  - The duration of the symptoms is a few weeks to months
  - Pathologic fractures (5% of cases)

Laboratory

- The serum alkaline phosphatase may be raised in the heavily osteoblastic tumors, but is often normal in the lytic cases
- A rise in alkaline phosphatase following excision may herald a recurrence

X-rays and Imaging Findings

- Radiographic appearances are diagnostic in ~ 2/3 of all cases
- Intramedullary lytic and sclerotic lesion with cortical breakthrough and associated matrix bone formation
- Some lesions may be purely lytic or sclerotic
- The margins vary from focally circumscribed to permeative
- The periosteum is often lifted to form a Codman's angle, "Codman's triangle"
- Rapid growth may result in an "onion skinning" appearance

Macroscopic

- Penetration of the cortex with an extraosseous soft tissue extension
- The intramedullary extension can be extensive and may be underestimated by radiologic studies
- Distant foci, within the marrow cavity of the same bone ("skip" lesions or skip-metastases) are important potential causes of recurrent disease
- Foci of hemorrhage and necrosis are common
- Large blood-filled areas may represent a telangiectatic component
- The periosteal reaction is frequently visible as spicules or lamellae of bone
- Epiphyseal penetration is an uncommon gross finding
- Joint extension may occur along the intra-articular ligaments (ligamentum teres in the femoral head, or the cruciate ligaments in the knee)

Microscopic

- Malignant neoplasms of bone composed of proliferating cells that produce osteoid, at least focally
- High-grade, anaplastic tumors with osteoid production
- Osteoblastic, chondroblastic, and fibroblastic differentiation is common
- The amount of osteoid production can be minimal or absent in otherwise typical osteosarcomas
  - Such lesions may be arbitrarily designated as osteosarcomas as opposed to malignant fibrous histiocytomas
  - Such lesions may produce heavily ossified metastases
- Spindle or oval anaplastic cells with atypical mitotic figures
- "Normalization" is the tendency of the osteoblasts to become smaller and less pleomorphic as they get incorporated into the osteoid
- Osteoid may have variable thickness and degrees of mineralization
- A thin, highly mineralized pattern (filigreed pattern) without osteoblastic rimming is suggestive of neoplastic osteoid
- Some osteosarcomas are composed of epithelioid-appearing cells
  - Rosette formation may give the appearance of gland formation
  - Immunohistochemical stains may be + for epithelial differentiation markers
  - Such osteosarcomas can be also seen as part of the sarcomatous component of a dedifferentiated chondrosarcoma
- Chemonecrosis of the tumor (following neo-adjuvant therapy)
  - Important to recognize and quantitate
  - The appearance of the tumor after chemotherapy depends on its original morphology:
    - Chondroblastic foci appear as acellular chondroid, often with ghost cells in the lacunae
    - Telangiectatic foci appear as acellular blood-filled cysts
    - Osteoblastic foci appear as acellular osteoid matrix
    - Atypical stromal cells may be scattered in all of these foci

Variants

- Osteosarcoma with prominent giant cells
  - Proliferation of uniform giant cells amidst a sarcomatous stoma
  - Osteoid production is usually sparse, encircling mononuclear pleomorphic stomal cells
- Osteosarcomas of the jaw bones (gnathic osteosarcomas)
  - Frequently chondroblastic
  - Thought to have a somewhat better outcome
  - The average age of patients is usually higher
  - The tumors tend to have less anaplasia and are often of a lower grade
  - The differentiation from benign lesions may be difficult in many cases
  - Cartilage differentiation in the jaw should always be viewed with suspicion

Differential Diagnosis

- Osteoblastoma
  - ~10% of osteosarcomas may appear radiologically benign

- Conversely, ~1/4 of osteoblastomas may be worrisome on X-rays
- Osteoblastic rimming favors osteoblastomas
- Lacks infiltration; cellular anaplasia, atypical mitotic figures

–Lacks cartilage

- Fracture callus
  - Callus can be extremely hypercellular, forming compact masses of osteoid in a mitotically active stroma
  - Zonation (a pattern of peripheral ossification with a fibrous or less ossified center)
  - Osteoblastic rimming
  - Lack atypical mitotic figures or significant atypia
  - Lack atypical or frankly malignant cartilage

Multifocal Osteosarcoma

- A small but distinct subgroup of osteosarcomas
- Divided traditionally into synchronous and metachronous types:
  - Synchronous lesions:
    - Arise (or are discovered) simultaneously (within 6 months)
    - May represent multifocal primary osteosarcomas
    - Subdivided into the "juvenile" and "adult" types
      - Juvenile (or childhood-adolescent) form
        - Typically found in the age group 5–17 years
        - Lesions are osteoblastic and of high grade
      - Adult form
        - Mean age 37 years
        - The tumors are better differentiated (resemble the low-grade intraosseous osteosarcoma)
  - Metachronous (asynchronous) lesions:
    - More common than the synchronous variant
    - Several long-term survivors are known

Telangiectatic Osteosarcoma

- Diagnostic criteria for this entity have been varied
- The incidence is low (<10%)
- Radiologically:
  - Purely lytic with features of rapid growth
  - Permeative margins, cortical destruction, and soft tissue extension
  - ABC-like appearance may be seen

Macroscopic

- Hemorrhagic-necrotic mass
- Multicystic with blood-filled spaces

Microscopic

- Two variants are described, corresponding to the gross appearances:
  - Hemorrhagic-necrotic variant
  - ABC-like variant

Small Cell Osteosarcoma

- A microscopically distinct variant of a high-grade intra-medullary osteosarcoma
- May contain hemangiopericytotoma-like pattern
- Hypocellular uniform spindle cells
- Islands of long parallel arranged trabecular bone without osteoblastic rimming
- Small round cells with delicate lace-like osteoid deposition
- Relationship with Ewings sarcoma is unclear
- Glycogen + and may share the t(11;22) chromosomal translocation

Intraosseous Well-Differentiated Osteosarcoma

- An intramedullary variant of osteosarcoma with better prognosis
- Low-grade fibrous and osseous tissue with only minimal cytologic atypia

Differential Diagnosis

- Desmoplastic fibroma: lack osteoid production
- Osteoblastoma:
  - Fibrovascular stroma and osteoblastic rimming
- Fibrous dysplasia:
  - Chinese-letter
  - Haphazard arrangement of short trabecullae
  - Lack osteoblastic rimming

Intracortical Osteosarcoma

- Rare variant
- Arises within and is confined to the cortex of a long bone (diaphysis of tibia and femur)

Periosteal Osteosarcoma

- Formerly called juxtacortical chondrosarcoma
- Predilection for the diaphysis of long bones in young patients (20s–30s)
- Radiographic:
  - Located on the external surface of the cortex and extends into the surrounding soft tissues
  - Predominantly lucent lesions
  - Mineralization, if any, is confined to the base of the tumor adjacent to the cortex
  - Characteristic spiculated (radiating) pattern of calcification (oriented perpendicular to the cortex)

  - Intramedullary extension is absent
- Macroscopic:
  - Sharply demarcated, lobulated, and cartilaginous tumor
- Microscopic:
  - Dominant chondrosarcomatous areas (Grade 2–3) with at least focal osteoid formation

High-Grade Surface Osteosarcoma

- A rare variant of osteosarcoma arising from the outer cortex of the bone
- Intramedullary extension is absent or minimal
- The lesions are often diaphyseal
- Presentation is similar to the high-grade, conventional intramedullary osteosarcoma
- Microscopically similar to conventional high-grade osteosarcoma

Parosteal Osteosarcoma

Clinical

- A well-differentiated, low-grade, fibro-osseous variant of juxtacortical osteosarcoma
- The prognosis is often much better compared to the conventional type
- Presentation:
  - Painless mass in female (usually around 40 years)
  - Most commonly situated in the posterior metaphysis of the distal femur (>2/3 of cases)
  - Other common sites include the tibia humerus

X-rays and Imaging Findings

- A dense mass of bone attached to the outer metaphyseal cortex by a broad base
- Plain X-ray has often underdiagnosed these lesions as osteochondromas
- There is dense mineralization, which is often less prominent peripherally
- The tumor tends to encircle the parent bone, a feature demonstrable by CT scanning
- A lucent line between the mass and the bone (string sign)
- Periosteal new bone is usually absent
- Intralesional lucencies are uncommon, suggesting dedifferentiation
- In dedifferentiated tumors, CT scan may demonstrate satellite lesions and intramedullary extension

Macroscopic

- Large, ossified exophytic mass with a broad base
- Less often, the tumor encircles the bone
- Resemblance to an osteochondroma may be considerable, including the presence of a cartilaginous cap
- The lesions are heavily ossified and may be lobulated

Microscopic

- Long, narrow trabeculae, or ill-defined areas of osteoid and woven bone separated by a fibrous stroma
- The trabeculae may show maturation (normalization), which may result in lamellar bone
- The spaces between the trabeculae are often filled with spindled fibroblastic tissue showing only minimal cytologic atypia
- Most lesions are grade 1
- High-grade areas resembling conventional osteosarcomas should be interpreted as evidence of dedifferentiation

Differential Diagnosis

- High-grade surface osteosarcomas
- Conventional osteosarcomas with a prominent extra-osseous component
- Periosteal osteosarcoma
- Osteochondromas:
  - The extension of the medullary cavity into the extracortical mass
  - Lack an atypical fibrous stroma/osteoid
  - Fat or hematopoietic marrow between trabeculae in continuity with involved parent bone
- Reactive soft tissue and periosteal processes:
  - May be difficult to differentiate on radiologic grounds
  - Such conditions include myositis ossificans and reactive periostitis
  - Evidence of zonation is helpful in diagnosing these conditions as benign

Cartilagenous Lesions

Osteochondroma (Osteocartilaginous Exostosis)

Clinical

- An outgrowth of bone with the combination of medullary and cortical bone
- Projects from the cortical surface and is covered with a cartilage cap
- Most often seen in the first 2 decades of life
- No predilection for gender
- Mostly long bones formed by enchondral ossification
- May originate from a displaced epihyseal cartilage that herniates through a periosteal defect
- Often asymptomatic and incidental findings
- Multiple osteochondromas:
  - Sporadic
  - Familial
    - Termed (multiple) hereditary exostoses or diaphyseal (or metaphyseal) aclasis

  - Autosomal dominant inheritance
  - Associated with a generalized osseous modeling defect
  - Associated with limb growth asymmetry
- Malignant transformation
  - Long-standing osteochondromas rarely show an aggressive (invasive or malignant) change
  - The incidence is probably <1% for solitary osteochondromas and slightly more for multiple osteochondromas

X-rays and Imaging Findings

- Located in the meta-diaphyseal region
- MRI scan is useful for measuring the thickness of the cartilage cap and locating the presence of wide fibrous septae within the osteochondroma
- MRI or CT scan can be used for establishing the continuation of the native medullary cavity into the marrow cavity of the osteochondroma

Macroscopic

- Entirely (extraperiosteally) resected lesions are covered by periosteum
- Well-defined bony stalk, capped by cartilage
- The marrow cavity of the parent bone continues into the osteochondroma
- Cartilage cap >2.0 cm in an adult is suspicious for a chondrosarcoma

Microscopic

- Presence of periosteum over the cartilage cap
- Linear cartilage bar with enchondral calcification
- The chondrocytes:
  - The cells occur in clusters and in lacunae in the superficial portion of the cap
  - Toward the base, the chondrocytes line up, simulating a growth plate
  - Below this, enchondral ossification is often seen
- A spindle cell proliferation occurring within an osteochondroma may be the result of a repair reaction from trauma

Differential Diagnosis

- Chondrosarcoma developing in an osteochondroma
- Parosteal osteosarcoma

Bizarre Parosteal Osteochondromatous Proliferation (Nora's Lesion)

Clinical

- An exophytic outgrowth from the cortex, consisting of a mixture of cartilage, fibrous tissue, and bone
- Occurs in patients 20–35 years of age, without gender predilection
- Predilection for the bones of the hands and feet, especially proximal phalanges of the hand
- Long bone involvement is less common

Macroscopic

- The lesions have a stalk and may have a well-defined cartilage cap
- The mass may sometimes show lobulations

Microscopic

- A triad of cartilage, bone, and a spindle cell element is seen
- The cartilage may form a cap and is often very cellular, with enlarged, bizarre nuclei at the peripheral of the lesion
- The chondrocytes often show bi- or multinucleation
- The interface with the underlying bone is irregular, with admixtures of bone and cartilage
- Occasionally, no cap is seen and the cartilage is admixed with bone and spindle cells
- The bone may show considerable osteoblastic prominence and is more irregular than is typically seen in osteochondromas
- A helpful clue is the blue tinctorial quality of the bone in routine Hematoxylin and Eosin sections
- Fibrous tissue and osteoclast-type giant cells may be intermixed within the lesion

Chondroma

Clinical

- Benign cartilaginous neoplasms occurring in either a central location within the bone (enchondroma) or on the surface (periosteal chondroma)
- There are lesions with overlapping features (enchondroma protruberans)
- The most frequent locations are the metaphysis or diaphysis of the hand and foot bones
- Periosteal chondromas are more frequent in the appendicular skeleton
- Flat bones are less often involved
- Ollier's disease:
  - Multiple enchondromas confined to one limb (unilateral)
  - 1/3 have malignant transformation
  - Often accompanied by parosteal chondroma
  - Associated with ovarian sex-cord stromal tumor
  - Histologically more cellular, more atypia, and more myxoid
- Maffuci's syndrome:
  - Multiple unilateral enchondromas associated with

soft tissue hemangiomas
  - Increased risk of astrocytoma and ovarian cancer (juvenile granulosa cell tumor of ovary)

X-rays and Imaging Findings

- Small lesions with well-defined margins, sometimes with lobulated edges
- Mineralization in the form of semicircles and circles ("Cs" and "Os")
- Often "hot" on technetium bone scans

Macroscopic

- Well-circumscribed, small (3–5 cm) cartilaginous lesions

Microscopic

- Lobules and islands of hyaline cartilage intermixed with normal bone trabeculae and marrow
- The lobular configuration of cartilage is characteristic:
  - The lobules are separated by fibrous or lamellar bony septae
  - These may be rimmed by reactive woven bone or calcification
- Enchondromas in the tubular long bones (excluding the hands and feet):
  - Small chondrocytes lying in lacunae
  - Round, regular nuclei, which are barely visible at low magnification
- Enchondromas of the hands and feet:
  - Can be alarmingly cellular
  - Chondrocytes may be present in clusters or even in sheets
  - Nucleomegaly, binucleation, and slight myxoid change of cartilage
  - Permeation of the cortex of the phalanges, however, is diagnostic of a chondrosarcoma
  - Extreme hypercellularity, nuclear pleomorphism, and extensive myxoid change are suggestive of malignancy
- Periosteal chondromas:
  - Well-demarcated lesions with no tendency to permeation
  - May also show cytologic atypia
  - Myxoid change is unusual
  - Lobules of hyaline cartilage in a fibrous stroma
- Multiple enchondromas:
  - Can also be cellular with spindle-shaped chondrocytes
  - Atypia and myxoid change are worrisome for chondrosarcoma

Differential Diagnosis

- Juxtacortical chondrosarcoma
- Periosteal osteosarcoma

Chondroblastoma

Clinical

- A benign cartilaginous neoplasm with predilection for the epiphysis (giant cell tumor, clear cell chondrosarcoma, osteomyelitis, and eosinophilic granuloma also show epiphysis predilection)
- The majority occur in patients <25 years of age
- Chondroblastomas in unusual locations may occur in older patients
- 20–30% of chondroblastomas occur in flat bones or the short tubular bones
- The most common benign tumor of the foot (in the talus or the calcaneus)
- Occasionally, lesions occur in the cranio-facial skeleton, especially the temporal bone
- Treatment = curettage and packing

X-rays and Imaging Findings

- Lytic geographic lesions, with Lodwick 1A or 1B margins
- Centered in the epiphysis but may grow into the metaphysis
- No matrix production in the majority of cases:
  - Fine matrix calcifications or trabeculations may be seen in ~1/3 of cases

Macroscopic

- Circumscribed, variegated lesions
- A secondary ABC component may be seen

Microscopic

- A spectrum of histologic appearances due to the inconstant amounts of matrix, ABC-like secondary changes and cytological variability
- The chondroblast:
  - Typically, a polygonal to oval cell with a sharp cytoplasmic border and lightly staining or clear cytoplasm
  - Some chondroblastomas lack this feature and may be referred to as the syncitial variant
  - The nucleus is round to oval, often with prominent grooves
  - Reticulin stains surround individual chondroblasts
  - Mitotic figures may be seen, but are not frequent
  - Epithelioid variants of chondroblastomas are comprised of cells with abundant pink cytoplasm
  - Focal aggregates of spindle cells may be seen
  - Scattered osteoclast-type giant cells may be seen
  - ~1/4 of chondroblastomas show a small number of cells with enlarged, hyperchromatic nuclei
    - Not related to an adverse outcome

  - Pigment is often prominent in lesions occurring in the cranio-facial and skull bones
- The matrix:
  - Has an eosinophillic quality in most cases
  - Calcification may be found focally, or more typically surrounding the chondroblast, especially in foci of necrotic chondroblasts
  - A characteristic "chicken wire" pattern of calcium deposition
- Mature chondrocytes are unusual
- Features suggestive of a chondromyxoid fibroma may be seen
- Focal cellular atypia or necrosis can be seen in up to 10% of cases
- Vascular invasion may be present, especially in lesions of the skull bones

Differential Diagnosis

- Giant cell tumor:
  - Generally occurs after the epiphyseal plate closes
  - Mononuclear stromal cells with folded nuclei
- Clear cell chondrosarcomas:
  - Broad sheets of cells with a voluminous clear cytoplasm

Chondromyxoid Fibroma

Clinical

- A benign, but locally aggressive cartilaginous tumor characterized by lobules of spindle-shaped or stellate cells in a myxoid (or chondroid) stroma
- The majority of the patients are <30 years of age
- Mild, transient, often long-standing pain
- Most cases occur in the long bones of the appendicular skeleton, especially the tibia
- 1/4 of cases are seen in the flat bones, especially the ilium
- Involvement of the short tubular bones of the hands and feet is not infrequent

X-rays and Imaging Findings

- Geographic and well-demarcated lesions
- Often eccentric and centered about the metaphysis
- Epiphyseal extension may be seen
- Chondro-myxoid fibromas of the hands and feet are often central and cause expansion of the short tubular bones
- Tumors of the flat bones are often irregularly lobulated
- Matrix calcification in any site should raise suspicion of a chondrosarcoma
- Surface lesions may be heavily mineralized

Macroscopic

- Small, circumscribed, and lobulated lesion with a semitranslucent quality

Microscopic

- Variable and may show several different components in varying proportions
- The chondroid lobules have hypercellular septae surrounding a hypocellular myxoid matrix
- The fibrous component is usually small, and often confined to the septae separating the lobules
- The septae occasionally contain blood vessels, osteoclast type giant cells, and osteoid
- The cells in the septae may be spindle or stellate
- Features suggestive of chondroblastomas may be seen
- The myxoid component within and between the lobules is variably cellular
- Pleomorphic cells are frequent and should not be overinterpreted
- Absence of cellularity in the center of the lobules
- Lack atypical mitotic figures
- Either chunky or fine, lace-like calcification and necrotic foci may be seen

Differential Diagnosis

- Chondrosarcoma;
  - Differentiation may be difficult on morphological ground
  - Both tumors can have a lobular growth pattern, peripheral cellularity, atypical cells, and a myxoid stroma
  - Reactive osteoid can be seen along the edges of the lobules in both lesions
  - Extreme hypercellularity in the central portion of the lobules is a feature of chondrosarcoma
  - Radiographic and clinical features are of utmost importance in differentiating the lesions
  - Features indicative of malignancy
    - Infiltrative margin or radiologic appearance with permeation of the cortex
    - Entrapment of (necrotic) bone
    - Infiltration of the Haversian system
  - Atypical mitotic figures and marked cytologic atypia
  - Invasion into soft tissue

Chondrosarcoma and Its Variants

Conventional Chondrosarcoma

Classification

- Primary:
  - Arising in a previously normal bone

- Secondary:
  - Arising in an underlying benign, usually cartilaginous neoplasm, such as osteochondroma
- According to location within the bone:
  - Central or intramedullary
  - Peripheral (must be differentiated from periosteal osteosarcomas)

Clinical

- A malignant tumor in which the neoplastic cells differentiate to form chondroid but not osteoid
- Occurs in age groups older than de-novo osteosarcomas
- Primary chondrosarcomas have a peak incidence in the 5th to 7th decades
- <2% chondrosarcomas occur in patients <20 years of age
- Presentation:
  - Central chondrosarcomas
    - Pain with or without a mass
  - Peripheral chondrosarcomas
    - Mass with or without pain
- Most frequent involvement seen in the bones of the pelvis and long tubular bones of the appendicular skeleton
- Involvement of the bones of the hands and feet is rare
- Chondrosarcomas are often centered around the trunk and proximal limbs
- ~2/3 of chondrosarcomas occur in the limb-girdles, femora, and humeri
- Chondrosarcomas have a slow biologic evolution, compared to dedifferentiated osteosarcomas
- A minority of chondrosarcomas give rise to highly malignant tumors, such as osteosarcomas, malignant fibrous histiocytomas, fibrosarcomas, etc. (dedifferentiation)
- Cartilagenous tumors of the sternum are almost always malignant, regardless of the histologic appearance
- Chondromas of the hands and feet, perosteal chondromas, enchondromas of Ollier's disease and Maffuci's syndrome, synovial chondromatosis, and soft tissue chondromas of the hands and feet are most often benign, in spite of sometimes alarming cellularity

X-rays and Imaging Findings

- Central chondrosarcomas arise in either the diaphysis or the metaphysis
- Epiphyseal origin and joint involvement is rare, except in the clear cell variant of chondrosarcoma
- Intramedullary spread is common and can be extensive
- Peripheral chondrosarcomas appear as masses protruding from the bone
- Matrix calcifications in the form of "Cs" and "Os" are common in tumors of cartilage origin
- The margins of the lesion can vary from irregular geographic (Lodwick 1) to permeated (Lodwick 3)
- Areas of increased lucency or inhomogeneity within the lesion should raise suspicion of dedifferentiation

Macroscopic

- A lobular large lesion with a hyaline quality
- Foci of hemorrhage, necrosis, and cystic or myxoid change may be present
- The matrix can vary in consistency from firm hyaline cartilage to thin mucus-like cartilage

Microscopic

- Lobules of neoplastic cartilage in a chondromyxoid stroma
- Myxoid cystic change is common
- Necrotic foci can later calcify
- Marked myxoid change, extensive necrosis, or cellularity suggests malignancy
- A low power view suggestive of infiltration or entrapment of native bone is one of the most helpful clues suggesting malignancy
  - The entrapped bone can also appear as islands of (usually necrotic) bone
- Peripheral/secondary chondrosarcomas often lack an infiltrative quality and frequently demonstrate a "pushing" border
- Chondrosarcomas tend to be more cellular than chondromas
- Soft tissue involvement (in the absence of fracture or previous surgery) is a definite sign of malignancy
- Calcification can be present, often around the lobules of cartilage
- Reactive woven bone may be present; however, malignant osteoid is a feature of an osteosarcoma
- When chondrosarcomas supervene on a previous osteochondroma:
  - The thickness of the cartilage cap increases
  - The normal columnar arrangement of chondrocyte columns is lost
  - Nodules of cartilage can sometimes be found in the adjacent soft tissues

Differential Diagnosis

- Chondroblastic osteosarcoma:
  - Identification of malignant osteoid is required for this distinction
  - The woven bone that surrounds chondrosarcoma lobules should not be overinterpreted
  - Osseous metaplasia is not diagnostic of an osteosarcoma
- Tophaceous pseudogout:
  - Finding of polarizable crystals and the presence of a granulomatous response

– Tissue processing for regular histology may dissolve the crystals

Variants

- Dedifferentiated chondrosarcoma:
  - Refers to chondrosarcomas with a high-grade, non-chondromatous sarcoma component presumably arising from a low-grade cartilaginous neoplasm
  - The non-chondromatous component may be
    - Osteosarcoma
    - Malignant fibrous histiocytoma (MFH)
    - Rhabdomyosarcoma
- Clear cell chondrosarcoma:
  - Malignant, but slow-growing tumors composed of neoplastic chondrocytes with abundant clear cytoplasm and a sparse intercellular matrix
  - Foci of conventional chondrosarcoma may also be present
  - Often mistaken clinically as well as histologically for chondroblastomas and osteoblastomas
- Mesenchymal chondrosarcoma:
  - Often occurs in young adults; jaw bone and ribs
  - Prognosis is good
  - Malignant, cartilage-forming tumors that are primarily composed of small, round to oval cells arranged in a hemangiopericytoma-like pattern
  - Small areas of osteoid may be present
  - Abrupt transition to low-grade cartilage from these small round cell areas

Vascular Lesions

Solitary Lymphangioma, Hemangioma, and Skeletal Angiomatosis

- Lymphangiomas and hemangiomas are benign proliferations of lymphatic or vascular channels that occur in and replace bone
- Angiomatosis is a multifocal or diffuse intra-osseous proliferation of benign hemangiomatous or lymphangiomatous channels
- There may be associated extra-osseous vascular malformations or combined "skeletal-extraskeletal" angiomatosis in continuity

Gorham's Disease (Massive Osteolysis)

- Predilection for mandible and rib
- A vanishing or disappearing bone disease resulting in massive osseous resorption
- Characterized by resorption of most or almost all of the bone associated with a proliferation of benign vascular channels
- The difference with skeletal angiomatosis is the extent of involvement
- Involves one or more contiguous bones in contrast to the multifocal nature of skeletal angiomatosis

Hemophilic Pseudotumor

- A tumor-like lesion that may mimic several aggressive bone neoplasms
- May cause massive bone destruction
- Not strictly a vascular proliferation; arise secondary to the large amounts of hemorrhage that occurs in bleeding disorders
- The hemorrhage is often intra-articular and associated with reactive synovitis and degenerative joint disease

Epithelioid (Histiocytoid) Hemangioendothelioma

- A low-grade malignant neoplasm composed of endothelial cells with conspicuous cytoplasm
- A variable degree of vasoformative features varying from vacuolization of cells to well-formed vascular channels
- Patients often have concomitant cutaneous, systemic, or soft tissue disease
- Multifocal disease is not uncommon
- Soft tissue or lung "metastases" should raise the question of possible multifocal primary tumors

Angiosarcoma

- A high-grade (sometimes surface) sarcoma of bone composed of cytologically malignant endothelial cells
- Multifocality is common
- Lytic, destructive, permeated lesions with frequent soft tissue extension
- Areas of well-formed anastomosing vascular channels lined by atypical endothelial cells, with large vesicular or hyperchromatic nuclei
- The vasoformative nature may not be evident in other solid, poorly differentiated areas

Hemangiopericytoma

- A potentially low-grade malignant vascular tumor consisting of pericyte-like cells with a prominent vascular pattern
- Occasionally, a paraneoplastic syndrome of hypophosphatemic osteomalacia may be present
- A variety of tumors can exhibit hemangiopericytoma-like areas:
  - Synovial sarcoma
  - Mesenchymal chondrosarcomas
  - MFH
  - Small cell osteosarcoma
  - Solitary fibrous tumor

Glomus Tumor

- A benign, highly vascular tumor composed of small, uniform, specialized smooth muscle cells resembling those of the glomus body
- Osseous glomus tumors are less frequent than their soft tissue counterparts
- Most commonly occur in the distal phalanges

Vascular Tumors in Immunocompromised Patients

- Both Kaposi's sarcoma and Bacillary angiomatosis have been described in bone

Giant Cell Lesions

Giant Cell Tumor (Osteoclastoma)

Clinical

- Giant cell tumors are more common in the skeletally mature adult population
- Peak incidence in the 3rd decade; occur in the region of the epiphysis
- Complaints are usually non-specific; there may be pain or a mass
- ~10% of patients present with a pathologic fracture

Laboratory

- Serum chemistries are generally normal
- Elevated serum calcium should raise the possibility of hyperparathyroidism
- Elevated serum alkaline phosphatase should raise the possibility of Paget's disease

Location

- ~1/2 of all giant cell tumors arise around the knee;
  - Other common sites include the distal radius, proximal femur, proximal humerus, and distal tibia
  - The flat bones most commonly involved are the sacrum and pelvic bones
- Most giant cell lesions of the gnathic skeleton are thought to be giant cell reparative granulomas rather than true giant cell tumors

X-rays and Imaging Findings

- Most lesions are epiphyseal, with frequent metaphyseal extensions
- 15% of patients are <20 years of age
- The tumors occur (for this age group) in a metaphysical or epi-metaphysical location
- Lytic lesions with Lodwick IB or IC margins
- May show lesional trabeculations
- Aggressive periosteal reactions and calcifications (sunburst, onion-skinning or Codman's angles) are not features of the giant cell tumor
- Lesions extending into the soft tissue often have a thin rim of bone ("egg-shell")
- Enneking's system
- Three stages of tumor:
  - Benign latent tumors:
    - Devoid of features of local aggressiveness
  - Benign active tumors:
    - Symptomatic
    - Show bone expansion on imaging studies
  - Aggressive tumors:
    - Correspond to the hypervascular lesions that erode into the soft tissues
    - May have an associated pathologic fracture

Macroscopic

- Hemorrhagic with focal aneurysmal bone cyst-like areas

Microscopic

- A locally aggressive neoplasm characterized by large numbers of osteoclast-type giant cells uniformly distributed in a population of plump, epithelioid, or spindle cells
- The diagnosis is made on the background population of stromal cells:
  - Stromal cells are round to oval, occasionally spindled, with storiform pattern
  - Nuclei resembling those of the giant cells
  - Mitotic figures may be abundant (2–3 per high power field)
  - No cytologic features of malignancy
- Giant cells are numerous and diffusely distributed with a few to hundreds of nuclei
- Occasional cases may have broad bands of collagen coursing throughout, especially in recurrent tumors

"Malignant Giant Cell Tumor"

- The term has been used;
  - To designate true bone sarcomas rich in giant cells
  - To describe a "dedifferentiated" giant cell tumor
  - To describe giant cell tumors that have metastasized
- The term is confusing and it is best to avoid its use

Differential Diagnosis

- Giant cell reparative granulomas:
  - Giant cells tend to be aggregated, mostly around areas of hemorrhage with less nuclei
  - The stroma is fibrotic, with hemorrhage and hemosiderin deposition
  - Foci of reactive bone are more common
- Non-ossifying fibroma:
  - Spindled stromal cells, stromal fibrosis, and xanthomatous foamy macrophages are more prominent

  - Occur in metaphysis of pediatric patients (rather than epiphysis)
- Benign fibrous histiocytomas:
  - A diagnosis of exclusion
  - Lack sheets of mononuclear stromal cells
- Aneurysmal bone cysts:
  - Non-epiphyseal tumor
  - Differentiation from a true ABC may be difficult in the spine
  - The Armed Forces Institute of Pathology tends to interpret most such cases as giant cell tumors with secondary ABC formation
- Osteosarcoma with prominent giant cells:
  - Osteoid production may be minimal, limited to thin strands encircling mononuclear pleomorphic stromal cells
  - The stromal cells usually have hyperchromatic nuclei, often with numerous atypical mitotic figures
  - The radiographic pattern suggests a permeative growth, not extending into the epiphyses
- Metastatic carcinoma:
  - Cytokeratin +

Giant Cell Reparative Granuloma

- A benign, reactive intraosseous proliferation characterized by granuloma-like aggregates of giant cells in a fibrovascular stroma
- The lesion is commonly seen in the gnathic skeleton
- Cherubism occurring bilaterally in the jaws of children, as well as the "solid" aneurysmal bone cyst may be other entities that are related to the giant cell reparative granuloma

Differential Diagnosis

- Giant cell tumor:
  - More uniform distribution of giant cells with more nuclei
  - Characteristic stromal mononuclear cells
  - Less stromal fibrosis and hemorrhage

Fibrous Lesions

Desmoplastic Fibroma

- Considered to be the bone counterpart of the soft tissue aggressive fibromatosis
- A non-metastasizing, but locally aggressive lesion
- Composed of cytologically typical fibroblasts in an abundantly collagenized stroma

Fibrosarcoma

- A malignant spindle cell lesion that exclusively exhibits fibrous differentiation
- Lacks osteoid and chondroid matrices
- The skeletal site distribution is similar to osteosarcoma
- The age of the patients is more evenly distributed from the 2nd to the 7th decades

Fibro-Histiocytic Lesions

Benign and Atypical Fibrous Histiocytoma

- Several lesions show common histologic features of a storiform pattern, histiocyte-like giant cells, foam cells, and a polymorphic infiltrate
- Such lesions are often grouped together under the general heading of benign fibrous histiocytomas
- These lesions may be unrelated to each other or to histiocytes

Malignant Fibrous Histiocytoma (MFH)

Clinical

- Wide age range with no predilection for gender
- Presentation: pain or a mass
- Some lesions arise in the setting of orthopedic implants, Paget's disease, fibrous dysplasia, and bone infarcts
- Associated with a pathologic fracture in up to 25% of cases

X-rays and Imaging Findings

- The metaphyseal regions of long bones are the most frequently involved
- Ill-defined, lytic lesions
- Cortical expansion and breakthrough with minimal periosteal reaction

Macroscopic

- A variegated tumor with hemorrhage and necrosis
- Margins are frequently permeative

Microscopic

- May exhibit a variety of patterns similar to soft tissue MFH
- Multinucleated malignant giant cells are present in most cases
- Histiocytic cells with grooved nuclei are frequent
- Fibrosis is variable
- Spindle cell areas with a storiform arrangement are common
- Chronic inflammatory cells are often seen
- Lack malignant osteoid or low-grade areas

Immunohistochemistry

- S100 protein ±, cytokeratin – (or focal +)

Differential Diagnosis

- Fibrosarcomas:

  - The fasicular arrangement or herringbone pattern
- Osteosarcoma:
  - Areas of malignant osteoid
- Metastatic spindle cell carcinoma and melanoma:
  - Immunohistochemistry is useful

Other Mesenchymal Lesions

Metaphyseal Fibrous Defect (Non-Ossifying Fibroma)

Clinical

- The incidence of these lesions may be age related
- Up to 35% of all children (if screened) are thought to have these lesions; most common between the ages of 4–8 years
- The majority of the lesions in this group are <0.5 cm in size
- The vast majority of lesions occur in the distal femur, distal and proximal tibia, and fibula

X-rays and Imaging Findings

- Most lesions are geographic, lytic lesions with Lodwick IA margins
- Varying amounts of sclerosis within the lesion in the healing phase

Microscopic

- Intracortical proliferation of fibrous tissue and histiocytes
- Predominantly fibrous lesions, often with a storiform arrangement
- Foamy histiocytes (xanthoma cells), hemosiderin-laden macrophages, and multinucleated giant cells
- Reactive woven bone may be present in the presence of fracture or in the healing phase

Differential Diagnosis

- Benign fibrous histiocytoma:
  - Intramedullary location, adult

Fibrous Dysplasia (FD, Jaffe-Lichtenstein Syndrome)

Clinical

- Mono-ostotic FD (80%):
  - May be seen at any age (usually <30 years old)
- Poly-ostotic FD (20%):
  - Generally presents before the age of puberty
- Presentation:
  - Pain, pathologic fracture, deformity (especially gnathic or upper femoral FD)
  - May be asymptomatic
  - Secondary sarcomas rarely develop
- Associated syndromes:
  - McCune-Albright syndrome
    - Poly-ostotic FD with macular skin lesions, precocious puberty, with or without fibromyxomatous soft tissue tumors
  - Mazabraud syndrome
    - Associated with a soft tissue or intramuscular myxoma
- Location:
  - Mono-ostotic
    - 33% involve the crani-facial bones
    - 33% involve the tibia and femur
    - 20% involve the ribs
  - Poly-ostotic
    - Femur, tibia, and pelvis are commonly involved
    - Small bones of the hands and feet, the ribs, and the skull may also be involved
- Pathogenesis:
  - Somatic point mutation in the α subunit of the GTP binding protein results in activation of GTPase in the absence of receptor activation

X-rays and Imaging Findings

- Intramedullary, geographic lesions with Lodwick 1A or 1B margins and a "ground-glass" matrix
- The lesions are intensely hot on bone scans

Microscopic

- Trabeculae of woven bone in a background of moderately cellular fibrous tissue
- The trabeculae often obtain a variety of shapes (Cs, circles, etc.) ("Chinese-letters")
- Osteoid tends to merge into the background ("metaplastic")
- Osteoblasts are interspersed in the woven bone, but are not conspicuous around the trabeculae
- Small foci of lamellar bone may be seen
- The fibro-osseous proliferation may show an infiltrative pattern at the junction with non-lesional bone
- The fibrous stroma may be highly or sparsely cellular, myxomatous, or show considerable collagenization
- The fibroblasts usually have plump, ovoid nuclei
- Multinucleated osteoclast type giant cells may be present
- Cartilage with peripheral enchondral ossification may be present
- Collections of foam cells are common

Differential Diagnosis

- Osteofibrous dysplasia:
  - A cortically based lesion
  - Most often affects the tibia or fibula in children (often <5 years)

- Reactive woven bone
- Osteoblastic rimming is more prominent

♦ Well-differentiated intraosseous osteosarcoma:
- The stromal cells have larger nuclei with cytologic atypia and atypical mitotic figures

♦ Desmoplastic fibroma:
- Usually heavily collagenized with prominent osteoblast rimming

Campanacci's Disease (Osteofibrous Dysplasia)

♦ A cortically based fibro-osseous proliferation

♦ Predilection for the tibia (and less frequently fibula) in children and infants

Fibrocartilaginous Mesenchymoma

♦ Consists of a combination of bone, spindle cells, and cartilage, predominantly in the chest wall

♦ The cartilage has a characteristic appearance of epiphyseal plate formation

♦ A dense, spindle cell proliferation is seen between well-formed bony trabeculae

♦ No or little collagen

Adamantinoma

♦ A low-grade malignant neoplasm with epithelial differentiation

♦ Shows marked predilection for the tibia

♦ Controversial relationship with Campanacci's disease or osteofibrous dysplasia

Ewing's Sarcoma

Clinical

♦ Affects patients in the first 2 decades of life

♦ Localized pain and a mass with fever, leukocytosis, and a raised sedimentation rate

♦ Up to 10% of patients may have skeletal metastases at the time of presentation

♦ Most often involves the diaphysis of long tubular bones (femur) as well as some flat bones (pelvis and ribs)

♦ Characteristic chromosomal translocation: t(11;22) (also seen in primitive neuroectodermal tumor [PNET] and ASKIN tumor of chest):
- Occurs in 85% of patients
- The EWS gene (located on chromosome 22q12) is translocated to the FL1 (a gene of the ETS family located on chromosome 11), resulting in the formation of a chimeric protein product

♦ A second, t(21;22), translocation has been identified in 15% of patients:
- Fusion of the EWS gene with a different member of the ETS family, the ERG gene located at chromosome 21q22, resulting in a chimeric EWS/ERG protein product

X-rays and Imaging Findings

♦ Ill-defined, lytic lesions with permeative margins

♦ A periosteal reaction of the onion-skin, sunburst, or other rapidly growing type

♦ A soft tissue component is detected by CT or MR scans

Microscopic

♦ Classic form:
- Sheets and large nests of uniform, small, round to polygonal cells with scanty cytoplasm
- The chromatin is finely dispersed, usually with no nucleoli
- Variable number of mitotic figures
- Perivascular cuffing may be evident in areas of necrosis
- Cytoplasmic glycogen, demonstrated by the PAS stain, is evident

Variants

♦ Large-cell type pattern:
- Cells may be larger and may have nucleoli

♦ Filigree pattern:
- Bi-cellular architecture, separated by stroma

Immunohistochemistry

♦ Mic-2 (CD99 or HBA 71) + (+ in PNETs, some rhabdomyosarcomas, acute lymphoblastic leukemia, pancreatic islets, and ependymoma)

♦ Vimentin +, CK –/+, neurofilament +, synaptophysin –/+, NSE ±

Electron Microscopy

♦ Nuclei with euchromatic pattern

♦ Scant cytoplasmic organelles and glycogen lake

Differential Diagnosis

♦ Small cell osteosarcoma and mesenchymal chondrosarcoma:
- Production of malignant osteoid or cartilage matrices

♦ Lymphoma:
- LCA +

♦ Metastatic neuroblastoma:
- More common than Ewing's sarcoma
- Patients are usually <5 years of age
- Homer-Wright pseudo-rosettes, pink fibrillary background, ganglion cell differentiation
- Neuritic cell processes containing neurofilaments, neural tubules, and dense core granules by electron microscopy
- Increased catecholamine metabolite levels in neuroblastoma

  - Demonstration of an adrenal mass on CT scan
- Primitive neuroectodermal tumor (PNET):
  - An entity closely related to Ewing's sarcoma, with neuroectodermal differentiation
  - Homer-Wright rosettes
  - Immunohistochemistry:
    - NSE +, synaptophysin +, neurofilament +, Mic-2 +
  - Ultrastructural evidence of dense core granules
  - Age/sex distribution and radiologic features are similar to Ewing's sarcoma

Conventional Chordoma

Clinical

- A low-grade malignant tumor occurring predominantly in the axial skeleton in the region of the embryonic notochord
- Particular predilection to the caudal and cranial extremes
- The clivus and the sacrum are the most common sites
- Vestigial rests of notochord-like tissue located in the spheno-occipital region are sometimes found and termed ecchordosis physaliphora

Microscopic

- Lobulated lesions with a myxoid background
- Cords, sheets, or occasionally haphazardly arranged cells
- Vacuolated cytoplasm (physaliphorous cells)
- Some cells may have abundant eosinophillic cytoplasm or may mimic signet ring cells
- Nuclear pleomorphism is mild and mitotic activity low to absent

Chondroid Chordoma

- A variant of conventional chordoma with foci of cartilaginous differentiation

Plasma Cell Dyscrasias (Plasmacytoma/Multiple Myeloma)

Clinical

- Most common tumor of the bone
- Pathogenesis involves osteoclastic activation by IL-6
- Multiple myeloma:
  - There may be bone lesions, marrow plasmacytosis, or foci of plasma cells
  - Secretion of monoclonal immunoglobulin chains into the blood
  - Anemia, bone pain, pathologic fracture, neurologic abnormalities, renal failure, and amyloid deposits are some other features
- Plasmacytoma:
  - Frequently, only a single deposit of clonally proliferating plasma cells
  - With or without secretion of immunoglobulins into the blood
- POEMS syndrome:
  - A variant consisting of sclerotic bone lesions along with polyneuropathies, endocrine abnormalities, and skin changes

X-rays and Imaging Findings

- Lytic (punched out) lesions in the diaphysis or metaphysis
- The radiological differential diagnosis:
  - Metastatic carcinoma
  - Malignant lymphoma
  - Hyperparathyroidism

Microscopic

- Sheets or aggregates of atypical plasma cells with a pink cytoplasm
- Multinucleated nuclei and prominent nucleoli may be present
- Amyloid deposits may be seen

Differential Diagnosis

- Osteomyelitis
- Malignant lymphoma

Non-Hodgkin's Lymphoma

- Bone lymphomas are very uncommon before the second decade
- Osseous lymphoma lesions are far more common as a secondary rather than a primary form of involvement

Langerhans' Cell Histiocytosis (LCH)

Clinical

- Terms such as histiocytosis X, eosinophilic granuloma, Letterer-Siewe disease, Hand-Schuller-Christian disease, etc. have been used
- The cells bear ultrastructural resemblance to Langerhan's cells of the skin, with the characteristic "Birbeck" granules
- Members of the group of the monocyte, phagocyte, and immune-regulator effector cell system (M-PIRE system)
- A clonal, neoplastic rather than a reactive process
- More common in the first three decades of life, although no age is completely exempt
- Pain and swelling are the most frequent presentations
- Systemic symptoms include diabetes insipidus, exophthalmos, skin lesions, and mastoiditis

X-rays and Imaging Findings

- Lytic, geographic lesions occasionally showing bony expansion

- Multiple punch out lesions

Microscopic

- Proliferation of histiocytoid cells with variable amounts of cytoplasm
- The cell borders may be well-defined or syncytium-like
- The nuclei have characteristic "grooves" and may be reniform or coffee-bean like
- Multinucleated giant cells may be present
- A variable number of mitotic figures may be seen
- Associated inflammatory response, often rich in eosionphils
- Lipid-laden histiocytes are sometimes seen

Immunohistochemistry

- S-100 protein +, CD1a+

Differential Diagnosis

- Granulomatous inflammation
- Osteomyelitis:
  - May be particularly difficult to distinguish on X-rays
  - Necrotic bone trabeculae
  - Predominantly neutrophil with less eosinophil
  - Frequently involves the skull
  - S-100 protein –, CD1a –
- Hodgkin's disease:
  - The diagnostic Reed-Sternberg cells
  - Distinct immunohistochemical profile

Erdheim-Chester Disease

- A condition of unknown cause that may be related to Langerhan's cell histiocytosis
- Most patients are male
- Presentation: weight loss and bone pain; may be asymptomatic
- Bilateral, symmetric sclerosis of the meta-diaphyseal regions of the long bones

Metastatic Bone Disease

Clinical

- Young children:
  - Neuroblastoma is most common
- Older adults:
  - Metastatic carcinoma predominates
- Most frequent primary sites:
  - Lytic lesions (majority of lesions):
    - Kidney
    - Thyroid
    - Gastrointestinal tract
  - Blastic lesions:
    - Prostate
    - Carcinoid tumors
    - Medulloblastoma
  - Blastic or lytic:
    - Breast
- Adult patients commonly present with pain, swelling, tenderness, or pathologic fracture
- The bones of the axial skeleton and proximal appendicular skeleton are more frequently affected
- IL-1, IL-6, TGF-β, PDGF, plasminogen activator, and bone morphogenetic proteins (BMPs) may be involved

X-rays and Imaging Findings

- Blastic, lytic, or mixed lesions
- Periosteal reactions are infrequent
- Lesions are often geographic and occasionally expansile

Macroscopic

- Metastatic lytic tumors tend to be more sharply demarcated
- Other metastatic tumors tend to be exquisitely vascular (kidney and thyroid tumors)
- Tumors can vary from hard, bony tumors to soft, fleshy, or friable

Microscopic

- Well-differentiated metastatic tumors do not pose a problem
- Renal cell or thyroid carcinomas can often be diagnosed without immunohistochemical stains
- Mucicarmine or immunostains for epithelial markers are helpful
- Reactive bone formation may mimic osteosarcoma
- Some sarcomas can be ± for epithelial markers such as cytokeratin (leiomyosarcomas, MFH, epithelioid osteosarcomas, epithelioid hemangioendotheliomas, etc.)

STAGING OF MUSCULOSKELETAL NEOPLASMS

- The system uses the GTM approach (Grade, SiTe, Metastasis) (Enneking system)
  - Grade:
    - G0: Benign
    - G1: Low grade
    - G2: High grade
  - Tumor site:
    - Particularly important
    - T1: Intracompartmental locations, including:
      - Intraosseous
      - Intraarticular
      - Paraosseous
      - Intrafascial (ray of hand, volar compartment of forearm, etc.)
    - T2: Extracompartmental locations
      - Evidence of soft tissue or fascial extension
      - Certain anatomic locations are always considered to be T2 locations
        - Popliteal and antecubital fossa
        - Femoral triangle
        - Mid and hind foot
        - Mid hand
        - Intrapelvic locations
        - Axilla
  - Metastasis:
    - M0: Absent
    - M1: Present

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Chapter 13

Soft Tissue Tumors

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Table of Contents

FIBROUS TUMORS

Classification of Fibrous Tumors

- See Table 13-1

Benign

Nodular Fasciitis

- Common, self-limiting, reactive proliferation of fibroblasts
- Histologically often mistaken for sarcoma

Clinical

- Typically, rapidly growing, often painful or tender subcutaneous nodule
- Duration: variable, most <10-12 weeks
- Most common in adults, 20-40 years; no sex predilection
- Common sites: upper extremities and trunk; head and neck in children
- Self-limiting, usually local marginal excision; 2% local recurrence

Macroscopic

- Well-circumscribed or stellate mass, usually <3 cm in diameter
- Cut surface: myxoid, centrally cystic or fibrous (depending on duration)

Microscopic

- Cellular myofibroblastic proliferation in short interweaving fascicles
- Loose, myxoid collagenous stroma (feathery appearance)
- Plump nuclei with occasional prominent nucleoli, no atypia
- Normal mitoses may be numerous
- Delicate thin-walled vessels (granulation tissue-like)

Table 13-1. Classification of Fibrous Tumors

Benign

Nodular fasciitis

Variants:

Ossifying fasciitis

Intravascular fasciitis

Cranial fasciitis

Proliferative fasciitis

Proliferative myositis

Ischemic fasciitis (atypical decubital fibroplasia)

Keloid scar

Elastofibroma

Fibroma of tendon sheath

Nuchal fibroma

Nasopharyngeal angiofibroma (see Head and Neck tumors)

Dermatofibroma (see Skin tumors)

Angiomyofibroblastoma (see Vulval tumors)

Myofibroblastoma (see Breast tumors)

Solitary fibrous tumor

Pediatric

Fibrous hamartoma of infancy

Infantile myofibromatosis

Variant: Solitary myofibroma

Fibromatosis colli

Juvenile hyaline fibromatosis

Infantile digital fibromatosis (inclusion body fibromatosis)

Infantile fibromatosis (desmoid-type)

Gingival fibromatosis

Calcifying aponeurotic fibroma

Calcifying fibrous pseudotumor

Fibromatoses

Superficial fibromatoses

Palmar fibromatosis (Dupuytren's contracture).

Plantar fibromatosis (Ledderhose's disease)

Penile fibromatosis (Peyronie's disease)

Knuckle pads

Deep fibromatoses (desmoid tumors)

Extra-abdominal fibromatosis (extra-abdominal desmoid)

Abdominal fibromatosis (abdominal desmoid)

Intra-abdominal fibromatosis (intra-abdominal desmoid)

Malignant

Fibrosarcoma

Variant: Infantile fibrosarcoma

- Extravasated red blood cells and scattered inflammatory cells
- Hyalinized stroma (variable)
- Multinucleated giant cells and reactive new bone formation (rare)

Immunohistochemistry

- Vimentin +, muscle-specific actin +, smooth muscle actin +
- Desmin –, S-100 protein –
- CD 68 ±

Variants

- Ossifying fasciitis (fasciitis ossificans)
  - Periosteal location
  - Features of both nodular fasciitis and myositis ossificans
- Intravascular fasciitis
  - Involves small or medium-sized veins or arteries
  - Predominant or focal intravascular growth
- Cranial fasciitis
  - Occurs predominantly in infants
  - Involves soft tissue of the scalp and underlying skull

Differential Diagnosis

- Sarcomas:
  - Rarely grow as rapidly, larger size and deep location
  - More cellular, densely packed, more nuclear atypia +/- necrosis
- Fibromatosis:
  - Larger, more infiltrative growth, usually involve skeletal muscle
  - Fascicular pattern with abundant collagen, slender fibroblasts
  - Less frequent mitoses
- Benign fibrous histiocytoma:
  - Whorled or storiform growth pattern, more polymorphous
  - Usually actin-

Proliferative Fasciitis

Clinical

- Peak incidence: 40-70 years; M:F equal
- Common sites: extremities, especially forearm and thigh
- Like nodular fasciitis grows rapidly within two or three weeks

Macroscopic

- Poorly circumscribed, subcutaneous, gray-white mass; 1-5 cm

Microscopic

- Similar to nodular fasciitis
- Numerous basophilic giant cells (ganglion cell-like)
- Septal distribution in subcutis

Immunohistochemistry

- Ganglion-like cells are actin negative

Differential Diagnosis

Pleomorphic rhabdomyosarcoma

- Rarely subcutaneous; more cytological atypia; atypical mitoses

Proliferative Myositis

Definition

- Deep or intramuscular counterpart of proliferative fasciitis

Clinical

- Peak: 5th and 6th decades; M=F
- Solitary, rapidly growing lesion, <4 weeks duration
- Mainly involves flat muscles of trunk and shoulder girdle
- Outlook is excellent; recur rarely

Macroscopic

- Poorly demarcated; 1-6 cm in diameter
- Scar-like induration involving muscle and overlying fascia

Microscopic

- Similar to proliferative fasciitis
- Along fibrous septa and between individual muscle fibers (uninvolved)
- Checkerboard appearance with atrophy of muscle fibers
- Foci of metaplastic bone or cartilage (10%)

Differential Diagnosis

Sarcoma

- More localized and does not preserve muscle fibers
- More cytological atypia and pleomorphism

Ischemic Fasciitis (Atypical Decubital Fibroplasia)

Clinical

- Occurs in debilitated, immobilized or bedridden patients
- Result of prolonged pressure and impaired circulation
- Chiefly over bony prominences: shoulder, sacrum and hip
- Painless soft tissue mass, mistaken for a neoplasm
- Slight female predilection; peak age: 70-90 years

- Local recurrence after excision may occur

Macroscopic

- Poorly circumscribed mass in deep subcutis, may extend into muscle

Microscopic

- Lobular or zonal growth pattern
- Vascular, inflamed granulation tissue with plump, atypical fibroblasts
- Prominent myxoid stroma and cystic changes
- Focal fibrinoid necrosis
- Fibrosis (variable, usually in older lesions)

Elastofibroma

Clinical

- Uncommon distinct reactive lesion
- Usually subscapular location, 10% bilateral
- Elderly, marked female predilection
- Slow-growing, ill-defined mass attached to periosteum of ribs
- Local recurrence rare

Macroscopic

- Ill-defined margins; range 5-10 cm in size
- Cut surface looks like dense fibrofatty tissue

Microscopic

- Irregular bands of dense, hypocellular hyalinized collagen
- Numerous thick, serrated, eosinophilic elastic fibers (diagnostic)
- Entrapped mature adipose tissue
- Myxoid matrix (variable)

Fibroma of Tendon Sheath

Clinical

- Relatively common in adults, peak: 20-50 years; M:F = 2:1
- Slow-growing, painless, hard nodule attached to tendon
- Mostly hands and feet
- Up to 25% recur after local excision

Macroscopic

- Well-circumscribed, firm and rubbery, attached to tendon
- Range: 1-2 cm in size

Microscopic

- Lobulated configuration
- Bland fibroblasts and myofibroblasts
- Densely collagenized stroma
- Thin, slit-like vessels between lobules
- Cellularity and mitosis (vary with duration)

Differential Diagnosis

- Giant cell tumor of tendon sheath:
  - Possibly a spectrum, more cellular and less hyalinized
- Nodular fasciitis:
  - Not attached to tendon, more cellular and zonation pattern
- Fibromatosis and Fibrosarcoma:
  - Not circumscribed or lobulated, no slit-like vessels

Nuchal Fibroma

- Rare, ill-circumscribed, subcutaneous fibrous growth
- Usually interscapular and paraspinal regions of adults
- May recur if incompletely excised

Solitary Fibrous Tumor

Clinical

- May occur in many sites other than pleura, including: peritoneum, retroperitoneum, mediastinum, and head and neck
- Usually adults, no sex predilection
- Slowly enlarging mass
- Usually benign clinical course, rare malignant transformation

Microscopic

- Large, well-circumscribed and lobulated
- "Patternless" growth pattern with variation in cellularity
- Spindle fibroblast-like cells with intervening collagen bundles
- Dense hyalinized stroma (variable)
- Hemangiopericytoma-like vascular pattern

Immunohistochemistry

- CD34+, actin-, S-100 protein –, desmin –

Keloid Scar

Clinical

- Reactive fibrous proliferation following local trauma or surgery
- Peak: 15-45 years; blacks>whites; may be familial
- Any anatomic location, especially head and neck region
- Treatment is difficult and up to 50% recur locally after excision

Macroscopic

- Excessive scar tissue

- Extends beyond the boundaries of the site of initial tissue damage

Microscopic

- Hypocellular, thick, glassy, hyalinized, eosinophilic collagen fibers
- Haphazardly arranged into broad bands or nodules
- Calcification (variable)

Differential Diagnosis

- Hypertrophic scar:
  - Less common, confined to the original site of tissue damage
  - More cellular scar tissue with nodular configuration
  - Less prone to local recurrence

Pediatric Fibrous Tumors

Fibrous Hamartoma of Infancy

Clinical

- First 2 years of life, usually <1 year; marked male predilection
- Usually solitary; involves dermis and subcutis; freely movable
- Commonly in axillary, upper arm and inguinal regions
- Cured by local excision; rarely recur

Macroscopic

- Poorly circumscribed; on average 3-5 cm in size

Microscopic

- Organoid growth pattern
- Composed of 4 components in varying proportions:
  - Myxoid foci with small round nests of undifferentiated spindle cells
  - Fascicles of myofibroblasts with wavy, tapering nuclei
  - Irregular fibrous trabeculae or septa with inflammatory cells
  - Islands of mature adipose tissue

Differential Diagnosis

- No real differential at this age and location

Infantile Myofibromatosis

- Hamartomatous myofibroblastic proliferation, may be hereditary

Clinical

- Usually <2 years, 30% congenital; M>F
- Solitary or multicentric (25%)
- Most involve skin and superficial soft tissue, or bone
- Common sites: head and neck and trunk
- Multicentric cases may involve viscera, mainly gut or lungs
- Soft tissue and bone lesions are benign and may regress spontaneously
- Multiple visceral lesions may have fatal outcome

Microscopic

- Most <3 cm, well-circumscribed
- Lobulated or multinodular pattern
- Peripherally, fascicles of bland eosinophilic myofibroblasts
- Centrally, primitive round cells around prominent hemangiopericytoma-like vessels
- Hyalinized and myxoid stroma (at periphery)
- Mitoses (few and typical)
- Necrosis (frequent)
- Intravascular growth (frequent)

Variant

- Solitary myofibroma:
  - Usually in head and neck region of adults
  - Firm, cutaneous, painful nodule
  - No tendency to local recurrence

Fibromatosis Colli

- Diffuse fibrous replacement of sternocleidomastoid muscle
- Usually neonates, 2-4 weeks; M = F; R>L
- Often associated with breech or forceps delivery
- Many resolve spontaneously, 10% develop torticollis (wry neck deformity)

Juvenile Hyaline Fibromatosis

- Exceedingly rare, hereditary disorder of infants and children

Infantile Digital Fibromatosis (Inclusion Body Fibromatosis)

- Distinct fibrous tumor in fingers and toes of infants
- Small digital nodule <2 cm, in dermis and subcutis
- 30% congenital, rarely in older children
- 60% recur following local excision; most regress spontaneously
- Ill-defined nodule composed of fascicles of myofibroblasts
- Intracytoplasmic rounded eosinophilic inclusions, close to nucleus

Infantile Fibromatosis (Desmoid-Type)

- Childhood counterpart of the desmoid-type fibromatosis

Clinical

- Usually deep, poorly-circumscribed, solitary mass
- Involves skeletal muscle or fascia
- Mostly <8 years; M>F
- Common sites: head and neck, shoulder, upper arm and thigh
- Locally aggressive: tend to recur locally, do not metastasize

Macroscopic

- Ill-defined, dense fibrous tissue, range: 1-10 cm in size

Microscopic

- Diffuse or mesenchymal form:
  - Infants, few months old
  - Haphazard arrangement of small cells
  - Primitive fibroblast-like cells in myxoid background
  - Diffuse infiltration of skeletal muscle
  - Atrophic muscle with fat replacement
- Fibroblastic form:
  - Cellular with bundles and fascicles
  - Plump spindle-shaped fibroblasts
  - Diffuse infiltration of skeletal muscle
- Desmoid form (like adult-type):
  - Less cellular and more collagenous
  - Usually children > 5 years
  - Behaves like adult-type

Differential Diagnosis

- Myxoid liposarcoma:
  - Rare in < 5 years, plexiform capillary pattern, presence of lipoblasts
- Lipoblastomatosis:
  - Lobular pattern, presence of lipoblasts
- Infantile fibrosarcoma:
  - Pushing margin, uniform cellularity, rapidly growing, mitotic activity and destructive behavior

Calcifying Aponeurotic Fibroma

Clinical

- Rare, slowly growing fibroblastic proliferation in hands or feet
- Mainly children and adolescents; M>F
- Poorly defined, painless mass involving aponeuroses and tendons
- Recur locally

Microscopic

- Usually <3 cm; infiltrative growth pattern
- Central calcified foci surrounded by chondroid-like areas (variable)
- Desmoid fibromatosis-like areas
- Plump myofibroblasts, may show cord-like orientation
- Osteoclast-like giant cells around calcification (variable)

Fibromatoses

- Locally aggressive neoplasms, commonly recur but do not metastasize
- Subclassified into superficial and deep types

Superficial Fibromatoses

Clinical

- Small, slow growing, benign myofibroblastic proliferations
- Usually in adults; 50% are bilateral
- Involve the superficial fascia or aponeurosis
- May cause flexion contractures
- May be associated with epilepsy, diabetes, alcohol abuse
- Local excision, usually fasciectomy; may recur

Microscopic

- Variable cellularity and collagenization
- Early active growth phase with plump myofibroblasts
- More hyalinized in later stage lesions with uniform fibroblasts
- Myxoid matrix and mitoses (variable, usually early lesions)
- Cartilaginous or osseous metaplasia (rare)

Variants

- Palmar fibromatosis (*Dupuytren's contracture*):
  - Involve hand or fingers, adults, M>F
- Plantar fibromatosis (*Ledderhose's disease*):
  - Involves feet, may occur between 5-15 years
  - No contraction deformities
  - Common local recurrence after surgery
- Knuckle pad:
  - Closely related to palmar fibromatosis, no treatment
- Penile fibromatosis (*Peyronie's disease*):
  - Involves shaft of the penis with pain and curvature
  - Mainly between 40-60 years, slow growing
  - More common in patients with palmar and plantar fibromatosis
  - No effective treatment except surgical excision

Differential Diagnosis

- No realistic differential diagnosis in the right clinical setting

Deep (Desmoid) Fibromatoses

Clinical

- Sporadic, multicentric, familial or associated with Gardner's syndrome
- Peak incidence: 25-35 years; M:F = 1:2
- Usually large, infiltrative masses involving deep musculature
- Wide complete excision +/- radiotherapy
- Recurrence rate range: 25-80%

Macroscopic

- Irregular large lesions (>5 cm), depending on location
- Cut surface: pale, whorled and fibrous
- Poorly-defined, infiltrative margins

Microscopic

- Usually hypocellular, fascicular or broad storiform growth pattern
- Pale eosinophilic fibroblasts and myofibroblasts
- Cellularity and mitotic activity (variable but usually low)
- Variably collagenous stroma, focally myxoid (variable)
- Thin-walled, elongated, compressed blood vessels
- Lymphoid aggregates, usually at the periphery
- Cartilaginous or osseous metaplasia (rare)

Subtypes

- Extra-abdominal fibromatosis (desmoid) - 60%:
  - Common sites: limb girdles, proximal extremities
- Abdominal fibromatosis (desmoid) - 25%:
  - Usually anterior abdominal wall
  - Usually females, frequently during or soon after pregnancy
  - May arise in a preceding scar (e.g., cesarean section)
- Intra-abdominal fibromatosis (desmoid) - 15%:
  - Usually involves mesentery, often after prior surgery
  - May be associated with Gardner's syndrome

Immunohistochemistry

- Actin+, Desmin-, S-100 protein -

Differential Diagnosis

- Nodular fasciitis:
  - Loose arrangement with microcystic stromal degeneration, zonation pattern, inflammation and hemorrhage
- Cellular neurofibroma and low grade malignant nerve sheath tumor:
  - Wavy, elongated nuclei and S-100+
- Fibrosarcoma:
  - More cellular, less collagenous, herringbone pattern and nuclear atypia

Malignant

Fibrosarcoma

Clinical

- Uncommon tumor, adult and infantile types

Macroscopic

- Usually well-circumscribed, <10 cm in diameter

Microscopic

- Typically cellular with herringbone fascicular pattern
- Monomorphic spindle cells with elongated, tapering nuclei
- Variable mitotic rate and minimal pleomorphism
- Limited collagen production
- Rare primitive, round, uniform cells (some childhood cases)
- Branching hemangiopericytoma-like vascular pattern (variable)

Immunohistochemistry

- S-100 protein –, EMA-, keratin- and desmin-
- Focally actin+ (some childhood cases)

Types

- Adult fibrosarcoma
  - Usually 4th to 6th decades, male predominance
  - Deep-seated, slow-growing mass
  - Common sites: thigh, trunk
  - 40% 5-year survival, depends on grade and resectability

Variants

- Sclerosing epithelioid fibrosarcoma
- Low grade fibromyxoid sarcoma:
  - Mostly adults; peak age: 30-60 years
  - Any location, usually superficial
  - Whorled growth pattern
  - Variable dense fibrous and myxoid stroma
  - Bland, uniform fibroblasts
  - Hypovascular and rare mitoses
  - Vimentin+, actin-, desmin-, CD34- and S100 –
  - May metastasize

Infantile Fibrosarcoma

- Within first two years of life, often congenital; M>F
- Large painless mass, may involve subcutis
- Predilection for distal extremities
- Better prognosis than adult type, 5-year survival >80%

Differential Diagnosis

- Usually a diagnosis of exclusion

FIBROHISTIOCYTIC TUMORS

Classification of Fibrohistiocytic Tumors

- See Table 13-2

Benign

Fibrous Histiocytoma

Clinical

- May be subdivided into:
  - cutaneous form (dermatofibroma - see skin chapter)
  - deep (<5%) within subcutis, skeletal muscle or abdominal cavity
- Principally adults, 20-40 years of age; M>F
- Commonest sites: lower limb and head and neck region
- 5-10% may recur after local excision

Macroscopic

- Well-circumscribed and pseudoencapsulated
- Usually <4 cm in diameter
- Central hemorrhage or cystic change (occasional)

Microscopic

- Storiform growth pattern with short fascicles
- Eosinophilic spindle cells with elongated or plump vesicular nuclei
- Foamy cells and giant cells (infrequent)
- Mitoses common, usually <5/10 HPF
- Foci of necrosis (occasional)
- Focal hyalinized or myxoid stroma
- Perivascular hyalinization or hemangiopericytoma-like vessels
- Hemorrhage; hemosiderin deposition
- Admixed inflammatory cells

Variants

- Aneurysmal Fibrous Histiocytoma:
  - Mainly in young adults; may grow rapidly to a large size
  - Numerous blood-filled cavernous cavities, no endothelial lining
  - Background of cellular fibrous histiocytoma
  - Abundant hemosiderin deposition
- Atypical Fibrous Histiocytoma (dermatofibroma with monster cells):
  - Clinically non-distinct variant with atypical cytological features
  - Bizarre hyperchromatic giant cells and histiocytes
- Epithelioid Benign Fibrous Histiocytoma:
  - Epithelioid cells with ample eosinophilic cytoplasm
  - Resembles Spitz nevi, however S-100 protein –
- Cellular variant of Benign Fibrous Histiocytoma:
  - Accounts for 5% of cases; may be mistaken for malignancy
  - Relatively monomorphic and fascicular

Table 13-2. Classification of Fibrohistiocytic Tumors

Benign	**Low-Grade Malignant**
Fibrous histiocytoma	Dermatofibrosarcoma protuberans (DFSP)
Variants:	Giant cell fibroblastoma
Dermatofibroma (cutaneous form—see Skin tumors)	Plexiform fibrohistiocytic tumor
Aneurysmal fibrous histiocytoma	Atypical fibroxanthoma (AFX)
Atypical fibrous histiocytoma	Angiomatoid malignant fibrous histiocytoma
Epithelioid fibrous histiocytoma	
Cellular variant of benign fibrous histiocytoma	**Malignant**
Juvenile xanthogranuloma	Malignant fibrous histiocytoma (MFH)
Reticulohistiocytoma	Storiform/Pleomorphic MFH
Xanthoma	Myxoid MFH (myxofibrosarcoma)
	Giant cell MFH
	Inflammatory MFH

- Recurs in up to 30% of cases

Immunohistochemistry

- Usually not helpful
- Scattered Factor XIIIa+ cells
- CD34-

Differential Diagnosis

- Nodular fasciitis:
  - Loosely arranged bundles with zonation pattern
- Neurofibroma:
  - More uniform bundles, slender wavy nuclei, thick wavy collagen bundles, S100 protein +
- Leiomyoma:
  - More distinct fascicular pattern, blunt-ended plumper nuclei
  - Actin+
- Dermatofibrosarcoma protuberans:
  - More extensive subcutaneous involvement
  - Uniform cellular population
  - Lacks giant cells, inflammatory cells and xanthoma cells
  - More infiltrative growth pattern
  - CD34+, Factor XIIIa-
- Malignant fibrous histiocytoma:
  - Deeper situated tumor
  - More cytological atypia, pleomorphism and abnormal mitoses

Juvenile Xanthogranuloma

Clinical

- Clinical features, self-limited, cutaneous or subcutaneous lesions
- 20% congenital; usually develop between 6-24 months; 15% in adults
- No sex predilection; solitary: multiple = 2:1
- Usually cutaneous, 5% deep soft tissue or other organs (e.g., eye)
- Usually self-limited, occasionally spontaneous involution

Macroscopic

- Usually >1 cm, may be massive
- Well-defined to infiltrative margins

Microscopic

- Diffuse, uniform population of histiocytes
- Eosinophilic, vacuolated or xanthomatous cytoplasm
- Mitotic figures common, sometimes frequent
- Touton giant cells, eosinophils, and plasma cells (all variable)
- Sclerosis with regression
- Overlying epidermis, usually uninvolved, rarely ulcerated

Differential Diagnosis

- Histiocytosis X:
  - Less cellular cohesion, no Touton giant cells, S-100+
- Fibrous histiocytoma:
  - Storiform growth pattern, more polymorphous cell population
- Xanthoma:
  - More uniform foamy cell population, no Touton giant cells

Reticulohistiocytoma

Clinical

- Uncommon cutaneous lesion
- Usually young or middle age adults; M<F
- Usually slowly-growing, solitary nodule (<1cm) on upper body
- May be multiple (20% associated with destructive arthritis)
- Benign or self-limiting course

Microscopic

- Well-circumscribed, uniform population of histiocytes within the dermis
- Abundant, ground-glass, eosinophilic cytoplasm with peripheral nuclei
- Multinucleated histiocytes, epithelioid cells and mixed inflammatory cells
- Diastase-resistant PAS-positive material in cytoplasm of giant cells

Differential Diagnosis

- Malignant fibrous histiocytoma:
  - More cytological atypia and pleomorphism with abnormal mitoses
- Malignant melanoma:
  - More cytological atypia and pleomorphism
  - S-100 protein + and HMB-45+

Xanthoma

- A reactive proliferation of histiocytes that contain intracytoplasmic lipid
- Frequently associated with hyperlipidemia
- Usually occur in skin and subcutis, may involve tendons or synovium
- The various types are related to type of lipid disorder and anatomic location: eruptive, tuberous, tendinous, plain xanthomas and xanthelasmas

Low-Grade Malignant

Dermatofibrosarcoma Protuberance (DFSP)

Clinical

- Involves dermis and subcutis of young adults, between 20-50 years
- No sex or racial predilection
- Most occur on trunk, groin, head and neck and lower extremity
- Slow-growing, commonly diagnosed after 5 years or more
- Local recurrences: 30-60%; complete local excision is required
- <5% metastasize to lungs and lymph nodes
- May transform to fibrosarcoma or MFH

Macroscopic

- Usually biopsied at nodular stage - solitary, protuberant, whitish mass
- Average size: 5 cm, occasionally >20 cm
- Overlying skin may be ulcerated
- Skeletal muscle extension is uncommon

Microscopic

- Poorly circumscribed with diffusely infiltrative margins
- Uniform population of spindle cells with monomorphous storiform pattern
- Extends into subcutis with infiltration and isolation of fat lobules
- Overlying epidermis separated by a Grenz zone
- Spindled fibroblast-like cells with amphophilic or pale cytoplasm
- Minimal cellular heterogeneity or hyperchromatism
- Rare foam cells, Touton giant cells and/or granular cells
- Low mitotic index, usually <5/10 HPF
- Myxoid or giant cell fibroblastoma-like (variable)

Variants

- Bednar tumor (5% of cases):
  - DFSP with heavy melanin-pigmented dendritic spindle cells
  - More common in black patients
- DFSP with myofibroblastic differentiation (myoid variant):
  - DFSP with nodules and bundles of myofibroblasts

Immunohistochemistry

- Vimentin+, CD 34+, Desmin-
- Actin- (except for myofibroblasts in myoid variant)
- S-100- (except in dendritic cells of Bednar tumor)

Differential Diagnosis

- Fibrous histiocytoma:
  - Usually smaller size, CD34–
  - More heterogeneous cell population with lipid and hemosiderin
- Atypical fibroxanthoma and MFH:
  - Prominent cytological pleomorphism and abnormal mitoses
- Fibrosarcoma:
  - Deeply-seated tumor, greater mitotic activity
- Myxoid liposarcoma:
  - Plexiform vascular network and presence of lipoblasts

Giant Cell Fibroblastoma

Clinical

- Primarily but not exclusively in children, usually boys
- Slowly growing painless mass in dermis and subcutis
- Frequently trunk
- Excision is often curative, but up to 50% may recur
- May be related closely to DFSP and shares similar clinicopathological and immunohistochemical features

Macroscopic

- Approximately 1-8 cm in diameter
- Overlying skin uninvolved

Microscopic

- Poorly circumscribed with a diffuse and/or fascicular pattern
- Classic pseudosinusoidal “angiectoid” spaces, no endothelial lining
- Cellularity (variable) diffuse, homogenous, spindle cells
- Multinucleated giant cells (frequently lining spaces)
- Fibrous to myxoid matrix
- Low mitotic index (<1/10 HPF)
- Occasional storiform foci resembling DFSP

Plexiform Fibrohistiocytic Tumor

Clinical

- Rare mesenchymal neoplasm occurring in children and young adults
- Female predominance; usually in upper extremities
- Involves the subcutis and may extend to dermis and/or skeletal muscle
- Wide local excision; prone to recur locally and may metastasize

Macroscopic

- Firm, fibrous, poorly circumscribed tumors
- Range: 0.5–8 cm in size, median 2 cm

Microscopic

- Plexiform proliferation of fibroblast-like, histiocyte-like and multinucleated giant cells (all variable)
- Usually mild cellular atypia without significant pleomorphism
- Mitotic activity (usually 3/10 HPF), occasional atypical mitoses
- Collagenous stroma between nodules
- Vascular invasion (rare)

Atypical Fibroxanthoma

Clinical

- Superficial (cutaneous) variant of MFH with an indolent course
- Usually rapidly enlarging, solitary nodule; ulceration is common
- Occurs in actinically damaged skin of head and neck in older adults
- Complete surgical excision with a uniformly good prognosis

Microscopic

- Usually 1-2 cm; often circumscribed, may be infiltrative
- Polypoid lesion in dermis with epidermal collarette
- Usually abut epidermis without a Grenz zone
- May extend focally (but not extensively) into superficial subcutis
- Haphazard, storiform or fascicular growth pattern
- Variably sized tumor cells with pleomorphic bizarre cells
- Abundant eosinophilic or amphophilic cytoplasm
- Frequent typical and atypical mitotic figures
- Touton giant cells (occasional)
- Collagenized and/or myxoid matrix (variable)
- Necrosis (rare)
- No vascular or perineural invasion

Immunohistochemistry

- Vimentin+, S-100-, HMB-45-, Desmin-, Cytokeratins-

Differential Diagnosis

- Squamous cell carcinoma:
  - Cytokeratins+
- Malignant melanoma:
  - S-100 protein+ and HMB-45+
- Leiomyosarcoma:
  - Desmin+ and smooth muscle actin+
  - Clinical setting: usually deep-seated large masses with necrosis
- Malignant fibrous histiocytoma:
  - Extensive involvement of subcutis, penetrates fascia and muscle
  - Necrosis and vascular invasion

Angiomatoid Malignant Fibrous Histiocytoma

Clinical

- Most often in children or adolescents; no sex predilection
- Occurs in subcutis and deep dermis of upper extremities
- May be associated with systemic features including pyrexia, anemia, weight loss or paraproteinemia
- Slowly growing, fluctuant, subcutaneous mass
- Excellent prognosis, provided lesion is completely excised
- 10-15% local recurrence rate
- <1% metastasize to lungs and lymph nodes

Macroscopic

- Well-circumscribed, multinodular, cystic masses
- Generally <3–4 cm in size

Microscopic

- Multiple nodules and sheets of uniform cells
- Collagenous stroma with fibrous pseudocapsule
- Large blood-filled pseudovascular spaces with cystic hemorrhage
- Histiocytoid cells with vesicular, spindled nuclei
- Infrequent mitoses and mild pleomorphism
- Giant cells (rare)
- Prominent lymphoid hyperplasia (peripheral) simulating lymph node
- Extensive hemosiderin deposition
- Focal myxoid change (variable)

Immunohistochemistry

- Desmin+, Muscle actin (HHF-5)+, Smooth muscle actin+/-

Differential Diagnosis

- Aneurysmal benign fibrous histiocytoma:
  - More superficial, more polymorphous cell population, desmin–
- Malignant fibrous histiocytoma:
  - More cytological atypia and pleomorphism with abnormal mitoses
- Metastatic melanoma:
  - S-100+ and HMB-45+

Malignant

Malignant Fibrous Histiocytoma (MFH)

Clinical

- Controversial entity, since it is largely a diagnosis of exclusion
- Arguably the most common sarcoma of adults
- Late adulthood: 50–70 years
- Primarily extremities
- Local recurrence rate: 40–60%
- Metastatic rate: 25–50%, frequently to lungs, lymph nodes and bone

Variants

Storiform/Pleomorphic MFH:

- Most common variant, may not be a cohesive entity
- Storiform pattern with short fascicles of fibroblasts
- Bizarre pleomorphic cells with atypical mitosis

Differential Diagnosis

- Benign fibrous histiocytoma
- DFSP
- Pleomorphic or dedifferentiated liposarcoma
- Pleomorphic rhabdomyosarcoma
- High grade sarcomatoid carcinoma

Myxoid MFH (Myxofibrosarcoma)

- Distinct entity, range from low to high grade histological features
- Mainly in extremities; may be subcutaneous
- Survival depends on grade; overall 60-70% 5-yr survival
- 10-20% hypocellular myxoid areas with prominent vasculature
- Perivascular tumor growth; vacuolated cells (pseudolipoblasts)
- Conventional MFH areas

Differential Diagnosis

- Intramuscular myxoma:
  - Hypocellular, hypovascular and no nuclear atypia
- Myxoid neurofibroma:
  - Less pleomorphic and S100+
- Myxoid liposarcoma:
  - Plexiform vascular pattern, lipoblasts, less nuclear atypia
- Low-grade fibromyxoid sarcoma:
  - Less vascular, more collagen, less nuclear pleomorphism

Giant Cell MFH

- May be a heterogeneous group of entities
- Multinodular growth pattern with osteoclast-like giant cells
- Conventional MFH areas
- Deep lesions have a poor prognosis

Differential Diagnosis

- Fibrous histiocytoma
- Extraskeletal osteosarcoma
- Giant cell tumor of bone with extraosseous extension
- Giant cell tumor of soft tissues
- Leiomyosarcoma with osteoclast-like giant cells

Inflammatory MFH

- Uncommon variant; predilection for retroperitoneum
- Behaves in a very aggressive fashion
- Large xanthomatous cells with atypical nuclei
- Prominent inflammatory component, especially neutrophils
- Conventional MFH areas

Differential Diagnosis

- Xanthogranulomatous pyelonephritis
- Inflammatory pseudotumor
- Malignant lymphoma
- Rosai-Dorfman disease

LIPOMATOUS TUMORS

Classification of Lipomatous Tumors

- See Table 13-3

Benign

Lipoma

Clinical

- Composed of mature adipose tissue and usually arises in subcutis
- Most common mesenchymal neoplasm
- Adults, >30 years of age. No sex predilection
- May occur anywhere, most frequently trunk and proximal limbs
- Rare in abdomen and retroperitoneum
- Most are solitary, 2–3% are multiple

Table 13-3. Classification of Lipomatous Tumors

Benign

- Lipoma
  - Variants
    - Intramuscular and intermuscular lipoma
    - Lipoma of tendon sheath
    - Synovial lipoma
    - Lumbosacral lipoma
    - Fibrolipomatous hamartoma of nerve (neural fibrolipoma)
    - Myolipoma
    - Chondroid lipoma
    - Myelolipoma
    - Angiomyolipoma
    - Angiolipoma
    - Spindle cell lipoma
    - Pleomorphic lipoma
    - Lipoblastoma
- Lipomatosis
- Hibernoma

Malignant

- Liposarcoma
  - Well-differentiated liposarcoma:
    - Lipoma-like type ('atypical lipoma')
    - Sclerosing type
    - Inflammatory type
      - High grade variant: Dedifferentiated liposarcoma
  - Myxoid liposarcoma
    - High grade variant: Round cell liposarcoma
  - Pleomorphic liposarcoma

- ♦ Local recurrence after excision is rare (1-2%)

Macroscopic

- ♦ Well-circumscribed, thinly encapsulated and lobulated
- ♦ Variable size, rarely >10cm

Microscopic

- ♦ Mature adipocytes with thin fibrous septa
- ♦ Myxoid change (variable, when prominent—myxolipoma)
- ♦ Fibrosis (variable, when prominent—fibrolipoma)
- ♦ Secondary fat necrosis and hemorrhage

Cytogenetics

- ♦ 12q translocations

Variants

- ♦ Intramuscular lipoma:
  - – Infiltrates skeletal muscle and fascia in the extremities
  - – Tend to recur if incompletely excised
- ♦ Lipoma of tendon sheath:
  - – Young adults; distal extremities; 50% bilateral
- ♦ Synovial lipoma (lipoma arborescens):
  - – Older adults; associated with chronic arthritis
- ♦ Lumbosacral lipoma:
  - – Children <10 years; associated with spina bifida
- ♦ Fibrolipomatous hamartoma of nerve (neural fibrolipoma):
  - – Mainly children and adolescents
  - – Infiltrate large peripheral nerves and their branches
  - – Primarily in hands and feet
- ♦ Myolipoma:
  - – Rare, benign fat and smooth muscle
  - – Common sites: trunk, inguinal region and pelvis
- ♦ Chondroid lipoma:
  - – Uncommon, benign, mistaken for sarcoma
  - – Mature and immature adipocytes with lipoblasts
  - – Myxohyaline, pseudochondroid matrix
- ♦ Extrarenal angiomyolipoma (see renal tumors):
  - – Rare examples arise in retroperitoneal and pelvic soft tissues
  - – May be mistaken for malignancy due to bizarre smooth muscle
  - – HMB 45+ in muscle cells
- ♦ Extra-adrenal myelolipoma (see adrenal tumors):
  - – Rare outside adrenal or liver
  - – Adult females, usually in retroperitoneum or pelvis
  - – No association with hematological abnormalities

Differential Diagnosis

- Myxoma:
  - Hypocellular without adipose tissue
- Intramuscular hemangioma:
  - Presence of intramuscular vascular proliferation
- Atypical lipoma:
  - Scattering of lipoblasts and atypical, hyperchromatic nuclei
- Well-differentiated liposarcoma:
  - Deep soft tissue: extremities, groin and retroperitoneum
  - Scattering of lipoblasts and atypical, hyperchromatic nuclei
- Myxoid liposarcoma:
  - Presence of lipoblasts and plexiform capillary pattern

Angiolipoma

Clinical

- Common, painful, subcutaneous lesion in young adults
- Male predominance
- Commonly in forearm, followed by trunk and upper arm
- Multiple in 60% of cases, <5% familial
- No tendency to local recurrence or malignant transformation

Macroscopic

- Encapsulated, usually <2 cm

Microscopic

- Mature adipose tissue with subcapsular vascular proliferation
- Prominent, small branching vessels with fibrin thrombi (diagnostic)
- Perivascular fibrosis (variable)

Differential Diagnosis

- Lipoma:
  - Lack of prominent, small, branching vessels with fibrin thrombi
- Intramuscular hemangioma:
  - Intramuscular location and poorly circumscribed
- Kaposi's sarcoma and angiosarcoma:
  - Larger, not encapsulated, no adipocytes or microthrombi

Spindle Cell Lipoma

Clinical

- Painless, slow-growing, well-defined, solitary mass
- Usually males, between 45–65 years
- Chiefly posterior neck and shoulder, in subcutis
- Local excision, recurrence uncommon

Macroscopic

- Average 3–5 cm in size
- Well-circumscribed, thinly encapsulated

Microscopic

- Admixture of mature fat and uniform, slender spindle cells
- Myxoid matrix (variable) and mast cells
- Birefringent, eosinophilic, hyaline collagen fibers

Differential Diagnosis

- Myxoma:
  - Hypocellular, less vascular and no adipocytes
- Neurilemmoma (schwannoma):
  - No adipocytes and S100+ spindle cells
- Myxoid liposarcoma:
  - Location, more vascular and lipoblasts

Pleomorphic lipoma

Clinical

- Closely related or variant of spindle cell lipoma
- Same clinical features as spindle cell lipoma

Macroscopic

- Same as spindle cell lipoma

Microscopic

- Mature adipocytes
- Variable number of multinucleated giant cells (floret cells)
- Collagen and sclerosis (hybrid appearance with spindle cell lipoma)
- Rare mitoses and lipoblasts
- Myxoid change (variable)
- Chronic inflammation

Differential Diagnosis

- Atypical lipoma and well-differentiated liposarcoma:
  - Deeper location, larger size and more adipocytic nuclear atypia

Lipoblastoma

Clinical

- Tumor of infancy, usually <3 years; M:F = 2:1
- Usually superficial, circumscribed, slowly-growing mass
- Involves limbs; approximately 5 cm in size
- Deeper lesions are larger and diffusely infiltrative (lipoblastomatosis)
- Infrequent local recurrence following excision

Microscopic

- Distinct lobular architecture with fibrous septa
- Variable admixture of mature and immature fat cells
- Lipoblasts range from primitive mesenchymal cells to univacuolated and multivacuolated cells
- Myxoid matrix and mast cells (variable)

Cytogenetics

- Deletions of chromosome 8

Differential Diagnosis

- Lipoma:
  - Absence of immature fat cells and lipoblasts
- Myxoid liposarcoma:
  - Rare in children, no lipocytic differentiation
  - May be impossible to distinguish on histological grounds

Hibernoma

Clinical

- Uncommon, usually young adults
- Primarily scapular region and also chest wall
- Slowly-growing, painless, subcutaneous mass, rarely intramuscular
- Cured by complete excision

Macroscopic

- Encapsulated, usually 5–10 cm diameter
- Tan-brown cut surface

Microscopic

- Distinct lobular pattern with a variable admixture of cells
- Large round cells with centrally located nuclei
- Granular to multivacuolated (lipoblast-like) eosinophilic cytoplasm
- Mature univacuolated adipocytes

Differential Diagnosis

- Adult rhabdomyoma:
  - Larger cells containing glycogen
- Granular cell tumor:
  - Absence of intracellular lipid vacuoles
- Myxoid and Round Cell Liposarcoma:
  - More cytological atypia and plexiform capillary pattern

Lipomatosis

- Rare condition, usually affects adult males, as different clinical forms
- Diffuse overgrowth of mature adipose tissue

Malignant

Liposarcoma

- One of the most common soft tissue sarcoma of adults
- Three major histologic subtypes:
  - Well-differentiated (dedifferentiated type - variant)
  - Myxoid (round cell type - variant)
  - Pleomorphic
- N.B subclassification is mandatory due to prognostic significance

Clinical

- Tumor of adulthood; M>F
- Peak age: 40-60 years, extremely rare in children
- Usually deep-seated; rate of growth parallels histologic grade
- Major sites: extremities, especially thigh and retroperitoneum
- Well-differentiated and myxoid types are low grade with multiple local recurrences and low metastatic rate
- High grade liposarcomas (dedifferentiated, pleomorphic and round cell types) behave more aggressively with short survival and metastases
- Recurrence rates depend on location and resectability

Well-Differentiated Liposarcoma

- Also known as atypical lipoma (see below) in superficial locations
- Two principle forms: lipoma-like, sclerosing and inflammatory subtypes
- Common sites: thigh, retroperitoneum and paratesticular regions

Macroscopic

- Usually large, well-circumscribed and coarsely lobulated
- Sclerosing type - pale and firm

Microscopic

- Mature adipocytes with variation in cell size
- Atypical, hyperchromatic nuclei
- Variable number of lipoblasts
- Multinucleated stromal cells
- Variable prominent fibrous septa with occasional bizarre cells
- Myxoid stroma (variable)
- Foci of metaplastic bone or smooth muscle differentiation (rare)
- Sclerosing liposarcoma - collagenous fibrous tissue with scattered mature adipocytes and bizarre hyperchromatic stromal cells

Variants

- Inflammatory type:
  - Numerous prominent lymphoplasmacytic aggregates
  - May simulate inflammatory pseudotumor or lymphoma
- Spindle cell type:
  - Usually located in the subcutis

Cytogenetics

- Ring chromosomes

"Atypical Lipoma"

- Controversial term for superficially located, well-differentiated liposarcoma - morphologically indistinguishable
- Occurs in subcutis of extremities or trunk
- Amenable to wide surgical excision and cure
- Cytogenetics: Ring chromosomes

Dedifferentiated Liposarcoma

- Well-differentiated liposarcoma which shows abrupt transition to high grade non-lipogenic sarcoma either in the primary tumor or in a recurrence
- 90% of cases occur de novo, 10% in recurrences
- Most often in retroperitoneum and groin

Macroscopic

- Both components are often easily distinguished
- Well-differentiated component has to be sampled for diagnosis in a primary tumor

Microscopic

- Dedifferentiated component usually looks like high grade MFH

Cytogenetics

- Ring chromosomes

Myxoid Liposarcoma

- Specific reciprocal chromosomal translocation t(12;16)(q13;p11)

Microscopic

- Multilobular architecture
- Prominent, delicate plexiform capillary pattern ("chicken-wire")
- Copious myxoid matrix with cystic, pseudolymphangiomatous spaces
- Univacuolated and multivacuolated lipoblasts
- Primitive round to angulated cells (variable)
- Mature adipocytes, variable, multinucleated giant cells (rare)
- Focal chondroid, smooth muscle or osseous metaplasia (rare)

Variant

- Round cell liposarcoma (>75% round cells areas):
  - Poorly differentiated form with same chromosomal translocation
  - Hypercellular with small uniform round cells with vesicular nuclei
  - Trabecular or adenoid pattern
  - Foci of transition to myxoid type (diagnostic)
  - Aggressive clinical course with tendency to metastasize

Differential Diagnosis

- Intramuscular myxoma:
  - Less vascular, no lipoblasts
- Myxofibrosarcoma (myxoid MFH):
  - More nuclear pleomorphism, more curvilinear vessels
- Anaplastic round cell malignancy (from round cell liposarcoma):
  - Lack of plexiform capillary network, mucin pooling and no lipoblasts

Pleomorphic Liposarcoma

- High grade liposarcoma with metastatic potential
- Accounts for 5% of liposarcomas
- High grade pleomorphic sarcoma with multivacuolated lipoblasts
- Marked cytological pleomorphism with numerous intracytoplasmic eosinophilic globules or droplets
- Cytogenetics: non-unique and very complex abnormalities

SMOOTH MUSCLE TUMORS

Classification of Smooth Muscle Tumors

- See Table 13-4

Benign

Leiomyoma

Microscopic

- Usually well-circumscribed

Table 13-4. Classification of Smooth Muscle Tumors

Benign	Malignant
Leiomyoma	Leiomyosarcoma
Variants:	Variants:
Pilar leiomyoma	Intra-abdominal leiomyosarcoma
Genital leiomyoma	Subcutaneous leiomyosarcoma
Deep leiomyoma	Cutaneous leiomyosarcoma
Angiomyoma (angioleiomyoma, vascular leiomyoma)	Vascular Leiomyosarcoma
Epithelioid leiomyoma (leiomyoblastoma)	Epithelioid leiomyosarcoma (malignant leiomyoblastoma)
Intravenous leiomyomatosis	
Peritoneal leiomyomatosis	
Palisaded Myofibroblastoma of Lymph Node	

- Interlacing bundles and fascicles of smooth muscle cells
- Blunt-ended cigar-shaped nuclei with eosinophilic cytoplasm
- Mitoses absent
- Degenerative pleomorphism (variable)
- Fibrosis and calcification (variable)

Variants

- Pilar leiomyoma:
  - Multiple, slow-growing, painful, cutaneous nodules
  - Mainly limbs and trunk of young adults; M=F
  - Irregular, ill-defined margins in the dermis
  - Associated with hair follicle
- Genital leiomyoma:
  - Involve nipple, vulva and scrotum
  - Nipple lesions—similar to pilar leiomyomas
  - Vulvar lesions—circumscribed with myxohyaline degeneration
  - Scrotal lesions—large, cellular and focally infiltrative
- Deep leiomyoma:
  - Uncommon, solitary, painless, slow-growing tumors
  - Peak age: middle-aged adults
  - Usually extremities, abdominal cavity and retroperitoneum
  - Well-circumscribed and typically >5 cm
- Angiomyoma (angioleiomyoma, vascular leiomyoma):
  - Solitary, painful, usually subcutaneous
  - Usually women, 40-60 years; extremities especially lower leg
  - Well-circumscribed; <3 cm in diameter
  - Mature smooth muscle cells around thick-walled blood vessels
  - Vessels lack elastic laminae
- Epithelioid leiomyoma (leiomyoblastoma):
  - Most arise in stomach, small intestine and mesentery
  - See gastrointestinal stromal tumors

Immunohistochemistry

- Smooth muscle actin+, Desmin+, Vimentin+

Intravenous Leiomyomatosis (see Uterine Tumors)

- Intravascular growth of benign smooth muscle in uterine or pelvic veins

Peritoneal Leiomyomatosis (Leiomyomatosis Peritonealis Disseminata)

- Multiple peritoneal nodules of benign smooth muscle cells
- Rare, usually incidental finding
- Usually premenopausal women, especially pregnant and black women
- Lesions regress with removal of estrogen and progesterone source

Palisaded Myofibroblastoma of Lymph Node

- Benign myofibroblastic proliferation in lymph nodes, usually groin
- Simulate neurilemmoma, due to palisading pattern
- Amianthoid fibers or thick collagen mats (distinctive)

Malignant

Leiomyosarcoma

Clinical

- Depends on location, see variants

Microscopic

- Usually well-circumscribed, except for cutaneous lesions
- Deep-seated types are larger with more necrosis
- Appearance varies with degree of differentiation or grade
- Interlacing fascicles and bundles of spindle cells
- Vesicular, ovoid to cigar-shaped nuclei with eosinophilic cytoplasm
- Nuclear pleomorphism and mitoses (variable)
- Epithelioid or round cells (rare)
- Hyalinization, myxoid change and necrosis (all variable)
- Multinucleated, osteoclast-like giant cells (rare)
- MFH-like areas (variable)

Immunohistochemistry

- Muscle specific actin+
- Smooth muscle actin+
- Desmin+
- S-100 protein +
- Keratin+/-
- EMA+/-

Variants

- Intra-abdominal leiomyosarcoma:
  - Retroperitoneum, mesentery or omentum
  - Peak: 50-70 years, M<F
  - Range: 7-35 cm; wide excision not possible
  - Metastasize to lungs and liver
  - 20-30% 5 year survival
- Subcutaneous leiomyosarcoma (deep soft tissue of limbs):
  - Most common in thigh
  - 50-70 years; slight male predominance
  - 50% metastasize; 60% 5 year survival
- Cutaneous leiomyosarcoma:
  - Usually limbs, especially lower leg, often painful
  - Mainly younger adults; male predilection
  - Commonly recur locally, rarely metastasize
- Vascular leiomyosarcoma:
  - Usually arise from inferior vena cava or large leg veins
  - Older adults; IVC tumors occur in women
  - Frequent metastases to liver, lymph nodes and lungs
  - 20% 5 year survival, depends on location and resectability
- Epithelioid leiomyosarcoma (malignant leiomyoblastoma):
  - See gastrointestinal stromal tumors

Differential Diagnosis

- Leiomyoma:
  - Smaller, less pleomorphism, rare mitoses and no necrosis
- Postoperative (reactive) myofibroblastic nodules:
  - Haphazard arrangement of cells, basophilic cytoplasm and lack of linear striations
- Malignant peripheral nerve sheath tumor:
  - No glycogen; wavy, buckled, asymmetrical nuclei
  - S-100 +, actin- and desmin-
- Fibrosarcoma:
  - No glycogen, tapered nuclei, actin- and desmin-

SKELETAL MUSCLE TUMORS

Classification of Skeletal Muscle Tumors

- See Table 13-5

Benign

Rhabdomyomatous Mesenchymal Hamartoma

- Extremely rare, peculiar striated muscle proliferation
- Cutaneous nodules in head and neck of neonates and infants

Cardiac Rhabdomyoma (see Chapter 16)

- Hamartomatous process often associated with tuberous sclerosis

Adult Rhabdomyoma

- Rare, slow-growing lesion in head and neck region
- Middle-aged adults; M>F
- 10% multifocal
- Occasionally recur after local excision
- Encapsulated, usually <5 cm

Table 13-5 Classification of Skeletal Muscle Tumors	
Benign	**Malignant**
Rhabdomyoma	Rhabdomyosarcoma
Rhabdomyomatous mesenchymal hamartoma	Embryonal rhabdomyosarcoma
Cardiac rhabdomyoma	Alveolar rhabdomyosarcoma
Adult rhabdomyoma	Pleomorphic rhabdomyosarcoma
Fetal rhabdomyoma	
Genital rhabdomyoma	

- Large, polygonal, eosinophilic cells with peripheral small nuclei
- Granular or vacuolated cytoplasm
- Cytoplasmic cross-striations (variable)
- Desmin+ and myoglobin+

Fetal Rhabdomyoma

- Rarer entity, presumable hamartomatous
- Any age, peak: <3 years
- Subcutis and submucosa of head and neck, especially behind ear
- Solitary, usually <5 cm
- Do not recur
- Zonation pattern with central primitive spindle cells in myoid matrix
- More mature eosinophilic rhabdomyoblasts at periphery
- Cellularity and fascicular pattern (both variable)
- No nuclear atypia and rare mitoses (unlike rhabdomyosarcoma)

Genital Rhabdomyoma

- Solitary, polypoid mass in vagina, vulva or cervix
- Young or middle-aged women; usually asymptomatic
- Slow-growing, usually <3 cm
- Do not recur
- Submucosal proliferation of elongated, eosinophilic rhabdomyoblasts
- Cytoplasmic cross-striations
- Mitoses absent
- Desmin+ and myoglobin+
- Differential diagnosis: Botyroid rhabdomyosarcoma

Malignant

Rhabdomyosarcoma (RMS)

- Malignant neoplasms which show evidence of skeletal muscle differentiation, in the absence of other differentiation
- Most common sarcoma of children and adolescents
- Three basic types:
  - Embryonal
  - Alveolar
  - Pleomorphic

Embryonal Rhabdomyosarcoma

Clinical

- Infants and children <15 years, peak: 4 years
- Male predominance
- Common sites: head and neck, paratesticular regions

Microscopic

- Infiltrative and haphazardly arranged
- Varying cellularity with alternating hypercellular and loose myxoid areas
- Undifferentiated, hyperchromatic, round or spindle-shaped cells
- Rhabdomyoblasts with eosinophilic, fibrillary cytoplasm
- Minimal collagen and myxoid matrix (variable)
- Cross-striations (in 30-60%)
- Mitoses and glycogen; nuclear pleomorphism (variable)

Cytogenetics

- 11q deletions

Variants

- Botyroid rhabdomyosarcoma:
  - Submucosal variant forming a polypoid (grape-like) mass
  - Hypocellular, myxoid areas with a cambium-layer (>50%)
- Spindle cell rhabdomyosarcoma:
  - Subtype with favorable clinical outcome; 90% 5-year survival
  - Usually paratesticular and head and neck region
  - Fascicular or storiform growth pattern
  - Eosinophilic, spindle rhabdomyoblasts

– Few mitoses and collagenized stroma

Alveolar Rhabdomyosarcoma

Clinical

- Mainly adolescents and young adults
- Usually deep-seated mass involving limbs
- Worse prognosis

Microscopic

- Circumscribed or infiltrative margins
- Ill-defined aggregates of round cells
- Fibrous septa with dyscohesive alveolar pattern
- Multinucleated giant cells with peripheral wreath-like nuclei
- Cross-striations (in 16-30% of cases)

Cytogenetics

- t(2;13)(q35;q14)

Variant

- Solid variant of alveolar RMS:
  - Densely packed tumor cells without alveolar pattern
  - Resemble embryonal RMS, however cells are larger

Pleomorphic Rhabdomyosarcoma

Clinical

- Rarest type; older patients >45 years

Microscopic

- Infiltrative growth pattern
- Haphazard, loose arrangement of cells
- Large, pleomorphic or spindle-shaped eosinophilic rhabdomyoblasts
- Collagenous stroma (variable)
- Cross-striations (rare)

Immunohistochemistry of RMS

- Desmin+, muscle-specific actin +
- Myoglobin+, MyoD1+
- Vimentin+, cytokeratin ±
- S-100 protein±, CD99 (MIC-2)+(15%)

Differential Diagnosis of RMS

- Ewings's sarcoma/primitive neuroectodermal tumor (PNET): CD99+
- Neuroblastoma: Chromogranin and synaptophysin+
- Angiosarcoma: CD31 and Factor VIII+
- Synovial sarcoma: Cytokeratin and EMA+
- Malignant melanoma: S-100 and HMB-45+
- Granulocytic sarcoma: CD45, myeloperoxidase, CD43 and CD68+
- Malignant lymphoma: CD45+
- Small cell carcinoma:
  - Low molecular weight cytokeratin (Cam 5.2)+
  - Location, age, lack of rhabdomyoblasts
- Rhabdoid tumor:
  - Cytokeratin+, desmin and myoglobin-
- Alveolar soft part sarcoma:
  - Alveolar pattern with intervening thin-walled vessels
  - Intracellular PAS with diastase-positive crystalline material
- Proliferative fasciitis/myositis
- Inflammatory reactive pseudotumor
- Granular cell tumor
- Myxoma:
  - Age and location usually provide correct diagnosis

Malignant Triton Tumor

- Malignant peripheral nerve sheath tumor with rhabdomyoblastic differentiation

Ectomesenchymoma

- Ganglioneuroblastoma with rhabdomyoblastic differentiation

VASCULAR TUMORS

Classification of Vascular Tumors

- See Table 13-6

Benign

Reactive

Papillary Endothelial Hyperplasia (Masson's tumor)

- Reactive lesion—unusual form of an organizing thrombus
- May arise in a dilated blood vessel or underlying vascular lesion
- Usually head and neck or fingers of young adults
- Commonly <2 cm and do not recur
- Well-circumscribed and commonly intravascular
- Papillary configuration with anastomosing endothelial-lined channels

Table 13-6. Classification of Vascular Tumors

Blood Vessel Tumors

Benign Tumors and Tumor-Like Conditions

- Reactive
  - Papillary endothelial hyperplasia (Masson's tumor)
  - Vascular transformation of lymph node (nodal angiomatosis)
  - Glomeruloid hemangioma
  - Bacillary angiomatosis
- Vascular ectasia
  - Nevus flammeus (nevus telangiectaticus)
  - Arterial spider (nevus araneus)
  - Hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu disease)
- Superficial hemangiomas
  - Capillary hemangioma
    - Variants:
      - Cellular hemangioma of infancy (strawberry nevus)
      - Tufted angioma
      - Verrucous hemangioma
      - Cherry angioma (senile angioma)
      - Lobular hemangioma (pyogenic granuloma)
  - Cavernous hemangioma
    - Variants:
      - Sinusoidal hemangioma
  - Arteriovenous hemangioma
  - Venous hemangioma
  - Epithelioid hemangioma (angiolymphoid hyperplasia with eosinophilia)
- Deep hemangiomas
  - Intramuscular hemangioma
  - Synovial hemangioma
  - Hemangioma of peripheral nerve
  - Intranodal hemangioma
  - Angiomatosis (Diffuse hemangioma)
  - Spindle cell hemangioendothelioma

Low Grade Malignant Tumor

- Epithelioid hemangioendothelioma
- Kaposiform hemangioendothelioma
- Malignant endovascular papillary angioendothelioma (Dabska's tumor)
- Kaposi's sarcoma

Malignant Vascular Tumors

- Angiosarcoma
  - Idiopathic superficial (head and neck)
  - Associated with lymphedema (Stewart-Trevers syndrome)
  - Angiosarcoma of breast
  - Radiation-induced
  - Angiosarcoma of deep soft tissues

Perivascular Tumors

- Glomus tumor
  - Variants:
    - Glomangiosarcoma
    - Glomangiomyoma
- Glomangiosarcoma
- Hemangiopericytoma

Lymph Vessel Tumors

- Lymphangioma
  - Variants:
    - Cavernous lymphangioma (cystic hygroma)
- Lymphangioma circumscriptum (cutaneous)
- Lymphangiomatosis
- Lymphangiomyoma
- Lymphangiomyomatosis

- ♦ Associated with thrombosis and fibrosis

Bacillary Angiomatosis

- ♦ Reactive epithelioid vascular proliferation
- ♦ Associated with neutrophilic infiltrate
- ♦ Usually in immunocompromised hosts
- ♦ Caused by Bartonella henselae

Capillary Hemangioma (Infantile Hemangioendothelioma)

- ♦ Most common benign vascular tumor of childhood
- ♦ Usually involves superficial soft tissue of head and neck region
- ♦ Usually presents soon after birth, grows rapidly
- ♦ 70% regress spontaneously
- ♦ Multilobulated architecture, cellular, closely packed capillaries
- ♦ Plump endothelial cells with mitoses
- ♦ Interstitial fibrosis (variable)

Variants

- ♦ Tufted angioma

- Verrucous hemangioma
- Cherry angioma (senile angioma)

Lobular Capillary Hemangioma (Pyogenic Granuloma)

- Common variant of capillary hemangioma
- Usually solitary, ulcerated, polypoid nodule < 2 cm
- Typically skin of fingers and skin and mucosa of head and neck; any age
- Do not regress and 10-15% may recur (including satellitosis)
- Well-circumscribed, lobular proliferation of capillaries
- Inflamed granulation tissue-like stroma
- Epithelial collarette and ulceration (variable)

Variants

- Intravascular pyogenic granuloma
  - Rare variant, usually adults
- Granuloma gravidarum:
  - Usually gingivae of pregnant women; regress postpartum

Cavernous Hemangioma

- Less common than capillary hemangioma
- Usually larger and more deep-seated and do not regress
- Any organ may be involved
- May be associated with:
  - Mafucci's syndrome with multiple enchondromas, lymphangiomas and spindle cell hemangioendothelioma
  - Kasabach-Merritt syndrome with consumption coagulopathy
  - Blue Rubber Bleb Nevus syndrome
- Poorly-circumscribed, dilated, thin-walled blood vessels
- Areas of capillary hemangioma (variable)
- Thrombosis and secondary dystrophic calcification (variable)

Variant

- Sinusoidal hemangioma

Epithelioid Hemangioma (Angiolymphoid Hyperplasia with Eosinophilia)

- Usually cutaneous red lesions in head and neck region
- Peak age: 30-60 years
- Solitary or multiple and involve dermis and subcutis
- Approximately 30% of cases recur
- Relatively circumscribed proliferation of small and medium-sized vessels
- Plump epithelioid endothelial cells with eosinophilic cytoplasm
- "Tombstone" appearance of nuclei
- Prominent lymphoid follicles with germinal centers, plasma cells and mast cells

Differential Diagnosis:

- Kimura's disease:
  - Involves lymph nodes, associated with eosinophilia and flat endothelial lining

Intramuscular Hemangioma

- Any age, usually <30 years, M=F
- Commonly lower limbs especially thigh
- Slowly growing mass, may be painful
- Radiographs: frequently calcified, probably phlebolith
- Recurrence common (up to 50%)
- Mixed capillary and cavernous vessels (variable)
- Ill-defined and admixed with adipose tissue

Differential Diagnosis

- Intramuscular lipoma - no vascular component, more indolent
- Angiosarcoma - no lobular architecture, more endothelial atypia

Angiomatosis (Diffuse Hemangioma)

- Rare lesion, usually in childhood or adolescence
- Probably malformation with a diffuse proliferation of blood vessels
- Involves large areas, usually limbs or visceral organs
- Clinically extensive, surgical treatment is difficult; common recurrences
- Diffuse infiltration of dermis, subcutis, skeletal muscle and bone
- Mixture of veins, capillaries and cavernous vascular spaces
- Mature adipose tissue (variable)

Differential Diagnosis:

- Intramuscular hemangioma - usually involves one muscle group
- Arteriovenous hemangioma - shunting, mixture of arteries and veins

Spindle Cell Hemangioendothelioma

- Initially described as low grade malignant, but probably non-neoplastic
- Solitary or multiple red nodules on distal extremities, especially hands
- Usually adolescents and young adults; M:F equal
- Indolent clinical course, may develop new lesions over many years
- Ill-defined lesion involving dermis and subcutis

- Irregular cavernous vascular spaces with flat endothelial lining, containing organizing thrombi
- Solid areas of bland spindle cells with eosinophilic cytoplasm
- Epithelioid endothelial cells with intracytoplasmic vacuoles
- May be an intravascular lesion
- Vascular lining and epithelioid cells: CD34 and CD31+
- Spindle cells: Vimentin+, CD34 and CD31-

Differential Diagnosis:

- Kaposi's sarcoma
  - No cavernous spaces, no epithelioid endothelial cells
  - CD34 and CD31+

Low Grade Malignant

Epithelioid Hemangioendothelioma

Clinical

- Low grade malignant vascular tumor that may involve any organ
- Usually solitary mass in soft tissue, associated with a blood vessel
- Commonly multiple in lung, liver and bone
- Wide range, usually adults; M:F equal
- Local recurrence >15%
- Metastatic rate >30%, usually to lymph nodes, lung, liver and bone

Microscopic

- Ill-defined and infiltrative
- Prominent myxoid to hyaline stroma (chondroid-like)
- Nests and trabeculae of epithelioid or spindle cells
- Eosinophilic cytoplasm with vesicular nuclei
- Intracytoplasmic vacuoles containing red blood cells
- Cytological atypia and mitosis (variable)
- May arise in a vessel with perivascular extension

Immunohistochemistry

- CD31+
- Cytokeratin+ (50%)
- Factor VIII+
- EMA-

Electron Microscopy

- Weibel-Palade bodies

Differential Diagnosis

- Metastatic carcinoma:
  - More nuclear atypia and mitosis, usually not angiocentric
  - CD31-, EMA+
- Melanoma:
  - More nuclear atypia and mitoses, usually not angiocentric
  - CD31-, S100 and HMB 45+
- Epithelioid angiosarcoma:
  - More nuclear atypia and mitoses, necrosis
  - Irregular anastomosing channels
- Epithelioid sarcoma:
  - Usual distal extremity of young patients
  - Nodular growth pattern with central necrosis
  - Dense collagenous stroma which blends with epithelioid cells

Kaposiform Hemangioendothelioma (Kaposi-like infantile hemangioendothelioma)

- Rare, distinctive tumor of childhood
- Usually retroperitoneum, upper limbs, chest wall and head and neck
- Mortality and morbidity associated with infiltrative growth
- Commonly associated with Kassbach-Meritt syndrome (consumption coagulopathy)
- Ill-defined nodules with proliferation of capillaries and vessels
- Scattered epithelioid endothelial cells
- Hemosiderin and hyaline globules (variable)

Differential Diagnosis

- Kaposi's sarcoma:
  - Rare in children, multicentric, not lobular
  - Prominent inflammatory infiltrate
- Capillary hemangioma:
  - Solid nodules of capillary proliferations
  - No spindle cell component

Kaposi's Sarcoma (see Skin Tumors)

- Probably represents a reactive, multifocal vascular proliferation
- Recently related to Human Herpes Virus 8
- 4 distinct clinical groups, where AIDS-related form is commonest
- All groups have similar histologic features with 3 stages

Malignant

Angiosarcoma

Clinical

- May be divided into 5 clinical groups:

Idiopathic Cutaneous Angiosarcoma

- Usually head and neck of elderly

- Multiple involving skin and subcutis
- Poor prognosis with disseminated, aggressive course

Lymphedema-associated angiosarcoma

- Also known as lymphangiosarcoma of Stewart-Treves
- Usually arm of females; 1-30 years post-radical mastectomy
- Poor prognosis

Radiation-induced angiosarcoma

- Rare, usually often a mean of 5 years after therapy
- Poor prognosis

Angiosarcoma of deep breast

- Rare, usually females; peak: 20-40 years
- May be low grade, survival rate depends on tumor grade

Angiosarcoma of deep soft tissue

- Rare, many extend from cutaneous forms
- Usually behave as high grade sarcomas

Microscopic

- All forms have similar histologic features
- Infiltrative tumors, usually multifocal
- Numerous, irregular, anastomosing vascular channels
- Dissecting pattern between collagen bundles
- Endothelial pleomorphism and hyperchromasia (variable)
- Tufting and papillary formation
- Mitoses and necrosis (variable)
- Solid areas without vascular architecture (variable)

Immunohistochemistry

- CD31+
- CD34+
- Factor VIII+/-

Electron Microscopy

- Weibel-Palade bodies

Differential Diagnosis

- Hemangioma
- Angiomatosis
- Angiolipoma
- Bacillary angiomatosis
- Epithelioid sarcoma
- Malignant melanoma
- Spindle cell sarcoma
- Sarcomatoid carcinoma

Variants

- Epithelioid angiosarcoma
  - Composed exclusively of epithelioid cells
  - Necrosis and hemorrhage
  - Aggressive clinical course with systemic metastases and death

Perivascular Tumors

Glomus Tumor

Clinical

- Common and usually adults 30-50 years
- M:F equal, except for subungual types (usually in women)
- Usually solitary, painful, <1 cm mass in dermis or subcutis of fingers
- 10% may recur after excision
- Rare malignant transformation (Glomangiosarcoma)

Microscopic

- Well-circumscribed and cellular (variable)
- Solid sheets or nests of round, uniform cells
- Pale, eosinophilic cytoplasm and central, round hyperchromatic nuclei
- Well-defined cell margins (PAS-positive cytoplasmic membranes)
- Edematous stroma with myxoid change

Variants

- Glomangioma:
  - Cavernous vascular spaces
  - Clusters of glomus cells around and lining vessels
  - Thrombi (variable)
- Glomangiomyoma:
  - Features of glomangioma and glomus tumor with smooth muscle proliferation

Immunohistochemistry

- Smooth muscle actin+
- Muscle specific actin+
- Desmin+/-
- Vimentin+

Differential Diagnosis

- Adnexal tumor:
  - Focal ductal differentiation, cytokeratin+
- Intradermal nevus:
  - Focal nesting pattern, maturation, S-100+

Hemangiopericytoma

Clinical

- Rare neoplasm, usually slowly growing, deep-seated mass
- Adults; M=F
- Commonly lower limb and retroperitoneum
- Also orbit, nose, paranasal sinuses and meninges
- Clinical behavior is difficult to predict based on histology

Microscopic

- Well circumscribed; lobulated appearance
- Numerous, thin-walled, branching vessels (staghorn configuration)
- Perivascular sheets or clusters of uniform cells
- Small, spindle cells with oval nuclei and ill-defined cytoplasm
- Myxoid stroma and fibrosis (variable)
- Features of malignancy:
  - Hypercellularity and nuclear atypia
  - Necrosis and hemorrhage
  - Mitoses >4/10 high power fields

Variants

- Infantile hemangiopericytoma:
  - Probably represents vascular form of infantile myofibromatosis

Immunohistochemistry

- Vimentin+
- CD34+ (variable, usually focal)
- Factor XIIIa+
- HLA-DR+

Differential Diagnosis

- Fibrous histiocytoma:
  - More prominent spindle cell pattern, storiform arrangement
  - More polymorphic cell population
- Synovial sarcoma
  - Focal biphasic pattern, more spindling, calcifications
  - Cytokeratin+, EMA+
- Mesenchymal chondrosarcoma:
  - Islands of well-differentiated cartilage
- Solitary fibrous pseudotumor (see fibrous tumors)
- Infantile fibrosarcoma (see fibrous tumors)
- Metastatic endometrial stromal sarcoma
  - Location and clinical history

SYNOVIAL TUMORS

Classification of Synovial Tumors

- See Table 13-7

Table 13-7. Classification of Synovial Tumors

Benign
Giant Cell Tumor of Tendon Sheath (Localized type)
Variant: Diffuse type (pigmented villonodular synovitis)
Malignant
Synovial sarcoma

Benign

Giant Cell Tumor of Tendon Sheath (Localized Type)

Clinical

- Very common; predominantly digits, mostly hand
- Painless, slow-growing and fixed to underlying tendon
- Peak age: 20-40 years; M:F = 1:2
- 10-20% recur after local excision

Macroscopic

- Multinodular, lobulated and well-circumscribed
- Usually 2-3 cm in diameter

Microscopic

- Sheets and nests of round, mononuclear stromal cells
- Multinucleated giant cells
- Foamy histiocytes and hemosiderin
- Chronic inflammation
- Collagenous stroma and hyalinization (variable)
- Cellularity and mitoses (variable)

Variant

- Diffuse tenosynovial giant cell tumor
  - Soft tissue variant of pigmented villonodular synovitis of joints
  - Uncommon, poorly circumscribed, infiltrative soft tissue mass
  - Aggressive behavior and 40-50% of cases recur

Malignant

Synovial Sarcoma

Clinical

- Any age; peak: 10-35 years; slight male predominance
- Deep-seated painful, slow-growing; usually close to large joint
- Common sites: lower limbs, abdomen, head and neck
- 20% involve bone; 30% are calcified
- 50% 5 year survival
- Late recurrences and metastases to lungs, lymph nodes, bone marrow
- Good prognostic signs: <5 cm, early clinical stage and <10 years of age

Macroscopic

- Well-circumscribed, multilobular with pseudocapsule
- Variable size

Microscopic

- Two histologic groups: biphasic and monophasic
- Hypercellular, monomorphic spindle cells arranged in fascicles and whorls
- High nuclear to cytoplasmic ratio with tapering nuclei
- Mitoses (variable)
- Collagenous stroma (variable)
- Focal stromal calcification or ossification
- Stromal mast cells
- Branching, hemangiopericytoma-like vascular pattern
- Biphasic: glandular structures lined by cuboidal to columnar epithelium

Immunohistochemistry

- Cytokeratin+
- EMA+

Cytogenetics

- t(X;18)(p11.2; q11.2)

Differential Diagnosis

- Epithelioid sarcoma
  - Superficial location, upper limb, multinodular with central necrosis
- Clear cell sarcoma (melanoma of soft parts)
  - Nesting pattern, pale nuclei with macronucleoli, intracellular glycogen
  - Cytokeratin- and S-100 protein+
- Malignant peripheral nerve sheath tumor
  - Usually associated with large nerve, neurofibroma or NF-1
- Fibrosarcoma
  - Not near joint, not multilobular, slender nuclei, no whorling
  - No mast cells or calcifications
- Carcinoma, especially adnexal origin
  - No spindle cell component
- Carcinosarcoma
  - Epithelial sarcomatous components are higher grade

PERIPHERAL NEURAL TUMORS

Classification of Peripheral Neural Tumors

- See table 13-8

Benign

Traumatic Neuroma (Amputation Neuroma)

- Reparative process arising from the proximal end of a nerve

Clinical

- Any location where peripheral nerve is severed without healing
- Usually trauma or surgery, especially amputation
- Small, painful nodule in superficial soft tissue

Microscopic

- Poorly circumscribed with disorderly arrangement of nerve fascicles
- Mixture of fibroblasts, Schwann cells and axons
- Collagenous stroma with myxoid change (variable)

Morton's Neuroma (Localized Interdigital Neuritis)

Clinical

- Severe lancinating pain in region of metatarsal heads
- Adults, with female predilection
- Reactive, sclerosing process involving peripheral nerves
- Resection is curative

Microscopic

- Irregular margins
- Marked perineural fibrosis with loss of axons
- Extension of fibrosis to adjacent fat and vessel walls

Digital Pacinian Neuroma

- Uncommon type of Pacinian neuroma

Table 13-8. Classification of Peripheral Neural Tumors

Benign

Traumatic neuroma (Amputation Neuroma)
Morton's neuroma (Localized interdigital neuritis)
Digital pacinian neuroma
Mucosal neuroma
Neuromuscular hamartoma (Benign Triton tumor)
Solitary circumscribed neuroma (Palisaded encapsulated neuroma)
Neurilemmoma (Schwannoma)
  Variants: Ancient (degenerated) schwannoma
  Cellular schwannoma
  Plexiform schwannoma
  Melanotic schwannoma
Solitary neurofibroma
  Variants: Epithelioid neurofibroma
  Pacinian neurofibroma
Diffuse neurofibroma
Plexiform neurofibroma
Perineurioma
Neurothekeoma
Nerve sheath myxoma
Ganglioneuroma
Granular cell tumor
  Variant: Malignant granular cell tumor
Heterotopic meningeal lesion (Ectopic meningioma)
Heterotopic glial nodules (Nasal gliomas)

Malignant

Malignant Peripheral Nerve Sheath Tumor (MPNST)
  Variants: Epithelioid MPNST
  Pigmented (melanotic) MPNST
  Malignant Triton tumor
Neuroblastoma and Ganglioneuroblastoma (See Adrenal Tumors)
Clear cell sarcoma (Malignant melanoma of soft parts)
Extraspinal (soft tissue) ependymoma

Mucosal Neuroma

- Rare, almost always part of MEN type IIb (Gorlin's Syndrome)

Solitary Circumscribed Neuroma (Palisaded Encapsulated Neuroma)

Clinical

- Long-standing, solitary, painless nodule; most 3 mm in size
- Usually on the face; peak age: 50-80 years

Microscopic

- Circumscribed, usually in the dermis
- Bland, spindle cells with small, wavy nuclei
- Fascicular growth in a fibrous stroma
- Artefactual clefts
- No nuclear palisading or zonation

Immunohistochemistry

- Schwann cells: S-100 protein +
- Axons: neurofilament+
- Capsule: EMA +

Neurilemmoma (Schwannoma)

- Benign, encapsulated nerve sheath tumor composed of Schwann cells

Clinical

- Peak: 20-50 years; M:F equal
- Usually, superficial or deep solitary, slow-growing mass; asymptomatic
- Common sites: head and neck and extremities
- Most solitary (unless NF-2)
- Usually do not recur after excision

Macroscopic

- Arise from nerve but usually easily separated at surgery
- Majority <5 cm in diameter; encapsulated

Microscopic

- Variable cellularity with fascicular or swirling pattern
- 2 components: Antoni A and B in varying proportions
- Antoni A:
  - Compact, cellular area with monomorphic eosinophilic spindle cells
  - Nuclear palisading around Verocay bodies
  - Collagenous stroma
- Antoni B:
  - Hypocellular, spindle cells in copious myxoid stroma
  - Blood vessels with thick hyalinized walls
- Mitoses (variable, usually few and not atypical)

- Nuclear hyperchromasia and mild pleomorphism
- Degenerative changes including hyalinization and stromal hemorrhage
- Infrequent microfoci of necrosis (not geographic like MPNST)

Immunohistochemistry

- S-100 strongly+

Variants

- Ancient (degenerated) schwannoma:
  - Benign schwannoma with severe degenerative changes
  - Significant nuclear atypia; no mitoses
- Cellular schwannoma:
  - May be mistaken for sarcoma; large deep tumors
  - Usually retroperitoneum or mediastinum
  - Hypercellular, fascicular pattern (predominant Antoni A)
  - Nuclear pleomorphism usually degenerative
  - Mitoses <10/10 HPF
  - Infrequent microfoci of necrosis (not geographic like MPNST)
  - S-100+; desmin- (unlike leiomyosarcoma)
- Plexiform schwannoma:
  - Uncommon type; usually not associated with neurofibromatosis
- Melanotic schwannoma - rare variant

Solitary Neurofibroma

- Benign nerve sheath tumor composed of mixture of Schwann cells, perineurial-like cells and fibroblasts

Clinical

- Solitary localized, painless, nodular, skin lesions
- Not associated with neurofibromatosis (NF)
- Peak age: 20-30 years
- Wide distribution, usually in dermis and subcutis
- Deeper lesions may be associated with NF and may undergo malignant change
- Arise within nerve; no tendency for local recurrence

Microscopic

- Circumscribed but not encapsulated
- Fusiform expansion of nerve trunk (variable)
- Uniform cellularity (variable) in a fibromyxoid stroma
- Elongated spindle cells with eosinophilic processes
- Tapering or wavy, hyperchromatic nuclei
- Small nerve fibers and mast cells
- Hyalinized stroma (variable)
- No mitoses
- S-100+ in 30-50% of cells

Variants

- Epithelioid neurofibroma (rare)
- Pigmented neurofibroma (rare
- Pacinian neurofibroma - possibly variant of schwannoma

Diffuse Neurofibroma

- Superficial variant of neurofibroma with ill-defined, infiltrative margins
- Peak age: 10-30 years
- 10% are associated with NF-1
- No tendency to undergo malignant transformation

Plexiform Neurofibroma

- Diffuse enlargement and distortion of nerves by neurofibromatous tissue
- Pathognomonic for NF-1; may be large and disfiguring
- Usually superficially and most common in head and neck region
- Large and deep-seated lesions have risk of malignant change

Soft Tissue Perineurioma (Storiform Perineurial Fibroma)

- A neoplasm composed of differentiated perineurial cells

Clinical

- Usually subcutaneous lesions in the extremities or trunk
- Typically middle-aged adults; M:F = 4:1
- Complete excision is curative, without recurrence

Microscopic

- Demarcated and unassociated with identifiable nerve
- Well-circumscribed, nodular or ovoid lesions; 1.5-20 cm in size
- Variable histology: elongated bundles, interweaving fascicles, loose whorls or storiform pattern
- “Cracking” artefact
- Wavy spindle cells dissecting collagenous stroma
- Mild nuclear hyperchromasia but no degenerative atypia
- Mitoses (rare)
- Myxoid change (infrequent)

Immunohistochemistry

- EMA+ (membranous staining)
- S100+ (axons and Schwann cells)
- Neurofilament+ (axons and Schwann cells)

Variant

- Intraneural perineurioma

Neurothekeoma

- Cutaneous, multilobulated, variably cellular neoplasm composed of clustered, spindle and epithelioid cells lacking Schwann cell differentiation

Clinical

- Usually solitary, cutaneous lesion in children and young adults
- Common sites: face, arm and shoulder
- No association with NF; local recurrence is uncommon

Microscopic

- Circumscribed with multilobular growth pattern; 0.5-3 cm in size
- Hypercellular with variably myxoid stroma
- Fascicles and whorls of spindle or epithelioid cells
- Multinucleated and hyperchromatic cells (frequent)
- Mitoses (variable)
- S-100 protein –

Variant

- Cellular Neurothekeoma:
  - Hypercellular variant without myxoid stroma
  - Infiltrative growth pattern
  - More nuclear pleomorphism and mitoses (up to 10/10 HPF)
  - Benign tumors, cured by resection

Nerve Sheath Myxoma

- Cutaneous, multilobulated, predominantly myxoid, spindle cell neoplasm exhibiting Schwann cell differentiation

Clinical

- Slow-growing, solitary, painless, lesions in adults: 30-60 years
- Common sites: hands, back, arm, face and neck
- No association with NF; local recurrence is uncommon

Microscopic

- Circumscribed with multilobular growth pattern; 0.5-3 cm in size
- Loose network of stellate, spindle and epithelioid cells
- Abundant myxoid stroma
- Eosinophilic, thin cytoplasmic processes
- Intranuclear and cytoplasmic vacuoles
- Mitoses (rare)
- S-100 protein+

Ganglioneuroma

- A benign neoplasm composed of mature autonomic ganglion cells and numerous axons with Schwann cells in a fibrous stroma

Clinical

- Peak age: 10-20 years; female predilection
- Most occur in the mediastinum, retroperitoneum and adrenal medulla
- Symptomatic due to mass effect and rarely due to endocrine activity
- Most arise de novo, a few may represent matured ganglioneuroblastoma
- May arise in association with schwannoma or pheochromocytoma
- Resection is curative

Microscopic

- Well-circumscribed mass with a fibrous capsule; most <15 cm
- Loose network with bundles of axonal processes with Schwann cells, resembling neurofibroma
- Nests or scattered mature ganglion cells
- Multinucleated cells, pleomorphism and vacuolation (all variable)
- Degenerative changes (variable)
- Adequate sampling to rule out ganglioneuroblastoma

Granular Cell Tumor

Clinical

- Common lesion; usually skin or subcutis
- Peak age: 40-70 years; slight female predominance
- Any anatomic site; commonly trunk, tongue and arms
- Usually solitary, 10% multiple
- Majority are benign and local recurrence is rare

Microscopic

- Usually <3 cm
- Poorly circumscribed or infiltrative margins
- Uniform appearance at any location
- Nests, trabecular or sheets of round to polygonal cells
- Copious granular, eosinophilic cytoplasm
- PAS with diastase+ intracytoplasmic granules
- Uniform, central, pyknotic nuclei
- Minimal nuclear pleomorphism and scattered mitoses
- Fibrosis (variable)
- Pseudoepitheliomatous hyperplasia of overlying squamous epithelium
- S-100, neuron-specific enolase (NSE) and laminin+

Variant

- Malignant granular cell tumor:
  - 2-3% of all cases; usually occur in deep soft tissue
  - 50% have a metastasizing, fatal clinical course
  - Similar morphologic features, usually infiltrative margins
  - Prominent nucleoli and frequent mitoses

Differential Diagnosis

- Adult rhabdomyoma:
  - No cytoplasmic granules; cross-striations and cytoplasmic glycogen
- Hibernoma and fibroxanthoma:
  - Presence of lipid droplets
- Reactive processes:
  - No nested or trabecular arrangement, inflammatory cells and necrosis
- Squamous cell carcinoma:
  - No underlying granular cells and more nuclear atypia

Heterotopic Meningeal Lesions (Ectopic Meningioma)

- Consists of three types:
  - Ectopic meningothelial hamartoma - usually over scalp and spinal column
  - Cutaneous meningioma - usually adults, mostly head
  - Spread of central nervous system meningioma to overlying skin or subcutis

Heterotopic Glial Nodules (Nasal Gliomas)

- Usually result of misplaced glial tissue in subcutis in head and neck

Malignant

Malignant Peripheral Nerve Sheath Tumor (Malignant Schwannoma or Neurofibrosarcoma)

Clinical

- 2 principal forms: sporadic or associated with NF-1 (30-50%)
- Peak age: 20-50 years; 10-15 years younger in patients with NF-1
- Sporadic form: M:F equal; NF-1: M:F = 4:1
- Common sites: proximal limbs and trunk
- May arise in a neurofibroma (NF-1) and rarely post-radiation
- 50% 5 year survival in sporadics and 20-25% in NF-1
- Metastases are usually to lung, liver, subcutis and bone

Macroscopic

- Usually large, fusiform, eccentric mass within a nerve
- Most >10 cm in diameter
- Fleshy, whitish cut surface with areas of hemorrhage and necrosis

Microscopic

- Fascicular spindle cell pattern (fibrosarcoma-like)
- Abrupt transition between cellular and myxoid areas
- Perivascular whorling of tumor cells
- Elongated cells with tapering or wavy, hyperchromatic nuclei
- Pale, ill-defined cytoplasm:
  - Mild nuclear pleomorphism and mitoses
  - Nuclear palisading (uncommon)
- Myxoid stroma and fibrosis (variable)
- Geographic necrosis (variable)
- Heterologous differentiation (10-15%):
  - Rhabdomyosarcoma (Malignant Triton tumor)
  - Osteosarcoma or chondrosarcoma
  - Angiosarcoma
  - Glandular differentiation

Immunohistochemistry

- S-100+ (50% of cases) and usually 20-30% of cells

Variants

- Epithelioid MPNST:
  - 5% of MPNSTs; 50% are superficial with better prognosis
  - Difficult differential diagnosis from carcinoma or melanoma
  - Usually S-100+, HMB 45 and keratin-
- Pigmented (melanotic) MPNST
- Malignant Triton tumor:
  - MPNST with rhabdomyoblastic differentiation

Differential Diagnosis

- Fibrosarcoma:
  - Uniform fascicular pattern, no neural differentiation, S-100-
- Synovial sarcoma:
  - Uniform fascicular pattern, no neural differentiation, calcification
  - Cytokeratin+
- Leiomyosarcoma:
  - Eosinophilic cytoplasm, central blunt-ended nuclei,
  - S-100-, actin+, desmin+
- Cellular neurofibroma (especially in NF-1):
  - No mitoses

- Cellular schwannoma:
  - Location, Antoni A and B pattern, perivascular hyalinization, encapsulation, strong and diffuse S-100 protein+

Clear Cell Sarcoma (Malignant Melanoma of Soft Parts)

Clinical

- Intimately associated with tendons and aponeuroses
- Peak age: 20-40 years; slight female predominance
- Common sites: distal extremities, especially foot and ankle
- Slowly growing, painful mass
- Repeated local recurrences due to incomplete excision
- 50% develop late metastases to lungs, lymph nodes or bone
- Poor long-term prognosis despite adjuvant therapy

Microscopic

- Usually <5 cm, associated with fascia and tendons
- Nests or fascicles of cells separated by fibrous septa
- Infiltrate into fibrotendinous tissue, subcutis or deep dermis
- Uniform cells with pale eosinophilic to clear cytoplasm
- Intracytoplasmic glycogen
- Round, polygonal to spindle cells
- Vesicular nuclei with prominent nucleoli
- Multinucleated giant cells (wreath-like nuclei)
- Melanin (variable)
- Fibrosis (variable)

Immunohistochemistry

- S-100+
- HMB 45+
- Neuron specific enolase (NSE)+

Cytogenetics

- t(12; 22) (q13; q13)

Differential Diagnosis

- Cutaneous melanoma:
  - Junctional activity; irregular growth pattern, more pleomorphism
- Fibrosarcoma:
  - No cellular aggregates, no intracytoplasmic glycogen
  - S-100-, HMB 45-
- MPNST:
  - Association with peripheral nerve or NF-1
  - No glycogen, more hyperchromatic nuclei and more mitoses
  - HMB 45-
- Metastatic renal cell carcinoma:
  - Less prominent nucleoli, no fusiform appearance
  - Cytokeratin (low molecular weight) and EMA+

Extraspinal (Soft Tissue) Ependymoma (see CNS tumors)

- Rare tumors; occur in subcutis dorsal to sacrum and coccyx
- Usually are of the myxopapillary type
- Greater tendency to metastasize than intraspinal counterpart
- Usually late metastasis (>10 years) to lung

CHONDRO-OSSEOUS TUMORS

Classification of Chondro-Osseous Tumors

- See Table 13-9

Benign

Osteoma Cutis

- Rare, usually multiple cutaneous nodules of mature bone
- Majority of bony nodules in skin are due to secondary ossification

Myositis Ossificans

Clinical

- Solitary, self-limiting, reactive, related to trauma (30%)
- Young adults with male predominance; uncommon in children
- Common sites: quadriceps and brachialis muscles
- Radiographs: well-circumscribed lesion with peripheral calcification and central lucency (variable with duration)

Macroscopic

- Well-circumscribed with edematous muscle at the periphery

Microscopic

- Zonation pattern
- Central zone - myofibroblastic proliferation (nodular fasciitis-like)
- Maturation towards periphery with osteoid production
- Mild nuclear atypia and mitoses

Table 13-9. Classification of Chondro-Osseous Tumors

Benign

Osteoma cutis

Myositis ossificans

Variants:

Panniculitis ossificans

Fibro-osseous pseudotumor of digits (florid reactive periostitis)

Fibrodysplasia (myositis) ossificans progressive

Soft tissue chondroma (Extraskeletal chondroma)

Malignant

Extraskeletal myxoid chondrosarcoma (chordoid sarcoma)

Extraskeletal mesenchymal chondrosarcoma

Extraskeletal osteosarcoma

- Hemorrhage (variable)
- Endochrondral calcification (variable)
- Entrapped, atrophic skeletal muscle fibers

Variants

- Panniculitis Ossificans:
  - Myositis ossificans in subcutis; usually upper limbs of women
- Fibro-osseous pseudotumor of the digits (florid reactive periostitis):
  - Rare heterotopic ossification in subcutis of digits
  - Young adults; M<F
  - Resembles myositis ossificans without zonation
- Fibrodysplasia (myositis) ossificans progressive:
  - Disseminated myositis ossificans
  - Rare, hereditary disease effecting children <10 years
  - Associated with skeletal abnormalities
  - Slowly progressive with poor long-term prognosis

Differential Diagnosis

- Extraskeletal osteosarcoma:
  - No zonation phenomenon or 'reversed' zonation
  - Marked nuclear pleomorphism and necrosis

Soft Tissue Chondroma (see bone tumors)

- Soft tissue counterpart of osseous tumors
- Exclusively hands and feet, usually fingers in adults
- Usually solitary and often associated with tendon

Malignant

Extraskeletal Myxoid Chondrosarcoma (Chordoid Sarcoma)

Clinical

- Painless, slow-growing, deep-seated mass
- Adults, peak age: 40-70 years; slight male predominance
- Common sites: lower limb (70%), trunk (20%) and upper limb (10%)
- Low grade tumor prone to local recurrences and infrequent metastases
- Metastasize to lungs, lymph nodes, bone and brain
- Bad prognostic factors: advanced age at presentation and >10 cm

Microscopic

- Well-circumscribed, multilobular, usually 5-15 cm
- Lobular growth pattern with fibrous septa
- Anastomosing cords, strands of small uniform chondroblast-like cells
- Copious myxoid matrix
- More cellular at periphery of lobules
- Round to spindle chondroblasts with eosinophilic cytoplasm
- Cartilaginous differentiation (variable)
- Cytoplasmic hyaline (rhabdoid) inclusions (variable)
- Mitoses and necrosis (variable)
- Intracytoplasmic glycogen (PAS+)

Immunohistochemistry

- S-100+ (focal, variable)

Differential Diagnosis

- Malignant mixed tumor of adnexal origin:
  - More superficial location, epithelial differentiation
  - Keratin, actin and S-100 protein+

Extraskeletal Mesenchymal Chondrosarcoma (see Bone Tumors)

- Highly malignant neoplasm, more common in bone
- Head and neck lesions in 25 year olds
- Deep musculature, especially thigh in >45 year olds
- Aggressive clinical course with metastases to lungs and lymph nodes

Extraskeletal Osteosarcoma

- 5% of all osteosarcomas arise in soft tissue
- Adults: 60-90 years; M>F
- Common sites: limbs, especially thigh and retroperitoneum

- ♦ May be radiation-induced
- ♦ Poor prognosis with aggressive, metastasizing clinical course
- ♦ Overall mortality: 60-70%
- ♦ Histology similar to bone tumors, commonest pattern is MFH-like

MISCELLANEOUS TUMORS

Classification of Tumors of Uncertain Histogenesis

- ♦ See Table 13-10

Benign

Tumoral Calcinosis

- ♦ Idiopathic disorder with tumor-like calcium deposition in periarticular soft tissue
- ♦ Unassociated with chronic renal failure or collagen vascular disorder

Clinical

- ♦ Peak age: 10-30 years: M>F
- ♦ 2/3 of cases involve blacks; siblings in 50%
- ♦ Usually around large joints: hip, shoulder and elbow.
- ♦ Slow-growing, firm, subcutaneous mass
- ♦ 2/3 are multiple and bilateral

Microscopic

- ♦ Unencapsulated, firm, rubbery mass; range: 5-15 cm in diameter
- ♦ Cut surface: calcified, chalky masses with dense fibrous tissue
- ♦ Proliferation of multinucleated and osteoclast-like giant cells and macrophages
- ♦ Dense fibrous tissue around calcified material
- ♦ Psammomatous calcifications (rare)

Differential Diagnosis

- ♦ Metastatic calcifications:
  - – Associated with chronic renal failure and secondary hyperparathyroidism
  - – Hyperphosphatemia with uremia on hemodialysis
  - – Hypercalcemia in hypervitaminosis D, hyperparathyroidism
- ♦ Calcinosis universalis and calcinosis circumscripta:
  - – Associated with collagen vascular disease
- ♦ Dystrophic calcifications:
  - – Smaller, usually in damaged tissue e.g.: injury or infection

Amyloidoma

Table 13-10. Classification of Tumors of Uncertain Histogenesis

Benign

- Tumoral calcinosis
- Amyloidoma
- Myxoma
  - Intramuscular myxoma
  - Juxta-articular myxoma
  - Dermal myxoma (cutaneous myxoid cyst)
  - Myxoma of the jaw
  - Cutaneous myxoma (superficial angiomyoma)
  - Ganglion
  - Aggressive angiomyxoma
- Ossifying Fibromyxoid Tumor

Malignant

- Alveolar Soft Part Sarcoma
- Epithelioid Sarcoma
- Primitive Neuroectodermal Tumor (Extraskeletal Ewing's sarcoma)
- Extrarenal Rhabdoid Tumor
- Desmoplastic Small Round Cell Tumor

- ♦ Rare in soft tissue; solitary or multiple
- ♦ May be primary or secondary

Myxoma

Intramuscular myxoma

Clinical

- ♦ Peak age: 30-70 years; female predominance
- ♦ Involve large muscles, usually thigh and limb girdles
- ♦ Slowly growing, painless mass.
- ♦ 5% multiple and associated with fibrous dysplasia
- ♦ Local recurrences are rare

Microscopic

- ♦ Circumscribed to ill-defined margins extending between muscle fibers

- Paucicellular and minimal vascularity
- Small, bland, spindle or stellate cells with hyperchromatic nuclei
- No pleomorphism or mitotic activity

Differential Diagnosis

- Myxoid liposarcoma:
  - Plexiform capillary network and lipoblasts
- Myxoid MFH (myxofibrosarcoma):
  - Hypercellularity, nuclear pleomorphism and mitoses

Juxta-articular Myxoma

- Uncommon variant
- Adjacent to large joints, usually knee, shoulder, elbow and hip
- Mainly males; peak age: 30-70 years
- Associated with cysts and degenerative joint disease
- May involve subcutis, tendons and joints
- Often recur locally
- Poorly marginated and may be more cellular

Dermal Myxoma (cutaneous myxoid cyst)

- Uncommon lesion on the finger of adults

Cutaneous Myxoma (superficial angiomyxoma)

- Usually sporadic, may be associated with Carney's complex
- Affects adults; usually head and neck or trunk
- Superficial nodule involving dermis and subcutis, <3-4 cm
- Commonly recur locally
- Multiple, poorly-defined myxoid nodules
- Numerous thin-walled vessels:
  - Entrapped epithelial elements

Ganglion

- Common, usually dorsum of wrist in young adults
- Frequently attached to joint capsule and tendon sheath

Aggressive Angiomyxoma (see Vulvar tumors)

- Involves vulva or pelvis of adult female

Ossifying Fibromyxoid Tumor

Clinical

- Usually subcutaneous nodule involving extremities
- Adults; M>F
- May recur locally

Microscopic

- Well circumscribed, multinodular; <5 cm in diameter
- Fibrous capsule and fibrous septa
- Shell of mature lamellar bone (90%)
- Nests and cords of cells
- Round cells with pale cytoplasm uniform, vesicular nuclei
- Minimal pleomorphism and scarce mitoses
- Abundant fibromyxoid stroma
- Chondroid metaplasia (variable)

Immunohistochemistry

- S-100 protein+
- Desmin+/-
- Actin+/-

Malignant

Alveolar Soft Part Sarcoma

Clinical

- Uncommon; <1% of all sarcomas
- Occurs in adolescents or young adults; M<F
- In adults usually in the lower extremities
- In children usually in head and neck region
- Slow-growing and painless
- May present with metastases to lungs or brain
- Indolent but bleak prognosis
- Children seem to have a better prognosis

Microscopic

- Well-circumscribed and lobulated
- Organoid pattern with nests and sheets of large cells
- Alveolar pattern due to central dyscohesion
- Fibrovascular septa
- Large, round cells with clear to eosinophilic granular cytoplasm
- Eccentric round nuclei with prominent nuclei:
- PAS-diastase+ intracytoplasmic crystals and granules
- Intracytoplasmic glycogen
- Necrosis and hemorrhage (variable)
- Mild nuclear pleomorphism and rare mitoses
- Vascular invasion, especially of dilated periphery veins

Differential Diagnosis

- Metastatic renal cell carcinoma:
  - More pleomorphism, lack intracytoplasmic crystals
  - Cytokeratin+
- Melanoma:
  - More pleomorphism, HMB-45 and S-100 protein+
- Paraganglioma:
  - No glycogen, chromogranin and synaptophysin+
- Granular cell tumor:
  - Not lobulated, less well-defined cells, less vascular, more granular cytoplasm, S-100 protein+

Epithelioid Sarcoma

Clinical

- Usually adolescents and young adults; male predominance
- Typically distal extremities, especially hand and wrist
- Solitary or multinodular, slow-growing, superficial mass
- Involve dermis, subcutis, fascia or tendons
- Pain and ulceration (common)
- Spreads along fascial planes or neurovascular bundles
- Treatment: radical surgery
- Slow, relentless course with multiple local recurrences
- Eventual metastases and death despite treatment
- 50% metastasize to lymph nodes, lung and soft tissue
- Tumor <5 cm have a better prognosis

Microscopic

- Ill-defined, multinodular firm mass with necrotic foci
- Usually <5 cm
- Diffusely infiltrative margins
- Nodules of monomorphic, eosinophilic, epithelioid to spindle-shaped cells
- Dense fibrous stroma
- Minimal nuclear pleomorphism
- Mitoses (variable)
- Central necrosis or myxohyaline degeneration
- Perineural and vascular invasion
- Cytoplasmic vacuolation (variable)
- Chondroid or osseous metaplasia (rare)

Immunohistochemistry

- Cytokeratin+
- Vimetin+
- EMA+
- S-100 protein ±
- Desmin-
- CD34-

Differential Diagnosis

- Infections or necrobiotic granuloma
  - No nuclear pleomorphism, no vascular and perineural invasion
  - Keratin and EMA-, CD68+
- Nodular fasciitis, fibrous histiocytoma and fibromatosis
  - No epithelioid features, no nodularity, cytokeratin-
- Squamous cell carcinoma:
  - Epidermal involvement, dyskeratosis, keratin pearls
  - More cytological pleomorphism
- Malignant melanoma:
  - More pleomorphism, S100+, HMB45+, cytokeratin-
- Synovial sarcoma:
  - Location, no dermal involvement and ulceration
  - Biphasic pattern, intracellular mucin, small cells not eosinophilic

Peripheral Primitive Neuroectodermal Tumor (Peripheral Neuroepithelioma, Askin tumor, Extraosseous Ewing's sarcoma)

- Family of lesions with specific and reproducible translocation t(11; 22)(q24;q12) and variable neuroectodermal differentiation

Clinical

- Wide age range; peak: 10-30 years; M=F
- Common sites: trunk and lower limbs
- Occasionally arise in association with nerve trunk
- Usually rapidly enlarging, deep-seated mass (unresectable)
- Susceptible to chemotherapy, the more primitive (Ewing's) respond well
- Overall 5-year survival is 20-30%
- Metastases occur to lungs and lymph nodes

Microscopic

- Variable depending on degree of neuroectodermal differentiation
- Lobules, trabecular and sheets of cells
- Prominent capillary network and scant stroma
- Necrosis (common)
- Primitive cells with round open to hyperchromatic nuclei
- Nucleoli (variable)
- Mitoses (variable)
- Pale, scanty to eosinophilic cytoplasm
- Intracytoplasmic glycogen (variable, typical in Ewing's)
- Homer-Wright rosettes and pseudorosettes (variable)

Immunohistochemistry

- MIC-2 (CD99)+
- LEU-7+
- Neuron-specific enolase (NSE)+
- Synaptophysin+
- Neurofilament+
- Chromogranin+
- S-100 protein +

Cytogenetics

- t(11;22)(q24;q12)

Molecular Genetics

- EWS-FLI-1 fusion protein

Differential Diagnosis

- Neuroblastoma:
  - Presence of neuropil, ganglionic differentiation, calcification,
  - MIC-2-
- Rhabdomyosarcoma:
  - Actin and desmin+, synaptophysin-
- Lymphoma:
  - No specific growth pattern, CD45+
- Neuroendocrine carcinoma:
  - Location, cytokeratin+, MIC-2-

Extrarenal Rhabdoid Tumor

- Rare, ill-defined entity (possibly a heterogeneous group)
- Usually infancy, wide age range
- Any location, usually trunk and proximal extremities
- Very aggressive clinical course with median survival of 6 months
- Metastases to lungs, liver, lymph nodes and soft tissue
- Hyaline globular cytoplasmic inclusions and large nucleoli
- Cytokeratin+, EMA+, vimentin+
- EM: Abundant paranuclear whorls of intermediate filaments

Desmoplastic Small Round Cell Tumor

Clinical

- Usually adolescents and young adults; male predominance
- Common sites: abdomen, pelvis, and omentum
- May be associated with widespread peritoneal implants
- Usually palpable, often painful mass
- Associated with distension, constipation, obstruction or ascites
- Highly aggressive neoplasm with a poor prognosis
- Widespread metastases (common)
- Normally not amenable to surgical excision
- Death despite treatment within a few years

Microscopic

- Solid, large multilobulated mass ± areas of necrosis
- Nests or masses of small rounded cells
- May have a trabecular or cord-like arrangement
- Intervening abundant fibrous stroma
- Hyperchromatic nuclei and scanty cytoplasm
- Cells may be vacuolated or contain PAS+ eosinophilic inclusions

Immunohistochemistry

- Cytokeratin +
- EMA+
- Desmin+ (usually paranuclear dot-like)
- Vimentin+
- S-100 protein ±
- CEA –

Cytogenetics

- (t(11;22)(q13;q12)

Differential Diagnosis

- Primitive neuroectodermal tumor (Ewing's sarcoma)
- Neuroblastoma
- Rhabdomyosarcoma
- Neuroendocrine carcinoma
- Seminoma
- Lymphoma

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Chapter 14

Tumor of the Salivary Glands

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INTRODUCTION TO SALIVARY GLAND TUMORS

- Salivary gland tumors are predominantly epithelial (Tables 14-1 and 14-2). Mesenchymal tumors most often involve glands by extension rather than arising within the gland. The latter are also found predominantly in children and adolescents. The most commonly encountered tumors in surgical pathology will be highlighted in this chapter. The non-pleomorphic salivary adenomas can be placed under the domain of monomorphic adenoma. These, in turn, can be divided into basaloid and non-basaloid tumors (Tables 14-3 and 14-4). There is also an inverse relationship between site of the affected salivary gland and the frequency of malignancy (Table 14-5)

Table 14-1. Salivary Gland Tumors

Benign		*Malignant*	
Epithelial	*Mesenchymal*	*Epithelial*	*Non-Epithelial/ Mesenchymal*
Pleomorphic adenoma (benign mixed tumor)	Angioma	Mucoepidermoid carcinoma	Sarcomas
Basal cell adenoma	Lipoma	Adenoid cystic carcinoma	Lymphomas
Canalicular adenoma	Fibrous histiocytoma	Acinic cell carcinoma	
Warthin's tumor	Neurofibroma and neurilemmoma	Terminal duct carcinoma (polymorphous low-grade adenocarcinoma)	
Oncocytoma	Hemangioma	Epithelial-myoepithelial carcinoma	
Myoepithelioma		Salivary duct carcinoma	
Sebaceous lymphadenoma and adenoma		Basal cell adenocarcinoma	
Ductal papillomas		Sebaceous carcinoma	
Cystadenoma		Oncocytic carcinoma	
		Adenocarcinoma, NOS (not otherwise specified)	
		Squamous cell carcinoma	
		Carcinoma ex-pleomorphic adenoma	
		Carcinosarcoma (sarcomatoid carcinoma)	
		Myoepithelial carcinoma (malignant myoepithelioma)	
		Undifferentiated carcinoma (small and large cell)	
		Nasopharyngeal-like carcinoma (undifferentiated carcinoma with lymphoid stroma)	

EPITHELIAL SALIVARY TUMORS

Table 14-2. Incidence of Primary Epithelial Salivary Gland Tumors in Different Sites (%)

Diagnosis	*Parotid*	*Submandibular*	*Sublingual*	*Minor*
Benign				
Pleomorphic adenoma	63.3	59.5	0	42.9
Warthin's tumor	14.0	0.8	0	0
Monomorphic adenoma	8.0	2.3	14	11
Malignant				
Mucoepidermoid carcinoma	1.5	1.6	0	8.9
Acinic cell carcinoma	2.5	0.4	0	1.8
Adenoid cystic carcinoma	2.0	16.8	28.6	13.1
Adenocarcinoma (NOS)	2.6	5.0	14.2	12.2
Squamous carcinoma	1.1	1.9	0	1.2
Undifferentiated carcinoma	1.8	3.9	14.2	2.1
Carcinoma ex pleomorphic adenoma	3.2	7.8	28.6	7.1

Pleomorphic Adenoma (Mixed Tumor)

Clinical

- Comprised of 55% to 70% of all salivary neoplasms
- More in females in 4th decade
- Painless, slow growing mass
- In parotid: 90% superficial lobe, 10% deep lobe

Macroscopic

- Well-defined, lobulated mass
- Multifocal in 0.5% of cases
- Variegated appearance, cartilaginous

Microscopic

- Biphasic epithelial and mesenchymal elements
- Epithelial cells:
  - Tubules, nests, ribbons, and files with occasional squamous, oncocytic, or sebaceous differentiation
- Myoepithelial cells:
  - Spindle or plasmacytoid cells
- Stroma: mucoid, myxoid, hyaline, or chondroid; rarely adipose tissue and bone
- Crystals: tyrosine-calcium oxyalate, collagenous spherules

Immunohistochemistry

- Generally non-contributory
- S-100 and SMA + in stromal and myoepithelial cells

Cytogenetics and Molecular Genetics

- Alteration, rearrangements, and LOH at 8q21 and 12q 14-15 regions

Differential Diagnosis

- Adenoid cystic carcinoma:
  - Lacks mesenchymal elements; clear demarcation between collagenous, epithelial, and mucoid materials
  - Propensity for perineural invasion
- Myoepithelioma:
  - Lacks ductal and mesenchymal elements
- Terminal duct carcinoma:
  - Variegated epithelial patterns; lacks mesenchymal features

Recurrent Mixed Tumor

- Histologically similar to primary
- Multiple nodules
- Extension to surrounding tissue

Myoepithelioma

Clinical

- Uncommon, 1.5% of all salivary tumors
- 2.2% to 5.7% of all benign tumors
- Male:female ratio = 1:1
- Most common sites: palate and parotid

Macroscopic

- Well-demarcated mass
- Tan, homogenous, and solid

Microscopic

- Comprised of >90% myoepithelial cells
- Cellular, mucoid, or hyalinized stroma may be present
- Lacks ductal differentiation
- Cell types: spindle, plasmacytoid, epithelioid, clear cells

Immunohistochemistry

- Keratin +, MSA +, S-100 +, desmin –

Electron Microscopy

- Microfilaments, 50 to 100 Å in size; pinocytic vesicles

Differential Diagnosis

- Spindle cell myoepithelioma:
  - Leiomyoma, nerve sheath tumors, synovial sarcoma, nodular fasciitis
  - Immunoreactivity for keratin excludes these mesenchymal tumors
- Plasmacytoid myoepithelioma:
  - Plasmacytoma: + for monoclonal light chain reaction, keratin –
- Clear cell myoepithelioma:
  - Metastatic renal cell carcinoma: vascular, cellular atypia, hemorrhage
  - Myoepithelial carcinoma: cellular atypia, infiltrative growth

Oncocytoma

Clinical

- Rare, 1% of all salivary tumors
- Women slightly more than men
- Bilateral in 7% of cases
- Main presentation is swelling

Macroscopic

- Solitary, encapsulated
- Reddish brown, smooth, and homogenous cut surface

Microscopic

- Large polygonal eosinophilic cells with central round nuclei
- Cord, ribbon, and acinar formation
- Focal mucinous or squamous metaplasia may be present
- Clear cell variant (clear cell oncocytoma)
- Oncocytic hyperplasia may occasionally be found at periphery

Immunohistochemistry

- Non-contributory

Electron Microscopy

- Large accumulation of mitochondria with lamellar structure
- Occasionally large glycogen particles:
  - Special stains
  - Phosphotangestic acid hematoxylin stain (PTAH) +

Differential Diagnosis

- Conventional oncocytoma:
  - Pleomorphic adenoma with oncocytic metaplasia: features of pleomorphic adenoma
  - Mucoepidermoid carcinoma: PTAH –; mucinous, intermediate, and squamous differentiation

Table 14-3. Types of Monomorphic Adenomas

Basaloid	*Non-Basaloid*
Basal Cell	Warthin's tumor
Tubulotrabecular	Oncocytoma
Solid	Sebaceous lymphadenoma
Canalicular	Sebaceous adenoma
Dermal analogue (membranous)	Ductal adenoma
	Myoepithelioma

Table 14-4. Differential Characteristics Between Basaloid Adenomas and Canalicular Adenoma

Feature	Basaloid		Canalicular
	Dermal analogue	*Other types*	
Sex			
Male:Female	10:1	1:1	1:1.7
Age (years)			
Range	34–74	1–83	34–88
Mean	58.1	58.6	65.1
Synchronous dermal lesions (%)	37.7	0	0
Site (%)			
Parotid	86.2	90.1	1.6
Submandibular	6.8	4.9	0
Upper lip	0	4.9	87.2
Other minor sites	6.8	0	24.7
Multicentricity (%)	48	0.9	24
Recurrences (%)	24	0	0
Malignant transformation (%)	28	3.9	0

Modified from Eveson & Caswon, 1985

- – Acinic cell carcinoma: acinar differentiation, PTAH granules
- – Oncocytosis and oncocytic hyperplasia: diffuse, lacks fibrous encapsulation, retains architecture

♦ Clear cell oncocytoma:

- – Epi-myoepithelial carcinoma: dual cellular differentiation (myoepithelial and ductal)
- – Metastatic renal cell carcinoma: high vascularity, history of renal cell carcinoma

Warthin's Tumor

Clinical

♦ Second most common benign tumor
♦ Superficial, slow-growing mass
♦ Exclusively parotid, 2% to 15% of all parotid tumors
♦ Bilaterality not uncommon
♦ Male:female ratio = 8:1

Macroscopic

♦ Well-circumscribed and cystic
♦ Brownish, creamy materials

Microscopic

♦ Oncocytic epithelial lined spaces with occasional papillary formation
♦ Lymphoid stroma with germinal centers
♦ Occasional globlet, squamous, and sebaceous cells

Immunohistochemistry

♦ Non-contributory

Electron Microscopy

♦ Enlarged mitochondria in oncocytes

Cytogenetics

♦ Structural alteration in chromosome 7

Differential Diagnosis

♦ Oncocytoma:

- – In stroma-deficient Warthin's tumor, lacks cystic formation

♦ Sebaceous adenoma, squamous carcinoma, and mucoepidermoid carcinoma:

- – Lack lymphoid stroma; minimal oncocytic features

Sebaceous Lymphadenoma

Clinical

- Rare, 0.1% of all adenomas
- Parotid is most common site
- Male:female ratio = 1:1
- Painless mass

Macroscopic

- Circumscribed and encapsulated mass

Microscopic

- Solid sebaceous or cystic nests and metaplastic ducts in lymphoid stroma
- Giant cell reaction to extravasated cystic content

Sebaceous Adenoma

Clinical

- Rare, 0.1% of all salivary gland tumors
- Males slightly more than females
- Parotid, submandibular, and oral cavity glands are most common sites

Macroscopic

- Solid, gray, well-circumscribed mass

Microscopic

- Benign, irregular, sebaceous, cellular nests in lymphoid stroma
- Large cystic formation

Basal Cell Adenoma

Clinical

- 1% to 3% of all major salivary gland tumors
- Mostly in women
- Parotid is most common site
- May present within cervical lymph node

Macroscopic

- Encapsulated, round, or oval mass
- Grayish or white homogenous cut surface
- Average size 2 cm
- Occasional cystic formation

Microscopic

- Trabecular, solid, mixed, and membranous cellular patterns
- Mixed variant common
- Monotonous, small, dark nuclei with scant basophilic cytoplasm
- Cords and nests with peripheral palisading
- Tubular pattern in minor glands
- Basement membrane materials between cell nests and stroma, marked in membranous type
- Vascular stroma

Dermal Analogue Tumor (Membranous Adenoma)

Clinical

- Mainly parotid and peri- or intra-parotid lymph nodes
- High recurrence rate
- Synchronous or metachronous skin adnexal tumors (e.g., dermal cylindromas, trichoepitheliomas, eccrine spiradenomas not uncommon)

Macroscopic

- Multicentric
- Unencapsulated nodule

Microscopic

- Hyaline materials between cellular nests
- Morula-like structure with keratinization

Immunohistochemistry

- Non-contributory

Electron Microscopy

- Reduplicated basal laminae

Table 14-5. Frequency of Epithelial Malignancy in Different Salivary Gland Sites (%)

Site	*Malignant*
Parotid	14.7
Submanidublar	37.0
Sublingual	85.7
Minor	46.1

- Ductal, myoepithelial, and basal cells features

Differential Diagnosis

- Adenoid cystic carcinoma:
  - Manifests invasive pattern; lacks vascularity
- Basal cell adenocarcinoma:
  - Similar cytomorphology, but shows invasive features

Canalicular Adenoma

Clinical

- 1% of all salivary gland tumors, 4% of all minor glands
- >73% in upper lip and buccal mucosa
- Male:female ratio = 1.0:1.7
- Painless swelling

Macroscopic

- 0.6 to 2 cm (1.7 cm) in size
- Circumscribed and encapsulated nodules (0.5 to 2 cm)
- Occasionally multinodular and multicentric
- Homogenous, tan, soft mass

Microscopic

- Cords of columnar cells with abundant cytoplasm
- Loose vascular stroma
- Cystic and papillary projection

Immunohistochemistry

- Non-contributory

Electron Microscopy

- Non-diagnostic
- Desmosomes, polysomes, and endoplasmic reticulum

Differential Diagnosis

- Basal cell adenoma:
  - Lacks columnar cell features
- Adenoid cystic carcinoma:
  - Lacks circumscription and vascularity
- Other benign adenomas
- Mucinous cystadenoma:
  - Mucin-lined cells

NON-EPITHELIAL SALIVARY TUMORS

Types

- Angioma, lipoma, neurofibroma, and hemangiopericytoma

Clinical

- Incidence less than 5%
- Mainly involves major glands

Macroscopic

- Poorly demarcated

Microscopic

- Similar to those of other locations

EPITHELIAL TUMORS

Malignant Mixed Tumor

- "Malignant mixed tumor" is a generic term for malignancy associated with mixed tumors. The carcinoma ex pleomorphic adenoma is, by far, the most frequent. Carcinosarcoma, on the other hand, are few in number. Metastasizing pleomorphic adenoma is a disputed case
- Incidence: 3% to 12% of all malignancy and 2% of all salivary tumors

Carcinoma Ex-Pleomorphic Adenoma

Clinical

- Painless, rapidly growing mass
- 5% to 10% of pleomorphic adenomas, 11.6% of all malignant tumors
- Mainly major salivary glands: parotid (82%), submandibular (18%), sublingual (0.3%)
- Minor glands: palate, sinonasal tract
- Facial nerve paralysis (38%)
- Fixation to surrounding structure is common

Macroscopic

- Poorly circumscribed and infiltrative mass
- Variegated cut surface, soft to firm
- Hemorrhage and necrosis

Microscopic

- Malignant features
  - Cellular atypia, infiltrative growth, necrosis, hemorrhage, hyalinization, and calcification

Histology
- Adenocarcinoma, NOS
- Squamous carcinoma
- Terminal duct carcinoma
- Undifferentiated carcinoma
- Mucoepidermoid carcinoma
- Salivary duct carcinoma
- Subtypes
  - Non-invasive (intratumoral carcinoma)
  - Invasive

Immunostaining
- Non-contributory

Differential Diagnosis
- Benign mixed tumors
- Carcinosarcoma

Carcinosarcoma (Concomitant Epithelial and Mesenchymal Malignancy)

Clinical
- Rapid onset
- Parotid is most common site
- Rare, 0.06% of salivary neoplasms and 0.16% of malignant tumors

Macroscopic
- Large mass
- Unencapsulated

Microscopic
- Infiltrative borders
- Biphasic epithelial and mesenchymal cells
- Malignant cellular features in both mesenchymal and epithelial components
- Cellular pleomorphism and mitosis
- Adenocarcinoma, chondrosarcoma, osteosarcoma, malignant fibrous histiocytoma, and unclassified sarcoma may be seen

Immunohistochemistry
- Keratin, EMA, desmin, SMA, +
- DNA content:
  – High proliferation and DNA aneuploidy

Differential Diagnosis
- Spindle cell carcinoma:
  – Keratin +, desmin and SMA –
- Primary sarcoma:
  – Keratin –
- Synovial sarcoma:
  – Uniform spindle and glandular components

Metastasizing Pleomorphic Adenoma

Clinical
- History of multiple recurrent pleomorphic adenoma
- Latent, average 16 years after primary excision

Microscopic
- Similar to benign mixed tumor

Macroscopic
- Non-encapsulated nodules

Differential Diagnosis
- Chrondroid hamartomas of lung:
  – Lacks myoepithelial cells
- Chondroid chordoma:
  – Usually afflicts vertebra; lacks duct component
- DNA flow cytometry:
  – Diploid with low proliferative activity

Myoepithelial Carcinoma

Clinical
- 0.2% of all epithelial neoplasms
- Parotid is most common site
- Male:female ratio = 1:1

Macroscopic
- Unencapsulated
- Hemorrhage, necrosis, and cystic degeneration

Microscopic
- Malignant spindle, plasmacytoid, clear, and epithelioid cells
- Marked pheomorphism, mitosis, and necrosis
- Invasive borders

Immunohistochemistry
- S-100 and actin +, keratin +/–

Electron Microscopy
- Microfilaments with focal dense bodies
- Desmosomes and pinocytic vesicles

Flow Cytometry
- Abnormal DNA content (aneuploidy)

Differential Diagnosis
- Leiomyosarcoma:
  – Keratin –, SMA +
- Nerve sheath tumor:

  - S-100 +, keratin –
- Spindle cell carcinoma:
  - Keratin +, S-100 –
- Metastatic melanoma:
  - HMB 45 +, keratin –
- Synovial sarcoma:
  - Biphasic features

Oncocytic Carcinoma

Clinical

- Rare, 5% of all oncocytic tumors
- 0.005% of all epithelial neoplasms
- Major salivary glands; parotid is most common site
- Male:female ratio = 1:1
- Pain, paralysis ($^1/_3$ of patients)
- Old age

Macroscopic

- Ill-defined, infiltrative mass
- Necrosis, hemorrhage

Microscopic

- Large cells with oncocytic cytoplasm
- Nuclear and cellular aytpia with pheomorphism, mitosis
- Vascular and soft tissue invasion

Immunohistochemistry

- Non-contributory

Differential Diagnosis

- Oncocytoma:
  - Lacks invasion; cellular atypia
- Salivary duct carcinoma:
  - Cribriform and apocrine features, PATH –

Carcinoma in Warthin's Tumors

Clinical

- Extremely rare
- Typically parotid or intraparotid lymph nodes
- Male:female ratio = 4.5:1
- Middle- and old-age individuals
- History of prior irradiation not uncommon

Macroscopic

- Solid, cystic, ill-defined mass
- Gray to light pink

Microscopic

- Oncocytic carcinoma, most common
- Squamous and adenocarcinoma, occasionally
- Undifferentiated carcinoma is rare

Immunohistochemistry

- Non-contributory

Differential Diagnosis

- Metastatic carcinoma:
  - History of primary tumor elsewhere
- Concomitant primary salivary gland tumor

Sebaceous Carcinoma

Types

- Sebaceous carcinoma
- Sebaceous lymphadenocarcinoma

Clinical

- Very rare
- Exclusively parotid
- Male:female ratio = 1:1
- Occasionally painful mass

Macroscopic

- Infiltrative, ill-defined mass
- Necrosis and hemorrhage

Microscopic

- Undifferentiated malignant cells with evidence of sebaceous differentiation
- Nerve invasion and soft tissue extension not infrequent

Special Studies

- Immunostaining:
  - Lactoferrin +
- Electron microscopy:
  - Lipid vacuoles and glandular features

Differential Diagnosis

- High-grade salivary gland carcinoma:
  - Lacks any sebaceous features
- Adnexal skin tumors

Basal Cell Adenocarcinoma

Types

- De novo
- Carcinoma ex-basal cell adenoma

Clinical

- 2% of malignant epithelial tumors, 1.6% of all salivary tumors
- Mainly parotid, occasionally in submandibular and minor glands

- Male:female ratio = 1:1
- Adults average 60 years
- Swelling, occasional pain and tenderness

Macroscopic

- Unencapsulated but well-circumscribed mass
- Occasionally infiltrative
- Homogenous mass with tan, cut surface, rarely cystic

Microscopic

- Small, round-to-ovoid cells with dark hyperchromatic nuclei and scant cytoplasm
- Peripheral palisading
- Minimal nuclear atypia
- Mitosis 1 to 10/10 HPF
- Focal squamous metaplasia 25%
- Infiltrative growth
- Perineural invasion 30%, vascular invasion 20%

Special Studies

- Non-contributory

Differential Diagnosis

- Basal cell adenoma:
  - Lacks invasive features
- Basal cell carcinoma of skin:
  - History of BCC
- Solid adenoid cystic carcinoma:
  - High-grade solid areas with foci of cribriform and tubular patterns
- Undifferentiated small cell carcinoma:
  - Neuroendocrine markers +
- Basaloid squamous carcinoma:
  - Comedo-necrosis, origin from dysplastic squamous epithelium

Acinic Cell Carcinoma (Table 14-6)

Clinical

- Parotid 99%, rarely in submandibular and oral cavity
- Ectopic: may present in middle and lower cervical lymph nodes

Macroscopic

- Circumscribed or infiltrative
- Homogenous mass with gray cut surface
- Multinodular

Microscopic

- Large cells with small, centralized nuclei
- Abundant basophilic cytoplasm with coarse granules; vacuolation and clear cytoplasm not uncommon
- Lymphoid infiltrate with germinal center

Electron Microscopy

- Three types of cells:
  - Ductal with few organelles and luminal microvilli
  - Serous with abundant granules
  - Undifferentiated

Special Stains

- Periodic acid schiff-diastase resistant granules

Immunostaining

- Non-contributory

Differential Diagnosis

- Terminal duct carcinoma:
  - Most common in minor salivary glands
  - Perineural invasion
  - Variegated patterns
  - Uniform cell populations
- Tumors with clear cell features:
  - Mucoepidermoid carcinoma: epidermoid features, mucinous and intermediate cells, and glandular formation
  - Metastatic renal cell carcinoma: vascular, history of RCC
  - Epi-myoepithelial carcinoma: ductal and myoepithelial cells, S-100 protein +
- Tumors with papillary features:
  - Cystadenocarcinoma: mucin +
  - Metastatic papillary thyroid carcinoma: thyroglobulin +, nuclear inclusion

Adenoid Cystic Carcinoma

Clinical

- 6.5% to 10% of all epithelial salivary gland tumors, 2% to 4% of parotid tumors, 15% of submandibular tumors, and 30% of minor gland tumors
- Slightly more in women, in submandibular gland
- Slowly growing mass
- Pain in approximately 18% of patients
- Facial nerve paralysis in 4% of cases

Macroscopic

- Circumscribed, but uncapsulated, size 1.5 to 4 cm
- Firm, monolobular mass
- Gray and homogenous cut surface

Microscopic

- Features and grades:
  - Tubular form:
    - Low grade
    - Monotonous cellular features, two cell types

Table 14-6. Characteristics of Acinic Cell Carcinoma

Feature		*Frequency (%)*
Pattern		
	Solid	50
	Microcystic	30
	Follicular	15
	Papillary-cystic	5
Cell type		
	Serous-acinar	75
	Ductal	20
	Vacuolated, clear	5
Male:Female		1:2
Incidence		
	All parotid tumors	2–4
	All parotid malignancies	12–17
Bilaterality		3
Local recurrence		45
Metastasis		20

- – Cribriform, cylindromatous:
  - Intermediate grade
  - Tumor nests with "sieve-like" or "Swiss cheese" configuration
  - Pseudoglandular spaces with hyaline materials
- – Solid:
  - Nests of basaloid high-grade tumor cells
  - Focal areas of tubular and cribriform patterns
  - Hyalized stroma, mucinous, and myxoid forms may be present

Immunohistochemistry

- ♦ Ductal cells: CEA, EMA, and keratin +; S-100 and SMA –
- ♦ Myoepithelial cells: SMA +, S-100 and keratin +

Flow Cytometry

- ♦ DNA aneuploid and high S-phase tumors, aggressive

Cytogenetics

- ♦ Translocation of t(6;9) chromosomes

Differential Diagnosis

- ♦ Terminal duct carcinoma:
  - – Variegated patterns, but no high-grade solid type
- ♦ Basal cell adenoma:
  - – One cell type, lacks infiltration
- ♦ Basaloid squamous carcinoma:
  - – Squamous differentiation, necrosis, origin from squamous dysplasia
- ♦ Small-cell undifferentiated carcinoma:
  - – Immunostaining positivity to neuroendocrine markers and EM granules
- ♦ Poorly differentiated mucoepidermoid carcinoma:
  - – Mucin +, epidermoid features

Mucoepidermoid Carcinoma

Clinical

- ♦ Most common malignant tumor, 15.5% of all salivary tumors
- ♦ Parotid 60% to 70%, oval cavity 15% to 20%, submandibular 6% to 10%
- ♦ Most common malignancy in children
- ♦ May present in mandible and paraparotid lymph node
- ♦ Average time to diagnosis: 6.8 years in low-grade tumors, 1.5 years in high-grade tumors

Macroscopic

- Low grade: well-circumscribed, cystic, and mucoid, rarely exceed 3.0 cm
- Intermediate and high grades: poorly circumscribed, infiltrative, and solid

Microscopic

- Grade I:
  - Macro- or microcystic
  - Mucin-producing cells abundant
  - Lack of pleomorphism and mitosis
  - Broad borders
  - Mucin pools
- Grade II:
  - No cyst formation
  - Intermediate cells with or without epidermoid features
  - Moderate nuclear pleomorphism
  - Invasive borders
  - Inflammation and fibrosis
- Grade III:
  - Rare mucin cells
  - Poorly differentiated, epidermoid, and glandular
  - Cellular pleomorphism
  - Invasive border

Immunohistochemistry

- Rarely required
- Proliferation markers, elevated in high grade

Cytogenetics

- Deletion of -5q

Differential Diagnosis

- Benign mixed tumors with squamous differentiation:
  - Stroma of mixed tumor and myoepithelial cells
- Squamous carcinoma:
  - Keratinization; lacks intermediate and mucinous cells
- Necrotizing sialometaplasia:
  - Preservation of lobular pattern; lacks malignant cellular features

Salivary Duct Carcinoma (Table 14-7)

Clinical

- Swelling and mass formation is common presentation

Macroscopic

- Poorly demarcated and infiltrative
- Light tan and firm

Microscopic

- Intraductal and infiltrative features, mimics mammary duct carcinoma:
  - Intraductal: comedo, cribriform, and solid forms
- Desmoplasia and hyalinization in invasive tumors
- Lacks myoepithelial and epidermoid cells
- Vascular and neural permeation not uncommon
- Goblet cells may be seen

Special Studies

- Mucin: generally negative
- Immunostaining: non-contributory
- Ki-67: high-growth fraction
- Estrogen receptor: typically negative
- Progesterone receptor: occasionally positive
- Flow cytometry: predominantly DNA aneuploid with elevated S-phase

Differential Diagnosis

- Mucoepidermoid carcinoma:
  - Lacks cribriform and intraductal component
  - Shows intermediate and epidermoid cells, contains goblet cells
- Acinic cell carcinoma:
  - Monotonous cells, no intraductal features
  - Lacks comedo-necrosis, characteristic granules
- Oncocytic carcinoma:
  - Large cells with granular cytoplasm, no papillary or cribriform features
- Mucin-producing adenopapillary carcinoma:
  - Columnar, goblet, and signet-ring cells
  - Lacks comedo-necrosis and intraductal component
- Metastatic breast carcinoma:
  - Most challenging differential diagnosis
    - Male predominance, favor primary
    - History of breast carcinoma

Epithelial-Myoepithelial Carcinoma

Clinical

- 1% of all salivary tumors
- Predominantly major glands: parotid 75%, submandibular and minor glands 25%
- Male:female ratio = 1:2
- Painless mass

Macroscopic

- Solitary, well-defined, circumscribed or lobulated, gray mass
- Size ranges from 2 to 8 cm

Table 14-7. Clinicopathologic Characteristics of Salivary Duct Carcinoma

Feature	*Frequency (%)*
Percent of:	
All epithelial neoplasms	0.2
All malignant tumors	0.5
Parotid malignancy	1–6
Male:Female	4:1
Age	27–83 (Median 63 y)
Site	
Parotid	83
Submandibular	12
Minor glands	5
Lymph node metastasis	57
Outcome: Death	53

- ♦ Recurrent tumors: lobulated, ill-defined borders with necrosis

Microscopic

- ♦ Variable intra- and intertumoral patterns
- ♦ Dual cell layers, inner ductal, and outer myoepithelial cells
- ♦ Ductal cells: cuboidal or columnar with eosinophilic cytoplasm
- ♦ Myoepithelial cells: ovoid with abundant clear cytoplasm surrounded by basal materials

Special Stains

- ♦ Mucin –
- ♦ PAS diastase resistant +

Immunohistochemistry

- ♦ Myoepithelial cells: SMA +, S-100 +, keratin weakly –
- ♦ Ductal: keratin +

Differential Diagnosis

- ♦ Mucoepidermoid carcinoma:
  - – Lacks dual cellular composition; cystic features in low grade
- ♦ Acinic cell carcinoma:
  - – Clear cell type, PAS +, diastase +, characteristic basophilic granules
- ♦ Sebaceous carcinoma:
  - – Fat stain +, occasional squamous differentiation
- ♦ Metastatic renal cell carcinoma:
  - – High vascularity, necrosis, history of renal cell carcinoma

Terminal Duct Carcinoma (Polymorphous Low-Grade Adenocarcinoma)

Clinical

- ♦ Incidence: 7.4% of all minor salivary gland tumors, 19.6% of malignant tumors
- ♦ Hard palate is most common site (Table 14-8)
- ♦ Occurs occasionally in major salivary gland

Macroscopic

- ♦ Small, lobulated mass
- ♦ Yellow-tan and firm

Microscopic

- ♦ Uniform cytology, but heterogeneous patterns
- ♦ Patterns: tubular, cribriform, papillary, solid, and fascicular features
- ♦ Mitosis, low; necrosis, rare
- ♦ Mucoid, hyaline, and mucohyaline stroma
- ♦ Perineural invasion common

Immunohistochemistry

- ♦ Non-contributory

Differential Diagnosis

Table 14-8. Differential Clinicopathologic Characteristics Between Terminal Duct Carcinoma (TDC) and Salivary Duct Carcinoma (SDC)

Category	*TDC*	*SDC*
Sex		
Male:Female	1:2	4:1
Age		
Range	23–79	27–83
Mean	(49)	(64)
Salivary Gland Site	Palate (65.5%)	Parotid (83.3%)
Behavior		
Recurrence	(12%)	55%
Cervical node metastasis	(10%)	66%
Distant metastasis	0	66%
	1.4%	70%

Modified from Batsakis & Luna, 1989

- Pleomorphic adenoma:
  - Epithelial and stromal elements
- Basal and canalicular adenomas:
  - Well-circumscribed
  - Uniform basal or columnar cellular pattern
- Adenoid cystic carcinoma:
  - Most difficult differential diagnosis, especially in low-grade tumors
  - Lacks varied patterns of terminal duct carcinoma
  - Manifests cribriform and solid features

Primary Squamous Cell Carcinoma

Clinical

- 0.9% to 4.7% of all malignancies; parotid gland 0.3% to 1.5% and submandibular 2.4% to 7.0%
- Male:female ratio = 3:1
- Symptoms: Mass (50%), pain (33%), nerve paralysis (17%)

Macroscopic

- Infiltrative, ill-defined, and firm mass
- Necrosis not uncommon

Microscopic

- Well to poorly differentiated squamous cells with keratinization
- Dysplastic ductal epithelium may be found

Differential Diagnosis

- Metastatic squamous carcinoma:
  - Circumscribed nodule within gland
  - History of squamous carcinoma
- Mucoepidermoid carcinoma:
  - Mucin-producing cells
  - Lacks keratinization
- Necrotizing sialometaplasia:
  - Lobular preservation of salivary structure
  - Lacks atypia and keratinization

Undifferentiated Carcinoma

- 1% to 30% of epithelial malignancy

Types

- Small cell
- Large cell
- Undifferentiated carcinoma with lymphoid stroma (lymphoepithelial carcinoma)

Differential Diagnosis

- Metastasis:
  - Merkel cell: history of Merkel cell carcinoma, keratin nodular +
  - Basal cell carcinoma: history of skin lesions
  - Solid adenoid cystic carcinoma: focal, tubular, and cribriform patterns

Table 14-9. Site and Ethnic Distribution of Lymphoepithelial Carcinoma of Major Salivary Glands

Feature		*Incidence (%)*
Site		
	Parotid	83.70
	Submandibular	15.00
	Unstated	1.25
Ethnicity		
	Eskimo-Greenlander	52.50
	Southern Chinese	20.00
	White	11.25
	Indian	2.50
	Japanese	2.50
	Black	2.50
	Others	8.75

Small Cell Carcinoma

Clinical

- Very rare: 1.7% of malignant parotid tumors, 2.2% of malignant submandibular tumors
- Mainly parotid
- Male:female ratio = 6:1

Macroscopic

- Light tan and soft nodule

Microscopic

- Identical to small cell carcinoma of lung

Immunohistochemistry

- Keratin, synaptophysin, and chromograinin +

Electron Microscopy

- Rare neurosecretory granules

Differential Diagnosis

- Lymphoma:
  - Keratin –, Leukocyte common antigen (LCA) +
- Adenoid cystic carcinoma, solid type:
  - Tubular and cribriform components may be present
  - Negative staining for neuroendocrine markers
- Merkel cell carcinoma:
  - History of primary
  - Keratin immunostaining

Large Cell Carcinoma

Clinical

- Predominantly parotid

Microscopic

- Cells larger than small cell carcinoma
- Abundant cytoplasm
- Cords and nests may be seen

Immunohistochemistry

- Keratin +, LCA –
- Neural markers occasionally +

Differential Diagnosis

- Melanoma:
  - S-100 and HMB-45 +, keratin –
- Undifferentiated carcinoma:
  - Neuroendocrine markers –

Lymphoepithelial Carcinoma (Table 14-9)

Clinical

- 0.4% of all salivary gland tumors
- Male:female ratio = 1.5:1
- Evidence of familial clustering
- Evidence of EBV-association

Microscopic

- Indistinguishable from nasopharyngeal carcinoma
- Lymphoid content varies

Table 14-10. Staging of Salivary Gland Malignancies

	Primary tumor (T)	*Regional lymph nodes (N)*
1	TX (cannot be assessed)	N0 (no node metastasis)
2	TO (no tumor detected)	N1, ≤3.0 cm in one lymph node
3	T1, ≤2.0 cm	N2 subtypes:
4	T2, <2.0 >4.0 cm	N2a, one ipsilateral lymph node >3.0 <6.0 cm
5	T3, >4.0 <6.0 cm	N2b, multiple ipsilateral lymph nodes <6.0 cm
6	T4, >6.0 cm	N2c, bilateral or contralateral, <6.0 cm in diameter
	NX (cannot be assessed)	N3, metastasis in lymph node >6.0 cm

Distant metastasis (M)
MX, metastasis (cannot be assessed)
M0, no metastasis
M1, distant metastasis

Table 14-11. Stage Grouping

Stage I:	T1 No Mo	Stage IV:	T4 No Mo
	T2 No Mo		T3 N1 Mo
Stage II:	T3 No Mo		T4 N1 Mo
Stage III:	T1 N1 Mo		Any T N2 Mo
	T2 N1 Mo		Any T N2 M1

Table 14-12. Prognostic Factors in Salivary Gland Carcinomas

Favorable features	*Unfavorable features*
Low-grade histology	High-grade
Low stage	High stage
Parotid location	Submandibular gland site
	Cervical node metastasis
	Facial nerve paralysis
	Skin involvement
	Recurrence
	Radio- and chemoresistant

Table 14-13. Frequency of Local Recurrence in Salivary Gland Carcinomas

Diagnosis	*Recurrence (%)*
Squamous cell carcinoma	64
Undifferentiated carcinoma	64
Adenoid cystic carcinoma	61
Carcinoma ex-pleomorphic adenoma	60
Adenocarcinoma, NOS	48
Acinic cell carcinoma	15
Mucoepidermoid carcinoma	5

Table 14-14. Frequency of Lymph Node Metastasis by Diagnosis of Salivary Gland Carcinomas

Histology	*Metastasis (%)*
Mucoepidermoid carcinoma	44
Adenocarcinoma, NOS	36
Undifferentiated carcinoma	23
Carcinoma ex pleomorphic adenoma	21
Acinic cell carcinoma	13
Adenoid cystic carcinoma	5

Johns, 1989

Table 14-15. Frequency of Distant Metastasis by Diagnosis of Salivary Gland Carcinomas

Histology	*Metastasis (%)*
Adenoid cystic carcinoma	42
Undifferentiated carcinoma	36
Adenocarcinoma, NOS	27
Carcinoma ex pleomorphic adenoma	21
Squamous cell carcinoma	15
Acinic cell carcinoma	14
Mucoepidermoid carcinoma	9

Table 14-16. Characteristics of Primary Salivary Gland Lymphoma

5% of all extranodal lymphomas

40% of all head and neck lymphomas

85% non-Hodgkin's B-cell origin ($^2/_3$ well-differentiated)

15% Hodgkin lymphoma, majority extranodal and parenchymal (MALT)

Table 14-17. Primary Sarcomas of Major Salivary Glands

Characteristic		*Incidence*
Sex	Male:Female	1 2 : 1
Age	Range	10–91 years
	Mean	36 years
Site	Parotid	91.8
	Submandibular	8.2
Most frequent subtypes	Rhabdomyosarcoma	21.6
	MFH	16.2
	Fibrosarcoma	12.1
	Neurosarcoma	9.4
	Angiosarcoma	6.7
Recurrence		22.9
Metastasis		32.4
Died of disease (DOD)		36.4

Modified from Luna, et al., 1991

- Occasional squamous differentiation
- Carcinoma demarcated from surrounding non-epithelial elements, epi-myoepithelial islands of lympho-epithelial lesions

Differential Diagnosis

- Metastasis from conventional sites

Rare Types of Adenocarcinoma

- Adenopapillary carcinoma
- Cystadenocarcinoma
- Adenosquamous carcinoma

Clinicopathologic Factors

- A number of clinicopathologic factors related to salivary gland carcinomas impact on the therapeutic outcome in patient prognosis. Clinical stage is probably the most important (Tables 14-10 and 14-11).

Salivary Gland Lymphoma (Table 14-16)

Primary Lymphomas (also see Chapter 7)

Clinical

- Rare (Table 14-16)
- Parotid:submandibular glands = 8:1
- Mainly older patients, 6th to 7th decade of life
- Intraparotid lymph node involvement staged as in cervical lymphoma

Microscopic

- Sclerosis, common in large type
- Small cell type arise in a background of benign lymphoepithelial lesions
- Plasmacytoma, very rare

Mesenchymal Tumors of Salivary Glands

- 5% of all tumors
- Both benign and malignant mesenchymal tumors affect children and adolescents (Tables 14-17 and 14-18)
- Location: mainly major salivary gland, especially the parotid glands
- Benign:
  - Angiomas, lipomas, neurofibromas, and hemangiopericytomas
  - Except for neurofibroma, exclusively parotid in origin
  - Usually ill-defined lesions
  - Histologically identical to soft tissue counterpart
- Sarcoma:
  - Rare
  - Ill-defined mass
  - Comparable microscopic characteristics to soft tissue counterparts

Table 14-18. Histologic Types of Salivary Gland in Children Under 16 years of Age

Epithelial (Total #394)	*Incidence (%)*	*Mesenchymal (Total #274)*	*Incidence (%)*
Benign (50%)		**Benign (93.8%)**	
Pleomorphic adenoma	46	Hemangioma	69.7
Embryoma	2	Lymphangioma	17.5
Warthin's tumor	0.70	Neurogenic	4
Cystadenoma	0.70	Lipoma	1.5
Lymphoepithelial lesions	0.70	Xanthoma	0.7
Monomorphic adenoma	0.25	Fibromatosis	0.7
Malignant (50%)		**Malignant Mesenchymal (6.2%)**	
Mucoepidermoid carcinoma	27.3	Sarcoma	5.5
Acinic cell carcinoma	6.8	Ganglioneuroblastoma	0.4
Adenocarcinoma	5.6		
Undifferentiated carcinoma	3.8		
Adenoid cystic carcinoma	2.8		
Carcinoma	2.3		
Ex-pleomorphic adenoma	1		
Squamous cell carcinoma	0.25		
Unclassified carcinoma			

Modified from Luna et al., 1998

SALIVARY GLAND TUMORS IN CHILDREN

General Features

- Comprise 5% of childhood tumors
- High incidence of benign non-epithelial tumors
- High incidence of epithelial malignancy
- Predominantly in parotid
- Vasoformative tumors, most common in neonates and infants
- Pleomorphic adenoma, mucoepidermoid, and acinic cell carcinomas in children between 10 and 16 years

Hemangioma

Clinical

- Most common postnatal tumor
- Commonly in girls with a left-side predilection
- Spontaneous involution not uncommon
- Angle of mandible common
- Recurrence uncommon
- 50% undergo spontaneous involution

Macroscopic

- Enlarged gland
- Purple-red and spongy

Microscopic

- Similar to other sites

Sialoblastoma (Embryoma)

Clinical

- Congenital or prenatal
- Newborn and first year of life
- Low-grade malignancy
- Major salivary glands
- 1.5 to 15 cm in size
- No gender preference
- Typically asymptomatic

Macroscopic

- Well-circumscribed, encapsulated, and lobulated mass
- Yellowish-tan and firm

Microscopic

- Primitive basaloid cells, resembling primitive epithelium
- Focal sebaceous differentiation occasionally
- Peripheral palisading is common
- Necrosis, perineural, or vascular invasions are not uncommon

Immunohistochemistry

- Non-contributory

Electron Microscopy

- Primitive features, free ribosomes, sparse endoplasmic reticulum

Differential Diagnosis

- Basal cell adenoma:
  - Less primitive cells, less mitotic activities, and primitive stroma
- Adenoid cystic carcinoma and basal cell adenocarcinoma are very rare

Malignant Epithelial Tumors

- Mucoepidermoid and acinic cell carcinomas account for 60% of salivary gland malignancy in children
- Adenoid cystic carcinoma, adenocarcinoma, and undifferentiated carcinomas very rare

METASTASIS TO SALIVARY GLANDS

General Features

- Routes
  - Lymphatic, hematogenous, local spread (sarcomas of facial bones or soft tissue and skin cancer)
- Parotid metastasis: lymphatic and hematogenous
- Submandibular gland metastasis rare
- Parotid is most common site because of lymphatic content
- Tables 14-19–14-22 present several types of metastases to the salivary glands

Table 14-19. Infraclavicular Primary Malignancy and Parotid and Parotid Node Metastasis

Primary	*Incidence (%)*
Lung	34.3
Kidney	31.4
Breast	11.4
Colorectal	11.4
Others	11.4

Table 14-20. Metastasis to Major and Minor Salivary Glands

Site	*Incidence (%)*
Intraoral Minor	85.7
Parotid	7.1
Submandibular	8.7
Submandibular space	1.5

Table 14-21. Supraclavicular Primary Tumors with Metastasis to Parotid Gland and Intraparotid Lymph Nodes

Site	*Diagnosis*	*Incidence (%)*
Skin & mucous membrane	Squamous carcinoma	68.9
	Melanoma	25.3
Nasopharynx	Carcinoma	4.9

Table 14-22. Metastatic Malignancy From Infraclavicular Primary to Submandibular Gland

Primary	*Incidence (%)*
Breast	38.9
Lung	27.7
Kidney	22.3
Other	11.1

IMMUNOHISTOCHEMISTRY IN ASSESSMENT OF SALIVARY GLAND TUMORS

General Features

- Immunohistochemistry can be a useful adjunct to routine light-microscopic evaluation of salivary gland tumors. It merits emphasis that the immunophenotype, by itself, should not be used alone to arrive at a diagnosis.
- Tables 14-23–14-25 are representative of some uses of immunohistochemistry

Table 14-23. Immunohistochemical Analysis of Tumors with Myxohyalinized Stroma

Marker	*PA*	*ADCC*	*BCA*
GFAP	+	–	–
S-100 protein	+	±	–
Keratin	±	+	+
SMA	±	+	+
Desmin	–	–	–

PA = Pleomorphic adenoma; ADCC = Adenoid cystic carcinoma; BCA = Basal cell adenoma

Table 14-24. Carcinoma with Basaloid Features

Markers	*Small cell*	*Adenoid cystic*	*Basaloid*
Keratin+	+	+	–
S-100	±	±	–
Chromogranin	+	–	–
SMA	–	±	–

SMA = Smooth muscle actin

Table 14-25. Immunohistochemistry in Differential Diagnosis of Salivary Gland Tumors with Clear Cell Features

Marker	*CCC*	*ME/MC*	*EMC*
CK	+	+	+
CK-CAM	+	+	+
CEA	±	–	+
EMA	+	±	+
S-100	–	+	+
SMA	–	+	+
MSA	–	+	+

CCC = Clear cell carcinoma; ME = Myoepithelioma; MC = Myoepithelial carcinoma; EMC = Epithelial-Myoepithelial Carcinoma; CK = Cytokeratin; CEA = Carcinoembryonic antigen; EMA = Epithelial membrane antigen; SMA = Smooth muscle actin; MSA = Muscle specific antigen

TUMOR-LIKE AND CYSTIC LESIONS (TABLE 14-26)

Table 14-26. Tumor-Like Lesions of Salivary Glands

- Sialolithiasis
- Sialadenitis
- Sialadenosis
- Oncocytosis
- Necrotizing sialometaplasia
- Benign lymphoepithelial lesions and Sjögrens Syndrome
- Salivary gland cysts (Table 14-27)
- Chronic sclerosing sialadenitis of submandibular gland (Küttner tumor)
- Cystic lymphoid hyperplasia in AIDS
- Inflammatory pseudotumors
- Others, nodular fasciitis, sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman disease), Wegener's granulomatosis

Modified from WHO Classification

Sialolithiasis

- ♦ Predominantly in submandibular gland
- ♦ Undulant and tender swelling
- ♦ Parotid less frequent and difficult to diagnose clinically

Microscopic

- ♦ Dilated ducts
- ♦ Squamous metaplasia
- ♦ Acinar atrophy and inflammation

Sialadenitis

- ♦ Acute and chronic non-specific inflammation:
  - – Bacterial: *Staphylococcus aureus*
  - – Viral: cytomegalovirus, paramyxovirus, Epstein-Barr virus, para and influenza viruses, and coxackievirus
- ♦ Granulomatous:
  - – Obstructive sialadenopathy:
    - • Ruptured mucoceles
    - • Extravasated mucin

- Infectious:
  - Myobacterial, cat-scratch, disease, tularemia, fungal, toxoplasmosis, and other
- Sarcoidosis
- Associated with systemic disease:
  - Wegener's granulomatosis, Crohn's disease, and others
- Associated with salivary tumor:
  - Acinic cell carcinoma
  - Mucoepidermoid carcinoma
  - Warthin's tumor
  - Lymphoepithelial lesions
- Foreign body granulomas:
  - Iatrogenic (sialography)

Sialadenosis

- Hypertrophy and hyperplasia of acini
- Associated with systemic and neural disorders
- Presents as bilateral painless and recurrent swelling
- Etiology: neurogenic, metabolic, or hormonal

Oncocytosis

- Oncocytic hyperplasia of ductal and acinar structure
- Unilateral or bilateral enlargement
- Preservations of lobular architecture
- Old age

Necrotizing Sialometaplasia

Clinical

- Benign self-limiting reactive inflammatory process
- Palate 81.7%, other oral sites 7.0%, major glands 7.8%, and other 3.5%
- Age: 40–60 years
- More men than women
- Uncertain etiology

Macroscopic

- Mucosal site, ulceration, and painful swelling
- Non-ulcerated: $^1/_3$ of lesions

Microscopic

- Lobular distribution
- Central ductal squamous metaplasia
- Peripheral necrotic and inflamed acini

Differential Diagnosis

- Squamous carcinoma:
  - Infiltrative, keratinization, cellular features of malignancy
  - Lacks lobular preservation
- Mucoepidermoid carcinoma:
  - Mucinous cells, infiltrative intermediate cells, and cystic formations

Benign Lymphoepithelial Lesions

Clinical

- Idiopathic, autoimmune disease, HIV infection
- Localized, systemic
- Older women
- Recurrent painful swelling
- The minor salivary glands rarely affected

Microscopic

- Focal periductal lymphoid proliferation
- Partial or total obliteration of acinar structure
- The lobular architecture is retained
- Epi-myoepithelial islands
- Marked lymphoreticular infiltrate with germinal centers
- Hyaline-like material deposits

Sjögren's Syndrome

Clinical

- High incidence of non-Hodgkin's lymphoma in women
- Associated with
  - Keratoconjunctivitis sicca
  - Xerostomia
  - Connective tissue disease
- Assessed by labial minor salivary gland biopsy
  - Focus score: number of inflammatory foci/4 mm of gland (focus is defined as >50 lymphocytes)

Differential Diagnosis

- Lymphoepithelial carcinoma
- Lymphoma (MALT)
  - Both tumors may arise in this setting

Chronic Sclerosing Sialadenitis of Submandibular Gland (Küttner's Tumor)

- Unilateral
- Lympho-plasmacytic periductal infiltrate with fibrosis
- Clinically tumor-like

Cystic Lymphoid Hyperplasia (HIV+ Subjects)

Clinical

- HIV-infected patients
- Hodular or diffuse enlargement of salivary glands

- ♦ Unknown pathogenesis
- ♦ Antigen infection

Microscopic

- ♦ Glandular atrophy
- ♦ Intense lymphocytic proliferation with follicular hyperplasia
- ♦ Cystic formation with epithelial lining from ductal inclusion
- ♦ Epi-myoepithelial islands

Inflammatory Pseudotumors

Clinical

- ♦ Firm, nodular swelling in the parotid

Microscopic

- ♦ Myofibroblastic proliferation and chronic inflammatory cells

Immunostaining

- ♦ SMA, MSA, and KPI CD68 +

SALIVARY CYSTS

General Features

- ♦ Non-neoplastic cysts and pseudocysts in salivary gland exceed cystic tumors in number and occur far more often in minor rather than major glands. Table 14-27 gives the location and frequency of these cysts. Table 14-28 does the same for the mucocele. A differential diagnosis of benign cystic lesions that can occur in the neck is given in Table 14-29.

Benign Cysts

- ♦ Types (Table 14-27)
  - – Dysgenetic: rare 2%
  - – Secondary/acquired, pseudocysts
    - • Mostly of secondary, pseudocysts are mucocele
    - • Two subtypes of mucoceles: the retention type and the extravasation type (Ranulas)

Dysgenetic Cysts

- ♦ Polycystic dysgenetic lesions:
  - – Mainly parotid
  - – Rare
  - – Multiple cysts lined by simple epithelial lining
  - – Female predominance
  - – Delayed clinical manifestation
  - – Bilateral
  - – Fluctuating, non-tender parotid swelling
  - – Diagnosis: sialogram, typically spare main salivary duct
  - – Surgical excision for diagnosis and treatment
  - – Etiology: most likely developmental
- ♦ Cyst of submandibular gland:
  - – Benign cyst lined by flattened epithelium
  - – Etiology: duct segmentation

Secondary Cysts

- ♦ Salivary duct cysts:
  - – Mainly parotid
  - – 10% of all non-neoplastic cysts
  - – More than $^{2}/_{3}$ male in 2nd decade of life
  - – Multilayered, cuboidal epithelial lining
  - – Occasional oncocytic and squamous metaplastic changes
  - – Cystic contents, spheroliths or crystalline precipitate
  - – Pathogenesis: ductal obstruction
- ♦ Lymphoepithelial cysts:
  - – Locations: parotid, intraparotid lymph nodes, floor of mouth
  - – Lining: flattened or multilayered epithelium surrounded by lymphocytes and lymphoid follides
  - – Sebaceous glands and goblet cells may be present
  - – Pathogenesis: displacement of epithelium into lymphoid tissue or proliferation of bronchial pouch epithelium
  - – Related to benign lymphoepithelial lesions, chronic myoepithelial sialadenitis, and HIV-related cystic lymphoid hyperplasia

Mucoceles

- ♦ Retention mucocele:
  - – Less common, 15%
  - – Older age, >20 years
  - – Site: minor salivary glands
  - – Cyst lined by flat, cuboidal, or multilayered epithelium surrounded by thick fibrous capsule
  - – Pathogenesis: obstruction
- ♦ Extravasation (Ranulas):
  - – Most common, 85%
  - – Sites: lip, cheek, and floor of mouth

– More in men (60%)
– Peak incidence: 2nd decade
– Initially ill-defined mucus lakes, followed by granuloma formation and muciphages, finally mucin-filled pseudocysts (no epithelial lining)

Cystic Neoplasms

- Cystic mucoepidermoid carcinoma
- Warthin's tumor
- Cystadenocarcinoma
- Sebaceous lymphadenoma

Table 14-27. Frequency and Location of Non-Neoplastic Salivary Gland Cysts

Type	*Site*	*Frequency (%)*
Mucocele	Minor glands	76
Salivary duct	Parotid	9
Lymphoepithelial	Parotid and oral cavity	7
Ranula	Sublingual gland	5
Congenital sialectasis	Parotid	1.5
Polycystic (dysgenetic)	Parotid	2

Batsakis & Raymond, 1989

Table 14-28. Frequency of Mucoceles by Site

Site	*Frequency (%)*
Lower lip	23.5
Cheek	13.2
Floor of mouth	12.6
Upper lip	15.4
Palate	8.8
Tongue	4.4
Other areas	16.1
No information	5.9

Modified from G. Seifert, 1991

Table 14-29. Benign Cystic Lesions of Neck

Type	*Characteristics*
Thyroglossal duct cyst	Midline, $^{2}/_{3}$ below hyoid bone, $^{1}/_{3}$ off midline, anteromedial to carotid artery and jugular vein
Bronchial cyst	Lateral neck, unrelated to hyoid, majority near angle of mandible; if small, anterior to sternomastoid, lateral to carotid artery and internal jugular vein
Parathyroid cyst	95% near inferior thyroid margin, off midline; anterior to carotid artery and internal jugular vein
Cervical thymic cyst	Off midline; low neck; anterior to carotid artery and internal jugular vein
Cystic hygroma	Off midline, usually posterior to carotid artery and internal jugular vein, may involve floor of mouth
Dermoid cyst	Near midline, usually upper neck
Benign teratoma	Usually near thyroid gland
Cervical ranula	Off midline and suprahyoid in submental and submandibular triangle

TNM CLASSIFICATION OF MAJOR SALIVARY GLANDS (1997 REVISION)

- T: Primary Tumor:
  - T1: Tumor ≤ 2 cm in greatest dimension without extraparenchymal extension
  - T2: Tumor > 2 cm but < 4 cm in greatest dimension. No extraparenchymal extension
  - T3: Tumor having extraparenchymal extension without seventh nerve involvement and/or > 4 cm but < 6 cm in greatest dimension
  - T4: Tumor invades base of skull, seventh nerve, and/or > 6 cm in greatest dimension
- N: Regional Lymph Nodes:
  - N0: No regional lymph node metastasis
  - N1: Metastasis in a single ipsilateral node, ≤ 3 cm in greatest dimesnion
  - N2: Metastasis in a single ipsilateral lymph node, > 3 cm but < 6 cm in geratest dimension, or in multiple ipsilateral lymph nodes, none > 6 cm in greatest dimension, or in bilateral or contra–lateral lymph nodes, none > 6 cm in greatest dimension:
    - N2a: Metastasis in a single ipsilateral lmph node > 3 cm but < 6 cm in greatest dimension
    - N2b: Metastasis in multiple ipsilateral lymph nodes, none > 6 cm in greatest dimension
    - N2c: Metastasis in bilateral or contraleteral lymph nodes, none > 6 cm in greatest dimension
  - N3: Metastasis in lymph node > 6 cm in greatest dimension
- M: Distant Metastasis:
  - M0: No distant metastasis
  - M1: Distant Metastasis

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Chapter 15

Mediastinum

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Table of Contents

CLASSIFICATION OF DISEASES

Table 15-1. Classification of Diseases

Non-Neoplastic Disorders

Inflammatory/infectious

- ♦ Acute mediastinitis
- ♦ Granulomatous mediastinitis
- ♦ Fibrosing mediastinitis

Cystic lesions

- ♦ Bronchogenic cyst
- ♦ Esophageal cyst
- ♦ Gastroenteric cyst
- ♦ Pericardial cyst
- ♦ Thymic cyst
  - – Unilocular
  - – Multilocular

Non-neoplastic lesions of thymus

- ♦ Thymic dysplasia
- ♦ Thymic aplasia
- ♦ Thymic hyperplasia
- ♦ Lymphoid hyperplasia

Lesions mimicking mediastinal tumors

- ♦ Substernal thyroid (mediastinal goiter)
- ♦ Mediastinal parathyroid lesions
- ♦ Cystic hygroma
- ♦ Thoracic skeletal lesions
  - – Chordoma
  - – Osseous tumors of thoracic spine
  - – Paravertebral abscess
  - – Myelomeningocele
- ♦ Extramedullary hematopoiesis
- ♦ Vascular lesions
  - – Aortic aneurysm
  - – Venous lesions
- ♦ Esophageal lesions
  - – Diverticula
  - – Leiomyoma
  - – Achalasia
  - – Carcinoma
- ♦ Pulmonary lesions
  - – Extralobar sequestration
  - – Hilar/mediastinal lymphadenopathy
  - – Lung cancer
- ♦ Subdiaphragmatic lesions
  - – Pancreatic pseudocyst
  - – Hiatal hernia

Other conditions

- ♦ Pneumomediastinum

Neoplasms

Thymus

- ♦ Thymoma (tumor of thymic epithelium)
  - – Circumscribed (usually benign) thymoma
  - – Invasive (malignant) thymoma
- ♦ Thymic carcinoma (cytologically malignant, tumor of thymic epithelium)
- ♦ Thymic carcinoid
- ♦ Thymic stromal tumors
  - – Thymolipoma
  - – Thymic stromal sarcomas

Neoplasms not limited to thymus

- ♦ Neurogenic tumors
  - – Peripheral nerve sheath tumors
    - • Schwannoma
    - • Neurofibroma
    - • Malignant peripheral nerve sheath tumor
  - – Tumors of sympathetic nervous system
    - • Neuroblastoma
    - • Ganglioneuroblastoma
    - • Ganglioneuroma
  - – Other (rare)
    - • Ependymoma
    - • Meningioma
- ♦ Paraganglioma
- ♦ Germ cell tumors
- ♦ Lymphoproliferative disorders
- ♦ Mesenchymal tumors
- ♦ Metastatic tumor

NON-NEOPLASTIC DISORDERS

Inflammatory/Infectious

Acute Mediastinitis

Clinical

- Life-threatening acute infection
- Most common causes by compartment:
  - Anterior: post-sternotomy after cardiac surgery
  - Middle: esophageal perforation, Boerhaave's syndrome (post-emetic rupture of esophagus)
  - Posterior: direct extension from lung or spinal infection
- Descending necrotizing mediastinitis:
  - Tracks through fascial planes from deep cervical infections originating in oropharynx
  - Mixed aerobic and anaerobic organisms

Macroscopic

- Purulent exudate layered on mediastinal structures
- Abscess formation
- Air crepitance secondary to pneumomediastinum (occasional)

Microscopic

- Acute fibrinopurulent inflammation
- Infectious agents identified by appropriate stains for fungi and bacteria

Differential Diagnosis

- Determine underlying etiology
  - Variable potential organisms (Gram, GMS stains, microbiologic cultures) depending on underlying etiology and immune status of patient

Granulomatous Mediastinitis

Clinical

- Disease of mediastinal lymph nodes
- Most common cause is Histoplasma capsulatum; less frequently, tuberculosis
- Complications: perforation and fistula formation, esophageal diverticula, erosion into bronchus and broncho-lithiasis

Macroscopic

- Frequently large, calcified, fibrocaseous mass of coalesced lymph nodes (mediastinal granuloma)

Microscopic

- Necrotizing granulomatous inflammation, fibrosis, and calcified caseonecrotic debris
- Acid fast bacilli (AFB) or yeast forms of H. capsulatum by special stains

Differential Diagnosis

- Histoplasmosis:
  - Thick fibrous capsule; yeast forms (GMS)
- Tuberculosis:
  - Thin fibrous capsule; acid-fast organisms
- Sarcoidosis:
  - Non-necrotizing granulomas; stains for microorganisms are negative
- Infected teratoma or bronchogenic cyst:
  - Necrosis may obscure typical identifying features
- Fibrosing mediastinitis:
  - Usually no caseous necrosis; ropy collagen present; superior vena caval obstruction; extension of fibrosis beyond lymph nodes

Fibrosing Mediastinitis

Clinical

- Young adults, female predominance
- Variety of compression syndromes due to involvement of mediastinal structures:
  - Superior vena caval syndrome
  - Tracheobronchial compression (hilar fibrosis)
  - Pulmonary artery or venous obstruction
- Associated with collagen vascular disease, pseudotumor of orbit, Riedel's struma, retroperitoneal fibrosis, and pulmonary hyalinizing granuloma
- May be idiopathic, or secondary reaction to documented fungal or mycobacterial infection

Macroscopic

- Firm gray fibrous tissue forms an ill-defined mass invading and compressing the mediastinal structures

Microscopic

- Dense hyalinized collagenous tissue (ropy collagen)
- Scant lymphocytic and plasmacytic inflammation
- Rare granulomas

Differential Diagnosis

- Nodular sclerosis Hodgkin's disease; other lymphomas with sclerosis
- Fungal/mycobacterial infection:
  - See granulomatous mediastinitis
- Secondary effects seen in open lung biopsy:
  - Hyalinizing granuloma, pulmonary hemosiderosis, venous infarcts, and venous and arterial sclerosis (simulates pulmonary veno-occlusive disease or pulmonary venous hypertension)
- Amyloidosis:

- Confirm with congo red or crystal violet stain
- Progressive massive fibrosis:
  - Due to coal or silica exposure
  - Usually within lung parenchyma; may extend to hilar or mediastinal structures
  - Associated pigment deposition
- Desmoplastic mesothelioma (rare)

Cystic Lesions

Bronchogenic Cyst

Clinical

- Most common congenital cyst of mediastinum
- Young adults
- Usual location is middle mediastinum

Macroscopic

- Spherical, unilocular or multilocular, clear or gelatinous fluid

Microscopic

- Respiratory epithelium, squamous epithelium; bronchial glands, smooth muscle, and cartilage may be present

Differential Diagnosis

- Esophageal cyst:
  - Absence of cartilage; double muscle layer +

Esophageal Cyst

Clinical

- Close association with esophageal wall in middle or posterior mediastinum

Macroscopic

- Spherical, unilocular

Microscopic

- Squamous and/or ciliated epithelium
- Esophageal glands
- Cartilage absent
- Double layer of muscle

Differential Diagnosis

- Bronchogenic cyst:
  - Presence of cartilage, no double muscular layer

Gastroenteric Cyst

Clinical

- Located in posterior mediastinum
- Often connected to vertebral column
- Associated with malformations of thoracic vertebrae (neuroenteric cyst)
- Symptoms related to nerve compression, peptic ulceration, and perforation

Macroscopic

- Unilocular cyst attached to or within esophageal wall

Microscopic

- Inner lining variable: gastric, duodenal, small intestinal, large intestinal, squamous, or respiratory epithelium
- Usually includes well-developed muscularis propria

Differential Diagnosis

- Differentiated from bronchogenic and esophageal cysts by location and gastric or intestinal epithelium

Pericardial Cyst (Coelomic Cyst)

Clinical

- Usual location in right cardiophrenic angle
- Rare in children

Macroscopic

- Spherical, unilocular, thin-walled cyst
- Usually no communication with pericardium
- Clear or straw-colored fluid

Microscopic

- Single layer of mesothelial cells overlying loose connective tissue

Immunohistochemistry

- Mesothelial cells strongly keratin +

Differential Diagnosis

- See bronchogenic, esophageal, and gastroenteric cysts
- Thymic cyst:
  - Located in superior mediastinum, thymic tissue in wall

Thymic Cyst

Unilocular Thymic Cyst (Developmental Origin)

Clinical

- Small; located in lateral neck more often than in mediastinum

Macroscopic

- Unilocular with thin and translucent wall

Microscopic

- Flat, cuboidal, columnar, or (rarely) squamous epithelial lining
- Thymic tissue present in wall
- Usually lack of inflammation

Multilocular Thymic Cyst (Acquired [Reactive] Process)

Clinical

- Asymptomatic large tumor-like mass in anterosuperior mediastinum
- Incidental finding on chest X-ray

Macroscopic

- Multilocular with thick fibrous septa containing cloudy to blood-tinged fluid

Microscopic

- Squamous (often), flat cuboidal, ciliated columnar, either single or stratified epithelial lining
- Acute and chronic inflammation with fibrovascular proliferation, necrosis, hemorrhage, cholesterol granulomas, and reactive lymphoid hyperplasia
- Thymic tissue present in wall

Differential Diagnosis

- Cystic thymoma:
  - Maintains features of thymoma with nodular proliferation of thymic epithelial cells in addition to prominent cystic changes
- Cystic teratoma (see germ cell tumors later)
- Cystic lymphangioma:
  - Prominent ectatic lymphatic channels
- Nodular sclerosis Hodgkin's disease and large cell lymphoma with cystic changes (see lymphoproliferative disorders later)
- Seminoma (germinoma) with cystic changes (see germ cell tumors later)
- Thymic carcinoma:
  - Invasive growth, malignant cytology

Non-Neoplastic Lesions of Thymus

Thymic Dysplasia

Clinical

- Present at birth
- Associated disease: usual X-linked or autosomal recessive form of severe combined immunodeficiency, ataxia telangiectasia, and related chromosomal instability syndromes; Nezelof syndrome; and incomplete form of DiGeorge syndrome (usually located ectopically)

Macroscopic

- Very small size (< 5g)

Microscopic

- Primitive-appearing epithelium without segregation into cortical and medullary regions
- Absence of Hassall's corpuscles
- Almost total absence of lymphocytes
- Small-sized vessels

Differential Diagnosis

- Acute thymic involution often seen at autopsy:
  - Results from stress and superimposed infections
  - Marked lymphocytic depletion with preservation of lobular architecture and of Hassall's corpuscles
  - Disproportionately large vessels compared to size of lobules
  - Scattering of inflammatory cells (particularly plasma cells) within interlobular and perilobular tissue

Thymic Aplasia

Clinical

- Present at birth
- Associated with complete form of DiGeorge syndrome

Macroscopic and Microscopic

- Complete absence of thymus gland

True Thymic Hyperplasia

- Enlargement of thymus gland (by weight and volume) beyond upper limit of normal for age

Clinical

- Unknown clinical significance; questionable immunologic rebound phenomenon
- Associated disease: pure red blood cell aplasia (single case report)

Macroscopic

- Enlarged thymus gland

Microscopic

- Normal thymic architecture
- Diagnosis made by increased size and weight

Differential Diagnosis

- Thymoma:
  - Preservation of thymic architecture in hyperplasia

Lymphoid Hyperplasia

Clinical

- Associated diseases: myasthenia gravis (most common), systemic lupus erythematosus, rheumatoid arthritis, scleroderma, allergic vasculitis, and thyrotoxicosis

Macroscopic

- Normal size and weight of thymus gland for age

Microscopic

- Increased number of lymphoid follicles with prominent germinal centers

Differential Diagnosis

- ♦ Thymoma:
  - – Preservation of thymic architecture in lymphoid hyperplasia
- ♦ Reactive lymph node hyperplasia or lymphoproliferative lesions:
  - – Reactive germinal centers with preserved thymic architecture in lymphoid hyperplasia

Lesions Mimicking Mediastinal Tumors

Substernal Thyroid (Mediastinal Goiter)

Clinical

- ♦ Located in superior mediastinum, usually connected to cervical goiter
- ♦ Can usually be excised via neck incision
- ♦ Compressive symptoms
- ♦ Radioactive iodine scanning + in half of cases

Macroscopic

- ♦ Features of adenomatous goiter (see Chapter 11)

Microscopic

- ♦ Nodular hyperplasia of thyroid tissue (see Chapter 11)

Differential Diagnosis

- ♦ Other thyroid lesions are rare (e.g., adenoma, carcinoma)

Mediastinal Parathyroid Lesions

Clinical

- ♦ Arise from ectopic parathyroid tissue in superior mediastinum
- ♦ Clinically associated with hyperparathyroidism and hypercalcemia

Macroscopic

- ♦ Enlarged parathyroid tissue

Microscopic

- ♦ Features of parathyroid adenoma or hyperplasia (chapter 11)

Differential Diagnosis

- ♦ Paraganglioma or carcinoid tumor:
  - – Not associated with hypercalcemia
  - – Histologically chief cells and/or water clear cells in parathyroid lesions

Other Conditions

Pneumomediastinum

Clinical

- ♦ Air within fascial planes of middle mediastinum, often in association with pulmonary interstitial emphysema, pneumopericardium, pneumothorax, and subcutaneous emphysema
- ♦ Major causes are mechanical ventilation (barotrauma), esophageal perforation, acute mediastinitis, and increased intrathoracic pressure (straining, valsalva maneuver)
- ♦ Chest X-ray and CT scan show mediastinal air outlining aorta, esophagus, and left heart border

Macroscopic

- ♦ Air bubbles and crepitance in mediastinal tissue at autopsy
- ♦ Tension pneumothorax often also seen in patients receiving mechanical ventilation

Microscopic

- ♦ Widened, empty interstitial spaces, track along broncho-vascular sheaths in lung

Differential Diagnosis

- ♦ Lymphangiectasia:
  - – Same distribution as interstitial air dissection
  - – Look for endothelial lining in lymphangiectasia vs. acute hemorrhage in air dissection
- ♦ Determine underlying cause (see clinical, above)

NEOPLASMS

Thymus

Histologic Features of Thymus

- ♦ Lobulated; encapsulated; subdivided into cortex and medulla
- ♦ Cell types:
  - – Epithelial cell:
    - • Endodermally derived
    - • Modulates differentiation of T lymphocytes
    - • Keratin +, HLA-DR +
    - • Subtypes:
      - ▪ Cortical: medium to large, round or polygonal, clear nuclei with nucleoli
      - ▪ Medullary: spindle nuclei
      - ▪ Epithelium forming Hassall's corpuscle
  - – Lymphocytes (traditionally known as thymocytes):
    - • Bone-marrow derived

- Subtypes:
  - Cortical: immature T cells (immunophenotyping: cytoplasmic CD3 +, CD1a +, terminal deoxynucleotidyl transferase (TdT) +, coexpresses CD4/8)
  - Medullary: mature T lymphocytes (immunophenotyping: surface CD3 +, either CD4 + or CD8 +)

– Other (minor) cell types:
- Interdigitating reticulum cells
- Langerhans' cells
- Mast cells
- Eosinophils (especially in neonates)
- Mesenchymal stromal cells

Thymoma

♦ Tumor of thymic epithelium; cytologically bland, with associated cortical-type T cells

♦ Major subtypes:

– Circumscribed (usually benign) thymoma:
- Histologic classification:
  - Lattes-Bernatz (L-B):
    - Predominantly spindle cell
    - Predominantly lymphoid
    - Predominantly mixed
    - Predominantly epithelial
  - Muller-Hermelink (M-H):
    - Medullary
    - Non-medullary:
      - Predominantly cortical (organoid)
      - Mixed
      - Cortical
      - Well-differentiated thymic carcinoma

– Invasive (malignant) thymoma: any of above histologic subtypes with evidence of invasion

Clinical

♦ Mainly adults

♦ Usually located in anterosuperior mediastinum

♦ Lobulated mediastinal mass on chest X-ray, CT, and MRI

♦ Associated diseases:

– Myasthenia gravis (almost exclusively associated with non-medullary thymoma)

– Hypogammaglobulinemia (mainly associated with medullary thymoma)

– Erythroid hyperplasia (mainly associated with medullary thymoma)

♦ Treatment:

– Surgery alone for entirely encapsulated (benign) thymoma (2% to 10% recurrence)

– Surgery with radiation for invasive thymoma

– Chemotherapy for metastatic disease

♦ Prognosis:

– Degree of tumor invasion (stage of disease) best prognostic factor

– Myasthenia gravis has no prognostic significance

Macroscopic

♦ Circumscribed thymoma:

– 2–20 cm

– Predominantly solid, yellowish gray, lobulated by connective tissue septa, encapsulated

– Cystic degeneration in larger tumors

♦ Invasive thymoma:

– Similar to circumscribed thymoma in addition to infiltration of surrounding structures

Microscopic

♦ General (applies to all histologic subtypes):

– Cellular lobules separated by fibrous septa

– Fibrous capsule complete in circumscribed thymoma, incomplete with capsular invasion in invasive thymoma

– Varying proportion of lymphocytes and neoplastic epithelial cells

– Perivascular spaces containing lymphocytes, proteinaceous fluid, red blood cells, foamy macrophages, or fibrous tissue

– Occasional gland or pseudogland structures

– Hassall's corpuscle-like structure

♦ Histologic subtypes:

– Predominantly spindle cell (medullary [M-H]):
- Predominantly spindle-shaped epithelial cells with few mature lymphocytes
- Variable patterns: storiform, hemangiopericytoma-like, rosette-like (without central lumen), glandular formation
- Capsular invasion rare

– Predominantly lymphoid (<33% epithelial cells, predominantly cortical [M-H]);
- Scattered large polygonal epithelial cells in diffuse, small, round lymphocytic background (CD1a +, coexpress CD4/8)
- Sparse foci of medullary differentiation containing tingible body macrophages ("starry sky" pattern)
- Capsular invasion rare

– Predominantly mixed (34% to 66% epithelial cells, mixed or cortical [M-H]):

- Mixed type (M-H):
  - Mixture of medullary and predominantly lymphoid pattern
  - Capsular invasion rare
- Cortical type (M-H):
  - Sheets of polygonal epithelial cells (large nuclei and prominent nucleoli) intermixed with lymphocytes
  - Minimal medullary differentiation
  - Capsular invasion may be present

– Predominantly epithelial (well-differentiated thymic carcinoma [M-H]):
- Sheets of polygonal epidermoid cells with large vesicular, hyperchromatic granular nuclei, nucleoli
- Slight to moderate cellular atypia
- Mitosis (up to 10/10 HPF)
- Usually invasive growth
- Considered to be variant of cortical thymoma

Electron Microscopic

♦ Neoplastic epithelial cells: branching tonofilaments; complete desmosomes; elongated cell processes and basal lamina

Immunohistochemistry (see Table 15-2)

♦ Neoplastic epithelial cells: keratin +, epithelial membrane antigen (EMA) +

♦ Nonneoplastic lymphocytes:
– Medullary: mature lymphocytes with features of medullary thymocytes (CD1a –, either CD4 + or CD8 +)
– Non-medullary: immature lymphocytes with features of cortical thymocyte (TdT +, CD1a +, coexpress both CD4 and CD8)

Differential Diagnosis

♦ Thymic carcinoma:
– Cytologically malignant; high mitotic rate with atypical mitoses, invasive growth, sclerosis in center of tumor, and coagulative necrosis
– CEA and B72.3 + in thymic carcinoma, but – in thymoma
– Infiltrating lymphocytes are mature lymphocytes and negative for CD1a (very useful criteria in needle biopsy)
– Usually not associated with myasthenia gravis

♦ Carcinoid:
– Unencapsulated; monomorphous cell population with true rosettes, ribbons, or festoons
– Positive staining for neuroendocrine markers
– Some associated with Cushing's syndrome

♦ Thymic Hodgkin's disease:
– Extensive fibrosis with rounded (as opposed to angulated) lobules
– Prominent cysts
– Reed-Sternberg cells or lacunar cells (CD15 +, CD30 +)
– Mixed inflammatory cells

♦ Lymphoblastic lymphoma:
– Diffuse growth or thin, separated lobules
– Numerous mitoses in lymphoid cells
– Positive for T-cell receptor or immunoglobulin chain gene rearrangement

♦ Diffuse large B-cell lymphoma with sclerosis:
– Diffuse growth
– Variable fibrosis with occasional compartmentalization
– Residual cystic thymus
– Lymphocytes with vesicular nuclei, prominent nucleoli, and variable cytoplasm
– Positive for B-cell markers (CD20)

♦ Thymic seminoma:
– Subdivided by fine fibrous trabeculae into variable-sized compartments
– Placental-like alkaline phosphatase (PLAP) +, keratin –

♦ Localized lymphoid hyperplasia (vs. thymoma, predominantly lymphoid subtype):
– Retention of normal cortical and medullary structure
– Presence of lymphoid follicles with germinal centers

♦ Fibrous histiocytoma and hemangiopericytoma (vs. predominantly epithelial or predominantly spindle-cell thymoma with storiform and hemangiopericytoma-like growth pattern):
– Keratin –

♦ Spindle epithelial tumor with thymus-like elements (SETTLE):
– Young age
– Occurrence in thyroid gland
– Mucous glands frequently present
– Lymphocytes lacking

Thymic Carcinoma

♦ Tumors of thymic epithelium, cytologically malignant, not associated with cortical-type immature T cells

Clinical

♦ Rarely associated with myasthenia gravis or other thymoma-related paraneoplastic syndromes

♦ Asymptomatic or nonspecific symptoms found by routine chest X-ray

Table 15-2. Immunohistochemistry Stain Profile of Mediastinal Tumors

	Thymoma		*Metastatic carcinoma*	*Thymic carcinoma*		*Thymic carcinoid*	*Germ cell tumor*	*HD nodular sclerosing type*	*LL*	*DLCL with sclerosis*
	Neoplastic epithelial cells	*Nonneoplastic lymphoid cells*		*Neoplastic epithelial cells*	*Nonneoplastic lymphoid cells*					
Keratin	+	–	+	+	–	±	+ except seminoma	–	–	–
EMA	+	–	+	+	–	±	–	–	–	–
LCA (CD45)	–	+	–	–	+	–	–	–	+	+
CD1a, TdT	–	+ except medullary	–	–	–	–	–	–	+	–
CD5	–	+	–	+	+	–	–	– (+ in background T cells)	+ (– in B-LL)	–
CD15, CD30	–	–	–	–	–	–	– embryonal Ca CD30 ±	+ (in R-S cells and variants)	–	–
PLAP	–	–	–	–	–	–	+	–	–	–
CEA	–	–	±	±	–	±	–	–	–	–
B72.3	–	–	±	±	–	±	–	–	–	–
Neuroendocrine marker	–	–	–	– (+ in small cell undifferentiated carcinoma)	–	+	–	–	–	–

Abbreviations: HD = Hodgkin's disease; LL = Lymphoblastic lymphoma; DLCL = Diffuse large cell lymphoma; B-LL = B-cell LL; R-S = Reed-Sternberg

- Superior vena cava syndrome (occasional)
- Metastatic sites:
  - Lymph nodes (mediastinal, cervical, and axillary), bone, lung, liver, and brain
- Treatment: surgery and radiation with or without chemotherapy
- Prognosis depends on histologic subtype:
  - Very aggressive: non-keratinizing carcinoma (including lymphoepithelioma-like tumors), sarcomatoid carcinoma, clear cell carcinoma, and undifferentiated (anaplastic) carcinoma
  - Intermediate: squamous cell carcinoma (SCC)
  - Relatively indolent: mucoepidermoid and basaloid carcinoma

Macroscopic

- Homogeneous, yellow to gray cut surface with hemorrhage, necrosis, and infiltrating borders

Microscopic

- Morphologically similar to carcinoma in other organ systems
- Cytologic features of malignancy; displays none of characteristic features of thymoma
- Lacks cortical-type T lymphocytes
- Subtypes:
  - Common:
    - Keratinizing SCC
    - Lymphoepithelioma-like (non-keratinizing) SCC:
      - Epstein-Barr virus associated (some cases)
  - Rare:
    - Mucoepidermoid carcinoma
    - Adenosquamous carcinoma
    - Basaloid carcinoma
    - Small cell undifferentiated carcinoma
    - Large cell undifferentiated (anaplastic) carcinoma
    - Sarcomatoid carcinoma
    - Clear cell carcinoma

Immunohistochemistry

- Neoplastic epithelial cells: keratin +, EMA +, CEA +, B72.3 +, and infrequently Leu-7 (CD57) +
- Thymic carcinoma cells are usually CD5 + (CD5 usually – in carcinomas other than thymic primary)
- Infiltrating lymphocytes: CD1a –

Differential Diagnosis

- Thymoma:
  - See above thymoma
- Carcinoma metastatic to or invading anterior mediastinum (particularly carcinoma of lung) and malignant mesothelioma:
  - Thymic squamous carcinoma often exhibits lobulated growth pattern, central sclerosis, and abrupt keratinization simulating Hassall's corpuscles
  - Other subtypes of thymic carcinoma cannot be differentiated based solely on histology (thymic carcinoma is a diagnosis of exclusion: in presence of malignant epithelial tumor located in thymic region in absence of known primary)
  - CD5 + for tumor cells supports diagnosis of primary thymic carcinoma
- Germ cell tumors:
  - PLAP +, human chorionic gonadotropin (HCG) ± (see section on germ cell tumors)
- Diffuse large cell lymphoma with sclerosis:
  - leuokocyte common antigen (LCA) +, CD20 (B cell marker) +, keratin –, EMA –
- Carcinoma with thymus-like elements (CASTLE):
  - Tumor of thyroid gland or soft tissues of neck of middle-aged adult
  - Histologically identical to thymic lymphoepithelioma-like carcinoma with better prognosis and more indolent course

Thymic Carcinoid (Including Atypical Carcinoid)

Clinical

- Adults
- Radiology:
  - Nonfunctional carcinoid:
    - Large, radiopaque, noncystic anterior mediastinal mass with/without fine calcification
  - Functional carcinoid (associated with Cushing's syndrome):
    - Usually of small size, detected by CT scan
- No reported cases of carcinoid syndrome
- Functional tumors have more aggressive course, invade locally, and metastasize infrequently
- Occasionally associated with multiple endocrine neoplasia syndrome (MEN) Type IIa or carcinoid tumors of other sites, such as bronchus and ileum
- Usually cured by excision
- Atypical carcinoids have increased metastatic potential and worse prognosis

Macroscopic

- Solid, well-circumscribed, but not encapsulated
- Lobulated, yellow-tan mass

Microscopic

- Typical carcinoid:

  - Rosette-like glands with central lumina, ribbon, and festoon formation
  - Uniform nuclei with low mitotic rate
  - Marked vascularization
- Atypical carcinoid (majority of tumors):
  - Nuclear pleomorphism
  - Increased mitotic rate and necrosis

Electron Microscopic

- Dense core neuroendocrine granules

Immunohistochemistry Stain

- Keratin +, neuron-specific enolase +, chromogranin +, adrenocorticotropic hormone (ACTH) + (for cases associated with Cushing's syndrome)

Differential Diagnosis

- Small cell undifferentiated carcinoma (vs. atypical carcinoid):
  - High mitotic rate; small nuclear size, with homogenous chromatin pattern
- Epithelial cell predominant thymoma with rosette-like structures:
  - Rosette-like structures frequently associated with lymphocytes, negative for neuroendocrine markers

Thymic Stromal Tumors

Thymolipoma

Clinical

- M:F = 2.3:l, young adult (mean age = 20–30 years)
- Benign, large, asymptomatic mass (>500 gm) of anterior mediastinum
- Association: myasthenia gravis, aplastic anemia, and Graves' disease
- Radiographically resembles cardiomegaly or pulmonary sequestration

Macroscopic

- Encapsulated, can be huge
- Appearance of lipoma with focal presence of whitish solid areas

Microscopic

- Admixture in various proportions of mature adipose tissue and unremarkable thymic tissue being in excess of that normally expected for age

Differential Diagnosis

- Lipoma:
  - Lacks thymic component
- Lymphoid hyperplasia:
  - Smaller size, less adipose tissue, prominent germinal centers

Thymic Stromal Sarcomas

- Rare, low-grade malignant mesenchymal tumors arising from thymic stroma, well-differentiated liposarcoma being the predominant component ("thymoliposarcoma")

Neoplasms Not Limited to Thymus

Neurogenic Tumors

- Account for ~19% of primary mediastinal masses; majority occur in posterior mediastinum

Peripheral Nerve Sheath Tumors

SCHWANNOMA

Clinical

- Typically in young adults
- Most common neurogenic tumor of mediastinum
- Usually asymptomatic, occasionally presenting as "dumbbell" tumor with extension through intervertebral foramen causing nerve root and spinal cord compression
- Radiography:
  - Well-circumscribed posterior mediastinal mass, usually single
- Multiple tumors associated with von Recklinghausen's disease
- Good prognosis, recurrence rare

Macroscopic, Microscopic, and Differential Diagnosis

- See Chapter 13

NEUROFIBROMA

Clinical

- Similar to schwannoma, second to schwannoma in frequency

MALIGNANT PERIPHERAL NERVE SHEATH TUMOR (MPNST)

Clinical

- Age range = 20–50 years
- Rare in mediastinum (<10% of thoracic neurogenic tumors)
- Poor prognosis: local invasion, recurrence, and metastasis
- Associated with von Recklinghausen's disease and prior radiation

Macroscopic, Microscopic, and Differential Diagnosis

- See Chapter 13

Tumors of Sympathetic Nervous System

Neuroblastoma

Clinical

- Most common mediastinal neurogenic neoplasm in children, particularly <1 year of age
- Usually symptomatic:
  - Esophageal or spinal nerve root compression, some with paraneoplastic neurologic syndrome known as opsoclonus myoclonus ("dancing feet and dancing eyes"); erosion of contiguous vertebral bones; failure to thrive; elevated level of catecholamine metabolites in urine or blood
- More than half with metastasis at time of diagnosis
- Frequent sites of metastasis: brain, liver, bone, or regional lymph nodes

Macroscopic, Microscopic, and Differential Diagnosis

- See Chapter 11

Ganglioneuroblastoma

Clinical

- Occurs in older infants and children
- Less aggressive than neuroblastoma

Macroscopic, Microscopic, and Differential Diagnosis

- See Chapter 11

Ganglioneuroma

Clinical

- Occurs in older children and young adults
- Usually asymptomatic, occasionally with spinal nerve root compression
- Usually good prognosis

Macroscopic, Microscopic, and Differential Diagnosis

- See Chapter 11

Paraganglioma

Clinical

- Two major types by location:
  - Anterosuperior mediastinum:
    - Associated with aorticopulmonary paraganglia
    - Average age = 49 years
    - Slight predilection for women
    - 3% of cases synthesize catecholamines
  - Posterior mediastinum:
    - Paravertebral location
    - Average age = 29 years
    - Men dominant
    - 50% of cases synthesize catecholamines
    - Secretory paragangliomas produce clinical symptoms similar to those of pheochromocytoma
- Carney triad:
  - Functional paragangliomas, pulmonary hamartomas, and gastrointestinal malignant stromal tumors
  - Most common in young women
- 50% of cases are fatal due to infiltrative growth and unresectability due to close association with great vessels

Macroscopic, Microscopic, and Differential Diagnosis

- See Chapter 11

Germ Cell Tumors

- Located in anterior and superior mediastinum
- Intimately associated with thymus
- Except for benign mature teratoma, almost exclusively occur in males
- Association with Klinefelter's syndrome
- Association with hematologic neoplasia [leukemia, anaplastic large cell (Ki-1) lymphoma]
- Symptoms due to compression or asymptomatic mass

Teratomas

Benign Mature Teratoma

Clinical

- Most common mediastinal germ cell tumor
- Affects adolescents and young adults
- Equal sex distribution
- Rarely erodes bronchus with expectoration of tumor content

Macroscopic

- Cystic, well-circumscribed, fibrous encapsulation; may contain fat, oily liquid, and hair

Microscopic

- Similar to gonadal teratoma
- Pancreatic and gastric tissue more common

Differential Diagnosis

- Metastatic teratoma
- Immature teratoma:
  - Embryonic tissue components
- Malignant teratoma:
  - Mixed germ cell or non-germ cell malignant components

Immature Teratoma

Clinical

- Male predominance, rarely affects women
- Benign

Macroscopic

- Large, solid, adherent to mediastinal structures
- Cut surface variegated

Microscopic

- Contains immature epithelial, mesenchymal, or neural elements with or without elements of mature teratoma

Differential Diagnosis

- See mature teratoma

MALIGNANT TERATOMA

Clinical

- Aggressive course with invasion of adjacent structures

Macroscopic

- Solid with areas of hemorrhage and necrosis

Microscopic

- Teratoma with components of other germ cell tumors (mixed germ cell tumor)
- Teratoma with malignant non-germ cell components (carcinoma, sarcoma)

GERMINOMA (SEMINOMA)

Clinical

- Males predominant, rare in females
- Second to fourth decades
- Responsive to radiation therapy (up to 100% 5-year survival)

Macroscopic

- Solid, homogeneous mass

Microscopic, Immunohistochemistry

- Identical to testicular seminoma

Differential Diagnosis

- Lymphoepithelioma-like carcinoma of thymus:
  - EMA +, cytokeratin +, PLAP –
- Diffuse large cell lymphoma:
  - Leukocytic common antigen +

EMBRYONAL CARCINOMA

Clinical

- Rare, highly malignant
- Affects males

Macroscopic

- Large, solid, hemorrhagic, and necrotic mass

Microscopic

- Poorly differentiated, with necrosis (identical to gonadal embryonal carcinoma)
- Usually mixed with other germ cell tumor components (mixed germ cell tumor)

Differential Diagnosis

- Metastatic adenocarcinoma:
  - PLAP –, alpha fetoprotein –, CD30–
- Yolk sac tumor:
  - Presence of Schiller-Duval bodies and reticular pattern

YOLK SAC TUMOR

Clinical

- Affects males in third and fourth decades
- High levels of serum alpha fetoprotein
- Poor prognosis

Macroscopic

- Large, necrotic, invasive mass

Microscopic

- Identical to gonadal yolk sac tumor
- Usually mixed with teratoma or other germ cell tumor elements

Differential Diagnosis

- Embryonal carcinoma:
  - Absence of Schiller-Duval bodies and reticular growth pattern; CD30 +

CHORIOCARCINOMA

Clinical

- Affects males in third decade
- Must exclude metastasis from occult testicular primary
- Elevated serum HCG
- Gynecomastia
- Poor prognosis; may be responsive to combination chemotherapy

Macroscopic

- Hemorrhagic mass

Microscopic

- Identical to gonadal choriocarcinoma

Differential Diagnosis

- Metastatic choriocarcinoma
- Mixed germ cell tumor
- Anaplastic carcinoma: HCG –

Lymphoproliferative Disorders (see chapter 7)

- Occur in all mediastinal compartments
- Malignant lymphoma: most common primary neoplasm of middle portion of mediastinum
- Lymphoma may be primary mediastinal process or manifestation of disseminated disease (see chapter 7)

Hodgkin's Disease (HD)

Clinical

- Involves thymus and/or lymph nodes
- Young adults, female predominant:
  - Local pressure symptoms (dyspnea, cough or chest pain) or an incidental finding on chest X-ray
- Nearly always nodular sclerosis type; cervical lymph nodes also frequently involved

Macroscopic

- Well-circumscribed with thick capsule; mimics thymoma
- Composed of single or multiple hard nodules with lobulated pattern
- Occasionally cystic (within thymus)

Microscopic

- Cellular nodules surrounded by fibrous bands
- Polymorphic cell population with diagnostic lacunar cells, Reed-Sternberg (R-S) cells with mixed inflammatory background

Immunophenotyping

- R-S cells and lacunar cells: CD15 +, CD30 +

Differential Diagnosis

- Thymoma: see thymoma earlier
- Thymic cysts: see thymic cyst earlier

Lymphoblastic Lymphoma (LBL)

Clinical

- Predilection for thymic region
- Presents with acute respiratory distress in children and adolescents due to large mediastinal mass
- Male predominant
- Bone marrow, lymph node, central nervous system, and gonadal involvement

Macroscopic

- Solid, soft, and nonencapsulated mass

Microscopic

- Diffuse and infiltrative pattern of atypical lymphocytic growth involving thymic parenchyma
- Neoplastic lymphocytes: medium-sized, very fine chromatin pattern with frequent nuclear convolutions
- Numerous mitotic figures and necrotic cells
- Starry sky pattern similar to that seen in Burkitt's lymphoma
- Neoplastic lymphocytes extending into perithymic fat and blood vessels

Immunophenotyping and Genotyping

- T cells (80% of cases):
  - Immunophenotyping similar to cortical thymocytes (CD1a +, coexpression of CD4/CD8)
  - Positive T-cell receptor gene rearrangement
- B cells (20% of cases):
  - TdT and B-cell marker (CD20) +
  - Positive immunoglobulin heavy chain and light chain gene rearrangement
- Rarely NK cell

Differential Diagnosis

- Thymoma, predominantly lymphoid:
  - Residual thymic lobules and Hassall's corpuscles in lymphoblastic lymphoma can mimic thymoma
  - Lymphocytes not atypical in thymoma
  - Presence of other features of thymoma such as perivascular spaces in thymoma
  - True thymoma rare in children
- Other lymphomas

Diffuse Large Cell Lymphoma With Sclerosis

Clinical

- Mass in thymus with or without lymph node involvement
- Young adult females (<35 years old)
- Presents with superior vena cava syndrome
- Radiology: large mass in anterior mediastinum
- Frequently invading large vessels, pericardium, pleura, lung, and chest wall
- Frequently recurs (usually involving kidney) after initial good response to chemotherapy and radiotherapy

Macroscopic

- Large (>10 cm), grossly invasive features; extension into pericardium, pleura, lung, sternum, and chest wall
- Firm with lobulation and foci of necrosis

Microscopic

- Lobules separated by wide fibrous bands
- Neoplastic lymphocytes with large, vesicular, irregularly shaped nuclei (indented, kidney-shaped, polylobated) and abundant pale to basophilic cytoplasm
- Frequent mitoses
- Entrapment of intrathymic and perithymic fat
- Invasion of blood vessel wall, pleura, or lung

- Sometimes abundant reactive histiocytic cells

Immunophenotyping and Genotyping

- Majority with B-cell phenotype (CD19 +, CD20 +, CD5 –, CD21 –)
- Surface immunoglobulins are often negative; when positive, are of IgG or IgA type, in contrast to other large cell lymphomas of nodal origin (IgM or D type)
- Positive for heavy chain and light chain gene rearrangements

Variants

- Anaplastic large cell lymphoma with T-cell phenotype (CD3 +)
- Clear cell lymphoma of B-cell type
- Pleomorphic large cell lymphoma of B-cell type

Differential Diagnosis

- Malignant thymoma: keratin +
- Germinoma: PLAP +
- Hodgkin's disease: CD15 +, CD30 +
- Metastatic undifferentiated carcinoma: keratin +
- Metastatic amelanotic melanoma: S-100 protein +, HMB45 +
- Other systemic lymphomas

Low-Grade B-Cell Lymphoma of MALT Type

Clinical

- Localized at diagnosis; cured by excision; indolent clinical course; some associated with Sjogren's syndrome

Macroscopic

- Encapsulated large masses (9–12 cm)
- Pale, tan, homogenous cut surface studded with fluid-filled cysts

Microscopic

- Normal architecture of thymus obscured by lymphoid infiltrate, in which Hassall's corpuscles remain
- Lymphoid infiltrate consists of reactive type of follicles and diffuse growth of predominantly "centrocyte-like lymphocytes" (monocytoid B cells), with abundant, clear, faintly granular cytoplasm, and sharp cell borders, admixed with scattered large transformed lymphocytes and scattered plasma cells
- Scattered cysts lined by attenuated epithelium or Hassall's corpuscles infiltrated by neoplastic lymphocytes

Immunophenotyping

- CD20 +, CD22 +, CD5 –, CD10 –

Granulocytic Sarcoma (Myeloblastoma, Chloroma)

Clinical

- Occurs de novo, as manifestation of acute myeloid leukemias at presentation or relapse, or as manifestation of blastic transformation of myeloproliferative disorder such as chronic myeloid leukemia
- Most common in pediatric patients
- Rarely presents in mediastinum

Macroscopic

- Greenish hue on cut surface

Microscopic

- Blastic lesions: composed of predominantly myeloblasts
- Immature lesions: composed of myeloblasts and promyelocytes
- Differentiated lesions: composed of promyelocytes and cells at later stages of maturation

Immunophenotyping and Enzyme Histochemical Stains

- CD43 +, myeloperoxidase +, lysozyme +, chloroacetate esterase +

Differential Diagnosis

- Large cell lymphoma, lymphoblastic lymphoma, and small non-cleaved cell lymphoma: see above lymphoproliferative disorders and chapter 7
- Undifferentiated carcinoma: keratin +

Extramedullary Plasmacytoma

Clinical

- Rarely involves mediastinum (more commonly occurs in head and neck, primarily in mucosa-associated sites)

Macroscopic, Microscopic, and Differential Diagnosis

- See chapter 7

Castleman's Disease (Angiofollicular Lymphoid Hyperplasia)

Localized Form—Hyaline-Vascular Type (90%)

Clinical

- Asymptomatic
- Children and adults of middle age
- Common in anterosuperior mediastinal lymph nodes
- Rarely centered in thymus

Macroscopic

- Single encapsulated mass; solid; homogenous; gray nodular and sometimes hemorrhagic

Microscopic

- Abnormal follicles and striking interfollicular vasculature
- Follicles with expanded mantle zones with atrophic germinal centers
- One or more small blood vessels entering from perifollicular tissue into follicles
- Vessels having hyalinized and thickened walls
- More than one small germinal center within single follicle

Localized form—plasma Cell Type

Clinical

- Similar to above type in addition to systemic manifestations:
  - Anemia, polyclonal gammopathy, elevated ESR, bone marrow plasmacytosis, and thrombocytosis
- Systemic manifestations disappear following excision of the mass

Macroscopic

- Several discrete matted nodes or a mass with adjacent smaller nodes

Microscopic

- Relatively well-preserved nodal architecture
- Interfollicular areas are densely infiltrated by polyclonal plasma cells
- Central region of follicle shows abundance of dendritic reticulum cells

Localized form—multicentric form

- Occurs in older patients
- Peripheral nodal disease
- Plasma cell type dominant
- More aggressive clinical course with development of malignancies such as Kaposi's sarcoma or lymphomas
- Some associated with POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes)

Differential Diagnosis

- For hyaline-vascular type:
  - Other lymphomas including mantle cell lymphoma, follicle center lymphoma, and angioimmunoblastic T-cell lymphoma discussion (page 15-7)
  - Thymoma: see earlier
- For plasma cell type:
  - Lymphadenopathy in patients with rheumatoid arthritis:
    - Clinical correlation
  - Lymphadenopathy in patients with syphilis:
    - Sarcoidal or necrotizing granulomas, spirochetes may be found
  - Lymphoplasmacytic lymphoma
- For both types:
  - Lymphadenopathy in patients with HIV infections

Mesenchymal Tumors

- Account for < 2% of primary tumors of mediastinum
- Many types of mesenchymal tumor have been described
  - All have similar clinical findings, including mediastinal mass and/or compressive symptoms

Benign (Low-Grade) Mesenchymal Tumors

Lipoma

Clinical

- Usually located in anterior compartment
- Tends to be bulky with extension to bilateral pleural cavities

Differential Diagnosis

- Thymolipoma:
  - Presence of thymic tissue in addition to adipose tissue
- Lipomatosis:
  - Diffuse accumulation of adipose tissue seen in association with obesity, Cushing's syndrome, and steroid therapy
  - Associated with "sabre-sheath" tracheal deformity
- Other benign adipose tissue tumors and low-grade liposarcoma (see chapter 13)

Lymphangioma

Clinical

- Anterosuperior mediastinum most frequent
- Usually in children, often includes cervical component

Macroscopic

- Circumscribed mass with large, cystic, smooth-walled spaces

Microscopic

- Endothelial-lined channels, lymphocytic infiltrate

Differential Diagnosis

- Hemangioma:
  - Blood-filled spaces
- Lymphangiomyomatosis:
  - Prominent smooth muscle component (HMB45 +) infiltrative; occurs exclusively in females

Hemangioma

Macroscopic

- Poor circumscription, large cystic spaces filled with blood

Microscopic

- Cavernous hemangioma more common in adults
- Thrombosis, calcification, and cholesterol granulomas common
- Cellular hemangiomas more common in children

Differential Diagnosis

- Lymphangioma (see earlier)
- Other vascular tumors include hemangiopericytoma, epithelioid hemangioendothelioma, and angiosarcoma (see Chapter 13)

Localized Fibrous Tumor

Clinical

- Anterior mediastinum
- May run aggressive course
- Some associated with hyperglycemia

Macroscopic

- Large, tan, firm, and well-circumscribed

Microscopic

- Bland-appearing short spindle cells and fibrous stroma with ropy collagen
- CD34 +

Differential Diagnosis

- Thymoma (hemangiopericytoma-like): keratin +, CD34 –
- Hemangiopericytoma: CD34 –
- Malignant mesothelioma: malignant appearing spindle cells, keratin +, CD34 –
- Fibromatosis: poor circumscription, CD34 –

Malignant Mesenchymal Tumors

Liposarcoma

Clinical

- Most common malignant mesenchymal tumor of mediastinum; may be associated with liposarcoma at other body sites

Differential Diagnosis

- Lipoma
  - Absence of lipoblasts
- Thymic liposarcoma or thymolipoma
  - Remnants of thymus gland

Synovial Sarcoma

Clinical

- Occurs in superior and middle mediastinum

Macroscopic, Microscopic

- Similar to soft tissue counterparts

Differential Diagnosis

- Biphasic malignant mesothelioma
- Fibrosarcoma (when monophasic)

Metastatic Tumors

Small Cell Undifferentiated Carcinoma of Lung

Clinical

- Frequently presents with mediastinal widening that overshadows lung involvement

Differential Diagnosis

- Thymic small cell undifferentiated carcinoma
  - Absence of recognizable lung primary; more solid mass (as opposed to lymph node involvement); lobulated appearance
- Lymphoma: LCA +, keratin –

Direct Extension of Tumors From Esophagus, Chest Wall, Vertebrae, Pleura, and Trachea

Metastases From Distal Sites

Clinical

- Especially problematic: metastatic germ cell tumor, melanoma, and prostatic carcinoma

Macroscopic

- Lymph node involvement often predominates with lesser degree of extranodal soft tissue spread

Differential Diagnosis

- Thymic carcinoma and primary germ cell tumors: must always rule out metastases

TNM CLASSIFICATION OF THYMOMA

TNM System Staging for Thymoma

- T: Primary tumor:
  - T1: macroscopically completely encapsulated and microscopically no capsular invasion
  - T2: macroscopic adhesion or invasion into surrounding fatty tissue or mediastinal pleura, or microscopic invasion into capsule
  - T3: invasion into neighboring organs, such as pericardium, great vessels, and lung
  - T4: pleural or pericardial dissemination
- N: Regional lymph node:

  - N0: no lymph node metastasis
  - N1: metastasis to anterior mediastinal lymph nodes
  - N2: metastasis to intrathoracic lymph nodes other than anterior mediastinal lymph nodes
  - N3: metastasis to extrathoracic lymph nodes
- M: Distant metastasis:
  - M0: no distal metastasis
  - M1: distal metastasis

Clinical Staging

Stage I:

- Completely encapsulated without microscopic capsular invasion (benign thymoma)

Stage II:

- Macroscopic invasion into surrounding fatty tissue or mediastinal pleura or microscopic invasion into capsule

Stage III:

- Macroscopic invasion into neighboring organs (i.e., pericardium, great vessels, or lung)

Stage IVa:

- Diffuse pleural or pericardial involvement

Stage IVb:

- Distal metastasis

THE DEFINITION OF WHO CLASSIFICATION OF THYMIC EPITHELIAL TUMORS*

Type A	A tumor composed of homogeneous population of neoplastic eptithelial cells having spindle/oval shape, lacking nuclear atypia, and accompanied by few or no non-neoplastic lymphocytes.
Type AB	A tumor in which foci having the features of type A thymoma are admixed with foci rich in lymphocytes; the segregation of the two patterns can be sharp or indistinct.
Type B1	A tumor which resembles the normal functional thymus in that it combines large expanses having an appearance practically indistinguishable from normal thymic cortex with areas resembling thymic medulla.
Type B2	A tumor in which the neoplastic epithelial component appears as scattered plump cells with vesicular nuclei and distinct nucleoli among a heavy population of lymphocytes; foci of squamous metaplasia and perivascular spaces are common.
Type B3	A tumor predominantly composed of epithelial cells having a round or polygonal shape and exhibiting mild atypia, admixed with a minor component of lymphocytes; foci of squamous metaplasia and perivascular spaces are common.
Type C	Thymic carcinoma

**The practical experience and clinical significance of this classification is limited. The readers should closely follow up the information regarding this classification.*

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Chapter 16

Cardiovascular Pathology

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Table of Contents

PATHOLOGY OF HEART

Congenital Heart Disease

- General information
  - 0.6 to 0.8 % of live births
  - No identifiable cause in most cases
  - Approximately 5% associated with chromosomal abnormality
  - First trimester rubella infection can lead to patent ductal artery, pulmonary stenosis
  - Down syndrome associated with septal defects (atrial and ventricular), defects of atrioventricular valves
  - Turner syndrome associated with coarctation of aorta
  - Drugs, such as alcohol and thalidomide, can also lead to congenital heart abnormalities

Aortic Stenosis

- Approximately 6% of congenital heart abnormalities
- May assume valvular and subvalvular forms
- Most common cause is bicuspid aortic valve

Atrial Septal Defect (ASD)

- Approximately 10% of congenital abnormalities
- Ostium secundum (OS) defect much more common than ostium primum (OP) defect
- Usually made clinically in both cases
- Often not detected in childhood, presenting in adult
- Results in increased pulmonary blood flow, systolic ejection murmur, widely split second heart sound, eventual right ventricular hypertrophy
- Most important complication is pulmonary hypertension; others include right heart failure, paradoxical embolization
- OP ASD presents in childhood, associated with mitral valve defects and mitral incompetence

Coarctation of Aorta

- Approximately 7% of congenital heart abnormalities
- More common in males
- Common in Turner's syndrome
- Approximately 60% will die (frequently of aortic rupture) by age 40 if not corrected
- 50% of cases associated with other congenital heart defects
- Coarctation located usually just distal to ductus arteriosus (adult type), but may occur just proximal to this structure in infantile type

Patent Ductal Artery (Patent ductus arteriosis, PDA)

- Manifestations depend on size of communication between aorta and pulmonary artery
- Indomethacin induce closure by inhibiting prostaglandin E (PGE) synthesis
- Small PDA results in small left-to right shunt, with "machinery" murmur
- Very mild symptoms in patients with small PDA
- Large PDA results in large shunt, with pulmonary hypertension, eventuating in shunt reversal with cyanosis

Pulmonary Stenosis

- Approximately 7% of congenital heart abnormalities
- Caused usually by valve cusp fusion
- In case of pulmonary atresia, right ventricle will be hypoplastic

Tetralogy of Fallot

- Most common cyanotic congenital anomaly
- Presents at birth with severe cyanosis
- Poor prognosis if not corrected surgically
- Four classic anatomical findings:
  - Ventricular septal defect (VSD)
  - Dextroposed aorta which overrides right ventricular outflow tract, and leads to:
  - Pulmonary stenosis, which leads to:
  - Right ventricular hypertrophy

Transposition of Great Arteries

- Approximately 4% of congenital heart defects
- Cyanosis at birth
- Child doesn't survive without some interatrial communication (PDA, VSD)
- Can be corrected surgically
- Grossly, aorta arises from morphologic right ventricle and is anterior and to right of pulmonary artery (normal lie posterior and to right of pulmonary artery)

Ventricular Septal Defect (VSD)

- Most common cardiac defect seen in children
- Classified according to size of defect, e.g., large, small (<5 mm)
- Most occur in membranous portion of interventricular septum
- May predispose to infective endocarditis

Small VSD

- Infrequent, minor symptoms usually
- Systolic murmur with mild shunt
- Pansystolic murmur
- May close spontaneously as patient gets older

Large VSD

- More serious than small VSDs
- Large left-to-right shunts producing:
  - Volume overload
  - Biventricular hypertrophy
  - Pulmonary hypertension
  - Eventual reversal of shunt with cyanosis (Eisenmenger's syndrome)

Myocardium

Ischemic Heart Disease

Clinical

- Most often due to coronary artery atherosclerosis
- Sometimes with demonstrable complication (plaque rupture, thrombosis, etc.) in acute setting
- May manifest as angina pectoris, myocardial infarct (MI), congestive heart failure, arrythmias, sudden death
- Complications include:
  - Arrythmia
  - Congestive heart failure
  - Hypotension
  - Post MI ventricular and/or papillary muscle dysfunction rupture
  - Extension of infarct
  - Pericarditis
  - Microbial colonization
  - Mural thrombosis/embolism
  - Ventricular aneurysm/rupture

Macroscopic

- Myocardial necrosis in an acute MI
- May be either transmural (most common), or subendocardial
- Usually no grossly detectable changes in first 6-12 hours
- After 18-24 hours, there may be either myocardial pallor, or a red-blue discoloration
- The infarcted zone begins to appear yellow as polymorphonuclear neutrophils move in (2-3 days)
- By 7-8 weeks cicatrization may be complete
- "Old" ischemic heart disease may manifest as an old MI, interstitial myocardial fibrosis, chamber dilation and compensatory hypertrophy

Microscopic

- Acute myocardial ischemia (see Table 16-1)
- Old myocardial ischemia (as interstitial fibrosis, vacuolar change in cardiac myocytes)
- Compensatory myocyte hypertrophy

Cardiomyopathy (Heart Muscle Disease of Unknown Cause)

Idiopathic Hypertrophic Cardiomyopathy

Clinical

- 50% familial (autosomal dominant), myosin heavy chain defect
- HLA linkage to chromosome 6
- Clinical evaluation needed to make diagnosis
- Symptoms of left ventricular outflow obstruction
- Cause of sudden death during exercise
- Treated by beta adrenergic blockage, septal myotomy or myomectomy

Macroscopic

- Asymmetric septal hypertrophy
- Plaque in the left ventricular
- Mitral valve thickening and enlarged left atrium

Microscopic

- Nonspecific myofiber disarray, hypertrophy, interstitial fibrosis

Differential Diagnosis

- Hypertensive disease
  - Shows usually concentric left ventricular hypertrophy

Idiopathic Dilated Cardiomyopathy

- Clinical evaluation needed to make diagnosis
- Often severe 4-chamber dilation grossly
- Biopsy may show non-specific, hypertrophy, interstitial fibrosis

Differential Diagnosis

- Rule out ischemia, other causes

Arrythmogenic Right Ventricular Cardiomyopathy [Arrythmogenic Right Ventricular Dysplasia (ARVD)]

- Asymptomatic, arrythmias, sudden death
- Can be familial
- Gross infiltration of right ventricular free wall by fat and/or fibrous tissue, with dilation and wall thinning
- Left ventricle may be involved also
- Myocyte loss, with presence of admixed myocytes, adipose and/or fibrous tissue
- Myocarditis may be present

Differential Diagnosis

- Normal fat infiltration of right ventricle, especially in obese persons

Hypertensive Heart Disease

Table 16-1: Sequence of Certain Microscopic Changes in Acute Myocardial Ischemia (approximate)

Time After Event	*Gross findings*	*Histopathologic findings*
1 day	Softening, pallor, and edema	Eosinophilic necrosis, edema, interstitial hemorraghe, contaction band change, nuclear pyknosis, beginning neutrophil infiltration.
2–3 days	Opaque with grey-yellow center and hemorrhagic border.	Marked neutrophil infiltrate, loss of nuclei and striations.
3 days to 1 week	Rubbery center with shrinkage.	Beginning macrophage infiltration, with phagocytosis and early fibroblastic response.
10 days	Thinning of myocardium with red-brown discoloration.	Extensive phagocytosis, granulation tissue formation.
2 months	Cicatrization	Cicatrization

- Secondary to long standing systemic hypertension
- Grossly, concentric left ventricular hypertrophy
- Microscopically, myocyte hypertrophy and interstitial fibrosis (not due to coronary ischemia)

Infiltrative Diseases

Amyloidosis

Clinical

- Depending upon type and degree of involvement
- May be asymptomatic or present with congestive heart failure, arrythmias, valve disease, ischemic disease, sudden death
- Amyloid in heart, which may be deposited in most types of amyloidosis, may be further characterized by identifying protein subclass, using immunohistochemical techniques
- In senile systemic amyloidosis with cardiac involvement, amyloid is composed of transthyretin
- In isolated atrial amyloid, it is composed of atrial natriuretic factor

Macroscopic

- Extensive deposits may lead to pale, firm and rubbery myocardium
- Valvular deposits may appear waxy and shiny

Microscopic

- Amorphous, extracellular, pink material on H&E section
- Deposits can be interstitial and/or intravascular, and may cause vessel stenosis
- By definition, deposits are Congo-red positive, with apple-green birefringence with polarized light
- Electron microscopy also definitive, but rarely necessary

Glycogen Storage Diseases

- Excess sequestration of various glycogen storage products lead to heart failure

Hemochromatosis/Hemosiderosis

- Systemic iron deposition with organ damage (usually in hemochromatosis)
- Iron stain to demonstrate reticuloendothelial iron in hemosiderosis, parenchymal iron in hemochromatosis

Myocarditis

- "Dallas criteria": leukocytic infiltrate (usually lymphocytic) with myocyte degeneration/necrosis

Clinical

- Viral (most often coxsackievirus B), bacterial, fungal, parasitic, collagen-vascular disease, drug reaction, radiation
- Complications include congestive heart failure, conduction defects, arrythmias, and sudden death

Macroscopic

- Range from normal to biventricular dilation/hypertrophy with pale "flappy" myocardium or fibrosis

Microscopic

- In most cases, a T-cell lymphocytic infiltrate admixed with histiocytes
- Occasionally with eosinophils, necessarily with myocyte damage
- Giant cells are seen in giant cell or Fiedler's myocarditis (idiopathic), as well as sarcoidosis
- Distinction between these two entities may be difficult

Variant

Giant Cell Myocarditis

- Occur in young and middle aged adults
- Present with arrythmias, conduction defects, cardiac failure, and sudden death (50%)

- Rapidly progressive and fatal, heart transplantation may be indicated
- Association: thymoma, SLE, thyrotoxicosis
- Microscopically, lymphohistiocytic infiltration and geographic myocyte necrosis
- Lack discrete granulomas or epithelioid histiocytes
- Giant cells are of both macrophage and myocyte origin

Differential Diagnosis

Cardiac sarcoidosis

- Myocardial necrosis associated with discrete non-necrotizing epithelioid granuloma
- Giant cells are exclusively of macrophage origin

Antracycline Cardiotoxicity

- Including doxorubicin (adriamycin) and daunorubicin
- Etiology unknown, may be due to lipid peroxidation of myofiber membrane
- Earliest changes include myocyte vacuolization secondary to sarcotubular system dilation
- Adria cells: myocyte with loss of cross striation and homogenous basophilic staining
- EM findings include cytoplasmic vacuolization, sarcotubular system dilation, and lysis of myofibrils
- Grading (0-3) based on the percentage of cells affected in 10 plastic embedded blocks of tissue

Angiokeratoma Corporis Diffusum Universale

- X-linked recessive inheritance
- Deficiency of lysosomal alpha-galactodase leading to ceramide trihexoside accumulation
- Skin, cornea, kidney, and heart affected
- Microscopically, myocyte vacuolization seen
- Intralysosomal concentric or parallel lamellae by electron microscope

Pericardium

Pericardial Effusion and Hemopericardium

Clinical

- Accumulation of fluid (serous, chylous, serosanguinous) and/or pure blood in pericardial sac, respectively
- If volume is rapidly increasing, cardiac tamponade may result

Macroscopic

- Excess fluid/blood in sac (>50 or so mL)
- Fibrinous exudate in fibrinous pericarditis (see below)
- Hemopericardium usually due to ruptured myocardial infarction, trauma, aortic rupture
- Serosanguinous exudate most often due to malignancy, but infection and renal failure need to be considered

Pericarditis

Acute Pericarditis

Clinical

- Fever, friction rub, heart failure, pain

Macroscopic

- Serous exudate: usually non-infectious
- Fibrinous: acute MI, post MI (Dressler's syndrome), uremia, radiation, trauma, lupus, rheumatic fever
- Purulent: usually infections
- Hemorrhagic: usually due to malignancy in pericardium, also tuberculosis in other countries
- Caseous: TB until proven otherwise, infrequently fungi

Chronic Pericarditis

- Healed phase of acute pericarditis
- May result in constrictive pericarditis
- Fibrosis, sometimes residual collections of lymphocytes

Valves and Endocardium

Acute and Chronic Rheumatic Heart Disease

- Included here, although effects valves as well as myocardium and/or pericardium, because long-term effects in survivors are predominantly valvular

Clinical

- Recurrent acute febrile disease of children following *Steptococcal* (group A) *pharyngitis*
- Etiology is due to an autoimmune mechanism
- Most common cause of mitral stenosis

Gross

- Subendocardial/perivascular areas of fibrinoid necrosis in acute form
- Later, lymphocytic then macrophage infiltrates which may become granulomatous
- These are called Aschoff's bodie, and they may contain characteristic "caterpillar cell"
- Small valvular vegetations may be present
- In chronic form, one may see (especially mitral) valvular fibrosis and thickening, calcification, with thickened and shortened chordae (see Mitral stenosis, below)

Aortic Valve Stenosis

Clinical

- Most common cause of left ventricular outflow obstruction

- Patients may develop concentric left ventricular hypertrophy, pulmonary hypertension, infective endocarditis, systemic embolization
- Associated with sudden death
- Most commonly a consequence of congenital bicuspid aortic valve (in persons younger than 70), and degenerative fibrosis and calcification (senile-type) in persons older than 70
- Other etiologies of aortic valve stenosis include congenital unicuspid valve, post-inflammatory (rheumatic) state, which occurs usually in association with mital valve involvement
- A small percentage of cases may preclude definitive assessment
- Congenital bicuspid aortic valves:
  - Rarely stenotic at birth
  - Tend to develop fibrosis and calcification with increasing age, resulting in stenosis
  - Prevalence of stenosis is proportional with age
  - Gross cusps are oriented either anterior-posterior, or right-left
  - A raphe may be seen in either right or anterior cusp, depending on orientation
  - Calcification and fibrosis may be severe
- Degenerative fibrosis and calcification (senile-type):
  - Occurs in three-cusped aortic valves
  - Usually affects patients older than 60 years
  - Gross calcification and fibrosis of valve cusps, with calcific deposits that may fill sinuses of Valsalva
  - Senile-type calcification and fibrosis may be associated with fusion of one or more commisures, making distinction from congenital bicuspid valve difficult
  - Helpful features are summarized in Table 16-2

Aortic Valve Insufficiency

- May result from a lesion of valvular cusps or dilation of aortic root itself
- Cusp lesions may include post-inflammatory (rheumatic) changes (the most common cause), infectious endocarditis, congenital bicuspid valve, and others

Carcinoid Heart Disease (CHD)

Clinical

- Occurs in setting of metastatic carcinoid tumor, in patients with the carcinoid syndrome
- Left sided lesions are associated with carcinoid tumors in lung
- The valvular lesions may cause pulmonary stenosis, tricuspid regurgitation, but rarely pure tricuspid stenosis

Macroscopic

- White endocardial or valvular plaques, usually of right atrium and/or ventricle

Microscopic

- Smooth muscle proliferation in proteoglycan-rich matrix

Differential Diagnosis

- Endocardial fibroelastosis:
  - Unlike CHD, occurs in infants and children (not adults)
  - Contains prominent elastin
  - Irraditation
  - History helpful here
  - Pericardial fibrosis may also be present

Endocarditis

Infectious

- Usually due to hematogenously transmitted infections by bacteria:
  - Most commonly Streptococcus (viridans, bovis, fecalis), which is less virulent than Staphylococcus aureus
- Approximately 30% occur on normal valves
- Usually there is some predisposition, such as:
  - Cardiac abnormality which creates turbulence, and presumably endothelial injury, such as valve stenosis/regurgitation, prosthesis, septal defects)
  - Clinical circumstance, such as immune suppression, cancers
  - IV drug use may lead to infectious endocarditis, usually of right sided valves
- Complications of infectious endocarditis include valve insufficiency (or stenosis less commonly), septic systemic embolization
- Grossly, friable vegetaions on side of direct flow, often near free edge, composed of thrombus material and bacteria (or fungi, etc.)

Non-infectious

- Non-bacterial thombotic endocarditis (marantic endocarditis):
  - Occurs in setting of cancer (especially mucinous adenocarcinoma) or other systemic wasting illness
  - May embolize
  - Grossly, small or large fibrin masses, without organisms, present at lines of closure on the aortic or mitral valves
  - Microscopically, fibrin and entrapped red blood cells, no inflammation
- Libman-Sacks disease (verrucous endocarditis):

Table 16-2: Helpful Distinguishing Features of Congenital and Bicuspid Aortic Valves

Acquired Commisural Fusion	*Congenital Bicuspid Valve*
Intercomissural distances are nearly equal in three cusps	Intercommisural distance of each fused cusp is smaller than unfused cusp
Cephalad height of raphe is equal to height of unfused commisures	Cephalad height of raphe is lower than height of unfused commisures
Raphe is wide and extends to cusp margin	Raphe is narrow and does not extend to cusp margin

- – Seen in systemic lupus erythematosus (SLE)
- – Multiple small leaflet vegetations, usually on non-flow side (ventricular surface) of mitral and/or tricuspid valves
- – Microscopically, fibrin intermixed with cellular debris and scattered inflammatory cells

Mitral Regurgitation

Floppy Mitral Valve

Clinical

- ♦ Most common cause of mitral regurgitation in one series
- ♦ Risk of developing severe regurgitation due to floppy valve increases with age, especially over 50
- ♦ Complications include ruptured chordae, infective endocarditis, thromboembolism, arrhythmias, and sudden death

Gross/Microscopic

- ♦ Excess valve cusp material, which is thick and hooded, with thickening or thinning of chordae
- ♦ Loose myxoid connective tissue expanding spongiosa layer, which may extend into the chordae

Other Causes of Mitral Regurgitation

- ♦ Papillary muscle dysfunction
- ♦ Infective endocarditis
- ♦ Chronic rheumatic valvular disease

Mitral Stenosis

Clinical

- ♦ Most common cause is rheumatic fever
- ♦ More common in women
- ♦ Latent period of several years followed by progressive stenosis, leading to conditions such as pulmonary hypertenion, left atrial thrombosis, systemic thromboembolism, and infective endocarditis

Macroscopic

- ♦ Pronounced fibrosis along valvular free edges and lines of closure, and fusion of posterior leaflet scallops, fused and shortened chordae tendinae
- ♦ New subendocardial blood vessel formation on valves themselves may be seen

Microscopic

- ♦ Fibrosis, thick-walled blood vessels, calcification, lymphocytes, and sometime myxomatous change

Prosthetic Valves

- ♦ Complications include mechanical fatigue, failure of valve, thrombosis and thromboembolism, infection (most commonly Staphylococcus), perivalvular leaks in suture area

Cardiac Transplantation

Acute Humoral Rejection (Hyperacute Rejection)

Clinical

- ♦ Abrupt failure of allograft, due to preformed recipient cytotoxic antibodies, ABO incompatibility, or major histocompatibility antigen mismatch
- ♦ Occur intraoperatively or immediately perioperatively

Macroscopic

- ♦ Dusky, edematous, hemorrhagic appearance

Microscopic

- ♦ Diffuse interstitial edema and hemorrhage
- ♦ Intravascular fibrin thrombi
- ♦ Myocyte necrosis

Immunohistochemistry/Immunofluorescence

- ♦ Myocardial deposition of cytotoxic antibody(ies)

Acute Cellular Rejection

Clinical

- ♦ Failure of allograft resulting cardiac dysfunction

Macroscopic

- ♦ May be grossly normal in mild cases
- ♦ Edema and endocardial hemorrhages

Microscopic

- ♦ Perivascular and interstitial myocardial lymphocyte infiltrate
- ♦ Myocyte degeneration/necrosis
- ♦ Five general levels (0-4) of severity which direct treatment (International Working Group for Cardiac Transplantation):
  - – Grade 0, no rejection
  - – Mild
    - • Grade 1A, focal (usually perivascular) lymphocyte infiltrate, without myocyte damage
    - • Grade 1B, diffuse interstitial lymphocyte infiltrate, without myocyte damage
  - – Moderate
    - • Grade 2, focal lymphocyte infiltrate, with associated myocyte damage
    - • Grade 3A, multifocal lymphocyte infiltrates, with associated myocyte damage
    - • Grade 3B, diffuse lymphocyte infiltrates, with myocyte damage
  - – Severe
    - • Grade 4, severe, diffuse lymphocyte infiltrate, associated with myocyte necrosis, and neutrophils, often with vasculitis and hemorrhage

Differential Diagnosis

- ♦ Old endomyocardial biopsy site with lymphocytic infiltrates associated with fibrosis
- ♦ Quilty effect
  - – Seen only in adults treated with cyclosporine
  - – Predominantly lymphocyte infiltrate centered in the surface endocardium
  - – Discrete endocardial lymphoid infiltrate with nodal organization
  - – Associated with myocardial degeneration and vascular proliferation
- ♦ Lymphoproliferative diseases

Humoral ("Vascular") Rejection

Clinical

- ♦ Failure of allograft, due to circulating recipient antibodies directed against the donor heart

Macroscopic

- ♦ Dilated cardiomegaly, edema

Microscopic

- ♦ Interstitial edema, hemorrhage, few inflammatory cells
- ♦ Capillaritis

Immunohistochemistry/Immunofluorescence

- ♦ IgG, IgM, C3, fibrinogen deposition on endothelium of intramyocardial vessels

Chronic Rejection

Clinical

- ♦ Failure of allograft (ischemic)
- ♦ Accelerated atherosclerosis is major long term complication of cardiac transplantation

Macroscopic

- ♦ Coronary stenosis, which may extend into intramyocardial branches

Microscopic

- ♦ Intimal hyperplasia/fibroplasias/atherosclerosis
- ♦ Intimal/adventitial chronic inflammatory cell infiltrate
- ♦ Myocyte degeneration and necrosis

Quilty Effect

Clinical

- ♦ Lesions of unknown etiology and of doubtful significance
- ♦ Should therefore be differentiated from allograft rejection

Microscopic

- ♦ Endocardial collections of lymphocytes (predominantly T-cells), with sometimes some around subendocardial myocytes
- ♦ Apparent myocyte necrosis may be present, distinguishing so-called Quilty B from Quilty A (no necrosis)
- ♦ Distinctive microvascular arrangement within aggregate, with lymphocyte streaming at perimeter

Epstein-Barr Virus (EBV)-Associated Post-transplant Lymphoproliferative Disorder

Clinical

- ♦ Occurs in about 10% of transplant cases
- ♦ May regress after withdrawal of immunosuppression

Microscopic

- ♦ Hyperplastic to lymphomatous collections of B-lymphocytes of endocardium
- ♦ Usually of B-cell type
- ♦ May involve other sites (e.g., lung, gastrointestinal tract, lymph nodes, etc.)

Post-transplantation Infection

Cytomegalovirus

- ♦ Most common infection of cardiac transplantation

- Characteristic viral inclusion bodies
- Immunohistochemical/*in situ* hybridization and PCR techniques (PCR is most sensitive) are helpful

Toxoplasmosis

- Characteristic appearance of organisms
- Immunohistochemical technique for identification available

Cardiac Neoplasms

Benign

Myxoma

Clinical

- Sporadic (usually middle-aged women) and familial types
- Comprise approximately 50% of primary tumors of heart
- Heart failure, secondary to valvular or chamber interference
- Constitutional symptoms (fever, malaise and weight loss) due to interleukin-6 production
- Thromboembolism
- May occur in younger patients with recurrence and extracardiac lesions (myxoma syndrome)
- Extracardiac lesions:
  - Myxoma of other organs
  - Breast myxoid fibroadenoma
  - Sertoli cell tumor of testis
  - Endocrine anomalies (adrenal cortical hyperplasia, pituitary adenoma with acromegaly)
  - Skin lesions (blue nevi, lentiginosis, psammomatous melanocytic schwannoma)

Macroscopic

- Most commonly left atrial (approximately 75%) and right atrial mass
- Located in fossa ovalis in atrial septum
- Attached to endocardium without deeper infiltration

Microscopic

- Myxoma cells (abundant eosinophilic cytoplasm with indistinct cell borders, ovoid nuclei, nucleoli variably present) forming trabeculae, syncytia, and rings in a myxoid and/or fibrous matrix
- Hemosiderin is present in hemosiderophages and sometimes myxoma cells
- Prominent vascularity
- Inflammation, extramedullary hematopoeisis may be present
- May show well-developed mucin producing glands (glandular myxoma), which may be confused with metastatic adenocarcinoma
- Immunohistochemically, positive staining has been reported for Factor VIII, vimentin, actin, desmin, smooth muscle myosin, alpha-1-antitrypsin, and alpha-1-antichymotrypsin
- Glandular areas may be positive for CEA, EMA, and keratin

Differential Diagnosis

- Myxoid sarcoma, myxoid hemangioma:
  - Both lack myxoma cells and fine capillary vasculature
- Mural (organized) thrombus:
  - May be indistinguishable with myxoma
- Papillary fibroelastoma:
  - No predilection for left atrium
  - Usually located on a valve cusp
  - Avascular papillary frond and laminated elastic fibers
  - Myxoid areas often located toward the peripheral of the lesion
- Fibroma:
  - Prominent elastic fibers with frequent calcifications

Papillary Fibroelastoma

Clinical

- Asymtomatic, incidental finding at surgery or autopsy
- May represent organized thrombi (similar to Lambl excrescence)
- May give rise to thromboemboli, rarely obstruction of a coronary ostium, with sudden death

Macroscopic

- Small, papillary structure usually occurs on surface of valves
- May also occur on other endocardial locations

Microscopic

- Papillary formation with a paucicellular hyalinized core covered by hyperplastic endocardial cells

Differential Diagnosis

- Lambl's excrescences:
  - Occur along the line of closure and free cuspal edge of valves
  - Smaller and less gelatinous

Fibroma

Clinical

- Occur in children, often < 1 year old and may present with congestive heart failure
- No sex predilection

- Probably represent hamartomaous lesions
- May be part of nevoid-basal cell carcinoma syndrome (Gorlin's syndrome)

Macroscopic

- Usually single, well-circumscribed, "fibroid"-like tumors of myocardium
- Located in the ventricular septum
- No hemorrhage or necrosis

Microscopic

- Fibrocytes, collagen, elastic tissue, sometimes calcification and bone-formation
- No necrosis, cellular pleomorphism, or prominent inflammatory infiltrate

Differential Diagnosis

- Old infarcts:
  - Usually contracted areas of fibrous tissue, and not expansile masses
- Inflammatory pseudotumors:
  - Prominent inflammation with plasma cells
- Papillary fibroelastoma:
  - Avascular papillary fronds with endothelial lining
- Fibrosarcoma:
  - Frequent mitotic figures
  - Usually occur in adults, but other age groups as well (cellular fibromas occur exclusively in early childhood)
  - Organized mural thrombi and cicatrized myxomas
  - Oriented endocardially, unlike intramural location of fibroma
- Solitary fibrous tumor of the pericardium:
  - Pericardial location

Rhabdomyoma

Clinical

- Seen mostly during first decade of life; many are congenital
- No sex predilection
- Associated with tuberous sclerosis and congenital heart disease
- Probably of myocyte origin

Macroscopic

- Single or multiple, firm, white, well-circumscribed nodules
- The most common locations are the left ventricle and ventricular septum

Microscopic

- "Spider cells," with radial cytoplasmic extensions:
  - Immunohistochemical positivity for myoglobin, actin, desmin, vimentin, and sometimes HMB-45

Lipomatous Hypertrophy of the Interatrial Septum

Clinical

- May represent acquired processes related to metabolic disturbance
- Often associated with obesity, advanced age and cardiomegaly
- May cause arrhythmia with sudden death

Microscopic

- Infiltrative, numerous vacuolated adipocytes with interspersed hypertrophic myocytes

Differential Diagnosis

- Liposarcoma:
  - Lipoblast and mitotic figures
- Lipoma:
  - Epicardial location

Cystic Tumor of the Atrioventricular Node

Clinical

- Usually occur in young adults with female predilection
- May cause complete heart block due to its location
- Believed to be a developmental abnormality
- May be associated with other congenital anomalies

Macroscopic

- Cyst-like lesion in the inferior interatrial septum in the region of AV node

Microscopic

- Ductules, cysts, and solid nests of epithelioid cells
- Positive for cytokeratin, epithelial membrane antingen (EMA), carcinoembryonic antigen (CEA), and B72. 3
- Negative for Factor VIII
- Electron microscopy shows desmosomes and microvilli (lesion once thought of as a type of mesothelioma)

Differential Diagnosis

- Bronchogenic and mesothelial cyst:
  - Usually occur on the epicardial surface
  - Larger lesion
- Teratoma:
  - Presence of neural and other ectodermal components

Paraganglioma (Extra-adrenal Pheochromocytoma)

Clinical

- Young adults

- Patients may have hypertension and elevated urine catecholamine levels

Macroscopic

- Most commonly a tumor of left atrium

Microscopic

- See Chapter 11

Others

- Granular cell tumor, hemangioma, lymphangioma, lipoma, angiolipoma, schwannoma, ganglioneuroma, teratoma, ectopic thyroid, and ectopic thyroid tissue

Malignant

- In general, primary cardiac sarcomas are very rare
- Some may defy classification with present-day diagnostic techniques
- Metastatic tumors to heart are much more common

Angiosarcoma

Clinical

- Probably most common primary malignant cardiac neoplasm
- Congestive heart failure, arrythmias, chamber obstruction

Macroscopic

- Large, hemorrhagic, invasive tumor, most frequently of right atrium and pericardium

Microscopic

- Malignant mesenchymal neoplasm, showing endothelial differentiation
- Most are poorly differentiated
- Immunohistochemistry for Factor VIII, CD34, CD31 is positive
- Electron microscopy: Weibel-Pallade bodies

Differential Diagnosis

- Papillary endothelial hyperplasia of hemangioma:
  - Lack mitotic figures or cytologic atypia

Lymphoma

Clinical

- Primary tumors are rare
- Secondary involvement by advance lymphoma or leukemia is much more common

Microscopic

- Usually diffuse large cell type

Neoplasms Metastatic to Heart

Clinical

- Far more common than primary cardiac tumors
- Most result from a primary tumor which is in thoracic cavity (e.g., extension from a contiguous carcinoma of lung)

Microscopic

- Depending on tumor type and includes malignant melanoma, carcinomas of kidney, lung, breast, choriocarcinomas, rhabdomyosarcoma, and others

Neoplasms Metastatic to Heart

Clinical

- Far more common than primary cardiac tumors
- Most result from a primary tumor which is in thoracic cavity (e.g., extension from a contiguous carcinoma of lung)

Microscopic

- Depending on tumor type and includes malignant melanoma, carcinomas of kidney, lung, breast, choriocarcinomas, rhabdomyosarcoma, and others

Others

- Leiomyosarcoma
- Rhabdomyosarcoma
- Malignant fibrous histiocytoma
- Osteosarcoma
- Fibrosarcoma
- Liposarcoma
- Synovial sarcoma
- Malignant peripheral nerve tumor
- Rhabdoid tumor

PATHOLOGY OF BLOOD VESSELS

Arteriosclerosis

- Means literally "hardening of arteries"
- Encompasses several entities, such as atherosclerosis, arteriolosclerosis (see under hypertensive vascular disease, below), and Mönckeberg's medial calcific sclerosis

Atherosclerosis

Clinical

- Accounts for more deaths in the West than any other disease

- Predominantly ischemic consequences of narrowed vessels, e.g. myocardial infarction, stroke, gangrene of extremities, etc.
- Aortic aneurysms are another important consequence

Gross

- Affects predominantly elastic, and large and small muscular arteries
- Lesions (atheroma) consists of a raised intimal plaque, with a lipid core of mostly cholesterol and cholesterol esters, and a fibrous cap
- The fatty streak, seen usually in children, thought to be precursor lesion
- In smaller vessels, atherosclerosis results in stenosis
- In larger vessels, lesion results in focal destruction and weakening of wall, with potential to aneurysm formation, thrombosis, and thromboembolism
- Abdominal aorta is affected more severely than thoracic

Microscopic

- Fibrous cap, containing smooth muscle cells and collagen, lipid core with cholesterol clefts and lipid-laden macrophages
- Dystrophic calcification, plaque rupture, intra-plaque hemorrhage, and luminal thrombosis

Hypertensive Vascular Disease

Hyaline Arteriosclerosis

Clinical

- Most severe in hypertensive subjects, but also seen in normotensive elderly persons
- Vascular narrowing leads to ischemic end-organ damage
- Most notably in kidneys (nephrosclerosis)

Microscopic

- Hyaline (pink, glassy) thickening of arteriole walls, concomitant with lumen narrowing

Hyperplastic Arteriolosclerosis

Clinical

- Seen in more severe and acute hypertension, such as "malignant hypertension," when diastolic pressures can exceed 110 mm/Hg

Microscopic

- "Onion-skinning" of arteriole walls by smooth muscle cells forming concentric layers which thicken and narrow vessel
- Basement membrane reduplicated
- Often accompanied by fibrinoid necrosis of vascular wall

Mönckeberg's Medial Calcific Sclerosis

Clinical

- Minor clinical significance, as this lesion rarely, if at all, produces vascular narrowing
- Occurs typically in individuals older than 50
- May be seen radiographically
- May co-exist in same vessel with atherosclerosis
- The cause is unknown

Macroscopic

- Usually affects femoral, tibial, radial, ulnar arteries, and vascular supply to genitalia
- Also seen frequently in arteries of thyroid gland

Microscopic

- Annular calcifications in media of medium to small muscular arteries
- Occasionally with bone and bone marrow formation lesion locally

Fibromuscular Dysplasia

Clinical

- Seen most often in young women (35 years old)
- May be found in virtually any artery of body
- Pathological end-effect is same as any other form of arterial stenosis
- Ischemia, related to degree of blockage
- Complications include aneurysm, emboli, sudden death
- Uncommon cause of renal artery stenosis
- More common in right renal artery with distal two-thirds of artery involved
- Etiology unknown
- Has a characteristic gross and radiographic appearance
- Manifest as a solitary narrowing, or as a grouped series

Gross/Microscopic

- Arterial wall thickening and consequent lumen narrowing
- Due to non-atheromatous and non-inflammatory fibrous or fibrous and smooth muscle hyperplasia, which can be present in intima, media (the most common location), or adventitia

Myxoid Medial Degeneration (Cystic Medial Necrosis) of Aorta

Clinical

- Cause unknown
- Develops with age
- Important complication of Marfan syndrome
- No necrosis or cyst formation
- Disintegration of elastic fibers (seen best with elastic stain) with "cystic" spaces containing mucopolysaccharide (appears myxoid on H&E section)

- Leads to weakening of aortic wall with potential for aneurysm formation and dissection
- Similar process can be seen in pulmonary artery and represents usually a normal, age related change of little, if any clinical consequence

Aneurysms

- Abnormal dilation of part of vascular wall
- Caused by an acquired or congenital weakness of media
- May assume certain shapes such as saccular, fusiform
- May predispose to dissection

Atherosclerotic Aneurysm of the Abdominal Aorta

Clinical

- Most occur in patients older than 50
- Most frequently seen aneuryms (along with those of common iliac arteries)
- May present as palpable abdominal mass and/or radiographic finding
- Most patients are men, and half are hypertensive
- Larger (>6 cm) are prone to rupture, with fatal internal hemorrhage
- Encroachment on renal, mesenteric, celiac, and/or iliac arteries may lead to ischemia of those respective distributions
- Atherosclerotic aneurysm of thoracic aorta is much less common

Macroscopic

- Most occur between renal artery ostia and iliac aortic bifurcation
- Usually fusiform
- May possess mural thrombus/thrombi

Microscopic

- Atherosclerosis with destruction of media, wall thinning
- Chronic inflammation

Berry Aneurysm of Cerebral Arteries

Clinical

- Associated with autosomal dominant (adult) polycystic kidney disease
- Clinically undetected aneurysms are found in as many as 25% of persons older than 55 years
- May present with focal neurologic deficits, headache, to fatal subarachnoid hemorrhage from a rupture

Macroscopic

- More than 90% are seen at various branch points in circle of Willis
- Multiple aneurysms are seen in approximately 20%
- Most commonly seen at junctions of anterior communicating with anterior cerebral arteries, trifurcation of middle cerebral arteries, and arterial branches of internal carotid artery (internal carotid complex)

Microscopic

- A discontinuity (thought to be congenital) of internal elastic membrane at branch point
- May seen eventual destruction of this membrane with wall thinning and a thin adventitial coat
- Mural thrombus may been seen

Infectious (Mycotic) Aneurysms

Clinical

- A complication of septicemia, and/or endocarditis with embolization of infectious material
- Occur in aorta, cerebral, mesenteric, splenic arteries, and elsewhere
- May also occur next to a nidus of tuberculosis or bacteral abscess
- Abscesses tend to rupture and hemorrhage

Microscopic

- Infectious destruction of vessel wall, with pattern of inflammation depending on type of organism, which can be bacterial, mycobacterial, fungal

Syphilitic Aneurysms

Clinical

- Rare in United States

Macroscopic

- "Tree-barking" of thoracic aorta, with aneurysm formation

Microscopic

- Vasitis vasorum (endarteritis/periarteritis of vasa vasorum) with plasma cells, lymphocytes, and macrophages
- Necrosis and scarring of media, and elastic fiber disintegration
- Not prone to dissection, unlike atherosclerotic aneurysms

Dissection

- Entrance of blood into vessel wall with extension along a certain length of that vessel
- Mistakenly called a "dissecting" aneurysm, when it really is a sort of hematoma

Clinical

- Typically sudden severe chest and/or back pain (in case of aortic dissection)
- May also see hypotension, shock, loss of arterial pulse, cardiac tamponade, and ischemic effects of encroachment upon vessel lumens
- Occurs three times more frequently in men

- Most common in sixth and seventh decades of life
- History of hypertension in common

Macroscopic

- Most often affects aorta, and/or its major branches
- Classified as Debakey's I (ascending aorta), II (ascending and descending aorta), and III (descending only)
- Also Stanford Type A (ascending only or ascending plus descending), and Type B (descending only)
- Aorta shows an intimal tear, typically a few centimeters above aortic ring
- Dissecting hematoma in media may extend into and compromise coronaries, carotids, renal, mesenteric, and/or iliac arteries
- Dissection may penetrate back into original aortic lumen, creating a "double-barrel" aorta
- Dissection into ascending aorta with adventitial tear may give rise to hemopericardium, hemomediastinum, hemothorax, and retroperitoneal hemorrhage
- Other risk factors for ascending thoracic aorta dissection:
  - Hypertension
  - Myxoid medial degeneration
  - Bicuspid aortic valve
- Other risk factors for abdominal aortic aneurysm:
  - Atherosclerosis
  - Hypertension

Vasculitis (also see Chapter 17)

- Classification of vasculitis based on size of involved vessel(s) is practical
- Specific cause can be identified in only a minority of cases
- Can be divided into infectious and non-infectious groups, with latter much more extensive
- There is a correlation between the type of antineutrophil cytoplasmic autoantibodies (ANCA) and the specific vasculitis syndrome
- C-ANCA (anti-proteinase 3) often seen in:
  - Active Wegener's disease
  - Microscopic polyarteritis
  - Churg-Strauss syndrome (allergic granulomatosis and angiitis)
- P-ANCA (anti-myeloperoxidase) often seen in:
  - Polyarteritis nododa
  - Primary glomerular disease (idiopathic crescentic glomerulonephritis
  - Kawaski's disease

Infectious Vasculitis

- Causes are bacterial (including syphilitic, with characteristic involvement of proximal aorta with vasitis vasorum and gross "tree-barking", with aortic root dilation and clinical insufficiency), rickettsial (Rocky Mountain spotted fever), mycotic, tuberculous (typically small vessels), and viral (herpes, CMV)

Non-infectious Vasculitis

MEDIUM TO LARGE SIZED VESSELS

- Large arteries (aorta and its main branches)

Giant Cell Arteritis/Aortitis (see also Temporal Arteritis, below)

Clinical/Macroscopic

- Most commonly seen in adults
- May be seen associated with rheumatoid arthritis, ankylosing spondylitis, scleroderma, and temporal arteritis
- Aortic insufficiency, aneurysms, dissection

Microscopic

- Chronic inflammation (multinucleated giant cells in giant cell aortitis, see Temporal Arteritis, below), with focal medial destruction

Kawasaki's Disease (Mucocutaneous Lymph Node Syndrome)

Clinical

- Occurs usually in infants (also named infantile polyarteritis nodosa)
- Fever, exanthema, conjunctivitis, reddened tongue, lips, oropharynx, cervical lymphadenopathy
- Sudden death from coronary involvement
- Due to necrotizing vasculitis leading to coronary artery aneurysm with rupture
- Leading cause of acquired heart disease in child
- Treated with i.v. gamma-globulin and aspirin

Macroscopic/Microscopic

- Necrotizing polyarteritis (cardiac and elsewhere), arterial aneurysms
- Recent and/or healed myocardial infarction

Takayasu's Disease

Clinical

- Occurs mostly in young Asian women
- Decreased/absent pulses in upper extremities
- Neurologic/ocular symptoms, renovascular hypertension

Macroscopic

- Involvement of aorta, aortic arch branches, pulmonary arteries and occasionally coronary arteries

Microscopic

- Chronic granulomatous vasculitis (may or may not have giant cells)
- Fibrosis of arterial wall in later stages

SMALL TO MEDIUM SIZED VESSELS

Churg-Strauss Syndrome

Clinical

- Probably a type of polyarteritis nodosa (see below)
- Triad of asthma, blood eosinophilia, eosinophilic vasculitis (pulmonary, systemic, and/or isolated organ involvement)

Microscopic

- Vasculitis with eosinophilic infiltrate
- Necrotizing granuloma
- Both arteries and veins involved

Polyarteritis Nodosa (PAN)

Clinical

- Ischemic, multiorgan system involvement
- History of hepatitis B infection
- Fever, hypersensitivity, eosinophilia (see also Churg-Strauss, above)
- Treated with steroids and cyclophosphamide

Macroscopic

- Visible/palpable nodular arterial thickenings, typically at branch points
- Involve predominantly renal and visceral muscular arteries and arterioles
- Pulmonary vessels spared

Microscopic

- Segmental necrotizing vasculitis of small to medium sized arteries
- Co-existent healing/healed lesions and segments of normal vessel (skip lesions)
- Medial destruction with interruption of elastic laninae

Differential Diagnosis

- Churg-Strauss syndrome:
  - Asthma, peripheral eosinophilia and pulmonary involvement
  - Both artery and vein involved
  - Microscopically, necrotizing granuloma and eosinophils

Microscopic Polyarteritis

Clinical

- Depending on severity of organ involvement
- Hemoptysis, hematuria/proteinuria (necrotizing glomerulonephritis), bowel pain/enterorrhagia, muscle pain and weakness, and/or palpable skin purpura may be seen
- Not hypertensive (in contrast to PAN)
- Immune reaction against an antigenic challenge (drugs, microorganisms, etc) can be postulated in many cases

Microscopic

- Vasculitis with fibrinoid necrosis of media and/or leukocytoclastic vasculitis (infiltration of polymorphonuclear neutrophils into vascular wall with neutrophil disintegration) of systemic arterioles, capillaries, and venules
- Lesions of the same age
- Smaller vessels (skin, lung, and kidney) involved than polyarteritis nodosa (PAN)
- Muscular and large arteries spared
- Usually without demonstrable immune complex deposition
- Skin-limited form called cutaneous leukocytoclastic vasculitis may be seen

Differential Diagnosis

- Polyarteritis nodosa
  - Lesions of various age with skip lesions

Temporal Arteritis (Giant Cell Arteritis)

Clinical

- Predominance in women, usually greater than 50 years of age
- Elevated sedimentation rate
- May be associated with polymyalgia rheumatica and giant cell aortitis (indicating systemic condition and not limited to temporal, cerebral, and retinal arteries)
- Blindness and central nervous system (CNS) manifestations
- Treated with steroids

Microscopic

- Segmental inflammatory destruction of vessel wall
- Destruction of elastica and presence of multinucleated giant cells
- Biopsy should include generous length (some say two centimeters) of superficial temporal artery, as lesion may be missed due to its segmental nature

Differential Diagnosis

- Takayasu's disease

Thromboangiitis Obliterans (Buerger's Disease)

Clinical

- Predominantly young men less than 40 years old
- Associated strongly with using tobacco

Macroscopic

- Segmental stenosis of small to medium sized arteries and veins of extremities, sometimes mesenteric vessels, rarely elsewhere
- Extremital ischemia

Microscopic

- Early stage shows arterial/venous thrombosis with inflammation
- Affecting entire wall of vessel, sometimes with multinucleated giant cells in thrombus itself
- Later stages may be difficult to distinguish from organizing thrombus of other etiology, or atherosclerosis

Wegener's Granulomatosis

Clinical

- Peaks in 5th decade, with pneumonitis, upper-airway inflammation and ulceration, and renal dysfunction (80%)
- C-ANCA detected in over 90% of patients who exhibit active disease
- Most patients die if untreated
- Responds well to immunosuppressive and cytotoxic medication

Microscopic

- Necrotizing vasculitis of small to medium-sized arteries and veins, with granulomatous features
- Pulmonary involvement leads to cavity formation and characteristic geographic necrosis
- Renal involvement may manifest as necrotizing and or crescentic glomerulonephritis
- Vascular and/or glomerular immune complexes may be seen in some patients

Differential Diagnosis

- Mycosis, tuberculosis, lymphomatoid granulomatosis

Other

- Vasculitis may be associated with connective tissue disease (e.g. SLE and rheumatoid arthritis), malignancy (lymphomas and others), cryoglobulinemia, and Henoch-Schonlein purpura

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Chapter 17

Lung

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Table of Contents

NONNEOPLASTIC DISEASES OF THE LUNG

Congenital Anomalies and Pediatric Lesions

Pulmonary Sequestration (Two Subtypes)

Intralobar

Clinical

- 90% lower lobes; 60% on left; equal incidence in both sexes
- 50% older than 20 years; usually presents with recurrent infections

Macroscopic

- Firm, cystic area within lobe
- Arterial supply from elastic artery from thoracic aorta or below the diaphragm
- No communication with normal tracheobronchial tree
- Invested by normal visceral pleura

Microscopic

- Young patients: pathology may be normal
- Older patients: pathology shows chronic obstructive pneumonia; honeycomb changes are common

Extralobar

Clinical

- 60% are found in children <1year; 90% on left side; M:F = 4:1
- Frequently found with repair of diaphragmatic defect
- 60% have other congenital anomalies such as diaphragmatic hernia or pectus excavatum (funnel chest)

Macroscopic

- Spongy, pyramidal mass outside of the normal pleura; invested by own pleura
- Systemic anomalous arterial supply; venous drainage through systemic or portal systems

Microscopic

- May appear normal; may resemble congenital adenomatoid malformation

Bronchogenic Cysts

Clinical

- Supernumerary lung buds from foregut; commonly found in subcarinal or middle mediastinum location; usually incidental findings on chest X-ray

Macroscopic

- Usually unilocular cysts with smooth margins; no communication with tracheobronchial tree

Microscopic

- Respiratory epithelium with smooth muscle, cartilage, and submucosal glands

Differential Diagnosis

- Lung abscess:
  - Frequent bronchial communication
- Enteric cysts:
  - Lined by gastric epithelium
- Esophageal cysts:
  - Squamous epithelium
  - Wall contains double layer of smooth muscle and no cartilage

Congenital Cystic Adenomatoid Malformation

Clinical

- Stillborn with anasarca and newborn with acute respiratory distress
- Most communicate with tracheobronchial tree

Macroscopic

- Three types of lesions:
  - Type 1: one or more large cysts; cured with surgical removal
  - Type 2: multiple, evenly spaced cysts; poor prognosis
  - Type 3: spongy tissue; no cysts; poor prognosis; mediastinal shift

Microscopic

- Pseudostratified, primitive epithelium; cartilagenous islands

Differential Diagnosis

- Extralobar sequestration:
  - Located outside of pleura
  - Have a separate arterial blood supply

Pulmonary Lymphangiomatosis

Clinical

- Occurs in young children; presents with wheezing and dyspnea; slowly progressive

Macroscopic

- Firm, lobulated lung

Microscopic

- Proliferation of dilated, endothelial-lined spaces; may have smooth muscle in walls in lymphatic distribution

Differential Diagnosis

- Lymphangiomyomatosis:
  - Occurs only in women of reproductive years

  - Smooth muscle is HMB 45 +
- Lymphangiectasis:
  - Dilated channels but not increased number

Airways and Obstructive Diseases

Emphysema

Clinical

- Pink puffer
- Four major types found in four different clinical settings:
  - Centrilobular (proximal acinar):
    - Smokers; upper lobes most affected
  - Panacinar:
    - Alpha-1-protease inhibitor deficiency (ZZ); lower lobes most affected
    - Can be seen in talc IV drug abuse and in Ritalin use
  - Distal acinar (Paraseptal):
    - May contribute to spontaneous pneumothoraces and bullae formation in tall, asthenic male adolescent
  - Scar (better known as pericicatricial airspace enlargement):
    - Most common type; around area of fibrosis

Macroscopic

- May manifest as bullae-alveolar spaces >1cm or blebs-representing airspaces made by dissection of loose connective tissue

Microscopic

- Alveolar wall destruction distal to terminal bronchioles; no fibrosis

Differential Diagnosis

- Congenital lobar overinflation:
  - No destruction of alveoli
- Honeycomb lung:
  - Fibrosis with metaplastic columnar epithelium

Large Airway Disease

Bronchiectasis

Clinical

- Causes include postinflammatory and postobstructive; seen in setting of cystic fibrosis, ciliary disorders, immunologic deficiencies, and idiopathic
- Recurrent pneumonias with productive cough; hemoptysis; recurrent fevers:
  - Cystic fibrosis (mucoviscidosis)

Macroscopic

- Diffuse or localized enlarged, fibrotic cartilaginous airways; dilated airways extend to pleural surface; commonly filled with mucopurulent material

Microscopic

- Ectatic, dilated airways; chronically inflamed wall; follicular bronchitis may be present
- Acute and organizing pneumonia is common

Differential Diagnosis

- Mucinous tumors of the airways:
  - Malignant epithelium

Chronic Bronchitis

Clinical

- "Blue bloater"

Microscopic

- Goblet cell hyperplasia, thickened basement membrane, submucosal gland hyperplasia, smooth muscle hypertrophy
- Reid index: thickness of mucous gland layer/thickness of bronchial wall (normal < 0.4)

Asthma

Clinical

- Nonproductive cough and wheezing; atopic, nonatopic, exercise, and occupational types
- Affects 5% of all children; 65% of asthmatics have symptoms before age 5
- M:F = 2:1

Macroscopic

- Mucous plugging of airways; overdistention with abundant air trapping
- May see saccular bronchiectasis, especially in upper lobe

Microscopic

- Thickened basement membranes; mucous plugs; goblet cell hyperplasia
- Submucosal gland hypertrophy; may show eosinophilic infiltrate
- Smooth muscle hypertrophy
- Curshman's spirals, Charcot-Leyden crystals, and Creola bodies

Differential Diagnosis

- Chronic bronchitis:
  - Histology very similar to asthma, except found only in smokers

Bronchocentric Granulomatosis

Clinical Features

- 50% of patients have asthma; also may have allergic bronchopulmonary aspergillosis

- ♦ High serum IgE; Type I and III reaction

Microscopic

- ♦ Bronchocentric granulomatous inflammation

Differential Diagnosis

- ♦ Wegener's granulomatosis:
  - – Angiocentric vasculitis
  - – c-ANCA +

Small Airway Disease

Respiratory Bronchiolitis (Smokers')

Clinical

- ♦ Incidental findings in smokers

Microscopic

- ♦ Pigmented macrophages within terminal bronchioles and surrounding alveoli
- ♦ Mild chronic inflammation, fibrosis

Respiratory Bronchiolitis-Associated Interstitial Lung Disease (RB-ILD)

Clinical Features

- ♦ Smokers' disease
- ♦ Dyspnea, cough, mild restrictive defects
- ♦ Chest X-ray usually normal; may present as interstitial infiltrates

Microscopic

- ♦ Pigmented macrophages accumulate within lumens of distal bronchioles and surrounding alveoli; mild chronic bronchiolar inflammation and fibrosis

Differential Diagnosis

- ♦ Desquamative interstitial pneumonia:
  - – Interstitial fibrosis, more peripheral Langerhans'
- ♦ Eosinophilic granuloma:
  - – Characteristic nodules with cells (S-100 protein +, CD1a +)

Follicular Bronchiolitis

Clinical

- ♦ Rare small airway disease; associated with collagen vascular diseases, including Sjögren's disease and rheumatoid arthritis, and with immunodeficiencies

Microscopic

- ♦ Marked chronic inflammatory infiltrate surrounding small bronchioles; germinal centers are frequent; acute inflammatory cells within lumen can be seen

Constrictive (Obliterative) Bronchiolitis

Clinical

- ♦ Complication of lung or bone marrow transplantation; drug toxicity; connective tissue disease and idiopathic disease

Microscopic

- ♦ Bronchiolar and peribronchiolar fibrosis with narrowing and eventual obliteration of the lumen; may be preceded by cellular bronchiolitis

Diffuse Panbronchiolitis

Clinical

- ♦ Seen almost exclusively in Japan; associated with HLA BW54:
  - – Etiology unknown; erythromycin offers some benefit

Microscopic

- ♦ Dense peribronchiolar infiltrate with characteristic foamy macrophages within the walls of the small bronchioles

Non-specific Chronic Bronchiolitis

Clinical

- ♦ Seen in association with many other lung disorders, rarely by itself

Microscopic

- ♦ Smooth muscle hypertrophy; scant inflammatory infiltrate
- ♦ May be part of a more significant lesion not seen on biopsy

Interstitial Diseases

Acute Lung Injury

Diffuse Alveolar Damage (DAD)/Acute Interstitial Pneumonia (AIP)

Clinical

- ♦ Pathologic correlate of adult respiratory distress syndrome; acute onset of dyspnea, diffuse pulmonary infiltrates, and rapid respiratory failure
- ♦ Causes include pulmonary edema, septic shock, oxygen toxicity, drugs (including chemotherapeutics), radiation, and trauma
- ♦ Idiopathic variant is known as acute interstitial pneumonia (AIP)—Hamman-Rich syndrome

Macroscopic

- ♦ "Respirator lung"-dense, red/grey diffuse consolidation

Microscopic

- ♦ Temporally uniform injury
- ♦ Two phases: acute and organizing:
  - – Acute: interstitial edema, Type I pneumocyte sloughing and hyaline membranes

- Organizing: proliferating Type II pneumocytes and interstitial fibroblasts with focal airspace organization:
  - Bronchiolar epithelial necrosis, re-epithelialization, and organization within airways
  - Acute and organizing thrombi within vessels are common

Differential Diagnosis

- Bronchiolitis obliterans organizing pneumonia:
  - More subacute clinical course
  - Process is patchy around bronchioles
  - Hyaline membranes are not seen
  - Organization is intraluminal

Bronchiolitis Obliterans Organizing Pneumonia (BOOP)

Clinical

- Causes include collagen vascular disease, toxic inhalants, post-infectious, bronchial obstruction, and idiopathic
- Subacute onset of cough, dyspnea, and fever; multiple patchy airspace opacities, usually bilateral, on chest X-ray
- Treated with steroids; excellent prognosis

Microscopic

- Temporally uniform injury
- Patchy, immature fibroblastic proliferation within bronchiolar lumens and peribronchiolar airspaces; usually sharply demarcated with adjacent normal parenchyma
- Foamy macrophages are commonly found in airspaces surrounding fibrosis
- Interstitial chronic inflammation and Type II pneumocyte hyperplasia in area of fibrosis

Differential Diagnosis

- Diffuse alveolar damage/acute interstitial pneumonia:
  - More acute clinical course
  - More diffuse process, involving both bronchioles and alveoli
  - Fibrosis is interstitial
- Usual interstitial pneumonia:
  - Temporally heterogenous injury
  - Interstitial fibrosis is randomly located
  - Collagen deposition honeycomb foci can be found

Idiopathic Interstitial Pneumonias

Desquamative Interstitial Pneumonitis (DIP)

Clinical

- Usually middle-aged adults, 90% are smokers; insidious onset of dyspnea
- Chest X-ray: bilateral, lower lobe, ground-glass opacities
- Favorable response to corticosteroids;
- Mean survival = 12 years

Microscopic

- Striking pigmented macrophages within alveolar spaces; Type 2 pneumocyte hyperplasia with subtle interstitial fibrosis
- Diffuse process; temporally uniform

Differential Diagnosis

- DIP-like reaction of usual interstitial pneumonitis (UIP):
  - Temporally heterogeneous pattern of injury
- Eosinophilic granuloma:
  - Patchy distribution; predominantly bronchiolar
  - Tightly packed macrophages
  - Can be found in patients <40 years of age
- Respiratory bronchiolitis-associated interstitial lung disease:
  - No interstitial fibrosis
  - Less macrophage accumulation and more airway centered

Usual Interstitial Pneumonia (UIP)

Clinical

- Insidious onset of dyspnea with chronic, progressive downhill course
- Most patients are 40–70 years of age; collagen vascular diseases are commonly present
- 60% of patients die; mean survival = 3 years

Macroscopic

- Honeycomb changes are most advanced at bases and periphery

Microscopic

- Temporally heterogenous pattern of injury; "variegated" low power appearance; fibrosis worse in subpleural and paraseptal regions
- Infiltrate is chronic with plasma cells; germinal centers commonly seen in rheumatoid arthritis
- Most fibrosis is dense collagen; intervening fibromyxoid fibroblastic foci are seen; large, ectatic airspaces with mucin pooling usually found in more advanced areas; areas of normal lung present centrally in lobule
- Smooth muscle hypertrophy and DIP-like reaction around bronchioles is common
- Vascular changes of intimal fibroplasia and medial

hypertrophy are common

Differential Diagnosis

- DIP:
  - Macrophage accumulation is diffuse
  - Process is temporally uniform
- BOOP:
  - Injury is temporally uniform
  - Clinical course is subacute
  - Areas of recent organizations are more pronounced
  - Areas of dense collagen deposition are absent
- Nonspecific interstitial pneumonia:
  - Injury is temporally uniform

Non-specific Interstitial Pneumonia/Fibrosis

Clinical

- Dyspnea and cough over several months; bilateral interstitial infiltrates on chest X-ray
- Middle-aged adults; underlying connective tissue disease is common; some probably represent hypersensitivity reactions; idiopathic
- Usually steroid responsive with good prognosis

Microscopic

- Temporally uniform process with interstitial pneumonitis and rare fibroblastic foci
- Patchy process; may be bronchiolocentric; may have increased numbers of alveolar macrophages
- More advanced stages have interstitial collagen deposition

Differential Diagnosis

- Usual interstitial pneumonia:
  - Injury is temporally heterogenous
  - Collagen deposition and honeycomb changes are seen
- Usual interstitial pneumonia:
  - Injury is temporally heterogenous
  - Granulomas usually not seen
- Sarcoidosis:
  - Rarely has interstitial pneumonia
  - Granulomas are well-formed in lymphatic distribution
- Lymphoid interstitial pneumonia:
  - Pathology is more diffusely distributed
  - Does not have areas of BOOP

Other Interstitial Diseases

Extrinsic Allergic Alveolitis (Hypersensitivity Pneumonitis)

Clinical

- Insidious onset of dyspnea with dry cough, fatigue, and malaise
- Exposure source not identified in 2/3 of cases diagnosed by pathology; diffuse interstitial infiltrates on chest X-ray
- Corticosteroids help after exposure has been eliminated

Microscopic

- Triad of features: interstitial pneumonitis; bronchiolitis with areas of organiziation (BOOP) and ill-formed, nonecrotizing granulomas or giant cells in parenchyma

Differential Diagnosis

Eosinophilic Pneumonia

Clinical

- Four clinical categories:
  - *simple:* Loeffler's syndrome; mild; self-limiting
  - *tropical:* found in tropics due to filarial infestation
  - *acute:* acute, febrile illness with respiratory failure; unknown etiology
  - *chronic:* subacute illness; blood eosinophilia; F > M; patchy, peripheral infiltrate (photographic negative of pulmonary edema); etiologic agents: drugs, fungal hypersensitivity, parasites, and idiopathic inhalants

Microscopic

- Filling of alveolar spaces with eosinophils and variable number of macrophages
- Eosinophilic abscesses and necrosis of cellular infiltrate; BOOP is common
- Features of DAD have been seen in acute form; mild, nonnecrotizing vasculitis of small arterioles and venules common

Differential Diagnosis

- Churg-Strauss disease:
  - Necrotizing granulomatous vasculitis is present
- Eosinophilic granuloma:
  - Infiltrate is interstitial and usually peribronchiolar
  - Seen only in smokers
- DIP:
  - Eosinophilic abscesses and necrosis of infiltrate rarely seen
  - Vasculitis not seen

Eosinophilic Granuloma (Pulmonary Histiocytosis-X/Langerhans' Cell Granulomatosis)

Clinical

- Occurs almost exclusively in smokers; M:F = 4:1; symptoms may be minimal; 4th decade
- Chest X-ray: multiple, bilateral nodules 0.5–1.0 cm in

upper lung lobes with cystic lesions

Microscopic

- Discrete, nodular/stellate lesions; bronchiolocentric Langerhans cell: convoluted (kidney-bean) nuclei

Immunohistochemistry

- S100 +, CDla +, HLR-DR +

Electron Microscopy

- Birbeck granule ("tennis racket" morphology)

Differential Diagnosis

- Respiratory bronchiolitis-associated interstitial lung disease:
  - Does not destroy bronchiole
  - Minimal fibrosis
  - No Langerhans cells

Sarcoidosis

Clinical

- Most common in young, black female (20–35 years)
- Deficient T cell response (cutaneous T cell anergy and decreased helper T cells)
- Associations: functional hypoparathyroidism; hypercalciuria ± hypercalcemia; erythema nodosum; uveitis
- Kveim test: granulomatous reaction following injection of human spleen extract
- Serum ACE (angiotensin converting enzyme)
- Radiologic stage:
  - Stage 0: normal chest X-ray
  - Stage 1: hilar/mediastinal adenopathy
  - Stage 2: hilar/mediastinal adenopathy + interstitial pulmonary infiltrate
  - Stage 3: interstitial pulmonary infiltrate only
  - Stage 4: endstage fibrosis with honeycombing

Microscopic

- Interstitial noncaseating granulomata distributed in lymphatic and bronchovascular pathways; vascular and pleural involvement common

Differential Diagnosis

- Chronic berylliosis:
  - Elevated beryllium levels on tissue quantitation
  - Clinical history of beryllium exposure
- Extrinsic allergic alveolitis:
  - Ill-formed granulomata; interstitial distribution
  - Accompanying interstitial pneumonia

Pulmonary Alveolar Proteinosis

Clinical Features

- Defect in alveolar macrophage (GM-CSF knockout mice)
- Etiologies: dust, drugs, immunodeficiency, leukemia, kaolin, idiopathic
- Bronchoalveolar lavage: treatment of choice
- Idiopathic or associated with infection

Microscopic

- Accumulation of granular eosinophilic material in alveoli; PAS + material

Electron Microscopy

- Lamellar body

Differential Diagnosis

- Pulmonary edema:
  - Interstitial/septal edema
- Mycobacterial, nocardial, or *Pneumocystis carinii* pneumonia:
  - + special stains or microbiologic cultures

Lymphangio(leio)myomatosis

Clinical

- Occurs exclusively in women of reproductive years
- Progressive dyspnea, chylous pleural effusions, recurrent pneumothoraces
- Chest X-ray: enlarged lungs; can show cystic or "honeycomb" changes
- Found in patients with tuberous sclerosis

Microscopic

- Haphazard proliferation of smooth muscle in lymphatics, blood vessels, bronchioles, and alveolar septa
- Hemosiderin-laden macrophages accumulate in the alveoli, especially in the subpleura

Immunohistochemistry

- HMB-45 +

Differential Diagnosis

- Benign metastasizing leiomyoma:
  - Discrete nodules, some contain entrapped pulmonary epithelium
- UIP with end-stage changes:
  - Small lungs, lower lobe predominant
  - Chronic inflammatory changes and fibrosis
  - Older age group; men and women

Goodpasture's Disease (Anti-Basement Membrane Antibody Disease [ABMA])

Clinical

- M:F = 9:1; young adults; smokers; DRw15, DQw6
- Cytotoxic, antibody-mediated, immune reaction; antibodies to basement membrane in serum cross react

to both kidney and lung
- Hemoptysis, anemia, azotemia, and diffuse lung infiltrates

Microscopic
- Capillaritis can be seen, but no large vessel vasculitis
- Extensive intraalveolar hemorrhage; nonspecific Type II pneumocyte hyperplasia

Immunofluorescence
- Linear staining of glomerular and pulmonary basement membranes for IgG

Differential Diagnosis
- Idiopathic pulmonary hemosiderosis:
  - Child and adolescent
  - Immunofluorescent linear pattern is absent
  - No acute hemorrhage

Idiopathic Pulmonary Hemosiderosis

Clinical
- Exclusively in children ≤ 16 years; M:F = 1:1
- Hemoptysis, chest infiltrates; iron deficiency anemia

Microscopic
- Intraalveolar hemosiderosis without capillaritis; alveolar wall thickening and Type II pneumocyte hyperplasia

Differential Diagnosis
- Goodpasture's Disease:
  - Linear immunofluorescence pattern (IgG)
  - Kidney involvement

Pneumoconioses
- A non-neoplastic reaction of the lungs to inhaled mineral or organic dust

Silicosis

Clinical
- Reaction in lung to inhaled crystalline silica: stonecutting, quarry work, or sandblasting
- 0.5–2 micron fibers: most fibrogenic
- Predisposed toward tuberculosis (TB)

Macroscopic
- Firm, discrete, rounded lesions with variable amounts of black pigment
- Nodules in lymphatic distribution: around bronchovascular bundles, in subpleural and interseptal areas

Microscopic
- Discrete foci of concentric layers of hyalinized collagen; dust-filled histiocytes are abundant; birefringent particles usually present
- When necrosis is present, consider complicating injection by myobacterial tuberculosis

Differential Diagnosis
- Inactive mycobacterial or fungal infections:
  - Giant cells and palisading histiocytes usually seen
- Hyalinizing pulmonary granuloma:
  - Collagen bundles are disorganized
  - Birefringent material is unusual

Asbestos-Related Reactions

Clinical
- Reactions of the lung to asbestos with accompanying cations (i.e., iron, calcium, magnesium, sodium); serpentine and amphibole are the most common types
- Fibrosis occurs 15–20 years after exposure and can progress after exposure stops

Macroscopic
- Firm, fibrotic lungs with areas of honeycomb change

Microscopic
- Marked interstitial fibrosis with minimal inflammatory infiltrate; UIP-like reactions common
- The presence of asbestos bodies, fibrosis, and exposure history are needed for definitive diagnosis
- Hyalinizing pleural plaques, pleural fibrosis, and rounded atelectasis can also be seen

Differential Diagnosis
- Usual interstitial pneumonia:
  - Temporally heterogenous
  - Lack of asbestos bodies

Coal Worker's Pneumoconiosis (CWP)

Clinical
- Simple: single nodule, <2cm
- Complicated: >2cm, including progressive massive fibrosis
- Caplan's syndrome: rheumatoid nodule with CWP (progressive massive fibrosis)

Microscopic
- Hyalinized nodule with anthracotic pigment in lung and lymph nodes
- Macules adjacent to bronchioles; may have centrilobular emphysema

Hard Metal Pneumoconiosis

Clinical
- Exposure to tungsten carbide and cobalt, usually in grinding, drilling, cutting, or sharpening
- Dyspnea with restrictive pulmonary function tests

Microscopic
- Giant cell interstitial pneumonitis with interstitial fibr-

Table 17-1. Differential Diagnosis of Granulomatous Lesions

	*NSG**	*Wegener's*	*Infection*	*Churg-Strauss Syndrome*
Sarcoidal granuloma	++	–	++	+
Vasculitis	++	++	±	++
Necrosis	++	++	++	++
Hilar Adenopathy	±	–	++	–
Cavitation	+	++	+	++
Asthma/peripheral eosinophilia	–	–	–	+

NSG: Necrotizing Sarcoid Granulomatosis

osis, peribronchiolar giant cells, and DIP-like reaction
- ♦ Giant cells are multinucleated and commonly engulf other inflammatory cells

Differential Diagnosis
- ♦ Viral bronchiolitis/pneumonitis:
  - – No history of tungsten carbide/cobalt exposure
- ♦ Hypersensitivity pneumonitis:
  - – Increased interstitial and peribronchiolar inflammatory infiltrate
  - – Non-necrotizing granulomas

Vascular Conditions

Vasculitides (also see Chapter 16)

Wegener's Granulomatosis

Clinical
- ♦ Triad: upper airway, lower airway (lung), and kidney; saddle nose; rarely lung only (so called "limited")
- ♦ 40% c-ANCA + (anti-proteinase 3) in remission; 90% c-ANCA + in active disease
- ♦ Chest X-ray: multiple well-demarcated peripheral nodules, lower lobes, rarely as a solitary pulmonary lobule

Microscopic
- ♦ Triad: parenchymal (basophilic) necrosis, vasculitis, granulomatous inflammation
- ♦ Variants: eosinophil rich, bronchiolocentric, solitary, capillaritis, and diffuse pulmonary hemorrhage

Differential Diagnosis (Table 17-1)
- ♦ Lymphomatoid granulomatosis:
  - – Atypical cytology
- ♦ Granulomatous infections:
  - – Well-formed, non-necrotizing granulomas
  - – Eosinophilic necrosis

Churg-Strauss Syndrome (Allergic Angiitis Granulomatosis)

Clinical
- ♦ Asthma, eosinophilia, systemic vasculitis, mono- or polyneuropathy
- ♦ Nonfixed lung infiltrate, paranasal sinus abnormalities; p-ANCA +

Microscopic
- ♦ Eosinophilic infiltrates, granulomatous inflammation, and necrotizing vasculitis

Differential Diagnosis (Table 17-1)
- ♦ Chronic eosinophilic pneumonia:
  - – Nongranulomatous
- ♦ Allergic bronchopulmonary aspergillosis:
  - – Bronchocentric
- ♦ Drug-induced vasculitis
- ♦ Polyarteritis nodosa:
  - – Rarely involves the lung
- ♦ Wegener's granulomatosis:
  - – Geographic necrosis

Necrotizing Sarcoid Granulomatosis (NSG)

Clinical
- ♦ F:M = 4:1; variable age presentation; cough, chest pain, weight loss, fever
- ♦ No systemic vasculitis
- ♦ Chest X-ray: bilateral lung nodules ± hilar adenopathy

Microscopic
- ♦ Lymphoplasmacytic or granulomatous vasculitis;

parenchymal necrosis without necrotizing vasculitis; numerous caseating sarcoid-like granulomas

Differential Diagnosis (Table 17-1)

- Wegener's granulomatosis:
  - No sarcoidal granulomas
- Infection
  - Vasculitis not prominent component
  - + organismal stains
- Churg-Strauss syndrome (allergic angiitis granulomatosis):
  - No hilar adenopathy
  - History of asthma
  - Peripheral eosinophilia

Necrotizing Capillaritis

Clinical

- Associated conditions: collagen vascular disease, especially systemic lupus eryhthematosis; Wegener's; Henoch-Schonlein purpura, cryoglobulinemia, Behcet's disease, drug reactions (sulfonamides), and Goodpasture's disease

Microscopic

- Focal necrosis of alveolar septa with neutrophilic infiltration, capillary fibrin thrombi, and interstitial hemorrhage/hemosiderosis
- Often associated with foci of DAD

Differential Diagnosis

- Acute hemorrhagic bronchopneumonia:
  - Neutrophils predominate in alveolar space

Pulmonary Hypertension

Plexogenic Arteriopathy

Clinical

- Congenital cardiac shunts
- Primary pulmonary hypertension (young female predominant)
- Aminorex fumarate
- Rare cases associated with cirrhosis of the liver
- Rare cases associated with portal vein thrombosis
- Rare cases associated with + HIV infection

Microscopic

- Grade 1: muscularization of pulmonary arteries
- Grade 2: cellular intimal proliferation
- Grade 3: intimal concentric laminar fibrosis
- Grade 4: plexiform lesions
- Grade 5: plexiform and angiomatoid lesions
- Grade 6: necrotizing arteritis (may actually precede Grades 4 and 5 developmentally)

Pulmonary Veno-Occlusive Disease with Secondary Pulmonary Arterial Hypertension

Clinical

- Rare form of pulmonary hypertension; 1/3 of all cases occur in children
- Causes include drug toxicity, especially chemotherapeutics, possibly viral etiology

Microscopic

- Congestive changes with hemosiderin-laden macrophages
- Pulmonary hypertensive changes
- Intimal fibrosis and thrombosis of veins

Thrombotic Arteriopathy

Microscopic

- Eccentric intimal fibrosis; collander lesions common; widespread small vessel thrombi
- Plexigenic lesions are rarely found (probably represents plexogenic arteriopathy with superimposed thrombi)

Pulmonary Capillary Hemangiomatosis

Clinical

- Rare cause of pulmonary hypertension; most patients between 20–40 years of age

Microscopic

- Proliferation of capillaries in interstitium; patchy hemosiderin

Infections

Viral

Cytomegalovirus

Clinical

- Found almost exclusively in immunocompromised patients

Microscopic

- Diffuse interstitial pneumonitis and nodular (miliary) pneumonia; diffuse alveolar damage
- Cytopathic changes include cytomegaly (2–3 times normal cell); ampholic/basophilic nuclear inclusions; basophilic cytoplasmic inclusions
- Inclusions found in pneumocytes; histiocytes and endothelial cells; PAS +; Grocott +

Differential Diagnosis

- Herpes viral inclusions:
  - Necrotizing pneumonia

- Adenoviral inclusions:
  - No cytoplasmic inclusions

Herpes Simplex Virus

Clinical

- Bloodborne or airborne dissemination; immunocompromised patient, inhalation injuries and chronic obstructive pulmonary disease patient
- Laryngotracheobronchitis, bronchopneumonia

Microscopic

- Military foci of necrosis
- Cytopathic changes: may be difficult to find in lung; mild nucleomegaly (1.25–1.5 times normal cell); dispersion of nuclear chromatin; condensation of nuclear chromatin on nuclear membrane
- Cowdry type A inclusions: intranuclear viral particles that coalesce
- Multinucleation may be absent in lung
- Epithelial cells mainly affected

Differential Diagnosis

- Cytomegalovirus pneumonia
  - Affects both epithelial and mesenchymal cells
  - Cytoplasmic inclusions

Measles Virus

Clinical

- Immunocompromised patient

Microscopic

- Diffuse alveolar damage; multinucleated cells (5–20 nuclei/cell); intranuclear and intracytoplasmic inclusions present (Feulgen –)
- Warthin-Finkeldey cell with lymphoid hyperplasia: CD4 + T cells

Differential Diagnosis

- Giant cell interstitial pneumonitis
  - Acute lung injury usually not present
  - Giant cells with 2–5 nuclei

Adenovirus

Clinical

- Generally found in children; can cause fulminent pneumonia in immunosuppressed

Microscopic

- Destruction of bronchioles with sloughing
- Cytopathic changes: smudge-Feulgen + round eosinophilic intranuclear inclusions

Electron Microscopy

- Lattice-like hexagonal viral particle

Respiratory Syncytial Virus

Clinical

- Usually seen in babies and young children; diagnosis usually made by serologies

Microscopic

- Cellular, lymphocytic bronchiolitis with intraluminal polymorphonuclear leucocytes
- Metaplastic bronchial epithelium; can show multinucleation
- Cytopathic effect: small, inconspicuous eosinophilic cytoplasmic inclusions in bronchiolar cells

Epstein-Barr Virus

Clinical

- Biopsy rarely performed for diagnosis; 10% of patients with mononucleosis show clinical symptoms of respiratory infection

Microscopic

- Perivascular (especially perivenular) chronic inflammation with plasmacytoid and/or immunoblastic features, cellular bronchiolitis, and interstitial infiltrates

Hantavirus Pulmonary Syndrome

Clinical

- Young, healthy adults; rapidly fatal; progressive pulmonary edema and hemorrhage
- Host: deer mice

Microscopic

- Pulmonary edema and pleural effusions; early DAD

Clinical

- Diagnosis usually made by culture or serologies; biopsy rarely done for diagnosis

Bacteria

Legionnaires' Disease

Clinical

- First recognized in large outbreak in American Legion convention in Philadelphia
- Acute pneumonic process with high fever, cough, chill and chest pain; gastrointestinal symptoms are prominent; renal failure is common
- Renal and bone marrow transplant patients at high risk

Microscopic

- Acute bronchopneumonia with characteristic intraalveolar exudate of neutrophils, macrophages, and karyorrhectic debris

Special Studies

- Small, pleomorphic Gram – bacillus; cultured in modified Mueller-Hinton agar
- Dieterle's silver stain best for visualizing organism; fluorescent studies of smears and scrapes are most sensitive for diagnosis

Nocardiosis

Clinical

- Localized abscess or miliary bilateral infection (common) in immunocompromised host

Microscopic

- Mixture of acute and chronic inflammation with microabscess formation
- Silver stain is best for diagnosis: fine, filamentous organisms—may be very difficult to find
- Weakly acid-fast (Fite's stain) and Gram +

Actinomycosis

Clinical

- Aspiration of oral or tonsillar organisms; patients with poor dentition or repeated tonsillitis
- May present like carcinoma

Microscopic

- Abscess in lung or mediastinum; sulphur granules found with palisading eosinophilic proteinaceous halo—Splendore-Hoeppli reaction

Malakoplakia

Clinical

- Nodular lesions in immunocompromised patients, particularly HIV-infected individuals; *Rhodococcus equi* is common etiologic agent

Microscopic

- Chronic infiltrate with plasma cells and lymphocytes with sheets of histiocytes containing abundant Michaelis-Gutmann bodies

Mycobacterial Tuberculosis (TB)

Clinical

- High risk factors include elderly, immigrants, lower socioeconomic groups, aboriginal races, HIV infection, silicosis, immunosuppressive therapies, diabetes mellitus, hemodialysis, gastrectomy, nutritional deficiency, IV drug abuse, and organ transplantation
- Clinical classification:
  - Primary TB: exogenous first infection; usually self-limiting
  - Progressive TB: inadequate acquired immunity (infants or elderly); progression of original infection; <10% of patients
  - Postprimary TB (reactivation;secondary): endogenous reactivation

Macroscopic

- Primary TB:
  - Ghon focus: single subpleural nodule, above or below interlobar fissure and enlarged hilar caseous lymph nodes
- Progressive TB:
  - Cavitation and progression of initial or reactivation nodule; consolidation or miliary spread can occur
- Postprimary TB:
  - Apical lesion (due to higher oxygen tension); miliary spread can occur

Microscopic

- Primary/postprimary TB:
  - Necrotizing granulomatous inflammation, airway-based; nonnecrotizing granulomas commonly present away from main mass
- Progressive TB:
  - Necrotizing granulomatous inflammation with cavitation and spread throughout lung; pleura commonly involved

Non-tuberculous Mycobacteria

- Most common are *Mycobacterium avium* complex (*M. intracellulare* and *M. avium*) and *M. kansasii*

Clinical

- Opportunistic infections in HIV-infected patients
- Other risk factors include COPD, bronchiectasis, and pneumoconioses
- Also found in patients without underlying lung disease (non-smoking women): more benign course

Macroscopic

- Can cause upper lobe cavitary lesion
- Non-cavitating form may be associated with local bronchiectasis

Microscopic

- Necrotizing granulomatous inflammation most common, with nonnecrotizing granulomas present
- Organizing pneumonia and nonnecrotizing granulomas can be seen

Special Studies

- Ziehl-Neelsen stain for acid fast organisms
- Auramine-rhodamine more sensitive

Differential Diagnosis

- Wegener's granulomatosis (Table 17-1):
  - No sarcoidal-like granulomas

- Basophilic necrosis
- ♦ Necrotizing fungal infections:
  - Results of special stains and microbiologic cultures +

Mycoplasma pneumoniae

Clinical

- ♦ Community-acquired pneumonia; dry cough with subacute course

Microscopic

- ♦ Cellular bronchiolitis with acute and chronic inflammation; plasma cells may be abundant
- ♦ Metaplastic bronchiolar epithelium without cilia; organism destroys cilia

Special Studies

- ♦ Complement fixation tests used for diagnosis; four-fold titer increase is diagnostic of infection
- ♦ Stains on Giemsa stain; DNA probe is best way to find organisms in tissue

Fungal

Aspergillosis

- ♦ *Asperillus*: thick-walled hyphae, septated and 45° branching; oxalic acid/calcium oxalate crystals seen with *A. niger*
- ♦ Four different pathologic patterns:
  - Allergic bronchopulmonary aspergillosis (ABPA):
    - Seen exclusively in asthmatics
    - Mucoid impaction, bronchocentric granulomatosis, and eosinophilic pneumonia
  - Aspergilloma:
    - Fungus ball growing in preexisting cavity, e.g. bulla
  - Chronic necrotizing aspergillosis;
    - Usually single, upper lobe lesion subacute clinical course
    - Chronic, granulomatous inflammation; eosinophils are prominent; hyphae should be readily apparent; no vascular invasion
  - Fulminant invasive aspergillosis:
    - Immunocompromised host; vascular invasion and infarction

Differential Diagnosis

- ♦ Mucormycosis:
  - Nonseptate, larger, right angle branching
  - Culture needed to distinguish, especially if Asp. is treated
- ♦ Alternaria:
  - Golden brown club-shaped macroconidia with longitudinal and transverse septation; bullous swelling near septation in hyphae

Mucormycosis (Phycomycosis)

Clinical

- ♦ Immunocompromised host: uncontrolled diabetes, burn injury, and renal failure

Microscopic

- ♦ Nonseptate hyphae 10–25 microns wide; irregular right angle branching; pleomorphic, collapsing walls; necrotizing bronchopneumonia with infarction

Differential Diagnosis

- ♦ Aspergillosis;
  - Septate, right angle branching

Candidiasis

Clinical

- ♦ Immunocompromised hosts, burns, trauma, catheters, and gastrointestinal surgery

Microscopic

- ♦ Yeast forms 2–6 microns; mycelial pseudohyphae forms are common
- ♦ Acute bronchopneumonia and emboli to other organs, especially kidney

Histoplasmosis

Clinical

- ♦ Can be seen in normal host; commonly found in Mississippi and Ohio River Valley; bird and bat feces

Microscopic

- ♦ Necrotizing granulomas, similar to *M. tuberculosis* yeast forms (2–5 microns), usually degenerating forms are seen; budding is unusual but seen

Coccidioidomycosis

Clinical

- ♦ Can be seen in normal host; southwest United States, dry arid climate (San Joaquin Valley Fever); inhaled arthrospores develop into spherules
- ♦ C. immitus usual organism; complement fixation tests positive in 90% of patients

Microscopic

- ♦ Necrotizing granulomas, resembling M. tuberculosis

Special Studies

- ♦ Spherules (20–200 microns) with endospores: PAS +, GMS +

Sporotrichosis

Clinical

- Male, alcoholic; infects preexisting lung disease (emphysema); *Sporothrix schenckii* usual organism; found in straw, moss, timber, and plants

Microscopic

- Single, necrotizing lesion; significant hilar adenopathy

Blastomycosis

Clinical

- Can be seen in normal host; *Blastomyces dermatitidis*, soil-growing fungus; North America around Mississippi and Ohio rivers and Southeast (Georgia)

Microscopic

- Necrotizing granulomas with central microabscess and multinucleated giant cells; yeast forms: broad-based, budding
- Bronchial lesions are common; bronchial stenosis is common

Cryptococcosis

Clinical

- Can be seen in normal host, most symptomatic cases are in immunocompromised hosts; predilection for CNS
- C. neoformans most common organism; source: pigeons

Microscopic

- Granulomatous lesions with acute inflammation; pleomorphic yeast forms (2–10 microns); single bud

Special Studies

- Silver +; mucicarmine + capsule

Protozoan

Pneumocystis carinii Pneumonia

Clinical

- Immunocompromised host, especially AIDS; insidious onset; bilateral infiltrates

Microscopic

- Frothy, eosinophilic intraalveolar exudate with faint blue dots
- Mild chronic interstitial pneumonitis
- Unusual reactions include granulomatous inflammation, diffuse alveolar damage, alveolar proteinosis, calcifications, and tissue invasion

Special Studies

- Cyst (5–8 microns) best seen on methenamine silver stain
- Trophozoite (1–2 microns) best seen on Giemsa stain

Differential Diagnosis

- Pulmonary alveolar proteinosis:
  - Methenamine silver stain –
  - Minimal interstitial reaction
  - PAS +

Dirofilarial (Dog Heart Worm) Granulomas

Clinical

- Dirofilaria immitis, dog heart worm; adult worm resides in right ventricle/pulmonary artery of dogs; microfilariae in dog blood transmitted to human via mosquito bites
- Asymptomatic coin lesion on chest X-ray

Microscopic

- Pathologic triad: spherical infarct, eosinophilic pneumonia, and endarteritis
- Dirofilarial parasite is present within branch of pulmonary artery within center of infarct
- 100–200mm thick cuticle with longitudinal ridges

Toxoplasma gondii Pneumonia

Clinical

- Immunocompromised host, especially AIDS and neonate; cats are carriers
- Infection of humans is via cat feces or raw meat

Microscopic

- Necrotizing nodules with central coagulative necrosis
- Tachyzoites are present within necrosis
- DAD can be seen

Special Studies

- Giemsa stains tachyzoites
- Immunohistochemical studies helpful for the identification of cysts

Paragonimiasis (Lung Fluke)

Clinical

- Endemic in South America, Africa, India, and Southeast Asia; in immigrants in North America
- "Endemic hemoptysis"; pleural and blood eosinophilia; benign clinical course

Microscopic

- Adult flukes in human lung: red/brown and fleshy; 0.8–1.4 cm in length
- Chronic abscess formation; upper lobes > lower lobes

Special Studies

- Ziehl-Neelsen stains eggshells

Lung Transplantation

Histologic Grading of Pulmonary Allograft Rejection

Acute Rejection

- Perivascular and interstitial mononuclear cell infiltrates:
  - Grade A0: normal pulmonary parenchyma
  - Grade A1: infrequent perivascular mononuclear infiltrates not obvious at low magnification
  - Grade A2: frequent perivascular mononuclear infiltrates surrounding venules and arterioles readily recognizable at low magnification
  - Grade A3: readily recognizable cuffing of venules and arterioles by dense perivascular mononuclear cell infiltrates, usually associated with endothelialitis; interstitial mononuclear cell infiltrates
  - Grade A4: diffuse perivascular, interstitial, and air space infiltrates of mononuclear cells and prominent alveolar pneumocyte damage usually associated with inflammatory cell debris

Airway Inflammation-Lymophocytic Bronchitis/Bronchiolitis

- Grade B0: no airway inflammation
- Grade B1: minimal airway inflammation
- Grade B2: mild airway inflammation
- Grade B3: moderate airway inflammation
- Grade B4: severe airway inflammation

Chronic Airway Rejection

- Active/inactive bronchiolitis obliterans (constrictive bronchiolitis)

Chronic Vascular Rejection-Accelerated Graft Sclerosis

- Fibrointimal thickening of arteries and veins of uncertain clinical significance

NEOPLASTIC DISEASES OF THE LUNG

Benign Tumors

Benign Epithelial Tumors

Squamous Papillomas and Papillomatosis

Clinical

- Upper airway–solitary; adult smoker
- Lower airway–multiple; papillomatosis: children and young adults

Macroscopic

- Multiple lobulated escrescences in bronchioles; distal bronchiectasis common

Microscopic

- Fibrovascular core with cytologically bland nonkeratinizing squamous epithelium; koilocytotic changes are common; mucus-secreting, transitional, or intermediate cells are sometimes interspersed

Differential Diagnosis

- Well-differentiated squamous cell carcinoma/verrucous carcinoma:
  - Lack of maturation
  - Marked cytologic atypia
  - Invasion into adjacent tissue
  - Increased dyskeratosis and hyperkeratosis

Papillary Adenoma of Type II Cells

Clinical

- Asymptomatic, coin lesion

Microscopic

- Circumscribed lesion of branching, papillary fronds lined by cytologically bland columnar cells; no mitoses, necrosis; intranuclear cytoplasmic inclusions common

Differential Diagnosis

- Metastatic papillary carcinoma:
  - Rule out primary ovarian, thyroid, kidney, colon, and breast
- Sclerosing hemangioma:
  - More diversity of pathology, with solid areas and blood-filled spaces
- Papillary adenocarcinoma:
  - Cytologic atypia, necrosis, and mitoses
  - Irregular, lepidic growth pattern

Alveolar Adenoma

Clinical

- Solitary nodule in women

Microscopic

- Multicystic, well-circumscribed with ectatic spaces filled with eosinophilic material; flat lining cells; interstitium contains collagenous matrix with myofibroblasts

Differential Diagnosis

- Lymphangioma:
  - Endothelial-lined spaces; cytokeratin –

Mucus Gland Adenoma

Clinical

- Occurs in both children and adults; more common in women
- Large airway obstruction/irritation

Macroscopic

- Polypoid, endobronchial lesions in lobar or segmental bronchi

Microscopic

- Cystic, mucous-filled glands with cytologically bland, mucus-secreting epithelium; oncocytic metaplasia can be seen

Differential Diagnosis

- Low-grade mucoepidermoid carcinoma:
  - Intermediate cells present
- Adenocarcinomas:
  - Cytologic atypia, necrosis, mitoses, lack of large cystic spaces

Mucinous Cystadenoma

Clinical

- Nodule in adult smokers

Macroscopic

- Mucus-filled cysts

Microscopic

- Cystic spaces lined by benign, mucus-secreting epithelium; no invasion into adjacent tissue; borderline lesions show increased cytologic atypia and areas of carcinoma (mucinous cystadenoma of uncertain malignant potential)

Differential Diagnosis

- Well-differentiated adenocarcinoma and mucinous bronchioloalveolar carcinomas:
  - No fibrous cyst wall
- Mucinous cystadenocarcinoma:
  - Invasive growth into surrounding lung

Benign Mesenchymal Tumors

Hamartoma

Clinical

- Two locations: central endobronchial and parenchymal
- Only central type causes symptoms

Macroscopic

- Well-circumscribed white, bulging nodules of cartilaginous consistency
- Calcium or bone may be present

Microscopic

- Usually composed predominantly of cartilage; fat, smooth muscle and fibromyxoid tissue can be seen
- Surrounded by clefts of benign ciliated or nonciliated epithelium, probably entrapped metaplastic epithelium

Cytogenetics

- 6p21 rearrangement activates high-mobility group gene (HMGI-Y)

Differential Diagnosis

- Bronchial chondromas as seen in young women with Carney's triad: pulmonary chondromas, gastric epithelioid tumors, and extra-adrenal paragangliomas:
  - Are usually connected to airway cartilage
- Benign metastasizing leiomyoma
  - Fat, cartilage, and other fibromyxoid elements are not seen
- Intrapulmonary solitary fibrous tumor

Lipoma

Clinical

- Usually arise in central bronchi; lead to obstruction, wheezing, and bronchiectasis
- Large variant completely enveloping bronchus can be sequelae of chronic bronchiectasis

Macroscopic

- More frequent in left main bronchus than on right side
- Smooth-walled polyps projecting into lumen

Microscopic

- Mature adipose tissue; can have giant cells

Differential Diagnosis

- Hamartoma:
  - Other mesenchymal elements present

Mesenchymal Cystic Hamartoma

Clinical

- Lung cysts causing hemoptysis, pneumothoraces, and pleuritic chest pain
- Can be seen in children

Macroscopic

- Small cysts with connections to bronchioles

Microscopic

- Normal respiratory or cuboidal epithelium; underlying primitive mesenchymal cells
- Hypertrophic arteries within mesenchyme

Differential Diagnosis

- Sequestration of the lung
- Congenital cystic adenomatoid malformation
- Cystic bronchiectasis:
  - None of the above contain primitive mesenchymal cells beneath epithelium
- Metastasis:

– Primary sarcoma (many of the reported cases have been metastases from uterine neoplasms)

Pre-Invasive Lesions

Squamous Dysplasia/Carcinoma In Situ

Microscopic

- Dysplasia: cytologic atypia, nuclear enlargement in lower, middle, and upper third of mucosa (grades: mild, moderate, and severe); superficial surface maturation
- CIS: entire mucosal involvement by dysplasia; no invasion below basement membrane

Atypical Adenomatous Hyperplasia

Microscopic

- May be precursor to adenocarcinoma
- Difficult to separate from nonmucinous variant of bronchioloalveolar carcinoma
- Focal lesions, often ≤5 mm; atypical cuboidal/low columnar epithelium; mitoses rare

Diffuse Idiopathic Pulmonary Neuroendocrine Cell Hyperplasia

Microscopic

- Increased number of neuroendocrine cells
- Precursor to the development of multiple tumorlets and carcinoids; typical and atypical carcinoids can arise in this setting
- Usually secondary to airway fibrosis and/or inflammation; rarely, seen as diffuse idiopathic variant

Malignant Tumors

Tumors of Salivary Gland Type

Mucoepidermoid Carcinoma

Clinical

- Half are in patients <30 years; symptoms of large airway obstruction/irritation

Macroscopic

- Tan/pink endobronchial nodule, most common in main or lobar bronchi
- Mucoid surface with underlying cystic areas; can ulcerate on surface

Microscopic

- Mucin-secreting squamous and intermediate cells:
  - Low grade: mitoses, nuclear pleomorphism, and necrosis are absent
  - High grade: mitoses (> 4/10 HPF), nuclear pleomorphism, and necrosis are present

Differential Diagnosis

- Bronchial mucous gland adenoma:
  - No intermediate or squamous cells
- Adenosquamous cell carcinomas:
  - Peripheral lesions with adjacent in-situ changes
  - Common to have keratinization

Adenoid Cystic Carcinoma

Clinical

- Most common salivary gland type tumor of the lower respiratory tract
- Lower trachea, mainstem bronchi, or lobar bronchi
- Large airway obstruction/irritation
- Recurrence is common

Macroscopic

- Tan/grey tumors intrude bronchial wall with sessile or annular lesions; can spread submucosally along bronchial wall and diffusely involve adjacent airways

Microscopic

- Small cells with hyperchromatic nuclei in cribriform, cylindromatous, trabecular, or glandular architecture; commonly infiltrates through airway cartilage; spaces contain alcian blue + basal lamina-type material; perineural invasion common

Differential Diagnosis

- Pleomorphic adenoma:
  - No cribriform or cylindromatous areas
- Mucoepidermoid carcinoma:
  - Smooth, well-circumscribed mass
  - Squamous and intermediate cells
- Adenocarcinomas of the lung:
  - Cytologic atypia, mitoses, and necrosis

Epithelial Tumors

- See Table 17-2 and TNM Classification of Lung Cancer for pathologic staging of non-small cell carcinomas

Squamous Cell Carcinoma

Clinical

- 2/3 are central; more commonly found in men; second most common bronchogenic carcinoma; strong association with smoking
- Hypercalcemia due to parathormone-related protein secretion by tumor

Macroscopic

- Vary from small to large, obstructive lesions; commonly cavitate
- Usually found in segmental or subsegmental bronchi

Microscopic

- Characterized by the presence of cytokeratin differentiation with keratinization and intercellular bridges by light microscopy
- Graded according to degree of squamous differentiation
- Spindle cells, osteoclastic-type and tumor giant cells, and clear cell changes can be seen
- Histologic variants include papillary, clear cell, small cell, and basaloid

Differential Diagnosis

- Squamous metaplasia;
  - Minimal cytologic atypia; maturation; lack of stromal invasion
- Adenosquamous carcinoma and mucoepidermoid carcinoma:
  - Glandular component
- Small cell carcinoma:
  - Lack nucleoli, increased nuclear molding, and crush artifact
  - Less cytoplasm

Adenocarcinoma

Clinical

- Most common form of bronchogenic carcinoma; most common lung cancer in women
- Hypertrophic pulmonary osteoarthropathy
- Smoking history is more variable than in other bronchogenic carcinomas

Macroscopic

- More commonly peripheral
- Desmoplasia can be prominent (but true "scar carcinomas" also occur)

Microscopic

- Characterized by heterogeneous differentiation within the same tumor
- Tubular, glandular, papillary, and acinar growth patterns can be seen, clear cell change is common

Immunohistochemistry

- Neuron specific enolase: 50% +; Leu 7: 33% +
- Chromogranin/Synaptophysin: 10–20% +
- Cytokeratin 7 + and Cytokeratin 20 ±
- Thyroid transcription factor –1 (TTF –1) +

Electron Microscopy

- Microvilli with glycocalx and rootlets

Molecular

- K-ras mutations

Differential Diagnosis

- Organizing diffuse alveolar damage with treatment-related cytologic atypia:
  - History of treatment (chemotherapy/radiation therapy)
  - Diffuse pattern on imaging studies
  - Heterogeneity of cell types
- Metastatic adenocarcinoma from kidney, gastrointestinal tract, and breast:
  - Clinical history
  - Mucin negative in renal cell carcinoma
  - Cytokeratin 7 positive in colorectal adenocarcinomas
  - See Table 25-2

Bronchioloalveolar Carcinoma

Clinical

- >50% of patients are asymptomatic
- May present as single or multiple nodules or consolidation of lobe
- Bronchorrhea may occur late in course

Macroscopic

- Nodules or areas of consolidation, more commonly peripheral
- Mucinous subtypes usually replace entire lobe and show preservation of underlying architecture with large pools of mucus within airspaces

Microscopic

- Considered a subtype of adenocarcinoma
- Separated into nonmucinous, mucinous, and mixed variants; epithelium is well-differentiated, uniform, and grows along intact alveolar walls
- No invasion into underlying stroma
- Aerogenous spread with microsatellite lesions is common

Differential Diagnosis

- Reactive Type II pneumocyte hyperplasia and other reactive bronchiolar inflammatory lesions:
  - No cytologic atypia
  - Cilia present
  - Lesions limited to bronchioles
- Atypical adenomatous hyperplasia:
  - Cytologic atypia is less marked
  - Typically <1 cm
- Bronchioloalveolar cell adenoma/alveolar adenomatous hyperplasia:
  - ≤ 5mm

Table 2. Stage Grouping–TNM Subsets*

Stage	*TNM Subset*
0	Carcinoma in-situ
IA	T1N0M0
IB	T2N0M0
IIA	T1N1M0
IIB	T3N0M0
	T2N1M0
IIIA	T3N1M0
	T1N2M0
	T2N2M0
	T3N2M0
IIIB	T4N0M0
	T4N1M0
	T4N2M0
	T1N3M0
	T2N3M0
	T3N3M0
	T4N3M0
IV	Any T Any N M1

**Staging is not relevant for occult carcinoma, designated TXN0M0*

- Adenocarcinoma, mixed type:
  - Invasion into stroma, pleura, or vessels

Small Cell Carcinoma

Clinical

- 20–25% of all lung cancer; strong association with smoking
- Inappropriate anti-diruetic hormone, Cushing's, and Eaton-Lambert syndrome
- Central tumors with early metastases; chemotherapy responsive

Macroscopic

- 70% of cases present as perihilar mass
- Extensive lymph node metastases are common
- Typically peribronchial; endobronchial lesions are uncommon

Microscopic

- Round to fusiform nuclei; nuclear molding; faint or absent nucleoli; scant cytoplasm
- Extensive necrosis
- Three histologic categories:
  - Small cell
  - Mixed small cell/large cell
  - Combined small cell/adeno- or squamous cell carcinoma

Immunohistochemistry

- Can show chromogranin +, synaptophysin +, and Leu 7 +; however, 25% of cases – for neuroendocrine markers

Cytogenetics

- 3p deletions

Differential Diagnosis

- Non-small cell carcinoma, including large cell neuroendocrine carcinoma:
  - Larger nuclei
  - Prominent nucleoli
  - Smaller nuclear/cytoplasmic ratio
  - Lack of nuclear molding

Large Cell Undifferentiated Carcinoma

Clinical

- 10–20% of lung carcinomas; strongly associated with smoking

Macroscopic

- Central or peripheral; typically large, with pleural invasion
- Rarely occult

Microscopic

- Sheets and nests growth pattern with extensive necrosis; large nuclei with prominent nucleoli; lack definitive evidence of squamous or glandular differentiation by light microscope
- Can have giant cell, clear cell, or spindle cell changes
- Variants include large cell neuroendocrine carcinoma (see neuroendocrine tumors), basaloid, lymphoepithelioma-like, and clear cell

Electron Microscopy

- 80% show glandular differentiation; 10% show squamous differentiation

Differential Diagnosis

- Melanoma:
  - – for cytokeratin by immunohistochemical studies
- Large cell lymphoma (including anaplastic type):
  - Nuclei tend to be smaller, with more irregular nuclear membranes

  - Negative for cytokeratin and + for CD45 (leucocyte common antigen) by immunohistochemical studies

Adenosquamous Carcinoma

Clinical

- 0.4–4.0% of lung carcinomas
- Strong association with smoking

Microscopic

- Contains well-defined squamous cell carcinoma and adenocarcinoma
- Each component must comprise at least 10% of the tumor

Differential Diagnosis

- Adenocarcinoma with metaplastic squamous changes:
  - Squamous metaplasia has benign features
- Squamous cell carcinoma with entrapped bronchial epithelium
  - Entrapped glandular epithelium is benign
- High-grade mucoepidermoid carcinoma:
  - Contains areas of low-grade mucoepidermoid carcinoma
  - Glandular component is usually goblet cell

Carcinomas with Pleomorphic, Sarcomatoid, and Sarcomatous Elements

Clinical

- Smokers

Macroscopic

- Usually large (>10 cm) and peripheral

Microscopic

- Poorly differentiated carcinomas associated with sarcoma or sarcoma-like elements
- Term for tumors with a continuum of epithelial and mesenchymal differentiation
- Includes:
  - Pleomorphic carcinoma (adeno-squamous cell carcinoma with spindle cells and/or giant cells)
  - Sarcomatoid carcinoma (monophasic and biphasic)
  - Spindle cell carcinoma (only spindle cells present—rare)
  - Giant cell carcinoma (large cell carcinoma with only giant cells—very rare)
  - Carcinosarcoma (carcinoma with sarcoma containing heterologous elements)
  - Pulmonary blastoma

Immunohistochemistry

- Cytokeratin of spindle cell elements can be –

Differential Diagnosis

- Metastatic sarcoma:
  - No epithelial differentiation by light or electron microscopy

Neuroendocrine Tumors

Carcinoid Tumorlet

Clinical

- Incidental microscopic findings
- Most common in adults; rarely in children

Microscopic

- Neuroendocrine cells embedded in fibrotic stroma
- $\leq$ 0.5 cm
- Usually adjacent to bronchiole

Differential Diagnosis

- Carcinoid tumor:
  - >0.5 cm
- Neuroendocrine cell hyperplasia:
  - Increased neuroendocrine cells within bronchiolar epithelium
- Bronchiolar metaplasia:
  - No evidence of neuroendocrine differentiation

Typical and Atypical Carcinoid

Clinical

- May present with postobstructive changes
- Most common in adults; can occur in children
- Paraneoplastic syndromes can occur
- Can occur in patients with Multiple Endocrine Neoplasia (MEN-I) (see Chapter 2)

Macroscopic

- Central and peripheral; central lesions have large, endobronchial component with postobstructive changes distally
- Peripheral lesions are usually subpleural
- Tan/yellow mass; danger of bleeding on biopsy

Microscopic

- Neuroendocrine cells with organoid, trabecular, insular, palisading ribbon, rosette-like architecture
- Round to oval nuclei with finely granular chromatin and inconspicuous nucleoli
- Stromal changes include bone, cartilage, dense fibrosis, and amyloid
- Atypical carcinoids have 2–10 mitoses/10 HPF, more prominent nucleoli, and focal necrosis
- Spindle cell variant is more common in peripheral lesions

Differential Diagnosis

- Spindle cell lesions (metastatic sarcoma and spindle cell carcinoma):
  - No neuroendocrine differentiation
- Metastatic carcinoma of the breast and prostate:
  - History of primary
  - Multiple lesions

Large Cell Neuroendocrine Carcinoma

Clinical

- Strong association with smoking; average age = 64 years

Macroscopic

- Can extensively replace lung; central or peripheral; can be multinodular

Microscopic

- Organoid, palisading, trabecular patterns
- Large, polygonal nuclei and low nuclear/cytoplasmic ratio; frequent nucleoli
- High mitotic rate (>10 mitoses/10 HPF); necrosis can be prominent

Immunohistochemistry

- Chromogranin: 80% +; Leu 7: 40% +; Synaptophysin: 40% +; Bombesin: 40% +; CEA 100% +; Cytokeratin: 100% +
- By definition, one of the above neuroendocrine markers must be positive

Differential Diagnosis

- Small cell carcinoma:
  - Smaller nuclei
  - No nucleoli
  - Increased nuclear/cytoplasmic ratio
- Atypical carcinoid:
  - 2–10 mitoses/10 HPF
  - Single cell necrosis or focal central necrosis
- Large cell undifferentiated carcinoma:
  - No evidence of neuroendocrine differentiation by light microscopy or immunohistochemical or ultrastructural analysis

Unusual Tumors with Neuroendocrine Differentiation

- Paraganglioma
- Primitive neuroectodermal tumor
- Neuroendocrine carcinoma with rhabdoid phenotype
- Amphicrine neoplasms
- Neuroendrocrine carcinoma with anemone features
- Pulmonary blastoma with neuroendocrine differentiation

Mesenchymal Tumors

Fibrous and Fibro-Histiocytic Tumors

Inflammatory Pseudotumor

Clinical

- 60% occur under the age of 40; represents the majority of benign tumors in children
- Usually an asymptomatic mass

Macroscopic

- Solitary, round, well-circumscribed but unencapsulated mass; can penetrate pleura or extend into adjacent mediastinal structures
- Calcification and foci of necrosis can be seen; xanthoma cells can cause yellow color

Microscopic

- Circumscribed, with pushing border of organizing pneumonia
- Mixture of plasma cells, lymphocytes, and macrophages with fibroblasts and connective tissue
- Fibrohistiocytic subtype:
  - Myofibroblasts and fibroblasts predominate and can show pinwheel or storiform architecture
  - Touton giant cells and xanthoma cells can be seen
- Plasma cell granuloma subtype:
  - Abundant plasma cells and lymphocytes
  - Fibroblasts and collagen
  - Mild nuclear atypia can be seen
  - Lymphoid follicles can occur

Differential Diagnosis

- Malignant fibrous histiocytoma:
  - Increased cytologic atypia, cellularity, and necrosis
  - Mitotic rate >3/50 HPF
- Pleomorphic (spindle cell) carcinoma:
  - Foci of epithelial differentiation
  - Reactivity for cytokeratin
- Pulmonary hyalinizing granuloma:
  - Usually multiple
  - Distinctive, hyalinizing lamellar collagen
- Inflammatory fibrosarcoma:
  - Increased spindle cell atypia
  - Increased cellularity
- Sclerosing hemangioma:
  - Interstitial collections of round, polygonal, or uniform cells
  - + epithelial membrane antigen

Malignant Fibrous Histiocytoma

Clinical

- Older presentation: 60–70 year old; primary is rare, always consider metastatic lesion

- Preoperative diagnosis is difficult due to – cytologic specimens

Macroscopic

- Usually solitary mass (2–10cm); peripheral location; rarely intrabronchial

Microscopic

- Spindle cells, pleomorphic giant cells, and histiocyte-like cells are present
- Storiform, fascicular, or pleomorphic architecture
- Inflammatory cells can be a significant component

Differential Diagnosis

- Pleomorphic carcinoma with spindle cells:
  - Evidence of epithelial (squamous or glandular) differentiation
  - Ultrastructural evidence of desmosomes, junctional complexes, microvilli within glands, or cytoplasmic tonofibrils
  - + for carcinoembryonic antigen
- Inflammatory pseudotumor-fibrohistiocytic type:
  - Lack cytologic atypia
  - <3 mitoses/50 HPF
  - No significant necrosis

OTHER FIBROUS OR FIBRO-HISTIOCYTIC TUMORS

Fibrosarcoma

- Rare in the lung; consider metastatic lesion

Cystic Fibrohistiocytic Tumor

- Two case reports; may actually represent low-grow metastatic sarcoma
- Multiple cystic masses

Smooth Muscle Tumors—Leiomyosarcoma

Clinical

- Rare; consider possibility of metastatic lesion, especially from uterus
- Symptomatic presentation: cough, hemoptysis

Macroscopic

- Large, circumscribed masses; most are parenchymal
- Propensity for hilar region

Differential Diagnosis

- Leiomyoma:
  - < 5 mitoses/50 HPF
  - No cytologic atypic
  - No significant necrosis
- Benign metastasizing leiomyoma:
  - Multiple nodules
  - Well-differentiated smooth muscle without mitoses/necrosis/cytologic atypia
- Lymphangioleiomyomatosis:
  - Seen exclusively in women
  - Multifocal, benign smooth muscle and cyst-like spaces

Skeletal Muscle Tumors—Rhabdomyosarcomas

Clinical

- Seen in both adults and children

Macroscopic

- Large, solid masses; may involve more than one lobe

Microscopic

- Cross striations are present; cells may be small, pleomorphic, or straplike
- Immunoreactive for desmin

Differential Diagnosis

- Metastatic rhabdomyosarcoma
- Carcinosarcoma:
  - Malignant epithelial component
- Pleuropulmonary blastoma:
  - 90% are found in children <10 years of age
  - May have focal malignant primitive epithelial component

Vascular Tumors and Related Conditions

Vascular Malformations

- Usually diagnosed radiographically; similar to those at other sites
- Multiple: Osler-Weber-Rendu

Epithelioid Hemangioendothelioma (Intravascular Bronchioloalveolar Tumors)

Clinical

- Multiple nodules in young women (M:F = 1:4)
- Has been seen in children; > 1/2 of patients are <40 years
- Concomitant multifocal disease can be see in bone, soft tissue, and liver

Macroscopic

- Discrete, firm white nodules (1–2mm); may resemble cartilage

Microscopic

- Circumscribed, pale eosinophilic nodules; stroma may resemble cartilage or amyloid
- Cells are cytologically bland with round nuclei and nucleoli; intracytoplasmic vacuoles are present; endothelial differentiation is present

Immunohistochemistry

- Factor VIII +, CD34 +, and CD31 +

Electron Microscopy

- Weibel-Palade bodies

Differential Diagnosis

- Adenocarcinoma:
  - Mucin + cytoplasmic vacuoles
  - Cytokeratin +
- Metastatic chondrosarcoma:
  - No endothelial differentiation
  - S-100 protein +
- Amyloid nodules:
  - Acellular
  - Congo red positivity
- Hamartoma:
  - Usually solitary
  - Entrapped epithelium is cytokeratin +
- Angiosarcoma:
  - Marked cytologic atypia
  - Predominantly intra-vascular

Kaposi's Sarcoma

Clinical

- Rare initial site of involvement; 25% of disseminated disease affects the lung
- Hemoptysis

Macroscopic

- Hemorrhagic bronchial plaques or nodules present in a lymphatic distribution

Microscopic

- Spindle cells with intercellular spaces containing red blood cells
- Hemosiderin and plasma cells

Immunohistochemistry

- Spindle cells are CD 34 + and CD 31 +

Differential Diagnosis

- Angiosarcoma:
  - Increased cytologic atypia
  - Patients lack risk factors for AIDS
- Benign granulation tissue:
  - Lack red blood cells within spaces
- Bacillary angiomatosis:
  - Bacteria identified by special stains

Angiosarcoma

Clinical

- Hemoptysis

Macroscopic

- Multiple, hemorrhagic nodules

Microscopic

- Atypical endothelial cells forming vascular spaces
- Intra-arterial or peri-arterial involvement is common
- Epithelioid variant

Differential Diagnosis

- Kaposi's sarcoma:
  - Lack cytologic atypia
- Metastatic sarcoma:
  - Primary lesion (e.g., heart or pulmonary artery)
- Primary/metastatic carcinoma:
  - Cytokeratin differentiation

Other Vascular Tumors

- Pulmonary artery and vein sarcomas:
  - Polypoid mass involving pulmonary vessels
  - 80% involve pulmonary trunk
- Hemangiopericytomas:
  - 10% of all primary hemangiopericytomas occur in lung
  - Poor prognosis associated with >5 cm and increased mitotic rate

Neurogenic Tumors

- All neurogenic tumors are rare as primary lung tumors
- Though the following can be found as primary lesions in the lung, the possibility of metastatic disease should be excluded first:
  - Malignant nerve sheath tumor
  - Malignant psammomatous melanotic schwannoma
  - Neuroblastoma and ganglioneuroblastoma
  - Meningioma
  - Neurilemmoma
  - Neuroma and ganglioneuroma

Cartilaginous Tumors

- All are rare lesions in the lung; consider metastatic disease before primary lung lesions:
  - Chondroma
  - Bronchial variant seen in Carney's triad
- Chondroblastoma
- Chondrosarcoma

Mixed Epithelial and Mesenchymal Tumors

Pulmonary Blastoma—Three Subtypes

1. Well-Differentiated Fetal Adenocarcinoma

Clinical

- Men and women affected equally; found mostly in adults
- Average age = 40 years; not in <10 years
- Strong smoking history

Macroscopic

- 1–10 cm; usually solitary; 85% are subpleural

Microscopic

- Branching tubules mimicking fetal lung and appear endometrioid
- Morules are usually present at base of glands; immature stroma present in 50% of tumors

Differential Diagnosis

- Adenocarcinoma:
  - No morules
  - Lack endometrioid appearance

2. Biphasic Pulmonary Blastoma

Clinical

- Rare; occurs mostly in smokers; symptomatic presentation; average age = 40 years

Macroscopic

- Large, solitary mass; favors upper lobes; usually peripheral
- Cystic breakdown and hemorrhage are common

Microscopic

- Malignant epithelium:
  - Endometrioid, cords, trabeculae, or solid sheets
- Malignant stroma:
  - Embryonic
  - Morules not common

Differential Diagnosis

- Carcinosarcoma:
  - Mature sarcomatous/carcinomatous elements
- Sarcomas with entrapped bronchial epithelium

3. Cystic and Pleuropulmonary Blastoma of Childhood

Clinical

- In children 1–9 years of age; usually symptomatic
- Family history of similar intrathoracic tumors or other solid tumors of childhood in 25–30% of cases

Macroscopic

- Large, multiloculated cystic mass; can be mediastinal or pleural

Microscopic

- Benign ciliated columnar epithelium with underlying primitive rhabdomyoblasts
- May contain anaplastic sarcomatous elements such as embryonal rhabdomyosarcoma, fibrosarcoma, chondrosarcoma, and anaplastic undifferentiated sarcoma

Differential Diagnosis

- Biphasic blastoma:
  - Adult
  - Smoking history
  - Malignant epithelium
  - Chromogranin +
- Congenital cystic adenomatoid malformation:
  - No malignant mesenchyme

Carcinosarcoma

Clinical

- 90% of patients are 50–90 years of age
- Strong association with smoking; may be peripheral or central

Macroscopic

- Solitary and well-circumscribed

Microscopic

- Biphasic—sarcomatous and carcinomatous component
- Epithelium is commonly squamous cell carcinoma
- Osteosarcoma, chondrosarcoma, and rhabdomyosarcoma are commonly part of sarcomatous element
- Carcinoma may be scant

Differential Diagnosis

- Spindle cell carcinoma:
  - Usually cytokeratin + in spindle cells
  - Lack heterologous sarcomatous element

Lymphoproliferative Lesions of the Lung

Benign/Hyperplastic Lesions

Pseudolymphoma (Nodular Lymphoid Hyperplasia)

Clinical

- Adults: 30–80 years; most are asymptomatic
- Can be associated with autoimmune diseases such as Sjögren's syndrome and lupus erythematosus
- May have polyclonal hypergammaglobulinemia

Macroscopic

- Most are solitary masses; can present as multinodular lesions or infiltrate
- Rarely >5 cm

Microscopic

- Heterogeneous inflammatory infiltrate; germinal centers are commonly seen
- Necrosis is rare; organizing pneumonia is common

Differential Diagnosis

- Low-grade B cell lymphomas of mucosa-associated lymphoid tissue (MALT):
  - Should be monoclonal by immunohistochemistry
  - Heavy chain rearrangements on molecular studies
  - Lymphoepithelial lesions
  - Granulomatous inflammation, and amyloid can be seen
  - Airway and vascular invasion

Lymphocytic Interstitial Pneumonitis (Diffuse Lymphoid Hyperplasia)

Clinical

- Symptoms of interstitial disease: cough and dyspnea
- Can be seen in children and adults
- Associated with many conditions, including congenital or acquired immunodeficiency syndromes, autoimmune diseases (e.g. Sjögren's), and drug-induced lung disease

Macroscopic

- Firm, consolidated lung

Microscopic

- Dense, diffuse lymphoplasmocytic infiltrates in alveolar walls
- Germinal centers with diffuse lymphoid hyperplasia; granulomas and giant cells can be seen

Differential Diagnosis

- Diffuse low-grade lymphoma:
  - Monomorphous population
  - Lymphatic distribution
  - Airway, vascular, and pleural invasion
- Extrinsic allergic alveolitis:
  - Areas of organization
  - Prominent bronchiolitis

Giant Lymph Node Hyperplasia (Castleman's Disease)

- Rare as primary pulmonary lesions
- Germinal center with characteristic hyaline vascular change

Lymphomas (also see Chapter 7)

Low-Grade Lymphoma of the Mucosa Associated Lymphoid Tissue (MALT)

Clinical

- Adults: 60 years; 1/2 are symptomatic
- 20% have monoclonal protein in serum
- Chest X-ray shows localized infiltrate or solitary lesion in 50%

Macroscopic

- Fleshy, nonnecrotizing mass; infiltrative growth pattern

Microscopic

- Dense, lymphoid infiltrate in lymphatic distribution; population may be monotonous
- Germinal centers are commonly seen; lymphoepithelial lesions can be seen
- Large mass lesions may be present
- Airway, vascular, and pleural invasion is common

Immunohistochemistry

- Light chain restriction can usually, but not always, be seen by immunohistochemistry

Molecular Studies

- Clonal B-cell rearrangements are usually seen by molecular studies

Differential Diagnosis

- Pseudolymphoma:
  - Heterogeneous and polyclonal population
  - Solitary nodule
- Lymphocytic interstitial pneumonitis:
  - Heterogeneous and polyclonal population
  - No bronchial, vascular, or pleural invasion
- Secondary pulmonary involvement by chronic lymphocytic leukemia:
  - Peripheral white blood cell count consistent with CLL

Angiocentric Immunoproliferative Lesions/Angiocentric Lymphomas/Lymphomatoid Granulomatosis/Polymorphic Reticulosis

Clinical

- Average age + 40–50 years; most present with multiple lung nodules
- Skin and CNS involvement is frequent
- Poor prognosis
- EBV infection implicated in high-grade progression

Macroscopic

- Nodular consolidation; nodules may have central necrosis

Microscopic

- Nodules or diffuse infiltrates of lymphoid cells
- Central necrosis and cavitation can be seen in larger

nodules; prominent vascular invasion (angiocentric pattern)
- Cell population may be heterogeneous; graded according to degree of cytologic atypia:
  - Grade 1: benign lymphocytic vasculitis
  - Grade 2: lymphomatoid granulomatosis, necrosis
  - Grade 3: angiocentric lymphoma

Immunohistochemistry

- Most cells are positive for T-cell markers (CD4,CD8); some are T-cell rich B-cell lymphomas

Molecular Studies

- Either immunoglobulin rearrangements (B-cell) or T-cell receptor rearrangements (T-cell)
- EBV DNA often detected by polymerase chain reaction

Differential Diagnosis

- Necrotizing granulomatous infections:
  - Well-formed granulomas
- Wegener's granulomatosis:
  - Giant cells and neutrophilic microabscesses
- Low-grade lymphomas of MALT:
  - Little necrosis
  - Predominantly lymphatic distribution, not angiocentric
- Hodgkin's disease:
  - Classic Reed-Sternberg cells
  - Classic background of lymphocytes and eosinophils
- Large Cell Lymphoma:
  - Distinction from high-grade angiocentric immunoproliferative lesion (AIL)/lymphomatoid granulomatosis (LYG) may be arbitrary

Post-Transplant Lymphoproliferative Disorder

Clinical

- Found in patients who have undergone organ transplantation
- Associated with EBV infection

Macroscopic

- Single or multiple nodules or infiltrates

Microscopic

- Varied appearance: small cell to large cell; can be polymorphous
- Necrosis and vascular invasion can be seen

Differential Diagnosis

- AIL/LYG:
  - Not restricted to immunosuppressed patients

Other Lymphoproliferative Lesions

Intravascular Lymphomatosis (Angiotropic Lymphoma)

- Aggressive, high-grade lymphoma with tumor cells proliferating within small vessels
- Skin and CNS involvement are most common, but pulmonary involvement is seen

Primary Pulmonary Hodgkin's Disease

- Usually involves lung by direct extension from mediastinum
- Primary lung involvement is rare
- Multiple nodules are common
- Histologic features of Hodgkin's Disease elsewhere

Plasmacytoma

- Extremely rare as primary lung lesion
- Plasma cell granuloma, pseudolymphoma, and pulmonary involvement by multiple myeloma should be ruled out

Mast Cell Tumor

- Very rare as primary lung lesion; should be distinguished from mast cell rich inflammatory pseudotumors

Tumors of Uncertain Histogenesis

Sclerosing Hemangioma

Clinical

- Female predominance (80% found in women); asymptomatic

Macroscopic

- Grey/red circumscribed mass; 1/2 are in lower lobes

Microscopic

- Solid, papillary sclerotic and hemorrhagic type; round, uniform epithelioid cells
- Mast cells may be numerous

Immunohistochemistry

- Epithelial cells in solid areas are EMA +; cytokeratin often –
- CEA and surfactant apoprotein often +

Differential Diagnosis

- Inflammatory pseudotumor:
  - Lack distinct epithelioid cells
  - Bronchioloalveolar carcinoma
  - No distinct cell population within stalk
  - Cytologic atypia

Benign Clear Cell (Sugar) Tumor

Clinical

- Incidental mass on chest X-ray; asymptomatic

Macroscopic

- Small, red/tan masses; shell out from surrounding lung

Microscopic

- Circumscribed mass with round cells with abundant eosinophilic cytoplasm
- Extracellular amorphous eosinophilic material
- May contain fine granular pigment; abundant PAS + material-glycogen
- Thin-walled blood vessels without a muscular coat

Immunohistochemistry

- HMB-45 +
- Cytokeratin –

Differential Diagnosis

- Primary lung cancer with clear cell change:
  - HMB-45 –
  - Glycogen not prominent
  - Cytologic atypia
- Renal cell carcinoma:
  - CEA –
  - Multiple, thick-walled vessels

Minute Pulmonary Meningothelial-Like Lesion (Minute Pulmonary Chemodectoma)

Clinical

- Incidental microscopic findings; female predominance

Microscopic

- Spindle or oval-shaped cell; perivenule location
- Zellballen pattern

Histochemistry

- Do not stain with argyrophil or argentaffin stains

Differential Diagnosis

- Carcinoid tumorlets:
  - Associated with bronchioles
  - Stain for neuroendocrine markers
- Angiomatoid lesions of pulmonary hypertension:
  - Associated with arteries/arterioles
  - CD34 (+) and CD31 (+)

Granular Cell Tumor (Granular Cell Myoblastoma)

Clinical

- Schwann cell lineage
- Usually solitary mass of trachea or bronchus; can be multicentric
- Also found in skin, breast, esophagus, and rectum; respiratory tract may be metastatic lesion
- Primary lung lesions may metastasize

Macroscopic

- Sessile or polypoid lesions with smooth surfaces; grow in walls of airways

Microscopic

- Large, granular foamy cells; some areas may have fusiform cells
- No mitoses

Immunohistochemistry

- S-100 +

Electron Microscopy

- Osmophilic inclusions

Differential Diagnosis

- Oncocytic carcinoid
  - + neuroendocrine immunohistochemistry

Masses and Tumor-Like Lesions

Pulmonary Amyloidosis

Clinical

- Patients have monoclonal proteins in serum or urine
- Associated diseases include multiple myeloma, lymphoid interstitial pneumonitis, low-grade lymphomas, and Sjögren's syndrome

Macroscopic

- Five types: nodular, diffuse, alveolar-septal, senile, tracheobronchial
- Waxy, hard irregular nodules

Microscopic

- Amorphous, eosinophilic material in vessels, airway, or as nodules
- Congo red shows apple green birefringence

Differential Diagnosis

- Kappa light chain disease:
  - Congo red stain not birefringent
- Pulmonary hyalinizing granuloma:
  - Congo red stain birefringent +

Pulmonary Hyalinizing Granuloma

Clinical

- Asymptomatic; adults
- 60% have serologic evidence of autoimmunity

Macroscopic

- Bilateral nodules; white/gray-"cotton balls"

Microscopic

- ♦ Lamellar collagen in storiform or whorled array—"donuts"; mild lymphoplasmacytic infiltrate

Differential Diagnosis

- ♦ Sclerosed plasma cell granuloma:
  - – Usually solitary
  - – More intense inflammatory infiltrate
- ♦ Nodular amyloidosis:
  - – Congo red stains for apple green birefringence
- ♦ Hyalinized infectious granulomas:
  - – Collagen arranged in parallel around center

Inflammatory Myofibroblastic Tumor

Clinical

- ♦ Usually solitary
- ♦ Most common in children

Microscopic

- ♦ Organizing myofibroblastic proliferation
- ♦ Inflammatory cell infiltrates are variable
- ♦ May have xanthogranulomatous appearance

Differential Diagnosis

- ♦ Malignant fibrous histocytoma:
  - – Cytologic atypia and numerous mitotic figures
- ♦ Sarcomatoid carcinoma:
  - – Cytologic atypia and numerous mitotic figures
  - – Cytokeratin +

Tracheobronchopathia Osteoplastica

Clinical

- ♦ Middle-aged or elderly men with hoarseness, stridor, and hemoptysis; possible relationship to tracheal amyloidosis

Macroscopic

- ♦ Hard, yellow-white papilla-like formations on cartilaginous portion of trachea or bronchi

Microscopic

- ♦ Nodules of bone and cartilage in submucosa

Table 17-3. Diagnosis of Mesothelioma versus Adenocarcinoma*

	Mesothelioma	*Adenocarcinoma*
Histochemical Studies		
Periodic and Schiff with Diastase digestion	–	+:40–50%
Mucicarmine	–	+:50%
Alcian Blue or Colloidal Iron	+	+
Alcian Blue or Colloidal Iron with Hyaluronidase digestion	–	+
Immunohistochemical Studies		
Carcinoembryonic antigen	–	+
Leu M1 (CD-15)	–	+
CAM 5.2	+	+
AE1/3	+	+
Ber EP4	–	+
B72.3	–	+
Calretinin	+	–
Thyroid Transcription Factor (TTF –1)	–	+
Ultrastructural Study	Lung, branching villi, length/diameter ≤10:1	Small microvilli
	Perinuclear intermediate filaments	Well-developed rootlets

** Although there are exceptions to each study, + and – signs signify the usual results of the study*

Benign Metastasizing Leiomyoma

Clinical

- Multiple nodules; invariably in women

Macroscopic

- Grey/white lobulated mass; shells out from lung parenchyma

Microscopic

- Well-differentiated smooth muscle; may have Type 2 epithelial inclusions
- ≤ 5 mitoses/50HPF

Differential Diagnosis

- Hamartoma:
  - Bronchial epithelium
- Metastatic leiomyosarcoma:
  - >5 mitoses/50 HPF
  - Primary sarcoma
  - Usually multiple lesions

Tumors of the Pleura (also see Chapter 20)

Malignant Mesothelioma

Clinical

- Asbestos is single most important cause of malignant mesothelioma; M > F
- Crocidolite and amosite asbestos are more carcinogenic than asbestos chrysotile

Macroscopic

- Tumor obliterates pleural space and encases lung

Microscopic

- Four main pathologic types:
  - Epithelial:
    - Most common
    - Subtypes: tubulopapillary and epithelioid are most common
  - Sarcomatoid
  - Mixed epithelial and sarcomatoid
  - Desmoplastic

Histochemistry and Immunohistochemistry

- See Table 17-3

Molecular

- Wilms' Tumor 1 (WT1) overexpression

Differential Diagnosis

- Epithelial type: Metastatic adenocarcinoma
- Sarcomatoid type: Sarcoma:
  - Sarcomas are cytokeratin –
- Desmoplastic: hyalinized pleural plaque:
  - Increased cellularity and cytologic atypia in desmoplastic mesothelioma

Localized Fibrous Tumor of the Pleura

Clinical

- Most are incidental masses
- Hypoglycemia due to insulin-like growth factor

Macroscopic

- Usually pedunculated; can be intrapulmonary
- Whorled and fibrous-appearing

Microscopic

- Spindle cells with short fascicles or haphazard pattern
- Pericytoma-like vasculature
- Varying amount of collagen; cytologic atypia and necrosis are absent
- Malignant features: >4 mitoses/10HPF; >10 cm; necrosis

Immunohistochemistry

- CD34+

TNM CLASSIFICATION OF LUNG CANCER (1997 REVISION)

- **T: Primary tumor:**
  - TX: Primary tumor cannot be assessed, or tumor proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy
  - TO: No evidence of primary tumor
  - Tis: Carcinoma in-situ
  - T1: Tumor ≤3 cm in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the labor bronchus* (i.e., not in the main bronchus)
  - T2: Tumor with any of the following features of size or extent:
    - >3 cm in greatest dimension
    - Involves main bronchus, 2 cm or more distal to the carina

- Invades the visceral pleura
- Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung

– T3: Tumor of any size that directly invades any of the following: chest wall (including superior suleus tumors), diaphragm, mediastinal pleura, parietal pericardium or tumor in the main bronchus <2 cm distal to the carina, but without involvement of the carina: or associated atelectasis or obstructive pneumonitis of the entire lung
– T4: Tumor of any size that invades any of the following: mediastinum, heart, great vessels, trachea, esophagus, vertebral body, carina: or tumor with a malignant pleural or pericardial effusion, or with satellite tumor nodule(s) within the ipsilateral primary tumor lobe of the lung

♦ **N: Regional lymph node**
– NX: Regional lymph nodes cannot be assessed
– NO: No regional lymph node metastasis
– N1: Metastasis to ipsilateral peribronchial and/or ipsilateral hilar lymph nodes, and intrapulmonary nodes involved by direct extension of primary tumor
– N2: Metastasis to ipsilateral mediastinal and/or subcarinal lymph node(s)
– N3: Metastasis to contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)

♦ **M: Distant metastasis**
– MX: Presence of distant metastasis cannot be assessed
– MO: No distant metastasis
– M1: Distant metastasis present

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Chapter 18

Breast

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NON-NEOPLASTIC DISEASES OF THE BREAST

Fibrocystic Change

Clinical

- Occurs in women 20–50 years of age
- May show clinical stages: swelling/tenderness, multiple nodules, larger cysts
- Involutes after menopause unless patient is on hormone replacement therapy
- Alteration of estrogen/progesterone ratio may be cause
- Viewed as aberration of normal involution and development
- No significant increase of cancer risk

Macroscopic

- Variably dense fibrous tissue with cysts 1 mm to 2 cm (blue-domed cysts) in size

Microscopic

- Fibrosis, cyst formation, frequently with apocrine metaplasia, atrophy of acini, variable chronic inflammatory infiltrate, and microcalcifications
- May have some epithelial hyperplasia on the spectrum of ductal intraepithelial neoplasia (DIN 1a—see discussion later)

Differential Diagnosis

- Lymphocytic mastitis
  - Dense lymphocytic infiltrate around lobules and vessels and atypical stromal cells

Microcalcifications

- May be associated with benign or malignant tissue
- Different patterns seen radiologically can be classified as most likely benign/indeterminate/malignant, but no pattern pathognomonic
- Within malignant breast disease:
  - Microcalcifications present in 94% of comedocarcinoma and 53% of cribriform (low-grade) type
  - Accordingly, mammographic estimation of the extent of DIN is better for higher grade lesions
  - Linear pattern is associated with high-grade DIN; granular pattern with lower grades
- Calcium phosphate:
  - Most common form (90%)
  - Easily visible on H&E
  - Present in benign and malignant lesions
- Calcium oxalate:
  - May be difficult to see on H&E
  - Requires polarized light
  - Usually associated with benign lesions
- Liesegang rings:
  - Laminated inclusions containing calcium, iron, silicone, and sulfur

Mucocele-Like Tumor

Clinical

- Uncommon lesion with no distinctive clinical pattern; microscopic diagnosis

Microscopic

- Single or multiloculated cyst with extravasated mucin
- Epithelium may be in detached strips; occasionally papillary fragments
- Epithelium is cytologically benign and has myoepithelial cells with it
- Cysts have fibrous wall with mild chronic inflammation

Differential Diagnosis

- Mucinous carcinoma:
  - Larger, cytologic atypia; more frequently papillary; cell clusters in lakes of mucin
- Intraductal papillary carcinoma with mucin production
- Infiltrating ductal carcinoma with mucin production

Juvenile Hypertrophy

Clinical

- Excessive and persistent enlargement of one or both breasts in young girls
- Age 11–14 years
- Usually coincides with menarche, but may precede it

Macroscopic

- Appears identical to surrounding breast tissue

Microscopic

- Proliferation of epithelium and stroma
- Proliferation of ductules similar to gynecomastia (see later)
- Proliferation of lobules
- Densely collagenous stroma is common
- Stroma may show pseudoangiomatous hyperplasia

Differential Diagnosis

- Fibroadenoma:
  - Better circumscribed grossly (shells out) and has an intracanalicular or pericanalicular pattern microscopically
- Normal breast tissue:
  - Clinical history may be necessary to distinguish juvenile hypertrophy from normal breast tissue

Gynecomastia

- Gynecomastia is unique to the male breast; other breast lesions/neoplasms may be found in males less commonly than females
- Lesions generally felt to be relatively more common in males include myofibroblastoma (see mesenchymal lesions)

Clinical

- Unilateral or bilateral (equal or unequal) breast enlargement
- Most frequent in adolescents and elderly males
- Etiology is either endogenous hormonal imbalance (puberty, senescence, hypogonadism, liver failure) or exogenous (drugs, chemotherapy)

Prognostic Significance

- Usually physiologic if in teens/elderly
- Otherwise requires evaluation of medical status/drug history
- Not a pre-malignant condition

Macroscopic

- Rubbery gray/white tissue, variable, well-defined

Microscopic

- Florid type:
  - Increased ducts with florid epithelial proliferation, cellular periductal stroma, and adipose tissue
- Fibrous type:
  - Dilated ducts, mild/moderate epithelial proliferation, hypocellular fibrous stroma, and no adipose tissue
- Hyperplasia is "gynecomastoid": angulated epithelial tufts with smallest cells at apex
- Myoepithelial layer preserved
- Apocrine and squamous metaplasia may occur
- Lobules are identified in 6% of cases
- Atypical intraductal hyperplasia is occasionally found

Differential Diagnosis

- Not a difficult diagnosis when you suspect it is a male patient

Metaplastic Changes

- Replacement of one cell type (mostly epithelium) with another mature cell type

Apocrine Metaplasia

- Cells with granular eosinophilic cytoplasm, round nuclei, and usually prominent nucleoli
- Sometimes shows decapitation secretion or coarse hyaline globules
- Frequently occurs in fibrocystic change
- Papillary morphology common in cysts; papillae with fibrovascular cores

Differential Diagnosis

- Apocrine hyperplasia:
  - Diagnosed when there is more than the normal one or two cell thickness
- Atypical apocrine metaplasia or hyperplasia:
  - Nuclei show a three-fold variation in size
- Apocrine intraductal carcinoma:
  - Atypia with luminal necrosis

Clear Cell Metaplasia

- Cytoplasm clear or vacuolated, rather than granular and eosinophilic
- May show PAS + globules in cytoplasm
- No association with clear cell carcinoma

Squamous Metaplasia

- Associated with:
  - Infarcted papilloma: may follow fine needle aspiration
  - Phyllodes tumor
  - Syringomatous adenoma
  - Ducts associated with periareolar abscess
  - May focally line a biopsy cavity

Mucinous Metaplasia

- Relatively uncommon
- Typically affects normal isolated lobule
- May occur focally in papillomas
- No known pre-neoplastic potential

Lactational Change (Lactational Metaplasia)

Clinical

- Usually reproductive-age females with recent history of pregnancy
- Rarely in postmenopausal females, possibly drug-related (digitalis, neuroleptics); males on stilbestrol
- May present as a mass during pregnancy or at postpartum examination

Macroscopic

- Sharply circumscribed, if involving a pre-existing tubular adenoma (= lactating adenoma), usually <5 cm
- Soft texture

Microscopic

- Lobules expanded
- Secretory pattern:

  - Eosinophilic material in lumen; cells with vacuolated cytoplasm
- Regressive pattern:
  - Less secretion; dilated acini with hobnail hyperchromatic nuclei

Differential Diagnosis

- May be mistaken for malignancy on FNA: look for history and foamy background to smear

Sclerosing Adenosis

Clinical

- Relatively common, often bilateral, lesion
- Occasionally forms a palpable mass <2 cm (nodular sclerosing adenosis) in size
- Usually a microscopic finding
- May be associated with increased risk of carcinoma, according to some investigators

Macroscopic

- Cannot be distinguished grossly from fibrocystic change

Microscopic

- Low-power retention of lobulocentric configuration is key to diagnosis
- Fibrosis may distort or obliterate lumens and make myoepithelial cells prominent

Immunohistochemistry

- Smooth muscle actin (SMA) will stain myoepithelial cells, which are preserved in sclerosing adenosis

Differential Diagnosis

- Atypical apocrine adenosis:
  - Shows involvement of lobules by atypical cells with apocrine features
- Invasive carcinoma:
  - No myoepithelial cell layer and no lobulocentric pattern

Microglandular Adenosis (MGA)

Clinical

- Palpable mass in women 28–52 years of age
- Usually 3–4 cm in size

Macroscopic

- No distinguishing features; variably dense, rubbery, fibrous tissue

Microscopic

- Proliferation of duct-like structures in a fibrocollagenous stroma
- PAS + eosinophilic material in lumen
- Single cell layer; cells with clear cytoplasm
- Stroma varies from hyalinized eosinophilic to loose and paucicellular

Immunohistochemistry

- No myoepithelial cell layer on staining with S-100 or SMA

Ultrastructure

- Preservation of basement membrane, which is often multilayered

Differential Diagnosis (see Table 18-1)

- Invasive tubular carcinoma:
  - MGA may also extend into fat
- MGA vs. tubular carcinoma:
  - Characteristic stroma: fibrocollagenous vs. fibroelastotic
  - Round glands vs. angulated
  - Luminal secretions vs. none
  - Clear cytoplasm in lining cells vs. eosinophilic
  - Truncated luminal cell border vs. apocrine snouting
  - Basement membrane vs. none
- Atypical MGA:
  - Some cases of MGA show cytologic atypia and mitotic figures: biologic potential unclear
- Secretory adenosis has a myoepithelial cell layer on immunostaining for actin

Complex Sclerosing Lesion/Radial Scar

Clinical

- Middle age to elderly women
- Frequently multiple and bilateral incidental microscopic findings

Radiology

- May form a stellate mass on mammogram, described as suspicious or malignant

Macroscopic

- May form a palpable mass indistinguishable from invasive carcinoma grossly

Microscopic

- Central fibroelastotic or fibrocollagenous scar
- Stellate arrangement of ducts; zonal pattern may be obscured if only part of lesion is sampled or in core biopsy
- Maximum epithelial proliferation is at periphery
- 30% have some atypical hyperplasia or carcinoma

Table 18-1. Distinguishing Features of Tubular Carcinoma, Sclerosing Adenosis, and Microglandular Adenosis

	Tubular carcinoma	*Sclerosing adenosis*	*Microglandular adenosis*
Shape of lesion	Stellate, irregular	Lobular, round	Irregular
Shape of glands	Angulated	Round to oval	Round
Luminal contents	Sometimes	Rarely	Frequent, "colloid"
Cell layers	1 (epithelial)	2 (epithelial and myoepithelial)	1 (epithelial)
Cell luminal surface	Snouting	Occasional snouting	Smooth
Cytoplasm	Eosinophilic	Inconspicuous	Clear
Stroma	Desmoplastic	Around lobules	Dense collagenous
Basement membrane	Usually none	Present	Prominent

Differential Diagnosis

- Tubular carcinoma:
  - Distinction may be impossible on needle biopsy
- RS/CSL shows preservation of myoepithelial layer on immunostaining

Duct Ectasia (Periductal Mastitis)

Clinical

- Majority of cases are subclinical
- Patients may have pain and tenderness around nipple or chronic nipple discharge or distortion

Macroscopic

- Periareolar (large) ducts affected
- Dilated ducts with yellow material in lumen, mimicking comedocarcinoma

Microscopic

- Acute stages rarely seen; acute inflammation around and in duct
- Fibrosis leads to duct distortion
- Periductal lymphoplasmacytic infiltrate, pigmented histiocytes
- Foam cells in epithelium and lumen
- Duct may be obliterated by process; "ectasia" a misnomer at this stage

Collagenous Spherulosis

- Incidental microscopic finding; importance is in differential diagnosis

Microscopic

- Spheres of eosinophilic material (20–100 mmm) surrounded by myoepithelial cells, in duct lumens or TDLU (terminal duct-lobular unit)
- Material may be fibrillar, asteroid, or dense and amorphous
- Eosinophilic "cuticle" at periphery characteristic
- Spheres may contain flocculent basophilic material: "mucinous spherulosis"
- The epithelial cell population around collagenous spherulosis may be benign, atypical, or malignant; judge separately from collagenous spherulosis

Immunohistochemistry

- Spheres + for collagen IV
- Surrounding myoepithelial cells + for S-100 or SMA

Differential Diagnosis

- Ductal carcinoma in situ, cribriform type:
  - May also show basophilic material in spaces; no myoepithelial cells around cribriform spaces
- Adenoid cystic carcinoma:
  - More cellular atypia, usually forms a mass
- Lobular neoplasia with signet ring cells:
  - Look for other cells with intracytoplasmic lumina

Mastitis

Acute Mastitis/Periareolar Abscess

Clinical

- Reproductive years
- Crack in skin of nipple, frequently in nursing women, allows bacterial entry
- Congential abnormality/inversion of nipple increases risk
- Rarely a surgical specimen

Microscopic

- Squamous metaplasia of large ducts
- Thick-walled abscess cavity
- Staph aureus and anaerobes are usual organisms

Granulomatous Mastitis

- Idiopathic accounts for most cases in the West
- Other causes include:
  - Tuberculosis: necrotizing granulomas; isolation of *M tuberculosis* required for diagnosis
  - Fungi and protozoa
  - Reaction to duct rupture
  - Reaction to carcinoma
  - Sarcoid: usually in context of established disease elsewhere, rule out other causes
  - Wegener's granulomatosis

Idiopathic Granulomatous Mastitis

Clinical

- Usually reproductive age, but wide range
- Tender, palpable nodule; may be bilateral
- Etiology unknown; epithelial damage may be primary event

Microscopic

- Granulomatous inflammation centered on lobules
- Mixed inflammatory cell infiltrate
- Diagnosis based on excluding other causes of granulomatous inflammation

Silicone Reaction

Clinical

- Leakage of silicone from implants/implant rupture usual cause
- Injection of silicone for augmentation no longer performed
- Reaction may be to additives and/or silicone

Microscopic

- Empty spaces or spaces with refractile foreign material
- Histiocytic or foreign-body giant-cell reaction with fibrosis
- Similar changes frequent in regional nodes

Differential Diagnosis

- Fat necrosis
- Metastatic mucinous carcinoma (lymph nodes or bone marrow)

Lymphocytic Mastitis (Diabetic Mastopathy, Fibrous Mastopathy)

Clinical

- Painless mass
- Wide age range of 24–72 years; occasional cases in males
- Associated with diabetes mellitus or autoimmune diseases

Macroscopic

- Dense rubbery fibrous tissue

Microscopic

- Extensive stromal fibrosis with atrophy of acini
- Dense lymphocytic infiltrate surrounds residual lobules; may have germinal centers
- Lymphocytic perivasculitis or vasculitis a constant feature
- Prominent epithelioid stromal cells, some binucleate

Immunohistochemistry

- Stromal cells – for keratin; may be KP-1 +
- Lymphocytes are B cells

Differential Diagnosis

- Infiltrating carcinoma:
  - Hypocellularity and atypia of stromal cells may suggest lobular carcinoma
- Fibrocystic change:
  - Inflammation in FCC more periductal than perilobular

Amyloid

Clinical

- May occur as an amyloid tumor (elderly women) or microscopic finding
- Patients have systemic disease (e.g., rheumatoid arthritis or amyloidosis)

Macroscopic

- Nodule with granular or waxy cut surface

Microscopic

- Amorphous eosinophilic material with giant cell reaction
- Vascular and adipose tissue deposition in non-nodular forms
- Pink on Congo Red stain, apple green birefringence on polarizing

Differential Diagnosis

- May be mistaken for carcinoma clinically and grossly
- Microscopically, elastosis may resemble amyloid
- Areas of collagen in lymphocytic mastitis may resemble amyloid

Fat Necrosis

Clinical

- Usually an incidental microscopic finding, occasionally a palpable mass
- History of trauma or radiotherapy in a minority
- May be accompanied by pain/tenderness/bruising/skin retraction

Macroscopic

- Well-defined, firm area < 2 cm in size
- Early lesions show hemorrhage
- Late lesions show scar with cyst formation

Microscopic

- Anucleate fat cells surrounded by foamy histiocytes
- Fibrosis and calcification in later lesions

NEOPLASMS

Benign Epithelial Neoplasms

Adenomas

- Benign, well-circumscribed proliferation of tubular structures, lined by epithelium and myoepithelium

Ductal Adenoma—See Sclerosing Papilloma

Syringomatous Adenoma—See Nipple Lesions

Nipple Duct Adenoma—See Nipple Lesions

Tubular Adenoma

Clinical

- 90% of patients <40 years; rare in males
- Mobile mass, may be tender; frequently discovered in pregnancy

Macroscopic

- Solid, firm, tan-yellow nodule >1 cm in size

Microscopic

- Encapsulated or well-defined
- Closely packed tubules
- Hypocellular stroma with scanty lymphocytes
- Epithelium may show mitotic figures, apocrine metaplasia, and lactational or secretory changes; atypia is rare

Differential Diagnosis

- Fibroadenoma has a neoplastic stromal component: Lesions with features of both may occur (combined tubular and fibroadenomas)
- Nodular adenosis: less well-defined/not encapsulated

Lactating Adenoma

Clinical

- Females in reproductive age group; discovered when pregnant or nursing

Macroscopic

- Well-circumscribed, yellow, soft

Microscopic

- May vary according to time of removal
- Sharply circumscribed, lobular arrangement maintained:
  - Pregnancy: secretory material in lumen, vacuolated cytoplasm
  - Postpartum: marked distention, hobnail cells, vacuolated cytoplasm
- Infarction may be seen
- Attenuated myoepithelial cell becomes inconspicuous

Differential Diagnosis

- Lactational change: more diffuse process, similar cytologically
- Carcinoma: pitfall on FNA, look for bubbly background

Pleomorphic Adenoma (Benign Mixed Tumor)

Clinical

- Rare
- Usually elderly female, but also reported in teenagers and males

Macroscopic

- Well-circumscribed, lobulated, myxoid or chondroid appearance

Microscopic

- Identical to those of the salivary glands morphologically
- Epithelial/myoepithelial proliferation in a myxochondroid background with focal ossification

Immunohistochemistry

- Cytokeratin: + in epithelial cells
- SMA/S-100: + in myoepithelial cells
- Glial fibrillary acidic protein: Myoepithelial cells are less commonly + than in salivary gland lesions

Hamartoma

Clinical

- Wide age range, usually 30s or 40s

- Detected on screening; well-delineated density on mammograms

Macroscopic

- Oval, usually approximately 3 cm in size; rubbery consistency

Microscopic

- Well-circumscribed, may be encapsulated
- Variable quantities of fibroadipose or glandular tissue, showing alterations seen in normal breast (fibrocystic change, adenosis)

Differential Diagnosis

- Normal breast:
  - May not be possible to distinguish unless sectioned to show capsule

Benign Mesenchymal Tumors

Fibromatosis

Clinical

- Less common in breast than other sites
- Females, median age = 25; occasionally bilateral
- Mass and skin retraction mimics carcinoma
- Stellate pattern on mammography also suggests carcinoma

Prognostic Significance

- May recur unless fully excised; inking and extensive sampling of specimen important

Macroscopic

- Ill-defined, soft, gray-white lesion, 1–10 cm in size

Microscopic

- Irregular margin with fingers extending into breast tissue and surrounding ducts
- Variably cellular, with intervening collagen; spindle cells are in sheets and occasionally show a storiform pattern of growth
- No or mild atypia
- Mitoses <3/10 HPF with no atypical forms
- No calcification or necrosis; chronic inflammatory cells frequent

Immunohistochemistry

- Spindle cells are + for vimentin and a minority for actin; – for keratin and S-100 protein

Differential Diagnosis

- Low-grade fibrosarcoma:
  - Difficult on occasion; fibrosarcoma has more mitoses and at least some nuclear atypia
- Spindle cell carcinoma:
  - More pleomorphism and mitotic figures with keratin + spindle cells
- Nodular fasciitis:
  - Rare diagnosis in breast, but may occur on adjacent chest wall; contains occasional multinucleated cells; inflammatory infiltrate is at periphery of lesion

Myofibroblastoma

Clinical

- Painless firm mass
- Occurs in males and females
- Excision is curative

Macroscopic

- Nodular, well-circumscribed, rubbery lesions

Microscopic

- Spindle cell proliferation arranged in fascicles and interspersed by bands of dense collagen
- Occasional cases show fat or cartilage.
- Some breast ducts may be entrapped in the lesion.

Immunohistochemistry

- Vimentin consistently +
- Variable positivity for actin, desmin, S-100, and CD 34
- Negative for cytokeratin

Ultrastructure

- Bundles of 6 nm diameter myofilaments and no tonofilaments
- Rare pinocytotic vesicles
- Elongated nuclei; cytoplasm with prominent rough endoplasmic reticulum and Golgi apparatus

Differential Diagnosis

- Fibromatosis:
  - Has a more infiltrative pattern
- Nodular fasciitis:
  - Stellate pattern, plumper mesenchymal cells
- Neurofibroma:
  - More angulated nuclei
- Neurilemmoma:
  - Antoni A and B areas
- Spindle cell lipoma:
  - Intermixed fat

Granular Cell Tumor

Clinical

- Uncommon in the breast; wide age range; females > males

- ♦ May be detected as stellate lesions on mammogram
- ♦ May be near the nipple, distorting it
- ♦ Cured by excision; <1% malignant

Macroscopic

- ♦ Frequently sharply circumscribed firm lesions
- ♦ May mimic carcinoma with a stellate shape and firm consistency

Microscopic

- ♦ Has a focally infiltrative margin in areas, despite gross appearance
- ♦ Sheets, nests, or cords of cells with granular eosinophilic cytoplasm
- ♦ Small central nuclei, occasionally mild pleomorphism
- ♦ Mitoses rare
- ♦ A highly infiltrative variant is often mistaken for carcinoma

Immunohistochemistry

- ♦ Diffuse positivity for S-100 protein
- ♦ – for cytokeratin and EMA

Differential Diagnosis

- ♦ Invasive ductal carcinoma:
  - – Principally mimics this on gross appearance and FNA
- ♦ Normal nipple:
  - – Small granular cell tumor may be difficult to see in this region
- ♦ Leiomyoma:
  - – May arise from smooth muscle in the periareolar region

Neurilemmoma (Schwannoma)

Clinical

- ♦ Rare in breast; males and females; wide age range

Microscopic

- ♦ Hypercellular (Antoni A) and hypocellular (Antoni B) areas, with Verocay bodies
- ♦ Identical to these tumors elsewhere
- ♦ Degenerative stromal and nuclear changes may occur.

Lipoma

Clinical

- ♦ Solitary soft mass; occurs in women in their 40s and 50s

Macroscopic

- ♦ Soft, yellow, well-demarcated

Microscopic

- ♦ Mature adipose tissue; thin fibrous capsule necessary to make the diagnosis
- ♦ Variants:
  - – Prominent spindle cells component: spindle cell lipoma
  - – Prominent vessels with fibrin thrombi: angiolipoma

Differential Diagnosis

- ♦ Normal breast adipose tissue

INTRADUCTAL EPITHELIAL PROLIFERATIONS

- ♦ General term = mammary intraepithelial neoplasia
- ♦ Divided into DIN and lobular neoplasia (LN)
- ♦ The designation of "mammary intraepithelial neoplasia" may be appropriate when an in situ proliferation has both ductal and lobular characteristics or does not quite match one or the other

Summary of Cytologic Characteristics

- ♦ See microscopic description of individual categories and Table 18-2

Features of Ductal Proliferations

- ♦ Distinct cell borders
- ♦ Secondary lumen formation (rosettes)
- ♦ Larger nuclei than lobular neoplasia
- ♦ Variants: stratified spindle cell, spindle cell, apocrine

Features of Lobular Proliferations

- ♦ Indistinct cell borders
- ♦ Solid or loosely cohesive pattern of growth
- ♦ Intracytoplasmic lumens
- ♦ Small, uniform nuclei
- ♦ Variants: pleomorphic lobular

Ductal Intraepithelial Neoplasia (see Table 18-3)

Clinical

- ♦ Discovered incidentally on biopsy specimen or following biopsy for mammographically detected microcalcifications
- ♦ DIN 1c and higher is a marker for ipsilateral breast tumor recurrence (IBTR); half of these are invasive (see Table 18-3)

Table 18-2. Intraductal Hyperplasia (IDH) versus Atypical Intraductal Hyperplasia (AIDH): Distinguishing Features

	IDH	*AIDH*
Cellular proliferation	Two cell types (mixed pattern)	Epithelial only (monotonous pattern)
Secondary lumina	Slit-like, irregular	Rigid "Roman bridges"
Cell borders	Indistinct	Distinct
Nuclei	Variable in shape	Round contour
Nucleoli	Usually absent	Frequently present
Necrosis	May be present	If present = ductal carcinoma in situ
High molecular weight cytokeratin	Present	Absent
Smooth muscle actin	+ throughout proliferation	+ at periphery of duct

Table 18-3. Spectrum of Preinvasive Mammary Ductal Proliferations (Ductal Intraepithelial Neoplasia, DIN)

Proposed DIN classification	*Current designation*	*Pleo-morphism*	*Necrosis*	*Abs risk of invasion*	*Molecular findings*	*Re-excision if + or close margin*
DIN 1a	IDH	–	– or +	1.9%	clonal*/LOH	no
DIN 1b	AIDH, flat type	*–f*	–	5.1–12%	clonal/LOH	no
DIN 1c	≤2mm AIDH, flat type >2mm DCIS, grade 1 (crib and micropap)	*–f*	–	10–32%	clonal/LOH	yes
DIN 2	DCIS, grade 2 (crib/micropap + necrosis or atypia)	*–f* +(–)	+ –	20–75%	clonal/LOH	yes
DIN 3	DCIS, grade 3 (anaplastic DCIS +/- necrosis)	+++ +++	+++ –	20–75%	clonal/LOH	yes

IDH = intraductal hyperplasia, AIDH = atypical intraductal hyperplasia, DCIS = ductal carcinoma in situ, LOH = loss of heterozygosity
f; no significant (moderate-severe) nuclear atypia is present, although a minor degree of atypia is assumed in all DCIS (as well as AIDH) proliferations
** A few cases of IDH have been shown to be clonal.*
Adapted from Tavassoli, FA. Ductal carcinoma in situ: introduction of the concept of ductal intraepithelial neoplasia. Mod Pathol. 1998;11:140–154

- Risk increases with increasing grade
- Risk for an individual patient depends on family history
- Adequacy of surgical margin is increasingly recognized as being of importance in determining the efficacy of breast-conserving therapy for DIN 1c and higher grades

DIN 1a: Intraductal Hyperplasia (IDH)

Microscopic

- Proliferation of cells characterized by difference in cell populations (epithelial and myoepithelial cells participate, heterogenous population), nuclear overlapping, indistinct cell borders, and irregular slit-like secondary lumina

Immunohistochemistry

- Cells react with high molecular weight (HMW) cytokeratins

DIN 1b: Flat Epithelial Atypia (AIDH, Flat Type)

Microscopic

- Monomorphous variant: so-called "clinging carcinoma;" frequently a single layer of abnormal cells around a duct space

Immunohistochemistry

- Cells do not react with HMW cytokeratin
- Cells react with E. cadherin

DIN 1c: AIDH and Low-Grade DCIS (Quantification Is Required when There Is Complete Duct Involvement)

Microscopic

- Proliferation with some cytologic (monotonous population, rounded nuclei, distinct cell borders) and architectural (rounded secondary lumina) atypia
- Quantitatively limited: maximum complete involvement of one or more ducts not exceeding 2mm in aggregate cross sectional diameter
- Uncommon: AIDH is usually focal
- Patterns of low-grade DCIS include cribriform and micropapillary patterns without necrosis

DIN 2

Microscopic

- Low-grade patterns promoted one grade by the presence of necrosis or low-grade patterns with moderate cytologic atypia
- Necrosis is nuclear debris of 5 or more cells; apoptosis of individual cells or granular amorphous luminal debris should not be used to diagnose it

Immunohistochemistry

- Cells negative for HMW cytokeratin
- Cells positive for E. cadherin

DIN 3

Macroscopic

- May be recognized grossly as multiple punctate yellow areas approximately 1 mm in size
- May be up to 8–9 cm in size, with fibrosis around ducts mimicking an invasive carcinoma

Microscopic

- Any case with severe cytologic atypia is grade 3
- Cases with moderate atypia and necrosis are also grade 3
- Comedocarcinoma should be reserved for grade 3 nuclei with necrosis
- Extensive periductal fibrosis and inflammation common

Immunohistochemistry

- Cells negative for HMW cytokeratin
- Cells positive for E. cadherin
- C-erb-B2 and p53 status correlates with grade
- ER/PR not generally performed on *in situ* lesions

Microinvasive Breast Carcinoma

- A cluster of tumor cells breaking through the basement membrane infiltrating the periductal stroma, with or without visible continuity with that duct, the diameter of the area not exceeding 2 mm
- If multiple, up to 3 foci, each up to 1 mm in diameter

Clinical

- If clearly defined, cases with microinvasion can be managed as DCIS
- Up to 3% of cases diagnosed as DCIS reportedly have lymph node metastases. These arise from areas of invasive carcinoma not detected in the biopsied or sampled areas

Macroscopic

- Cannot be distinguished from intraductal carcinoma

Microscopic

- Tongue-like projection from a duct or small group of cells beside a duct with DCIS
- Stroma frequently fibroblastic and myxoid

Variants of DCIS

Intraductal Papillary Carcinoma

- See separate section (Papillary Lesions)

Apocrine Intraductal Carcinoma

Clinical

- No definitive clinical significance; importance is in differential diagnosis
- High proportion have androgen receptors and are devoid of estrogen and progesterone receptors

Microscopic

- Apocrine cytology: granular eosinophilic cytoplasm, prominent nucleoli
- Apical snouting and cytoplasmic vacuolization variable
- Architectural patterns include solid or cribriform, rarely papillary types
- Two variants described:
  - Necrotic variant shows luminal necrosis and severe atypia
  - Non-necrotic variant has more variable atypia, usually solid or cribriform

Differential Diagnosis

- Apocrine metaplasia/hyperplasia:
  - No nuclear atypia; papillary fronds have fibrovascular cores

- Atypical apocrine metaplasia:
  - Atypia = 3-fold variation in nuclear size
- Atypical apocrine hyperplasia:
  - Atypia and more than 2 cell layers
  - Epithelial bridges lacking fibrovascular cores, even with bland cytology; imply a diagnosis of atypical apocrine hyperplasia

Intraductal Clear Cell Carcinoma

Microscopic

- Cells with optically clear cytoplasm and distinct cell borders
- May be mixed with other patterns
- May have associated invasive clear cell carcinoma

Intraductal Signet Ring Carcinoma

Microscopic

- Rare variant, composed of cells with a signet ring morphology

Differential Diagnosis

- Intraductal papillary carcinoma:
  - May have a signet ring component
- Mammary intraepithelial neoplasia:
  - Proliferation may have mixed ductal and lobular features
- Collagenous spherulosis:
  - Flattened myoepithelial cell nuclei at periphery of aggregates of collagen may mimic signet ring cells

Intraductal Carcinoma with Secretory Features

Microscopic

- Rare variant
- Dilated ducts with eosinophilic luminal secretion
- Epithelial tufting (papillary), cribriform growth most usual
- Mitotic figures present
- Moderate nuclear atypia
- Cytoplasmic vacuolization

Differential Diagnosis

- Lactational change:
  - More generalized change (but not invariably); cribriform growth not a feature

Intraductal Spindle Cell Carcinoma

Microscopic

- Rare variant; importance lies in differential diagnosis
- Monotonous proliferation of elongated cells, forming solid pattern
- Often admixed with a relatively solid variant of cribriform DCIS

Differential Diagnosis

- Intraductal hyperplasia:
  - Has a spindle cell population, but does not display the monotony of spindle cell IDCA
- Solid papillary carcinoma:
  - May have spindle cell component

Lobular Intraepithelial Neoplasia (LIN)

Clinical

- A pathologic diagnosis
- Occurs in 0.3–3.8% of all breast biopsies
- Natural history difficult to determine
- Marks patients as being at increased risk of invasive carcinoma, both lobular and ductal, in both breasts, rather than as an obligate precursor
- Patients with grade 3 lesions are at higher risk
- Ductal involvement is not a risk factor for recurrence
- Role of family history in increasing risk not determined

Macroscopic

- Not detectable macroscopically

Microscopic

- Generally, a population of small uniform cells lacking nucleoli
- Intracytoplasmic lumina present
- Cell borders indistinct; cells frequently loosely cohesive
- Extension into terminal ducts found in approximately $^{2}/_{3}$ of cases
- Necrosis or calcification rare
- "Clover-leaf pattern" due to unfolding of TDLU

Immunohistochemistry

- Cells are negative for E. cadherin
- Cells are positive for HMW cytokeratin

Grading

- LIN grade 1:
  - Partial or complete replacement of normal acinar epithelium; lobules are not distended
- LIN grade 2:
  - Distention of some acini, but preservation of interlobular stroma
- LIN grade 3:
  - Massive distention and confluence of acini
  - Signet ring cell form also graded as 3

Differential Diagnosis

- Atypical intraductal hyperplasia:
  - See cytologic features listed above
  - Some cases may be impossible to distinguish from AIDH:
    - Use the designation "mammary intraepithelial neoplasia"
- Collagenous/mucinous spherulosis:
  - Increased difficulty when LIN involves a pre-existing benign lesion that alters architectural pattern (e.g., sclerosing adenosis, complex sclerosing lesions)

INFILTRATING CARCINOMA

Infiltrating Ductal Carcinoma

- Most cases are "not otherwise specified" (NOS); to be regarded as a subtype, a pattern should comprise >90% of the tumor

Reporting of Infiltrating Breast Carcinoma

- Essential features include:
  - Laterality
  - Type of biopsy specimen
  - Size of tumor (maximum dimension in cm)
  - Grade of tumor
  - Margin status
  - *In situ* component
  - Presence or absence of lymphovascular invasion
  - ER/PR status

Grading of Invasive Carcinomas

- Modified Scarff-Bloom-Richardson system is the one most commonly used
- Tumor is graded by scoring each of the following features:
  - Tubule formation:
    - >75% = 1
    - 10–75% = 2
    - <10% = 3
  - Nuclear pleomorphism:
    - This is both a qualitative and a quantitative assessment
    - Uniform small regular nuclei = 1
    - Moderate variation in size and shape, occasional nucleoli = 2
    - Marked variation in size and shape, prominent nucleoli = 3
  - Mitotic activity:
    - Unequivocal mitotic figures are counted at the periphery of the tumor
    - At least 10 high power fields are counted
    - The range of figures that gives each score correlates with field diameter (and field area); for example, for Olympus BX 40, HPF (x400) = 0.55 mm diameter, scores are
      - 0–7/10 HPF = 1
      - 8–15/10 HPF = 2
      - >15/10 HPF = 3
- The scores are added to give the grade:
  - 3–5 = well-differentiated, Grade 1
  - 6–7 = moderately differentiated, Grade 2
  - 8–9 = poorly differentiated, Grade 3

Axillary Lymph Node Status

Clinical

- Clinical assessment of nodal status is incorrect in 50% of cases
- Nodes should be submitted entirely, unless grossly involved (sampled)
- Highest node should be designated by the surgeon (i.e., level 2 or level 3)

Macroscopic

- Metastatic tumor gives firm yellow-white appearance
- Sinus histiocytosis (especially with previous biopsy) may give soft enlarged pale node

Microscopic

- Metastatic tumor fills and expands sinuses first, may replace node
- May resemble primary tumor pattern or show variation in pattern
- Extracapsular extension should be documented in report

Differential Diagnosis

- Negative lymph node:
  - Deeper levels will increase yield in 9–33% of cases
  - Immunostain for keratin may be necessary to detect small metastases, especially lobular carcinoma
- Sinus histiocytosis:
  - Bland reniform nuclei, sinuses expanded

- Metastatic melanoma:
  - Breast cancer may also be S-100 +; only melanoma is HMB-45 + also
- Benign inclusions:
  - Epithelial or melanocytic, located in capsule of node

Infiltrating Ductal Carcinoma NOS (Table 18-4)

Clinical

- Increasing proportion detected mammographically
- Many detected on clinical examination; average size has decreased from 2 cm to 1.2 cm
- If there is "extensive ductal carcinoma *in situ*" (i.e., DCIS comprising >25% of the tumor and extending beyond the invasive component), conservative therapy is less likely to be successful
- Mutations in *BRCA1* (located on chromosome 17q21) and *BRCA2* (located on chromosome 13q12-13) genes are responsible for approximately 80% of familial early-onset cases
- Individuals who carry BRCA1 mutation have high risk (up to 85%) of developing breast cancer by age 70
- Patients with Her-2/neu oncogene amplification may have worse prognosis

Macroscopic

- Firm, gray, stellate nodule
- Adjacent fat shows deep yellow-orange tinge
- Cutting gives a texture described as "unripe pear"
- May have punctate yellow foci representing *in situ* component with comedo necrosis

Microscopic

- Proliferation of epithelial cells with varying degrees of glandular differentiation and nuclear atypia
- Intraductal carcinoma present in 80% of cases, confirms a primary breast neoplasm
- Variable lymphoplasmacytic reaction

Immunohistochemistry

- ER/PR can be performed on formalin-fixed paraffin embedded material, called + if ≥10% of tumor cell nuclei are +
- SMA may be useful in confirming invasive carcinoma
- Neuroendocrine markers (chromogranin A and synaptophysin) confirm neuroendocrine differentiation in some tumors: no definitive prognostic significance
- Gross Cystic Disease Fluid Protein-15 is +

Differential Diagnosis

- Intraductal carcinoma:
  - Most important differential; establishing this is more important than keeping frozen tissue for markers
- Specific subtypes of breast carcinoma (see below)
- Metastatic carcinoma:
  - *In situ* component is not present

Variants of Infiltrating Ductal Carcinoma

Tubular Carcinoma

Clinical

- Over-represented in carcinomas detected by screening/ carcinomas <1 cm (8%)
- Appears as a stellate lesion on mammogram
- Median age is slightly younger than other breast carcinomas

Prognostic Significance

- Lower incidence of axillary nodal metastases (8–20%, 1.4% if tumor is <1 cm)

Table 18-4. Infiltrating Ductal Carcinoma versus Infiltrating Lobular Carcinoma*

	Ductal carcinoma	*Lobular carcinoma*
Relative frequency	80–85%	< 10%
Pattern of infiltration	Nests/sheets of cells	Single file, "targetoid"
Intervening stroma	Often scanty	Extensive
Tubule formation	Present	Absent
Cell size	Moderate to large	Usually small
Signet ring cells	Rare	Frequent
Associated lesions**	Ductal carcinoma in situ	Lobular neoplasia

** Borderline forms occur (i.e., ductal carcinoma with lobular features); rarely, the two types coexist. A combined pattern—tubulolobular carcinoma—occurs*
*** An in situ component is not necessary for diagnosis*

- Excellent survival (>90% 10 years) for pure variety
- Misdiagnosis as radial scar is a pitfall

Macroscopic

- No distinguishing features from other ductal carcinomas; usually small, firm, gray/white lesion

Microscopic

- Requirement of a pure pattern for this diagnosis ascertains a distinctive category with excellent prognosis
- Many authors also accept up to 25% of other (usually cribriform) component
- Haphazard arrangement of tubules with open lumens, frequently comma-shaped
- Single cell lining
- Nuclei show little pleomorphism; mitoses rare
- Apical snouting common
- Classic lesions show a reactive fibroblastic stroma, but it may be densely collagenous, or show smooth muscle metaplasia
- Basement membrane patchy/absent (PAS stain)

Differential Diagnosis (see Table 18-1)

- Radial scar:
  - Similar mammographic appearance; immunostain for actin shows myoepithelial layer present in radial scar
  - Secondary features that help make the distinction include elastotic core in RS
- Mixed tubular carcinoma (75–99% tubular):
  - Term is used where tubular pattern is not pure (solid areas, higher grade nuclei)
- Sclerosing adenosis:
  - Retains a lobulated outline, lumens compressed/obliterated, two cell layer present
- Microglandular adenosis:
  - More rounded glands with central secretory material and stroma densely collagenous

Mucinous (Colloid) Carcinoma

Clinical

- Rare carcinoma (1–6% of infiltrating ductal carcinomas)
- Mean age = 60 years, slightly older than other forms

Prognostic Significance

- Low rate of axillary node metastases (3–15%) in pure form
- Better survival (>80% at 10 years) than ductal carcinoma NOS
- Increased size, hypercellularity, and nodal metastases predict more aggressive course

Macroscopic

- Well-circumscribed, gray, gelatinous nodule; may be multiple

Microscopic

- May occur in pure or mixed (with infiltrating ductal carcinoma NOS) forms
- Pure form can be divided into hypocellular and hypercellular variants
- Small clusters of tumor cells, in solid, papillary, or glandular patterns, floating in abundant extracellular mucin

Immunohistochemistry

- Chromogranin and S-100 protein frequently +
- ER + in ~50–75% of cases, PR + in 14%

Differential Diagnosis

- Infiltrating ductal carcinoma NOS
- Mucocele-like lesions:
  - A ruptured cyst with benign epithelial and myoepithelial elements in mucus
  - Usually <5 mm in size
  - Immunostain for actin may help in the demonstration of myoepithelial cells

Medullary Carcinoma

Clinical

- Uncommon (5–7% of ductal carcinomas); see below
- Occurs at average age (50 years)

Prognostic Significance

- Better prognosis: 80–90% 10-year survival
- In contrast, "atypical medullary carcinoma" does not differ in prognostic terms from ductal carcinoma NOS

Macroscopic

- Well-circumscribed, soft, fleshy tumor, yellow/hemorrhagic appearance; may show necrosis and cyst formation

Microscopic

- When strict criteria are used in diagnosis, this is a rare tumor
- Essential features:
  - Circumscribed, non-infiltrative periphery
  - Lymphoplasmacytic infiltrate of at least moderate degree at periphery
  - Syncytial growth pattern makes up >75% of tumor mass; no discrete cell borders
  - Fine (not dense) collagen bands intersect tumor
  - Grade 2-3 nuclei; usually vesicular with prominent nucleoli
  - Absence of intraductal component

- Also seen are:
  - Lymphoplasmacytic infiltrate extending into fibrous septa
  - Necrosis/cyst formation
  - Prominent mitoses
  - Squamous metaplasia
  - Granulomatous reaction

Immunohistochemistry

- ER + in $<^1/_3$ of cases

Differential Diagnosis

- "Atypical medullary carcinoma":
  - An infiltrating ductal carcinoma with some, but not all, of the above features; far more common than true medullary carcinoma

Apocrine Carcinoma

- Carcinoma composed predominantly of cells with abundant granular, eosinophilic cytoplasm; distinct cell borders; and central nuclei with prominent nucleoli

Clinical

- Frequency depends on application of definition, probably < 0.5% of carcinomas
- Males and females, generally older ages

Prognostic Significance

- No conclusive evidence of better or worse behavior than ductal carcinoma NOS

Macroscopic

- Firm, partly cystic, occasionally tan color

Microscopic

- Apocrine cytology as above
- Nuclear pleomorphism may be marked and overlap with that seen in benign apocrine lesions
- Cytoplasm may contain coarse eosinophilic granules and lipofuscin
- Luminal/cystic areas show decapitation secretion
- Intraductal component is usually apocrine IDCA

Immunohistochemistry

- Gross cystic disease fluid protein (GCDFP-15) staining is variable (~75%)
- Androgen receptor +; high-grade lesions loose AR expression
- B72.3, CEA, cytokeratins also +
- S-100 protein –

Differential Diagnosis

- Apocrine metaplasia, with or without atypia, in sclerosing adenosis:
  - Definite infiltrative pattern should be seen for a diagnosis of invasive carcinoma
- Sclerosing adenosis:
  - Lobular configuration retained
- Histiocytoid (pleomorphic lobular) carcinoma:
  - Has eosinophilic cytoplasm, intracytoplasmic lumina, and mucin
- Lipid-rich carcinoma:
  - More vacuolated and foamy cytoplasm
- Squamous cell carcinoma:
  - Cytologically may be similar, but contains glycogen on PAS staining
- Granular cell tumor:
  - Small nuclei, S-100 +

Histiocytoid Carcinoma

- see Lobular Carcinoma, Pleomorphic Variant

Lipid-Rich Carcinoma

- Invasive carcinoma, in which at least 80% of cells contain neutral lipid and show cytoplasmic vacuolization; extremely rare subtype

Clinical

- Little distinctive features; chalky elastotic foci less likely

Prognostic Significance

- May be a more aggressive variant; too few cases reported to reach a definitive conclusion

Microscopic

- Fixed material shows cells with foamy cytoplasm and nuclei with prominent nucleoli
- Frozen tissue stained with oil-red O (ORO) demonstrates fat. Diagnosis must be considered at time of frozen section to enable confirmation by optimal ORO stain

Immunohistochemistry

- ER/PR –

Differential Diagnosis

- Ductal carcinoma NOS:
  - May have sebaceous foci and lipid on ORO staining
- Pleomorphic lobular carcinoma

Secretory Carcinoma

Clinical

- Younger age (median = 25 years) than other breast carcinomas
- Has been reported in males pre- and post-puberty

Prognostic Significance

- Age dependent: patients <20 years do well, recurrences may be years later and the course indolent; axillary node metastases rare in children, but occur in adults
- Course resembles ductal carcinoma NOS in older patients

Macroscopic

- Firm, usually well-circumscribed, gray-white lesions; can mimic fibroadenoma

Microscopic

- Abundant intra- and extracellular eosinophilic secretory material
- Bland nuclei; scanty mitotic figures
- Intraductal component may be present and have a secretory pattern
- Papillary pattern may be present
- Pushing margin
- Histochemistry: PAS and DPAS +, alcian blue +, focal mucicarmine positivity

Clear Cell Carcinoma

Clinical

- Uncommon variant; middle aged to elderly females

Prognostic Significance

- More aggressive than ductal carcinoma NOS; higher incidence of nodal metastases; more aggressive course

Macroscopic

- Mass 2–8 cm, no specific gross features

Microscopic

- 90% of cells should have clear or finely granular eosinophilic cytoplasm for diagnosis
- Clear pattern is due to glycogen (PAS +, removed by diastase)
- Grows in solid nests, occasionally papillary formations
- Intraductal clear cell component may be present
- Nuclei are usually grade 2; tumor is usually grade 3 on SBR grading

Differential Diagnosis

- Ductal carcinoma NOS with clear cell areas comprising < 90% of tumor
- Adenomyoepithelioma:
  - Shows positivity for actin and/or S-100
- Clear cell hidradenoma (eccrine acrospiroma):
  - Look for two cell types and evidence of duct differentiation
- Lipid-rich carcinoma:
  - ORO and PAS stains +
- Metastatic clear cell tumors, especially renal cell carcinoma; look for intraductal component

Immunohistochemistry

- Few cases studied are ER/PR –

Carcinoma with Osteoclast-Like Giant Cells

Clinical

- No specific features: uncommon variant
- Frequently well-circumscribed on mammography

Prognostic Significance

- Recurrences and metastases in $^1/_3$ of cases: no significant prognostic difference from ductal carcinoma NOS

Macroscopic

- Soft, hemorrhagic, red-brown tumor in contrast to most breast carcinomas

Microscopic

- Numerous osteoclast-like giant cells present adjacent to tumor cells
- Characteristic hemorrhagic fibroblastic stroma with chronic inflammatory cell infiltrate
- Giant cells may be present in metastatic deposits

Immunohistochemistry

- Giant cells are acid phosphatase, KP-1 and α-1-antitrypsin + and keratin –, confirming histiocytic origin

Differential Diagnosis

- Metaplastic carcinoma:
  - May have giant cells in addition to chondroid and osseous differentiation
- Poorly differentiated carcinoma with tumor giant cells:
  - Keratin +
- Granulomatous inflammation with giant cells:
  - Keratin –

Inflammatory Carcinoma

Clinical

- Characterized by the clinical appearance of red, tender/painful, warm lesion with skin dimpling/peau d'orange, and diffuse induration of the breast
- The clinical diagnosis is more frequent (5–10%) than the pathologic counterpart (0.5–1%) (see below)

Prognostic Significance

- Axillary nodal metastases are present in most cases
- Tumors with either clinical or pathological features of inflammatory carcinoma are aggressive; fatal within 2 years before chemotherapy
- Currently, 25–50% 5-year survival; worse than ductal carcinoma NOS

Macroscopic

- Large tumor or diffuse mammary involvement
- Skin thickening apparent
- Changes may spread to chest wall

Microscopic

- Invasive ductal carcinoma with plugging of dermal lymphatics by tumor emboli is the usual pathologic finding
- This may be prominent or focal
- May show a mononuclear infiltrate
- Increase in dermal collagen and lymphatic dilatation also seen
- There is not an absolute correlation between the clinical and pathological picture; there may be clinically inflammatory carcinoma without lymphatic plugging and vice versa

Immunohistochemistry

- ER – in > $^1/_2$ of tumors, PR – in $^2/_3$

Differential Diagnosis

- Clinical picture resembles acute inflammation/erysipelas; skin does not contain neutrophils

Adenoid Cystic Carcinoma

Clinical

- Rare tumor in this location
- Presents as painless mass, occasionally of some years duration; median age = 50–63 years; females > males

Prognostic Significance

- Much less aggressive than its salivary gland counterpart; reason unclear
- Lymph node or pulmonary metastasis rare but long-term follow-up required
- Most cases treated by mastectomy; has usually been curative

Macroscopic

- Variable size, mean = 2 cm
- Well-circumscribed, firm, gray/yellow mass; occasionally cysts present

Microscopic

- Histologically identical to salivary gland ACCs
- Two cell types:
  - Basaloid cells and cells with eosinophilic or clear cytoplasm
- Lumens contain three types of material in very variable proportions:
  - Hyaline bodies: dense eosinophilic, PAS + replicated basal lamina
  - Mucoid secretory material
  - Eosinophilic "cuticle" with or without luminal material
- Sebaceous differentiation seen in a minority of tumors
- Perineural invasion occasionally seen
- Histologic grading of limited use: low grade show dominant cribriform pattern; high grade show predominant solid basaloid pattern

Immunohistochemistry

- Basaloid cells are vimentin + and variably + for actin and S-100
- Eosinophilic cells are keratin and EMA +

Differential Diagnosis

- Collagenous spherulosis:
  - Usually an incidental microscopic finding; spherules are surrounded by myoepithelial cells with no atypia
- Cribriform carcinoma:
  - Does not have two cell types

Carcinoma of the Male Breast

Clinical

- ~1% of incidence of breast cancer in women
- Occurs in an older age group than in women (mean = 60+ years vs. 50+ years)
- May present as an asymptomatic mass, nipple discharge, or Paget's disease
- Most are located centrally in the breast
- Risk factors include Klinefelter's syndrome (47 XXY); 3–6% develop breast carcinoma

Prognostic Significance

- Formerly thought to have a much worse prognosis; more recent studies suggest it is similar to stage-matched female patients
- High incidence of metastases (55%)
- Central location means increased internal mammary lymph node metastases
- Tumors should be graded as in carcinomas from female patients

Macroscopic

- Most tumors < 3 cm

Microscopic

- All tumor types except in situ and invasive lobular carcinoma are found
- Most are infiltrating ductal carcinoma
- Papillary carcinomas comprise a greater percentage than in women

Immunohistochemistry

- A higher proportion are ER + (80–90%) than in women and >50% of these are hormone-responsive
- PR are + 25–75% of cases
- Prostate-specific antigen (PSA) has been demonstrated in primary breast carcinomas

Differential Diagnosis

- Metastatic adenocarcinoma:
  - Especially from prostate, in a male treated with estrogen for prostate cancer
  - Less common with antiandrogen treatment (now preferred)
  - Clinical history and PSA and PSAP needed for diagnosis

Metaplastic Carcinomas

- Malignant tumors with an epithelial or mesenchymal population different from or in addition to adenocarcinoma
- Histogenesis is uncertain and designation is on the basis of morphology and immunohistochemistry and/or ultrastructure
- Traditionally, the more common metaplastic carcinomas (i.e., apocrine carcinomas) are not designated as such

Squamous Cell Carcinoma

Clinical

- Very rare tumor in pure form; significantly < 1% of primary breast carcinomas

Prognostic Significance

- Variable reports claiming better or worse than ductal carcinoma NOS; prognosis may be more related to grade than squamous features

Macroscopic

- Characteristic feature is multiple cysts

Microscopic

- Variable appearance: Keratinizing, acantholytic, and spindled are described
- Intercellular bridges and keratohyaline granules seen in benign or well-differentiated squamous elements
- Mixtures of these types are common
- Central cyst and prominent reactive stroma are frequent

Immunohistochemistry

- Keratin: + in squamous cells
- Vimentin ± actin, desmin in mesenchymal cells

Ultrastructure

- Squamous cells show desmosomes and tonofilaments

Differential Diagnosis

- Primary squamous cell carcinoma of the skin
- Metastatic squamous cell carcinoma
- Carcinosarcoma (see separate section)
- Syringomatous adenoma: usually near nipple, infiltrative, but cytologically bland

Adenosquamous Carcinoma (Mucoepidermoid Carcinoma)

Clinical

- No significant difference from ductal carcinoma NOS
- Incidence unknown; squamous component may not be reported if small

Prognostic Significance

- Low-grade tumors mainly recur
- High-grade tumors are aggressive and metastasize

Macroscopic

- Poorly defined mass median = 2.5 cm with variable foci of white keratinous debris

Microscopic

- Variable mixture of adenocarcinoma (often peripheral) and squamous carcinoma (often more central)
- Mucin stains demonstrate adenocarcinomatous component
- Histologic grading of tumor should be performed

Adenocarcinoma with Spindle Cell Metaplasia

Prognostic Significance

- Too few cases reported to provide clear information

Microscopic

- Adenocarcinoma cells merge with malignant spindle cells

Immunohistochemistry

- Necessary for diagnosis, demonstration of cytokeratin in the spindle cell component

Carcinoma with Chondroid Metaplasia

Clinical

- Rare tumors, cases show wide age range and may reach a large size (20 cm)

Prognostic Significance

- Difficult to ascertain, as studies have not always separated them from carcinosarcomas (vi)
- Many cases within this group are categorized with carcinomas displaying osseous differentiation; again, prognostic significance is uncertain

Microscopic

- Variable extent and distribution of cartilage
- Associated carcinoma is usually an infiltrating ductal carcinoma

Infiltrating Lobular Carcinoma

Clinical

- Less common pattern: 0.7–14% of invasive carcinomas
- Same median age (5th and 6th decades) as invasive ductal carcinoma
- Detection may be difficult:
  - Lack of calcification hampers mammographic detection
  - Tumor may be poorly defined on palpation
  - Tumor may be multifocal

Prognostic Significance

- Studies vary as to survival; may be better or the same as infiltrating ductal
- Pattern of metastases differ: Lobular has predilection for viscera, bone marrow, and meninges; ductal for lung/pleura
- Metastases in nodes and other sites may be difficult/impossible to detect on H&E; keratin immunostain useful
- Histologic variants may have slightly poorer prognosis than classic form

Macroscopic

- Small foci are not visible
- Larger tumors appear as indurated, ill-defined masses
- Less commonly a multinodular texture "grains of sand"

Microscopic

- Classic form and variant forms:
  - Classic:
    - Small cells with ovoid nuclei and little cytoplasm, arranged in single file, frequently in a targetoid pattern around ducts
    - Intracytoplasmic lumens present in a minority of cells; mucin stains useful
    - Signet ring forms occasionally seen
    - Stroma is desmoplastic, but with an overall eosinophilic appearance
    - Lobular neoplasia present in 90% of all cases
  - Solid:
    - Closely packed small cells forming large nests with thin fibrous trabeculae
  - Alveolar:
    - Smaller, closely packed islands of uniform small cells
- Mixed patterns common (30% of cases); a pattern should comprise >70% of the tumor to justify designation as a subtype
- Variants show a lower incidence of coexistent lobular neoplasia in some series:
  - Histiocytoid variant (pleomorphic lobular carcinoma):
    - Bland, histiocytoid-appearing cells
    - Comprises ~5% of infiltrating lobular carcinoma
    - Larger cells, more pleomorphic nuclei than other variants
    - Similar growth pattern, intracytoplasmic lumens, association with LN, and/or admixture with classic pattern confirm its interpretation as a lobular carcinoma variant
- Grading:
  - Should be performed as for infiltrating ductal carcinoma
  - Lobular carcinoma will score 3 for tubules; usually has little pleomorphism or mitoses, so it qualifies as a well- or moderately differentiated carcinoma

Immunohistochemistry

- 70–90% are ER +; ≥70% are PR +
- 60% + for S-100 protein
- As with other carcinomas, keratin and EMA + and LCA –

Differential Diagnosis

- Inflammation:
  - Lobular carcinoma cells can resemble lymphocytes, especially on frozen section
- Lymphoma:
  - Especially solid variant, lymphoma cells do not have intracytoplasmic lumens (but rare signet ring forms have been described); immunostains for LCA and keratin useful
- Infiltrating ductal carcinoma:
  - So-called tubulolobular variant is a well-differentiated ductal carcinoma with lobular features
- Infiltrating apocrine carcinoma:
  - Differential with pleomorphic lobular carcinoma, which does not have nucleoli

Papillary Lesions

- Lesions characterized by an arborizing growth pattern and fibrovascular cores
- May be either central, in large peri-areolar ducts/lactiferous sinuses (frequently solitary), or peripheral (usually smaller and multiple)
- Differential diagnosis is of lesions on the spectrum and is discussed below

Intraductal Papilloma

Clinical

- Most frequent in females >50; may occur in males
- Serous or serosanguinous discharge from the nipple in a majority (87%) of cases

Macroscopic

- Papillary lesion frequently visible in dilated duct
- If duct is dilated such that it appears like a cyst, the term intracystic papilloma is appropriate

Microscopic

- Epithelial and myoepithelial cell layer supported by fibrovascular core
- Secondary changes are common:
  - Torsion/hemorrhagic infarction of papilloma
  - Squamous metaplasia secondary to infarction
  - Sclerosis/hemosiderin deposition in duct wall and papillary stalk; occasionally, extensive sclerosis dictates the diagnosis of "sclerosing papilloma"
- "Ductal adenoma": well-circumscribed, fibrotic nodule, frequently within a duct lumen, but extensive fibrosis may obscure this:
  - Prominent myoepithelial proliferation, epithelial component resembles sclerosing adenosis
  - Apocrine metaplasia, sometimes with atypia, may occur
  - Most likely a variant of sclerosing papilloma

Intraductal Papillomatosis

Clinical

- Occurs in women ~10 years younger than solitary papilloma
- Associated with a discharge from the nipple in a minority (33%) of cases

Prognostic Significance

- Not completely established: currently believed not to have a significantly increased risk for cancer unless there is associated atypia

Macroscopic

- Not visible grossly

Microscopic

- Papillary fronds with a myoepithelial cell layer; in multiple TDLUs
- Ducts smaller and walls less sclerotic
- Multiple foci of mural attachment and smaller size mean degenerative changes less prominent

Atypical Papilloma

- Atypical papilloma contains papillary lesions with:
  - Up to $^1/_3$ of papillary fronds lacking myoepithelial cells, or
  - Up to $^1/_3$ of area composed of an atypical intraductal proliferation, or
  - Fronds covered by a stratified spindle cell proliferation
- Carcinoma arising in a papilloma:
  - Similar changes involving 33–90% of lesion
  - Recent study suggests a similar course for lesions in categories 1 and 2. These can be combined under the designation of atypical papilloma
- Papillary carcinoma:
  - >90% of lesion involved

Papillary Carcinoma

Clinical

- Accounts for ~2% of carcinomas
- Similar demographics to papilloma; nipple discharge less common ($^1/_4$ patients)
- May present with nipple distortion or a mass if invasive

Prognostic Significance

- Criteria for atypical papilloma and carcinoma arising in a papilloma are arbitrary; complete excision is advisable; behavior of these entities may not differ significantly
- Presence of atypia in adjacent ducts increases risk of subsequent invasive carcinoma
- Invasive papillary carcinoma is only rarely associated with nodal metastases. These are in lower axillary nodes and systemic metastases/death is rare

Microscopic

- Myoepithelial layer is central diagnostic point
- Cytology may be bland, but cellular monotony is a key factor in recognition
- Patterns of papillary carcinoma include:
  - Cribriform proliferation between fibrovascular stalks
  - Solid: may be difficult to see few residual stalks; minority of cells have eosinophilic cytoplasmic granules
  - Spindle cell proliferation: often associated with mucin production
  - Transitional cell: rare variant
- Adjacent duct spaces often contain atypical intraductal hyperplasia

Immunohistochemistry

- Myoepithelial layer stains for SMA
- With very fine fibrovascular cores, actin + endothelial cells may cause problems; endothelial cells are Factor

VIII +, but they are negative for S-100 protein, which stains myoepithelial cells
- Some solid and spindle cell variants are positive for chromogranin and synaptophysin

Invasion in Papillary Carcinoma
- Occurs in minority of cases
- Unequivocal invasion is tumor cells infiltrating outside duct into fat
- Irregular tubules trapped in sclerotic duct wall or stalk is common; these retain a myoepithelial cell layer
- Invasion of tumor into sclerotic wall is called "early stromal invasion"

Differential Diagnosis
- Application of percentage criteria distinguishes benign/atypical/carcinoma
- Application can be on H&E slides or actin
- If diagnosis of carcinoma is made, should be qualified as either "intraductal" or "invasive"
- Skin adnexal tumors may mimic central papillomas, especially eccrine acrospiroma (clear cell hidradenoma)
- "Ductal adenoma" may be mistaken for invasive carcinoma

Biphasic Tumors (Table 18-5)

Fibroadenoma

Clinical
- Women in reproductive age range, average 25–35 years
- African American > Caucasian
- Usually presents as a solitary mobile breast mass

Prognostic Significance
- Myxoid variant: increased risk of recurrence; may be part of complex of myxomas (cardiac and cutaneous), spotty pigmentation, and endocrine overactivity (Carney's syndrome)
- Carcinoma arising in a fibroadenoma: rarely results in death from tumor, may be managed conservatively

Macroscopic
- Gray/white, well-circumscribed nodule "shells out"
- Characteristic bulging surface
- Lesions from older women more fibrous and may be calcified

Microscopic
- A proliferation of mesenchymal and epithelial elements
- Fully developed form shows different patterns of stromal proliferation (no clinical significance):
  - Intracanalicular: around compressed cleft-like spaces
  - Pericanalicular: around tubular ducts
- Margin is usually pushing, with some irregularities
- Myxoid change may occur in stroma: association with Carney's syndrome
- Epithelium shows two cell layers and hyperplasia is frequent
- Apocrine metaplasia seen in some fibroadenomas (11%)
- Benign changes such as sclerosing adenosis are found in fibroadenomas
- Multiple adjacent TDLUs may show these changes without a well-defined mass; this is called fibroadenomatoid change
- Fibroadenomas in elderly women often show stromal hyalinization, epithelial atrophy, and calcification
- Carcinoma arising in fibroadenoma: >50% of these are lobular in type; there is often (50%) invasive carcinoma elsewhere in the breast

Differential Diagnosis
- Phyllodes tumor: leaf-like processes, cystic spaces, stromal hypercellularity
- Juvenile fibroadenoma (occurs in adolescent females): rapid growth, cellular stroma, pericanalicular growth pattern usual

Phyllodes Tumor
- Previously called cystosarcoma phyllodes; however, many do not behave like a sarcoma
- Phyllodes = leaf-like; phylloides = leafy

Clinical
- Accounts for 2.5% of fibroepithelial breast tumors
- Wide age range, but on average 20 years older (45 years) than women with fibroadenoma
- Present as painless breast mass, often longstanding with sudden enlargement
- Median size = 6.4 cm, but size is not a diagnostic criterion

Macroscopic
- Fleshy, white tumor, with bulging leaf-like processes

Microscopic
- Leaf-like processes and cystic spaces lined by epithelium with two-cell layer
- Squamous metaplasia more frequent than in fibroadenoma
- Stromal overgrowth is assessed differently by different authors; should be confined to cases where there is extensive (multiple low-power fields, multiple slides) proliferation of sarcomatous elements
- Hypercellular stroma: Assessment of this is subjective
- Chondroid, osseous, and lipoid metaplasia more frequent than in fibroadenoma
- Rare variant shows stromal cells with intracellular

Table 18-5. Biphasic Neoplasms—Diagnostic Features

	Fibroadenoma	*Low-grade phyllodes*	*High-grade phyllodes*
Size	Variable	Variable	Variable
Spaces	Tubular or slit-like	Leaflike, cystic	Leaflike, cystic
Stromal cellularity	Variable	Moderate to high	High
Margins	"Pushing"	"Pushing"	Infiltrative
Stromal overgrowth	Absent	Absent	Present in some
Stromal nuclear atypia	Minimal	Mild to moderate	Moderate to severe
Mitotic figures	Variable	< 3/10HPF	≥+ 3/10 HPF
Benign heterologous elements	Rare	Frequent	Frequent

accumulations of actin (identical to infantile digital fibromatosis)

Grading

- No single feature is predictive of biologic behavior
- Low-grade tumors may recur, but do not metastasize:
  - Pushing margin
  - <3 mitoses per 10 HPF
  - Lack of moderate or severe cytologic atypia
- High-grade tumors tend to recur and may metastasize:
  - Infiltrative margin
  - Moderate to severe cytologic atypia
  - 3 or more mitoses/10 HPF
  - Presence of specific sarcoma subtypes (liposarcoma, osteosarcoma) classify a tumor as high-grade
- Metastases:
  - Wide range, probably <10% of cases
  - Hematogenous, especially to lungs; axillary node dissection unnecessary

Periductal Stromal Sarcoma

- Term has been used loosely; when defined as below, it is a rare biphasic tumor

Prognostic Significance

- Not well-defined

Microscopic

- Proliferation of stromal spindle cells around tubules with open lumens
- Leaf-like pattern not apparent
- Intervening normal fibro-adipose tissue

Nipple Lesions

- Lesions that are usually, but not exclusively, found in the region of the nipple

Paget's Disease

Clinical

- Presents as unilateral, eczematoid change of nipple, ulceration or distortion of nipple, or more diffuse irregularity of the nipple/periareolar area
- 1–5% of breast carcinomas

Macroscopic

- See clinical ~50% have an underlying mass
- If a mass is felt in a case of Paget's, an invasive carcinoma is extremely likely

Microscopic

- Intraepithelial proliferation of malignant cells, with or without an associated intraductal or infiltrating carcinoma (usually ductal)
- Paget cells are large, with pale cytoplasm and large nuclei
- Present singly or in basally located nests, undermining native epithelium
- Occasional acinar formation
- Paget cells are positive for mucin (PAS, mucicarmine) in 50–60% of cells

Immunohistochemistry

- Paget cells are positive for Cam 5.2 and CK 7
- Variable positivity is seen for EMA and polyclonal CEA
- They are negative for S-100 protein and HMB-45

Differential Diagnosis

- Eczema:
  - Particularly due to clinical appearance
- Toker cells
  - Normal variant, clear cells in nipple epithelium; these are not cytologically malignant

- Squamous cell carcinoma:
  - Rare in nipple
- Melanoma:
  - Rare in nipple also, immunos as above confirm Paget's

Nipple Duct Adenoma (Erosive Adenomatosis)

Clinical

- Uncommon lesion; females > males; 5th decade
- Nipple discharge, induration, or ulceration may occur
- ~25% of cases are asymptomatic/incidental findings

Prognostic Significance

- Clinically, may be mistaken for Paget's disease; not a pathologic diagnosis
- May recur if incompletely excised
- May occur in association with carcinoma, but not generally felt to be pre-malignant

Macroscopic

- Well-circumscribed lesion; may cause cystic dilatation of ducts

Microscopic

- Proliferation of tubules replacing the nipple
- Sclerosis of adjacent stroma
- Associated papilloma formation/papillomatosis
- Epithelial hyperplasia and squamous metaplasia frequent
- Atypia may also be present

Immunohistochemistry

- Actin confirms retention of myoepithelial cell layer

Differential Diagnosis

- Infiltrating carcinoma, especially tubular carcinoma; use actin to differentiate
- Papilloma: Adenoma component of NDA may be quite focal
- Sclerosing adenosis
- Syringomatous adenoma:
  - Tubules are closer together in NDA
  - Syringomatous adenoma permeates the nipple stroma; NDA replaces it

Syringomatous Adenoma

Clinical

- Uncommon lesion, unilateral, in region of nipple in 80% of cases
- Presents as a firm mass; nipple discharge or pain less common
- Females > males
- May recur locally if incompletely excised

Macroscopic

- Poorly defined gray nodule; may have small cystic areas
- Tend to be small in size (1–3 cm)

Microscopic

- Irregular, angulated tubules widely separated by fibrous stroma
- Occasional connections to surface epithelium, but erosion/ulceration rare
- Permeates nipple structures
- Tubules have myoepithelial cell layer
- Squamous metaplasia common; squamous cysts may develop
- Stroma usually has few or no mitoses, with chronic inflammatory infiltrate in occasional cases

Differential Diagnosis

- Tubular carcinoma:
  - Single cell layer, apical snouting, squamous metaplasia less common
  - Rarely occurs in the nipple
- Nipple duct adenoma:
  - Displaces/destroys rather than permeates the nipple

Skin Adnexal Tumors

Clinical

- Rarely involve nipple

Macroscopic

- No distinguishing features

Microscopic

- Basal cell carcinoma:
  - Hyperchromatic basaloid cells with stromal retraction and peripheral palisading
- Eccrine acrospiroma (clear cell hidradenoma):
  - Clear cells and eosinophilic cells
  - May show solid or papillary pattern
  - Differential diagnoses includes papillary transitional cell carcinoma

Myoepithelial Lesions

- Classified as myoepitheliosis, adenomyoepithelioma, and malignant myoepithelioma
- Differential diagnosis and ultrastructural features are discussed for the whole group

Prognostic Significance

- Myoepitheliosis
  - No recurrences or malignant change reported
- Adenomyoepithelioma
  - Tubular variant appears most likely to recur:

histologic features do not predict which cases will recur
  - Metastases may develop from carcinoma arising in this lesion
- Malignant myoepithelioma
  - Small number of cases, but a risk of nodal metastases exists

Myoepitheliosis

Clinical

- Does not form a palpable mass
- It is the most common of the three groups in this class

Macroscopic

- May be detected as firm areas within breast biopsy specimen

Microscopic

- Multifocal proliferation of spindle cells in TDLU
- Intraductal or periductal pattern
- Epithelial cells may be entrapped and lumens obliterated
- No atypia or mitotic figures seen in spindle cells

Immunohistochemistry (see Table 18-6)

- Strong positivity for S-100 protein
- Moderate positivity for actin
- Weak positivity for keratin
- Negative for GFAP

Adenomyoepithelioma

Clinical

- Females; median age = 62 years
- Solitary, centrally located lesions
- May have an associated nipple discharge

Macroscopic

- Usually well-circumscribed, white-gray nodules 1–7 cm in size

Microscopic

- Spindle cell, tubular, and lobulated types:
  - Spindle cell:
    - Solid mass with small foci of epithelium, frequently apocrine in type
  - Tubular:
    - Rounded tubules lined by both epithelial and myoepithelial cells
    - Myoepithelial cells may be hyperplastic and obliterate lumens
    - Up to 3 mitoses per 10 HPF seen
    - Margin shows focal irregularity
  - Lobulated:
    - Solid nests with fibrous capsule, some margin irregularity
    - Myoepithelial cells are clear, eosinophilic, or plasmacytoid
    - Stroma is hyalinized, with frequent calcification or infarction
    - Mitoses usually <3/10 HPF, occasionally more

Immunohistochemistry (see Table 18-6)

- Strong positivity for S-100 protein (less in clear cells)
- Weak positivity for actin and keratin
- Generally negative for GFAP, unlike the salivary gland counterpart

Malignant Myoepithelioma (Myoepithelial Carcinoma)

Clinical

- Female, middle aged to elderly
- Central breast mass, with or without nipple discharge

Macroscopic

- Stellate or well-circumscribed masses 1–21 cm in size
- Satellite nodules may be visible grossly

Microscopic

- Spindle cell proliferation only
- Cellular pleomorphism present; cells may be plump or oval
- Mitotic figures > 3/10 HPF
- Infiltrative margins

Immunohistochemistry (see Table 18-6)

- Positive for actin and/or S-100 protein

Ultrastructure

- Features vary somewhat according to cell type studied
- Constant features are
  - Multilayered basal lamina
  - Desmosomes and hemidesmosomes
  - Aggregates of myofibrils with dense bodies
  - Pinocytotic vesicles (fewer in clear cells)
  - Occasional tonofilaments (in malignant myoepithelioma)

Differential Diagnosis

- Myoepitheliosis is an incidental microscopic finding and blends with myoepithelial prominence in sclerosing adenosis
- Lobulated adenomyoepithelioma may be mistaken for high-grade ductal carcinoma. Look for hyalinized stroma and clear/plasmacytoid cells

Table 18-6. Myoepithelial Lesions of the Breast

	Myoepitheliosis	*Adenomyoepithelioma*	*Myoepithelial carcinoma*
Frequency	Common	Uncommon	Rare
Gross	Usually not seen	Solitary mass	Mass(es)
Microscopic	Spindle cells	Variable, usually spindle	Spindle cells
S100 protein	+++	+++	++
Smooth muscle actin	++	+	++ - +++
Cytokeratin	+	+	+

+ = weakly positive; ++ = moderately positive; +++ = strongly positive

- Malignant myoepithelioma resembles:
  - Spindle cell carcinoma: This shows stronger staining for keratin
  - Fibromatosis: more infiltrative, little or no atypia, <3 mitoses/10 HPF, – for keratin and S-100 protein
  - Stromal (spindle cell) sarcoma: – for epithelial markers
- Ultrastructural demonstration of pinocytotic vesicles strongly favors myoepithelial origin over epithelial origin

Carcinoma Arising in Adenomyoepithelioma

- Either component (epithelial or myoepithelial) may give rise to carcinoma
- Epithelial tumors reported include ductal carcinoma and adenoid cystic carcinoma

Vascular and Vascular-Like Lesions

Pseudoangiomatous Hyperplasia

Clinical

- Most cases are incidental microscopic findings (23% of breast biopsies)
- Symptomatic cases present as a painless mass in women with a mean age of 40 years

Macroscopic

- Firm, rubbery lesion, 2–7 cm in size

Microscopic

- Usually discrete and multifocal, resembling a vascular lesion on low power
- Dense collagenous stroma with slit-like channels lined by stromal, not endothelial, cells

Immunohistochemistry

- Lining cells are vimentin and PR +, – for vascular markers Factor VIII and CD34

Vasculitis

Clinical

- Rare, accompanied by systemic symptoms
- Tender nodules, cord-like lesion if a superficial vein (Mondor's disease)

Microscopic

- Giant cell arteritis and polyarteritis nodosa have been described
- Mondor's disease involves a vein

Prognostic Significance

- Arteritis should prompt systemic assessment
- Mondor's disease may be secondary to trauma and needs symptomatic treatment only

Microscopic Hemangioma

Microscopic

- Incidental microscopic findings < 5mm in size
- Perilobular hemangioma is most common form: aggregate of red blood cell-filled vascular channels in perilobular stroma
- No atypia or endothelial proliferation

Palpable Hemangioma

Clinical

- Definition: >5mm in size
- Female > male

Prognostic Significance

- No convincing evidence that hemangiomas are precursors of angiosarcoma
- Atypical hemangiomas do not recur or require reexcision

Macroscopic

- May be apparent as well-defined blood-filled lesions

Microscopic

- Vascular proliferation in intra- and interlobular stroma
- Cavernous, capillary, and arteriovenous forms described
- Some lesions show focal endothelial hyperplasia or anastomosing channels: "atypical hemangiomas"

Atypical Vascular Lesion

Clinical

- Solitary or multiple skin or breast nodules
- Occurs 2–5 years after radiotherapy to the breast
- Not associated with skin discoloration

Prognostic Significance

- Atypical vascular lesion does not recur and has no metastatic potential

Macroscopic

- Pink or tan-white nodules

Microscopic

- Located in dermis or present as circumscribed lesions in breast
- Dilated vascular spaces with anastomosing pattern
- Endothelium is plump, with occasional projections or tufting
- No endothelial mitoses or stromal blood lakes

Differential Diagnosis

- Angiosarcoma: more atypia, endothelial proliferation

Angiomatosis

Clinical

- A rare, congenital lesion; often manifests in young females, mean age = 33 years
- One case reported in a male

Microscopic

- Extensive in distribution
- Proliferation of irregular vascular channels
- No anastomosing pattern or endothelial atypia
- Does not dissect into lobular stroma

Differential Diagnosis

- Low-grade angiosarcoma (see below)

Hemangiopericytoma

Clinical

- Rare lesion; males and females

Prognostic Significance

- Complete local excision appears adequate; no recurrence reported
- Follow-up is recommended when there is hemorrhage, necrosis, or significant mitotic activity

Macroscopic

- Well-circumscribed, pink/tan mass

Microscopic

- Well-circumscribed cellular lesions
- Densely packed spindle cells surround endothelial-lined spaces
- Larger spaces classically show a staghorn shape; smaller may be slit-like
- Hemorrhage, necrosis, and significant mitotic activity are uncommon
- Stroma may have myxoid change

Immunohistochemistry

- + for vimentin, CD 34, and Factor XIIIa
- Tumor cells are – for Factor VIII or Ulex (endothelial cells are + for these) and – for keratin and SMA

Angiosarcoma

Clinical

- Rare neoplasm; females > males; mean age = 35 years
- May present as a well-defined, painless, rapid growing mass
- A minority present with diffuse discoloration of the overlying skin
- May develop post-radiotherapy (typically after 12 years, but reported within 4 years of treatment)

Prognostic Significance

- Well- and moderately differentiated lesions have median cancer-free survival of 12–15 years
- Poorly differentiated lesions have 15 months median survival
- Metastases to lungs, liver, skin: axillary nodes rarely involved

Macroscopic

- Spongy, hemorrhagic tissue in breast; may extend to overlying skin
- Extensive sampling is necessary for grading (vi)

Microscopic

- Variable appearance makes up basis for grading
- Low grade (well differentiated):
  - Anastomosing vascular channels
  - 1–2 cell layer lining
  - No necrosis or pleomorphism; mitoses rare
  - No blood lakes
- Intermediate grade (moderately differentiated):
  - Solid areas comprise <20% of total tumor mass

  - Endothelial tufts present
- High grade (poorly differentiated):
  - Predominance of solid spindle cell areas
  - Mitoses, pleomorphism, necrosis, and hemorrhage present

Immunohistochemistry

- Positivity for vascular markers (FVIII-related antigen, Ulex, CD 31) is maximal in better differentiated tumors, and very variable in poorly differentiated ones

Ultrastructure

- Malignant cells show pinocytotic vesicles, desmosomes, tight junctions, and Weibel-Palade bodies. The latter are seen mainly in some low-grade lesions

Differential Diagnosis

- Pseudoangiomatous hyperplasia:
  - Does not infiltrate lobules and is – for vascular markers
- Hemangioma (microscopic, perilobular):
  - No angiosarcomas have been found with this pattern
- (Post radiation) atypical vascular lesion:
  - Lacks atypia, mitoses, or endothelial proliferation and does not infiltrate subcutis
- Angiolipoma:
  - Well-demarcated/non-infiltrative, vessels contain microthrombi
- Angiomatosis:
  - Lacks atypia, mitotic activity (<1mitosis/10HPF, if any), endothelial cell proliferation, and dissection into lobular stroma

Lymphoid Lesions

- May be primary in the breast or in an intramammary/axillary node

Lymphoma

Clinical

- Primary lymphoma is rare. There is concurrent axillary node disease in 30–50% of all cases
- Secondary involvement of the breast by disseminated disease is more common
- Primary: bimodal incidence reported (38 and 58 years)
- Usually unilateral, but may be bilateral; small number in males
- Presentation can be with mass, pain, or constitutional (B-type) symptoms

Prognostic Significance

- Prognosis depends on stage and type
- Primary mammary lymphoma recurs locally in ~50% of all cases

Macroscopic

- Fleshy, gray-white tissue

Microscopic

- Non-Hodgkin's lymphoma (NHL) is much more common than Hodgkin's lymphoma
- B-cell is far more common than T-cell
- NHL types include diffuse large cell and diffuse, non-cleaved, small cell (Burkitt's like)
- No histologic features can distinguish primary from secondary forms
- Lymphocytic infiltration of epithelium may be seen in benign and malignant breast disease

Immunohistochemistry

- Appropriate panel to type lymphoma should be performed (see chapter 7)
- Immunoglobulin or T-cell receptor gene rearrangement studies as needed

Differential Diagnosis

- Poorly differentiated carcinoma: keratin +, LCA –
- Solid and alveolar variants of infiltrating lobular carcinoma: keratin +, intracytoplasmic lumens best seen in periphery, mucicarmine +
- "Pseudolymphoma": Many of these atypical lymphoid proliferations evolve into lymphoma; they have a mixed cell population
- Lymphocytic mastitis: localized; no atypia; associated with dense collagen and atypical epithelioid stromal cells

Plasmacytoma

Clinical

- Rare lesion in the breast; may be presentation of myeloma

Microscopic

- Similar to extramedullary plasmacytoma at other sites; cellular aggregate of variably atypical plasma cells (see lymph nodes, chapter 7)

Granulocytic Sarcoma

Clinical

- Uncommon; occurs either synchronously with, or shortly prior to, onset of acute myeloid leukemia
- Presents as a unilateral breast mass in patients aged 34–56 years

Macroscopic

- May show the characteristic green color

Microscopic

- Immature myeloid cells: mononuclear forms with granular eosinophilic cytoplasm, chloroacetate esterase (Leder) stain +

Sinus Histiocytosis with Massive Lymphadenopathy (Rosai-Dorfman Disease)

Clinical

- Rare in breast, but may involve axillary nodes
- Occurs at any age, but especially younger women

Microscopic

- Selective involvement of sinuses with expansion by S-100 + histiocytes
- Emperipolesis: engulfment of lymphocytes by histiocytes is characteristic
- Prominent polyclonal plasmacytosis

TNM CLASSIFICATION OF CARCINOMA OF THE BREAST*

- T: Primary Tumor:
  - Tis: *In situ* carcinoma
  - T1: ≤ 2 cm in greatest dimension
    - T1 mic: ≤ 0.1 cm
    - T1a: > 0.1 cm, ≤ 0.5 cm
    - T1b: > 0.5 cm, ≤1 cm
    - T1c: > 1 cm, ≤ 2 cm
  - T2: > 2 cm, ≤ 5 cm
  - T3: > 5 cm
  - T4: extension to chest wall/skin
    - T4a: chest wall
    - T4b: skin edema/ulceration, satellite skin nodules
    - T4c: both 4a and 4b
    - T4d: inflammatory carcinoma
- N: Regional Lymph Nodes
  - N1: moveable axillary nodes involved
    - pN1a: micrometastasis only, ≤ 0.2 cm
    - pN1b: metastasis to lymph node >0.2 cm**
  - N2: fixed axillary nodes involved
  - N3: internal mammary nodes involved

**Tumor, Nodes, Metastasis system: adapted from Hermanek P, Hutter RVP, Sobin LH, et al. eds. TNM Atlas: Illustrated Guide to the TNM/pTNM Classification of Malignant Tumors. 4th ed. Berlin: Springer-Verlag; 1997:201-212.*
p = pathologist staged
*** This group may be further subdivided according to the number of nodes involved*

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Chapter 19

Vulva, Vagina, Uterus and Fallopian Tube

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VULVA

Benign Lesions of the Vulva

Infection (see Table 19-1)

Human Papillomavirus Infection

Clinical

- Responsible for condyloma acuminatum and some cancer precursor lesions
- 3–50% of patients with vulvar condyloma acuminatum have a cervical HPV infection
- Commonly associated with vaginitis, pregnancy, diabetes mellitus, oral contraceptive use, and immunosuppression
- Lesions best seen with colposcopic examination after application of 3–5% topical acetic acid

Macroscopic

- Papillary, verrucous, or papular lesions
- Almost always multiple; frequently confluent
- May see red, granular areas that turn white after acetic acid is applied

Microscopic

- Koilocytotic cells: enlarged nuclei, wrinkled nuclear membrane, and perinuclear halos/cavitation
- Acanthosis, dyskeratosis, parakeratosis, hyperkeratosis, and prominent granular layer
- Squamous cells often binucleated and multinucleated
- Parabasal crowding, but minimal basal or parabasal cell atypia
- Mitotic figures may be increased, but are not atypical
- Superficial dermal chronic inflammatory infiltrate often seen

Differential Diagnosis

- Vulvar intraepithelial neoplasia (VIN):
  - Abnormal mitoses, marked variation in nuclear size and shape
  - Hyperchromasia

Herpes Virus Infection

Clinical

- Causative agent is herpes simplex virus (HSV), usually Type 2, but Type 1 may be involved
- ~600,000 new cases of genital herpes occur each year in the United States
- Sequential appearance of vesicle, pustules, and painful shallow ulcers
- In addition to the vulva, the lesions can involve the anus, urethra, bladder, cervix, and vagina
- ~2/3 of women who culture + for HSV have diagnostic genital vesicles and ulcers
- Recurrent episodes are common after primary infection

Microscopic

- Infected epithelial cell initially has homogenous chromatin ("ground glass" appearance) and then progresses to eosinophilic intranuclear inclusion body
- Characteristic intranuclear inclusions seen at the periphery of the lesion
- Clusters of multinucleated cells
- Cells eventually undergo karyorrhexis and lysis
- Cannot histologically distinguish primary from secondary infection or HSV1 from HSV2

Table 19-1. Infectious Diseases of the Vulva

Infectious disease	*Causative organism*	*Microscopic features*
Syphilis (primary lesion, chancre)	*Treponema pallidum*	Ulcerated epidermis, chronic dermal inflammation, perivascular inflammation
Condyloma lata (secondary syphilitic lesion)	*Treponema pallidum*	Similar to chancre, but with epithelial hyperplasia
Granuloma inguinale	*Campylobacterium granulomatis*	Ulcer, noncaseating granuloma, Donovan bodies (histiocytes with encapsulated bacilli), pseudoepitheliomatous hyperplasia
Lymphogranuloma venereum	*Chlamydia*	Nonspecific giant cells, lymphocytes, plasma cells, no organisms seen
Chancroid	*Haemophilus ducreyi*	Ulcer, noncaseating granuloma, Gram – organisms
Tuberculosis	*Mycobacterium tuberculosis, atypical mycobacterium*	Caseating granuloma, acid-fast bacilli

Other Viral Infections

- *Varicella* (herpes zoster, vulvar shingles)
- Cytomegalovirus infection
- Epstein-Barr infection
- *Molluscum contagiosum*

Other Infectious Diseases

- Fungal infections:
  - *Candida* and dermatophytes
- Vaginitis causing vulvar inflammation:
  - *Trichomonas*, *Chlamydia*, *Candida*
- Erythrasma:
  - Chronic bacterial infection, often in obese diabetic patients, *Corynebacterium minutissimum*
- Parasitic infections:
  - *Enterobius vermicularis*, *Schistosoma masoni*

Benign Epithelial Disorders

Lichen Sclerosus

Clinical

- Dermatosis of unknown etiology
- Most frequently on the genitalia, but may affect the trunk or extremities
- Most common in postmenopausal women

Macroscopic

- Pale, white, flat, plaque-like areas
- Vaginal mucosa is not involved

Microscopic

- Considerable variation related to the age of lesion, excoriation, and treatment
- Progressive thinning of the epithelium, with blunting or loss of rete ridges
- Homogeneous subepithelial edema with fibrin deposition
- Underlying dermal zone of chronic inflammation

Differential Diagnosis

- Lichen planus:
  - Inflammatory infiltrate at the dermal-epidermal junction
  - Colloid bodies common
  - Involves mucosal, as well as nonmucosal, sites
- Morphea (scleroderma):
  - Usually lacks subepithelial edema
  - Perivascular and deep dermal inflammation

Squamous Cell Hyperplasia

Clinical

- Formally called hyperplastic dystrophy
- Diagnosis of exclusion; epithelial thickening of the vulva that cannot be otherwise classified
- Usually found in adult women, 30–60 years of age

Macroscopic

- Gray-white or reddened, with adjacent gray-white epithelium
- May be confined to a focal area, usually involving the labia majora

Microscopic

- Epithelial thickening with acanthosis
- Hyperkeratosis and parakeratosis may be present
- No significant inflammatory infiltrate

Differential Diagnosis

- Fungal (chronic candidiasis) or dermatophyte infection:
  - Silver stain or PAS stain
- Psoriasis:
  - Uniform acanthosis
  - Collections of neutrophils within the epidermis (Munro abscesses)
- Regressing or early flat condyloma:
  - Koilocytosis
  - Prominent granular layer

Other Dermatoses

- Lichen planus
- Psoriasis
- Contact dermatitis
- Fixed drug eruption (dermatitis medicamentosa)
- Atopic dermatitis
- Fox-Fordyce disease
- Plasma cell vulvitis (vulvitis of Zoon)
- Vulvar vestibulitis (vulvar vestibular syndrome)
- Bechet syndrome
- Crohn's disease
- Necrotizing fasciitis
- Hidradenitis suppurativa
- Mites and lice

Bullous and Bullous-Like Diseases

- Pemphigus (pemphigus vulgaris)
- Pemphigus vegitans
- Pemphigoid (bullous pemphigoid)
- Herpes gestationis
- Erythema multiforme (Steven-Johnson syndrome)
- Darier disease (keratosis follicularis)
- Benign chronic bullous disease of childhood (linear IgA disease)

Cystic Lesions

Bartholin Duct Cyst

- Results from obstruction
- Mucoid, translucent liquid that fails to grow bacteria
- Squamous (most common), transitional, or low cuboidal mucinous epithelial cyst lining
- May be recurrent and require marsupialization
- May be associated with a carcinoma of the Bartholin gland in postmenopausal women

Keratinous Cyst (Epithelial Inclusion Cyst)

- May occur at any age, including infants
- Generally seen on the labia majora; usually multiple
- Usually contains white-pale yellow keratinous debris without hair
- Stratified squamous epithelial lining with a granular layer
- Foreign body giant-cell reaction may be seen in adjacent tissue due to leakage of keratinous material from the cyst

Mucous Cyst

- Usually solitary and seen within the vestibule
- Lined by mucous-secreting cuboidal to columnar epithelium
- Squamous metaplasia may be present
- Probably arises due to occlusion of the minor vestibular glands

Mesonephric-Like Cyst (Wolffian-Like Duct Cyst)

- Seen on the lateral aspects of the vulva and vagina; usually solitary
- Thin-walled, containing a clear fluid
- Cuboidal to columnar, non-ciliated epithelial lining
- Smooth muscle layer usually present beneath the basement membrane

Cyst of Canal of Nuck (Mesothelial Cyst)

- Thought to arise from inclusions of the peritoneum at the inferior insertion of the round ligament into the labia majora (analogous to spermatic cord hydrocele)
- Generally found in the superior aspect of the labia majora or inguinal canal
- Thin-walled cyst lined by flattened mesothelial cells
- Associated with inguinal hernia in ~1/3 of cases

Benign Squamous Lesions

Condyloma Acuminatum

- See Human Papillomavirus Infection

Differential Diagnosis

- Squamous cell carcinoma, especially verrucous type:
  - May be deeply infiltrative and locally destructive; koilocytosis absent
- Keratoacanthoma:
  - Central keratin plug, irregular epidermal proliferation extending downward into the dermis
- Vulvar intraepithelial neoplasia:
  - Nuclear pleomorphism, abnormal mitotic figures, variable cellular crowding
- Epidermolytic acanthoma:
  - Rare, benign vulvar lesion
  - Prominent acanthosis and hyperkeratosis
  - Prominent granular layer containing many irregularly shaped keratohyaline bodies

Squamous (Vestibular) Papilloma

Clinical

- Typically occurs on the vestibule
- Almost exclusively in women of reproductive age
- Solitary or multiple
- Etiology unknown

Microscopic

- Delicate fibrovascular connective tissue core
- Covered by either nonkeratinized or slightly keratinized epithelium
- Epithelium often glycogen-rich, but no koilocytosis

Differential Diagnosis

- Condyloma acuminatum
- Hymenal tags

Fibroepithelial Polyp (Acrochordon)

Clinical

- Also known as "skin tag"
- Rare on vulva
- Usually arises in hair-bearing skin, but may be seen on the labia minora

Macroscopic

- Papillomatous growths; vary from small to large and pedunculated
- Flesh-colored to hyperpigmented
- Soft and fleshy on cut section

Microscopic

- Epithelial surface may be thickened with papillomatosis, hyperkeratosis, and acanthosis or attenuated and flattened with multiple folds
- Prominent fibrovascular stroma component

Other Benign Squamous Lesions

- Seborrheic keratosis
- Keratoacanthoma

Benign Glandular Lesions

Papilloma Hidradenoma (Hidradenoma Papilliferum)

Clinical

- Apocrine sweat gland origin
- Presents after puberty; predominantly in Caucasian women

Macroscopic

- Well-circumscribed subcutaneous nodule measuring 0.5–1 cm

Microscopic

- Composed of numerous tubules and acini lined by a single or double layer of cuboidal cells
- Outer layer is myoepithelial
- Pseudocapsule formation from compression of the adjacent stroma
- May see mild nuclear pleomorphism and minimal mitotic activity

Differential Diagnosis

- Skin appendage adenocarcinomas
- Metastatic carcinomas
- Endometriosis
- Ectopic breast tissue

Nodular (Clear Cell) Hidradenoma

Clinical

- Eccrine sweat gland origin

Macroscopic

- Solitary, predominantly solid, subcutaneous nodule, usually 0.5–2 cm
- Gray-white on cut section

Microscopic

- Lobules of large clear cells divided by delicate strands of collagen-rich connective tissue
- Mitotic figures are unusual

Differential Diagnosis

- Metastatic clear cell adenocarcinoma
- Metastatic renal cell carcinoma
- Clear cell leiomyoma

Other Benign Glandular Lesions

- Syringoma
- Trichoepithelioma
- Trichilemmoma
- Adenoma of minor vestibular glands

Benign Mesenchymal Lesions

Angiomyofibroblastoma

- Benign vulvar tumor that may present as a Bartholin cyst or mass
- Well-circumscribed
- Spindled to oval stromal cells with bland nuclei
- Numerous capillary-like blood vessels, some with vessel wall thickening and collagen hyalinization
- May see cellular areas, concentrated around blood vessels, and adjacent hypocellular areas
- Absent or rare mitotic figures

Differential Diagnosis

- Aggressive angiomyxoma:
  - Less cellular, fewer blood vessels, lacks vascular wall thickening and hyalinization, infiltrative growth

Other Benign Mesenchymal Lesions

- Lipoma/fibrolipoma
- Capillary and cavernous hemangioma
- Pyogenic granuloma
- Angiokeratoma
- Lymphangioma
- Leiomyoma
- Granular cell tumor
- Neurofibroma
- Schwannoma (neurilemmoma)
- Glomus tumor
- Fibrous histiocytoma (dermatofibroma)
- Rhabdomyoma
- Desmoid tumor

Tumor-Like Lesions

Pseudoepitheliomatous Hyperplasia

Clinical

- Proliferative epidermal reactive process that mimics squamous cell carcinoma
- Identified in ~50% of vulvar granular cell tumors
- Adequate skin biopsy is essential

Microscopic

- Exuberant hyperplastic squamous epithelium with downgrowth of rete pegs into underlying papillary dermis
- Bland nuclei and few mitotic figures

Differential Diagnosis

- Squamous cell carcinoma:
  - Nuclear atypia, increased and/or abnormal mitoses

Other Tumor-Like Lesions

- Endometriosis
- Langerhan cell histiocytosis
- Benign xanthogranuloma
- Verruciform xanthoma
- Nodular fasciitis

Premalignant and Malignant Lesions of the Vulva

Vulvar Intraepithelial Neoplasia (VIN, Dysplasia, Carcinoma In Situ*)*

Clinical

- The labia minora and perineum are the most common sites
- Perianal involvement in ~1/3 of cases
- 70% of lesions are multifocal
- May be adjacent to superficially or deeply invasive squamous cell carcinoma
- Spontaneous regression may occur, especially in young or pregnant women

Macroscopic

- Variable appearance: 50% are white, others are red, black, brown, or gray
- Often macular or papular

Microscopic

- Nuclear enlargement, pleomorphism, and hyperchromasia
- Abnormal mitotic figures
- Crowded cells with disordered maturation
- Coarse chromatin with radial dispersion toward nuclear membrane
- Involves skin appendages in >50% of all cases
- Grading depends on the extent of replacement of the epithelium by abnormal cells in the most severely involved areas:
  - VIN 1: mild dysplasia; lower third of the epithelium
  - VIN 2: moderate dysplasia; $^1/_2$–$^2/_3$ of the epithelium
  - VIN 3: severe dysplasia; >$^2/_3$ of the epithelium
  - VIN 3: carcinoma in situ; full thickness, but not surface layers
- Subclassified into three types:
  - Basaloid: small, uniform cells with hyperchromatic, coarse chromatin; nucleoli are rare
  - Warty: larger cells, pleomorphic; koilocytosis, binucleation, prominent granular layer with dyskeratosis, parakeratosis, and/or hyperkeratosis
  - Well-differentiated: large, pleomorphic keratinocytes with abundant, eosinophilic cytoplasm; prominent nucleoli
  - May see a mixed pattern of the three types

Differential Diagnosis

- Basal cell carcinoma
- Superficial spreading malignant melanoma
- Paget's disease

Malignant Squamous Tumors

Squamous Cell Carcinoma

- By far, most common malignancy of the vulva
- Divided into two categories: superficially invasive and frankly invasive carcinoma (see below)
- Epidemiologically, two broad groups:
  - Younger women (mean age = 55 years): VIN associated with carcinoma, 75% associated with HPV; tend to be heavy cigarette smokers
  - Older women (mean age = 77 years): no associated VIN or history of heavy smoking, rarely contain HPV; often have associated squamous cell hyperplasia

Superficially Invasive Squamous Cell Carcinoma

Clinical

- Depth of invasion of ~1 mm and a diameter of ~2 cm
- Does not include patients with more than one site of invasion
- Zero risk of lymph node metastasis in several large studies

Macroscopic

- May present as an ulcer, red macule or papule, white hyperkeratotic plaque, or in association with VIN
- No clinical findings that specifically separate VIN from VIN with superficial invasion

Microscopic

- Depth of invasion is defined as the measurement from the epithelial–stromal junction of the adjacent dermal papillae to the deepest point of invasion
- Thickness of the tumor is defined as the measurement from the surface, or the granular layer if a keratinized surface is present, to the deepest point of invasion
- If possible, both depth of invasion and tumor thickness should be measured
- Isolated squamous cells in the stroma

Invasive Squamous Cell Carcinoma

Clinical

- Recognized risk factors: advancing age, immuno-

Table 19-2. FIGO Staging of Vulva Carcinoma (1989)

Stage 0	Tis	Carcinoma in situ, intraepithelial carcinoma
Stage I[a]	T1 N0 M0	Tumor confined to the vulva and/or perineum, ≤2 cm in greatest dimension, nodes are not palpable
Stage II	T2 N0 M0	Tumor confined to the vulva and/or perineum, >2 cm in greatest dimension, nodes are not palpable
Stage III	T3 N0 M0 T3 N1 M0 T1 N1 M0 T2 N1 M0	Tumor of any size with: 1. Adjacent spread to the lower urethra and/or the vagina, or the anus (T3) and/or 2. Unilateral regional lymph node metastasis (N1)
Stage IVA	T1 N2 M0 T2 N2 M0 T3 N2 M0 T4 any N M0	Tumor invades any of the following: urethra, bladder mucosa, rectal mucosa, pelvic bone (T4), and/or bilateral regional node metastasis (N2)
Stage IVB	Any T, any N, M1	Any distant metastasis including pelvic lymph nodes

[a]*Tla: stromal invasion ≤ 1 mm; Tlb: stromal invasion >1mm (1997 TNM Revision)*

deficiency, condyloma acuminatum, cigarette smoking, and genital granulomatous disease
- Solitary in 90% of all cases
- Survival is primarily related to the stage of the disease

Macroscopic
- Exophytic, papillomatous mass, or ulcer

Microscopic
- Typical squamous cell carcinomas are almost always well-differentiated and keratinizing
- Many histologic subtypes (see Table 19-2)

Differential Diagnosis
- Malignant melanoma
- Metastatic squamous cell carcinoma
- Epithelioid sarcoma
- Pseudoepitheliomatous hyperplasia
- Keratoacanthoma
- Skin appendage involvement by VIN

Histologic Subtypes of Squamous Vulvar Carcinoma
- Squamous cell carcinoma (NOS)
- Basaloid carcinoma
- Warty (condylomatous) carcinoma
- Verrucous carcinoma
- Giant cell carcinoma
- Spindle cell carcinoma
- Acantholytic squamous cell carcinoma
- Lympohoepithelioma-like carcinoma
- Basal cell carcinoma

Basaloid Carcinoma

Clinical
- Increased prevalence of HPV, mainly Type 16
- Frequently associated with adjacent VIN
- Associated with synchronous or metachronous squamous tumors of the cervix and vagina

Macroscopic
- Similar to typical squamous cell carcinomas

Microscopic
- Squamous cells with little or no maturation
- Irregular-shaped clusters and cord of cells surrounded by fibrous stroma
- Basal-type cells uniform in size, with scant cytoplasm and increased nuclear-cytoplasmic ratio

Differential Diagnosis
- Basal cell carcinoma
- Metastatic small cell carcinoma
- Merkel cell tumor

Verrucous Carcinoma

Clinical

- Synonym = giant condyloma of Buschke-Lowenstein

Macroscopic

- Papillary exophytic growth
- May be very large, distorting or obscuring the vulva

Microscopic

- Bland cytology, minimal nuclear pleomorphism
- Large nests of squamous epithelium with pushing tumor-dermal border
- Surface maturation, parakeratosis, and hyperkeratosis
- Abundant eosinophilic cytoplasm
- Koilocytosis and fibrovascular cores absent

Differential Diagnosis

- Squamous cell carcinoma (NOS):
  - Greater nuclear pleomorphism
  - More irregular infiltration of stroma
- Warty carcinoma:
  - Fibrovascular cores within the papillary fronds
  - Koilocytosis and greater nuclear atypia
- Condyloma acuminatum:
  - Complex branching papillary architecture with vascular papillae
  - Koilocytosis typically present

Warty (Condylomatous) Carcinoma

Clinical

- Occurs in younger women
- Associated with HPV, especially Type 16

Macroscopic

- Large, exophytic, with papillary architecture

Microscopic

- Papillary surface covered by hyperkeratotic squamous epithelium
- Fibrovascular cores within the epithelium
- Irregular nests of squamous epithelium at tumor-stroma interface
- Mild to marked koilocytotic atypia

Differential Diagnosis

- Verrucous carcinoma
- Keratinizing squamous cell carcinoma

Basal Cell Carcinoma

Clinical

- 2–4% of all vulvar carcinomas
- Elderly women

Macroscopic

- Well-circumscribed, raised or ulcerated

Microscopic

- Variable
- Relatively small, hyperchromatic tumor cells with peripheral palisading
- Squamous differentiation may be seen focally

Differential Diagnosis

- Squamous cell carcinoma
- Merkel cell tumor
- Metastatic small cell carcinoma

Malignant Glandular Tumors

Extramammary Paget's Disease

Clinical

- Can develop anywhere along the milk line (axilla to perineal area)
- ~2% of all vulvar neoplasms
- Typically seen in postmenopausal women
- May be associated with underlying invasive adenocarcinoma, but majority in vulva are not

Macroscopic

- Eczematoid pink to red lesion with irregular margin
- Foci of white hyperkeratotic epithelium often seen

Microscopic

- Pale cell, grouped and singly, located predominately in the epithelium within the basal and parabasal zones
- Fine granular cytoplasm, usually with one or more enlarged nucleoli

Differential Diagnosis

- Superficial spreading malignant melanoma
- Vulvar intraepithelial neoplasia

Bartholin Gland Tumors

- Adenocarcinoma
- Squamous cell carcinoma
- Adenoid cystic carcinoma
- Transitional cell carcinoma
- Adenosquamous carcinoma

Malignant Mesenchymal Tumors

Embryonal Rhabdomyosarcoma (Sarcoma Botryoides)

Clinical

- Almost always in infants and children; rare in vulva and vagina beyond 10 years of age

- Usually arises in the perineal or labial area (classified as vaginal in origin if the labia minora is involved)

Macroscopic

- Polypoid usually solid
- May simulate a bunch of grapes (more common in the vagina)

Microscopic

- Thin squamous epithelial surface overlying the edematous or myxomatous tumor
- "Cambium zone": dense cellular subepithelial layer
- Embryonal rhabdomyoblasts: round to spindled-shaped cells, eosinophilic cytoplasm, and pleomorphic nuclei
- Rhabdomyoblasts with cross-striations seen in <15% of all cases
- Cytoplasm of tumor cells usually reactive for myoglobin, desmin, and muscle-specific actin

Aggressive Angiomyxoma

Clinical

- Usually presents in second to third decade
- Locally aggressive, but not a true sarcoma
- Local recurrences in ~50% of all cases

Macroscopic

- Soft myxoid appearance

Microscopic

- Spindled fibroblasts and myofibroblasts without significant atypia or mitotic activity
- Myxoid stroma with prominent variably sized blood vessels

Differential Diagnosis

- Intramuscular myxoma
- Myxoid MFH
- Angiomyofibroblastoma

Leiomyosarcoma

Clinical

- Rare, but most common sarcoma of the vulva
- Tends to recur locally

Macroscopic

- Often ≥5 cm when diagnosed

Microscopic

- Interlacing bundles of spindle cells with pleomorphic, hyperchromatic nuclei
- Typically, high mitotic rate; often >10/10 high-power fields
- Myxoid and epithelioid variants described

Other Malignant Mesenchymal Tumors

- Dermatofibrosarcoma protuberans
- Malignant fibrous histiocytoma
- Epithelioid sarcoma
- Malignant rhabdoid tumor
- Malignant schwannoma
- Angiosarcoma
- Hemangiopericytoma
- Liposarcoma
- Alveolar soft part sarcoma
- Granular cell tumor

Miscellaneous Malignant Tumors

Malignant Melanoma

Clinical

- Mostly in postmenopausal women; ~1/3 occur in women <50 years of age
- Account for ~9% of all malignant tumors of the vulva

Macroscopic

- Slightly elevated or nodular mass
- Pigmented or nonpigmented

Microscopic

- Three distinct histopathologic types:
  - Superficial spreading: radial growth involving four or more adjacent rete ridges
  - Nodular: vertical growth
  - Acral lentiginous: vertical and radial growth
- Cells may be epithelioid, dendritic (nevoid), or spindled; pure or mixed populations within an individual tumor

Differential Diagnosis

- Paget's disease
- Vulvar intraepithelial neoplasia
- Dysplastic nevus
- Squamous cell carcinoma with spindle cells or giant cells

Other Miscellaneous Malignant Tumors

- Malignant lymphoma
- Yolk sac tumor
- Merkel cell tumor
- Metastatic tumors:
  - Primary site usually in genital tract
  - 50% originate within the cervix

VAGINA

Benign Lesions of the Vagina

Infection (Table 19-3)

Vaginitis

- Most common reason for gynecologic visits
- May be caused by virus, bacteria, fungus, or parasites (see below)

Bacterial Vaginosis

- Due to an overgrowth of multiple bacteria (*Gardnerella*, variety of anaerobes) rather than a single organism
- Inflammation is usually absent
- Diagnosis made if three of four criteria are present:
  - Homogenous, thin, malodorous discharge
  - Vaginal pH >4.5
  - "Clue cells": vaginal epithelial cells with numerous attached bacteria
  - Fishy odor when vaginal secretions are alkalinized

Malakoplakia

Clinical

- Closely related to xanthogranulomatous pseudotumor
- Due to infection by Gram negative or positive bacilli, usually *E. coli*

Macroscopic

- Yellow, polypoid nodules on vaginal mucosa

Microscopic

- Same histologic findings as in other sites
- Collections of histiocytes with abundant pale to granular foamy cytoplasm
- Plasma cells and lymphocytes interspersed
- Variable number of intracellular and extracellular laminated basophilic spheres (Michaelis-Gutman bodies)

Toxic Shock Syndrome

Clinical

- Systemic disease associated with localized infection with strains of staphylococcus
- Related to the use of tampons during menses, but ~10% of reported cases are not menstrual-related
- 4% mortality rate

Macroscopic

- Focal ulceration and/or discoloration of vaginal and cervical mucosa

Microscopic

- Extensive epithelial desquamation
- Vasculitis, perivascular inflammation, and platelet thrombi

Atrophic Vaginitis

Clinical

- Thinned epithelium due to decreased estrogen in postmenopausal women
- Little resistance to altered flora, including streptococci, staphylococci, and E. coli
- Minor trauma may facilitate infection

Macroscopic

- Pale mucosa with petechiae
- Loss of rugal folds

Table 19-3. Selected Sexually Transmitted Pathogens

Bacteria	Fungi
N. gonorrhoeae	*C. albicans*
C. trachomatis	Viruses
M. hominis	Herpes simplex virus
U. urealyticum	Hepatitis B virus
T. pallidum	Cytomegalovirus
G. vaginalis	Human papillomavirus
H. ducreyi	*Molluscum contagiosum* virus
Shigella	Protozoa
Group B Streptococcus	*T. vaginalis*
	E. histolytica

Microscopic

- Reduction or loss of superficial and intermediate squamous epithelial layers
- May see small ulcers with acute inflammation and granulation tissue
- Dense submucoasl infiltration by lymphocytes and plasma cells

Differential Diagnosis

- High-grade squamous intraepithelial lesion

Tumor-Like Lesions

Postoperative Spindle Cell Nodule

Clinical

- Typically arises 1–3 months following surgery in the area
- No local recurrences even if excision is incomplete

Macroscopic

- Poorly defined, polypoid, subepithelial

Microscopic

- Intersecting fascicles of plump spindle cells
- Mitoses variable, but usually numerous (1–25/10 high-power fields)
- Delicate network of small blood vessels
- Overlying epithelium often ulcerated

Differential Diagnosis

- Leiomyosarcoma (and other sarcomas)
  - Nuclear pleomorphism, abnormal mitoses

Other Tumor-Like Lesions

- Endometriosis
- Vault granulation tissue:
  - Often after hysterectomy
- Prolapsed fallopian tube:
  - Often after hysterectomy
- Decidual reaction

Cystic Lesions

Keratinous Cyst (Squamous Epithelial Inclusion Cyst)

- Most common vaginal cystic lesion
- Lined by stratified squamous epithelium

Müllerian Cyst

- Lined by columnar, mucin-secreting, endocervical-type epithelium
- Ciliated, tubal-type epithelium and squamous metaplasia may also be seen

Mesonephric (Gartner's Duct) Cyst

- Located on the anterolateral wall or lateral wall
- Lined by nonmucin-secreting cuboidal epithelium
- Cilia absent
- Squamous metaplasia very uncommon

Urothelial Cyst

- Lined by transitional epithelium
- Sometimes admixed with stratified cuboidal or columnar epithelium
- Cilia absent

Benign Squamous Lesions

Squamous Papilloma

Clinical

- More often multiple than single
- Often clustered around hymenal ring
- Not related to HPV infection

Macroscopic

- Similar to condyloma
- Polypoid; several millimeters to 2 cm

Microscopic

- Single papillary frond with central fibrovascular core
- Lack koilocytosis

Differential Diagnosis

- Condyloma acuminatum-koilocytosis, complex branching papillae

Condyloma Acuminatum

- See Benign Squamous Lesions of the Vulva and Benign Squamous Lesions of the Cervix

Müllerian Papilloma

- Arises in the vagina and cervix of infants and young girls
- Benign papillary tumor composed of complex, branching fibrovascular cores
- Cores covered by bland cuboidal or mucinous epithelium; occasionally with hobnail-like cells
- Epithelium may form solid masses and/or glandular lumina

Benign Glandular Lesions

Adenosis

Clinical

- Presence of glandular epithelium (or its secretory products) in the vagina
- Related to prenatal exposure to diethystilbestrol (DES); occurs in $^1/_3$ of exposed offspring

- ♦ May arise in women unexposed to DES
- ♦ Spontaneously regresses in most cases

Macroscopic

- ♦ Multiple cysts (0.5–4.0 cm) or diffusely red granular mucosa

Microscopic

- ♦ Replacement or covering of surface squamous epithelium by glandular epithelium or glands in lamina propria
- ♦ Glands lined by mucinous (endocervial type) or ciliated (tuboendometrial type) epithelium
- ♦ Metaplastic squamous epithelium is usually present

Atypical Adenosis

- ♦ Often adjacent to clear cell adenocarcinoma, but no definitive proof that atypical adenosis is premalignant
- ♦ Occurs in tuboendometrial-type epithelium
- ♦ More complex glands lined by enlarged, pleomorphic, hyperchromatic cells with prominent nucleoli

Benign Mesenchymal Lesions

Leiomyoma

- ♦ Most common mesenchymal tumor in the vagina of adult women
- ♦ Usually solitary and submucosal
- ♦ Similar gross and microscopic appearance as those in the uterus

Other Benign Mesenchymal Lesions

- ♦ Rhabdomyoma
- ♦ Granular cell tumor
- ♦ Neurofibroma
- ♦ Paraganglioma
- ♦ Glomus tumor
- ♦ Hemangioma

Benign Miscellaneous Lesions

Fibroepithelial Polyp (Mesodermal Stromal Polyp, Psuedosarcoma Botryoides)

Clinical

- ♦ Almost always in adults; mean age at diagnosis = 40 yr
- ♦ ~25% of cases involve pregnant women
- ♦ Pathogenesis unclear

Macroscopic

- ♦ Usually solitary; from 0.5–4.0 cm in size
- ♦ Polypoid or pedunculated
- ♦ Gray-white, soft, rubbery

Table 19-4. FIGO Staging of Vaginal Carcinoma (1978)

Stage 0	Intraepithelial
Stage I	Limited to vaginal wall (T1)
Stage II	Extends to subvaginal tissue, but not to pelvic side wall (T2)
Stage III	Extends to pelvic side wall (T3)
Stage IV	Extends beyond the true pelvis or involves mucosa of bladder or rectum (T4)
Stage IV-A	Adjacent organs involved
Stage IV-B	Distant sites involved

Microscopic

- ♦ Edematous fibrovascular stroma covered by stratified squamous epithelium
- ♦ Stroma contains numerous dilated blood vessels and scattered enlarged fibroblasts
- ♦ ~50% of the cases contain atypical fibroblasts with large, hyperchromatic, pleomorphic, often multiple, nuclei
- ♦ Lack cambium layer and rhabdomyoblasts

Differential Diagnosis

- ♦ Embryonal rhabdomyosarcoma

Other Miscellaneous Benign Lesions

- ♦ Benign mixed tumor
- ♦ Melanocytic nevus
- ♦ Mature cystic teratoma
- ♦ Villous adenoma

Premalignant and Malignant Lesions of the Vagina (Table 19-4)

Vaginal Intraepithelial Neoplasia (VAIN, Dysplasia, Carcinoma In Situ*)*

Clinical

- ♦ Relatively rare
- ♦ ~5% of VAIN cases progress to invasive vaginal carcinoma
- ♦ ~75% have preceding or coexisting squamous carcinoma of the cervix or vulva
- ♦ Risk factors:
  - – Immunosuppression
  - – HPV infection or squamous neoplasia elsewhere in the genital tract
  - – History of pelvic irradiation

Macroscopic

- Usually no grossly identifiable vaginal lesion
- Occasionally raised, roughened, pink or white mucosa

Microscopic

- Features analogous to those of squamous intra-epithelial lesion (SIL), with identical grading criteria (see Premalignant Lesions of the Cervix)
- VAIN 1 (mild dysplasia) designated as low-grade squamous intraepithelial lesion (LSIL)
- VAIN 2 or 3 (moderate or severe dysplasia or carcinoma in situ) designated as high-grade squamous intraepithelial lesion (HSIL)

Differential Diagnosis

- Atrophy
- Immature squamous metaplasia in a woman with adenosis
- Radiation change
- Reactive squamous atypia

Malignant Squamous Tumors

Squamous Cell Carcinoma

- Represents ~90% of primary vaginal malignancies, but much less common than primary squamous cell carcinoma of the cervix or vulva
- Must not involve cervix or vulva to be classified as primary tumor of the vagina
- Same risk factors as for VAIN
- Single most important indicator of outcome is clinical stage

Macroscopic

- Commonly located in the upper (proximal) $^1/_3$ of the vagina
- Ulcerative in 50% of cases; exophytic in 30%

Microscopic

- Similar histology as squamous cell carcinoma arising in the cervix
- Majority are nonkeratinizing and moderately differentiated
- No correlation found between grade and prognosis
- Microinvasive squamous carcinoma:
  - Carcinoma invading stroma to a depth of 3 mm or less
  - No vascular invasion
  - Not a distinct entity, but these have a low likelihood of nodal metastases

Verrucous Carcinoma

Clinical

- Well-differentiated variant of squamous cell carcinoma
- Invades and recurs locally, but rarely metastasizes

Macroscopic

- Exophytic, fungating masses
- Coarsely granular surface

Microscopic

- Squamous cells with bland cytologic features
- Arranged in broad, bulbous squamous masses
- Pushing border at tumor-stroma interface
- No koilocytosis or fibrovascular cores

Differential Diagnosis

- Pseudoepitheliomatous hyperplasia
- Condyloma acuminatum
- Warty (condylomatous) carcinoma:
  - Papillary mass with fibrovascular cores
  - Koilocytosis, nuclear pleomorphism
  - Infiltrative pattern at stromal interface

Malignant Glandular Tumors

Clear Cell Carcinoma

Clinical

- Peak age of 19–20 years; rare before 12 years and after 30 years of age
- History of prenatal exposure to DES and related nonsteroidal estrogens, but risk of carcinoma in exposed population (up to 24 years of age) is low at 0.014– 0.14%
- ~60% confined to vagina (others in cervix or vagina and cervix)

Macroscopic

- Majority are polypoid and nodular; others are flat or ulcerated

Microscopic

- Most frequent pattern is tubulocystic: tubules and cysts lined by hobnail, flat, or clear cells
- Other patterns include solid and papillary
- Atypical adenosis is identified adjacent to the tumor in >90% of cases

Differential Diagnosis

- Microglandular hyperplasia (see Benign Glandular Lesions of the Cervix):
  - Benign; usually develops in cervix, but can arise in foci of vaginal adenosis
  - Associated with the use of oral contraceptives and occasionally with pregnancy
  - Usually, history of prenatal DES exposure

Other Malignant Glandular Tumors

- Mucinous adenocarcinoma
- Endometrioid and endocervical adenocarcinomas

- Mesonephric carcinoma
- Adenoid cystic carcinoma
- Adenosquamous carcinoma

Malignant Mesenchymal Tumors

Embryonal Rhabdomyosarcoma (Sarcoma Botryoides)

Clinical

- Rare, but most common vaginal sarcoma
- Almost exclusively in infants and children; mean age at diagnosis = 2 years

Macroscopic

- Multiple polypoid masses, 3–4 cm each
- Gray, myxoid tissue on cut section

Microscopic

- Tumor covered by a thin layer of squamous epithelium with dense, subepithelial, cambium layer of tumor cells
- Small round or spindled tumor cells in myxoid stroma beneath a cambium layer
- Rhabdomyoblasts (racquet-shaped or strap cells with prominent eosinophilic cytoplasm) found in stroma and cambium layer
- Cross-striations may not be identified; not necessary for diagnosis
- Tumor cells (cytoplasm) usually immunoreactive for myoglobin, desmin, and muscle-specific actin

Differential Diagnosis

- Fibroepithelial polyp
- Rhabdomyoma
- Mullerian papilloma

Other Malignant Mesenchymal Tumors

- Leiomyosarcoma
- Endometrial stromal sarcoma
- Malignant schwannoma
- Fibrosarcoma
- Malignant fibrous histiocytoma
- Angiosarcoma
- Alveolar soft part sarcoma

Malignant Mixed Epithelial and Mesenchymal Tumors

- Malignant mixed tumor resembling synovial sarcoma
- Adenosquamous carcinoma
- Malignant mixed müllerian tumors

Miscellaneous Malignant Tumors

Malignant Melanoma

Clinical

- Represents <5% of all malignant tumors of the vagina and <1% of all melanomas

Macroscopic

- Nodular, polypoid, or fungating
- Black or blue-gray, soft masses
- Often ulcerated

Microscopic

- No distinctive histologic features in the vagina
- Usually pigmented, but may be amelanotic

Differential Diagnosis

- Squamous cell carcinoma
- Malignant lymphoma

Metastatic (Secondary) Tumors

- Much more common than primary vaginal tumors
- Direct extension or lymphatic or hematogenous spread
- Most common metastatic carcinomas are from the cervix, endometrium, and vulva

Other Miscellaneous Malignant Tumors

- Yolk sac tumor (see chapter 26)
- Malignant lymphoma (see chapter 7)

UTERUS—CERVIX

Benign Lesions of the Cervix

Non-Infectious Cervicitis

- Usually chemical irritation or mechanical trauma
- Nonspecific inflammatory response

Acute Cervicitis

- Swollen, erythematous, friable cervix
- May see purulent endocervical discharge
- Stromal edema, vascular congestion
- Neutrophilic infiltration of stroma and epithelium

Chronic Cervicitis

- Extremely common in adult females
- Preferentially affects the squamocolumnar junction and endocervix

- Hyperemic cervical mucosa
- May contain erosions or ulcerations
- Significant chronic inflammatory reaction; consisting predominantly of lymphocytes, plasma cells, and histiocytes
- Granulation tissue and stromal fibrosis (variable amounts)

Follicular Cervicitis

- Seen in non-infectious and infectious cervicitis (*C. trachomatis* is major cause)
- Lymphoid follicles with germinal centers beneath the cervical epithelium

Infectious Cervicitis

- Central role in pathogenesis of sexually transmitted diseases
- Initial event in pelvic inflammatory disease
- Associated with spontaneous abortion, stillbirth, premature delivery, chorioamnionitis, and neonatal septicemia and pneumonia
- Bacterial and chlamydial infections are the most common causes of infectious cervicitis
- Organisms causing ectocervicitis or endocervicitis tend to differ, but some agents may cause both
- Endocervicitis (mucopurulent cervicitis): yellow endocervical discharge with many neutrophils, erythema, and friable cervical ectropion
- Ectocervicitis: either ulcerations and necrosis or diffuse punctate erythema

Chlamydial Infection

Clinical

- Caused by *Chlamydia trachomatis*
- Most common cause of infectious cervicitis (along with bacteria)
- Frequently find concurrent bacterial infection, especially *Neisseria gonorrhea*
- $^2/_3$ of all cases are asymptomatic
- Associated endometritis in 40%; associated salpingitis in 11% of all cases
- Usually diagnosed by culture, direct immunofluorescence staining of smears, or enzyme-linked immunosorbent assay (ELISA)

Macroscopic

- Yellow-green endocervical exudate (if symptomatic)
- Erythema, friable cervical ectropion, atypical transformation zone

Microscopic

- Epithelium and stroma infiltrated by acute and chronic inflammatory cells; may obscure epithelial-stromal junction
- Atypia of endocervical and metaplastic squamous cells
- May see intracytoplasmic inclusions (not specific)
- Follicular cervicitis often present

Actinomyces Infection

Clinical

- Caused by *Actinomyces israeli*
- Due to clinical abortion, surgical instrumentation, intrauterine contraceptive devices, or direct extension from parametrial or appendiceal lesions or from the anus

Macroscopic

- Yellow granular lesions in the center of large abscesses ("sulfur granules")

Microscopic

- Organism composed of branching, Gram + filaments with peripheral palisading "clubs"
- Occasional granuloma formation
- May have significant fibrosis and scarring with chronic actinomyces infections

Tuberculosis

Clinical

- Almost always secondary to tuberculous salpingitis and endometritis
- Prevalence of 5% in the United States (much higher in other areas)

Macroscopic

- Unremarkable or erythematous
- May simulate invasive carcinoma

Microscopic

- Multiple granulomas (tubercles) with central caseous necrosis, epithelial histiocytes, and multinucleated giant cells
- Noncaseating granulomas may be present
- Lymphoplasmacytic infiltrate around the periphery of the granuloma
- Diagnosis requires the demonstration of the mycobacterium organisms

Differential Diagnosis

- Foreign body giant cell granulomas (due to sutures, cotton, etc.)
- Sarcoidosis
- Lymphogranuloma venereum
- Schistosomiasis

Other Granulomatous Infections

- Syphilis, lymphogranuloma venereum, granuloma inguinale, and chancroid
- Clinically, all may resemble carcinoma

Herpes Virus Infection

Clinical

- Caused chiefly by herpes simplex virus, type 2 (HSV-2)
- Up to 70% of HSV-2 infections are asymptomatic
- Cervix is involved in 90% of primary infections, but only 12–20% of recurrent infections
- May result in spontaneous abortion, fetal morbidity, or mortality
- Diagnosed by culture, Pap smear, or serology

Macroscopic

- Multiple painful vesicles evolving into shallow ulcerations
- May involve vulva, perineum, vagina, and/or cervix

Microscopic

- Papanicolaou smear shows large multinucleated cells with ground glass intranuclear inclusions
- Cervical biopsy during vesicular phase may show intraepidermal vesicles filled with serum, degenerated epithelial cells, and multinucleated giant cells

Fungal Infection

- Majority caused by *Candida albicans*
- Usually occurs as part of a generalized lower genital tract infection with white vaginal discharge and vulvar pruritis
- Fungal overgrowth promoted by alkanization of vaginal pH, antibiotic therapy, and poorly controlled diabetes
- Aspergillus infection prevalent only in immunosuppressed host

Trichomonal Infection

- Cervical infestation by *Trichomonas vaginalis*
- Associated most often with concurrent trichomonal vaginitis
- Foamy, yellow-green vaginal discharge
- Acute infection may produce intense inflammatory response with prominent reparative atypia in squamous and endocervical cells
- Diagnosis is made by wet mount or identification of the organism on Pap smear

Parasitic Infection

- Schistosomiasis (bilharziasis) of the cervix is very common in Egypt, South America, Puerto Rico, and Asia
- Caused by *Schistosoma mansoni*
- Associated with sterility and urinary schistosomiasis
- Noncaseating granulomas with ova surrounded by multinucleated giant cells
- Ova often calcified
- May be associated with extensive pseudoepitheliomatous hyperplasia of cervical squamous epithelium

Human Papillomavisrus

Clinical

- > 60 HPV types have been characterized, with > 20 types capable of infecting the lower anogenital tract
- Resulting infections produce a variety of lesions
- Linked to a variety of cervical diseases, ranging from condyloma acunimatum to invasive squamous cell carcinoma and its precursors
- Most prevalent anogenital HPVs have been divided into three "oncogenic risk" groups::
  - Low risk: 6,11, 42–44; frequently associated with condyloma acuminatum, occasionally associated with LSIL, rarely associated with HSIL
  - Intermediate risk: 31,33,35,51,52; frequently associated with all grades of SIL, but infrequently with invasive squamous cell carcinoma
  - High risk: 16,18,45,56; most frequently associated with invasive squamous cell carcinoma of the anogenital tract
- "Gold standard" for HPV identification is Southern blot hybridization

Microscopic

- Morphological hallmark of HPV infection is koilocytosis:
  - Koilocyte = superficial or intermediate mature squamous cell with sharply demarcated perinuclear vacuolization and enlarged nucleus with wrinkled nuclear membrane; may be binucleated or multinucleated

Condyloma Acuminatum

Clinical

- Benign papillary neoplasm caused by HPV
- HPV types 6 and 11 are found in 70–90% of all cases
- Usually, spontaneously regress, with good response to conservative therapy
- Recurrences are unpredictable; may be persistent

Macroscopic

- Vast majority are exophytic
- Appear white and display extensive vascular loops after application of 3–5% acetic acid

Microscopic

- Arborizing fibrovascular cores covered by acanthotic squamous epithelium
- Marked papillomatosis
- Parakeratosis and hyperkeratosis

- Koilocytosis may be focal
- Usually mild cytologic atypia, occasionally may be marked

Tumor-Like Lesions

Mesodermal Stromal Polyp (Pseudosarcoma Botryoides)

- Much less common in the cervix than in the vagina (see Miscellaneous Benign Lesions of the Vagina)
- Arise in the ectocervix of reproductive-aged women, especially pregnant women
- Benign exophytic lesion composed of edematous stroma covered by squamous epithelium
- Small, bland, spindle-shaped cells scattered with the stroma
- Occasionally large, multinucleated, hyperchromatic fibroblasts within the stroma (resemble sarcoma botryoides)
- Cambium layer and rhabdomyoblast are absent

Microglandular Hyperplasia

Clinical

- Benign proliferation of endocervical glands
- Often incidental finding on cervical biopsy, cone biopsy, or hysterectomy specimen
- Most common in women of reproductive age; usually with history of oral contraceptive use or in pregnant or postpartum patients

Macroscopic

- Polypoid, 1–2 cm (if visible)
- Single or multiple

Microscopic

- Densely crowded small glands lined by single layer of cuboidal cells with variable amounts of mucin
- Uniformly small, round nuclei
- Stroma commonly edematous and infiltrated by acute and chronic inflammatory cells
- Squamous metaplasia often present
- Mucinous, solid, or hyalinized patterns sometimes seen, but associated with more typical areas

Differential Diagnosis

- Clear cell carcinoma:
  - Papillary, more open glands and tubules, often with hobnail cells
  - Increased mitotic figures

Mesonephric Remnants

Clinical

- Seen in up to 20% of cervices (sampling dependent)
- Asymptomatic, incidental findings
- Cannot be seen grossly
- Differentiation between remnant and hyperplasia not clinically important

Microscopic

- Most commonly seen deep in the lateral wall beneath junction or ectocervix and endocervix
- Small tubules or cysts often arrange in clusters around a main branching duct (lobular pattern)
- Tubules lined by nonciliated, low columnar, or cuboidal epithelium
- Tubules surrounded by prominent basement membrane
- Tubular lumina filled with pink, homogenous, PAS + secretions
- May become hyperplastic, resulting in a florid tubuloglandular proliferation that may extensively involve the cervix

Differential Diagnosis

- Minimal deviation adenocarcinoma of the endocervix
- Mesonephric adenocarcinoma
- Cervical adenocarcinoma

Endometriosis

Clinical

- Lesions composed of ectopic endometrial glands and stroma
- Mechanism unknown, but frequently develop after cervical trauma

Macroscopic

- Single or multiple
- Usually located on portio or in endocervical canal
- Small, blue or red nodule, several millimeters in diameters

Microscopic

- Glands and stroma almost always resemble proliferative endometrium
- Hemosiderin-laden macrophages
- Decidua may be seen in pregnancy or with progestin therapy

Tubal Metaplasia

Clinical

- Found in up to 31% of all cases

Microscopic

- Architecturally normal endocervical glands lined by cells resembling those of the fallopian tube mucosa
- Ciliated or clear cells, nonciliated cells, and intercalary (peg) cells may all be seen

- Usually involves a few glands near the squamocolumnar junction, but may be quite extensive
- Absent or rare mitotic figures

Differential Diagnosis

- Endocervical gland carcinoma

Arias-Stella Reaction

Clinical

- Typically occur in the endometrium, but can develop in both endocervical glands and ectopic endometrial glands within the cervix
- Occurs in association with pregnancy, including ectopic pregnancies and gestational trophoblastic disease

Microscopic

- Identical to endometrial reaction
- Glands lined by vacuolated epithelial cells with hypersecretory features
- Enlarged, pleomorphic, hyperchromatic nuclei; often project into the glandular lumen in a hobnail pattern
- Mitotic activity rare

Differential Diagnosis

- Clear cell carcinoma:
  - Mass lesion with stromal invasion and increased mitoses
  - Classic tubular and papillary areas
- Adenocarcinoma in situ:
  - More uniform nuclei, less cytoplasmic vacuolization, and increased mitoses

Postoperative Spindle Cell Nodule

- Clinically and histologically identical to those found more commonly in the vagina
- May develop in the cervix after trauma (i.e., biopsy or curettage)
- Loose, actively proliferating spindle cells with interlacing bundles often separated by edema
- Variable size of nuclei, may be hyperchromatic
- Mitotic figures common
- Often have prominent neutrophils and erythrocytes

Tunnel Clusters

Clinical

- Benign aggregates of dilated endocervical glands
- Fairly common; more prevalent in pregnant women and with increasing age
- Asymptomatic, incidental findings

Microscopic

- Well-demarcated nodular aggregate of closely packed, uniform, round, open glands
- Glands lined by a single layer of flat to cuboidal mucinous cells
- Glands filled with a concentrated mucous fluid
- Lack nuclear atypia and mitotic activity
- Superficially located, close to the cervical surface epithelium

Differential Diagnosis

- Minimal deviation adenocarcinoma of the cervix:
  - Nuclear atypia, increased mitotic activity, and deep stromal invasion

Lymphoma-Like Lesion (Pseudolymphoma)

- Rare
- Markedly inflammatory lesions, extensive enough to be confused with a lymphoproliferative lesion
- Composed of a superficial band of large lymphoid cells admixed with mature lymphocytes, plasma cells, and neutrophils
- Rarely infiltrate deeper than 3 mm
- Germinal centers and macrophages commonly seen
- Polyclonal staining pattern with immunohistochemistry

Nabothian Cyst

Clinical

- Most common cervical cyst
- Develop within the transformation zone due to obstruction from squamous metaplasia overlying endocervical glands

Macroscopic

- Usually superficial
- Yellow or white cysts; frequently multiple
- Measure up to 1.5 cm in diameter

Microscopic

- Cysts lined by a flattened, single layer of mucin-producing (endocervical) epithelium

Other Tumor-Like Lesions

- Decidual nodule (pseudopolyp)
- Placental-site tropoblasic nodule
- Amputated (traumatic) neuroma
- Glial polyp

Benign Squamous Lesions

Squamous Papilloma (Fibroepithelial Polyp)

Clinical

- Benign papillary tumor found more commonly on vulva or vagina

Macroscopic

- Usually solitary; 1–2 mm to 2 cm in diameter
- Found on ectocervix or squamocolumnar junction

Microscopic

- Central fibrovascular stalk covered by mature squamous epithelium
- Koilocytes absent

Differential Diagnosis

- Condyloma acuminatum: koilocytosis, complex branching papillae

Squamous Metaplasia

Clinical

- Replacement of endocervical epithelium by undifferentiated subcolumnar reserve cells that differentiate into squamous epithelium
- Most active during late fetal life, adolescence, and pregnancy
- Lower (acid) pH in the vagina thought to be the initial stimulus for metaplasia

Macroscopic

- Smooth, slightly pink epithelium that appears white after application of 3–5% acetic acid

Microscopic

- Initially, proliferation of reserve cells immediately beneath the columnar epithelium (immature squamous metaplasia):
  - Cuboidal to low columnar cells, uniform round to oval nuclei, and scant cytoplasm
- Increased eosinophilic cytoplasm as reserve cells mature into squamous epithelial cells
- Metaplastic squamous epithelium usually lacks intracytoplasmic glycogen
- Overlies endocervical glands, eventually replacing the endocervical epithelium on the surface and extending into (endocervical) glandular clefts

Differential Diagnosis

- CIN 1 with koilocytosis: enlarged, atypical, eccentrically placed nuclei

Transitional Metaplasia

Clinical

- Usually seen in association with atrophy
- Usually on ectocervix, but sometimes may fill endocervical glands

Microscopic

- Full thickness involvement by basal and parabasal cells
- Ovoid, often grooved, nuclei
- Palisaded basal layer
- Lacks cytologic atypia and high mitotic rate

Differential Diagnosis

- High-grade CIN: cytologic atypia, increased mitotic rate

Benign Glandular Lesions

Endocervical Polyp

Clinical

- Found most often during the fourth to sixth decades and in multigravidas
- Often asymptomatic, but may be associated with postcoital bleeding or discharge
- Carcinoma arising in polyps is extremely rare (0.2–0.4%)

Macroscopic

- Rounded or elongated, with smooth or lobulated surface
- Most are single; 1–2 mm to 2–3 cm

Microscopic

- Variety of patterns
- Most commonly, endocervical mucosal polyp: tall, columnar, mucinous epithelium covers the surface and lines the crypts; with or without cystic change
- Frequently see squamous metaplasia involving the surface or glands
- Stroma is composed of loose fibrous tissue and is usually infiltrated by chronic inflammation
- Thick-walled blood vessels are present at the base of the polyp

Glandular Atypia

Clinical

- May be associated with inflammation or irradiation

Microscopic

- Glands lined by single layer of epithelial cells with enlarged, pleomorphic, hyperchromatic nuclei, often with prominent nucleoli
- Multinucleation may be present
- Mitotic figures are rare

Differential Diagnosis

- Atypical endocervical hyperplasia and adenocarcinoma in situ: epithelial stratification and increased nuclear atypia and mitotic activity

Benign Mesenchymal Lesions

Leiomyoma

Clinical

- Represents ~8% of all uterine leiomyomas
- Usually asymptomatic, but may produce vaginal bleeding or discharge

Macroscopic

- Usually solitary, producing unilateral enlargement of cervical portio
- Large tumors may protrude below the os and fill the vagina
- Discrete, firm, white nodule
- Whorled appearance on sectioning
- Superficial erosions, edema, and infarction are seen more commonly in the cervix than in the corpus

Microscopic

- Similar histology as those in the myometrium (see Benign Mesenchymal Lesions of the Uterine Corpus): fascicles of smooth muscle cells, uniform spindled cells with tapered or blunt ends
- Increased mitoses in prolapsed or ulcerated tumors

Other Benign Mesenchymal Lesions

- Capillary and cavernous hemangioma
- Benign schwannoma
- Lipoma and lipoleiomyoma
- Paraganglioma

Benign Miscellaneous Lesions

Papillary Adenofibroma

Clinical

- Uncommon in the endocervix; most occur in the endometrium

Macroscopic

- Papillary or sessile; protruding into the endocervical canal
- May exceed 5 cm in diameter
- Usually firm, rubbery, tan-brown
- Spongy or mucoid appearance on sectioning

Microscopic

- Lobulated papillary architecture
- Broad, fibrous, relatively acellular fronds covered by flattened cuboidal epithelium
- Small, uniform stromal cells
- Focal columnar mucinous or squamous differentiation in some
- Absent or low mitotic activity

Differential Diagnosis

- Adenosarcoma: periglandular stromal hypercellularity with atypia

Blue Nevus

Clinical

- At least 50 cases described; age ranges from 22–73 years old
- Usually incidental findings

Macroscopic

- Blue to black, flat lesions
- Usually 2–3 mm, but may be as large as 2.0 cm
- Majority (80%) are single
- Usually found in lower posterior endocervix

Microscopic

- Collections of wavy, dendritic nevus cells located in the stroma just below the endocervical epithelium
- Cells arranged singly and in clusters
- Cytoplasm filled with fine brown melanin pigment
- Macrophages also found in the stroma

Differential Diagnosis

- Melanosis:
  - Benign pigmented melanocytes confined to the basal layer of the epithelium (stroma not involved)
- Malignant melanoma:
  - Junctional activity and stromal infiltration by malignant cells

Premalignant and Malignant Lesions of the Cervix (Table 19-5)

Squamous Intraepithelial Lesions (SIL)

Clinical

- Historically, classified as dysplasia (mild, moderate, and severe) and carcinoma *in situ* or cervical intraepithelial neoplasia (CIN, grades 1–3)
- SIL encompasses the entire morphologic spectrum of preinvasive squamous lesions
- Linked to HPV infection: detected in ~90% of HSIL lesions (usually HPV 16)
- Begins in the transformation zone and replaces adjacent squamous and glandular epithelium
- Natural history of SIL (difficult to study):
  - ~50% of LSIL regress
  - ~10% progress to high-grade lesions
  - ~1% progress to invasive cancer
  - Fewer high-grade lesions regress and more progress to invasive cancer

Macroscopic

- Best seen grossly by colposcopic examination after application of 3–5% acetic acid
- Variety of colposcopic patterns depending on epithelial changes and underlying vasculature
- Occurs twice as often on the anterior lip of the cervix as on the posterior lip; rare laterally

Microscopic

Table 19-5. FIGO Staging of Carcinoma of the Uterine Cervix (1988 Modification)

Stage	*Description*
I	Carcinoma strictly confined to the cervix (extension to the corpus should be disregarded)
*IA	Preclinical carcinomas of the cervix (i.e., those diagnosed only by microscopy)
IA1	Minimal microscopically evident stromal invasion
IA2	Lesions detected microscopically that can be measured; the upper limit of the measurement should not show a depth of invasion of >5 mm taken from the base of the epithelium, either surface or glandular, from which it originates, and a second dimension, the horizontal spread, must not exceed 7 mm; larger lesions should be classified as stage IB
IB	Lesions of greater dimensions than stage IA2 or clinically visible lesion confined to the cervix+
II	Carcinoma that extends beyond the cervix but has not extended to the pelvic wall; the carcinoma involves the vagina but not as far as the lower third
IIA	No obvious parametrial involvement (T2a)
IIB	Obvious parametrial involvement (T2b)
III	Carcinoma that extends to the pelvic wall. On rectal examination, there is no cancer-free space between the tumor and pelvic wall; the tumor involves the lower third of the vagina; all cases with hydronephrosis or nonfunctioning kidney are included unless they are known to be due to other causes
IIIA	No extension to the pelvic wall (T3a)
IIIB	Extension to the pelvic wall and/or hydronephrosis or nonfunctioning kidney (T3b)
IV	Carcinoma that extends beyond the true pelvis or has clinically involved the mucosa of the bladder or rectum (T4)
*T1a1:	Stromal invasion ≤3mm, horizontal spread ≤7mm
T1a2:	Stromal invasion >3mm, ≤5mm, horizontal spread <7mm
+T1b1:	Clinically visible lesion ≤ 4cm in greatest dimension
T1b2:	Clinically visible lesion > 4cm in greatest dimension (1997 TNM Revision)

(1997 Revision, TNM Classification)

- Abnormal cellular proliferation beginning in the basal and parabasal layers; increased immature parabasal cells variably extending into intermediate and superficial layers
- Abnormal maturation with loss of polarity and cellular disorganization
- Degree of maturity inversely related to severity of lesion
- Microscopic grading of SIL:
  - Based on extent of replacement of epithelium by abnormal proliferating parabasal cells, degree of nuclear atypia, and level at which mitotic figures are found
  - Most clinically important distinction is between LSIL and HSIL
- LSIL:
  - Includes condyloma and CIN1
  - Thickened epithelium (acanthosis) and koilocytic atypia in the mid and upper portions of the epithelium
  - Koilocytic atypia:
    - Nuclear atypia with variation in nuclear size and shape, perinuclear cavity, wrinkled nuclear membrane, and binucleate forms
  - Few mitoses, rarely atypical, found in lower half of epithelium
  - Evenly spaced parabasal nuclei
  - Hyperchromatic, but uniform in intensity
  - Variable nuclear size, but uniform contour
- HSIL:
  - Includes CIN2 and CIN3
  - Nuclear atypia in all layers of the epithelium, in at least a portion of the lesion:
    - Lesions with koilocytic atypia or maturation are equivalent to CIN2
    - Lesions without discernible maturation are

equivalent to CIN3
- – Epithelial surface often contains horizontally arranged parakeratotic cells with abnormal nuclei
- – Frequent mitoses, often atypical and often in the upper half of the epithelium
- – Parabasal nuclear crowding and overlapping
- – Hyperchromatic with coarse, uneven intensity
- – Variable nuclear size with variable nuclear contour

Differential Diagnosis

- ♦ Immature metaplasia:
  - – Full epithelial thickness composed of immature parabasal cells
  - – Unlike HSIL, no nuclear pleomorphism and no abnormal mitotic figures
- ♦ Atrophic epithelium:
  - – Basal and parabasal cells with no differentiation, nuclear pleomorphism, atypia, or mitotic activity
- ♦ Normal metaplasia:
  - – Squamous epithelium with prominent glycogen vacuolization, normal maturation and stratification
  - – Unlike LSIL, no atypical or enlarged nuclei
- ♦ Microinvasive carcinoma:
  - – May look similar to HSIL with extensive gland involvement

Malignant Squamous Tumors

Microinvasive Squamous Cell Carcinoma

Clinical

- ♦ Controversial with lack of agreement over diagnostic criteria
- ♦ Most recent modification based on FIGO staging system:
  - – Stage IA1: minute focus of invasion (up to 1mm)
  - – Stage IA2: invasion not exceeding 5mm in depth and 7mm in horizontal dimension
- ♦ Presence of vascular/lymphatic invasion does not influence the stage, but should be indicated in the report

Macroscopic

- ♦ Similar grossly to CIN on colposcopic examination
- ♦ Variety of patterns seen, including abnormal vessels

Microscopic

- ♦ Irregularly shaped epithelial tongues invading underlying stroma
- ♦ The intraepithelial lesion is usually CIN3
- ♦ Invasive cells have increased eosinophilic cytoplasm and may show keratinization
- ♦ May have associated desmoplasia and/or inflammatory infiltrate

Differential Diagnosis

- ♦ CIN3 with gland involvement:
  - – Usually no necrosis or pearl formation within the squamous epithelium (if present, should search for nearby microinvasion)

Invasive Squamous Cell Carcinoma

Clinical

- ♦ Incidence and mortality has decreased dramatically in the United States over the last three decades
- ♦ Increased risk with increased number of sexual partners, decreased age at time of initial sexual intercourse, promiscuity of male partner, and smoking
- ♦ Uncommon before age 30, but $^1/_2$ of patients are <50 years old at diagnosis
- ♦ Cervical biopsy necessary for diagnosis

Macroscopic

- ♦ Either on ectocervix or in endocervical canal
- ♦ Exophytic, infiltrative, or ulcerative

Microscopic

- ♦ Considerable morphologic variation
- ♦ Usually nests of neoplastic squamous epithelium with keratinization or necrosis
- ♦ Nuclei vary from uniform to pleomorphic
- ♦ Increased mitotic figures; atypical mitoses common
- ♦ Subtyped into keratinizing and non-keratinizing: depends on presence or absence of keratin pearls

Differential Diagnosis

- ♦ Squamous metaplasia with extensive gland involvement
- ♦ Marked decidual reaction
- ♦ Clear cell carcinoma

Verrucous Carcinoma

Clinical

- ♦ Type of well-differentiated squamous cell carcinoma that recurs locally but does not metastasize
- ♦ More common on vulva
  - – Associated with HPV 6

Macroscopic

- ♦ Large bulky tumors with warty, fungating appearance
- ♦ Occasionally ulcerated

Microscopic

- ♦ Rounded masses of squamous cells with central keratinization
- ♦ Lacks fibrovascular cores
- ♦ "Pushing" deep margin

- Little to no nuclear atypia; koilocytosis usually not present
- Low mitotic activity

Differential Diagnosis

- Condyloma acuminatum
  - Presence of fibrovascular cores, koilocytosis

Warty (Condylomatous) Carcinoma

- Squamous cell carcinoma with condylomatous appearance grossly and histologically
- May also occur in the vagina and vulva
- Less aggressive behavior than typical well-differentiated squamous cell carcinoma
- Many of the malignant cells have koilocytotic atypia
- Features of squamous cell carcinoma at deep margin

Papillary Squamous (Transitional) Cell Carcinoma

Clinical

- Rare variant of squamous cell carcinoma
- Superficial resemblance to transitional cell carcinoma of the urinary bladder
- Aggressive and capable of metastasizing

Microscopic

- Papillary architecture with papillae covered by several layers of atypical basaloid cells
- Little maturation; abundant mitotic figures
- Hyperchromatic nuclei with scant cytoplasm
- Invasive squamous cell carcinoma evident at the base of the tumor

Differential Diagnosis

- Verrucous carcinoma
- Condyloma acuminatum
- Squamous papilloma with atypia

Lymphoepithelioma-Like Carcinoma

- Composed of nests of undifferentiated cells surrounded by a prominent inflammatory infiltrate
- Sharply circumscribed tumor margin
- Abundant cytoplasm, uniform vesicular nuclei
- Indistinct cell borders forming syncytia
- Inflammatory infiltrate composed of lymphocytes, plasma cells, and eosinophils

Differential Diagnosis

- Glassy cell carcinoma
- Lymphoproliferative disorder

Malignant Glandular Tumors

Adenocarcinoma *In Situ* (AIS)

Clinical

- Comprises up to 25% of adenocarcinoma in the cervix
- Usually asymptomatic and found on abnormal cervical smears
- Patients are usually 1–2 decades younger than those with invasive adenocarcinoma
- CIN or invasive squamous cell carcinoma coexists with AIS in ~2/3 of all cases
- ~90% contain HPV, usually type 16 or 18

Macroscopic

- No distinctive gross appearance
- Often superior to squamocolumnar junction
- Usually multifocal

Microscopic

- Replacement of glandular epithelium by cytologically malignant epithelial cells
- Spreads along surface without invading stroma
- Most common type of AIS is endocervical (mucinous) type:
  - Basal nuclei with nuclear enlargement, pale granular cytoplasm, hyperchromasia, increased mitoses, increased density of cells lining glands, sharply demarcated from uninvolved glands
- Other types include intestinal (goblet cells) and endometrioid (no mucin or goblet cells, marked nuclear stratification)
- Can show widely variable morphologic features

Differential Diagnosis

- Atypical hyperplasia
- Arias-Stella reaction
- Glandular atypia due to inflammation or irradiation
- Microglandular hyperplasia
- Endometriosis
- Tubal metaplasia
- Mesonephric remnants
- Adenocarcinoma with early invasion

Atypical Hyperplasia (Glandular Dysplasia)

- Closely resembles AIS, but nuclei are not cytologically malignant and mitoses are less abundant
- Prominent pseudostratification of hyperchromatic, enlarged cells, but uniform size and shape
- Slight nuclear atypia, but not fully malignant
- Usually no cribiform or papillary patterns

Invasive Adenocarcinoma

Clinical

- Represents up to 25% of primary carcinomas of the cervix
- ~90% of cases contain molecular evidence of HPV (similar to squamous cell carcinoma)
- Mean age of patients at diagnosis is between 47–53 years
- May have vaginal bleeding or watery discharge, but up to $^1/_2$ will be asymptomatic
- At diagnosis, up to 85% will have stage I (limited to the cervix) or stage II (extending into parametrium or upper vagina) disease
- Up to 15% of all cases may be asymptomatic (may still be deeply infiltrative)

Macroscopic

- ~50% of all cases are exophytic, papillary, or polypoid
- May be nodular with ulceration or diffusely enlarged

Microscopic

- Variety of histologic patterns and cell types
- Designation of type based on predominant cell type
- Combination of types is common: designated mixed cell type if second cell type comprises 10% or more of the tumor
- Mucinous adenocarcinoma:
  - Most common type
  - Three subtypes:
    - Endocervical type:
      - Pale granular cytoplasm, basal nuclei resembling normal endocervix
    - Intestinal type:
      - Pseudostratified epithelium, small amounts of mucin; may have goblet cells; cells form glands with papillae or infiltrate throughout the stroms
    - Signet-ring cell type:
      - Rarely occurs in pure form; usually present as minor component of endocervical or intestinal type
- Endometrioid adenocarcinoma:
  - May resemble typical adenocarcinoma of the endometrium with squamous differentiation and lack of intracytoplasmic mucin
- Microscopic grading based on nuclear features and architecture (degree of gland formation)

Differential Diagnosis

- Microglandular hyperplasia
- Mesonephric remnant hyperplasia
- Adenocarcinoma *in situ*
- Metastatic adenocarcinoma to the cervix
- Extension of endometrial adenocarcinoma

Clear Cell Carcinoma

Clinical

- Accounts for ~4% of the cervical adenocarcinoma
- Up to $^2/_3$ of cases have history of in utero exposure to DES or related substances
- In those with DES exposure, median age = 19 years (range = 7–31 years)
- Up to 50% of cases associated with vaginal adenosis
- >85% of cases are stage I or II at diagnosis

Macroscopic

- Varies from a nodular erythematous mass to small punctate ulcerating lesions

Microscopic

- Variety of patterns: papillary, microcystic, solid, tubular
- Cells with clear or eosinophilic cytoplasm
- Hobnail-shaped cells often present: bulbous nuclei with scant cytoplasm; nucleus appears to protrude into the glandular lumens
- Tubules lined by single layer of cells
- Low number of mitotic figures

Differential Diagnosis

- Squamous cell carcinoma with abundant glycogen
- Microglandular hyperplasia
- Arias-Stella reaction
- Mesonephric remnants (hyperplasia)

Minimal Deviation Adenocarcinoma

Clinical

- Very well-differentiated adenocarcinoma, originally termed adenoma malignum
- Rare, comprises 1–3% of cervical adenocarcinoma
- Increased incidence of coexisting ovarian neoplasm (usually mucinous adenocarcinoma or sex cord stromal tumor)
- Usually need deep conization or hysterectomy specimen to adequately evaluate deep margin
- Associated with Peutz-Jeghers syndrome and ovarian sex cord tumors with annular tubules

Macroscopic

- Ulcerative, polypoid, or ill-defined irregularity
- Cervix may appear normal in early lesions
- Occasionally, cervix may be stenotic

Microscopic

- Diagnosis based on:
  - Variably sized and shaped glands with bland cytology

  - Increased mitotic figures
  - Hyperplastic glands at the surface
  - Increased number of glands located deeper than the normal endocervical glands (lower level of normal is >5 mm)
- Minimal amount of desmoplasia usually present

Differential Diagnosis

- Deeply seated nabothian cysts
- Microglandular hyperplasia
- Mesonephric remnants hyperplasia
- Tunnel clusters
- Atypical hyperplasia/adenocarcinoma in situ

Well-Differentiated (Papillary) Villoglandular Adenocarcinoma

Clinical

- Tends to occur in young women, usually <40 years, some <30 years
- Usually superficially invasive, but deep invasion does occur

Macroscopic

- Usually polypoid or broad-based papillary masses
- Others appear as eroded nodular lesions

Microscopic

- Complex branching papillary lesion
- Papillae usually lined by stratified columnar cells (endocervical, endometrial, or intestinal cell type)
- Minimal cytologic atypia
- Desmoplastic or myxoid stroma

Differential Diagnosis

- Other papillary carcinomas (serous, mucinous, clear cell types)
- Hyperplastic reactive glands

Other Malignant Glandular Tumors

- Serous adenocarcinoma:
  - Rare, identical to counterparts in the endometrium and ovary
- Mesonephric adenocarcinoma:
  - Rare, carcinoma arising in mesonephric remnants

Other Malignant Epithelial Tumors

Adenosquamous Carcinoma

Clinical

- Tumor containing malignant squamous and glandular elements
- Accounts for 5–25% of all cervical cancers
- Found in both old and young women; may be associated with pregnancy
- Similar risk factors as those of cervical squamous cell carcinoma (e.g., multiple sexual partners, smoking, etc.)

Macroscopic

- Ulcerated and nodular or polypoid

Microscopic

- Glandular component is usually poorly differentiated, with minimal mucinous differentiation
- Squamous component is also poorly differentiated, with scant keratinization

Differential Diagnosis

- Extension of poorly differentiated endometrial adenocarcinoma with squamous differentiation
- Collision tumor of adenocarcinoma with intraepithelial neoplasia or squamous cell carcinoma

Glassy Cell Carcinoma

Clinical

- Poorly differentiated form of adenosquamous carcinoma
- Accounts for <1% of all cervical carcinomas
- Younger mean age (31–41 years) than patients with cervical adenocarcinoma or squamous cell carcinoma
- Reportedly worse prognosis than adenocarcinoma or squamous carcinoma, but difficult to assess based on the few number of cases
- Similar prognosis as other types of adenosquamous carcinoma of the cervix

Macroscopic

- Commonly bulky, exophytic masses

Microscopic

- Invasive sheets and nests of cells
- Moderate amounts of pale eosinophilic cytoplasm with ground-glass or granular appearance
- Large nuclei with prominent single or multiple nucleoli
- Distinct cell borders
- Cells often separated by delicate fibrovascular septae
- Numerous mitotic figures
- Stromal inflammatory infiltrate with many eosinophils and plasma cells

Differential Diagnosis

- Poorly differentiated nonkeratinizing squamous cell carcinoma

Small Cell Carcinoma

Clinical

- Accounts for 2–5% of all carcinomas of the cervix
- Clinically aggressive neoplasm with early metastases

- Often associated with HPV type 18, but type 16 is also reported
- Several reported paraendocrine (paraneoplastic) syndromes in association with cervical small cell carcinoma

Macroscopic

- Often ulcerative and infiltrative

Microscopic

- Very cellular, with sheets of densely packed small cells
- Scant cytoplasm
- Hyperchromatic, round to oval nuclei with smudged appearance
- Increased mitotic activity
- Necrosis common
- May see areas of glandular or squamous differentiation, but comprises <5% of the tumor

Differential Diagnosis

- Nonkeratinizing squamous cell carcinoma
- Poorly differentiated adenocarcinoma with carcinoid features

Other Malignant Epithelial Tumors

- Adenoid cystic carcinoma
- Adenoid basal carcinoma
- Adenocarcinoma with features of carcinoid tumor (carcinoid tumor)
- Metastasis

Malignant Mesenchymal Tumors

Leiomyosarcoma

Clinical

- ~20 reported cases, but most common primary sarcoma in the cervix
- Usually in perimenopausal women and associated with vaginal bleeding
- Poor prognosis

Macroscopic

- Large, soft, polypoid masses
- May have areas of hemorrhage or necrosis

Microscopic

- Dense, interlacing bundles of smooth muscle cells
- Atypical, large, hyperchromatic nuclei
- Increased mitotic activity
- Same histologic criteria as those found in the uterine corpus (see Malignant Mesenchymal Tumors of the Uterine Corpus):
  - Nuclear atypia
  - Increased mitotic activity
  - Coagulative tumor necrosis

Other Malignant Mesenchymal Tumors

- Endocervical stromal sarcoma
- Sarcoma botryoides (embryonal rhabdomyosarcoma)
- Alveolar soft-part sarcoma
- Osteosarcoma

Malignant Miscellaneous Tumors

Malignant Mixed Mesodermal Tumors

Clinical

- Usually involve the cervix as an extension from the endometrium
- ~25% of uterine MMMT involve the cervix
- Perimenopausal or menopausal women
- May have distant history of prior irradiation for cervical squamous cell carcinoma
- Highly aggressive

Macroscopic

- Large polypoid, partially necrotic mass obscuring the cervix

Microscopic

- Mixture of malignant epithelium and sarcomatous stroma
- Sarcoma usually predominates
- May have squamous differentiation focally
- Up to 50% of cases contain heterologous elements, usually rhabdomyosarcoma, but may see chondrosarcoma, liposarcoma, and mixtures

Malignant Melanoma

Clinical

- Primary melanoma of the vulva and vagina is five times more common than that of the cervix
- Up to 50% of cervical melanomas involve the vagina when diagnosed
- Poor prognosis

Macroscopic

- Ulcerated grayish-blue or black nodules

Microscopic

- Similar histologic features as those in the skin, vulva, and vagina
- Small cell and spindle cell variants seen
- Junctional activity seen in <50% of all cases

Differential Diagnosis

- Metastatic melanoma involving the cervix (usually primary vulva or vagina):

- Lacks junctional activity

Metastatic (Secondary) Tumors

- Up to 50% arise as a result of direct extension from an endometrial primary tumor:
  - Poorly differentiated endometrial adenocarcinoma is most common
- Coexistent endometrial hyperplasia supports endometrial origin; coexistent cervical intraepithelial neoplasia or adenocarcinoma in situ supports cervical origin
- Ovarian carcinoma is the second most common source of metastases
- Metastases from extragenital tumors infrequently involve the cervix (ovary and vagina are more common metastatic sites)
- Breast carcinoma is most common extragenital tumor to metastasize to the cervix
- Majority with metastases to the cervix will have widespread disease

Other Miscellaneous Tumors

- Adenosarcoma
- Lymphoma and leukemia
- Yolk sac tumor (endodermal sinus tumor)

UTERUS—CORPUS

Normal Endometrial Cycle

Proliferative Phase

- Preovulatory phase; variable in length
- Cannot distinguish day-to-day changes, but may divide into early, middle, and late stages:
  - Early (4th–7th day in 28-day cycle): thin regenerating surface epithelium; straight, short, narrow glands with mitoses; compact stroma with some mitotic activity and large nuclei with scant cytoplasm ("naked nuclei")
  - Middle (8th–10th day): columnar surface epithelium; longer, curving glands; variable amount of stromal edema; numerous mitoses in naked nuclei stroma
  - Late (11th–14th day): somewhat undulent surface; tortuous glands showing active growth and pseudostratification of the epithelium; moderately dense, actively growing stroma

Secretory Phase

- Postovulatory phase
- Daily, progressive changes in the endometrium
- Dating assumes a classic 28-day cycle with ovulation occurring on the 14th day and menstruation on the 28th day:
  - 36–48 hours after ovulation: no appreciable microscopic changes
  - 16th day (2nd postovulatory day): subnuclear vacuolation of the gland epithelium becomes prominent
  - 17th day: orderly row of nuclei with homogenous cytoplasm above them and large vacuoles below
  - 18th day: vacuoles decrease in size; nuclei approach base of cell
  - 19th day: few vacuoles remain; intraluminal secretion appears
  - 20th day: intraluminal acidophilic secretory material peaks
  - 21st day: tissue edema appears rather abruptly
  - 22nd day: edema reaches its peak; small, dense stromal cells
  - 23rd day: spiral arterioles become much more prominent
  - 24th day: collections of predecidual cells appear around arterioles
  - 25th day: predecidua begins to appear under the surface epithelium
  - 26th day: predecidual islands coalesce; polymorphonuclear infiltration appears
  - 27th day: predecidua appears as a solid sheet of well-developed cells; polymorphonuclear infiltration becomes prominent; areas of focal necrosis and hemorrhage begin to appear
  - 28th day: necrosis and hemorrhage prominent

Menstrual Phase

- Normally lasts 3–5 days
- Endometrial mucosa rapidly degenerates, with 50% of the menstrual detritus expelled in the first 24 hours of menses
- The upper $^2/_3$ of the endometrium gradually involutes, degenerates, and undergoes necrosis
- Tissue shedding is followed by regeneration
- On cycle days 28–2, the upper $^2/_3$ of the endometrium contains degenerative predecidual cells admixed with epithelial glandular cells and acute and chronic inflammatory cells

Inactive Endometrium

- Endometrium is as thick as early- to midproliferative-phase endometrium, but lacks morphologic features of active proliferation or secretion

- Uniformly dense endometrial stroma with no clear-cut separation between upper functionalis and lower basalis layers
- Glands and stroma resemble midproliferative phase endometrium, but with few glands
- Epithelium at the surface and lining the glands is columnar or cuboidal, with pseudostratified nuclei, occasional ciliated cells, and no mitotic figures

Atrophic Endometrium

- Most common cause of abnormal uterine bleeding in postmenopausal women
- Thinned endometrial mucosa
- Decreased number of glands and decreased stromal volume
- Epithelium lining the glands and surface is low cuboidal
- Stroma may be fibrocellular and collagenized
- Glands may be cystically dilated

Benign Lesions of the Uterine Corpus

Acute and Chronic Endometritis

Clinical

- Usually result from ascending infection through the cervix
- Cervical barrier is compromised during parturition, abortion, menses, and instrumentation
- Clinically significant acute endometritis is usually associated with pregnancy or abortion
  - Acute endometritis is usually caused by *Streptococcus, Staphylococcus, Neisseria gonorrheae,* or *Clostridium welchii*
- Chronic endometritis may be asymptomatic or may present with menometrorrhagia, mucopurulent cervical discharge, or uterine tenderness:
  - Chronic endometritis most commonly caused by *Chlamydia trachomatis* and *Neisseria gonorrheae*
  - Chronic endometritis likely represents an intermediate stage of pelvic inflammatory disease between cervicitis and salpingitis
- Microorganisms identified based on culture

Microscopic

- Acute endometritis diagnosis is based on finding moderate to large numbers of polymorphonuclear cells (PMNs) in nonbleeding endometrium or finding microabscesses (aggregates of PMNs) in the stroma
- Chronic endometritis diagnosis is based on identifying plasma cells that may be scant; variable numbers of lymphocytes, PMNs, and macrophages are also seen
- Two features suggesting chronic endometritis:
  - Spindled stromal cells surrounding glands in a pinwheel arrangement
  - Inability to date secretory endometrium
- The clinical significance of finding a small number of plasma cells in an asymptomatic woman needs further clarification

Specific Types of Chronic Endometritis

Chlamydia Infection

- Increased numbers of plasma cells
- Lymphoid follicles with transformed lymphocytes

Mycoplasma

- Mycoplasma hominis, mycoplasma fermentans, ureaplasma urealyticum

Tuberculosis

- Part of systemic disease
- Second most commonly affected female genital tract site after the fallopian tubes
- Focal or diffuse granulomatous infection

Fungal Infection

- Blastomycosis and coccidiomycosis
- Granulomatous endometritis as part of a disseminated infection

Viral Infection

- Herpes virus, cytomegalovirus, human papillomavirus

Parasitic Infection

- *Schistosoma*, *Enterobius vermicularis*, *Echinococcus granulosus*:
  - Rare in the United States; endemic cause of endometritis in parts of Central America, Africa, the Middle East, and the Far East
- Toxoplasmosis

Miscellaneous Infections

- Xanthogranulomatous (histiocytic) inflammation
- Malakoplakia

Endometrial Metaplasia

- Benign variety of cytoplasmic changes in the endometrial epithelium
- Metaplastic and hyperplasia often coexist, most likely because both may result from hyperestrinism
- Usually focal when not associated with hyperplasia
- Often diffuse when associated with hyperplasia (not necessary to describe metaplastic changes in hyperplasia because it doesn't affect prognosis)
- Mitotic activity minimal or absent
- Many types of metaplasia

Eosinophilic Metaplasia

- Most common type of metaplasia
- Glands lined partially or completely by eosinophilic cells
- May form intraglandular tufts and bridges in hyperplastic lesions

Papillary Syncytial Metaplasia

- Tends to occur at or near the endometrial surface
- Surface epithelium is stratified due to a proliferation of small eosinophilic cells with uniform bland nuclei
- Small glandular pseudolumina (microcystic spaces) may be formed and are often infiltrated by neutrophils
- May have prominent papillae due to cellular stratification, but these papillae lack stromal cores
- Squamous metaplasia often present
- Minimal or absent mitotic activity

Squamous Metaplasia

- Seen in hyperplasia, especially atypical forms, and in endometrial carcinoma, especially low grade
- Rarely present in normal endometrium or in hyperplasia without atypia
- Cytologically bland squamous cells usually with moderate amount of eosinophilic cytoplasm enclosed by a well-defined cell membrane
- Squamous morules may be present, reflecting immature or incomplete squamous differentiation

Ciliated Cell Metaplasia

- Resembles fallopian tube epithelium with ciliated cells and intercalated (peg) cells
- Frequently seen in simple, complex, or atypical hyperplasia

Clear Cell (Hobnail) Metaplasia

- Uncommon
- Polygonal cells with abundant clear cytpolasm containing glycogen and small bland nuclei
- Usually focal and found lining glands or on the endometrial surface
- Usually associated with pregnancy or exogenous hormone use

Secretory Metaplasia

- Columnar cells with sub- or supranuclear vacuoles with clear glycogenated cytoplasm
- Resemble glandular cells of early secretory endometrium
- Seen most often in association with hyperplasia or carcinoma

Mucinous Metaplasia

- Uncommon
- Mucin-containing cells focally or extensively lining glands
- Epithelium resembles that of the endocervix

Differential Diagnosis

- Endometrial hyperplasia:
  - Irregular, complex, glandular outlines
  - Stratified epithelium due to proliferative nature of the process
  - Cytological atypia in the atypical hyperplasias
- Endometrial carcinoma:
  - Stromal invasion with desmoplastic response
  - Confluent glandular pattern

Endometrial Hyperplasia

Clinical

- Heterogeneous group of abnormal endometrial proliferations that develop as a result of estrogenic stimulation
- Usually presents with abnormal bleeding
- Proliferation of glands of irregular size and shape, with an increased gland to stroma ratio compared to proliferative endometrium
- The hyperplastic process may not involve the entire endometrium
- Subdivided:
  - Simple hyperplasia vs complex hyperplasia
  - Atypical hyperplasia vs hyperplasia without atypia
- Atypia based on cytologic features; simple versus complex based on extent of glandular complexity and crowding
- ~23% of atypical hyperplasias progress to carcinoma, whereas <2% of hyperplasias without cytologic atypia progress to carcinoma

Simple Hyperplasia

- Cystically dilated glands with glandular outpouchings
- In some cases, the glands are focally crowded but only minimally dilated
- Pseudostratified columnar cells without cytologic atypia line the glands
- Variable mitotic activity

Complex Hyperplasia

- Crowded glands with little intervening stroma
- Characteristically have back-to-back glands with papillary intraluminal infoldings
- Variable mitotic activity, usually <5 mitotic figures per 10 high-power fields
- No cytologic atypia

Atypical Hyperplasia

- Simple or complex glandular architecture

- Glands lined by cytologically atypical cells (increased nuclear:cytoplasmic ratio, prominent nucleoli, nuclear stratification)
- Confluent glands
- Variable mitotic activity

Differential Diagnosis

- Disordered proliferative phase:
  - Irregularly shaped and enlarged glands focally interspersed among normal proliferative glands
  - The normal glands may be focally crowded
- Hyperplastic endometrial polyp:
  - Often have areas of simple or complex hyperplasia
  - Dense fibrous stroma with thick-walled blood vessels
- Ciliated metaplasia:
  - Often seen in association with endometrial hyperplasia
- Endometrial and stromal breakdown:
  - Due to estrogen withdrawal
  - Proliferative-type glands appear back-to-back because of loss of intervening endometrial stroma
  - Unlike hyperplasia, usually see glandular fragmentation, nuclear dust, and clusters of stromal cells
- Atypical polypoid adenomyoma:
  - Slight architectural complexity
  - Squamous morules and glands surrounded by smooth muscle
- Well-differentiated carcinoma:
  - Three helpful criteria:
    - Desmoplastic stromal response to invasion
    - Confluent glandular pattern uninterrupted by stroma; may be cribiform
    - Extensive papillary pattern

Tumor-Like Lesions

Adenomyosis

Clinical

- Common non-neoplastic condition where endometrial glands and stroma are found within the myometrium
- Commonly associated with abnormal menstrual bleeding, dysmenorrhea, and uterine enlargement, but may be asymptomatic
- Often seen with leiomyomata and endometriosis

Macroscopic

- Usually moderately enlarged uterus
- Myometrium usually thickened, with a trabeculated cut surface
- Lesions may be visible grossly as small, soft, pink or gray-white areas within the myometrium
- Hemorrhagic foci and small cysts may be seen

Microscopic

- Exact criteria for histologic diagnosis are not clear
- Some recommend one medium-power (X100) microscopic field below the endometrial-myometrial junction as the dividing line between adenomyosis and normal penetration of the endometrium into the myometrium
- Some recommend that the distance between the lower border of the endometrium and the adenomyosis be $^1/_2$ of a low-power field (~2.5 mm)
- Usually inactive or proliferative endometrium
- Hemorrhage or hemosiderin pigment usually absent
- Important to differentiate between carcinoma and other tumors that penetrate into tongues of adenomyosis from a malignant tumor with true myometrial invasion

Differential Diagnosis

- Normal uterus
- Low-grade endometrial stromal sarcoma: "gland poor" adenomyosis may mimic endometrial stromal sarcoma

Lymphoma-Like Lesions

Clinical

- Non-neoplastic proliferation of lymphoid tissue within the endometrium
- By definition, no history of malignant lymphoma
- Most likely an unusual form of chronic endometritis

Macroscopic

- Usually no gross mass

Microscopic

- Endometrium infiltrated by lymphoid aggregates with germinal centers and many large mitotically active lymphoid cells
- Admixed with histiocytes and plasma cells
- Chronic endometritis usually in the background
- Myometrial involvement is absent

Differential Diagnosis

- Malignant lymphoma

Arias-Stella Change

Clinical

- Endometrial changes seen in both normal and abnormal (including ectopic) pregnancies
- Also seen in endometriosis, adenomyosis, vaginal adenosis, endocervical epithelium, tubal epithelium, and other müllerian epithelium

Microscopic

- Glands show stratification, hypersecretion, and cytomegaly (enlarged nuclei and cytoplasm)
- Large, hyperchromatic nuclei with smudged appearance
- Paucity of mitotic figures

Differential Diagnosis

- Clear cell adenocarcinoma:
  - More atypical mitotic activity
- Cytomegalovirus infection of the endometrium:
  - More focal, usually individual cells within a gland; cytoplasmic and nuclear inclusions
- Adenocarcinoma *in situ*

Other Tumor-Like Lesions

- Inflammatory pseudotumor
- Postoperative spindle-cell nodule

Benign Miscellaneous Lesions

- Arteriovenous malformation
- Heterologous tissues
  - Bone, cartilage, smooth muscle, glial tissue
- Giant cell arteritis
- Langerhans' cell histiocytosis

Benign Epithelial-Nonepithelial Tumors

Endometrial Polyp

Clinical

- One of the most common pathologic lesions of the uterine corpus
- Benign nodular lesion above the endometrial surface
- Due, in part, to estrogenic stimulation
- Usually seen in perimenopausal or postmenopausal women

Macroscopic

- Sessile or pedunculated; usually solitary
- Located anywhere within the uterine cavity
- Surface usually smooth, tan, and glistening
- May have focal erosions, hemorrhage, and/or necrosis
- Often fragmented in curettage specimens

Microscopic

- Composed of irregularly distributed endometrial glands and stroma
- Glands may be sparse, focally dilated, and irregularly distributed; lined by atrophic, inactive, or proliferative endometrium
- Stroma either focally or diffusely fibrotic; may contain variable amounts of smooth muscle (classified as adenomyoma if stroma is predominantly smooth muscle)
- Variable degrees of stromal atypia
- Characteristic thick-walled blood vessels, usually dilated
- Many variations from classic appearance

Differential Diagnosis

- Polypoid carcinoma or sarcoma
- Atrophic or proliferative endometrium
- Endometrial hyperplasia
- Adenomyoma
- Adenofibroma
- Adenosarcoma

Adenofibroma

Clinical

- Rare
- Seen at any age, but most frequent in postmenopausal women

Macroscopic

- Usually arise from the endometrium, but ~10% originate in the cervix
- Usually broad-based polypoid masses
- Spongy cut surface

Microscopic

- Composed of broad, club-shaped papillae projecting into the endometrial cavity
- Histologically benign mixture of epithelial and stromal elements
- Usually proliferative endometrial epithelium; may be flattened or show metaplastic changes
- Stroma composed of cells resembling fibroblasts or benign endometrial stromal cells or both
- Variable stromal cellularity and sclerosis, but no atypia
- Mitotic activity minimal or absent

Differential Diagnosis

- Endometrial polyp
- Adenosarcoma

Adenomyoma

- Nodular, well-circumscribed aggregate of smooth muscle, endometrial glands, and, commonly, endometrial stroma
- Located within either the myometrium or the endometrium, where it may grow as a polyp

Atypical Polypoid Adenomyoma

Clinical

- Rare variant of the adenomyoma
- Usually occurs in premenopausal women (average age = 39 years)

- Typically presents with abnormal vaginal bleeding

Macroscopic

- Polypoid mass, pedunculated or sessile
- Often located in the lower uterine segment or endocervix

Microscopic

- Admixture of endometrial glands and stroma
- Endometrial glands show architectural atypia with variable sizes and shapes; may show cytological atypia
- Myofibroblastic or smooth muscle stroma
- Squamous metaplasia usually present and often extensive
- Adjacent endometrium may show hyperplasia

Differential Diagnosis

- Endometrial carcinoma invading the myometrium
- Adenofibroma
- Adenosarcoma

Benign Mesenchymal Tumors

Leiomyoma

Clinical

- Benign smooth muscle tumor
- Most common neoplasm of the uterus
- Occurs in ~20–40% of women >30 years of age
- Rare in women <18 years of age
- Pain, dysmenorrhea, menorrhagia, metrorrhagia, or constipation may be seen with larger or multiple leiomyomas

Macroscopic

- Solitary or multiple (multiple in $^{2}/_{3}$ of patients)
- Well-circumscribed
- May be submucosal, intramural, or subserosal:
  - Submucosal tumors may project into the cervix or vagina
- Firm pearly white to tan cut surface with whorled trabecular pattern
- Degenerative changes include hemorrhage, hyalinization, necrosis, calcification, and myxoid or cystic changes

Microscopic

- Composed of smooth muscle cells arranged in anastamosing whorled fascicles
- Nuclei are uniform, elongated, and cigar-shaped, with blunt or tapered ends
- Usually more cellular than the surrounding myometrium
- Mitotic figures infrequent or absent
- Vascular component quite variable

Leiomyoma Variants

Vascular

- Very prominent blood vessel proliferation

Myxoid

- May be difficult to identify as a smooth muscle tumor or to distinguish it from myxoid leiomyosarcoma

Cellular

- Significantly more cellular than surrounding myometrium
- Do not differ clinically or grossly from other leiomyomas

Hemorrhagic Cellular (Apoplectic)

- Type of cellular leiomyoma
- Occurs in young women who are taking oral contraceptives or are pregnant
- Discrete areas of hemorrhage
- Increased mitotic activity adjacent to hemorrhagic areas
- No nuclear atypia

Epithelioid

- Tumors composed of round or polygonal cells
- Often contains epithelioid and classic spindle cell foci
- Includes**:**
  - Leiomyoblastoma: round cells with eosinophilic cytoplasm
  - Clear cell leiomyoma: polygonal cells with abundant clear cytoplasm
  - Plexiform leiomyoma: cords or nests of round cells with scant cytoplasm
- Behavior is difficult to predict; uncertain malignant potential

Atypical

- Other names include bizarre, pleomorphic, or symplastic leiomyoma
- Benign smooth muscle tumor with pleomorphic giant tumor cells
- Huge dark nuclei with smudged chromatin
- By definition, mitotic figures are not numerous (<5 mitotic figures per 10 high-power fields) and are not atypical

Lipoleiomyoma

- Rare, usually occurs in postmenopausal women
- Typical leiomyoma with significant amount of fat

Intravenous Leiomyomatosis

Clinical

- Very rare, benign smooth muscle proliferation extensively involving myometrial veins

- By definition, the vascular invasion extends outside the confines of the leiomyoma
- May extend outside the uterus within venous channels
- May cause significant morbidity and sometimes mortality

Macroscopic

- Complex nodular growth within the myometrium with convoluted, worm-like extensions into the uterine veins in the broad ligament or other pelvic veins
- Varies from soft and spongy to rubbery and firm, pink-white to gray
- May extend into the interior vena cava or even the right side of the heart

Microscopic

- Tumor found within venous channels, but not found in arteries
- May resemble typical uterine leiomyoma, but the histologic appearance is highly variable and may show any of the histologic variants
- Most have areas of hyalinization or fibrosis
- Mitotic figures are minimal or absent

Differential Diagnosis

- Leiomyosarcoma

Diffuse Leiomyomatosis

- Rare, benign smooth muscle lesion
- Numerous, confluent small leiomyomas replacing much of the uterine parenchyma
- Uterus usually massively enlarged
- Minimal atypia, mitotic activity, or intravenous growth

Differential Diagnosis

- Intravenous leiomyomatosis
- Leiomyosarcoma

Adenomatoid Tumor

Clinical

- Tumor of the uterine serosa and myometrium
- Originates from serosal mesothelium
- Occurs in women of reproductive age
- Usually an incidental finding, seen in up to 1% of uteri

Macroscopic

- Gray or tan, with rubbery consistency
- Resembles small leiomyoma, but margins are ill-defined

Microscopic

- Most common pattern is adenoid or tubular with dilated tubules and lined by flattened or cuboidal cells without atypia
- Other patterns include angiomatoid, solid, and cystic
- The stroma surrounding the tubules is rich in collagen, elastic fibers, and smooth muscle
- Mitotic activity is minimal or absent
- No desmoplastic response

Differential Diagnosis

- Lymphangioma
- Adenocarcinoma: primary or secondary

Endometrial Stromal Nodule

Clinical

- Rare benign mesenchymal neoplasm (malignant counterpart called endometrial stromal sarcoma—see Malignant Mesenchymal Tumors)
- Represent <25% of endometrial stromal tumors
- ~75% occur in premenopausal women; average age = 47 years
- Usually presents with abnormal bleeding and menorrhagia, but ~10% are asymptomatic

Macroscopic

- Usually single fleshy, yellow or tan nodule that bulges above the surrounding myometrium
- Size ranges from 0.8–15 cm, average = 4 cm
- May see cystic change, but hemorrhage or necrosis are not commonly seen
- ~5% are multiple
- Cervix is seldom involved

Microscopic

- Composed of cells that are very similar to normal proliferative phase endometrial stromal cells
- Uniform cells with minimal atypia
- Margin is expansile and compresses the adjacent endometrium and myometrium
- Tumor does not infiltrate the myometrium
- Mitotic activity is usually low, but a few may have higher mitotic rates (doesn't affect behavior)

Uterine Neoplasm Resembling an Ovarian Sex Cord Tumor

Clinical

- Heterogenous group of uterine tumors resembling ovarian sex cord tumors
- Most are endometrial stromal tumors with epithelial-like differentiation
- Usually occur in women of reproductive age, but peri- or postmenopausal women can also be affected
- Most have behaved in a benign fashion, but a few have recurred or metastasized

- Behavior likely related to cytologic features, stage, and tumor margin (circumscribed or infiltrating)

Macroscopic

- Usually enlarged uterus with myometrial masses
- Masses usually solid and well-circumscribed, occasionally cystic

Microscopic

- Generally, cells with small regular nuclei and variable cytoplasm forming cords, tubules, trabeculae, and solid nests
- No evidence of endometrial stromal or smooth muscle differentiation
- Mitotic activity rare

Capillary Hemangioma

- Most common uterine vascular tumor
- Dilated vascular spaces may extend through the myometrium and into the broad ligament

Malignant Lesions of the Uterine Corpus

Endometrial Carcinoma (Table 19-6)

- Classification of endometrial carcinoma
  - Endometrioid adenocarcinoma:
    - Villoglandular
    - Secretory
    - Ciliated cell
    - Endometrioid adenocarcinoma with squamous differentiation
  - Serous carcinoma
  - Clear cell carcinoma
  - Mucinous carcinoma
  - Squamous carcinoma
  - Mixed types of carcinoma
  - Undifferentiated carcinoma

Clinical

- Endometrial carcinomas are the most common invasive malignant tumors of the female genital tract
- By far, the most common type is endometrioid adenocarcinoma
- Risk factors include**:**
  - Unopposed estrogen stimulation, including ovarian lesions associated with increased estrogen production
  - Obesity
  - Nulliparity or low parity
  - Hypertension
  - Possible diabetes mellitus
- Most occur in perimenopausal and postmenopausal women:
- Almost always present with abnormal bleeding
- Clinically and epidemiologically, there appears to be two different forms of the disease:
  - Type I (estrogen-related):
    - Unopposed estrogen present
    - Pre- and perimenopausal
    - Hyperplasia present
    - Tends to be low grade, with minimal invasion
    - Endometrioid subtype
    - More stable behavior
  - Type II (non-estrogen-related):
    - Unopposed estrogen absent
    - Postmenopausal
    - Hyperplasia absent
    - Tends to be high grade, with deep myometrial invasion
    - Serous and clear cell subtypes
    - More aggressive in behavior

Macroscopic

- Almost all histologic subtypes look similar grossly
- Usually a single dominant mass and at least partially exophytic
- More frequently seen on posterior than anterior wall
- Surface often focally ulcerated with soft, friable, gray-white tumor mass below

Microscopic (Endometrioid Type)

- Endometrioid is most common type seen
- Comprised of small, round, fairly uniform glands
- The glands of a well-differentiated endometrioid carcinoma are usually lined by uniform cells with single or moderately stratified nuclei
- Occasionally may see increased nuclear atypia
- Mitiotic activity variable, but usually similar to that seen in benign proliferative or hyperplastic en dometrium
- Distinguished from complex or atypical hyperplasia by the presence of glandular confluence, stromal fibrosis, or stromal necrosis
- Subtypes of endometrioid carcinoma:
  - Papillary or villoglandular carcinoma
    - Short, blunt papillae
    - Lack nuclear pleomorphism, cellular stratification, or necrosis
  - Secretory adenocarcinoma:
    - Well-differentiated glands resembling early to midsecretory endometrium
    - May be focal
    - Associated with favorable prognosis

Table 19-6. FIGO Staging of Endometrial Cancer (1988)

Stage		*Description*
Stage IA	G123	Tumor limited to the endometrium (T1a)
Stage IB	G123	Invasion to <1/2 of the myometrium (T1b)
Stage IC	G123	Invasion to >1/2 of the myometrium (T1c)
Stage IIA	G123	Endocervical glandular involvement only (T2a)
Stage IIB	G123	Cervical stromal invasion (T2b)
Stage IIIA	G123	Tumor invades serosa and/or adnexae and/or + peritoneal cytology (T3a)
Stage IIIB	G123	Vaginal involvement (T3b)
Stage IIIC	G123	Metastases to pelvic and/or para-aortic lymph nodes (T3c)
Stage IVA	G123	Tumor invasion of bladder and/or bowel mucosa (T4)
Stage IVB	G123	Distant metastases including intraabdominal and/or inguinal lymph nodes

G1 = no more than 5% of the tumor is composed of solid masses; G2 = 6–50% of the tumor is composed of solid masses; G3 = >50% of the tumor is composed of solid masses.

  - Ciliated carcinoma:
    - Tumor composed predominantly of ciliated cells
  - Endometrioid adenocarcinoma with squamous differentiation:
    - By definition, the squamous element constitutes at least 10% of a tumor
    - Can be seen in low-grade or high-grade tumors
- Grading of the glandular component:
  - Grade I: 5% or less of tumor has a nonsquamous, nonmorular solid growth pattern
  - Grade II: 6–50% of tumor has a solid growth pattern
  - Grade III: >50% of tumor has a solid growth pattern

Differential Diagnosis

- Endometrial hyperplasia
- Normal menstrual endometrium:
  - Often fragmented, with crowded glands and stroma
  - Mixed with blood and necrotic debris
- Reactive glandular atypia:
  - May be seen in association with endometritis, after curettage or radiation therapy
- Endometrial metaplastic changes
- Carcinosarcoma (malignant mixed mullerian tumor)
- Atypical polypoid adenomyoma

Other Histologic Subtypes of Endometrial Carcinoma

Serous Carcinoma

- Comprises 5–10% of all endometrial carcinomas
- Aggressive, with deep myometrial invasion and early dissemination
- Often invades into vascular and lymphatic spaces
- Commonly grows in complex papillary fronds with central fibrovascular cores
- May also see smaller papillae and buds or a complex papilloglandular pattern with slit-like lumina
- Psammoma bodies seen in ~30% of all cases
- Necrotic foci and frequent mitotic figures are common
- Frequently see macronucleoli and multinucleated tumor cells

Clear Cell Carcinoma

- Comprises ~4% of all endometrial carcinomas
- Usually occurs in postmenopausal women
- Often associated with poorer prognosis due to higher stage
- See large tumor cells with clear cytoplasm due to glycogen accumulation
- Hobnail cells may be prominent
- Often see large, very pleomorphic nuclei
- May have prominent extracellular mucin and dense hyalinized stroma
- Architectural patterns include solid, papillary, mixed, or tubular
- Only nuclear grade used for grading these tumors
- Often mixed with serous subtype

Mucinous Carcinoma

- Uncommon variant of endometrial carcinoma

- Abundant mucin both within the gland lumina and in the cytoplasm of the glandular cells
- By definition, >50% of the tumor must contain intracytoplasmic mucin

Squamous Cell Carcinoma

- Rare primary carcinoma of the endometrium
- Diagnosed only in the absence of cervical squamous cancer
- Tumor should be thoroughly sampled to rule out adenosquamous carcinoma
- Extremely poor prognosis
- Histologically resembles squamous cell carcinoma found in other sites

Mixed Carcinoma

- Carcinoma containing >1 of the cell types
- The second cell type must comprise at least 10% of the total tumor volume

Undifferentiated Carcinoma

- Tumors failing to show evidence of either glandular or squamous differentiation

Malignant Mesenchymal Tumors

Leiomyosarcoma

Clinical

- Represents ~30% of all uterine sarcomas
- Usually occurs in postmenopausal women, average age = 52 years (a decade older than women with leiomyoma)
- Presenting symptoms include abnormal bleeding, lower abdominal pain, or pelvic or abdominal mass (occasionally rapidly growing)

Macroscopic

- Usually large, solitary, poorly circumscribed
- Most are intramural
- Soft fleshy appearance with variegated cut surface
- Gray-yellow or pink with hemorrhagic and/or necrotic areas
- May grossly extend beyond the uterus

Microscopic

- Very cellular tumor composed of intersecting fascicles of large atypical spindled cells
- Atypical hyperchromatic nuclei with rounded ends, coarse chromatin, and prominent nucleoli
- Multinucleated giant cells found in 50% of cases
- Hemorrhagic and necrotic foci may be prominent
- Many have at least focal infiltration into adjacent myometrium
- Three main criteria for diagnosis:
  - Mitotic activity: usually have 10 or more mitotic figures/high-power field
  - Significant nuclear atypia
  - Hypercellularity

Differential Diagnosis

- Benign leiomyoma and variants:
  - Less cellular, decreased cytologic atypia, minimal mitotic activity
- Intravenous leiomyomatosis
- High-grade endometrial stromal sarcoma
- Poorly differentiated endometrial carcinoma
- Other sarcomas (e.g., malignant fibrous histioctyoma, rhabdomyosarcoma)

Leiomyosarcoma Variants

Epithelioid Leiomyosarcoma

- Round or polygonal cells with abundant eosinophilic or clear cytoplasm
- Increased mitotic activity

Myxoid Leiomyosarcoma

- Large, gelatinous tumor with abundant myxoid stroma that may obscure the smooth muscle origin
- Non-myxoid areas generally appear more obviously like smooth muscle and show more atypia and increased mitotic activity
- May appear benign, but usually see microscopic invasion of surrounding myometrium
- Same unfavorable prognosis as typical leiomyosarcoma

Endometrial Stromal Sarcoma (Low-Grade and High-Grade)

Clinical

- Endometrial stromal tumor that infiltrates the myometrium (endometrial stromal nodule is the benign counterpart—see Benign Mesenchymal Lesions)
- Divided into two patterns: low-grade (LGSS) and high-grade (HGSS) endometrial stromal sarcoma
- Comprises <10% of all uterine sarcomas; $^{2}/_{3}$ are low-grade, $^{1}/_{3}$ are high-grade
- The mean age = 42–53 years
- Presenting symptoms include abnormal bleeding, worsening cyclic menorrhagia, and abdominal pain
- Occasionally may present with abdominal or pulmonary metastases
- LGSS is slow growing, with a median survival of 11 years; recurrence may occur many years after diagnosis

- HGSS often rapidly progresses and recurrence is usually evident within 2 years of diagnosis

Macroscopic

- LGSS:
  - Usually soft, tan, and polypoid
  - Commonly intramural
  - Three main patterns:
    - Diffusely thickened myometrium with no clearly defined tumor
    - Nodular tumor with soft, tan or yellow-orange cut surface
    - Poorly-circumscribed mass with pink, tan, or yellow tumor nodules infiltrating the myometrium
  - May infiltrate beyond the uterus
- HGSS:
  - Soft, tan, fleshy polypoid tumor
  - Bulges into and often fills the endometrial cavity
  - May infiltrate beyond the uterus

Microscopic

- LGSS:
  - Composed of cells resembling the stromal cells of proliferative-phase endometrium
  - Uniform cells with round to oval nuclei and small nucleoli
  - Mitotic activity usually <3 mitotic figures/10 high-power fields
  - Can have prominent vascularity
  - Hyalinized zones are common
  - Invades the myometrium and characteristically invades lymphatic and vascular channels
  - ~25% have areas of epithelial-like differentiation
- HGSS:
  - More cytologic atypia than LGSS, but still consists exclusively of cells that resemble endometrial stromal cells
  - Cells have large vesicular nuclei with prominent chromatin clumping and nucleoli
- Increased mitotic activity commonly with 10–20 mitotic figures/10 high-power fields
- Destructive myometrial invasion with necrosis and hemorrhage

Other Malignant Mesenchymal Tumors

- Malignant fibrous histiocytoma
- Rhabdomyosarcoma
- Angiosarcoma
- Liposarcoma
- Osteosarcoma

Malignant Mixed Epithelial-Nonepithelial Tumors

Müllerian Adenosarcoma

Clinical

- Rare tumor with benign epithelial component and malignant stromal component
- Average age = ~57 years
- Extrauterine adenosarcoma (fallopian tube, ovary) occurs in younger women and is more aggressive than those found in the uterus
- Most commonly present with abnormal vaginal bleeding
- Recurrence seen in 25–40% of all cases

Macroscopic

- Soft or firm polypoid mass that fills the endometrial cavity and enlarges the uterus
- Cut surface is fleshy, tan or gray, and contains small cysts
- ~25% have foci of hemorrhage and necrosis

Microscopic

- Surface often papillary and may have a leaf-like appearance
- Epithelial component consists of small dilated glands admixed with compressed slit-like glands usually lined by inactive or proliferative-type endometrium
- Stromal component cytologically malignant, composed of spindled or round cells with variable nuclear atypia
- Periglandular stromal hypercellularity is a characteristic feature
- Mitotic figures are easily identified in most tumors
- Foam cells, smooth muscle cells, and sex cord-like elements may be present
- Heterologous elements, especially striated smooth muscle (rhabdomyosarcoma), is identified in 20–25% of the cases
- ~10% will have "stromal overgrowth" (one-sided proliferation of the sarcomatous component of the tumor); usually associated with increased cellularity, nuclear atypia, and mitotic activity
- Myometrial invasion seen in 15–20% of the tumors and both glands and stroma are seen in these areas
- Distant metastses are usually composed purely of the sarcomatous element

Differential Diagnosis

- Adenofibroma:
  - Decreased cellularity, mitoses, and stromal nuclear atypia
  - No periglandular stromal cuffing
- Malignant mixed mullerian tumor

Malignant Mixed Müllerian Tumor (Carcinosarcoma)

Clinical

- Comprises <1.5% of malignant tumors of the uterus, but is the most common uterine sarcoma
- Well-recognized association with prior pelvic radiation
- Mostly occurs in postmenopausal women; average age = 65 years
- Usually present with abnormal vaginal bleeding, but may have abdominal pain, abdominal distention, and/or a palpable mass
- Poor prognosis: many present with advanced stage disease (staging is the same as for endometrial carcinoma)

Macroscopic

- Large, bulky, polypoid mass that usually fills the endometrial cavity and often protrudes through the external cervical os
- Commonly soft and friable with a tan, fleshy, variegated cut surface
- Hemorrhage and necrosis often present
- May grossly recognize bone or cartilage

Microscopic

- Composed of malignant epithelium and sarcomatous stroma
- The epithelial component is usually an adenocarcinoma of endometrioid type, but may see any of the endometrial carcinoma subtypes
- The sarcoma component is commonly endometrial stromal sarcoma or fibrosarcoma
- May have foci of heterologous elements consisting of foci of rhabdomyosarcoma, chondrosarcoma, osteosarcoma, liposarcoma, or a mixture of these types
- Rarely, these tumors may be confined to a polyp

Differential Diagnosis

- Poorly differentiated endometrial carcinoma
- Pure sarcoma
- Adenosarcoma

Miscellaneous Malignant Tumors

Glassy Cell Carcinoma

- Uncommon
- Variant of a mixed adenosquamous carcinoma
- Poorly differentiated, with little glandular or squamous differentiation
- Composed of masses and nests of polygonal cells separated by fibrous stroma, often with abundant inflammatory cells
- Cells have granular eosinophilic or amphophilic cytoplasm with ground-glass appearance
- Nuclei are large, with prominent eosinophilic nucleoli
- Increased mitotic activity with atypical mitoses
- Highly aggressive behavior

Giant Cell Carcinoma

- Rare
- Multinucleated giant cells accounting for substantial part of the tumor
- Other areas may contain more differentiated endometrial carcinoma or undifferentiated carcinoma
- Resembles giant cell carcinomas in other sites such as lung, thyroid, pancreas, and gall bladder

Choriocarcinoma

- Rarely develops in postmenopausal women
- Highly malignant epithelial tumor, arising from the trophoblast
- Cases have shown focal glandular differentiation among solid areas of poorly differentiated tumor
- Human chorionic gonadotropin (hCG) is elevated in the serum and found in the syncytiotrophoblastic cells

Yolk Sac Tumor

- Thought to arise in the uterus as a result of aberrant migration of primordial germ cells
- Alpha-fetoprotein (AFP) is elevated in the serum and found in the tumor cells

Lymphoma

- Rarely involves the endometrium as the initial presentation
- If first seen in the endometrium, the cervix will often be the presenting site
- Usually diffuse large cell or follicular small cleaved cell

Differential Diagnosis

- Leoimyosarcoma with heavy lymphocytic infiltrate
- Lymphoma-like lesion:
  - Polyclonal heterogenous population of lymphoid cells

Metastatic (Secondary) Tumors

Metastatic Ovarian Carcinoma

- Should distinguish between:
  - Metastases from endometrium to ovaries (occurs more often than the reverse)
  - Metastases from ovary to endometrium
  - Independent primary tumors (occurs in ~$^1/_3$ of cases)
- Important to distinguish because prognosis and treatment differ
- Increased likelihood of metastases from endometrium to ovaries with:

- Small ovaries (<5cm)
- Bilateral ovarian involvement
- Deep myometrial invasion
- Vascular invasion
- Fallopian tube involvement

Metastases from Extragenital Site

- Metastatic breast cancer most common followed by (in descending order) stomach, melanoma, colon, pancreas, and kidney
- Usually associated with other evidence of dissemination
- May involve endometrium or myometrium

FALLOPIAN TUBES

Non-Neoplastic Lesions of the Fallopian Tube

Acute Salpingitis

Clinical

- Usually due to the direct passage of bacteria from uterine cavity into tubal lumen, but may spread via lymphatic or hematogenous route
- Polymicrobial etiology: *N. gonorrhoeae*, *C. trachomatis*, anaerobic bacteria, *E. coli* and others
- Typically, onset of pain several days after menses
- Recurrent infections result in chronic salpingitis
- Close association with chronic endometritis

Macroscopic

- Enlarged, edemetous, erythematous tube(s)
- Frequently show fibropurulent serosal and luminal exudate
- May be adherent to adjacent structures, including ovary
- Tubo-ovarian abscess may result

Microscopic

- Initial marked neutrophilic transmural and mucosal infiltration with intraluminal exudate
- Associated congestion and edema
- Possible tubal mucosal ulceration
- Subsequent lymphoplasmocytic infiltrate
- Surface fibrin deposition resulting in adherence of mucosal plicae

Chronic Salpingitis

- Caused by chronic, recurrent infections
- Large dilated tube with shaggy lining and thick walls
- Healing and organization lead to permanent bridging between plicae with resulting follicular salpingitis (adherent tubal plicae, variably-sized follicle-like spaces)
- Fimbriae may occlude completely and form pyosalpinx
- Multiple tuboovarian adhesions; may progress to tuboovarian abscess
- Resolution of purulent salpingitis:
  - Severely scarred tube
  - Hydrosalpinx:
    - Obliterated fimbriated end with dilated tube
    - Clear serous fluid within tube
    - Low cuboidal epithelial lining with occasional remaining plicae
    - Unlikely recovery of tubal function
    - Often bilateral
- Rarely, massive intraluminal hemorrhage may lead to the formation of hematosalpinx:
  - Should be distinguished from much more common form due to ruptured tubal pregnancy

Granulomatous Salpingitis

- Caused by a variety of organisms or noninfectious processes

Mycobacterium tuberculosis

- Most common etiology
- Usually due to secondary spread from primary pulmonary infection
- Preferentially involves the tubes rather than other parts of the genital tract; commonly bilateral
- Early lesions show typical granulomatous inflammation with epithelioid histiocytes, lymphocytes, giant cells, and caseous necrosis
- Mucosal extension to serosa may occur, with adhesions forming between the tube and ovary
- Hematosalpinx or hydrosalpinx may result
- Almost always results in sterility

Actinomycosis

- Associated with intrauterine contraceptive devices
- Abscess formation: single or multiple
- Gram +, filamentous, sulfur granules may be identified
- May disseminate to liver and lung
- Abscess wall contains histiocytes, plasma cells, and lymphocytes

Parasitic Infection

- *Enterobius vermicularis* (pinworm)
- Schistosomiasis
- *Echinococcus granulosus*
- Cysticercosis

Sarcoidosis

- Tubal involvement rarely with disseminated disease

Crohn's Disease

- May secondarily produce granulomatous salpingo-oophoritis

Foreign Body

- Introduced during gynecologic exam, especially hysterosalpingography
- Phagocytic reaction with accumulation of subepithelial foamy histiocytes
- Infectious cause should be excluded

Salpingitis Isthmica Nodosa

Clinical

- Average age at diagnosis = 30 years
- Single or multiple diverticula of tubal epithelium in the isthmic region
- Possibly adenomyosis-like process, but exact etiology unknown
- Associated with infertility and ectopic pregnancy

Macroscopic

- Yellow-white nodular swellings in the isthmus, 1–2 cm in diameter
- Smooth serosa
- Bilateral in up to 85% of cases

Microscopic

- Cross-sectioned diverticula appear as isolated glands lined by tubal epithelium and separated by broad bands of smooth muscle
- Usually no connection with serosal surface

Ectopic Pregnancy

Clinical

- 1–2% of all conceptions are ectopic
- >95% occur in the fallopian tube
- Majority (75–80%) occur in the ampulla, 10–15% isthmic, 5% at the fimbriae
- Previous history of pelvic inflammatory disease in 35–45% of all cases
- If not recognized, rupture typically occurs around the eighth gestational week

Macroscopic

- If unruptured, grossly seen as irregular dilation of bluish-colored tube (from hematosalpinx)
- Chorionic villi usually identified within blood-filled, dilated lumen
- ~$^{2}/_{3}$ contain identifiable embryo (grossly or microscopically)

Microscopic

- Chorionic villi and extravillous trophoblast can grow intraluminally or penetrate deeply into the muscularis
- Commonly see trophoblastic invasion into tubal wall and blood vessels, but is not clinically significant
- Evidence of chronic salpingitis found in ~50% of all cases
- Tubal wall should be examined for evidence of salpingitis isthmica nodosa
- Rupture may result in reactive mesothelial proliferation with papillae and psammoma body formation (should not be misinterpreted as metastatic ovarian serous carcinoma)

Walthard Cell Nests

Clinical

- Incidental finding
- Mesothelial inclusion cyst filled with metaplastic polygonal epithelial cells

Macroscopic

- Usually multiple
- Subserosal, yellowish white nodules, 1–2 mm in size

Microscopic

- Epithelial cells with irregular, ovoid nuclei with longitudinal grooves
- May see cystic nests lined by nonciliated, nonmucinous columnar cells

Metaplastic Papillary Tumor

- Associated with pregnancy
- Occasionally seen in tubes removed in the immediate postpartum period
- Papillary oncocytic and mucinous metaplastic process
- Benign behavior

Paratubal Cysts

- Mesothelial or paramesonephric (müllerian) in origin:
  - Mesothelial cysts:
    - Includes large majority of paratubal cysts >3 cm
    - Lined by flat cells and surrounded by thin fibrous wall
  - Paramesonephric cysts:
    - Also known as hydatids of Morgagni
    - Small (2–10 cm) round cysts attached by pedicle

to the fimbriae
- Thin translucent wall containing clear serous fluid
- Lined by ciliated and nonciliated cells
- Cyst wall may contain papillary infoldings

Endosalpingiosis

- Ectopic location of tubal-type epithelium involving peritoneal surfaces
- Likely represents a proliferative mesothelial process

Tubal Prolapse

- Occasionally occurs after a prior hysterectomy (vaginal hysterectomy in 80% of cases)
- Grossly see lesion resembling granulation tissue around the vaginal apex

Other Non-Neoplastic Lesions

- Endometriosis
- Decidual reaction
- Arias-Stella reaction

Benign Tumors of the Fallopian Tube

Adenomatoid Tumor (Benign Mesothelioma)

Clinical

- Most frequent benign tubal tumor
- Presumed mesothelial derivation

Macroscopic

- Nodular swelling (1–2 cm) beneath tubal serosa
- Yellow or whitish gray on section

Microscopic

- Multiple dilated slit-like spaces lined by single layer of cuboidal or flattened mesothelial cells
- May grow into stroma in an infiltrative-type manner
- Marked smooth muscle hyperplasia may be present

Differential Diagnosis

- Infiltrating adenocarcinoma

Leiomyoma

- Uncommon in the fallopian tube
- May originate from tubal or broad ligament smooth muscle or from the blood vessel walls of either
- Histologically identical to uterine counterpart, including possible degenerative changes

Epithelial Papilloma

- Rare
- Delicate, branched papillary core
- Core lined by single layer of uniform nonciliated columnar or oncocytic cells
- Malignant potential unknown
- Should be differentiated from papillary hyperplasia associated with inflammation and hyperestrinism

Teratoma

Clinical

- Rare
- Usually nulliparous and in the fourth decade
- Majority are mature

Macroscopic

- Most frequently located within the lumen, but may be intramural or attached to the serosa
- Usually cystic
- Size ranges from 1–20 cm in diameter

Microscopic

- Similar histology to benign counterpart in the ovary
- Mixture of well-differentiated ectodermal, mesodermal, and endodermal tissues

Other Benign Tumors

- Mucinous cystadenoma
- Hemagioma
- Lipoma
- Angiomyolipoma
- Adenofibroma
- Sex-cord tumor with annular tubules

Premalignant and Malignant Tumors of the Fallopian Tube (Table 19-7)

Carcinoma In Situ

- Often not recognized until after invasion has occurred
- Accurately diagnosed only when epithelial cells have lost their polarity and are forming papillae with hyperchromatic, irregular, large nuclei (nuclear crowding and atypia may be seen in normal tubes)
- Intact basement membrane
- May be seen adjacent to tubal carcinoma or malignant mixed mesodermal tumor

Invasive Adenocarcinoma

Clinical

- Rare; accounts for <1% of primary genital tract malignancies
- Direct tubal extension by uterine or ovarian carcinoma is 10 times more common
- Diagnosis rarely made preoperatively
- Usually postmenopausal, sixth or seventh decade

- Classic triad seen in <50% of cases:
  - Pain
  - Vaginal discharge
  - Palpable adnexal mass

Macroscopic

- Swollen tube due to marked intraluminal growth
- Lumen usually filled and dilated by solid or papillary growth
- Frequently bilateral

Microscopic

- Usual histologic appearance similar to that of an invasive papillary serous adenocarcinoma of the ovary:
  - Branching papillae covered by epithelium with enlarged, pleomorphic, hyperchromatic nuclei
  - Increased and atypical mitoses
- May see abrupt transition from normal to neoplastic epithelium
- Other carcinoma subtypes are uncommon

Differential Diagnosis

- Tubal extension by primary uterine or ovarian carcinoma

Malignant Mixed Mesodermal Tumor

Clinical

- Rarely primary in the fallopian tubes
- Must clearly identify normal ovary to rule out primary ovarian origin
- Poor prognosis

Macroscopic

- Distended tube
- Usually evidence of extension to adjacent pelvic and abdominal structures

Microscopic

- Mixture of carcinoma (squamous, glandular, or both) and spindle-cell sarcomatous stroma
- Mitotically active

Differential Diagnosis

- Poorly differentiated carcinoma with spindle-cell metaplasia

Metastatic (Secondary) Tumors

- Usually from direct extension of ovarian or endome-

Table 19-7. FIGO Staging of Fallopian Tube Carcinoma

Stage 0	Carcinoma *in situ* (limited to tubal mucosa)
Stage I	Growth limited to fallopian tubes
Stage IA	Growth limited to one tube with extension into submucosa and/or muscularis but not penetrating serosal surface; no ascites (T1a)
Stage IB	Growth limited to both tubes with extension into submucosa and/or muscularis but not penetrating serosal surface; no ascites (T1b)
Stage IC	Tumor either Stage IA or IB but with extension through or onto tubal serosa or with ascites containing malignant cells or with + peritoneal washings (T1c)
Stage II	Growth involving one or more fallopian tubes with pelvic extension
Stage IIA	Extension and/or metastases to uterus and/or ovaries (T2a)
Stage IIB	Extension to other pelvic tissues (T2b)
Stage IIC	Tumor either Stage IIA or IIB and with ascites containing malignant cells or with + peritoneal washings
Stage III	Tumor involving one or both fallopian tubes with peritoneal implants outside pelvis and/or positive retroperitoneal or inguinal nodes; superficial liver metastasis equals Stage III; tumor appears limited to true pelvis but with histologically proved malignant extension to small bowel or omentum
Stage IIIA	Tumor grossly limited to true pelvis with – nodes but with histologically confirmed microscopic seeding of abdominal peritoneal surfaces
Stage IIIB	Tumor involving one or both tubes with histologically confirmed implants of abdominal peritoneal surfaces, none exceeding 2 cm in diameter; lymph nodes are –
Stage IIIC	Abdominal implants >2 cm in diameter and/or + retroperitoneal or inguinal nodes
Stage IV	Growth involving one or both fallopian tubes with distant metastases; if pleural effusion is present, cytological fluid must be + for malignant cells to be Stage IV; parenchymal liver metastasis equals Stage IV

trial carcinoma
- Much more common than primary tubal carcinoma
- May also see hematogenous metastases from breast or other extrapelvic carcinomas

Other Malignant Tumors
- Leiomyosarcoma
- Choriocarcinoma
- Malignant lymphoma
  - Usually secondarily involved by systemic disease

Tumors of the Broad Ligament

Adnexal Tumor of Probable Wolffian Origin

Clinical
- Incidental finding or associated with palpable mass and abdominal pain
- Age range = 29–58 years
- Usually benign behavior, but may have multiple local recurrences
- Rarely metastasizes

Macroscopic
- Typically seen within the leaves of the broad ligament or attached to the fallopian tube by a pedicle
- Predominantly solid and lobulated; 1–12 cm (average size = 8 cm)
- Encapsulated
- Usually rubbery or soft

Microscopic
- Epithelial cells growing in diffuse, trabecular or tubular patterns
- Tongues of tumor may invade capsule

Other Broad Ligament Tumors
- Leiomyoma
- Borderline serous papillary tumor
- Papillary cystadenoma associated with von Hippel-Lindau disease

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Chapter 20

Ovary and Peritoneum

Kevin Wu, MD
and Gary Keeney, MD

Table of Contents

OVARY

General

Mesodermal Origin Except Germ Cell Component (Endodermally Derived)

Macroscopic

- Outer cortex, inner medulla, hilus, cystic follicles, corpora lutea, corpora albicantia
- Adult premenopausal ovaries vary from 3–5 cm in greatest dimension
- Average weight during reproductive years is 5–8 g

Microscopic

- Surface epithelium (germinal epithelium):
  - Continuous with peritoneal mesothelium
- Stroma: cortex and medullary regions:
  - Spindle-shaped cells
  - Luteinized cells
  - Adipose cells
  - Neuroendocrine cells
- Germ cells: primordial follicles:
  - Primary
  - Secondary
  - Tertiary
  - Graffian follicles
  - Oocytes
  - Granulosa cells
  - Internal and external theca cell layers
  - Leydig cells
  - Rete ovarii

Inflammatory Lesions

Bacterial Infections

- Often related to pelvic inflammatory diseases with subclinical infections common
- Neisseria, chlamydia, and coliform bacteria most common
- Often secondary to salpingitis
- May lead to tubo-ovarian abscesses, tubo-ovarian cysts, fibrous adhesions, hydrosalpinx, or pyosalpinx

Uncommon Infections

- Actinomycosis: associated with intrauterine devices (IUDs); branching gram + filamentous rods, sulfur granules
- Syphilis
- Schistosomiasis
- Enterobius vermicularis
- Tuberculosis
- Cytomegalovirus: intranuclear/cytoplasmic inclusions
- Mumps oophoritis
- Malacoplakia: Michaelis-Gutmann bodies
- Echinococcus
- Fungi: blastomycosis, coccidiomyocosis, aspergillus
- Mycobacterium leprae (leprosy)

Noninfectious Granulomatous Inflammation

- Foreign body granulomas:
  - Secondary to starch granules
  - Contrast material
  - Keratin (ruptured dermoid cysts)
  - Free bowel contents
- Systemic disease:
  - Sarcoidosis
  - Crohn's disease: due to direct extension of bowel inflammatory process
  - Cortical granulomas: see later

Miscellaneous Inflammatory Lesions

- Xanthogranulomatous oophoritis:
  - Foamy macrophages
  - Plasma cells
  - Lymphocyte infiltrate secondary to chronic ovarian abscess
- Autoimmune oophoritis:
  - Plasma cells and lymphocytes around developing ovarian follicles
    - Associated with other autoimmune phenomena such as Addison's disease, diabetes, hypothyroidism, pernicious anemia, and others
- Giant cell arteritis

Benign Ovary

Gonadal Dysgenesis

Abnormalities of Sexual Development

- Testicular feminization:
  - XY males with end organ testosterone receptor defects:
    - Cryptorchid testes, vagina, no uterus
    - Increased risk of testicular malignancy
- Kleinfelter's 47, XXY
- Turner's syndrome:
  - 45, XO
  - 45, XX/XO mosaic

- Streak gonads: increased incidence of gonadoblastoma
- Hermaphroditism

Adrenal Cortical Rest

- Small round yellow mass in ovary or fallopian tube (more common)
- Nests of adrenal-type cells with foamy cytoplasm

Ectopic/Supernumerary Ovary

- Ovarian tissue located away from normal ovary
- Sites include pelvis, bladder, retroperitoneal, periaortic, and mesentery
- May be multiple or bilateral
- Associated with other genitourinary disorders
- Differentiate from accessory ovary (ovarian tissue immediately adjacent or connected to the native ovary)

Ovarian Remnant Syndrome

- Associated with previous oophorectomy (often bilateral) complicated by pelvic adhesions
- Cyclic pelvic pain
- May have elevated follicle-stimulating hormone (FSH) and Leutenizing hormone (LH) levels despite prior oophorectomy
- Abdominal exploration may reveal cystic mass adherent to pelvic sidewalls and intra-abdominal organs
- Ovarian tissue present histologically

Follicle Cysts

Clinical

- Common after menarche
- Seen in childhood to menopause
- May be seen in cases of precocious puberty
- Benign

Macroscopic

- Corpus follicle:
  - Physiologic secondary ovarian follicle <1 cm
- Cystic follicle:
  - Physiologic secondary follicle 1–3 cm in size
- Follicular cyst:
  - Unilocular smooth-walled cyst or cysts 3–10 cm
- Associated with metrorrhagia and endometrial hyperplasia

Microscopic

- Cyst wall lined by inner theca layer and outer granulosa layer

Differential Diagnosis

- Surface epithelial inclusion cyst:
  - Flattened epithelium and/or tubal metaplasia
- Epidermoid cyst:
  - Squamous epithelium
  - Considered monodermal teratoma
- Endometriosis:
  - Endometrial stroma and glands with hemorrhage
- Unilocular cystic granulosa cell tumor:
  - Call-Exner bodies, nuclear grooves, granulosa cells

Polycystic Ovarian Disease (POCD)/Multiple Follicular Cysts/Stein-Leventhal Syndrome

Clinical

- Young women presenting with symptoms/signs of ovarian failure:
  - Oligomenorrhea or amenorrhea
  - Infertility
  - Hirsutism
- Incidence in up to 7% of women
- Dysregulation of ovarian 17-hydroxylase, 11 beta-hydroxylase, and C-17,20 lyase described
- Associated with hypothyroidism in some
- Responds to hormonal therapy
  - Oophorectomy no longer treatment of choice
- Endometrium may be weakly proliferative or show cystic atrophy, atypical hyperplasia, or well-differentiated carcinoma

Macroscopic

- Normal to slightly enlarged ovaries
- Multiple cysts usually <1 cm
- Often no coropora lueta or follicular cysts

Microscopic

- Fibrous hypocellular ovarian cortex
- Multiple cysts with inner layer(s) of nonluteinized granulosa cells and prominent outer layer of luteinized theca cells
- Hyperthecosis often present
- Primordial follicles can be identified.

Differential Diagnosis

- Chronic anovulation
- Hypothalamic-pituitary axis disorders

Large Solitary Luteinized Follicle Cyst of Pregnancy and Puerperium

Clinical

- Palpable adnexal mass
- Seen in pregnancy:
  - Related to human chorionic galadotropin (hCG) stimulation

- No associated clinical endocrine abnormalities

Macroscopic

- Grossly resembles follicular cyst except cyst may be large (>25 cm)

Microscopic

- Single to multiple layers of luteinized cells and/or focal atypia

Differential Diagnosis

- Unilocular cystic granulosa cell tumor:
  - Call-Exner bodies, nuclear grooves, no luteinization

Corpus Luteoma/Corpus Lutuem Cyst

Clinical

- Most common during reproductive years
- Rarely reported to be seen at birth
- Rare rupture with hemoperitoneum

Macroscopic

- Often yellow coloration of cyst wall and/or hemorrhage
- Corpus luteum/cystic corpus luteum 1–2.5 cm (physiologic)
- Corpus luteum cyst >2.5 cm

Microscopic

- Physiologic cyst lined by luteinized granulosa cells and theca layer and/or hemorrhage and central necrosis

Treatment

- None
- Commonly removed for suspicious cystic adnexal mass

Hyperreactio Luteinalis (Multiple Luteinized Follicle Cysts)

- Enlarged ovaries with multiple luteinized follicles and stromal edema
- Due to hCG stimulation
- Common with hydatidiform mole; also described in choriocarcinoma and twin pregnancies
- Usually regresses after pregnancy or treatment of gestational disease

Pregnancy Luteoma

Clinical

- Adnexal mass during pregnancy
- Benign, regresses after pregnancy
- Related to hCG stimulation
- No association with gestational trophoblastic disease

Macroscopic

- Bilateral, multifocal nodule

Microscopic

- Coalescing masses of luteinized cells
- May represent an exaggerated luteinization of pre-existing stromal hyperthecosis

Differential Diagnosis

- Steroid cell tumor (stromal luteoma and Leydig cell tumor)

Epithelial Inclusion Glands/Cyst in Ovarian Cortex

Clinical

- Occurs at any age but most common in older women
- Occasionally seen in infants and children
- Often incidental finding

Macroscopic

- Multiple small thin-walled cysts in ovarian cortex
- Usually <1 cm:
  - Most are identified only microscopically

Microscopic

- Thin-walled cysts lined by attenuated to slightly columnar epithelium
- Epithelium may show tubal metaplasia or rare psamomma bodies

Differential Diagnosis

- Endometriosis:
  - Endometrial glands and stroma, hemorrhage
- Surface epithelial tumors:
  - Epithelial atypia and stratification

Surface Nodular/Papillary Stromal Proliferation

- Most commonly seen in older women
- Hyalinized ovarian stroma with overlying single layer of benign surface epithelium producing a small nodular surface protuberance
- No clinical significance

Cortical Granuloma (Hyaline Scar)

- Common incidental finding in peri/postmenopausal women
- Pathogenesis unknown
- No known clinical significance

Stromal Hyperplasia (Hyperthecosis, Diffuse Thecomatosis)

Clinical

- May present as virilization with/without steroidogenic

effects such as obesity, hypertension, diabetes, and so forth
- More resistant to treatment than POCD; may require oophorectomy

Macroscopic
- Nodularity or enlargement of both ovaries
- Stromal thecomas or luteomas may also be present

Microscopic
- Bilateral nodular to diffuse proliferation of ovarian stromal cells and/or luteinization

Differential Diagnosis
- Polycystic ovarian disease:
  - Multiple follicle cysts
- Thecoma/fibroma:
  - Unilateral distinct mass

Stromal/Hilar Leydig Cell Hyperplasia

Stromal Leydig Cell Hyperplasia
- Microscopic aggregates of Leydig cells with Reinke crystalloids in ovarian stroma often showing changes of hyperthecosis

Hilar Leydig Cell Hyperplasia
- Nodular aggregates of hilar Leydig cells seen during pregnancy and sometimes in postmenopausal women
- Stromal hyperthecosis or hilar cell tumor may be present

Granulosa Cell Proliferation
- Focal proliferation of granulosa cells found incidentally in ovary
- Associated with pregnancy
- Differential includes adult granulosa cell tumor: forms a mass; majority occur in postmenopausal patient

Ectopic Decidual Reaction
- May occur in ovary during pregnancy
- Corpus luteum usually present in one ovary

Rete Ovarii (Rete Adenoma/Cyst)
- Benign
- Female analogue of rete testis in male
- Found in hilus of all ovaries
- Cords, tubules, and cysts lined by flat to columnar epithelium with smooth muscle bundles
- May form small nodules (rete adenoma) or cysts

Massive Ovarian Edema

Clinical
- Young women ~20 years
- Pelvic/abdominal pain, and/or abdominal swelling
- Unilateral palpable adnexal mass
- Ovarian torsion present in 50% of cases
- Conservative treatment; may require oophorectomy

Macroscopic
- Enlarged soft, edematous ovary up to 35 cm
- White surface coloration with tan cut surface and "weeping fluid"

Microscopic
- Stromal edema surrounding ovarian follicles and/or focal necrosis

Differential Diagnosis
- Edematous fibroma: older patients
- Myxoma: rare; hypocellular without follicular derivatives

Ovarian Fibromatosis

Clinical
- Young women ~20–30s
- Abdominal pain, abnormal menses, usually unilateral adnexal mass

Macroscopic
- Enlarged, firm, solid ovary 6–12 cm
- White coloration

Microscopic
- Spindle cell proliferation with variable amounts of collagen surrounding follicles

Differential Diagnosis
- Fibroma: older patients, few ovarian follicles, rim of normal surrounding tissue

Endometriosis

Clinical
- Women in reproductive years
- Ovary is the most common site of involvement
- Often present with pain and fertility problems
- May give rise to hyperplasia or carcinoma as in uterus
- Hormonal therapy is often initial treatment

Macroscopic
- Bluish-red macules on serosal surfaces or "chocolate cysts" in ovary

Microscopic
- Three components: endometrial type glands, endometrial stroma, and hemorrhage/hemosiderin-laden macrophages

Table 20-1. Immunohistochemical Profiles In Ovarian Neoplasms

	Keratin	*Vimentin*	*AFP*	*Inhibin*	*CEA*	*HCG*
Serous Carcinoma	+	+	–	–/+	+/–	–
Endometriod Carcinoma	+	+/–	–	–	–/+	–
Mucinous Carcinoma	+	–	–	–	++	–
Dysgerminoma	–	–	–	–	–	+/–
Yolk sac	+	–	+	–	–	+
Embryonal	+	–	+	–	–	+
Granulosa cell	-/+	+	–	+	–	–
Sertoli-Leydig	+	–	–	+	–	–
Brenner	+	–	–	–	+	–
Clear cell	+	+	–/+	+/–	+/–	–
Choricarcinoma	+	–	–	–/+	–	+
Fibrothecoma	–/+	+	–	+	–	–

Note: AFP = alpha fetoprotein; CEA = carcinoembryonic antigen; hCG = human chorionic gonadotropin.

Neoplasms of Ovary (Table 20-1)

Surface Epithelial-Stromal Tumors (Table 20-2)

General

- 2/3 of all ovarian tumors; 90% of all malignant ovarian tumors
- Thought to originate from surface epithelial invaginations
- Tumor classification based on:
  - Cell type: serous, mucinous, endometrioid, undifferentiated, and so forth
    - Tumors with multiple cell types comprising <10% should be classified under predominant cell type
  - And/or presence of prominent fibrous stromal component
  - Pattern of growth: exophytic tumors = "surface," cystic, papillary, combination
  - Presence/absence of invasion: benign, borderline (see below), malignant

Borderline Surface Tumors of the Ovary

- Atypical proliferating, of low malignant potential
- Show intermediate features between benign and malignant neoplasms
- Epithelial proliferation greater than that in benign tumors
- Cellular stratification with epithelial budding and tufting:
  - Cellular buds may appear detached from lining.
  - May have cribriform patterns
  - Mild-moderate nuclear atypia
  - Mitotic figures rare to prominent
- No destructive stromal invasion
- Rare lymphatic metastases ("implants")
- Benign and borderline tumors generally diploid; carcinomas aneuploid
- Prognosis generally good even with advanced disease (similar to benign serous tumors); some, however, may kill patient; typically, long clinical course (bowel obstruction, etc.); rare (?1%) true malignant transformation
- Differential Diagnosis
  - Low-grade ovarian carcinomas: absence of destructive stromal invasion helps distinguish borderline tumors from low-grade carcinomas

Treatment

- Benign and most borderline ovarian tumors:
  - Benign course
  - Benign tumors treated by unilateral salpingo-oophorectomy alone to preserve fertility in young patients
  - Borderline tumors in the past were treated by salpingo-oophorectomy; many now treated similar to benign tumors (dependent on stage)
  - Adjuvant therapy controversial

Table 20-2. Summary of Surface Epithelial Tumors

	Incidence	*Relative size*	*Cell type*	*Squamous diff.*	*Psamomma*	*Bilaterality*
Serous	50% to 70%	Small-mod	Flat-cuboidal	Rare	30%	30% to 50%
Mucinous	15% to 25%	Large	Columnar	Rare	Rare	10% to 20%
Endometrioid	5% to 10%	Small-mod	Columnar	30%	Rare	10% to 30%

- Carcinomas:
  - Many cases advanced with poor outcome
  - Treated by hysterectomy and bilateral salpingo-oophorectomy with surgical staging by biopsy of pelvic, peritoneal, diaphragmatic, omental surfaces and lymph nodes (pelvic and retroperitoneal)
  - Peritoneal washings for cytologic examination also routinely performed
  - Adjuvant therapy with chemotherapeutic agents and radiation given for high-stage or high-grade lesions
  - Serum marker CA125 found to be elevated in malignancies and particularly useful in following patients for recurrence of ovarian neoplasms

Prognosis

- Poor prognosis due to patients presenting with advanced disease due to lack of symptoms early in disease
- 5-year survival rate overall <30%
- Factors adversely influencing survival include:
  - Older age: more likely to have higher grade/stage lesions
  - Clinical stage
  - Tumor grade
  - DNA ploidy of tumor: aneuploid tumors more aggressive than diploid tumors
  - Presence of ascites
  - Overexpression of p53 and HER-2/neu correlated with worse prognosis in some studies and no statistical differences in others

Serous Tumors

General

- Serous tumors account for ~50--70% of ovarian neoplasms
- Approximately 70% of serous tumors are benign, 25% are carcinomas, and 5% to 10% are borderline tumors

Benign Serous Tumors

Clinical

- May occur at any age with peak incidence around 50 years
- Adnexal mass

Macroscopic

- Predominantly unilateral (bilateral in 30% to 50% of cases)
- Unilocular thin-walled cyst, occasionally multilocular, 1–30 cm
- Thin watery to slightly viscous fluid
- Moderate size
- And/or small polypoid excrescenses

Microscopic

- Cysts and papillary fronds lined by stratified, cuboidal, columnar, or tubal epithelium
- ± Psamomma bodies (30%), usually inconspicuous
- ± Fibrous stroma

Variants

- Serous cystadenoma/papillary cystadenoma:
  - Endophytic growth pattern
- Serous surface papilloma:
  - Exophytic growth pattern
- Cystadenofibroma:
  - Cystic tumor with firm, hard nodules with fibrous stroma
- Adenofibroma:
  - Firm, solid tumor with fibrous stroma without prominent cysts
- Adenoacanthofibroma:
  - Squamous differentiation

Borderline Serous Tumors

- Borderline serous tumors more likely to have slightly finer papillae and viscous fluid grossly
- More prominent epithelial proliferation/stratification and cellular atypia microscopically
- Absence of stromal invasion
- Up to 40% may have cystic/papillary serous lesions arising in omentum, lymph nodes, or pelvic organs (implants), which does not change prognosis
- Should be distinguished from endosalpingiosis or mesothelial hyperplasia

- Tumor implants may be noninvasive or invasive (worse prognosis): often difficult to distinguish:
  - Noninvasive implants that are more common are either epithelial (peritoneal surface) or desmoplastic (tumor cells with dense reactive stroma)
  - Both noninvasive types show sharp demarcation with tumor and stroma in contrast to invasive implants showing infiltration of adjacent tissue and often higher grade cytology
  - Tumor classification based on primary tumor in ovary
  - Tumors with invasive implants are more likely to have progression of disease than noninvasive implants
- Some borderline serous tumors may have areas of microinvasion of stroma in a background of typical borderline tumor:
  - Characterized by papillary clusters, single eosinophilic neoplastic cells in papillae or cribriform clusters, or infrequently, lymphatic invasion
  - Microinvasion should not exceed 3 mm
  - Prognosis is similar to tumors without microinvasion

Variants

- Borderline cystic tumor and papillary cystic tumor
- Borderline surface papilloma
- Borderline adenofibroma and cystadenofibroma

Differential

- Low-grade serous carcinoma: stromal invasion

Malignant Serous Tumors

Clinical

- Occur at slightly older age than benign serous lesions, 50–60 years
- Bilateral ovaries in 2/3 of cases
- Most patients present with advanced stage disease

Macroscopic

- Any size from few millimeters to >20 cm
- Cystic, papillary with turbid and hemorrhagic fluid, necrosis
- Surface papillae may be present.
- Psamomma bodies usually present ~70%

Microscopic

- Tumors with stromal invasion, nuclear atypia, numerous mitoses, and complex architectural features (slit-like glandular lumina, tight nests, etc.)

Variants

- Adenocarcinoma
- Papillary adenocarcinoma
- Papillary cystadenocarcinoma
- Adenocarcinofibroma and cystadenocarcinofibroma
- Surface papillary adenocarcinoma

Serous Psammocarcinoma

- Rare form of low-grade serous carcinoma typically involving peritoneum
- Appears to behave more like serous borderline tumors rather than serous cancer
- Four criteria necessary for diagnosis:
  - Invasion
  - Nuclear atypia
  - Solid epithelial nests <15 cells thick
  - Psamomma bodies in at least 75% of nests or papillae

Differential Diagnosis

- Mesothelioma:
  - No psamomma bodies or columnar epithelium
  - Presence of cytoplasmic neutral mucins (mucicarmine or PAS-D)
- Serous borderline tumor/carcinoma of peritoneal primary:
  - Extensive involvement of peritoneum with no or minimal involvement of ovaries

Mucinous Tumors

General

- 15% to 25% of ovarian tumors
- 85% of mucinous tumors are benign
- Bilateral in 10% to 20% of cases

Benign Mucinous Tumors

Clinical

- Adnexal mass
- Most frequent around 30–50 years (borderline mucinous tumors 40–70 years)
- Association with Brenner tumors, Peutz-Jehger's syndrome, pseudomyxoma peritonei (intestinal type), and teratoma

Macroscopic

- Tendency toward larger size when compared to serous tumors (up to 50 cm)
- Often multilocular with thin-walled cysts and thick mucinous fluid
- Papillations not a prominent feature

Microscopic

- Cyst wall lined by columnar epithelium with basal nuclei similar to endocervix or intestinal-type lining (borderline tumors) with occasional goblet cells, Paneth cells, or mixed types

- Stroma shows variable degrees of fibrous component, usually not prominent
- Minor nuclear atypia may be seen in mucinous tumors without other features of borderline tumors/carcinomas
- Some mucinous tumors may contain mural nodules that microscopically resemble high-grade sarcomas/carcinomas or have giant cells

Variants

- Mucinous cystadenoma
- Adenofibroma
- Cystadenofibroma

Borderline Mucinous Tumors

Clinical

- Peak incidence around 30 years

Microscopic

- Greater epithelial proliferation than benign mucinous tumors
- Borderline tumors more likely to have solid areas or excrescences
- Lining epithelium more likely to be intestinal type (89%); müllerian (15%)
- Tumors of intestinal type associated with pseudomyxoma peritonei
  - Müllerian type associated with extraovarian implants
- Some tumors may show foreign body giant cell reaction due to mucin extravasation
- Occasional cases show mural nodules containing numerous sarcoma-like osteoclast-type giant cells; should be differentiated from true sarcomas or poorly differentiated carcinomas that, unlike the former, carry a worse prognosis

Variants

- Borderline cystic tumor
- Borderline adenofibroma
- Borderline cystadenofibroma

Malignant Mucinous Tumors

Clinical

- Women 40–70 years
- 10% to 20% bilateral
- Pseudomyxoma peritonei:
  - Synchronous tumor of appendix usually identified
  - Consider metastasis if appendiceal primary present

Macroscopic

- Necrosis and hemorrhage more commonly associated with carcinoma
- Solid areas and mural nodules more common

Microscopic

- Malignant tumors show nuclear atypia, epithelial stratification, architectural complexity, and ± invasion
- CEA positivity seen in 100% malignant mucinous tumors as compared to 30% of endometrioid and serous types

Variants

- Adenocarcinoma
- Cystadenocarcinoma
- Adenocarcinofibroma
- Cystadenocarcinofibroma

Differential Diagnosis

- Endometrioid carcinoma:
  - Has only minor intracellular mucin and/or focal mucinous-type epithelium
  - Squamous differentiation favors endometrioid carcinoma
- Metastatic mucin-producing tumor:
  - Usually gastrointestinal primary
  - Mixture of borderline and benign components favors ovarian primary
  - Cytokeratin may be useful in differentiating metastatic colon cancer from ovarian primary (see Table 20-3)

Endometrioid Tumors

Clinical

- 5% to 10% of ovarian neoplasms; account for 10% to 20% of ovarian carcinomas
- Most (>75%) are malignant with benign and borderline endometrioid tumors rare
- Origin in endometriosis seen in 10% of cases
- May be associated with independent uterine carcinoma or represent spread from uterus (33%)
- Most carcinomas are well-differentiated, low stage, with good prognosis

Macroscopic

- Solid and/or cystic mass
- Often hemorrhagic
- May grossly resemble adenofibromas

Microscopic

- Tubular glands resembling endometrial adenocarcinoma/hyperplasia
- Pseudostratified, non-mucinous epithelium (rarely focal mucin)
- ± squamous differentiation (30%):
  - Usually benign
  - Occasionally malignant
- Secretory change may be present; not to be confused

Table 20-3. Colonic Versus Ovarian Carcinoma

*Tumor type**	*Cytokeratin 7*	*Cytokeratin 20*
Colonic	–	+
Ovarian	+	±

**See Table 25-2 for detailed description in other cancers*

with clear cell carcinoma
- Adenofibroma-like stroma

Variants
- Benign:
  - Cystadenoma with squamous differentiation
  - Adenofibroma and cystadenofibroma ± squamous differentiation
- Borderline (rare);
  - Adenofibroma
  - Cystadenfibroma
- Malignant:
  - Adenocarcinoma
  - Cystadenocarcinoma
  - Adenocarcinofibroma and cystadenocarcinofibroma
  - Endometrial stromal sarcoma
  - Mesodermal mixed tumors (carcinosarcoma)

Malignant Mixed Müllerian Tumors
- Postmenopausal women
- Similar macro- and microscopic appearance as in uterus:
  - Heterologous type: malignant heterologous component (most commonly chondrosarcoma compared to rhabdomyosarcoma in uterus)
  - Homologous type: malignant epithelium and malignant stroma without specific features (carcinosarcoma)
- Stage most important but poor prognosis overall
- Differential includes malignant teratoma: younger patients, presence of immature neural and other germ cell components
- Mullerian adenosarcoma: malignant stroma and benign glandular component

Differential Diagnosis
- Poorly differentiated serous carcinoma
- Mucinous carcinomas:
  - Squamous differentiation favors diagnosis of endometrioid neoplasm.
- Sertoli-Leydig cell tumors:
  - No squamous differentiation or true gland formation, less nuclear atypia and mitotic activity
- Metastatic adenocarcinoma:
  - Bilaterality, multiple tumor nodules, cribriform patterns with central necrosis, diffuse CEA positivity, lack of squamous differentiation and cytokeratin staining pattern (Table 20-3 and 25-2)
- Clear cell carcinoma:
  - Hobnail pattern, prominent clear cell change

Clear Cell (Mesonephroid) Tumor
Clinical
- Uncommon (5% of ovarian tumors)
- Benign, borderline, and malignant categories
- Benign and borderline clear cell tumors are uncommon
- Most commonly occur in ages 50–70
- Usually unilateral, infrequently bilateral (<10%)
- Malignant clear cell carcinoma associated with pelvic endometriosis or endometriotic cyst
- Prognosis based on stage, similar to epithelial tumors

Macroscopic
- Gross resemblance to adenofibromas with white/yellow color and/or hemorrhage, necrosis; may be spongy or cystic
- Average diameter = ~15 cm
- Often unilocular thick-walled cyst with solid nodules in cyst wall
- Occasional tumors multilocular or solid neoplasms
- May arise in endometriotic cyst

Microscopic
- Clear cell adenofibroma:
  - Fibrous stroma with glands lined by flat to slightly hobnail cells and clear cells
- Clear cell carcinoma:
  - Fibrous stroma with prominent hobnail cells and clear cells
  - Complex papillae with hyalinized cords
  - Diffuse, tubulocystic, papillary, and trabecular patterns
  - Hyaline bodies may be present (25%)

- Few to moderate mitoses
- Often seen in association with endometrioid carcinoma

Immunohistochemistry

- Keratin +, LEU-M1 +, alpha-fetoprotein ±

Variants

- Clear cell cystadenoma
- Adenofibroma and cystadenofibroma
- Borderline cystic tumor
- Borderline adenofibroma
- Cystadenofibroma adenocarcinoma
- Adenocarcinofibroma
- Cystadenocarcinofibroma

Differential Diagnosis

- Endometrioid adenofibroma/carcinoma: clear cell change not prominent, no hobnail cells
- Germ cell tumors (younger age, <20):
  - Yolk sac tumors: primitive nuclei, no hyaline papillary cores, strong AFP +
  - Dysgerminoma: lymphocytes present, no mucin
- Metastatic renal cell carcinoma
  - Renal mass, bony metastases

Transitional Cell Tumors

Brenner Tumors

Clinical

- <2% of all ovarian tumors
- Women 40–80 years old
- Slow-growing neoplasm, often incidental finding
- Associated with mucinous tumors
- Most are benign, with <2% borderline or malignant.
- May have signs of estrogen hyperstimulation

Macroscopic

- Typically unilateral (6% bilateral) and small (<2 cm)
- Predominantly solid, firm, white/yellow color resembling fibromas
- Small cysts with yellowish fluid
- ± calcifications
- May arise as solid nodule in mucinous cystadenoma

Microscopic

- Nests of bland round/polygonal cells surrounded by dense fibroblastic stroma
- Transitional cell-like cells with sharply defined borders, clear cytoplasm, and distinct nucleus with longitudinal groove (similar to Walthard nest)
- Abundant mucinous change and prominent cystic change without papillary fronds or nuclear atypia = metaplastic Brenner tumor

Immunohistochemistry

- Keratin +, glycogen + (PAS), EMA +, CEA +

Differential Diagnosis

- Low-grade stromal sarcoma:
  - Concentric pattern of cells around vessels
- Thecoma/fibroma
  - Fascicles of spindle cells with central nuclei and moderate pale cytoplasm, no clear cells
- Granulosa cell tumor:
  - Call-Exner bodies, nuclear grooves
- Good prognosis for benign, metaplastic, proliferating, and borderline tumors

Atypical Proliferating Brenner Tumor

- Borderline Brenner tumors are typically a unilocular cyst to multilocular cyst with papillary nodules protruding into the cyst
- Rarely solid
- Histology similar to Grade 1–2 (of 3) papillary transitional cell carcinoma of the bladder
- No invasion

Malignant Brenner Tumor

- Brenner tumors with invasion and identifiable benign Brenner component

Transitional Cell Carcinoma (TCC)

- Uncommon
- Solid or cystic
- Primary surface epithelial origin with histology similar to TCC at other sites
- Squamous or glandular differentiation common within tumor
- No identifiable benign Brenner component

Differential

- Metastatic transitional cell carcinoma of urinary tract
  - Clinical history of invasive urinary tract TCC neoplasm
  - Bilateral ovarian involvement
  - May be more responsive to chemotherapy than surface epithelial cancers

Germ Cell Tumors

Dysgerminoma

Clinical

- Young patients (children and young adults <30)
- ± elevated hCG
- Arise in both normal and abnormal gonads (gonadoblastoma)

- Female counterpart of seminoma in males
- Usually unilateral, 15% bilateral
- Good prognosis, >95% survival rate
- Oophorectomy treatment of choice, + chemotherapy, ± radiotherapy

Macroscopic

- Solid, grayish-white surface with fibrous capsule
- Focal hemorrhage or necrosis can be seen

Microscopic

- Similar appearance to seminoma in testis
- Nests of uniform cells with large nuclei and prominent nucleoli and clear cytoplasm
- Fibrous septae intermixed with lymphocytes, separate tumor nests
- Focal hemorrhage, necrosis, and infrequently, calcification
- Other germ cell components occasionally seen
- Nests of hCG + syncytiotrophoblast giant cells seen (<10%)

Immunohistochemistry

- Placental alkaline phosphatase +, scattered hCG + syncytiotrophoblastic cells, ± glial fibrillary acidic protein (GFAP), occ. keratin + (focal), alpha fetoprotein (AFP) – (presence of AFP indicates yolk sac)

Differential Diagnosis

- Lymphoma:
  - Large cells in dysgerminoma negative for leukocyte common antigen
- Other germ cell components should be ruled out by adequate sampling of tumor

Yolk Sac Tumors (Endodermal Sinus Tumors)

Clinical

- Young patients, most <20 years
- Elevated serum AFP
- Normal hCG
- Highly aggressive tumor with tendency for widespread metastasis; stage most important prognostic factor

Macroscopic

- Smooth external surface, often partially cystic
- Foci of necrosis and hemorrhage
- Average size ~15 cm

Microscopic

- Cuboidal cells with loose reticular pattern and microcystic areas
- Schiller-Duval bodies (papillary processes with central vessels)
- PAS + droplets in cytoplasm
- Myxoid background
- Polyvesicular vitelline pattern
- Cystic structures lined by columnar or cuboidal cells separated by spindle stroma
- Hepatoid pattern with nests or sheets of large polyhedral cells and glandular lumina
- Glandular pattern
- Resembles secretory or typical endometioid carcinoma

Immunohistochemistry

- Keratin +, AFP +, alpha-1-antitrypsin ±, hCG + (in scattered syncytiotrophoblast cells if present)

Differential Diagnosis

- Clear cell carcinoma

Embryonal Carcinoma

Clinical

- Young patients <20 years
- Elevated serum AFP
- Elevated human chorionic gonadotropin (β-hCG)
- Aggressive malignant tumor with early metastases

Macroscopic

- Median size = 17 cm
- Smooth external surface, predominantly solid
- Variegated cut surface with necrosis and hemorrhage

Microscopic

- Sheets or nests of large undifferentiated cells with abortive glandular formations
- Large and prominent centrally located nucleus
- Numerous mitoses
- Syncytiotrophoblastic giant cells sometimes present

Immunohistochemistry

- Keratin +, hCG +, AFP + CD30+, EMA –

Differential Diagnosis

- Dysgerminoma:
  - AFP and keratin –, lymphocytic infiltrate

Polyembryoma

- Rare germ cell tumor, usually unilateral
- Young patients
- Numerous embryoid bodies microscopically (structures composed of embryonic disk, amnionic sac, and yolk sac)
- Highly malignant tumor with aggressive clinical course

Choriocarcinoma

Clinical

- Most ovarian choriocarcinomas represent metastases

from the uterus.

- ♦ May arise as choriocarcinomatous differentiation in germ cell tumor or pure ovarian primary
- ♦ Young women
- ♦ Elevated hCG
- ♦ Aggressive neoplasm; gestational tumors associated with better prognosis than non-gestational type

Macroscopic

- ♦ Solid grayish-white mass with hemorrhage and or necrosis

Microscopic

- ♦ Syncytiotrophoblastic and cytotrophoblastic cells
- ♦ Necrosis and prominent hemorrhage

Immunohistochemistry

- ♦ hCG +, keratin +

Differential Diagnosis

- ♦ Germ cell tumors with choriocarinomatous differentiation

Teratoma

Mature Teratoma

- ♦ Mature teratoma, solid type:
  - – Common tumor comprising up to 30% of ovarian tumors (85% of childhood ovarian tumors)
  - – Young women in second decade
  - – Usually unilateral
  - – Grossly solid with multiple small cysts
  - – Microscopically composed of mature, adult tissues
  - – Tumor should be sampled adequately to exclude immature elements (immature malignant teratoma)
  - – Good prognosis
- ♦ Mature teratoma, cystic type (dermoid cyst):
  - – Most common childhood ovarian neoplasm
  - – Usually unilateral
  - – Multiloculated mass with teeth (Rokitansky's protuberance), hair, and caseous-like keratinous material
  - – Fetiform teratoma:
    - • Cystic teratomas with identifiable body-like structures
  - – Microscopically, many mature tissues seen from all three germ cell layers:
    - • Skin and neural-type tissue and cartilage most often seen
    - • Foci of immature neural-type tissue may be found, which does not generally affect good prognosis; need to distinguish from immature teratoma, which has greater amount of immature elements
  - – Squamous cell carcinomas most common malignancy to arise in cystic teratomas
  - – Epidermoid cyst:
    - • Cystic teratoma with skin epithelium without skin adnexae or other elements.
- ♦ Immature teratoma (malignant):
  - – Adult and primitive or embryonal-type tissues seen microscopically
  - – Grossly solid, solid and cystic, or mostly cystic
  - – Immature neural type tissue most often seen but any immature tissue from ectoderm, mesoderm, or endoderm can be encountered
  - – The amount of immature tissue should be reported relative to all tissues examined
  - – GFAP can be useful to identify glial tissues, both mature and immature.
  - – Prognosis based on amount and type of immature components; best when a predominance of neural tissues is seen
  - – Grading:
    - • Grade 1: predominantly mature tissues with loose mesenchymal tissue, immature cartilage, and tooth anlagae
    - • Grade 2: fewer mature tissues; focal neuroepithelial tissue with mitotic figures <3/HPF
    - • Grade 3: few to no mature tissues and abundant neuroepithelium
  - – Cellular stroma occupies ≥ 4 low power fields
  - – Malignant neuroectodermal tumors are tumors with an exclusive malignant neural component
  - – Teratomas exclusively composed of ependymal structures are designated as ependymomas

Struma Ovarii

Clinical

- ♦ Overgrowth of thyroid tissue in association with teratoma
- ♦ Associated with Brenner tumor, mucinous cystadenoma, and carcinoid tumors

Macroscopic

- ♦ Gross appearance of thyroid tissue with red, meaty consistency
- ♦ Occasionally cystic

Microscopic

- ♦ Normal to nodular thyroid tissue that can show features of thyroiditis, hyperplasia, carcinoma
- ♦ Cystic changes may be prominent

Treatment/Prognosis

- ♦ Surgical removal
- ♦ Prognosis same as in other teratomas

Carcinoids

Clinical

- Carcinoid tumors may arise as an element of a teratoma, a metastasis, or a primary ovarian neoplasm.
- Carcinoid syndrome (flushing, wheezing, etc.) may occur due to a release of serotonin and other neuropeptides.
- Strumal carcinoids are tumors that show features of struma ovarii and carcinoid tumors

Macroscopic

- Solid mass with yellow-tan color
- Average diameter = 10 cm

Microscopic

- Nests of round cells forming trabecular or acinar groups
- Nucleus with "salt and pepper" chromatin
- Similar appearance to carcinoid tumors in gut, lung, and so forth
- May have abundant fibrous stroma

Immunohistochemistry

- Chromogranin +, neuron-specific enolase +, synaptophysin +, serotonin +

Differential Diagnosis

- Granulosa cell tumor:
  - Call-Exner bodies, nuclear grooves
- Brenner tumor:
  - Grooved nuclei, presence of mucinous epithelium
- Metastatic carcinoid tumor:
  - May be difficult to differentiate met vs. primary: presence of teratomatous component favors latter; bilateral tumors favors metastatic; clinical history important
- Sertoli-Leydig cell tumor:
  - Less well-formed trabecular cords; lack of neuroendocrine differentiation

Sex Cord Stromal Tumors

General

- Approximately 5% of all ovarian tumors
- Tumors that show differentiation following sex cords or stroma
- Granulosa and Sertoli-Leydig type cells
- Inhibin (TGF-B family of peptides) positivity found in many sex cord-stromal tumors by immunhistochemical techniques that may be useful in differential diagnosis

Granulosa Cell Tumors

- Two subtypes:
  - Adult and juvenile granulosa cell tumors
- Cytogenetic studies of tumors associated with trisomy 12

Treatment/Prognosis

- Treated by hysterectomy and salpingo-oophorectomy for adult form; conservative treatment for younger patients
- Prognosis dependent on tumor stage

Adult-Type Granulosa Cell

Clinical

- Most commonly in postmenopausal women
- Associated with symptoms of hyperestrinism (metrorrhagia) and endometrial hyperplasia
- Rarely androgenic effects
- Most low stage at presentation (Stage 1); good prognosis
- Recurrences tend to be late (>5 years)

Macroscopic

- Unilateral >90%
- Solid mass with smooth external surface
- Small cysts with thin fluid sometimes present
- Cysts occasionally large
- Grey to yellow color cut surface

Microscopic

- Variable architectural patterns with microfollicular (Call-Exner bodies), macrofollicular, diffuse, trabecular. Nuclei with folds or grooves "coffee bean nuclei" (inconspicuous in diffuse pattern)
- Occasional bizarre multinucleated cells that probably represent degenerative changes may be seen.
- Variable leuteinization

Immunohistochemical

- Vimentin +, progesterone +, estrogen +, keratin –/+ (dot-like pattern), smooth muscle actin +, S-100 + (50%), inhibin +

Differential Diagnosis

- Carcinoid tumors:
  - "Salt and pepper" chromatin, no nuclear grooves
- Poorly differentiated surface epithelial carcinomas
  - Strong cytoplasmic keratin positivity, more atypia, high mitotic rate, bilateral involvement, psamomma bodies favor carcinoma
- Endometrial stromal sarcoma
- Small cell carcinoma:
  - High mitotic rate, lack of features seen in typical granulosa cell tumors

- Fibroma/thecoma:
  - Exclusive spindle cell component
- Metastatic carcinoma

Juvenile Granulosa Cell Tumors

Clinical

- Diagnosed in women <20 years, many prepubertal
- Associated with precocious puberty
- Very good prognosis; may be treated conservatively with unilateral salpingo-oophorectomy
- Recurrence tends to be early (<5 years)

Macroscopic

- Similar to adult type

Microscopic

- Diffuse pattern most common with larger cells and abundant eosinophilic luteinized cytoplasm
- Nuclear grooves and Call-Exner bodies less common than in adult form
- Nuclear atypia and numerous mitoses more common
- Inhibin +

Differential Diagnosis

- Small cell carcinoma:
  - Scanty cytoplasm, high mitotic rate

Fibrothecoma

Thecoma

Clinical

- Postmenopausal women
- Usually unilateral
- Associated with excesses of estrogen (e.g., endometrial hyperplasia)
- Luteinized theomas may be associated with sclerosing peritonitis
- Benign

Macroscopic

- Firm, encapsulated mass
- Generally solid, may have few small cysts
- Yellow color
- Calcification ±

Microscopic

- Spindle cells with varying amounts of collagen production
- Hyaline plaques may be present.
- Stromal hyperplasia of ovary may be prominent.
- Luteinized cells sometimes seen (luteinized thecoma)
- Inhibin +

Fibroma

Clinical

- Any age; account for ~4% ovarian tumors
- Arise from ovarian stromal cells
- Unilateral
- Patients may have endometrial hyperplasia.
- Associated with:
  - Gorlin's syndrome (basal nevus cell syndrome)
  - Meig's syndrome (fibroma, ascites, pleural effusion)
- Benign clinical course

Macroscopic

- Firm, solid, white-colored mass; average size = 12 cm
- Some with cystic or myxoid changes

Microscopic

- Spindle cells with storiform pattern or intersecting bundles
- Hypercellular fibromas referred to as cellular fibromas
- Mitoses should not exceed >3 per 10 HPF (= fibrosarcoma)
- Inhibin +

Differential Diagnosis

- Thecoma:
  - –Yellow in color, fibromas tend to be white in color
- Fibrosarcoma:
  - Hypercellularity with mitoses >3/10 HPF, necrosis
- Fibromatosis:
  - Young patients
- Massive edema:
  - Younger patient
  - Differentiate from edematous fibroma (older patients)

Sclerosing Stromal Tumor

- Younger patients (20–30 years)
- Rarely hormonally active
- Sharply defined gray mass with cellular pseudolobules, alternating hypercellular areas, and numerous dilated thin- walled vessels with hemangiopericytomatous-like vascular pattern separated by collagenous to fibrous stroma with round lipidized cells and spindle cells

Sertoli-Leydig Cell Tumors (Androblastoma, Arrhenblastoma)

Clinical

- Uncommon tumor (<0.5%)
- Young women, rarely postmenopausal
- Predominantly unilateral

- Symptoms of androgen excess (hirsutism, acne, balding, etc.) in 30% to 40% of cases
- Relatively good prognosis, most Stage I

Macroscopic

- Solid and cystic mass, 5–15 cm

Microscopic

- Variable histology/clinical behavior; most categorized as follows:
  - Well-differentiated or Meyer's Type I (11%):
    - Tubular formations lined by Sertoli-like cells with clusters of Leydig cells
  - Intermediate type or Meyer's Type II (54%):
    - Sertoli-like cells in sheets or cord formations separated by Leydig cells and spindled cells
  - Poorly differentiated or Meyer's Type III (13%):
    - Spindle cells with sarcomatoid appearance
  - Retiform (15%):
    - Sertoli and Leydig cell elements with irregular clefts resembling rete testis
  - With heterologous elements (22%):
    - Sertoli-Leydig cell elements and other tissue elements such as skeletal muscle, gastrointestinal epithelium, cartilage, liver, and so forth
  - Pure sertoli cell tumor:
    - Similar appearance as well-differentiated sertoli cell tumor but without Leydig cells or spindle stroma; abundant cytoplasmic lipid sometimes seen

Immunohistochemical

- Testosterone and estradiol +, keratin + (sertoli cells), inhibin +
- EMA, PLAP, CEA, and S100 –

Differential Diagnosis

- Metastatic carcinoma:
  - Signet ring cells, abundant mucin, and atypia
- Carcinoid tumors: Neuroendocrine markers +
- Granulosa cell tumor:
  - Lack of prominent tubules or Leydig cells, greater number of granulosa cells, nuclear grooves
- Yolk sac tumor:
  - May be confused with retiform variant of Sertoli-Leydig cell tumor (SLCT), AFP +
- Teratoma:
  - May be confused with heterologous SLCT; SLCT lacks neural type tissues

Gynandroblastoma

- Rare
- Sex cord-stromal tumor with Sertoli-Leydig cell and granulosa cell components in similar proportions

Sex Cord Tumor With Annular Tubules

- Associated with Peutz-Jehger's syndrome (30%)
- Simple and complex tubules surrounding hyaline material, which may be partially calcified
- Hyperestrinism may be present clinically
- Two types:
  - Unilateral large tumor often mixed with germ cell tumor elements
  - Small bilateral microscopic and multifocal lesions associated with Peutz-Jehger's syndrome

Differential Diagnosis

- Gonadoblastoma:
  - Sex cord tumor with annular tubules may have sex cord elements, hyaline bodies, and calcification resembling gonadoblastoma, but does not have germ cell elements

Ovarian Tumor of Wolffian Origin

- Epithelial cells with oval to elongated nuclei forming cystic or tubular structures, imparting a "sieve-like" appearance microscopically
- Occurs in broad ligament, ovary, and retroperitoneum
- Probably arises from Wolffian/mesonephric derivatives
- Behaves in benign fashion

Lipid (Steroid) Cell Tumors

- Leydig cell and adrenal cortical types
- Occur at any age, often virilizing clinically
- Unilateral yellowish/yellow-brown nodules separated by fibrous trabeculae
- Large round to polyhedral cells with lipid-rich cytoplasm (+ for fat stains)
- Reinke's crystalloids may be present (Leydig cell tumors).
- Vimentin +, keratin + (50%)
- Most follow benign course
- Differential includes stromal luteoma, fibrothecomas, and granulosa cell tumors with luteinization

Stromal Luteoma

- Postmenopausal women
- >1/2 are estrogenic, with associated ovarian hyperthecosis
- Most tumors are circumscribed small lesions up to 3 cm in size

- Aggregates of eosinophilic luteinized cells in nests and cords with little stroma intervening:
  - Pseudovascular spaces may be present secondary to degenerative changes within tumor

Unclassified Sex Cord-Stromal Tumors

- Tumors with features that do not fit into a well-defined category

Other Tumors

Myxoma

- Cystic and solid myxoid mass
- Microscopic appearance similar to myxomas elsewhere
- Benign

Gonadoblastoma (Dysgenetic Genadoma)

Clinical

- Occurs in patients with gonadal dysgenesis (XY gonadal dysgenesis and XO-XY mosaicism):
  - Rarely in normal individuals
- Described in ataxia-telangiectasia

Macroscopic

- Bilateral in 1/3 cases
- Small mass, may be incidental finding

Microscopic

- Mixture of germ cells and sex-cord stromal elements with features of granulosa or sertoli cells
- Calcification and or hyalinization present

Sarcomas

- Primary ovarian sarcomas are rare
- Fibrosarcoma:
  - High mitotic rate (>3/10 hpf), necrosis; aggressive clinical course
- Endometrial stromal sarcomas:
  - Spindle cells arranged around vessels
  - High- and low-grade types as in uterus
- Chondrosarcomas, rhabdomyosarcoma, and leiomyosarcomas also described

Metastatic Tumors

- >50% bilateral
- Gastrointestinal tract, breast, lung, uterus, and skin common sites of origin
- Krukenberg tumor:
  - Metastatic carcinoma, often bilateral, with numerous signet ring cells

Lymphoma/Leukemia

- Primary involvement rare:
  - Usually result of generalized disease
- Lymphomas predominately non-Hodgkin's type

Differential Diagnosis

- Dysgerminoma, poorly differentiated carcinoma, or granulosa cell tumor

Small Cell Carcinoma

Clinical

- Young women with average age = 22 years
- Two types:
  - Hypercalcemic type
    - Hypercalcemia resolves after surgery.
  - Pulmonary type:
    - Resembles small cell carcinoma of lung
- Poor prognosis for both types

Macroscopic

- Usually bilateral
- Large and solid mass with necrosis and hemorrhage

Microscopic

- Small cells with scanty cytoplasm
- Follicle-like structures and larger pleomorphic cells may be seen.
- Keratin +, vimentin +, EMA +, chromogranin +, S100 –

Differential Diagnosis

- Juvenile granulosa cell tumor
- Lymphoma: LCA +

Hepatoid Carcinoma

- Rare tumor with aggressive clinical course
- Features resemble hepatocellular and gastric hepatoid carcinomas
- Most postmenopausal women
- AFP +
- Differentiate from metastatic hepatic tumors to ovary

PERITONEUM

General

- The peritoneum is the mesodermally derived mesothelial lining that covers the abdominal cavity and intrabdominal organs:
  - Visceral peritoneum
  - Parietal peritoneum
- Immunohistochemical studies of peritoneal tissues are characteristically + for cytokeratin and vimentin and – for CEA, LEU-M1, and B72.3
- Electron microscopic studies show desmosomes, tonofillaments, and long surface microvilli

Inflammation

Peritonitis

- Generalized inflammation of peritoneal tissues due to a variety of causes that may resolve completely or result in adhesions or abscess cavities:
  - Chemical: bile, pancreatic, or gastrointestinal fluids
  - Bacterial:
    - Primary: streptococci, mostly children and adults with severe liver disease
    - Secondary: perforation of a viscus, mycobacteria, fungi
  - Foreign substances: granulomatous inflammation due to talc, starch granules, keratin (endometrioid adenocarcinomas with squamous differentiation)
  - Schlerosing peritonitis (mesenteric panniculitis):
    - Idiopathic fibrous thickening of mesentery, rare; characterized by chronic inflammatory infiltrate, fat necrosis, foamy histiocytes, and myofibroblasts
- Associated with luteinized thecomas of the ovary

Differential Diagnosis

- Desmoplastic mesothelioma:
  - More atypia, necrosis, invasion
- Fibrous/hyaline plaques:
  - Paucicellular plaques most commonly found on splenic capsule

Mesothelial Hyperplasia and Metaplasia

Mesothelial Hyperplasia

- Diffuse or nodular proliferation of mesothelial cells due to irritation/inflammation, viral infection, collagen vascular disease, or chronic peritoneal effusions (e.g., liver disease):
  - Nodular hyperplasia sometimes seen in strangulated hernia sacs
- Nests, papillary, or tubule formations microscopically
- Psamomma bodies may be present

Differential Diagnosis

- Mesothelioma:
  - Features favoring malignancy over hyperplasia are
    - Necrosis and severe nuclear atypia
    - Grossly apparent nodules
    - Invasion
- Serous borderline tumor of peritoneal primary:
  - Hyperplasia of mesothelium common with nearby ovarian tumors
  - Psamomma bodies, columnar type epithelium favor serous tumor

Mesothelial Metaplasia

- Squamous metaplasia
- Mullerian metaplasia (exclusively in pelvis of females):
  - Endometriosis
  - Endosalpingiosis
  - Ectopic decidual reaction
- Cartilaginous metaplasia

Cysts

Pseudocyst

- Cyst without an epithelial lining
- Probably due to resolved inflammatory process

Solitary Cyst

- Small cyst ranging in size from 1–6 cm
- Attached to abdominal wall or free in pelvis
- Also likely to be related to inflammatory process

Cystic Lymphangioma

- Multiloculated thin-walled cyst filled with milky white fluid
- Cyst wall lined by flattened endothelial cells and may have wisps of smooth muscle bundles
- Originates from lymphatic vessels
- Benign

Endometriosis/Endometriotic Cyst

- See ovary section

Cyst of Müllerian Origin

- Cystic mass in males lined by epithelium resembling fallopian tubal epithelium
- Located in pelvis in the region of the bladder or rectum and also mesentery
- Thought to originate from persistence of Müllerian tissues

Neoplasms of Serous Membrane

Solitary Fibrous Tumor

- Benign
- Thought to arise from submesothelial fibroblasts
- Histologically identical to tumors seen in pleura:
  - Spindle cells separated by bundles of collagen
  - Hemangiopericytomatous vascular pattern
  - Thick-walled vessels
- Tumor cells stain + for CD34, – for cytokeratin
- Differential includes fibrosarcoma, which shows more atypia, CD34 –

Adenomatoid Tumor

- "Localized epithelial meosthelioma" characterized by smooth muscle and glandular proliferation as seen in genital tract
- Benign
- Uncommon

Multilocular Peritoneal Inclusion Cysts (Multicystic Benign Mesothelioma)

Clinical

- Predominantly a disease of young women
- Present with chronic pelvic pain and/or mass

Macroscopic

- Multiple thin-walled translucent cysts (<1–20 cm) with thin serous fluid
  - Usually in pelvis

Microscopic

- Cystic spaces lined by cuboidal to flattened mesothelial cells
- May have focal areas with mesothelial hyperplasia
- Foci of chronic inflammatory cells in cyst wall

Differential Diagnosis

- Cystic lymphangioma:
  - Located in mesentery; cysts with milky fluid; cyst wall may have smooth muscle bundles
- Cystic malignant mesothelioma
- Greater mesothelial proliferation and atypia

Treatment/Prognosis

- Benign but tend to recur

Primary Serous Papillary Carcinoma of Peritoneum

- Histologically similar to ovarian serous papillary carcinoma with tubular and papillary pattern, epithelial tufting, and psamomma bodies
- Some tumors may resemble serous borderline tumors:
  - Differentiate borderline tumors from carcinoma by high-grade cytology and desmoplastic stromal invasion of the latter
  - Generally have good prognosis
  - Prognosis for serous carcinoma similar to Stage III ovarian carcinoma
- Ovaries are minimally (surface granularity) or not involved by tumor
- Differentiation from mesothelioma aided by immunohistochemistry (see Table 17-3)

Malignant Mesothelioma

Clinical

- Male predilection
- Less common than in thoracic cavity
- Present with ascites, abdominal pain, and weight loss
- Associated with asbestos exposure; long latency
- May metastasize to regional lymph nodes and rarely to lung

Macroscopic

- Multiple nodules and plaques studding peritoneal surface
- Combined pleural and peritoneal involvement may be seen occasionally

Microscopic

- Histologic types:
  - Epithelial:
    - Tubulopapillary and epithelioid
    - Most common subtype
  - Sarcomatous
  - Biphasic
  - Undifferentiated

Electron Microscopy

- Elongated, thin, bushy microvilli
- Length/diameter of microvilli >15:1
- Numerous tonofillaments

Immunohistochemistry (also see Table 17-3)

- LEU-M1 –, CEA –, B72.3 –, and Ber-EP4 –
- EMA +, cytokeratin +, vimentin +, calretinint
- Rare mesotheliomas + for bcl-2
- Positive for human milk fat globulin (HMFG) with membranous staining pattern
- Presence of hyaluronic acid is suggestive of mesothelioma

Variants

- Desmoplastic mesothelioma:
  - Abundant collagen deposition (>50%)

  - Differential includes fibromatosis
- Well-differentiated papillary mesothelioma:
  - Rare
  - Mostly in women
  - Lacks stratified epithelium or significant cytologic atypia
  - Rare to no mitoses
  - Most follow benign clinical course
- Malignant mesothelioma of tunica vaginalis testis:
  - Papillary or tubular pattern involving tunica vaginalis
  - Rare
  - Clinically may act in indolent or agressive course
- Deciduoid peritoneal mesothelioma
  - Rare aggressive tumor of young women with prominent decidual change

Differential Diagnosis

- Mesothelial hyperplasia:
  - Less atypia
  - No necrosis or invasion
  - No gross nodules
  - Smaller nuclei
- Metastatic adenocarcinoma:
  - See Table 17-3
- Primary peritoneal serous carcinomas:
  - Female patients
  - Histologically indistinguishable from ovarian primary
  - Psamomma bodies and bizarre nuclear features favor peritoneal serous carcinomas

Treatment/Prognosis

- Poor prognosis, especially sarcomatoid variant
- Chemotherapy
- Radiotherapy ineffective

Intra-Abdominal Desmoplastic Small Round Cell Tumor

Clinical

- Young adults
- Males > females
- Abdominal pain, and/or abdominal mass or ascites
- Associated with t(11;22) translocation

Macroscopic

- Large solid mass with multiple small peritoneal implants
- White to gray coloration
- Focal necrosis and hemorrhage

Microscopic

- Nests of uniform small cells with scanty cytoplasm and slightly epithelioid or spindled cells within a fibrous stroma
- Numerous mitotic figures
- Necrosis
- Lymphatic invasion common

Immunohistochemistry

- Positive for cytokeratin, NSE, desmin (dot-like paranuclear), vimentin, EMA
- Chromogranin/synaptophysin ±
- Negative for actin

Electron Microscopy

- Paranuclear intermediate cytoplasmic filaments
- Dense core granules

Treatment/Prognosis

- Aggressive course with poor prognosis
- Tumor debulking with chemotherapy and radiation

Miscellaneous Lesions of Peritoneum

Endosalpingiosis

Clinical

- Presence of fallopian tubal epithelium outside the fallopian tube
- Occurs in many locations:
  - Ovary
  - Omentum
  - Pelvic peritoneum
  - Upper female genital tract

Macroscopic

- Often incidental finding on microscopic exam

Microscopic

- Three cell types as in fallopian tubal epithelium:
  - Secretory cells
  - Peg cells
  - Ciliated epithelial cells
- ± occasional psamomma bodies

Differential Diagnosis

- Borderline serous tumor of ovary
  - Cellular stratification/tufting, more atypia
- Mesonephric remnant
  - Cuboidal nonciliated epithelium
- Salpingiosis isthmica nodosa (see fallopian tube section)
- Endometriosis

  - Endometrial glands and stroma with evidence of hemorrhage

Infarcted Appendix Epiploica

- Mesenteric adipose tissue that becomes twisted, leading to infarction
- Infarcted tissue may be attached to the abdominopelvic wall or lay loose in pelvis
- May become calcified

Leiomyomatous Peritonealis Disseminata

- Rare
- Nodular submesothelial proliferation of benign smooth muscle cells
- Uterine leiomyomata commonly present
- May rarely involve regional lymph nodes; differentiate from metastatic leiomyosarcoma

Inflammatory Psuedotumor/Myofibroblastic Tumor

- Young patients, benign course
- Systemic symptoms include weight loss, fever, anemia/thrombocytopenia, and polyclonal hypergammaglobulinemia
- Histological examination shows plasma cells, lymphocytes, and "myofibroblastic" type spindle cells

Walthard Nest

- Benign
- Women of any age
- Tunica vaginalis of men
- Small nests of transitional type epithelium as in ovary/fallopian tube

Urachal Remant

- Developmental defect characterized by sinus tract or cyst formation connecting the bladder (dome) and umbilicus or as blind sinuses originating from either site
- Cyst wall may be transitional or glandular type
- May give rise to adenocarcinomas or squamous or transitional carcinoma

Endocervicosis

- Benign endocervical type glands within peritoneum or smooth muscle of pelvic viscera, usually around uterus and bladder
- Rare
- Benign
- Differential includes metastatic low-grade adenocarcinoma

Tailgut Cyst (Retrorectal Cystic Hamartoma)

- Benign, developmental anomaly
- Precoccygeal multiloculated cyst with squamous, transitional, or glandular epithelium and smooth muscle
- Differential includes teratoma:
  - Other germ cell layer elements present

Necrotic Pseudoxanthomatous Nodule

- Peritoneal nodules with an outer rim of palisaded pseudoxanthoma cells and fibrous tissue surrounding necrotic centers
- Evidence of endometriosis may be sparse or absent.
- Condition may be seen after treatment or spontaneously
- Infection should be ruled out

Ectopic Decidual Reaction

- Seen during pregnancy as whitish peritoneal nodules on peritoneal surface
- Nodular aggregates of submesothelial decidualized cells

Metastatic Tumor

- Most common primary site is from ovary
- Other sites include gastrointestinal tract, breast, lung, skin (melanoma) and others

Pseudomyxoma Peritonei

- Mucinous neoplasm involving peritoneum (jelly belly)
- Appendiceal (most common) or ovarian primary (borderline or mucinous carcinoma)
- Pools of mucin with intestinal type epithelium

TNM CLASSIFICATION OF OVARIAN CARCINOMA (1997 REVISION)

- T1:
  - Tumor confined to ovaries
  - T1a: Unilateral tumor, capsule intact, no external involvement of ovary by tumor, no ascites
  - T1b: Bilateral tumor, capsule intact, no external involvement by tumor, no ascites
  - T1c: Unilateral or bilateral tumor with *external involvement* of ovary, or ruptured capsule, or ascites with cytologic involvement by tumor
- T2:
  - Tumor involving one or both ovaries with pelvic extension of tumor
  - T2a: Tumor extension or metastatic implants on uterus or fallopian tubes
  - T2b: Tumor extension to other pelvic tissues
  - T2c: Stage IIA or IIB + tumor involving ovarian surface, or capsular rupture, or malignant cells present in peritoneal washings
- T3:
  - Intraperitoneal tumor outside of the pelvis and/or metastases to retroperitoneal lymph nodes or pelvic tumor with involvement of omentum or small bowel
- M1:
  - Distant metastases

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Chapter 21

Placenta and Gestational Trophoblastic Disease

Raymond W. Redline, MD

Table of Contents

GESTATIONAL TROPHOBLASTIC DISEASE (GTD)

Precursor Lesions

Partial Hydatidiform Mole

Clinical

- Diandric triploidy only
  - Three complete haploid sets of chromosomes (n = 69)
  - Two sets derived from the father
- Never seen in digynic triploid
- Trophoblast hyperplasia results from unbalanced overexpression of paternal gene products (genomic imprinting)
- Presentation:
  - Late first or early second trimester spontaneous abortion
  - Occasionally presents with increased maternal human chorionic gonadotropin (hCG)
- 1/13 spontaneous abortions are triploid
  - 2/3 of these are diandric; 1/2 fulfill diagnostic criteria for partial mole
- Overall prevalence: 1/39 spontaneous abortions
- Incidence of persistent GTD requiring chemotherapy = 0.5% to 20%
- Subsequent invasive mole, choriocarcinoma, and placental site trophoblastic tumors are rare

Macroscopic

- Spongy villous tissue with small 1–2 mm fluid-filled vesicles (as in hydropic abortus and complete hydatidiform mole)
- Fetal fragments or malformed fetus may be seen occasionally

Microscopic

- Diagnostic criteria:
  - Villous trophoblast hyperplasia (usually predominantly syncytiotrophoblast)
  - Dimorphic population of large and small villi without intermediate forms
  - Hydropic villi >0.5 mm
  - Irregular villous contour often with multicellular trophoblast inclusions within villous stroma
- Other features:
  - Mazelike villous capillary vascular pattern
  - Atypical implantation site trophoblast
  - Molar villi with well-delineated central cisterns
  - Villous stromal karyomegaly (nuclei 2–3 times normal size)

Flow Cytometry or Image Analysis

- Occasionally helpful in differentiating partial versus complete mole or partial mole versus hydropic abortus (modal DNA index = 1.5 vs. 1.0 for the other two conditions)

Differential Diagnosis

Hydropic Abortus

- Lacks dimorphic population of large and small villi without intermediate forms
- Generally lacks villous trophoblast hyperplasia
- Focal trophoblast hyperplasia can be seen in approximately 3% of nonmolar abortions:
  - May require a limited hCG follow-up, depending on severity
- Lacks atypical implantation site (intermediate trophoblast with enlarged irregular hyperchromatic nuclei)

Complete Hydatidiform Mole

- Uniformly hydropic villi with central cisterns
- Lacks second population of small villi
- Villous trophoblast hyperplasia is generally more diffuse and atypical, and involves cytotrophoblast and syncytiotrophoblast equally.

Complete Hydatidiform Mole

Clinical

- Diandric diploid gestation (two sets of chromosomes with both sets derived from the father; Karyotype 46,XX or XY)
- Trophoblast hyperplasia results from an overexpression of paternally derived gene products and/or a lack of maternally derived gene products (genomic imprinting)
- Early presentation (<8 weeks):
  - Anembryonic missed abortion by ultrasound
- Late presentation (>8 weeks):
  - Large for dates
  - Vaginal bleeding
  - Elevated hCG
  - Occasionally: hyperemesis, preeclampsia, thyrotoxicosis, or bilateral adnexal masses (theca lutein cysts)
- Incidence of persistent GTD requiring chemotherapy = 20% to 30%
- Rate of subsequent choriocarcinoma is approximately 1/40

Macroscopic

- Usually a discohesive collection of swollen grape-like molar villi up to 5–10 mm in diameter. Occasionally at <8 weeks, hydropic/molar changes are inconspicuous

Microscopic

- Classic complete hydatidiform mole:
  - Diffuse, circumferential villous trophoblast hyperplasia
  - Involves both cytotrophoblast and syncytiotrophoblast
  - Uniformly hydropic villi, many with well-defined central cisterns
  - Lack of fetal vessels and nucleated red blood cells
  - Frequent atypical implantation site
- Early complete hydatidiform mole:
  - Focal cytotrophoblast and syncytiotrophoblast hyperplasia of both villi and the undersurface of the chorion
  - Redundant bulbous terminal villi (± focal hydrops)
  - Hypercellular myxoid villous stroma often with stromal karyorrhexis
  - Labyrinthine network of villous stromal canaliculi
  - Atypical implantation site
  - Fetal vessels or nucleated red blood cells may be seen
- Tumor grading: lacks prognostic value in current practice and is not routinely performed

DNA Studies

- PCR-based microsatellite analysis on microdissected maternal and fetal tissue removed from the paraffin blocks can be used to confirm diandric origin (not routinely available).

Differential Diagnosis

- Partial hydatidiform mole:
  - See earlier
- Hydropic abortus:
  - Generally lacks trophoblast hyperplasia and atypical implantation site
  - Degenerative features:
    - Hypocellular villous stroma and intervillous fibrin
- Early spontaneous/elective abortion:
  - Generally lacks trophoblast hyperplasia and atypical implantation site
  - Lacks villous stromal hypercellularity and canaliculi

Malignant Trophoblastic Tumors

Choriocarcinoma

Clinical

- Rapidly growing and invasive, with frequent metastases
- Generally curable with multiagent chemotherapy
- Can follow any pregnancy at any stage
- Frequency of preceding pregnancy types:
  - Hydatidiform mole 45%
  - Term pregnancy 25%
  - Spontaneous abortion 25%
  - Ectopic pregnancy 5%
- Cytogenetics:
  - Diploid or near diploid, with frequent polyploid subpopulations
  - Gains or losses of chromosomes 1, 3, 8, 10, and 12
- Three partially overlapping definitions:
  - Clinical:
    - Radiologically confirmed metastatic GTD following pathologically confirmed molar pregnancy
  - Pathologic:
    - Biphasic avillous trophoblast at any site with cytologic features of malignancy
  - Primary placental:
    - Parenchymal nodules of biphasic malignant trophoblast in a normal placenta
- Clinical Staging:
  - 0 Elevated hCG only
  - 1 Uterine corpus involvement
  - 2 Lung metastases
  - 3 Pelvic and/or vaginal metastasis
  - 4 Distant metastasis
- Adverse prognostic factors:
  - Older age
  - Preceding nonmolar pregnancy
  - Longer interval to preceding pregnancy
  - Tumor size (>5cm)
  - hCG level (>$10^5$1o/liter)
  - Number of metastases
  - Metastasis to brain, liver, or GI tract
  - Previous chemotherapy
- Clinical management:
  - Serial maternal serum hCG determinations
  - Metastatic workup and chemotherapy instituted if hCG levels plateau or rise

Macroscopic

- Grossly hemorrhagic, ill-defined lesions within the uterovaginal wall or in the parenchyma of other organs
- Often difficult to detect nonhemorrhagic tumor tissue

Microscopic

- Biphasic tumor composed of malignant villous cytotrophoblast and syncytiotrophoblast

- Classic pattern:
  - Groups of 10–50 cytotrophoblast:
    - Uniformly enlarged central nuclei, prominent nucleoli, and margination of chromatin
    - Scant, watery, clear cytoplasms
  - Surrounded by a wreath-like arcade of multinucleate syncytiotrophoblast:
    - Enlarged irregular hyperchromatic nuclei and glassy eosinophilic cytoplasm
- Extensive tumor hemorrhage, necrosis, and perpendicular invasion of myometrial fibers (especially useful in the absence of classic pattern described above)

Immunocytochemistry

	Cytotrophoblast	Syncytiotrophoblast
Cytokeratin	+	+
hCG	–	+
Human placental lactogen (hPL)	–	+
Placental alkaline phosphatase (PLAP)	–	variable
Desmin	–	–
Vimentin	–	–
Carcinoembryonic antigen (CEA)	–	–
Alpha fetoprotein (AFP)	–	–

Differential Diagnosis

- Intervillous X-cell nodules:
  - Aggregates of intermediate trophoblast found in term placentas:
    - Lack nuclear atypia
    - Dense eosinophilic to purplish cytoplasm
    - Fibrinoid matrix
- Placental site trophoblastic tumor (PSTT):
  - Less hemorrhagic by gross exam
  - Tumor cells have dense eosinophilic cytoplasm and larger, more irregular and hyperchromatic nuclei than malignant cytotrophoblast
  - Syncytiotrophoblasts are rare
- Epithelioid trophoblastic tumor (atypical choriocarcinoma):
  - Tumors with features intermediate between choriocarcinoma and PSTT
  - Extremely rare; tumors are often seen in patients with previously treated choriocarcinomas (poorly characterized)

Placental Site Trophoblastic Tumor

Clinical

- Rare, generally indolent tumors
- 15% to 20% manifest malignant behavior (local invasion and distant metastasis)
- Resistant to chemotherapy
- Low serum hCG, generally <10,000 mIU/ml
- Usually follow term pregnancy (95% of cases), often with a long interval (up to 15 years)
- Precursor lesions:
  - Rarely if ever molar pregnancy
  - Possibly derived from placental site nodules

Macroscopic

- Presents as a uterine mass; generally nodular or polypoid
- Occasionally diffusely infiltrative

Microscopic

- Cohesive sheets of mononuclear intermediate trophoblast
- Often associated with zonal necrosis and prominent vascular invasion and remodelling (recapitulates normal implantation site)
- Individual cells generally mononuclear
- Occasionally binucleate, with abundant eosinophilic cytoplasm
- Enlarged, round to oval nuclei with coarse clumped chromatin and prominent nucleoli
- Tumors with a mitotic rate >5/10 high power fields, prominent necrosis, and less dense eosinophilic cytoplasm may have a worse prognosis

Immunocytochemistry

- Cytokeratin, hPL: diffusely +; hCG: weak or focal positivity only

Differential Diagnosis

- Placental site nodule (involuting or remote implantation site):
  - Well-circumscribed aggregates of intermediate trophoblast embedded in a fibrinoid matrix
  - Low cellularity
  - Bland cytologic features
  - Cytokeratin +; hPL, hCG, PLAP: variable
- Exaggerated implantation site (recent implantation site):
  - Seen with abortions (spontaneous or elective)
  - Intermediate trophoblast infiltrate decidua and myometrium as single or small groups of cells
  - Multinucleate placental site giant cells seen in specimen
  - Lacks necrosis and destructive myometrial invasion

PLACENTA

Acute Chorioamnionitis

Clinical

- Leading cause of preterm birth
- 40% of infants <1.5 kg have placentas with chorioamnionitis
- Pathogenesis:
  - Ascending infection (common)
  - Hematogenous (rare)
  - Transuterine from UTI (possible)
- Risk factors:
  - Racial and genetic predisposition
  - Incompetent cervix; premature cervical dilation
  - Change in cervicovaginal flora-bacterial vaginosis
- Organisms:
  - Predominantly normal flora: anaerobes, mycoplasmas
  - Less common: Group B streptococci, *E. coli*
  - With foreign body (cerclage, IUD): candidal species
  - Rare: *Listeria monocytogenes*, *Campylobacter fetus* spp.

Macroscopic

- Grayish discoloration of membranes
- Haziness and blurring of chorionic plate vessels
- Frank yellow-green exudate if severe
- Candida:
  - Yellow microabsesses on umbilical cord surface
- *L. monocytogenes* and *C. fetus*:
  - Intervillous abscesses and septic infarcts

Microscopic

- Maternal inflammatory response:
  - Membranes (from decidual postcapillary venules)
    - Early: diffuse band of PMNs in chorion
    - Intermediate: diffuse PMN in chorion and amnion
    - Late: necrosis and sloughing of amniocytes (necrotizing chorioamnionitis)
  - Chorionic plate (from intervillous space)
    - Early: PMNs in subchorionic fibrin
    - Intermediate: PMNs in chorionic plate and amnion
    - Late: Necrosis of amniocytes, PMN karyorrhexis
- Fetal inflammatory response:
  - Chorionic plate (from chorionic vessels)
    - Early: PMNs in vessel wall
    - Late: Vessel wall damage and mural fibrin deposits
  - Umbilical cord (from umbilical vessels)
    - Early: PMNs in umbilical vein only
    - Intermediate: PMNs in all vessels
    - Late: Degenerating PMNs in arcs around vessels (necrotizing or subnecrotizing funisitis)
- Candidal species:
  - Peripheral funisitis with microabsesses
- *L. monocytogenes*/ *C. fetus*:
  - Acute intervillositis/perivillitis

Special Stains and Cultures

- Candida (GMS and/or PAS of cord and membranes)
- Group B streptococci, L. monocytogenes (tissue gram stain)
- Anaerobes, C. fetus, other bacteria (Silver stains: Dieterle, Warthin-Starry, or Steiner)
- Bacterial cultures generally not useful

Differential Diagnosis

- Ischemic necrosis of decidua:
  - Degenerating PMNs, often focal
  - Predominantly confined to membranous decidual layer
- Isolated umbilical phlebitis:
  - Occasionally seen with meconium exposure
  - Lacks PMNs in amnion, chorion, and subchorionic fibrin

Meconium and Subacute Hypoxia

Clinical

- Pathogenesis:
  - Cord occlusion
  - Umbilical vein collapse
  - Vagally mediated intestinal vasoconstriction
  - Reflex defecation
- Predisposing factors:
  - Large active babies
  - Long umbilical cord
  - Decreased amniotic fluid (common postdates, > 42 weeks)
- Common (10% to 20% of all term deliveries); rarely if ever seen prior to 34 weeks
- Meconium aspiration syndrome:
  - Occurs in 8.6% of meconium-stained infants

- Respiratory distress in a term infant requiring oxygen with an abnormal CXR

♦ Severe meconium aspiration syndrome/birth asphyxia:
- Occurs in 2.9% of meconium-stained infants
- Chemical pneumonitis
- Extrapulmonary air leaks
- Pulmonary hypertension
- Hypoxic-ischemic encephalopathy
- High morbidity and mortality
- Often coexistent with other placental findings indicative of subacute (in utero) hypoxia

Macroscopic

♦ Green staining of membranes and chorionic plate (focal or diffuse)

♦ Green staining of umbilical cord (with prolonged exposure)

♦ Slippery edematous membranes with chorion-amnion separation

♦ Occasionally with signs of umbilical cord compression:
- True knots, hypercoiling, focal attenuation, or edema

Microscopic

♦ Meconium:
- Pigment-laden macrophages, often with cytoplasmic vacuoles

  Early: amnion only

  Late (≥3hrs): amnion, chorion, and decidua
- Number of macrophages correlates with amount of meconium within the first few hours after discharge

♦ Peripheral vascular necrosis:
- Degenerative changes in vascular smooth muscle cells (cellular dehiscence, nuclear pyknosis, cytoplasmic eosinophilia)
- Seen at the periphery of umbilical or chorionic vessels (bad prognostic sign)

♦ Subacute hypoxia:
- Increased nucleated red blood cells:
  - Indicator of significant in utero hypoxia leading to erythropoietin release
- Chorangiosis:
  - Numerical increase in the number of capillaries per terminal villus
  - >10 capillaries in >10 villi in several areas of the placenta
  - Seen in women delivering at high altitudes
  - Capillary proliferation in response to decreased oxygen availability or other angiogenic factors

Differential Diagnosis of Green Color

♦ Severe acute chorioamnionitis

♦ Chronic marginal separation/abruption with hemoglobin breakdown products

♦ Immune hemolytic anemia with bilirubin

♦ Pigment-laden macrophages:
- Hemosiderin (chronic marginal separation/abruption)
- Nonspecific (lipofuschin)

Maternal Arteriopathies and Preeclampsia

Clinical

♦ Primary (pregnancy-specific):
- Superficial implantation
- Failure of trophoblast to remodel spiral arteries predisposing to hypoxia and trophoblast-induced endothelial damage with subsequent fibrinoid necrosis of spiral arteries ("acute atherosis")

♦ Secondary (underlying maternal disease):
- Coagulopathy: antiphospholipid antibodies, others
- Essential hypertension
- Insulin-dependent diabetes mellitus
- Autoimmune disease
- Chronic renal disease

♦ Risk factors for primary disease:
- Primiparity (or multiparity with different father)
- Positive family history
- Obesity

♦ Presentations:
- Preeclampsia (hypertension, edema, and proteinuria)
- Intrauterine growth retardation (IUGR)
- Placental insufficiency and chronic fetal hypoxia
- Abruptio placenta
- Preterm labor

Macroscopic

♦ Placental weight less than expected for gestational age

♦ Old and recent infarcts

♦ Retroplacental hematoma consistent with abruptio placenta

♦ Thin umbilical cord indicative of fetal volume depletion

Microscopic

♦ Membrane decidua:
- Fibrinoid necrosis ("atherosis") of spiral arterioles
- Smooth muscle hypertrophy of spiral arterioles

♦ Villous parenchyma:
- Villous infarcts
- Accelerated maturation

- Increased syncytial knots
- Microinfarcts
- Decreased terminal villi

♦ Basal plate:
  – Excessive immature intermediate trophoblast
  – Nonremodelled spiral arteries with intact smooth muscle

Differential Diagnosis (Villous Infarcts)

♦ Increased perivillous fibrin:
  – Lack villous agglutination, karyorrhectic trophoblast, and PMN debris

♦ Intervillous thrombi:
  – Spherical, nonbasal, and show only focal pressure-related infarction of adjacent villi

Hemorrhagic Lesions

Intervillous Thrombus (Fetomaternal Hemorrhage)

Clinical

♦ Pathogenesis:
  – Traumatic rupture of terminal villous vessels with fetal bleeding into maternal circulation

♦ Kleihauer-Betke acid elution technique:
  – Quantifies volume of fetomaternal hemorrhage by staining for cells containing fetal hemoglobin in the maternal circulation

♦ Intervillous thrombi and small fetomaternal hemorrhages common

♦ Volume of hemorrhage correlates with number and size of thrombi

♦ Massive fetomaternal hemorrhage (associations):
  – Nonimmune hydrops fetalis
  – Intrauterine fetal death
  – Abnormal fetal monitoring (sinusoidal heart rate)

Macroscopic

♦ Spherical lesions displacing and surrounded by villi:
  – Recent: firm, glassy, dark red
  – Old: firm, light red, laminated

Microscopic

♦ Recent or organizing hemorrhage in the intervillous space

♦ Surrounded by and displacing villi without significant adjacent villous infarction

♦ Significance is enhanced by the findings of increased nucleated red blood cells and changes suggestive of hydrops fetalis (villous edema, cytotrophoblast proliferation, and increased Hofbauer cells)

Differential Diagnosis

♦ Villous infarct with central hemorrhage

♦ Retroplacental hemorrhage with intraplacental extension:
  – Irregular with focal extension to basal plate

♦ Massive subchorial thrombus:
  – Laminated expansile subchorionic hemorrhages elevating the chorionic plate
  – Probably due to ruptured stem villous vessels
  – Associated with very bad prognosis

♦ Septal cyst:
  – Clear-blood-tinged fluid-filled cyst of villous parenchyma
  – Surrounded by intermediate trophoblast

Retroplacental Hemorrhage Consistent With Abruptio Placenta

Clinical

♦ Classical presentation:
  – Vaginal bleeding, uterine rigidity, abdominal pain, hypotension/anemia

♦ Pathogenesis:
  – Premature rupture of one of the major arteries supplying the intervillous space, resulting in forceful separation of the placenta from the uterus

♦ Risk factors:
  – Preeclampsia/maternal arteriopathy
  – Substance abuse: cocaine and smoking
  – Physical trauma

♦ Clinicopathologic correlation recommended:
  – Only 1/2 of clinical abruptio placentae are pathologically apparent
  – Only 1/2 of pathologic retroplacental hematomas are associated with clinical abruptio placenta

♦ Sequela:
  – Acute birth asphyxia
  – Intrauterine fetal death
  – Neurologic impairment

Macroscopic

♦ Retroplacental hematoma

♦ Usually central or eccentric, indenting or rupturing into the villous parenchyma

♦ Concave indentation of the basal plate without a retroplacental hematoma

♦ Irregular basal intervillous thrombus

♦ Occasionally: overlying recent (red) villous infarction

Microscopic

♦ Basal plate: intradecidual hemorrhage, rupture through

basal plate, maternal arteriopathy (rare)

- Parenchyma: recent villous infarction, intravillous stromal hemorrhage, irregular basal intervillous thrombus

Differential Diagnosis

- Acute marginal separation:
  - Marginal hematoma without significant indentation or rupture of basal plate
  - No intradecidual hemorrhage

Retroplacental Hemorrhage Consistent With Marginal Separation

Acute Marginal Separation (Marginal Abruption)

Clinical

- Classical presentation:
  - Preterm labor with vaginal bleeding
  - Premature rupture of membranes
  - Rapid delivery at any gestation
- Pathogenesis:
  - Rupture of dilated tortuous marginal veins as a consequence of increased venous pressure
  - Collapse of the gestational sac following rupture of membranes, or acute inflammation
- Risk factors:
  - Premature rupture of membranes
  - Acute chorioamnionitis
  - Prior history of preterm birth
- Clinicopathologic correlation: probably accounts for the poor correlation between clinical abruptio placenta and its sequela: preterm delivery

Macroscopic

- Marginal retroplacental hematoma without significant indentation of villous parenchyma

Microscopic

- Marginal decidual venous dilatation, hemorrhage, and ischemic necrosis

Differential Diagnosis

- Abruptio placenta:
  - Usually central or paracentral, indentation of parenchyma
  - Overlying villous ischemia (stromal hemorrhage or infarction)

Chronic Marginal Separation (Chronic Abruption)

Clinical

- Classical presentation:
  - Recurrent vaginal bleeding throughout pregnancy, often with preterm labor and watery vaginal discharge (due to clot retraction)
- Pathogenesis:
  - Chronic marginal venous hemorrhage without progression to retroplacental separation; possibly related to abnormal, poorly supported implantation
- Risk factors:
  - Prior history of pregnancy loss
- Sequela:
  - IUGR
  - Preterm labor

Macroscopic

- Old, pale brown, marginal blood clot
- Circumvallate membrane insertion (complete or partial)
- Greenish discoloration of chorionic plate

Microscopic

- Hemosiderin-laden macrophages in membranes and chorionic plate
- Ridge of old blood clot pushing membranes away from margin (circumvallation)

Special Stains

- Iron stain to confirm hemosiderin deposition

Differential Diagnosis

- Circummarginate membrane insertion: membranes inserted away from the placental margin, but lacking the ridge of old blood clot and hemosiderin deposits; often accompanied by redundant folding of membranes at the placental margin

Fetal Thromboocclusive Lesions

Thrombotic Arteriopathy

Clinical

- Pathogenesis:
  - Thrombosis of chorionic plate or stem villous arteries resulting in downstream hyaline fibrosis and loss of fetal capillaries
- Risk factors:
  - Coagulopathy:
    - Maternal antiphospholipid or antiplatelet antibodies
    - Inherited fetal defect in coagulation cascade
    - Hypoxia or traumatic endothelial damage
  - Acute chorioamnionitis with severe chorionic vasculitis
  - Villous inflammation: chronic villitis, L. monocytogenes

  - Diabetes mellitus
- Sequela:
  - Intrauterine fetal death
  - Fetal thromboembolic disease (especially CNS)
  - Subacute asphyxia

Macroscopic

- Occasional: thrombus in chorionic plate artery (arteries travel over veins)
- Segmental or arcuate region of relative villous pallor

Microscopic

- Vascular thrombi (adherent, laminated, and/or calcified)
- Large or small groups of avascular terminal villi with stromal hyalinization

Differential Diagnosis

- Venous thrombooclusive changes ("hemorrhagic endovasculitis") (see below)
- Maternal infarct:
  - Collapsed intervillous space
  - Aggregated villi
  - Karyorrhexis, PMN debris, and trophoblast necrosis
- Villitis of unknown etiology:
  - Villi are often avascular but villous stroma shows chronic lymphohistiocytic infiltrate

Changes Consistent with Venous Stasis (Hemorrhagic Endovasculitis)

Clinical

- Pathogenesis:
  - Decreased flow through terminal villi
  - As a consequence of umbilical or chorionic venous occlusion, venous stasis mimicking changes accompanying stillbirth
- Risk factors:
  - Chronic compression of umbilical cord or chorionic vein
  - Fetal heart failure (hydrops fetalis)
  - Venous thrombosis
- Sequela:
  - Acute or subacute fetal hypoxia
  - Intrauterine fetal death

Macroscopic

- Large, congested, and often meconium-stained placenta and cord

Microscopic

- Terminal villi:
  - Karyorrhectic debris
  - Old and recent hemorrhage
  - Increased Hofbauer cells
  - Hypovascularity
- Chorionic plate and stem villous vasculature:
  - Fibromuscular sclerosis
  - Intimal fibrin cushions
  - Recent thrombi

Differential Diagnosis

- Changes due to recent stillbirth:
  - The diagnosis of venous thromboocclusive disease (hemorrhagic endovasculitis) in stillborns should be made with caution and depends on seeing nonaffected areas of the placenta
- Changes consequent to improper placental storage:
  - Fresh or incompletely fixed placentas stored for prolonged periods without refrigeration also mimic stillbirth and venous thromboocclusive change
- Fetal thrombotic arteriopathy:
  - Avascular villi with bland fibrosis
  - Lack hemorrhage or significant karyorrhexis

Chronic Inflammation and Coagulation

Congenital Infection

Clinical

- TORCH (pnemonic for organisms and serologic screening test):
  - Toxoplasma gondii
  - Others (syphilis, organisms rarely found in the United States)
  - Rubella virus
  - Cytomegalovirus
  - Herpes viruses (herpes simplex, EBV, varicella zoster)
- Pathogenesis:
  - Hematogenous infection of the fetus and placenta with a diffuse fetal inflammatory response in the placenta and direct teratogenic effects on the fetus
- Typical features:
  - All: hepatosplenomegaly, cytopenias, pneumonitis
  - T. gondii: CNS calcifications, retinitis
  - Rubella: congenital heart disease, cataracts, skin rash
  - Cytomegalovirus: CNS calcifications, retinitis, ascites
  - Herpes simplex: IUGR, microcephaly, hepatic necrosis
  - Syphilis: bone, skin, and mucosal membranes; GI lesions

  - Varicella zoster: limb and radicular skin defects
- Recurrence risk: Most TORCH infections are primary and confer protective immunity, preventing recurrence.

Macroscopic

- Small for gestational age placenta: herpes viruses, rubella
- Large for gestational age placenta: syphilis, *T. gondii*, CMV

Microscopic

- Common:
  - Diffuse lymphohistiocytic villitis with villous fibrosis and calcification
  - Chronic choriodeciduitis
  - Increased nucleated red blood cells
- Specific:
  - *T. gondii*: umbilical cord pseudocysts
  - Rubella: viral inclusions, endothelial necrosis
  - Cytomegalovirus: viral inclusions, villous plasma cells
  - Herpes simplex: viral inclusions. prominent necrosis
  - Syphilis: necrotizing umbilical periphlebitis, proliferative stem villous periarteritis

Special Studies

- Immunocytochemistry: CMV, HSV
- Silver stains (Warthin-Starry, Dieterle, Steiner): syphilis

Differential Diagnosis

- Villitis of unknown etiology:
  - Nonuniform patchy involvement
  - Predominantly lymphocytic
  - More intervillositis, less choriodeciduitis, less necrosis
  - Later gestational age, no fetal anomalies
- Nonspecific increase in Hofbauer cells (especially common with hydrops):
  - Lack lymphocytes, fibrosis, necrosis, or choriodeciduitis

Villitis of Unknown Etiology (VUE)

Clinical

- Presentation:
  - Nonhypertensive IUGR
  - Intrauterine fetal death
  - Recurrent reproductive failure
- Pathogenesis:
  - Infiltration of fetal villous stroma by maternal T-lymphocytes derived from the intervillous space
  - Basis for transepithelial migration and recurrence is poorly understood
- Relatively common (3% to 5% of term pregnancies), with 20% to 30% recurrence risk
- IUGR and other fetal morbidities parallel the extent of involvement
- Focal VUE relatively benign

Microscopic

- Nonuniform chronic inflammation of terminal and stem villi
- Lymphocytic, lymphohistiocytic, granulomatous, and active (with PMNs) variants
- Basal and diffuse subtypes
- Chronic intervillositis and perivillous fibrin common
- Plasma cells common in decidua, never in villi

Massive Chronic Intervillositis

Clinical

- Rare lesion associated with spontaneous abortion and recurrent reproductive failure
- May be related to autoimmune disease and/or maternal alloimmune responses to oncofetal antigen

Microscopic

- Diffuse infiltration of intervillous space by monocyte-macrophages
- Abundant perivillous fibrin and trophoblast necrosis
- Lacks a significant component of VUE

Differential Diagnosis

- Placental malaria:
  - Same histology; malarial pigment present
  - No history of recurrent reproductive failure
- VUE with prominent chronic intervillositis:
  - Villous inflammation
  - Polymorphous intervillous infiltrate (lymphs, monocytes, PMN)
- Acute (infectious) villitis and intervillositis:
  - Predominance of neutrophils, often with prominent eosinophils and plasma cells; stainable organisms

Massive Perivillous Fibrinoid (Maternal Floor Infarction)

Clinical

- Presentation:
  - Recurrent reproductive failure
  - Severe normotensive intrauterine growth retardation
- Pathogenesis (poorly understood):
  - Anomalous procoagulant expression on trophoblast
  - Inappropriate secretion of fibrinoid by trophoblast

  - Intervillous stasis due to relative maternal hypovolemia
- Very high recurrence risk:
  - Requires vigorous early fetal surveillance with early elective delivery or experimental therapy (steroids, aspirin, heparin, IVIG)

Macroscopic

- Placenta generally small for gestational age
- Placenta occasionally large (depending on the volume and distribution of fibrin)
- Classic maternal floor infarction has diffuse "orange rind-like" thickening of the basal plate.
- Most cases show diffuse parenchymal thickening.

Microscopic

- Extensive fibrin(oid) surrounds and displaces terminal villi
- Diffuse infiltration of fibrin(oid) by intermediate trophoblast (X cells)
- Accentuation of fibrin(oid) near and within the basal plate

Differential Diagnosis

- Massive chronic intervillositis:
  - Presence of intervillous monocyte macrophages
  - Generally lacks X cells
- VUE with chronic intervillositis:
  - Presence of polymorphous inflammatory infiltrate
  - Absence of X cells
- Stasis-related fibrin deposition of chorionic plate and stem villi:
  - Focal; spares basal region; does not involve terminal villi
- Perivillous fibrin associated with placental atrophy:
  - Focal change associated with thinning and attenuation of placental parenchyma
- Old villous infarcts:
  - Collapsed intervillous space
  - Abundant karyorrhectic debris
  - Well-circumscribed
- Nodular perivillous fibrin ("fibrinoid necrosis of villi"):
  - Nodular aggregates of fibrin(oid) eccentrically protruding from and incorporated within terminal villi
  - Accelerated placental maturation and other signs of maternal arteriopathy

Multiple Pregnancy

General

- Monochorionic twin placentas are monozygous:
  - Derived from a single fertilized egg
  - Usually have twin-twin anastomoses
- Dichorionic twin placentas:
  - Either dizygous (derived from two independent fertilized eggs) or monozygous
  - Never have vascular anastomoses

Clinical

- Dizygous twinning (depends on ovarian function):
  - Familial
  - Increased with African ancestry
  - Seen with ovulation induction (clomiphene) and in vitro fertilization techniques
- Monozygous twinning (error in embryogenesis):
  - Sporadic
  - Spectrum extends from conjoined twins to monochorionic monoamnionic twins to monochorionic diamnionic to dichorionic diamnionic, depending on the exact timing of the error
- Clinical syndromes:
  - Cord entanglement and IUFD:
    - Monoamnionic twins only
  - Twin oligohydramnios polyhydramnios syndrome (TOPS):
    - Twin-twin transfusion syndrome:
      - Monochorionic only; usually diamnionic
      - Size discrepancy with circulatory imbalance
      - Due to vascular anastomoses (1 small twin/1 large twin)
      - Often with hydrops of either or both twins
    - Non-TTS:
      - Dichorionic twins with asymmetric placental insufficiency resulting in worsening IUGR of the disadvantaged twin (1 small twin/1 normal twin)
      - Increased incidence of preterm labor, preeclampsia, and cerebral palsy for all twins

Macroscopic

- Separate placentas (dichorionic):
  - No assessment of dividing membranes required; injection studies not indicated
- One placenta with dividing membrane (mono- or dichorionic):
  - Peel dividing membrane (2 vs. 3 layers):
    - Three layers = diamnionic dichorionic:
      - Divide placentas, weigh, and process separately
      - Injection studies not necessary
      - Submit dividing membrane for histology

- Two layers = diamnionic monochorionic:
  - Look for surface anastomoses
  - Perform air (or other) injection studies for vascular anastomoses
  - Do not separate placentas
  - Take sections from each twin's vascular territory
  - Submit dividing membrane for histology

♦ One placenta without dividing membrane = monoamnionic:
  – Process as described above for diamnionic monochorionic twins (except for dividing membrane)

Microscopic

♦ Monochorionic:
  – Dividing membrane has two layers of amnion only.
  – Rule out fetal thrombotic arteriopathy or asymmetry of villi secondary to differences in vascular perfusion

♦ Dichorionic:
  – Dividing membrane has two layers of amnion separated by a fused layer consisting of two chorions
  – Look for causes of placental insufficiency with TOPS syndrome or other morbidities affecting one infant only.

Air Injection Studies

♦ Select twin with lower birth weight (or smaller umbilical cord)

♦ Ligate and serially inject air distal to the ligation for each of the two to four arteries branching off cord (arteries travel over veins)

♦ Look for air appearing in veins (or arteries) of the second twin

♦ If negative, repeat with arteries from the second twin

Differential Diagnosis

♦ Monochorionic placenta with twins of different sexes:
  – Consider 46,XY/45,XO with loss of an X chromosome in one twin

♦ Separate placentas with vascular anastomoses:
  – Consider severe atrophy of the region between the umbilical cords in a monochorionic placenta

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Chapter 22

Prostate

David G. Bostwick, MD
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Table of Contents

INFLAMMATORY LESIONS

Acute Bacterial Prostatitis

Clinical

- Sudden onset of fever, chills, pain, and irritative and obstructive symptoms
- Swollen, tender, and indurated on digital rectal examination
- *E. coli* infection accounts for 80% of cases
- Diagnosis confirmed by culture of midstream urine and/or prostatic secretions
- Biopsy contraindicated

Microscopic

- Microabscess formation and heavy infiltrate of acute and chronic inflammatory cells
- Acinar destruction and epithelial cell degeneration
- Stromal hemorrhage and edema

Chronic Bacterial and Non-Bacterial Prostatitis

Clinical

- Chronic nonbacterial prostatitis is more common than bacterial prostatitis (*E. coli*)
- Chlamydia trachomatis and ureaplasma urealyticum are common etiologic agents
- Often follows an indolent clinical course with relapses and remissions

Microscopic

- Epithelial degeneration and metaplasia
- Chronic inflammation

Differential Diagnosis

- High-grade prostatic intraepithelial neoplasia (HGPIN):
  - Partial acinar involvement, nuclear stratification, and prominent nucleoli
  - Caution is urged in diagnosing PIN in the setting of inflammation

Granulomatous Prostatitis

Clinical

- Prior history of urinary tract infection is common (Table 22-1)
- Suspicious for carcinoma on digital rectal examination
- Probably caused by blockage of prostatic ducts and stasis of secretion

Microscopic

- Specific etiology often cannot be determined from histologic examination
- Glandular disruption, epithelial degeneration, and metaplasia
- Granulomatous inflammation with or without necrosis
- Polymorphous chronic inflammation composed of multinucleated giant cells, histiocytes, lymphocytes, plasma cells, and neutrophils
- Intracellular and extracellular Michaelis-Gutman bodies in malakoplakia highlighted by PAS and von Kossa stains
- Stellate and geographic granulomas with palisading histiocytes and vasculitis are often seen in Wegener's granulomatosis
- Necrotizing vasculitis with fibrin deposition and tissue eosinophilia is often seen in Churg-Strauss vasculitis
- Central zone of fibrinoid necrosis surrounded by peripheral palisading epithelioid histiocytes is often seen in postsurgical granuloma

Table 22-1. Etiology of Granulomatous Prostatitis

Infections	
Bacterial	Tuberculosis (AFB staining), syphilis
Fungal	Coccidioidomycosis, cryptococcosis, histoplasmosis
Parasitic	Schistosomiasis
Viral	Herpes zoster
Iatrogenic	
Post-surgery or radiation	
Post-BCG treatment	
Malakoplakia	
Systemic granulomatous disease	
Allergic	
Sarcoidosis	
Systemic vascular diseases	
Wegner's granulomatosis	
Polyarteritis nodosa	
Churg-Strauss syndrome	
Idiopathic	

Variants

- Xanthoma:
  - Incidental findings in elderly men
  - Clusters and sheets of lipid-laden histiocytes in a nodular configuration
  - CD68 +, cytokeratin –
- Xanthogranulomatous prostatitis:
  - Non-specific granulomatous prostatitis
  - Composed predominantly of sheets of epithelioid histiocytes
  - Polymorphous inflammatory infiltrate
  - Associated with atrophy and acinar disruption

Immunohistochemistry

- PSA –, PAP –, Cytokeratin –

BENIGN LESIONS AND MIMICS OF ADENOCARCINOMA

Benign Prostatic Hyperplasia (BPH)

Clinical

- Occurs in 50% or more of men >50 years
- Often presents with lower urinary tract symptoms
- Develops in transition zone, resulting from stromal and epithelial proliferation
- Etiology and pathogenesis not completely understood
- Hormonal regulation is mainly via dihydrotestosterone (DHT), derived from testosterone by the activity of 5-alpha-reductase
- Growth factors also play an important role in the development of BPH
- Epidermal growth factor (stimulatory) and transforming growth factor-ß (inhibitory) after prostatic growth

Macroscopic

- Yellow-gray rubbery to firm and bulging nodules in the transition zone and periurethral region
- For transurethral resection specimens, submit a minimum of six cassettes for the first 30 g of tissue and one cassette for every 10 g thereafter

Microscopic

- Epithelial and stromal hyperplasia in the transition zone and periurethral region
- Stromal nodules consist of fibromuscular spindle cell proliferation with thin- or thick-walled vessels and scattered lymphocytic infiltrate (mainly T-helper cells)
- Often associated with prostatic infarct with squamous and urothelial metaplasia
- At least part of a nodule should be present for the diagnosis to be made on biopsies (uncommon)

Metaplasia

Squamous Metaplasia

- Often seen at edges of prostatic infarct and after hormonal therapy
- Common in the region of prostatic urethra in patients with an indwelling catheter
- Syncytial aggregates of polygonal cells with abundant eosinophilic cytoplasm and hyperchromatic nuclei

Mucinous Metaplasia

- Cluster of columnar cells with mucin production
- Focal involvement of acini and lack of involvement of the entire lobular unit of acini
- Negative immunostaining for PSA and PAP
- High molecular weight cytokeratin 34ßE12 +
- Mucicarmine +, PAS with diastase +, alcian blue +

Urothelial Metaplasia

- Presence of urothelium beyond the normal urothelial-columnar junction
- Stratified epithelium with streaming effect of nuclei
- Ovoid cells with pale cytoplasm, uniform nuclei, nuclear grooves, perinuclear halos, fine granular chromatin, and inconspicuous nucleoli
- The long axis of the cells is perpendicular to the basement membrane

Nephrogenic Metaplasia

- Suburethral location; composed of exophytic mass of small tubules or papillae with solid and cystic appearance
- Uniform nuclei with fine granular chromatin and inconspicuous nucleoli
- Edematous and often inflamed stroma without desmoplasia
- Often associated with proliferative papillary urethritis
- Negative immunoreactivity for PSA, PAP, and CEA
- High molecular weight cytokeratin 34ßE12 +

Atrophy

- Often located in the peripheral zone
- Lobular configuration of atrophic glands with open ectatic lumina in a sclerotic stroma
- Variable acinar architectural distortion and irregularity
- Cystic dilation of acini and ducts lined by flattened

attenuated epithelial cells with scant cytoplasm, hyperchromatic nuclei, and inconspicuous nucleoli
- Basal cell layer may be fragmented

Post-Atrophic Hyperplasia

- Occurs in all zones with predilection for the peripheral zone
- Occurs in 18% of radical prostatectomy specimens
- Lobular cluster of atrophic acini surrounding central dilated larger acini in a hyalinized stroma
- Variable acinar architectural distortion and irregularity
- Acini lined by a single layer of secretory cells with proliferative changes
- Moderate cytoplasm with luminal apocrine blebs
- Enlarged nuclei with evenly distributed fine granular chromatin and occasional enlarged nucleoli
- Fragmented basal cell layer
- Often associated with adjacent inflammation

Basal Cell Proliferation

- Basal cells probably contain the regenerative or stem cells of the prostate
- Occurs in 6% of biopsies and 9% of transurethral resection specimens

Basal Cell Hyperplasia (BCH)

- Often occurs in the transition zone
- Proliferation of basal cells with multiple layers (≥ 2)
- Often eccentrically located with partial involvement of acini, retaining the overlying columnar or cuboidal secretory cells
- Basal cells have enlarged nuclei, fine powdery chromatin, and occasional nuclear grooves
- Nuclear "bubble" artifact or intranuclear vacuole often seen in formalin-fixed tissue but not in frozen section
- Often associated with chronic inflammation

Atypical Basal Cell Hyperplasia (ABCH)

- Same as basal cell hyperplasia but with prominent nucleoli
- Require >10% of cells displaying prominent nucleoli for diagnosis

Basal Cell Adenoma

- Variant of BPH
- Nodule formation with basal cell hyperplasia
- Well-circumscribed solid nests and aggregates of hyperplastic basal cells in a condensed fibrous stroma
- Plump nuclei, high nucleocytoplasmic ratio, and inconspicuous nucleoli
- High molecular weight cytokeratin 34ßE12 +
- PSA ± (patchy), PAP ± (patchy)
- S100 and chromogranin ±

Cribriform Hyperplasia

- Often occurs in the transition zone
- Cribriform pattern of acinar proliferation with intact basal cell layer
- Uniform cells with clear or granular cytoplasm and inconspicuous nucleoli

Sclerosing Adenosis

Clinical

- Incidental findings in 2% of transurethral resection specimens
- Occurs in transition zone, usually solitary and microscopic
- The only prostatic lesion with myoepithelial differentiation of basal cells

Microscopic

- Well-circumscribed proliferation of small acini in a densely myofibroblastic stroma
- Thickened basement membrane with prominent myoepithelial cells
- Acini appear to merge with adjacent pale staining cellular stroma with abundant loose ground substance
- Compressed and distorted glands imparting a pseudoinfiltrative pattern
- Occasional nuclear and nucleolar enlargement
- Moderate amount of clear to eosinophilic cytoplasm

Electron Microscopy

- Myoepithelial differentiation with aggregates of thin filaments

Immunohistochemistry (Table 22-2)

- High molecular weight cytokeratin 34ßE12 +
- Muscle-specific actin (MSA) +
- S-100 protein +

Differential Diagnosis

- Atypical adenomatous hyperplasia:
  - Lacks densely hyalinized stroma and fragmented basal cell layer
  - MSA –, S-100 protein –
- Prostatic adenocarcinoma:
  - Cytologic atypia with nucleomegaly and prominent nucleoli
  - Lacks hyalinized stroma
  - Absence of MSA, HMW cytokeratin, and S-100 protein staining

Table 22-2. Immunohistochemical Profiles of Benign Lesions in the Prostate

	PSA/PAP	*HMW CK*	*Cytokeratin* Protein*	*S-100*	*SMA*	*Zonal predilection*
Xanthoma/ xanthogranulomatous prostatitis	–	–	–	–	–	Peripheral
Nephrogenic metaplasia	–	+	+	–	–	Periurethral
Post-atrophic hyperplasia	+	+	+	–	–	Peripheral
Atypical basal cell hyperplasia	±	+	+	±	–	Transition
Cribriform hyperplasia	+	+	+	–	–	Transition
Sclerosing adenosis	+	+	+	+	+	Transition
Stromal hyperplasia with atypia	–	–		–	+	Transition
Hyperplasia of mesonephric remnants	–	+	+	–	–	Unknown
Verumontanum mucosal gland hyperplasia	+	+	+	–	–	Verumontanum
Seminal vesicles/ejaculatory ducts	–	+	+	–	–	Seminal vesicles
Cowper's gland	–	+	+	–	–	Urogenital diaphragm
Paraganglion	–	–	±	±	–	Base>apex

** Broad spectrum cytokeration*
Note: PSA/PAP = prostate-specific antigen/prostate acid phosphatase, HMW CK = high molecular weight cytokeratin (34ßE12), SMA = smooth muscle actin

Stromal Hyperplasia With Atypia

- Often occurs in the transition zone
- Increased stromal cellularity with bizarre giant cells and nuclear degenerative changes
- Nuclear pleomorphism, nuclear hyperchromasia, and pyknosis
- Lacks the circumscription of leiomyoma
- No mitotic figures

Hyperplasia of Mesonephric Remnants (Florid Mesonephric Hyperplasia)

- Occurs in all zones, mainly in the transition zone
- Rare lobular proliferation of small acini lined by single layer of cuboidal cells
- Two growth patterns:
  - Closely packed small round to oval tubules lined by cuboidal hobnail cells with eosinophilic cytoplasm
  - Proliferation of small acini with empty lumens or solid nests
- May have haphazard arrangement at periphery, imparting pseudoinfiltrative growth pattern
- Ectatic tubules with lumenal colloid-like eosinophilic inclusions and micropapillary infoldings
- Uniform cells with occasional nuclear and nucleolar enlargement
- PSA –, PAP –, high molecular weight cytokeratin 34ßE12 +

Verumontanum Mucosal Gland Hyperplasia

- Located in the posterior wall of the mid prostatic urethra
- Used as a landmark during transurethral resection of the prostate (resection is proximal)
- Recognized in 14% of radical prostatectomy specimens
- Rare in biopsies and not seen in transurethral resection specimens
- Often intimately associated with urothelium
- Multifocal lobular proliferation of closely packed small (>25) acini usually with intact basal cell layer
- Uniform cells with basophilic cytoplasm and lack of cytologic atypia
- Numerous corpora amylacea and distinctive orange-red non-laminated concretions that are often fragmented

- Luminal secretory cells may contain lipofuscin pigment
- Intact basal cell layer
- PSA +, PAP +, high molecular weight cytokeratin 34ßE12 +

Seminal Vesicles and Ejaculatory Ducts

Microscopic

- Well-circumscribed
- Complex papillary folds with irregular convoluted lumens
- Lined by non-ciliated pseudostratified columnar epithelium
- Ejaculatory ducts have large lumens with more prominent mucosal folding and prominent circumferential layer of muscular wall
- Stromal (eosinophilic) hyaline bodies:
  - Often seen within the muscular wall, resulting from smooth muscle degeneration
  - Highlighted by Masson's trichrome and PAS stain
- Bizarre smudged cells with granular refractile golden yellow lipofuscin pigment
- Enlarged nuclei with nuclear hyperchromasia, coarse granular chromatin, prominent nucleoli, and occasional nuclear halos
- Multinucleated giant cells with pyknotic nuclei and a lack of mitotic figures
- DNA aneuploid in 6.7% of seminal vesicles

Immunohistochemistry

- PSA –, PAP –, HMW cytokeratin (34βE12)+

Differential Diagnosis

- Pigmented prostatic epithelium:
  - Scant, finely granular, yellow-brown pigment
  - PSA +, PAP +, 34βE12 –
- Post-atrophic hyperplasia:
  - Lobular arrangement of acini surrounding central dialted acini; proliferative change
  - Lacks lipofuscin or cytologic atypia
- High-Grade PIN:
  - Lacks lipofuscin; displays significant nuclear pleomorphism
- Adenocarcinoma:
  - Lacks lipofuscin; displays nuclear degeneration; bizarre nuclei uncommon
  - PSA +, PAP +, 34βE12 –

Senile Seminal Vesicle Amyloidosis

Clinical

- Occurs in up to 8% of men 46–60 years, 23% between age 61–75 years, and 40% >75 years
- Derived from secretory protein of the epithelium
- Benign; not associated with systemic amyloidosis

Microscopic

- Linear or nodular subepithelial deposition of amorphous eosinophilic amyloid
- Basement membrane thickening

Immunohistochemistry

- Congo red +, crystal violet +, toluidine blue +, PAS +

Cowper's Glands

Microscopic

- Located within the urogenital diaphragm; seen in apex biopsies
- Not present in transurethral resection specimens
- Equivalent to Bartholin's glands of female genital tract
- Small paired bulbomembranous urethral glands surrounded by skeletal muscle
- Well-circumscribed small acinar proliferation
- Uniform cells with abundant apical mucinous cytoplasm
- Lack nuclear and nucleolar enlargement

Immunohistochemistry

- PSA –, high molecular weight cytokeratin +, mucicarmine +, PAS with diastase +

Differential Diagnosis

- Mucinous metaplasia:
  - Focal involvement of a small number of acini
  - Lacks skeletal muscle
- Mucinous adenocarcinoma:
  - Nests and clusters of epithelial cells floating in extravasated mucin pool
- Well-differentiated adenocarcinoma:
  - Prominent nucleoli

Paraganglia

- Located closer to the base than the apex of the prostate
- Usually associated with neurovascular structures
- Solid nests and organoid arrangement of closely packed polygonal cells with abundant clear cytoplasm
- Centrally located uniform nuclei with or without prominent nucleoli
- PSA –, PAP –, cytokeratin –, neuroendocrine markers +

Prostatic Urethral Polyp

Proliferative Papillary Urethritis

- Papillary proliferation of urothelium with metaplastic changes and reactive atypia
- Inflammation and stromal edema

Ectopic Prostatic Tissue (Benign Polyp With Prostatic-Type Epithelium)

- Adolescents or young adults present with hematuria
- Delicate papillae with fibrovascular core and prostatic epithelial lining

Nephrogenic Metaplasia (Described Elsewhere)

Benign Urothelial Papilloma

- Patient <50 years with solitary lesion <2 cm in greatest dimension
- < 7 cells in thickness with intact superficial (umbrella) cell layer
- No significant cytologic atypia (no more than Grade 1 urothelial carcinoma)

Inverted Papilloma

- Patients present with hematuria and urinary obstructive symptoms
- Smooth contoured invaginated cords and columns of urothelial cells with intact overlying urothelium
- Peripheral palisading basaloid cells and thickened basement membrane
- Squamous metaplasia and microcystic change
- Scant stroma
- Lacks fibrovascular cores

PUTATIVE PRECURSORS OF ADENOCARCINOMA

High-Grade Prostatic Intraepithelial Neoplasia (HGPIN)

Definition

- Precancerous end of the morphologic continuum of cellular proliferations within preexisiting prostatic ducts, ductules, and acini

Clinical

- Divided into low-grade (formerly PIN 1) and high-grade (formerly PIN 2 and 3)
- Some pathologists prefer not to report low-grade PIN, recognizing the difficulty in separating this lesion from benign epithelium and reactive atypia
- Morphometrically, PIN is genotypically and phenotypically linked to cancer
- Precedes the onset of carcinoma by 5–10 years
- Multifocal (63% of cases) and co-exists with cancer in 86% of prostatectomy specimens
- Occurs in the nontransition zone (63% of cases) and all zones (36%)
- Present in up to 4.2% of transurethral resection specimens (2.8% without cancer, 10.2% with cancer)
- The volume of HGPIN increases with the pathologic stage, Gleason grade, and positive surgical margins in patients with prostate cancer
- More prevalent and extensive and occurs approximately a decade earlier in African American men than Caucasian men
- Prevalence and extent of HGPIN are decreased after androgen deprivation therapy
- No influence on serum PSA concentration
- Occurs in up to 16% of contemporary needle biopsies
- The diagnosis of HGPIN confers a 35% to 50% predictive value for cancer on repeat biopsy
- Follow-up is suggested at 3- or 6-month intervals, and thereafter at 12-month intervals for life after diagnosis

Patterns of Growth

- Tufting (97% of specimens with HGPIN, most common)
- Micropapillary (66%)
- Flat (21%)
- Cribriform (19%)

Pattern of Spread

- Replacement of normal luminal secretory cells with preservation of the basal cell layer
- Direct invasion with disruption of the basal cell layer
- Pagetoid spread (rare)

Microscopic

- Nuclear and nucleolar enlargement are the cytologic hallmark of HGPIN
- Cellular crowding, irregular spacing, nuclear stratification, and overlapping
- Partial acinar involvement may be seen
- Cells usually display cytoplasmic blebs along the luminal surface
- Disruption of the basal cell layer is highlighted by high molecular weight cytokeratin

Differential Diagnosis

- Inflammatory reactive atypia

  - Metaplastic (eosinophilic) changes and inflammatory background
- Urothelial metaplasia:
  - Lacks prominent nucleoli
- Seminal vesicles and ejaculatory ducts:
  - Bizarre cells with lipofuscin pigment
  - Nuclear hyperchromasia, nuclear pleomorphism, and degenerative changes
  - PSA and PAP –
- Cribriform hyperplasia:
  - Occurs in transition zone; sieve-like pattern
  - Uniform cells with clear cytoplasm
  - Lacks nuclear and nucleolar enlargement
- Post-atrophic hyperplasia:
  - Lacks prominent nucleoli
- Atypical basal cell hyperplasia:
  - Small solid nests or eccentric expansion of the basal cell layers between normal columnar secretory cells and basement membrane
  - The long axis of basal cells is usually parallel to the basement membrane
  - Enlarged nuclei with delicate stippled chromatin, occasional nuclear grooves, and nuclear "bubble" artifact
  - Often associated with inflammatory background
  - Cytokerain 34ßE12 +
- Low-grade PIN:
  - The epithelium lining ducts and acini are heaped up, crowded, and irregularly spaced
  - Lacks prominent nucleoli and less nuclear hyperchromasia
  - Intact basal cell layer without disruption
- Ductal (endometrioid) prostatic adenocarcinoma:
  - Lacks basal cell layer
- Large gland variant of Gleason pattern 3 carcinoma and cribriform variant:
  - More extensive involvement, infiltrative growth pattern
  - Often associated with small acinar carcinoma
  - Lacks circumferential basal cell layer

Atypical Adenomatous Hyperplasia (AAH)

Clinical

- Usually occurs in the transition zone and is found in ~23% of prostatectomy specimens
- Multicentric in ~46% of cases
- The biologic significance is uncertain and was proposed as a putative precursor lesion
- The extent and zonal distribution of AAH and carcinoma share a weak but significant association
- Shares less frequent, but similar allelic imbalance with prostatic adenocarcinoma
- May be associated with a subset of low-grade carcinoma arising in the transition zone
- The identification of AAH should not influence or dictate therapeutic decisions

Microscopic

- Requires most or all of the focus to be present for diagnosis of AAH on biopsy
- Well-circumscribed nodular proliferation of small acini at the peripheral of BPH
- Parent gland with larger branching lumina in the central location
- Lacks diffuse nucleolar enlargement
- Infrequent intraluminal mucin secretions and crystalloids
- Basal cell layer fragmented

Differential Diagnosis

- Verumontanum mucosal gland hyperplasia:
  - Located in the posterior wall of the distal prostatic urethra
  - Back-to-back arrangement of small acini with prominent corpora amylacea
  - Fragmented nonlamellated orange-red concretions
  - Cytoplasmic lipofuscin
  - Intact basal cell layer and intimately associated with urothelial-lined ducts
- Post-atrophic hyperplasia:
  - Lobular cluster of atrophic acini with proliferative change
  - Not intimately associated with nodular hyperplasia
  - Associated with adjacent atrophy with inflammation, stromal fibrosis, or smooth muscle atrophy
- Sclerosing adenosis:
  - Biphasic pattern with hyalinized periacinar stroma
  - S-100 protein +, actin +
- Low-grade small acinar prostatic adenocarcinoma:
  - Nucleolar enlargement
  - Lacks basal cell layer

ATYPICAL SMALL ACINAR PROLIFERATION (ASAP), SUSPICIOUS FOR MALIGNANCY

Clinical

- A diagnostic category encompassing a spectrum of histologic abnormalities that fall below the threshold for the diagnosis of cancer
- The incidence of ASAP is ~2.5% in contemporary prostate biopsies
- Predicts ~45% likelihood for cancer on repeat biopsy
- Many ASAP foci may represent marginally sampled cancer
- 99% of cancers were diagnosed on second and third biopsy, usually within 6 months after the ASAP diagnosis (73%)
- 41% of cancers were detected exclusively in other sites of initial ASAP lesion
- The entire prostate should be rebiopsied due to random sampling variation

Microscopic

- Lacks the full complement of requisite architectural and cytologic features of cancer
- Usually very small in size
- The focus often disappears on deeper levels
- Lacks unequivocal cytologic features of malignancy
- Enlarged nucleoli are often difficult to find
- Clustered growth of acini
- May represent partial sampling of AAH, sclerosing adenosis, or low-grade cancer
- Treatment-induced atypia
- Confounding acinar atrophy and prominent inflammation in the immediate vicinity of suspicious acini, and poor histologic preparations
- Features that may be present include:
  - Infiltrative growth
  - Variation in acinar size
  - Nucleomegaly
  - Nucleolar enlargement
  - Microvacuolated cytoplasm
  - Intraluminal proteinaceous secretions
  - Luminal mucin
  - Crystalloids

Immunohistochemistry

- High molecular weight cytokeratin (34ßE12) may be helpful

Differential Diagnosis (see Prostatic Adenocarcinoma)

- Prostatic adenocarcinoma:
  - Usually requires a minimum of three malignant acini for the diagnosis, unless:
    - Prominent cytologic anaplasia was present
    - No confounding inflammation
    - Persistence of cancer on serial sections
    - The possibility of seminal vesicle/ejaculatory ducts and other mimics has been excluded
- HGPIN
- Atrophy and post-atrophic hyperplasia
- Sclerosing adenosis
- Basal cell hyperplasia
- Atypical adenomatous hyperplasia

MALIGNANT TUMORS

Prostatic Adenocarcinoma

Clinical

- Most common non-skin cancer in American men
- Accounted for 198,100 newly diagnosed cancers and 31,500 cancer deaths in 2001
- One in six men will develop clinically evident prostate cancer during his life
- Prevalence increases from 10% at age 50 years to ~80% at age 80 years
- Proposed risk factors include age, family history, race, dietary fat, heavy metal exposure (cadmium, zinc), vasectomy, obesity, alcohol, and HGPIN or ASAP on biopsy
- The American Cancer Society recommended in 1997 that men age 50 with a minimum life expectancy of 10 years undergo digital rectal examination and PSA screening annually
- An abnormal serum PSA concentration is most commonly defined as a value >4.0 ng/ml
- Up to 25% of men with cancer have normal serum PSA (<4 ng/ml)
- Serum PSA half-life is 2–3 days
- 70% to 80% of prostate cancers arise in the peripheral zone (often referred to as the posterior lobe in the older literature), 15% to 25% in the transition zone, and 10% in the central zone

- ♦ Prostatic carcinoma in the transition zone is usually well-differentiated

Macroscopic

- ♦ Yellow-white mass with a firm consistency in the peripheral zone
- ♦ Many are grossly inapparent

Gleason Grading

- ♦ Based on the degree of architectural differentiation
- ♦ The predominant grade is recorded as the primary grade, and the nondominant grade is assigned secondary grade
- ♦ When only one pattern exists (frequently encountered on biopsies), then double the grade
- ♦ Gleason score = primary grade + secondary grade
- ♦ Needle biopsy underestimates tumor grade in 33% to 45% cases, and overestimates grade in 4% to 32% cases

Reporting

- ♦ Biopsy specimens:
  - – Biopsy site
  - – Histopathologic type of carcinoma
  - – Gleason grade
  - – Extent of cancer
    - • % of specimen involved
    - • Number of cancer foci
  - – Perineural invasion (not an independent predictive factor)
  - – Extraprostatic extension (rare)
  - – Associated conditions (e.g., post-atrophic hyperplasia)
  - – Ancillary studies (e.g., DNA ploidy by digital imaging analysis)
- ♦ Transurethral resection specimens
- ♦ Weight:
  - – 12 g, embed totally; >12 g, a minimum of six cassettes for the first 12 g, and thereafter one cassette for every 10 g; if cancer involves <5% of tissue submitted, all remaining tissue should be examined)
- ♦ Histopathologic type of carcinoma:
  - – Gleason grade
  - – Extent of cancer (% of specimens)
  - – HGPIN
- ♦ Radical prostatectomy specimens:
  - – Weight and size of the prostate
  - – Histopathologic type of carcinoma
  - – Gleason grade
  - – Location of cancer:
    - • Bilateral vs. unilateral (left or right)
    - • Anterior vs. posterior
    - • Peripheral zone vs. transition zone
  - – Estimated cancer volume (% of specimens)
  - – Extraprostatic extension (EPE):
    - • Location and extent
    - • Definition of EPE:
      - ▪ Cancer in adipose tissue
      - ▪ Cancer in perineural spaces of the neuromuscular bundles outside the prostate
      - ▪ Cancer in anterior muscle beyond the rounded interface between the fibromuscular stroma and skeletal muscle
  - – Seminal vesicle invasion:
    - • Cancer in the adventitia but not in the muscular wall of the seminal vesicle does not qualify for seminal vesicle invasion
  - – Surgical margin status:
    - • Positive margins are defined as cancer cells at the inked surface
    - • Sites and extent of margin involved may be used.
  - – Vascular invasion
  - – HGPIN
  - – Associated conditions (e.g., nodular hyperplasia)
  - – Lymph node status:
    - • Anatomic sites
    - • Number of positive nodes
    - • Size of nodal metastasis
    - • Extranodal extension (we exclude this because of recent data)
  - – Ancillary studies (e.g., DNA ploidy by digital imaging analysis or flow cytometry)
  - – Pathologic stage

Microscopic

- ♦ The diagnosis of cancer is made in the presence of ≥3 malignant acini in most cases
- ♦ Angulated and distorted acini with an irregular haphazard arrangement and infiltrative growth pattern
- ♦ Acini vary in size, shape, and spacing, and lack basal cell layer
- ♦ Enlarged nuclei with large eccentrically located prominent nucleoli (>1 μm)
- ♦ The presence of multiple nucleoli is strong evidence of malignancy
- ♦ Vacuolated or microvacuolated cytoplasm
- ♦ Collagenous micronodules are a specific finding of prostatic adenocarcinoma, correlated with mucin production by the tumor (0.6% of biopsies and 12.7% of prostatectomies)

- Perineural invasion is of diagnostic value, but has no apparent clinical significance
- Complete circumferential perineural growth, intraneural and/or ganglion invasion are diagnostic for cancer
- Intraluminal crystalloids and amorphous wispy basophilic acid mucin secretions are helpful, but not specific findings of cancer
- Neuroendocrine cells with large eosinophilic granules are seen focally in 10% of cases, but have no diagnostic or prognostic significance
- Co-exists with HGPIN in 86% of cases
- Adenocarcinoma with atrophic features:
  - Occurs in up to 2% of contemporary needle biopsies
  - Not considered as a specific clinicopathologic entity
  - Similar prognosis as conventional prostatic adenocarcinoma
  - Haphazard arrangement of small dilated acini resembling sclerotic pattern of atrophy
  - Acini lined by flattened, attenuated epithelium with scant cytoplasm
  - Nucleomegaly, nuclear hyperchromasia, and prominent nucleoli
  - Lacks basal cell layer
  - Considered to be Gleason pattern 3 if no glandular fusion
- Cribriform pattern of carcinoma:
  - Used as a descriptive term, not a specific entity
  - Considered as Gleason pattern 3 or 4 carcinoma
  - Lacks basal cell layer
  - Associated with other patterns of acinar adenocarcinoma

Immunohistochemistry (Table 22-3)

- PSA (located in endoplasmic reticulum, vesicle vacuoles, lumina) +
- PAP (lysosome) +
- High molecular weight cytokeratin (34ßE12) –

Differential Diagnosis

- Inflammatory reactive atypia:
  - Associated with inflammation and metaplasia
  - Lacks nucleolar enlargement
  - High molecular weight cytokeratin (34ßE12) +
- Xanthoma and xanthogranulomatous prostatitis:
  - Sheets of foamy histiocytes
  - PSA/PAP –, cytokeratin –, macrophage markers (CD68) +
- Post-atrophic hyperplasia (PAH):
  - Lobular clusters of atrophic acini with epithelial proliferative changes
  - Central large dilated atrophic acini or ducts
  - Moderate cytoplasm with occasional apical cytoplasmic blebs
  - Lacks diffuse nucleolar enlargement
  - Background of inflammation, atrophy, and stromal fibrosis
  - Intact or fragmented basal cell layer
- Atypical basal cell hyperplasia:
  - Proliferation of basal cells between normal columnar secretory cells and basement membrane
  - Eccentric expansion of multiple basal cell layers
  - The long axis of basal cells is often oriented parallel to the luminal surface
  - Clear cytoplasm
  - Enlarged nuclei with fine powdery chromatin, occasional nuclear grooves, and nuclear "bubble" artifact
  - Often associated with inflammation
  - High molecular weight cytokerain (34ßE12) +
- Atypical adenomatous hyperplasia (AAH):
  - Lobular architecture maintained with fragmented basal cell layer
  - Closely packed small acini
  - Lacks cytologic features of malignancy
  - Intimately associated with nodular hyperplasia with similar cytologic findings
- Seminal vesicles and ejaculatory ducts:
  - Circumscribed pushing border rather than haphazard arrangement
  - Bizarre cells with golden-yellow lipofuscin pigment
  - Nuclear hyperchromasia, nuclear pleomorphism, and degenerative changes
  - Negative immunoreactivity for PSA or PAP
- Paraganglion:
  - Closely associated with nerves or blood vessels
  - Lobular cluster of polygonal cells with abundant clear cytoplasm
  - Centrally located nuclei with prominent nucleoli
  - PSA –, PAP –, cytokeratin –, neuroendocrine markers +
- Clear cell changes:
  - Atypical adenomatous hyperplasia (AAH)
  - Cribriform hyperplasia
  - Basal cell hyperplasia
  - Cowper's glands
  - Mucinous metaplasia
  - Paraganglion
  - Xanthoma and xanthogranulomatous prostatitis (PSA – and cytokeratin –)

Table 22-3. Immunohistochemical Profiles of Preinvasive and Malignant Lesionsin the Prostate

	PSA/PAP	*HMW CK*	*Cytokeratin**	*SMA*	*Desmin*
HGPIN	+	± (fragmented)	+	–	–
Atypical adenomatous hyperplasia	+	± (fragmented)	+	–	–
Prostatic adenocarcinoma	+	–	+	–	–
Ductal adenocarcinoma	+	–	+	–	–
Mucinous adenocarcinoma	+	–	+	–	–
Small cell carcinoma	±	–	±	–	–
Signet ring cell carcinoma	+	–	+	–	–
Squamous cell carcinoma	±	–	+	–	–
Sarcomatoid carcinoma	±	–	+	±	±
Adenoid cystic/basal cell carcinoma	±	+	+	–	–
Urothelial carcinoma	–	+	+	–	–
Phyllodes tumor	+	+	+	±	+
Leiomyosarcoma	–	–	±	+	+
Lymphoma	–	–	–	–	-

** Broad spectrum cytokeration*
Note: PSA/PAP = prostate-specific antigen/prostate acid phosphatase, HMW CK = high molecular weight cytokeratin (34βE12), SMA = smooth-muscle actin

  - Metabolic storage disease
  - Sclerosing adenosis
- Basal cell layer disruption:
  - HGPIN
  - Inflammatory atypia
  - Atypical adenomatous hyperplasia
  - Atrophy and post-atrophic hyperplasia (PAH)
- Sclerosing adenosis:
  - Compressed and distorted acini in cellular fibrous stroma
  - Lobular pattern is retained, and lacks cytologic atypia
  - HMW cytokeratin (34ßE12) +, S100 +, MSA +
- Hyperplasia of mesonephric remnants:
  - Lobular arrangement of small tubular acini
  - Often contains intraluminal eosinophilic colloid-like material
- Nephrogenic metaplasia:
  - Polypoid proliferation of small tubules and papillae lined by hobnail cells
  - Thickened basement membrane and intraluminal eosinophilic secretions
  - Edematous stroma and cystic dilation of some tubules
  - Associated with adjacent urothelium-lined ducts
- Urothelial carcinoma:
  - Often co-existing urothelial dysplasia and carcinoma *in situ*
  - May have history of bladder carcinoma
  - Nuclear pleomorphism, eosinophilic cytoplasm
  - Often associated with heavy inflammation
  - PSA/PAP –, HMW cytokeratin (34ßE12) +

Prostatic Adenocarcinoma Variants

Ductal (Endometrioid) Adenocarcinoma

Clinical

- Accounts for 0.8% of prostatic adenocarcinomas
- Similar clinical presentation and prognosis as conventional acinar carcinoma
- Occurs almost exclusively in elderly men with urinary obstructive symptoms
- Most cases have concurrent invasive acinar carcinoma
- Serum PSA concentration is often normal. probably due to secretion of PSA directly into the prostatic urethra by tumor cells

Macroscopic

- Polypoid tumor located in the urethra at or near the verumontanum

Microscopic

- Considered Gleason pattern 3 (no necrosis) or 5 (with necrosis) cancer
- Cribriform and papillary proliferation of medium to large-sized acini
- Acini lined by stratified tall columnar cells with cytologic atypia
- May have prominent central necrosis and frequent mitotic figures

Immunohistochemistry

- PSA +, PAP +, CEA + (focal)

Differential Diagnosis

- Cribriform hyperplasia:
  - Lacks cytologic atypia
- HGPIN (Cribriform pattern):
  - Less extensive; lacks infiltrative growth
  - Basal cell layer is focally present
- Urothelial carcinoma:
  - Dysplasia and carcinoma *in situ* of adjacent urothelium
  - PSA –
- Large gland variant of Gleason pattern 3 adenocarcinoma
- Ectopic prostatic tissue (prostatic urethral polyp):
  - Lacks cytologic atypia
- Proliferative papillary urethritis:
  - Lacks cytologic atypia
  - PSA –

Mucinous Adenocarcinoma

Clinical

- Accounts for 0.04% of prostate carcinoma (pure mucinous pattern)
- Similar clinical presentation as typical acinar carcinoma
- Aggressive, may not respond well to radiotherapy or androgen deprivation
- Elevated serum PSA concentration and bone metastasis

Macroscopic

- Often located in peripheral zone

Microscopic

- Usually considered Gleason pattern 4 adenocarcinoma
- Requires 25% of tumor to contain extracellular mucin, excluding non-dilated glands with mucin for diagnosis
- The presence of epithelial nests or glands in mucin pools is diagnostic
- May present with acinar or cribriform carcinoma with luminal distention
- Collagenous micronodules are often seen

Immunohistochemistry

- PSA +, PAP +

Differential Diagnosis

- Metastatic or contiguous spread of mucinous adenocarcinoma (e.g., colon cancer)
  - PSA –, PAP –
- Cowper's glands
  - Circumscribed lobules of closely packed small uniform acini
  - Embedded in skeletal muscle
  - Uniform cells with mucinous cytoplasm and basally located small nuclei
  - PSA –, high molecular weight cytokeratin +

Small Cell Carcinoma (High-Grade Neuroendocrine Carcinoma)

Clinical

- Highly aggressive; most patients dead within 2 years
- May present with paraneoplastic syndromes
- May develop after radiation therapy for acinar adenocarcinoma
- Serum PSA varies according to cancer volume and stage

Microscopic

- Considered Gleason pattern 5 adenocarcinoma
- Infiltrating cords and sheets of small cells with high N/C ratio and crush artifact
- Nuclear hyperchromasia, nuclear molding, and inconspicuous nucleoli

Immunohistochemistry

- Neuroendocrine markers (chromogranin A, synaptophysin, serotonin) +
- PSA ±, PAP ±

Signet Ring Cell Carcinoma

Clinical

- Similar clinical presentation as typical acinar carcinoma
- High stage presentation with unfavorable prognosis

Microscopic

- Considered Gleason pattern 5 adenocarcinoma
- Requires 25% tumor with signet ring cells for diagnosis

Immunohistochemistry

- PSA +, PAP +, CEA ±, mucin ±, oil-red O ±

Differential Diagnosis

- Paraganglion:
  - Organoid nests of polygonal cells with centrally located nuclei
- Vacuolated smooth muscle cells or lymphocytes:
  - PSA –, PAP –

Squamous Cell Carcinoma

Clinical

- Extremely rare in the prostate
- Accounts for <0.5% of cases of prostatic carcinoma
- Similar clinical presentation as typical acinar carcinoma
- Patients often have a prior history of hormonal or radiation therapy
- May be associated with schistosomiasis
- Aggressive; patients often present with osteolytic bone metastasis and are refractory to hormonal therapy
- Serum PSA may be normal even in the presence of metastasis

Macroscopic

- Often located in the periurethral region

Microscopic

- Usually high grade
- Nests and cords of malignant cells with squamous differentiation
- Requires the absence of acinar carcinoma and bladder involvement for diagnosis

Immunohistochemistry

- PSA ±, PAP ±, high molecular weight cytokeratin ±

Differential Diagnosis

- Squamous metaplasia:
  - Lacks significant nuclear pleomorphism
- Metastatic squamous cell carcinoma:
  - PSA –, PAP –

Carcinosarcoma

Clinical

- Often occurs in elderly patients with urinary obstructive symptoms
- Patients often have prior history of hormonal or radiation therapy
- Highly aggressive, with median survival of 12 months
- No differences in outcome for those with or without heterologous elements

Microscopic

- Considered Gleason pattern 5 adenocarcinoma
- Spindle cell proliferation with epithelial differentiation
- Nuclear pleomorphism and numerous mitotic figures
- Heterologous components variable, including osteosarcoma, leiomyosarcom, etc.

Immunohistochemistry

- PSA ±, PAP ±, cytokeratin +

Differential Diagnosis

- Postoperative spindle cell nodule:
  - Clinical history of prior surgery
  - Lacks significant nuclear pleomorphism
- Sarcoma:
  - Lacks evidence of epithelial differentiation

Adenoid Cystic/Basal Cell Carcinoma

Clinical

- Similar clinical presentation as typical acinar carcinoma
- Considered cancer of low malignant potential
- Serum PSA concentration is not elevated.

Microscopic

- Irregular and infiltrating nests of basal cells in a myxoid stroma
- Predilection for perineural invasion
- Often coexistence of adenoid cystic pattern with rounded fenestrations and basaloid pattern with cell nests and peripheral palisading
- Elongated cells with crowding, stippled chromatin, and inconspicuous nucleoli
- May be associated with squamous differentiation with keratin production
- Two cell populations: peripheral basaloid cells and inner columnar ductal cells

Immunohistochemistry

- PSA ±, PAP ±, high molecular weight cytokeratin +

Differential Diagnosis

- Basal cell hyperplasia/adenoma:
  - Solitary, well-circumscribed nodules associated with benign prostatic hyperplasia (BPH)
  - Uniformly distributed solid nests of hyperplastic basal cells
  - Condensed stroma at the peripheral of nodules

Urothelial Carcinoma

Clinical

- Accounts for <1% of prostate cancers

- Patients present with hematuria and urinary obstructive symptoms
- Poor prognosis, with osteolytic bone metastasis; most die within 2 years of diagnosis
- Refractory to hormonal therapy
- Serum PSA concentration is normal

Microscopic

- Marked cytologic atypia with nuclear pleomorphism and high mitotic figures
- Often associated with prominent stromal response
- Dysplasia and carcinoma in situ common in adjacent urothelium
- Usually coexistent bladder cancer

Immunohistochemistry (also see Table 25-2)

- CEA +, PSA –, PAP–, high molecular weight cytokeratin (34βE12) +, cytokeratin 20 ±

Differential Diagnosis

- Prostatic adenocarcinoma:
  - Acinar differentiation with less nuclear pleomorphism
  - PSA +, PAP +, high molecular weight cytokeratin –
- Inverted papilloma:
  - Complex arborizing invagination with peripheral palisading
  - Lack fibrovascular core
- HGPIN

Leiomyosarcoma

Clinical

- Most common prostatic sarcoma in adults; accounts for 26% of all prostatic sarcomas
- Aggressive; usually recurs and results in death

Microscopic

- Similar to leiomyosarcoma of other sites
- Interlacing fascicles of spindle cells with eosinophilic cytoplasm and fusiform nuclei
- Necrosis, cytologic atypia, and increased number of mitotic figures

Immunohistochemistry

- Smooth muscle-specific actin +, desmin +

Differential Diagnosis

- Symplastic leiomyoma:
  - Multinuclear giant cells and bizarre cells with nuclear degeneration
  - Mitotic figures inconspicuous
- Stromal hyperplasia with atypia:
  - Bizarre hyperchromatic nuclei with inconspicuous nucleoli, rarely vacuolated
  - No mitotic figures or necrosis
- Postoperative spindle cell nodule:
  - Small size of lesion
  - Fascicles of relative uniform spindle cells in a myxoid stroma
  - Cells with abundant cytoplasm
  - Enlarged nuclei with fine granular chromatin and prominent nucleoli
  - Mitotic figures may be frequent
  - Lacks atypical mitotic figures and nuclear pleomorphism
  - Prominent vasculature and associated with inflammation
- Blue nevi:
  - Pigmented dendritic bipolar cells in fibrous stroma

Phyllodes Tumor

Clinical

- Patients usually present with urinary obstructive symptoms
- Potentially aggressive and often recurrent
- May dedifferentiate after recurrence (stromal overgrowth)
- Histogenesis is uncertain

Macroscopic

- Cystic and spongy tumor with prostatic enlargement, similar to BPH

Microscopic

- Biphasic growth of stromal and epithelial components
- Interlacing fascicles of spindle cells with leaf-like projections into duct-like spaces
- Increased stromal cellularity and overgrowth with compressed, elongated channels
- Uniform nuclei with inconspicuous nucleoli
- Grading is not reliable in predicting recurrence.
- May undergo sarcomatous transformation after recurrence (stromal overgrowth)

Immunohistochemistry

- Stroma: actin +, vimentin +, desmin –, S-100 protein –
- Luminal epithelial cells: PSA +, PAP +, keratin +

Differential Diagnosis

- Stromal hyperplasia with atypia:
  - Increased stromal cellularity and nuclear atypia
  - Bizarre cells with nuclear degenerative change
  - Associated with BPH

- Nodular hyperplasia with fibroadenoma-like areas:
  - Cystically dilated acini associated with hyperplastic epithelium
- Multilocular prostatic cystadenoma:
  - Epithelial cell-lined cyst in a fibrous stroma
  - Lacks stromal cellularity
- Leiomyosarcoma:
  - Lacks biphasic growth pattern of Phyllodes tumor
- Seminal vesicle cyst (lateral location) and Mullerian duct cyst (midline location):
  - Unilocular cyst
  - No stromal cellularity
  - PSA –, PAP –

Lymphoma

Clinical

- Occurs in elderly patients presenting with urinary obstructive symptoms
- Secondary involvement more common than primary involvement (55% vs. 35%)
- Poor prognosis (median survival = 23–28 months) regardless of age, histologic type, treatment, clinical stage at presentation, or type of involvement (primary vs. secondary)
- Criteria for the diagnosis of primary lymphoma:
  - Absence of hematopoeitic involvement (spleen, lymph nodes, peripheral blood, or liver) within 1 month prior to diagnosis
  - Limited to the prostate and adjacent soft tissue

Macroscopic

- Diffusely enlarged with firm to rubbery consistency

Microscopic

- Diffuse large cell and small lymphocytic lymphoma are two most common types
- Diffuse irregular infiltrates of monotonous lymphocytes
- Preservation of acini

Differential Diagnosis

- Granulomatous prostatitis:
  - Acinar destruction with polymorphous inflammatory infiltrate
- Granulocytic sarcoma (chloroma):
  - Chloracetate esterase and lysozyme +
- Rhabdomyosarcoma:
  - Very rare, occurs mainly in pediatric patients
  - Embryonal rhabdomyosarcoma is most frequent type
  - Sheets of immature spindle cells and occasional rhabdomyoblasts in myxoid stroma
  - Myoglobin +, MSA +, desmin +, PSA –, PAP –

TREATMENT EFFECTS

Androgen Deprivation Therapy

Benign

- Acinar atrophy and distortion
- Decreased ratio of acini to stroma, with stromal fibrosis and hyalinization
- Atypical basal cell hyperplasia, squamous metaplasia, and urothelial metaplasia
- Acinar rupture with preservation of basal cell layer
- Cytoplasmic vacuolization and nuclear shrinkage

Cancer

- Linear arrays and ragged infiltrate of malignant acini with cytoplasmic vacuolization, nuclear pyknosis, and hyperchromasia
- Nucleoli may be inconspicuous
- Malignant glands are often dilated, with atrophic features and a hemangiopericytoma-like pattern
- Lacks basal cell layer
- Reduced incidence and extent of HGPIN

Immunohistochemistry

- PSA +, PAP +, high molecular weight cytokeratin– (cancer)

Differential Diagnosis

- Clear cell change
  - AAH
  - Cribriform hyperplasia
  - Basal cell hyperplasia
  - Cowper's glands
  - Mucinous metaplasia
  - Paraganglion
  - Xanthoma and xanthogranulomatous prostatitis
  - Metabolic storage disease
  - Sclerosing adenosis

Radiation Therapy

Benign

- Lobular and acinar atrophy, decreased acini to stroma ratio, stromal edema, and fibrosis
- Atypical basal cell hyperplasia, squamous and transitional cell metaplasia
- Acinar rupture with extravasation, dystrophic calcification
- Vascular myointimal proliferation
- Cytoplasmic clearing with nuclear pyknosis

Cancer

- Linear arrays and ragged infiltrate of malignant acini with cytoplasmic vacuolization, nuclear pyknosis, and hyperchromasia
- Nucleoli may be inconspicuous
- Lacks basal cell layer
- Reduced incidence and extent of HGPIN
- Grading of salvage prostatectomy specimens is predictive of survival

Immunohistochemistry

- PSA +, PAP +, high molecular weight cytokeratin–(cancer)

TNM CLASSIFICATION OF PROSTATE CANCER (1997 REVISION)

- T: Primary tumor:
  - Tx: primary cancer cannot be evaluated
  - T1: incidental finding, non-palpable, nor visible by imaging:
    - T1a: ≤ 5% of tissue resected
    - T1b: >5% of tissue resected
    - T1c: detected by needle biopsy due to screening for PSA (incidental tumor identified in both lobes by needle biopsies, but not palpable or reliably visible by imaging)
  - T2: palpable or visible cancer clinically confined within the capsule:
    - T2a: involves one lobe
    - T2b: involves both lobes
  - T3: extends outside the prostate:
    - T3a: extraprostatic extension (unilateral or bilateral)
    - T3b: seminal vesicle invasion
- T4: fixed or invades adjacent structures other than seminal vesicles: bladder neck, external sphincter, rectum, or levator muscles
- N: Regional lymph nodes:
  - N1: regional lymph node(s) metastasis
- M: Distant metastasis:
  - M0: No distant metastasis
  - M1: Distant metastasis:
    - M1a: non-regional nodes
    - M1b: bone
    - M1c: other sites

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Chapter 23

Non-Neoplastic Renal Diseases

Donna J. Lager, MD

Table of Contents

GLOMERULAR DISEASES

Morphologic Classification (Table 23-1)
Primary Glomerular Diseases

Minimal Change Disease (MCD)

Clinical

- The most common cause of the nephrotic syndrome in children (Table 23-2)
- Mild periorbital edema, prior to the rapid onset of the nephrotic syndrome
- Proteinuria is "selective" or composed primarily of albumin
- Microscopic hematuria is rare; hypertension is unusual

Microscopic

- Light microscopy:
  - The glomeruli, tubules, and interstitium appear normal
- Immunofluorescence microscopy:
  - Usually negative, mesangial IgM may occasionally be present
- Electron microscopy:
  - Diffuse effacement of the epithelial cell (podocyte) foot processes (also see chapter 4)

Differential Diagnosis

- An early membranous lesion may look normal by light microscopy

Focal Segmental Glomerulosclerosis (FSGS)

Clinical

- Focal segmental glomerulosclerosis may be primary (idiopathic) or secondary to a number of etiologic agents, including:
  - Unilateral renal agenesis
  - Renal ablation
  - Sickle cell disease
  - Morbid obesity (with or without sleep apnea)
  - Reflux nephropathy
  - HIV nephropathy

Microscopic

- Light microscopy:
  - Focal and segmental glomerular sclerosis with capillary loop collapse, hyaline and lipid deposition, and often adhesion to Bowman's capsule
  - The remainder of the glomerular tuft appears normal
  - Lesions begin or are more common near the cortico-medullary junction
- Immunofluorescence microscopy:
  - Deposition of IgM and C3 in mesangium or in segmental sclerosis
  - May be negative

Table 23-1. Morphologic Classification

Normal glomeruli by light microscopy
- Minimal change disease
- Thin Glomerular Basement Membrane Disease
- Early Alport disease
- (Early membranous glomerulonephritis)

Focal/segmental lesions
- Focal segmental glomerulosclerosis
  - Idiopathic vs. secondary
- Focal segmental proliferative glomerulonephritis
- Focal segmental necrotizing and crescentic glomerulonephritis

Diffuse glomerulonephritis
- Membranous glomerulonephritis
  - Idiopathic vs. secondary
- Proliferative glomerulonephritis
  - Mesangial proliferative glomerulonephritis
    - IgA nephropathy
    - Mesangial proliferative lupus nephritis
  - Endocapillary proliferative glomerulonephritis
    - Acute post-infectious glomerulonephritis
  - Mesangiocapillary glomerulonephritis
    - Membranoproliferative glomerulonephritis (MPGN)
    - Diffuse proliferative lupus nephritis
    - Cryoglobulinemic glomerulonephritis
    - Chronic thrombotic microangiopathy

Crescentic glomerulonephritis
- Immune complex mediated crescentic glomerulonephritis
- Pauci-immune (Antineutrophil cytoplasmic antibody-associated) crescentic glomerulonephritis
- Anti-glomerular basement membrane antibody mediated

Diffuse/nodular mesangial expansion
- Diabetic glomerulosclerosis
- Light chain deposition disease
- Fibrillary glomerulonephritis
- Amyloidosis

- ♦ Electron microscopy: (also see chapter 4)
  - – Effacement of podocyte foot processes
  - – Podocyte denudation may be present focally as an early lesion
  - – Segmental sclerosis may also be seen

Differential Diagnosis

- ♦ May be secondary (see earlier) and may be end result of segmental necrotizing disease

Membranous Glomerulonephritis (MGN)

Clinical

- ♦ A major cause of the nephrotic syndrome in adults
- ♦ May occur in association with a number of disorders or exposure to antigenic substances, including:
  - – Systemic lupus erythematosus
  - – Malignant neoplasms
  - – Exposure to gold and mercury
  - – Penicillamine, captopril and NSAIDS
  - – Hepatitis B
  - – In association with metabolic disorders
- ♦ Thought to be a chronic antigen-antibody mediated disease in which the antigens are planted within the subepithelial space of the glomerular capillary loops

Microscopic

- ♦ Light microscopy:
  - – The glomeruli may appear normal if the deposits are small (early disease)
  - – Capillary walls are thickened, with subepithelial spikes on silver stain
- ♦ Immunofluorescence microscopy:
  - – Bright granular staining of the capillary loops with anti-IgG and C3
- ♦ Electron microscopy: (also see chapter 4)
  - – Subepithelial electron dense deposits with intervening basement membrane spikes
  - – Stage of disease correlates with incorporation of deposits into the glomerular basement membrane (GBM)

Differential Diagnosis

- ♦ Secondary causes of MGN are common, especially systemic lupus euthematosus
- ♦ In SLE, see mesangial deposits and reticulotubular structures
- ♦ An early lesion may be confused with minimal change disease (MCD) by light microscopy

IgA Nephropathy (IgAN)

Clinical

- ♦ Most common form of primary glomerulonephritis in the world
- ♦ Geographically variable
- ♦ May be related to a genetic or acquired abnormality of immune regulation leading to increased mucosal IgA synthesis in response to respiratory or gastrointestinal exposure to environmental agents
- ♦ Occurs with increased frequency in patients with:
  - – Celiac disease
  - – Dermatitis herpetiformis
  - – Liver disease
- ♦ Patients usually present with one of three syndromes:
  - – Macroscopic hematuria concurrent with an upper respiratory infection; so-called synpharyngitic hematuria
  - – Asymptomatic microscopic hematuria and variable proteinuria, including the nephrotic syndrome

Table 23-2. Classification of Primary Glomerulonephritis by Predominant Clinical Manifestations

	Nephrotic syndrome	*Nephritic syndrome*
Minimal change disease	+++++	–
Focal segmental glomerulosclerosis	++++	+
Membranous glomerulonephritis	++++	+
IgA nephropathy	+++	++
Membranoproliferative GN	++	+++
Acute post-infectious GN	+	++++
Crescentic glomerulonephritis	+	++++

  - Henoch-Schonlein purpura is the systemic form of the disease process causing IgA nephropathy, and occurs more frequently in children than adults
    - Patients with Henoch-Schonlein purpura manifest skin, joint, and intestinal involvement

Microscopic

- Light microscopy:
  - The glomeruli show some degree of mesangial hyper-cellularity
  - Segmental proliferation, segmental sclerosis, and necrosis with crescents may be seen
- Immunofluorescence microscopy:
  - Mesangial deposits of IgA; IgG and C3 are variably present
- Electron microscopy:
  - Deposits are present in the mesangium
  - Deposits often "paramesangial," beneath the basement membrane as it covers mesangium

Differential Diagnosis

- Mesangial deposits may also be seen in SLE (WHO Class II lupus nephritis) and post-infectious glomerulonephritis (later disease)

Membranoproliferative (Mesangiocapillary) Glomerulonephritis (MPGN)

Clinical

- Chronic progressive glomerulonephritis in older children and adults
- Circulating immune complexes have been identified in 50% of patients
- Activation of the complement system with hypocomplementemia is a hallmark of MPGN
- Patients may present with:
  - Nephrotic syndrome
  - Abnormal urinary sediment with non-nephrotic proteinuria
  - Acute nephritis
- May be primary or associated with other systemic disorders (secondary)
- Secondary causes of MPGN include:
  - Hepatitis B and hepatitis C infection
  - Infected ventriculoatrial shunts
  - Schistosomiasis
  - Alpha-1-antitrypsin deficiency
  - Chronic liver disease
- Patients with partial lipodystrophy may develop Type II MPGN

Microscopic

- Three types of MPGN (Types I, II, and III) have been described. All types feature mesangial hypercellularity and matrix expansion, and mesangial interposition beneath the endothelium with formation of double contours:
  - Type I MPGN:
    - Subendothelial and mesangial deposits that frequently contain C3 and immunoglobulins
    - Most cases of secondary MPGN are Type I
  - Type II MPGN (dense deposit disease):
    - Electron dense deposits within lamina densa of the GBM contain C3 in a linear pattern in the peripheral capillary loops with ring-like patterns in the mesangium
  - Type III MPGN:
    - Prominent mesangial, subendothelial, and subepithelial immune deposits
    - Type III is the least common form of MPGN

Post-Infectious Glomerulonephritis (PIGN)

Clinical

- May be caused by a number of infectious agents
- Post-streptococcal glomerulonephritis is primarily a disease of children, 6 to 7 years of age:
  - The onset is usually abrupt, with a latent period of 7 –21 days between infection and the development of nephritis
  - During epidemics, the clinical attack rate is 10% to 12%, but subclinical disease occurs four times more frequently than overt disease; asymptomatic contacts may have hematuria
- Common initial clinical manifestations of post-streptococcal glomerulonephritis are:
  - Hematuria (microscopic or macroscopic)
  - Edema
  - Hypertension
  - Oliguria
- The acute clinical episode of post-streptococcal glomerulonephritis is usually self-limited, and complement levels, which are usually depressed acutely, return to normal within 6 weeks
- In most patients, hematuria disappears by 6 months, but proteinuria may persist for 2 years in one-third of patients

Microscopic

- Light microscopy:
  - The glomeruli show diffuse mesangial proliferation and endocapillary proliferation with infiltration of neutrophils and mononuclear inflammatory cells
  - Crescents may also be present
- Immunofluorescence microscopy:

- Granular deposits of C3 and IgG along the capillary loops and in the mesangium

♦ Electron microscopy:
- Large subepithelial, "hump-like" deposits as well as mesangial deposits
- The capillary loop deposits become less frequent after a few weeks, but the mesangial deposits persist for a longer period

Crescentic Glomerulonephritis

Clinical

♦ May be:
- Immune complex mediated
- Pauci-immune (ANCA associated)
- Mediated by anti-glomerular basement membrane antibody

♦ Patients with crescentic glomerulonephritis secondary to anti-glomerular basement membrane disease may also have pulmonary hemorrhage (Goodpasture's disease)

♦ The prognosis depends on the number of crescents present in the biopsy; a more diffuse crescentic process predicts a worse prognosis

Microscopic

♦ Light microscopy:
- Disruption of the glomerular capillary loops with extravasation of blood and cells into Bowman's space, forming a cellular crescent

♦ Immunofluorescence microscopy:
- Bright linear staining of GBM for IgG in anti-glomerular basement membrane mediated disease
- Negative in ANCA-associated crescentic GN
- Other immune complexes present in immune complex mediated disease

♦ Electron microscopy:
- Disruption of capillary wall with ± immune deposits

Fibrillary Glomerulonephritis

Clinical

♦ Most patients are 40–50 years of age, with a slight female predominance and a greater frequency in whites

♦ Most patients present with proteinuria, and occasionally the nephrotic syndrome, or with symptoms of nephritis

♦ Renal insufficiency is progressive, with renal failure usually occurring within 2–4 years

Microscopic

♦ Light microscopy:
- The glomeruli show mesangial matrix expansion, variable hypercellularity, and capillary wall thickening

♦ Immunofluorescence microscopy:
- Mesangial and capillary wall staining for IgG and C3 are present

♦ Electron microscopy:
- There is glomerular deposition of fibrils that are thicker than amyloid fibrils and lack congo red birefringence
- The 18–22 nm thick fibrils are randomly oriented and non-branching and are present in the mesangium and at least segmentally along the capillary loop basement membranes

Secondary Glomerular Diseases

Diabetes Mellitus (Diabetic Nephropathy)

Clinical

♦ Major cause of end-stage renal failure in the United States

♦ Approximately one-third of patients entering dialysis programs have lost renal function as a result of diabetes

♦ Patients with diabetes mellitus rarely develop clinically detectable glomerular injury before 10 years

♦ Nodular mesangial sclerosis (Kimmelstiel-Wilson lesion)

Microscopic

♦ Light microscopy:
- Thickened tubular and glomerular basement (after 2–3 years)
- Interstitial fibrosis and expansion of mesangial regions with formation of mesangial nodules begins after 3–5 years; parallels progressive loss of renal function

♦ Electron microscopy:
- Diffuse thickening of the capillary loop basement membranes and mesangial matrix expansion

Paraproteinemia

♦ A group of disorders characterized by tissue damage associated with the overproduction of monoclonal immunoglobulin proteins and their components

♦ The renal manifestations occur as a result of the interaction of the abnormal protein with normal tissue components

Amyloidosis

♦ Extracellular deposition of insoluble fibrillar proteins with a characteristic β-pleated sheet configuration; most proteins have an α-helical structure:
- Primary or AL amyloid is caused by a plasma cell

dyscrasia with overproduction of a monoclonal immunoglobulin light chain, which in most patients is λ light chain; overt myeloma is present in 20% of these patients

– Secondary or AA amyloid occurs in chronic infections and chronic inflammatory states, including rheumatoid arthritis, ankylosing spondylitis, tuberculosis, osteomyelitis, and intravenous drug abuse

Microscopic

♦ Light microscopy:

– Amyloid deposits occur predominantly in glomeruli and appear as amorphous, eosinophilic nodules within the mesangium, and as thickened capillaries

– The amyloid deposits do not stain with the silver stain (non-argyrophillic) and show green birefringence under polarized light with the congo red stain

♦ Electron microscopy:

– The amyloid deposits are composed of nonbranching, randomly oriented, twisted fibrils that measure 8– 12 μm in diameter

– They accumulate first in the mesangium and later in the subendothelial space and may penetrate the basement membrane, producing long silver-positive bundles that extend subepithelially, perpendicular to the basement membrane (spicules)

Light Chain Deposition Disease

♦ A systemic disease caused by overproduction of a monoclonal immunoglobulin light chain (usually κ), which deposits in various sites

Microscopic

♦ Light microscopy:

– The glomeruli contain eosinophilic mesangial nodules similar to the nodules seen in diabetic nephropathy and in amyloidosis

– Like amyloid, the mesangial nodules in light chain deposition disease are non-argyrophillic

♦ Immunofluorescence microscopy:

– There is bright linear staining of tubular basement membranes for κ light chains and less intense staining of the glomeruli; other immunoglobulins may be present rarely

♦ Electron microscopy;

– Punctate granular deposits in the lamina rara interna of the glomerular basement membrane with extension into the lamina densa and lamina rara externa less commonly:

• Mesangial deposits are less prominent

– The deposits are more consistently present in the tubular basement membranes and have a similar granular appearance

Cryoglobulinemic Glomerulonephritis

♦ Cryoglobulins are circulating immunoglobulins that precipitate on cooling and resolubilize on warming

♦ Three types of cryoglobulinemia have been described:

– In Type I cryoglobulinemia, the immunoglobulin is a single monoclonal immunoglobulin usually without associated antibody activity

– In Type II cryoglobulinemia, a monoclonal immunoglobulin (usually IgM-κ) is directed against polyclonal immunoglobulin (usually IgG)

– In Type III cryoglobulinemia, a polyclonal immunoglobulin is directed against a polyclonal immunoglobulin

Clinical

♦ Type I cyroglobulinemia is most often associated with lymphoproliferative disorders such as multiple myeloma, Waldenstrom's macroglobulinemia, and chronic lymphocytic leukemia

♦ Mixed cyroglobulinemia (Types II and III) occurs in a variety of settings, including lymphoproliferative disorders, collagen-vascular diseases, and infections including Hepatitis B, C, and Epstein-Barr virus

♦ Several studies have demonstrated an increased incidence of hepatitis C virus infection in patients with mixed cryoglobulinemia:

– Antibody to hepatitis C virus has been detected in serum from 91% to 98% of patients with mixed cryoglobulinemia, and hepatitis C virus RNA in 81%

Microscopic

♦ Light microscopy:

– The acute glomerular lesion of mixed cryoglobulinemia is a diffuse proliferative glomerulonephritis with prominent subendothelial and intraluminal deposits

– The mesangial proliferation and mesangial interposition results in a lobular architecture resembling Type I membranoproliferative glomerulonephritis; infiltrating monocytes and occasional neutrophils are also present

– Renal arteritis may also be present and is found in ~30% of patients

♦ Immunofluorescence microscopy:

– The composition of the glomerular deposits corresponds to that of the circulating cryoglobulin; mixed cryoglobulins contain IgG, IgM, C3, C1q, and C4

– Because of the presence of a monoclonal IgM-κ component, staining for these immunoglobulins is often more intense than for IgG and λ

– Staining involves the subendothelial aspect of the

glomerular capillary wall with focal globular intraluminal deposits and smaller mesangial deposits

- Electron microscopy:
  - The deposits are typically subendothelial. Mesangial deposits are usually smaller and less numerous. Intramembranous and subepithelial deposits may also be seen
  - Often the deposits have a characteristic substructure with curved tubular structures, ~30 μm in diameter, that cluster in curvilinear bundles

Systemic Lupus Erythematosus (Lupus Nephritis)

Clinical

- Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by the overproduction of antibodies to endogenous antigens, usually derived from cell components; the kidneys are almost always affected, giving rise to lupus nephritis

Microscopic

- There are six morphologic classes:
  - Class I: Normal glomeruli:
    - Minor glomerular abnormalities by light microscopy may be accompanied by deposits identified on immunofluorescence or electron microscopy
    - IA: nil (by all techniques)
    - IB: normal by light microscopy but deposits present
  - Class II: Mesangial lupus nephritis:
    - IIA: mesangial widening and/or mild hypercellularity (+)
    - IIB: moderate hypercellularity (++)
  - Class III: Focal and segmental proliferative lupus nephritis:
    - IIIA: active necrotizing lesions
    - IIIB: active and sclerosing lesions
    - IIIC: sclerosing lesions
  - Class IV: Diffuse proliferative lupus nephritis:
    - IVA: without segmental necrotizing lesions
    - IVB: with active necrotizing lesions
    - IVC: with active and sclerosing lesions
    - IVD: with sclerosing lesions
  - Class V: Diffuse membranous lupus nephritis:
    - VA: pure membranous lupus nephritis
    - VB: associated with lesions of category II (A or B)
    - VC: associated with lesions of category III (A,B, or C)
    - VD: associated with lesions of category IV (A,B,C, or D)
  - Class VI: Advanced sclerosing lupus nephritis:
    - This class represents a late stage and resembles any case of advanced glomerulonephritis, usually lacking the specific features of lupus nephritis

HIV Nephropathy

Clinical

- Human immunodeficiency virus (HIV) nephropathy occurs in 5% to 10% of patients with HIV infection and occurs more frequently in blacks
- The clinical presentation of HIV nephropathy is characterized by heavy proteinuria, which is in the nephrotic range in 90% of patients, accompanied by rapid progression to renal failure over 6–12 months
- Therapy with antiviral agents has been attempted with limited success, and immunosuppressive therapy is not generally considered safe because of the immune compromise already present in these patients

Microscopic

- Light microscopy:
  - Swelling and hypertrophy of podocytes with PAS + inclusion droplets
  - Focal segmental glomerulosclerosis and global collapse of the glomerular tufts
  - Microcystic, dilated tubules containing hyaline occlusive casts
  - Prominent lymphocytic infiltration of the interstitium
- Electron microscopy:
  - Reticulotubular inclusions in endothelial cells and interstitial leukocytes

Hereditary Systemic Disorders With Renal Involvement

Fabry's Disease

Clinical

- Fabry's disease (Anderson-Fabry's Disease, Alpha-Galactosidase A Deficiency, Angiokeratoma Corporis Diffusum Universale) is an uncommon disorder caused by an inborn error in the catabolism of glycosphingolipids, resulting in glycosphingolipidosis
- The central defect is a complete or partial deficiency in α-galactosidase A activity
- It is inherited as an X-linked disorder and is caused by a variety of mutations in the α-galactosidase gene on the long arm of the X chromosome; it has an incidence of 1:40,000
- Diagnosis can be made in the setting of typical skin lesions (angiokeratoma corporis diffusum), corneal dystrophy, and birefringent inclusions in urinary sediment:

  - Confirmation of the diagnosis is made by measuring the α-galactosidase A activity in peripheral blood leukocytes
- Renal manifestations include polyuria and polydipsia with a dilute urine:
  - Proteinuria may be mild and insidious in onset
  - Patients eventually progress to renal failure, usually by the time they reach 50 years of age
- Hemizygous males usually develop the disease as children and heterozygous females may develop a more mild form of the disease:
  - Caucasian males with ABO types B or AB usually present with more severe disease

Microscopic

- Light microscopy:
  - The glomeruli show podocyte swelling with cytoplasmic vacuolization
  - Vacuoles are also present in the cells lining Bowman's capsule, endothelial and mesangial cells, and in cells of the distal convoluted tubule and loop of Henle
  - With disease progression, the glomeruli undergo segmental and global glomerulosclerosis accompanied by interstitial fibrosis and tubular atrophy
- Electron microscopy:
  - Numerous whorled osmiophilic structures (myelin figures, zebra bodies) are present within lysosomes in the cell cytoplasm
  - Foot processes are generally effaced depending on the degree of proteinuria
  - Myelin figures may be seen within Bowman's space and in the interstitium and tubular epithelium

Lecithin Cholesterol Acyltransferase (LCAT) Deficiency

Clinical

- An autosomal recessive disorder that results from inadequate enzymatic activity of lecithin cholesterol acyltransferase, which is responsible for forming lipoprotein cholesterol esters
- Clinical features include corneal opacities, anemia, proteinuria, and premature atherosclerosis
- Renal involvement is common and almost all patients with renal involvement progress rapidly to chronic renal failure, usually by the fifth decade of life ;
  - Atherosclerotic vascular disease is a significant and early cause of morbidity and mortality
- There is no known treatment;
  - Renal transplantation is of benefit, but does not reverse the lipid abnormalities, and histologic lesions may recur by 6 months post-transplantation

Microscopic

- Light microscopy:
  - The renal lesion is characterized by mesangial expansion and sclerosis, irregular thickening of the capillary loops with numerous bubbles or holes and foam cells
- Electron microscopy:
  - Electron-dense, lamellar structures are present within the mesangium and capillary walls and are associated with surrounding lucent spaces
  - Podocyte foot process effacement is also present

Nail-Patella Syndrome

Clinical

- Nail-Patella syndrome, or osteo-onychodysplasia, is a hereditary disorder characterized by:
  - Iliac horns or prominent iliac crests (80%)
  - Hypoplastic or absent patellae (60%) and patellar tendons
  - Dysplasia of elbows (60-90%)
  - Fingernail and less commonly toenail dystrophies (80% to 90%)
  - Renal disease (50%)
- An autosomal dominant disorder with full penetrance and an incidence of approximately 1:50,000:
  - The gene is located on chromosome 9 and is closely linked to the ABO blood group and adenylate cyclase loci
- Most patients with renal disease present with proteinuria, microscopic hematuria, edema, and hypertension:
  - An abnormal urinary sediment, impaired urinary concentrating ability, and abnormalities in urinary acidification have also been described

Microscopic

- Light microscopy:
  - The glomeruli are frequently normal in appearance but capillary loop thickening may be apparent
  - Mesangial sclerosis, segmental sclerosis, tubular atrophy, and interstitial fibrosis may also be present and correlate with the degree of renal functional impairment
- Immunofluorescence microscopy:
  - Generally negative, but occasional nonspecific staining for IgM, C3, or C1q may be present
- Electron microscopy:
  - The pathognomonic renal lesion is the finding of multiple mottled and lucent areas within the glomerular basement membrane and less commonly the mesangium
  - These lucent areas contain clusters of collagen fibrils that are best visualized following phosphotungstic acid staining

Lipodystrophy

Clinical

- An uncommon disorder that may be partial or total, and congenital or acquired, and may be associated with:
  - Hyperinsulinism and insulin resistance
  - Hyperlipidemia
  - Hyperproteinemia
  - Euthyroid hypermetabolism
  - Increased basal free fatty acid levels
- Other manifestations include:
  - Tall stature
  - Muscular hypertrophy
  - Hirsutism
  - Macroglossia
  - Abdominal distention
  - Subcutaneous nodules
  - Acanthosis nigricans
  - Hepatomegaly
  - Cirrhosis
  - Clitoral or penile enlargement
  - Adenopathy
  - Neurologic abnormalities
- In the congenital form, which has an autosomal recessive inheritance pattern, lipoatrophy is present at birth and diabetes mellitus develops later in adolescence
- The acquired forms of general lipodystrophy and partial lipodystrophy do not have a heritable basis:
  - Partial lipodystrophy most often presents in young girls between 5–15 years of age
  - In addition to lipoatrophy and renal disease, these patients may have some of the symptoms seen in the generalized lipodystrophy group

Microscopic

- In partial lipodystrophy, the incidence of renal involvement is 15% to 30%, with dense deposit disease or membranoproliferative glomerulonephritis Type II being the predominant lesion, occurring in 80%, and Type I MPGN in the remainder
- Approximately 10% of patients with dense deposit disease have partial lipodystrophy

Hereditary Nephritis

- The term hereditary nephritis encompasses a heterogeneous group of disorders that have in common microscopic hematuria, but differ markedly in clinical course and outcome

Alport Syndrome

Clinical

- A hereditary disorder of basement membrane collagen that is characterized clinically by hematuria, progressive renal failure, and frequently, hearing loss and ocular abnormalities
- In most cases, the disease is inherited as an X-linked trait; absence of a family history is noted in 10% to 15% of patients and these cases may represent new mutations:
  - The gene frequency is estimated at 1:5,000–10,000
- The X-linked form of Alport's syndrome has been shown to be caused by mutations in the gene COL4A5 encoding for the $\alpha 5$ chain of Type IV collagen present in the glomerular basement membrane; the gene has been mapped to chromosome Xq22
- Microscopic hematuria is present from birth in affected males and has a 93% penetrance in heterozygous females
- Proteinuria is variable, but occasionally reaches nephrotic range; hemizygous males inevitably progress to end-stage renal failure; heterozygous females are generally less severely affected
- Non-renal features of Alport syndrome include:
  - Bilateral high-frequency hearing loss
  - Ocular defects including lenticonus and retinal flecks
  - Leiomyomatosis, particularly leiomyomas of the esophagus and female genital tract

Microscopic

- Light microscopy;
  - In the early stages of the disease, the glomeruli may appear entirely normal or may show mesangial widening
  - Progression of the disease is characterized by segmental sclerosis and glomerular obsolescence, tubular atrophy, and interstitial fibrosis
  - Interstitial foam cells are often present but are a non-specific finding
- Immunofluorescence microscopy:
  - Direct immunofluorescence microscopy may be normal or there may be non-specific deposition of IgM and C3
- Electron microscopy:
  - The characteristic ultrastructural changes of the glomerular basement membranes consist of both thickening and thinning, and in early cases, this may be the only abnormality
  - The lamina densa is replaced by irregular lamellae and fragmented strands of lamina densa-like material
  - The extent of lamellation and fragmentation of the lamina densa in the glomeruli is variable, ranging from involvement of short segments to widespread involvement in severely affected cases

Thin Glomerular Basement Membrane Syndrome

Clinical

- Familial thin glomerular basement membrane syndrome, or benign recurrent hematuria, is an autosomal dominant basement membrane glomerulopathy characterized by a glomerular basement membrane that is uniformly thinned to approximately half of the normal thickness
- Some cases consistent with autosomal recessive inheritance have been reported
- The overall incidence is not known; however, it is relatively common (20%) in patients with hematuria
- Patients present with continuous or intermittent microscopic hematuria usually in childhood but rarely as an adult
- Episodic gross hematuria may occur and is usually concurrent with an upper respiratory infection
- A distinction must be made between thin glomerular basement membrane syndrome and Alport syndrome:
  - This is usually accomplished by the lack of renal insufficiency, sensorineural hearing loss, and ocular abnormalities that characterize Alport syndrome

Microscopic

- Light microscopy:
  - The glomeruli appear normal and the tubules contain red blood cells
- Electron microscopy:
  - The glomerular capillary loop basement membranes show focal and segmental or diffuse thinning of the lamina densa (<200 μm in an adult, <180 μm in a child 2–10 yr. old)
  - The inner and outer contours of the glomerular basement membrane are smooth, and no disruption or lamellation of the glomerular basement membrane is present

Congenital and Infantile Nephrotic Syndrome

- The term congenital nephrotic syndrome is used to describe infants who develop nephrotic syndrome at birth or before 3 months of age
- Infantile nephrotic syndrome describes infants with a later onset of nephrotic syndrome (4–12 months of age)
- Causes of congenital and infantile nephrotic syndrome are listed in Table 23-3

Congenital Nephrotic Syndrome of the Finnish Type

Clinical

- Described worldwide, although the highest incidence is in Finland, with a gene frequency of 1:200 and an incidence of 1.2:10,000 live births
- Both sporadic and autosomal dominant forms occur and diagnosis is based on family history, perinatal presentation, placental size, and renal pathology
- Common clinical and gestational findings include:
  - Unremarkable pregnancy except for elevated alpha-fetoprotein at week 16–20
  - Premature delivery (usually 35–38 wk)
  - Small for gestational age
  - Breech presentation is more common
  - Low Apgar score including asphyxia
  - Meconium staining (more common)
  - Large placenta, 25% larger than infant by weight
  - Classic appearance (may be due in part to loss of thyroid binding globulin in urine):
    - Low bridged nose
    - Wide cranial sutures
    - Large fontanels
    - Delayed ossification
    - Flexion deformities of the extremities
  - Signs of disease develop in the first 3 months of life
- Renal manifestations include massive proteinuria detectable at birth that is resistant to corticosteroids and immunosuppression
- The pathogenesis is not well understood, but is assumed to be the result of a hereditary error in glomerular basement membrane metabolism that is expressed early in gestation (16–18 weeks)

Microscopic

- Light microscopy:
  - The glomeruli show mesangial proliferation, dilatation of Bowman's space, and microcysts in the cortical tubules
  - Scattered microglomeruli may also be found
- Electron microscopy:
  - Diffuse podocyte foot process effacement, microvillous transformation, and mesangial expansion; no immune deposits are present
  - The capillary loop basement membranes show widening of the lamina rara interna and focal splitting and thinning of the lamina densa

Diffuse Mesangial Sclerosis

Clinical

- Unlike congenital nephrotic syndrome of the Finnish type, diffuse mesangial sclerosis is not associated with premature birth, low birth weight, or placental enlargement

Table 23-3. Causes of Congenital Nephrotic Syndrome

Congenital nephrotic syndrome	*Infantile nephrotic syndrome*
Primary	*Primary*
Finnish-type	Minimal change disease
Diffuse mesangial sclerosis	Focal segmental glomerulosclerosis
Minimal change disease	Mesangial proliferative GN
Focal segmental glomerulosclerosis	Membranous GN
Mesangial proliferative GN	Diffuse mesangial sclerosis
Membranous GN	
Secondary	*Secondary*
Drash Syndrome	Membranous GN
Diffuse mesangial sclerosis	Syphilis
Membranous GN	Fanconi's syndrome
Syphilis	Proliferative GN
Systemic lupus erythematosus	Syphilis
Toxoplasmosis	Cytomegalovirus
Nail-patella syndrome	Alpha-1-antitrypsin deficiency
Hemolytic uremic syndrome	Mercury poisoning
	Drash syndrome
	Diffuse mesangial sclerosis
	Hemolytic uremic syndrome

- Most patients present between 3–11 months of age with proteinuria, renal insufficiency, and rapid progression to end-stage renal failure, usually within 6 months of onset
- Approximately 25% of cases are associated with male psuedohermaphroditism, Wilms tumor, and nephropathy—a constellation of features referred to as the Denys-Drash syndrome or Drash syndrome, which appears to be the result of a single gene defect involving WT1, a tumor suppressor gene isolated on chromosome 11p13
- Infants with diffuse mesangial sclerosis, with or without Drash syndrome, demonstrate a rapid decline in renal function within 6 months of diagnosis

Microscopic

- Light microscopy:
  - The early glomerular lesion is characterized by an increase in mesangial matrix without hypercellularity
  - Later, the glomerular tuft becomes an avascular sclerotic mass surrounded by a layer of podocytes, often accompanied by a dilated Bowman's space
  - The tubules show marked ectasia with attenuation of the epithelium and eosinophilic hyaline casts in the lumens
  - A zonal distribution of lesions has been described
- Electron microscopy:
  - The glomeruli show podocyte damage characterized by diffuse effacement of foot processes, microvillous transformation, and pseudocyst formation
  - The glomerular basement membranes show thickening, collapse, subendothelial and subepithelial widening, and foci of lamina densa splitting and lamellation

TUBULOINTERSTITIAL DISEASES OF THE KIDNEY

Acute Infectious Pyelonephritis (Ascending or Hematogenous Infection)

- Acute infectious pyelonephritis is rarely seen grossly except at autopsy

Macroscopic

- The kidney may be enlarged with a bulging cut surface
- Microabscesses may be present in the cortex and studding the subcapsular surface of the kidney
- The cut section of the kidney demonstrates pus-filled collecting ducts that extend into the underlying medulla
- The pelvicaliceal system is dilated and the renal papillae are diffusely blunted, with an inflamed lining mucosa

Microscopic

- There is a dense interstitial and intratubular infiltrate of acute inflammatory cells with tubular destruction

Chronic Pyelonephritis

Chronic Obstructive Pyelonephritis

- May be caused by obstruction of the ureter by calculi (stones), tumor within the ureter, or extrinsic compression

Macroscopic

- The kidney shows pelvicaliceal dilatation and parenchymal thinning, with blunting of papillae
- Coarse cortical and medullary scars are situated over dilated calices
- Staghorn calculi may complicate and contribute to obstruction

Chronic Non-Obstructive Pyelonephritis (Reflux Nephropathy)

- Results from reflux of urine from the bladder into the ureter and renal pelvis

Macroscopic

- Morphologically, it is characterized by coarse, sharply demarcated segmental scarring overlying dilated calices
- The kidney may be reduced in size and process may involve one kidney
- Scarring is more prominent and extensive at the poles of the kidney

Microscopic

- Characterized by tubular atrophy, interstitial fibrosis, chronic inflammation, and periglomerular fibrosis
- Focal segmental glomerulosclerosis has been associated with reflux nephropathy

Acute Tubulointerstitial Nephritis

- An acute inflammatory disease involving the renal tubules and interstitium; glomeruli and vessels are generally spared
- Acute pyelonephritis is a form of acute tubulointerstitial nephritis; however, a number of other etiologic agents have been identified
- The most common causes of non-infectious acute interstitial nephritis include:
  - Immune mediated:
    - Drug exposure
    - Diuretics
    - Antibiotics
    - Phenytoin
    - Phenobarbital
    - Probenicid
    - Allopurinol
    - Cimetidine
    - Nonsteroidal anti-inflammatory agents
  - Miscellaneous:
    - Sarcoidosis
    - Lymphoma
    - Leukemia

Microscopic

- The interstitium contains an infiltrate of mixed inflammatory cells composed predominantly of lymphocytes with admixed plasma cells and usually eosinophils
- Interstitial edema and tubulitis are also present
- Granulomatous forms of intersititial nephritis also occur

Acute Tubular Necrosis (ATN)

Ischemic Injury

- May complicate a number of primary disorders, many of which are associated with circulatory shock and hypovolemia
- Conditions that may be complicated include:
  - Extensive trauma and burns
  - Pancreatitis
  - Incompatible blood transfusions
  - Dehydration following diarrhea, vomiting, and excessive sweating
  - Rhabdomyolysis

  - Shock
  - Septicemia
  - Hemolysis
- ♦ The straight segment of the proximal tubule is most vulnerable to ischemia

Microscopic

- ♦ Single cell necrosis with desquamation
- ♦ Loss of the proximal tubule brush border
- ♦ Tubular dilatation
- ♦ Pigmented (brown) casts in distal tubules
- ♦ Crystals in distal tubules and collecting ducts
- ♦ Mild interstitial edema and inflammation
- ♦ Accumulation of leukocytes in the vasa recta

Nephrotoxic Injury

- ♦ May be defined as acute renal failure caused by a dose-dependent toxic renal injury
- ♦ Causes include:
  - Antimicrobials:
    - Aminoglycosides
    - Tetracyclines
    - Amphotericin
    - Polymyxin
    - Cephalosporins
  - Heavy metals:
    - Mercury
    - Lead
    - Arsenic
    - Gold salts
    - Barium
  - Miscellaneous:
    - Cisplatin
    - Doxorubicin
    - Streptozocin
    - Methoxyflurane
    - Halothane
    - Heat stroke
    - Ethylene glycol
    - Carbon tetrachloride
    - Radiographic contrast agents
    - Myoglobinemia
    - Transfusion reactions
    - Snake and spider bites

Light Chain Cast Nephropathy (Myeloma Kidney)

- ♦ Results from the overproduction of immunoglobulins or fragments of immunoglobulins (light chains) by a clone of malignant B cells (plasma cells)
- ♦ Filtration of excessive light chains can cause direct toxic damage to renal tubular cells, and tubular obstruction from cast formation

Microscopic

- ♦ The term "myeloma kidney" or "cast nephropathy" refers to renal damage that occurs as a result of large numbers of light chain casts forming primarily in the distal tubules
- ♦ These casts incite a giant cell inflammatory reaction within the tubules that may cause tubular degeneration and extend into the interstitium
- ♦ Volume depletion predisposes to the formation of light chain casts

VASCULAR DISEASES OF THE KIDNEY

Benign Nephrosclerosis

- ♦ Estimates suggest that 15% to 25% of adults in the United States are hypertensive
- ♦ Less than 95% of individuals with persistently elevated blood pressure are classified as having essential hypertension

Macroscopic

- ♦ The kidneys are usually normal to slightly smaller than normal, and in long-standing cases, may be markedly reduced in size
- ♦ The subcapsular surface is finely granular and the capsule is often adherent
- ♦ The cut surface reveals thinning of the cortex and v-shaped subcapsular scars

Microscopic

- ♦ The areas of scarring show varying degrees of glomerular ischemic wrinkling and hyalinization, tubular atrophy, and interstitial fibrosis
- ♦ Arterioles show hyaline deposits; larger arteries show elastic fragmentation and reduplication with subendothelial fibrosis, intimal thickening, and focal lipid deposits

Malignant Nephrosclerosis

- ♦ Malignant hypertension (papilledema in the presence of diastolic blood pressure >125 mm Hg) develops in 1% to 7% of hypertensive individuals

- Approximately 50% of patients with malignant hypertension have a history of essential hypertension and only 1% to 2% develop the disease de novo

Microscopic

- The glomeruli show wrinkling and duplication of the capillary loop basement membranes and fibrinoid necrosis of the vascular pole
- The blood vessels show proliferative endarteritis in small arteries and arterioles, arteriolar necrosis, and mucoid intimal thickening of medium-sized and small arteries

Renovascular Hypertension (Renal Artery Stenosis)

- Defined as stenotic lesions of the main or segmental renal arteries inducing chronically elevated blood pressure that normalizes after correction of the stenosis
- Approximately two-thirds of renovascular hypertension in adults is due to atherosclerosis, which affects more men than women
- Fibromuscular dysplasia accounts for approx 25% of cases and is the most common cause of renovascular hypertension in young people and is found predominantly in young women

Atherosclerosis

- Atherosclerotic stenosis of the renal artery is usually located in the proximal renal artery, and in 50% of patients, is present at the ostium, where the renal artery arises from the aorta

Microscopic

- The involved segments of the renal artery are narrowed by an eccentric plaque that is characterized by subendothelial intimal thickening overlying cell debris, lipid, cholesterol clefts, and foam cells
- Medial and adventitial fibrosis may also be present. The atherosclerotic plaque may be complicated by hemorrhage and dissection
- Calcification, and in some cases, osseous metaplasia, may occur

Fibromuscular Dysplasia (FMD)

- Patients with fibromuscular dysplasia are younger (mean age = 35) and are predominantly women
- There are intimal, medial, and adventitial forms of fibromuscular dysplasia:
  - Intimal fibroplasia (2% to 4%)
  - Medial fibroplasia (25%):
    - Affects distal portion of artery
    - Aneurysmal dilatations
    - Often bilateral
    - Fibromuscular ridges alternate with a thinned media
  - Perimedial fibroplasia (4% to 5%):
    - Circumferential fibrosis of the outer third of the media
    - Affects women in second and third decades (not men)
  - Medial hyperplasia (1% to 2%):
    - Increased medial smooth muscle cells with little fibrosis
    - Medial dissection
      - Associated with the above forms of fibromuscular dysplasia
  - Adventitial fibroplasia (<1%):
    - Adventitial proliferation of fibrous connective tissue
    - May be related to retroperitoneal fibroplasia

Thromboembolic Diseases

- Vascular occlusion producing infarction of the renal parenchyma is a relatively rare occurrence
- Thrombosis of major vessels as a consequence of trauma is more common in younger individuals; occlusion as a complication of atherosclerotic vascular disease is more often seen in older persons
- Emboli to the renal artery or one of its major branches is the most common cause of renal artery obstruction, and occurs predominantly in the setting of cardiac disease and arrhythmias
- Cholesterol atheroemboli from peripheral vessels, thrombotic microangiopathy, and sickle cell disease are all causes of small vessel occlusion

Cortical Infarcts

- Sudden complete occlusion of the main renal artery results in infarction of much of the renal parenchyma; occlusion of smaller renal artery branches results in necrosis of wedge-shaped segments of the renal parenchyma

Macroscopic

- The infarcted kidney appears enlarged and pale
- Regions of segmental infarction are pale, with a hyperemic border

Microscopic

- The infarct shows coagulation necrosis with adjacent parenchyma showing changes of acute tubular necrosis
- Hemorrhage and acute inflammation are often present at the edge of the infarct, and there may be a rind of more preserved parenchyma overlying the infarct, that is supplied by penetrating capsular vessels
- Within days to weeks, the infarct becomes fibrotic, with eventual shrinkage of the affected parenchyma:
  - This area contains dense, globally sclerotic glom-

eruli with intervening dense fibrous tissue and tubule loss. The adjacent parenchyma may show tubular atrophy and varying degrees of glomerular sclerosis

Renal Cholesterol Microembolism Syndrome

Clinical

- Can occur spontaneously or as a complication of aortic surgery or major vessel angiography in patients with diffuse atherosclerosis
- Renal cholesterol embolism may be diagnosed clinically when renal failure develops following identifiable predisposing factors and when there is evidence of systemic involvement in the form of focal digital ischemia, retinal embolism, and lower extremity livedo reticularis

Microscopic

- The characteristic renal lesion in disseminated cholesterol microembolism syndrome is the finding of atheromatous material in the form of cholesterol clefts within arcuate and interlobular arteries

Thrombotic Microangiopathy

Clinical

- Encompasses a group of disorders characterized by microangiopathic hemolytic anemia, thrombocytopenia, and microvascular thrombi:
  - Hemolytic uremic syndrome (HUS)
  - Thrombotic thrombocytopenic purpura (TTP)
  - Disseminated intravascular coagulation (DIC, shows fibrinolysis)
  - Malignant hypertension
  - Scleroderma
  - Pregnancy associated
  - Therapy associated
  - Chronic transplant glomerulopathy

Morphologic Features

- Thickening of capillary walls with the formation of "double contours"
- Capillary thrombosis
- Fragmented red blood cells
- Mesangiolysis with microaneurysm formation
- Mucoid intimal thickening of arteries with glomerular ischemia

Vasculitis

- Renal involvement in systemic vasculitis is characterized by necrotizing and crescentic glomerulonephritis
- Crescentic glomerulonephritis may be immune complex mediated, mediated by anti-glomerular basement membrane antibody, or characterized by little or no immune deposits (pauci-immune type):
  - Pauci-immune crescentic glomerulonephritis comprises nearly 50% of cases of crescentic glomerulonephritis, and is frequently associated with both polyarteritis and Wegener's granulomatosis, but may also be diagnosed as an isolated renal disease (idiopathic crescentic GN)
  - Most pauci-immune crescentic glomerulonephritis is associated with a detectable anti-neutrophil cytoplasmic antibody (ANCA) in the serum:
    - ANCA-associated vasculitis includes:
      - Wegener' granulomatosis >90% of cases
      - Microscopic polyarteritis >90%
      - Polyarteritis nodosa 30% to 50%
      - Idiopathic crescentic glomerulonepheritis >90%
      - Kawasaki disease 50%
      - Churg-Strauss syndrome 50% to 60%
    - Wegener's granulomatosis is a necrotizing, granulomatous vasculitis that classically involves the upper and lower respiratory tract and the kidney; other sites such as the eyes, ears, heart, nervous system, skin, and joints are less commonly affected:
      - Clinical signs of renal disease are present in the majority of patients with Wegeners granulomatosis; patients usually present with the acute nephritic syndrome with renal functional impairments ranging from mild to overt renal failure
      - Morphologically, the typical renal lesion in Wegener's granulomatosis is a focal and segmental necrotizing and crescentic glomerulonephritis that lacks immune deposits
    - Involvement of vessels in the kidney in polyarteritis nodosa is frequent, but the caliber of vessel involved varies; this vascular involvement may lead to focal infarction. Significant renal functional impairment more commonly results from necrotizing and crescentic glomerulonephritis. The necrotizing glomerulonephritis of polyarteritis is morphologically indistinguishable from that of Wegener's granulomatosis

DEVELOPMENTAL AND CYSTIC DISEASES OF THE KIDNEY

Renal Dysplasia

Clinical

- A developmental abnormality that results from aberrant metanephric differentiation
- Although the pathogenesis is unknown, possibilities include in utero urinary tract obstruction and a defect in inducer, the ampullary bud, responder tissue, or metanephric blastema
- Renal dysplasia occurs sporadically and may be associated with obstruction, multi-malformation syndromes (Meckel's syndrome), chromosomal anomalies (trisomy 9 or 13), or hereditary malformation syndromes (chondrodysplasia syndromes)
- Unilateral multicystic renal dysplasia is the most common cause of a renal mass in childhood; bilateral lesions may present in utero or shortly after birth with oligohydramnios and Potter's syndrome
- Adults are usually asymptomatic but may have flank pain or a nonfunctioning small kidney
- The clinical outlook depends on the extent of dysplasia if bilateral, and the function of the contralateral kidney if unilateral
- The recurrence rate in siblings is approx. 2% but may be much greater in syndromic dysplasias

Macroscopic

- Dysplastic kidneys may be unilateral or bilateral, large or small, reniform or irregular, and solid or cystic

Microscopic

- The overall architecture is disorganized. There may be primitive ducts, aberrant glomeruli, cysts lined by flattened epithelium, and immature cartilage, tubules, or mesenchymal tissue, as well as relatively normal tubules and glomeruli

Autosomal Dominant Polycystic Kidney Disease (ADPKD)

Clinical

- The most common cystic renal disease, with an estimated frequency between 1:500 and 1:1000 and a nearly complete penetrance
- Occurs slightly more frequently in Caucasians than in African Americans
- There is some genetic heterogeneity but >90% of cases in Caucasians are associated with a defect in chromosome 16p
- The disease course is variable, ranging from cases that are fatal in newborns to cases with minimal functional disturbance at old age; 25% of patients lack a family history
- In children, the process may be nonuniform and the patient may appear to have a unilateral lesion early in the course, even radiographically
- Most patients present in the third to fourth decade with dull abdominal pain and bilaterally palpable kidneys, as well as variable renal insufficiency, gross or microscopic hematuria, hypertension, infection, and mild proteinuria:
  - Other associated manifestations include cardiac abnormalities, congenital intracranial aneurysms (10% to 36%), and cysts of the liver, lungs, pancreas, and spleen
- Renal failure occurs in 50% of patients an average of 10 years after clinical detection
- Patients with ADPKD account for 10% of patients in the United States on dialysis and 6% of renal transplants

Macroscopic

- The kidneys are large, ranging from 250–4000 g, and usually maintain a somewhat reniform shape
- Variable numbers of spherical, unilocular cysts are present within the cortex and medulla
- The calices, pelvis, and papilla are often greatly distorted

Microscopic

- 1% to 2% of the nephrons show cystic dilation of primarily the collecting tubules, proximal convoluted tubules, and Bowman's space interspersed with normal or compressed renal parenchyma
- Frequently, there is focal hyperplasia of the epithelial lining and polyp formation
- Renal cell carcinoma may also occur

Autosomal Recessive Polycystic Kidney Disease (ARPKD)

Clinical

- Occurs in 1/6,000 to 1/14,000 live births and has a 2:1 female predominance
- The etiology and pathogenesis are unknown, but the kidneys appear to have a normal distribution and number of nephrons and collecting ducts
- The clinical presentation is variable depending on the extent and duration of disease:
  - Many affected newborns have severe disease with a grossly enlarged abdomen, kidneys, and signs of oligohydramnios (pulmonary hypoplasia, flattened nose, low set ears, micrognathia, hip dislocation). In the first days of life, these neonates develop fatal respiratory distress, congestive heart failure, and hypertension

  - Older children and adults show a variable course with approx. 30% having an insidious onset of renal failure, which is often associated with anemia, renal osteodystrophy, growth retardation, hypertension, and congestive heart failure
- Also associated with congenital hepatic fibrosis, and there is an inverse relationship between the extent of renal cystic change and the extent of hepatic fibrosis
- Older patients have a smaller number of large cysts with marked, progressive hepatic fibrosis; although liver function is usually well maintained, severe portal hypertension, hepatosplenomegaly, and esophageal varices may develop by 5–10 years of age

Macroscopic

- The renal capsule is smooth with numerous 1–2 mm cysts visible
- On sectioning, the cysts are 1–8 mm, cylindrical, and extend radially throughout the cortex, obscuring the corticomedullary junction
- In older patients, the surface becomes irregular

Microscopic

- In the younger patient, the kidney is almost entirely composed of dilated terminal branches of the collecting ducts; these appear cylindrical in the cortex and round to oval within the medulla:
  - The cysts are lined by cuboidal epithelium, which may have foci of hyperplasia or polyp formation
  - The glomeruli and proximal nephron may be compressed but are otherwise unremarkable
- In older patients, the cysts are fewer in number but are larger and are associated with tubular atrophy, interstitial fibrosis, and glomerular sclerosis:
  - The hepatic lesion is diffuse but is limited to the portal triads, where there is variable fibrosis and increased numbers of irregularly shaped bile ducts

Juvenile Nephrophthisis (Medullary Cystic Disease)

Clinical

- Juvenile nephronophthisis, or medullary cystic disease, is a complex of progressive renal diseases affecting children, characterized by nephrosclerosis, renal failure, and medullary cysts
- May present as a single morphology and clinical picture, differing only in the pattern of inheritance (sporadic, autosomal recessive, or autosomal dominant)
- Clinical presentation usually occurs between 5–35 years of age with anemia, polyuria, enuresis, and polydipsia secondary to the decreased concentrating ability of the tubules
- Occasionally, patients will present with associated abnormalities of the retina, skeletal, or central nervous system
- Proteinuria, hematuria, infection, stone formation, and pain are not usually present

Macroscopic

- The kidneys in medullary cystic disease are symmetrically small and firm with a finely granular surface, a thin cortex and medulla, and indistinct corticomedullary junction, which is the site of a variable number of cysts

Microscopic

- There is severe, widespread tubular atrophy and interstitial fibrosis with diffuse thickening of the basement membranes and scattered sclerotic glomeruli
- The cysts are lined by cuboidal to flattened epithelium with surrounding fibrosis and inflammation

Acquired Renal Cystic Disease

Clinical

- Affects patients on hemodialysis and peritoneal dialysis as well as azotemic nondialyzed patients
- Cysts develop in 35% to 47% of patients on maintenance hemodialysis and development appears to be dependent on the duration of dialysis
- Acquired cysts occur in as many as 92% of patients who have been dialyzed more than 8 years
- Cyst formation is three to four times more common in males
- Most patients have no symptoms referable to the cysts but may present with renal bleeding or pain
- The cysts form primarily from the proximal convoluted tubules, and are associated with multiple small diverticula elsewhere in the tubule

Macroscopic

- Overall, the kidneys are variably sized, but in a single patient, are usually of equal size
- The kidneys contain a variable number of clear, fluid-filled cysts with some having a few large subcapsular cysts and others having numerous small cysts throughout the parenchym
- The cysts can be uni- or multilocular and mainly involve the cortex, but can also affect the corticomedullary junction and medulla; often there is evidence of acute or past hemorrhage

Microscopic

- The kidneys show end-stage renal disease with sclerotic glomeruli, tubular atrophy, and interstitial fibrosis
- Calcifications, hemosiderin, and arterial intimal and medial hyperplasia may also be present

- The cysts are lined by flattened to cuboidal epithelium and may contain deposits of calcium oxalate
- There is an increased incidence of renal cell carcinoma, particularly papillary renal cell carcinoma, in patients with end-stage renal failure and acquired cystic disease

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Chapter 24

Tumors of the Kidney

Liang Cheng, MD
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CHILDHOOD TUMORS OF THE KIDNEY

Cystic Nephroma (Multilocular Cyst of Kidney, Solitary Multilocular Cyst)

Clinical

- Often occurs in children (<2 year, M:F = 2:1) and in adult females (M:F = 1:3)
- Benign; surgical excision is curative

Macroscopic

- Multicystic, well-circumscribed tumor surrounded by a fibrous capsule
- Often located in the upper pole of the kidney

Microscopic

- Unifocal, unilateral, multilocular, and cystic
- Variable-sized (5–10 cm) cysts lined by cuboidal or hobnail cells
- Cysts do not communicate with the renal pelvis
- No normal mature renal parenchymal components in the fibrous septa
- Fibrous septa may contain differentiated tubules
- No blastema
- The presence of even a small amount of clear cells is incompatible with cystic nephroma

Immunohistochemistry

- Cytokeratin +
- Epithelial membrane antigen (EMA) +

Differential Diagnosis

- Polycystic kidney disease:
  - Normal renal parenchymal in the fibrous septa
- Cystic hamartoma of renal pelvis:
  - Occurs in adults, with female predominance (M:F = 1:7)
  - More complex epithelioid structure with branching and micropapillae
  - Spindle smooth muscle and thick-walled vessels in the septae
  - Interspersed epithelial tubules lined by cuboidal and columnar cells
- Multilocular cystic renal cell carcinoma:
  - Clear cells invariably seen
- Cystic partially differentiated nephroblastoma (CPDN):
  - Blastema in the wall of septae and skeletal muscle

Mesoblastic Nephroma

Clinical

- Most common kidney tumor in the first 3 months of life; rare after 6 months
- Comprises 5% of pediatric renal neoplasms
- M = F; benign tumor; may recur
- Presents with abdominal mass, hematuria, anemia, vomiting, jaundice, and hypertension
- Cytogenetics: trisomy 11
- More aggressive in older children
- Increased cellularity, mitotic figures, atypia, and necrosis may be associated with recurrence and metastasis in older children (>3 months)
- Complete surgical excision is critical in the clinical management
- Associations:
  - Polyhydramnios
  - Premature birth
  - Hyperenism
  - Hypercalcemia (due to prostaglandin E production)

Macroscopic

- Unilateral leiomyoma-like rubbery whorled tumor adjacent to the hilum
- May have finger-like projections with indistinct borders and cystic change

Microscopic

- Infiltrative growth
- Monophasic interdigitating spindle cell proliferation resembles fibromatosis or leiomyoma.
- Surrounded by scattered lymphocytes
- Coarse chromatic pattern; lacks prominent nucleoli; no skeletal muscle component
- May contain cartilaginous component (also seen in Wilms' tumor and renal dysplasia), foci of hematopoiesis, and squamous differentiation
- Frequent entrapment of isolated glomeruli and renal tubules
- Large tortuous vascular spaces
- Two patterns of growth:
  - Classic pattern:
    - Fascicles of elongated spindle cells with infiltrative border
  - Cellular pattern:
    - More common than classic pattern, not seen in adults
    - Rounded, plump cells with pushing border and increased mitotic figures
- Adult type (vs. congenital):
  - Only classic pattern is reported
  - Encapsulated or well-circumscribed, with more prominent tubular component

- Lower cellular density and more collagenized
- May have clear cell change and polypoid growth

Electron Microscopy

- Anastomosing rough endoplastic reticulum

Immunohistochemistry (Table 24-1)

- Vimentin +
- Desmin ±
- Muscle-specific actin ±
- Cytokeratin –
- S-100 protein –

Differential Diagnosis

- Wilms' tumor:
  - Occurs in older patients; bilateral and multicentric
  - Circumscribed tumor with pushing margin
  - Triphasic: blastemal, epithelial, and stromal (skeletal muscle) components
- Leiomyosarcoma:
  - Rare in children; atypia; numerous mitotic figures
- Clear cell sarcoma:
  - Occurs in older patients; delicate fibrovascular septa
  - Fine open chromatin, cytoplasmic vacuoles, and pale cytoplasm
- Angiomyolipoma:
  - Triphasic tumor
- Renal cell carcinoma with sarcomatoid features:
  - High-grade tumor with fine vasculature

Ossifying Tumor of Infantile Kidney

Clinical

- Rare, occurs in infants < 4 months old
- Clinical presentation: hematuria
- Benign without recurrence after complete resection

Macroscopic

- Small (2–3 cm) calcified mass with indistinct border in the pelvic region

Microscopic

- Sheets of plump spindle cells with eosinophilic cytoplasm
- Associated with osteoid and bone formation

Wilms' Tumor (Nephroblastoma)

Clinical

- M:F = 1:1; peak age 2–4 years; highest incidence in African Americans
- Usually occurs between 6 months and 3 years of age; rare after age 3
- Comprises 85% of pediatric renal neoplasms and 5% of childhood cancers
- 5% multicentric, 5% bilateral, and 5% anaplastic
- Focal anaplasia does not have a worse prognosis
- Lung metastases common
- Associated with cryptorchidism, hypospadias, hemihypertrophy, aniridia, renal ectopia, and horseshoe kidney
- Risk (see Chapter 2 for syndromes):
  - Beckwith-Wiedemann (hemihypertrophy): WT2 gene, 5% develop Wilms tumor
  - Wilms-aniridia-genital anomaly-retardation syndrome (WAGR): WT1 gene
  - Denys-Drash syndrome (glomerulonephritis, pseudohermaphroditism, and nephroblastoma): WT1 gene
  - Trisomy 18
  - Multicystic dysplastic kidney
- Cytogenetics: chromosome 11p13 deletion common:
  - WT1:
    - Located on chromosome 11p13, putative tumor suppressor gene
    - 30–40% Wilms' tumors show loss of heterozygosity (LOH) at 11p13

Table 24-1. Immunohistochemical Profile of Pediatric Renal Neoplasms

	Mesoblastic Nephroma	*Wilms' Tumor*	*Rhabdoid Tumor*	*Clear Cell Sarcoma*
Cytokeratin	–	+	±	–
Vimentin	+	+	+	–/+
EMA	–	+	±	–
Desmin	+	+ (in skeletal muscle component)	–	–

Note: EMA = epithelial membrane antigen

- Encoding 45-49 kd protein, homologous to early growth response 1 (EGR1)
- Involved in transcription regulation with sequence-specific DNA binding

– WT2:
- Located on chromosome 11p15.5
- Putative tumor suppressor gene
- Genomic printing and loss of maternal allele
- IGF2 and H19 were putative candidate genes for WT2

– WT3:
- Located on chromosome 16q
- LOH is associated with cancer progression
- LOH on chromosome 1p
- Trisomy 18

Macroscopic

♦ Large (usually >5 cm) circumscribed tumor with variegated and nodular appearance

♦ 10% multicentric

Microscopic

♦ Triphasic:

– Blastema:
- Three growth patterns: nodular (organoid), serpentine, and diffuse (no prognostic significance)
- Small, densely packed small cells with little cytoplasm
- Oval to elongated nuclei, overlapping nuclei, and numerous mitotic figures

– Epithelial component:
- Abortive tubules and glomeruli
- May show mucinous, squamous, neural, or neuroendocrine differentiation

– Stroma:
- Skeletal muscle (most common), spindle cells, or cartilage

– Note: Cartilage in the kidney may also be seen in mesoblastic nephroma and renal cystic dysplasia

♦ Often multicentric (also seen in lymphoma and angiomyolipoma)

♦ Pushing border except diffuse blastemal pattern

♦ Anaplasia:

– Only criterion for placing Wilms' tumor into unfavorable histological categories

– Indicates increased resistance to therapy rather than increased aggressiveness

– Definition of anaplasia:
- Atypical multipolar mitotic figures
- Enlarged nuclei (three times larger than adjacent blastemal cells in both axes)
- Marked nuclear hyperchromasia

♦ Focal versus diffuse anaplasia:

– Focal (Faria et al. AJSP 20:909; 1996.)
- Anaplasia limited to one or more discrete foci within the primary tumor and not present in any tumor extensions beyond the original tumor capsule
- No evidence of anaplasia or marked nuclear atypia elsewhere in the tumor
- If multiple foci of anaplasia detected, each focus should be surrounded by a non-anaplastic tumor
- Anaplasia is confined to discrete foci within the original primary tumor and surrounded by non-anaplastic or necrotic tumor cells in treated patients

– Diffuse:
- More diffuse anaplasia
- Anaplasia or marked nuclear atypia (nuclear unrest) elsewhere in the tumor
- Anaplasia present in a random biopsy or incomplete tumor sample
- Nondemarcated anaplasia at the edge of more than one section; the pathology report does not document that the involved sections were from the same tumor focus
- Anaplasia beyond the original tumor capsule, or at invasive margin, vessels, extrarenal sites, or metastatic deposits

Immunohistochemistry (Blastema)

♦ Vimentin +

♦ Neuron-specific enolase (NSE) +

♦ Cytokeratin +

Variants

♦ Cystic Partially Differentiated Nephroblastoma (CPDN):

– Slight male predominance; excellent prognosis

– Sharply demarcated, no expansile nodules as seen in classic Wilms' tumor

– Hobnail cell-lined cysts with blastemal component in immature mesenchymal stroma

– Differential diagnosis:
- Polycystic kidney disease:
  - Glomeruli in septa, no blastema
- Cystic nephroma:
  - No blastema, no skeletal muscle
- Monomorphic epithelial variant:
  - Elongated ovoid nuclei with tapered ends and molding

- Fetal rhabdomyomatous variant:
  - This subdivision is controversial
  - 30% bilateral, usually male; may have a better prognosis
  - Predominant mature skeletal muscle component, lacks rhabdomyoblasts
  - Often seen after chemotherapy
- Teratoid variant:
  - This subdivision is controversial.
  - Tumor contains >50% heterologous elements
  - Fat, squamous epithelium, and cartilage

Differential Diagnosis

- Small blue cell tumors of childhood:
  - Neuroblastoma:
    - Often arises from the adrenal medulla; often unifocal and unilateral
    - Bone metastasis common (Note: lung metastasis common in Wilms' tumor)
    - True rosette formation with central neurofibrils
    - Vimentin –
    - Neuron-specific enolase (NSE) +
    - Synaptophysin +
    - Neurofilament +
  - Ewing's sarcoma:
    - Mic2 (HBA71) +
  - Rhabdomyosarcoma:
    - Desmin +
  - Lymphoma:
    - Leukocyte common antigen (LCA) +
- Clear cell sarcoma of kidney:
  - Infiltrative scalloped border and entrapped normal tubules within the lesion
  - Lack of overlapping nuclei and more intense reticulin stain around tumor cells
  - Fibrovascular septa with chicken wire-like vasculature
- Rhabdoid tumor:
  - Infiltrative sheets of large polygonal cells with a single prominent central nucleoli
  - No nodular or serpentine growth pattern; no triphasic components
  - Hyaline cytoplasmic inclusions
- Mesoblastic nephroma:
  - Common in the first 3 months of life; no blastema or skeletal muscle
  - Infiltrative border in classic mesoblastic nephroma
  - Not bilateral or multicentric
- Renal cell carcinoma:
  - Round nuclei, usually with clear cells and delicate vasculature
  - (Elongated nuclei in monomorphic Wilms' tumor)

National Wilms' Tumor Study System for Staging of Pediatric Renal Tumors (NWTS-5)

Stage I

- Confined to kidney and completely resected:
  - Renal capsule is not penetrated by tumor
  - Lacks invasion of vessels of renal sinus
  - Focal soft tissue invasion of sinus with negative medial sinus margins
  - Prior fine needle aspiration is acceptable for stage I

Stage II

- Extends beyond kidney, but is completely resected with surgical margins:
  - Penetrates through renal capsule, or renal vessels involved, but margins clear
  - Extensive renal sinus invasion that approaches, but does not definitively involve, the medial sinus margin
  - Prior core needle or open biopsy
  - Local spillage limited to the flank and does not contaminate the peritoneum

Stage III

- Residual tumor confined to the abdomen:
  - Diffuse peritoneal involvement by implantation, spillage, or direct tumor growth
  - + surgical margins
  - Abdominal lymph node involvement

Stage IV

- Hematogenous metastasis
- Involvement of nodes beyond renal drainage region (e.g., mediastinal nodes)

Stage V

- Bilateral (tumor in each kidney should be separately substaged)

Nephrogenic Rest

- Abnormal persistence of small foci (< 300 μm in diameter) of embryonal cells
- Considered as a precursor of Wilms' tumor
- Perilobar nephrogenic rest:
  - Occurs in 1% of infants <3 months; multifocal
  - Associated with Beckwith-Wiedemann syndrome and synchronous bilateral Wilms' tumor

  - Peripheral location with sharply defined margin; multiple
  - Diffuse blastemal component without stromal or epithelial differentiation
- Intralobar nephrogenic rest:
  - Associated with metachronous bilateral Wilms' tumor
  - Randomly distributed in the cortex and medulla with indistinct margins; solitary
  - Predominantly stromal component
  - Dilated dysplastic tubules and collections of blastemal cells in a fibrous stroma
- Nephroblastomatosis: presence of diffuse or multifocal nephrogenic rests:
  - Perilobar nephroblastomatosis: 5% develop Wilms in contralateral kidney
  - Intralobar nephroblastomatosis: 16% develop Wilms in contralateral kidney
  - Wilms with nephroblastomatosis: 5% develop Wilms in contralateral kidney

Differential Diagnosis

- Wilms' tumor:
  - Pushing border (except diffuse blastemal pattern)
  - Triphasic (blastemal, stromal, and epithelial)

Clear Cell Sarcoma of Kidney (Bone-Metastasizing Renal Tumor of Childhood)

Clinical

- M:F = 1.6:1; peak at 2–3 years of age; rare before 6 months
- Comprises 4% of pediatric renal neoplasms
- Poor prognosis, with frequent bone metastases (17%) and high mortality rate
- 10 times higher risk of bone metastasis than other pediatric renal tumors
- Treatment of choice is doxorubicin

Macroscopic

- Well-circumscribed, tan-gray, firm unilateral tumor with frequent cyst formation

Microscopic

- Zonation:
  - Entrapped, isolated individual nephron/collecting ducts at central lesion
  - Infiltrative nests, trabeculae, palisading, and cords of monomorphic small round or spindle polygonal cells at periphery
- Chicken wire-like, evenly distributed network of fibrovascular septa composed of spindle cells with dark nuclei
- Few mitotic figures; intra- and intercellular vacuoles
- Amphophilic cytoplasm with accumulation of mucopolysaccharides
- No overlapping nuclei (in contrast to Wilms' tumor)
- Different patterns of growth, including epithelioid, spindle, sclerosing, myxoid, and palisading

Immunohistochemistry

- Cytokeratin –
- Vimentin –/+
- Epithelial membrane antigen (EMA) –
- Alpha 1 antichymotrypsin +
- Desmin –
- Muscle-specific actin (MSA) –

Differential Diagnosis

- Cellular mesoblastic nephroma:
  - No prominent nucleoli
- Wilms' tumor:
  - More cellular, blastemal component, with overlapping nuclei
  - Heterogeneous tissue (muscle and cartilage)
  - Bilateral and multicentric, pushing border
  - May present with more widely infiltrative border in diffuse blastemal pattern
- Rhabdoid tumor:
  - More infiltrative pattern, single prominent huge nucleoli
  - Vimentin +
  - Cytokeratin +

Rhabdoid Tumor of Kidney

Clinical

- M:F = 1.5:1; 90% of patients < 3 years of age; peak at 1 year
- Comprises 2% of pediatric renal neoplasms
- Aggressive; poor prognosis, often die within 1 year of diagnosis
- Histogenesis unknown, may arise from renal medullary cells
- Cytogenetics: chromosome 22 anomalies
- Associations:
  - Primitive neuroectodermal tumor (PNET)
  - Medulloblastoma
  - Hypercalcemia with elevated parathyroid hormone serum levels

Macroscopic

- Infiltrative, medially located unilateral tumor with frequent necrosis and hemorrhage
- Satellite nodules

Microscopic

- Infiltrative, diffuse sheets of monomorphous large noncohesive polygonal cells in sclerotic hyalinized stroma
- Large vesicular nuclei with prominent central huge nucleoli and nuclear membrane thickening
- Abundant eosinophilic cytoplasm with distinct scalloped cell borders
- Juxtanuclear hyaline cytoplasmic inclusions/globules
- No well-differentiated skeletal (striated) muscle (if present, then Wilms)
- Patterns of growth include sclerosing, epithelioid, spindle, and lymphomatoid

Immunohistochemistry

- Cytokerain ±
- Vimentin +
- EMA +
- S-100 protein –
- Actin –
- Desmin –
- Myoglobin –

Electron Microscopy

- Tangles and whorls of intermediate filaments (hyaline globules)
- Lack myofilaments

Differential Diagnoses

- Wilms' tumor:
  - Pushing border; multifocal and bilateral
  - Triphasic tumor; may contain skeletal muscle component
  - Dense smaller blastemal cells with overlapping nuclei in a fibromyxoid stroma
- Mesoblastic nephroma:
  - Lacks large central prominent nucleoli and thick nuclear membrane
- Clear cell sarcoma of the kidney:
  - Cytokeratin –
  - Vimentin –
  - Inconspicuous nucleoli; less infiltrative margin
  - Prominent chicken wire-like vasculature

ADULT RENAL NEOPLASMS

Benign Epithelial Neoplasms

Papillary Adenoma

Clinical

- Cut point of size for malignancy uncertain
- Lesions <5 mm in diameter are benign for practical purposes
- Often asymptomatic; incidental findings; occurs in up to 23% of autopsy patients
- May arise in the background of acquired renal cystic disease and nephrosclerosis
- Cytogenetics: identical to papillary renal cell carcinoma (+7, +17, -4)

Macroscopic

- Well-cricumscribed subcortical nodule

Microscopic

- Tubular and papillary growth of small cells with uniform nuclei and little cytoplasm
- Cytologically indistinguishable from low-grade papillary renal cell carcinoma
- Clear cell change is incompatible with diagnosis
- No distinguishable components of clear cells, chromophobe, or collecting duct renal cell carcinoma

Differential Diagnosis

- Renal cell carcinoma
- Solid growth of clear cells with higher nuclear grade

Renal Oncocytoma

Clinical

- M:F = 2:1; comprises 5% of adult renal tumors in surgical series
- Benign; surgical resection is curative
- Characteristic angiographic findings include:
  - Spoke-wheel pattern of vascularity in a well-demarcated tumor
  - Uniform capillary nephrogram phase
  - Lack of pooling of contrast media and arteriovenous shunting
- Cytogenetics: LOH on chromosome 1p and 8p
- Bilateral and multifocal in 3.6% of cases

Macroscopic

- Well-circumscribed large tumor with stellate central scar and uniform mahogany brown color
- No gross hemorrhage, necrosis, or cystic change; usually unilateral

Microscopic

- Compact solid or nesting (organoid) arrangement of large cells in an edematous and hyalinized stroma
- Cells with uniform nuclei and abundant eosinophilic cytoplasm
- Occasional degenerative bizarre nuclei; grading is not recommended
- No extensive papillary structures, prominent nucleoli, or lipid/glycogen accumulation
- Mitotic figures inconspicuous
- Small foci of cytoplasmic clearing may be seen in 9% of cases

Immunohistochemistry

- Vimentin –
- Periodic acid-Schiff (PAS) –
- Cytokeratin AE1/3 +
- Low molecular weight (LMW) cytokeratin +
- Carbonic anhydrase +
- Band 3 anion exchange protein +

Electron Microscopy

- Numerous mitochondria

Differential Diagnosis

- Renal cell carcinoma and/or papillary renal cell carcinoma:
  - Mitotic figures, clear cell change, papillae, vimentin +
  - Gross vascular invasion or extension into perirenal fat
- Eosinophilic variant of chromophobe renal cell carcinoma:
  - Solid sheets of cells with perinuclear halos and reticular cytoplasm
  - Hale's colloidal iron stain +, microvesicles by electron microscopy
  - Lacks compact nests, acini, or tubular arrangement of cells

Metanephric Adenoma

Clinical

- M:F = 1:2; adults; mean age = 41 years; incidental findings
- No consistent cytogenetic anomalies
- Associated with polycythemia due to increased erythropoietin production
- Accounts for many previously designated monomorphic Wilms' tumor in adults
- Histogenetic relationship with papillary adenoma/papillary renal cell carcinoma and Wilms' tumor uncertain

Macroscopic

- Well-circumscribed nodule with frequent hemorrhage
- Often larger than renal cortical adenoma

Microscopic

- Closely packed small tubules lined by cuboidal cells in the sclerotic stroma
- Uniform cells contain round, uniform nuclei and scant basophilic cytoplasm
- Lacks fibrous pseudocapsule; may contain psammoma bodies
- Mitotic figures inconspicuous; cystic change may be prominent
- May form tubular, glomeruloid, polypoid, and papillary structures
- Tumor may regress and be replaced by a hyalinized scar with dystrophic calcification.

Immunohistochemistry (Table 24-2)

- Cytokeratin +
- Vimentin +
- EMA –
- Carcinoembryonic antigen (CEA) –
- Smooth muscle actin ±
- Desmin –
- Glycogen (PAS) –
- Oil red 0 –
- S-100 protein –
- NSE –
- Chromagranin –
- Neurofilament –

Variant

- Nephrogenic adenofibroma
  - Mean age = 16 years; no gender predilection
  - Often presented with polythemia vera
  - Biphasic tumor with both epithelial and spindle stromal component
  - Muscle specific actin – (in contrast to mesoblastic nephroma)

Differential Diagnosis

- Adult Wilms' tumor:
  - Larger cells with less nuclear hyperchromasia and frequent mitotic figures
  - Stromal and blastemal components
  - Lacks sclerotic stroma and psammoma bodies
- Renal adenoma:
  - Tubulopapillary structures lined by cuboidal small cells
  - Lacks acellular sclerotic stroma
  - EMA +

Table 24-2. Immunohistochemical Profile of Adult Renal Neoplasms

	Metanephric Adenoma	*Oncocytoma*	*Clear Cell RCC*	*Papillary RCC*	*Chromophobe RCC*	*Collecting Duct Carcinoma*	*Urothelial Carcinoma*
Mucin	–	–	–	–	–	+	–
Hale's iron stain	–	–	–	–	+	–	–
PAS (glycogen)	–	+	+	–/+	–	+	–
HMW cytokeratin	±	+	–	–	–	+	+
LMW cytokeratin	±	+	+	+	+	+	+
Vimentin	+	–/+	+	+	–	+	–
EMA	–	+	+	+	+	+	+
			(membranous)		(apical intracytoplasmic)		
CEA	–	–	–	–	–	–/+ (focal)	+
UEA-1		–	–	–	–	±	–
Carbonic anhydrase		+	–	–	–/+	+	–

Note: RCC = renal cell carcinoma, PAS = periodic acid-Schiff, HMW = high molecular weight, LMW = low molecular weight, EMA = epithelial membrane antigen, CEA = carcinoembryonic antigen, UEA-1 = Ulex europaeus agglutinin 1 lectin

- Papillary renal cell carcinoma:
  - Larger eosinophilic cells with cytologic atypia and foamy cells
  - Frequent hemorrhage and necrosis
  - Cytokeratin 7 +, trisomy 7 and 17
- Carcinoid:
  - Nesting or insular growth pattern with more abundant cytoplasm
  - Lacks sclerotic stroma
  - Neuroendocrine markers are +
- Perilobar nephrogenic rests:
  - Occur in younger patients; multiple; risk for Wilms' tumor
  - May be indistinguishable from metanephric adenoma histologically
- Embryonal hyperplasia in end-stage kidneys:
  - Occurs in patients on long-term hemodialysis
  - May be indistinguishable from metanephric adenoma histologically

Cystic Hamartoma of Renal Pelvis

Clinical

- Adult female (M:F = 1:7) presenting with flank pain
- Benign; complete surgical excision is curative

Macroscopic

- Cystic expansile lesion with pseudocapsule

Microscopic

- Variable-sized cysts and tubules lined by cuboidal and columnar cells, forming micropapillae
- Cellular spindle cell stroma and thick-walled vessels in the septae
- Irregular small epithelial tubules
- Lacks blastema or clear cells
- The presence of even a small amount of clear cells is incompatible with cystic nephroma

Immunohistochemistry

- Cytokeratin +
- EMA +
- Smooth muscle actin +

Differential Diagnosis

- Cystic nephroma:
  - Similar gender predilection and location, with propensity for herniation into the renal pelvis
  - Less complex, less variable epithelial elements
  - Fibrous septa with infrequent spindle cell elements
- Polycystic kidney disease:
  - Normal renal parenchyma in the fibrous septa

- Mesoblastic nephroma:
  - Occurs in infants (<3 months)
  - Epithelial elements more densely distributed at the periphery of the tumor
  - Infiltrative border
- Cystic Partially Differentiated Nephroblastoma (CPDN):
  - Blastoma in the wall of septae and skeletal muscle
- Multilocular cystic renal cell carcinoma:
  - Clear cells are invariably seen

Cystic Nephroma (see Childhood Tumors)

Mesoblastic Nephroma (see Childhood Tumors)

Benign Soft Tissue Tumors

Renomedullary Interstitial Cell Tumor (Medullary Fibroma)

Clinical

- Occurs in patients >20 years; may arise in response to hypertension
- Derived from smooth muscle; produces prostaglandins (antihypertensive)

Macroscopic

- Well-circumscribed, small (< 1 cm) gray-white nodule in the renal medulla

Microscopic

- Cellular neoplasm composed of ovoid spindle stromal cell with interlacing fibers and elongated cytoplasmic processes
- Thin-walled vessels in a loose basophilic stroma

Electron Microscopy

- Electron-dense granules (lipid droplets)

Juxtaglomerular Cell Tumor

Clinical

- M:F = 2:1; young adults and adolescents with hypertension and elevated plasma renin level
- Derived from smooth muscle
- Benign without risk of metastasis or extra renal extension

Macroscopic

- Unilateral, solitary, well-circumscribed, solid, rubbery tumor, often <3 cm
- May have small cyst-like cavities

Microscopic

- Cords and trabeculae of polygonal and spindle cells in a myxoid stroma with lymphocytic infiltrate
- Organoid/hemangiopericytoma-like growth pattern with prominent vasculature
- Cells with uniform central nuclei and granular eosinophilic cytoplasm or pale cytoplasm
- May have papillary architecture

Immunohistochemistry

- Renin +
- S-100 protein –
- NSE –
- Cytokeratin –
- Smooth muscle actin +
- Muscle specific actin +
- Vimentin +
- Desmin –

Electron Microscopy

- Rhomboid crystalline membrane-bound granules (renin)

Angiomyolipoma

Clinical

- M:F = 1:2; mean age = 45–55 years in sporadic cases, 25–35 years in patients with tuberous sclerosis
- Considered as a type of choristoma (fat is not present in the normal kidney)
- Recent X-chromosome inactivation data suggest clonal origin (neoplastic process)
- Benign; may involve lymph nodes as a manifestation of multicentricity
- Acute hemorrhage (10–25%) as the most common serious complication
  - Complications also include renal failure and rare malignant transformation
- 40–50% of patients have tuberous sclerosis: bilateral, smaller, multiple, younger
  - 40–80% of tuberous sclerosis patients have angiomyolipoma
- Sporadic form: middle-age women; larger, solitary, unilateral, tumor
- Diagnosis can be made by fat attenuation on CT scan and hyperechogenicity on ultrasound
- Cytogenetics: LOH on chromosome 16p13.3

Macroscopic

- Well-circumscribed subcapsular or perirenal yellow nodules with frequent hemorrhage

Microscopic

- Triphasic growth of thick-walled vessels, smooth muscle, and mature fat
- Concentric arrangement of smooth muscle around vessels

- Nuclear atypia, necrosis, and mitotic figures are compatible with diagnosis
- Nuclear pleomorphism and mitotic figures have no prognostic significance

Immunohistochemistry

- HMB45 + (in smooth muscle, perimembranous pattern)
- S-100 protein –
- PAS + with diastase
- Desmin +
- Muscle specific antigen +
- High molecular weight (HMW)/LMW cytokeratin –
- Epithelial membrane antigen (EMA) –
- Vimentin +

Variant

- Epithelioid angiomyolipoma:
  - May recur, metastasize, and cause cancer death
  - Sheets of polygonal epithelioid cells and large mononuclear cells
  - Cells with eccentric nuclei and prominent nucleoli, resembling ganglion cells
  - Mitotic figures, hemorrhage, and necrosis may be prominent

Differential Diagnosis

- Renal cell carcinoma with sarcomatoid change:
  - Cytokeratin +, fine vasculature, cytologic atypia
- Lipoma:
  - Lacks vascular and smooth muscle component of angiomyolipoma
- Leiomyosarcoma:
  - Cytologic atypia and numerous mitotic figures

Malignant Neoplasms

Conventional (Clear Cell) Renal Cell Carcinoma

Clinical

- M:F = 2:1; peak in the sixth and seventh decade
- Comprises 70% of all renal cell neoplasms (23,000 newly diagnosed cases annually)
- Cytogenetics:
  - Deletion of 3p13
  - Somatic mutation or inactivation of the von Hippel-Lindau gene (tumor suppressor gene RAF-1 at 3p25)
- Arises from renal tubular epithelium, differentiated toward proximal tubular epithelium
- Often presents with hematogenous metastases in unusual sites
- Most common malignancy to receive metastasis from other sites
- Classic triad: hematuria (40% of patients), flank pain (40%), and palpable mass (35%)
- Paraneoplastic endocrine syndromes:
  - Polycythemia (due to erythroipoiedin production)
  - Hypercalcemia (often seen in advanced stage)
  - Hypertension (due to renin production)
  - Cushing's syndrome
  - Sex hormonal imbalance (feminization, gynecomastia, or masculinization)
- Risk for development of renal cell carcinoma:
  - Cigarette smoking
  - Long-term phenacetin and acetaminophen use
  - Obesity
  - Acquired renal cystic disease
  - Renal stone
  - Long-term hemodialysis
  - Tuberous sclerosis
  - von Hippel Lindau syndrome
  - Cystic nephroma
  - Adult polycystic kidney
- Tumor-related prognostic factors:
  - TNM stage
  - Surgical margins
  - Nuclear grade
  - Sarcomatoid features

Macroscopic

- Solitary, well-circumscribed; often located in the upper pole of the kidney
- Variegated appearance with hemorrhage, necrosis, cystic change, and calcification

Fuhrman Nuclear Grading

- Grade I:
  - Nuclei 10 μm in diameter; inconspicuous nucleoli
  - Nuclei round, small, and uniform
- Grade II:
  - Nuclei 15 μm in diameter; conspicuous (uniform) nucleoli at 40x magnification
  - Nuclei irregular
- Grade III:
  - Nuclei 20 μm in diameter; large prominent nucleoli at 10x magnification
  - Nuclei markedly irregular
- Grade IV:
  - Nuclei >20 μm in diameter; macronucleoli
  - Pleomorphic giant cell, multilobated, spindle nuclei, bizarre cells

Microscopic

- Compact growth pattern with solid and cystic appearance
- Abundant clear cytoplasm with accumulation of lipid and glycogen
- Prominent fine delicate vasculature
  - Note: Sarcomatoid change is the common pathway of tumor progression and is no longer considered as a distinct histologic type

Immunohistochemistry (see table 24-2)

- LMW cytokeratin +
- Vimentin +
- HMW cytokeratin –
- S-100 protein –
- Epithelial Membrane Antugen, (EMA) +
- PAS/glycogen +
- Placental alkaline phosphatase (PLAP) ±
- Oil red O (lipid) +
- CEA –
- Mucin –

Variant

- Multilocular cystic renal cell carcinoma:

Clinical

- Favorable prognosis after nephrenectomy, with minimal risk for recurrence or metastases

Gross

- Multilocular cyst fills with clear fluid or blood

Microscopic

- Cystic component comprises >50% of the tumor (arbitrary cut point)
- Multiloculated cyst lined by simple cuboidal cells and clear cells
- Collections of clear cells in the fibrous septa with hyalinized stroma
- Small papillae may extend into the cysts

Differential Diagnosis

- Adrenocortical carcinoma:
  - EMA –
  - Cytokeratin –
  - Vimentin +
- Urothelial carcinoma of the renal pelvis:
  - High-grade urothelial carcinoma (sarcomatoid change) may be indistinguishable from renal cell carcinoma
  - Low-grade urothelial carcinoma often retains features of urothelial differentiation
  - Less clear cell change; *in situ* component may be seen
  - Lacks prominent vasculature of renal cell carcinoma
  - CEA +
  - HMW cytokeratin +, cytokeratin 20+
- Monomorphic epithelial variant of Wilms' tumor:
  - Elongated nuclei with tapered ends (vs. round nuclei in renal cell carcinoma)
- Xanthogranulomatous pyelonephritis:
  - Women age 50–60 years present with flank mass, pain, fever, and anemia
  - Associated with urinary tract infection (*E. coli*) and staghorn renal calculi
  - Polymorphous inflammatory cell infiltrate
  - Zonation with central area of necrosis and outer zone of granulation and foamy histiocyte with lipid-laden vacuolated cytoplasm rather than clear cytoplasm; cytokeratin –
  - Lacks delicate vasculature and cytologic atypia
- Malakoplakia:
  - Michaelis-Gutaman bodies in eosinophilic histiocytes
  - Lacks cytologic atypia and fine vasculature
- Cystic nephroma:
  - Lacks clear cell change
- Wilms' tumor:
  - Elongated nuclei with tapered ends rather than spherical nuclei in renal cell carcinoma
  - Blastema component and skeletal muscle may be seen
- Melanoma:
  - HMB-45 +. S-100 protein +, melan A+
  - Cytokeratin –
  - EMA –

Papillary Renal Cell Carcinoma

Clinical

- M:F = 2:1; mean age = 50–55
- Comprises 15% of all renal cell neoplasms (second most common renal cell carcinoma)
- Hypovascular or avascular by angiography
- Associated with end-stage renal disease
- Cytogenetics:
  - Gain of chromosome 7, 17
  - Loss of chromosome Y
- May have better prognosis than clear cell renal cell carcinoma

Macroscopic

- Well-circumscribed cortical tumor with frequent hemorrhage and necrosis
- Often multifocal and bilateral, size >3 cm

Microscopic

- Papillary growth in >50–75% of tumor component
- Fibrovascular cores may be sclerotic or expanded by foamy macrophages, psammoma bodies, iron deposition, and stromal edema
- Papillae lined by small cuboidal cells with high nuclear/cytoplasmic ratio, basophilic cytoplasm, and larger cells with abundant eosinophilic cytoplasm
- Uniform round nuclei, low nuclear grade

Immunohistochemistry (see Table 24-2)

- Cytokeratin AE1/3 +
- LMW cytokeratin (cytokeratin 7) +
- Vimentin +
- HMW cytokeratin –
- Mucin –
- Ulex europaeus lectin –
- Glycogen +

Differential Diagnosis

- Renal papillary tumors:
  - Renal papillary adenoma
    - Tumor size <5 mm
    - Histologically indistinguishable from papillary renal cell carcinoma
  - Collecting duct carcinoma:
    - Infiltrative tumor in renal medulla
    - Tubulopapillary architecture, prominent desmoplasia, and acute inflammation
    - Dysplastic change in the adjacent ducts
    - Frequent vascular invasion
    - Mucin +
    - HMW cytokeratin +
- Metanephric adenoma:
  - Closely packed tubules lined by cells with uniform nuclei and scant cytoplasm
  - Lacks extensive papillae with fibrovascular cores

Chromophobe Renal Cell Carcinoma

Clinical

- M = F; mean age = 55 years
- Comprises 5% of all renal cell carcinomas
- Third most common malignancy of renal tubular epithelium
- Cytogenetics: loss of chromosomes 1 and 2
- Renal failure with cystic disease is a risk factor for development of chromophobe renal cell carcinoma
- May have a better prognosis than clear cell renal cell carcinoma

Macroscopic

- Well-circumscribed nodule without extensive necrosis or hemorrhage

Microscopic

- Solid (most common) and tubuloalveolar growth pattern with focal hemorrhage
- Large polygonal cells with delicate pale flocculent reticular cytoplasm and sharply defined cell borders
- Concentration of large cells around blood vessels
- Intermediate nuclear grade (Fuhrman grade 2), low nuclear/cytoplasmic ratio
- Fewer mitotic figures, hemosiderin-laden macrophages, and calcification

Immunohistochemistry (see Table 24-2)

- Hale's colloidal iron stain (acid mucopoly–saccharides) +
- LMW cytokeratin +
- Cytokeratin AE1/3 +
- Vimentin – (renal cell carcinoma: vimentin +)
- EMA +
- Lipid and glycogen (PAS) –
- Band 3 protein –
- Alcian blue +
- Carbonic anhydrase C –/+

Electron Microscopy

- Numerous cytoplasmic microvesicles (150–300 nm) of unknown origin

Variant

- Eosinophilic variant of chromophobe renal cell carcinoma
  - Prognosis similar to other types of renal cell carcinoma
  - Prominent tubular architecture
  - Cells with abundant eosinophilic cytoplasm and perinuclear halos

Differential Diagnosis

- Oncocytoma:
  - Nesting growth pattern; lacks condensation of cytoplasmic border
  - Hale's colloidal iron stain –
- Clear cell renal cell carcinoma:
  - Lacks perinuclear halo and dense eosinophilic rims along peripheral cell membranes
  - Vimentin +
  - Hale's colloidal iron stain (acid mucopoly-saccharides) –

Collecting Duct Carcinoma

Clinical

- M:F = 2:1; mean age = fifth to seventh decade
- Comprises 1% of all renal cell carcinomas
- Similar prognosis as clear cell renal cell carcinoma after controlling for stage and grade
- LOH at 1q and 6p

Macroscopic

- Infiltrative gray-white tumor located in the renal medulla

Microscopic

- Tubulopapillary architecture with irregular channels
- Lined by atypical cells with hobnail appearance and prominent nucleoli
- Atypical hyperplastic change (dysplasia) in the adjacent collecting ducts occasionally
- Abundant basophilic stroma with intense desmoplastic response and inflammatory infiltrate
- Frequent angiolymphatic invasion

Variant

- Medullary carcinoma of the kidney:
  - Young blacks ranging from 11–39 years of age
  - M:F = 3:1 before age 24; M = F after age 24
  - Associated with sickle cell trait and with chromosome 3 and 11 anomalies
  - Aggressive; most patients die within 1 year of diagnosis (mean survival = 15 weeks)
  - May arise from the collecting ducts of the renal medulla
  - Microcystic pattern with yolk sac-like and adenoid cystic appearance
  - Prominent stromal desmoplasia, angiolymphatic invasion, and neutrophil infiltrate

Immunohistochemistry (see Table 24-2)

- Mucin +
- Vimentin +
- EMA +
- Peanut lectin +
- LMW cytokeratin (CAM5.2) +
- Ulex europaeus lectin +
- HMW cytokeratin (cytokeratin 19)+
- CEA focal +
- LeuM1 –
- Cytokeratin 13 –
- HMW cytokeratin (CK19 and 34ßE12) +
- Cytokeratin 19 +

Differential Diagnosis

- Papillary renal cell carcinoma:
  - Well-circumscribed tumor in cortical location, often multifocal
  - Lower nuclear grade; may contain clear cytoplasm, foamy cells, and psammoma bodies; mucin –
  - Lacks desmoplastic and inflammatory stroma
  - HMW cytokeratin –
- Metanephric adenoma:
  - Closely packed tubules lined by cells with uniform nuclei and scant cytoplasm
- Urothelial carcinoma of the renal pelvis:
  - In situ component and atypia in adjacent urothelium
  - Often composed of intestinal-type epithelium
  - Lacks hobnail cells; vimentin –, cytokeratin 13 +, cytokeratin 19 +
- Clear cell renal cell carcinoma:
  - Lacks prominent stromal desmoplasia
  - Ulex europaeus lectin –
- Metastatic carcinoma:
  - Well-circumscribed, multifocal
  - Lacks dysplastic change of the adjacent collecting ducts

Renal Cell Carcinoma, Unclassified

- Comprises 4–5% of all renal cell carcinomas
- Assignment of carcinoma to this category includes:
  - Predominant sarcomatoid change without recognizable epithelial elements
  - Unrecognizable cell types

TNM CLASSIFICATION OF RENAL CELL CARCINOMA (1997 REVISION)

- Tx: Primary tumor cannot be assessed
  - T0: No primary tumor
  - T1: Tumor ≤7 cm in greatest dimension and confined to the kidney
  - T2: Tumor >7 cm in greatest dimension and confined to kidney
  - T3a: Tumor extends to adrenal or perinephric tissue, but not beyond Gerota's fascia

  - T3b: Tumor extends into renal vein or lower inferior renal cava (below the diaphragm)
  - T3c: Tumor extends into inferior renal cava above the diaphragm
  - T4: Tumor extends beyond Gerota's fascia
- N: Regional lymph nodes cannot be assessed
  - N0: No lymph node involvement
  - N1: Metastasis in a single regional lymph node
  - N2: Metastasis in more than one regional lymph node
- M: Distant metastasis cannot be assessed
  - M0: No distant metastasis
  - M1: Distant metastasis

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Chapter 25

Urinary Bladder

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CONGENITAL ANOMALIES

Urachal Abnormalities

- The urachus is the vestigial remnant of the connection from the apex of the bladder to the allantois (located at the umbilicus)
- Derived from the ventral cloaca and allantois
- Normally, the urachus closes by the fourth month of fetal life
- A spectrum of anatomic abnormalities may result in abnormal persistence or malformation, and presents in children
- A number of malformations have been described:
  - Patent urachus:
    - Communicating duct between the bladder and the umbilicus that allows the flow of urine
    - Predisposes to infection
    - Spontaneous closure may occur, but usually requires surgical intervention
  - Urachal cyst:
    - Presents as a suprapubic palpable mass
    - Usually located in the lower part of the urachus
    - Lined by columnar or urothelial cells
  - Blind sinuses and vesicourachal diverticuli:
    - An external opening of the urachal duct
    - History of chronically infected urachal cyst
    - Vesicourachal diverticuli are associated with the prune-belly syndrome
  - Hamartomatous polyp:
    - Presents as polypoid mass in the bladder near the urachus
    - Composed of nests and glands of urothelial cells
- A variety of tumors may arise from urachal remnants:
  - Villous adenoma
  - Adenocarcinoma
  - Urothelial carcinoma
  - Squamous cell carcinoma

Exstrophy

Clinical

- Congenital malformation in which the anterior bladder wall and abdominal wall are absent
- Thought to arise from failure of the midline to close properly in development
- Associated with other urogenital abnormalities (e.g., epispadia, bilateral inguinal hernia, bifid clitoris, vaginal stenosis)
- The exposure of the bladder mucosa to the external environment, with subsequent risk of infection and carcinoma (usually adenocarcinoma)

Macroscopic

- Anterior abdominal wall defect with simultaneous absence of anterior bladder wall, resulting in exposure of the bladder mucosa to the environment
- Usually accompanied by some degree of bladder eversion

Microscopic

- Squamous metaplasia and cystitis glandularis

CYSTITIS

- Refers to a variety of benign inflammatory lesions
- Often descriptive and non-specific
- May be associated with proliferative and metaplastic conditions

Acute Cystitis

- Predominantly neutrophilic infiltration of the lamina propira and urothelium
- Edema of lamina propria
- Frequent urothelial denudation

Variants

- Ulcerative cystitis:
  - The urothelium is denuded and ulcerated
- Suppurative membranous cystitis:
  - The surface urothelium is covered by exudate and necrotic debris
- Emphysematous cystitis:
  - Inflammatory condition caused by infection by gas-forming bacteria such as *Clostridium perfringens*
  - Usually limited to patients with predispositions to unusual infections, including diabetes, neurogenic bladder, and chronic urinary tract infection
  - Gas-filled blebs with giant cell reaction in the lamina propria
- Hemorrhagic cystitis:
  - Inflammatory condition seen in patients treated with cyclophosphamide (up to 8% of patients)

- May result in severe, intractable hematuria, which may require cystectomy
- Results from the direct topical effects of cyclophosphamide metabolites that are excreted in the urine
- May be associated with adenovirus infection
- Diffuse, severe hyperemia with edema and ulceration endoscopically
- Marked edema and extensive hemorrhage within the lamina propria
- Areas of ulceration common

Chronic Cystitis

- Chronic inflammatory infiltrate of lamina propria
- Edema and fibrosis of the lamina propria
- Often associated with urothelial hyperplasia

Variants

- Proliferative papillary cystitis (papillary-polypoid cystitis):
  - History of indwelling catheter or vesical fistula
  - Located in the dome or posterior wall
  - Broad papillary projection of inflamed lamina propria with overlying hyperplastic urothelium
  - Superficial umbrella cell preserved
  - Prominent stromal edema, congestion, and inflammatory infiltrate
- Follicular cystitis:
  - Incidental finding
  - May be associated with history of infection, biopsy, or intravesical Bacillus Calmette-Guerin (BCG) therapy
  - Bladder mucosa may appear normal or have a finely nodular appearance endoscopically.
  - Subepithelial lymphoid follicles with germinal centers microscopically
- Encrusted cystitis:
  - Associated with infection of urea-splitting bacteria in alkalinized urine
  - The ulcers are coated with calcium and phosphate salt
  - Mononuclear cell infiltrate and foreign body giant cell reaction
  - May extend into muscularis propria

Granulomatous Cystitis

- Etiology:
  - Infection:
    - Bacterial:
      - Tuberculosis, syphillis
    - Fungal:
      - Coccidiodomycosis, histoplasmosis
    - Parasitic:
      - *Schistosoma hematobium*
    - Viral:
      - Herpes simplex virus and adenovirus
  - Iatrogenic:
    - Post surgery or radiation
    - Post intravesical (BCG) therapy
  - Malakoplakia
  - Systemic granulomatous disease:
    - Crohn's disease
    - Sarcoidosis
    - Rheumatoid disease
  - Chronic granulomatous disease of childhood
  - Xanthoma (with elevated serum cholesterol)
  - Vasculitis:
    - Wegener's granulomatosis
    - Polyarteritis nodosa
    - Churg-Strauss Syndrome
  - Idiopathic

Tuberculous Cystitis

Clinical

- Secondary to generalized spread from pulmomary infection by *Mycobacterium tuberculosis*
- Associated with renal tuberculosis
- Common cause of bladder disease worldwide
- Complications include scarring, obstruction, and fistula formation

Macroscopic

- Solitary or confluent ulcerated mucosal lesions, usually in the region of the ureteral orifices (trigone)

Microscopic

- Caseating granulomatous inflammation and fibrosis involving the lamina propria
- Ulceration of the overlying mucosa
- Special stains (auramine-rhodamine or other AFB stain) demonstrate acid-fast bacilli

BCG-Induced Cystitis

Clinical

- Clinical history is critical in determining the etiology
- Used to treat patients with superficial bladder carcinoma
- Symptoms include dysuria, frequency, fever, and other systemic reactions (e.g., pneumonitis, hepatitis, rash, and arthralgia)

Macroscopic

- Erosion and ulceration

Microscopic

- Sarcoid-like non-necrotizing granuloma with giant cells
- Edema, congestion, and chronic inflammatory infiltrate in the lamina propria

Post-Surgical Granuloma

Clinical

- History of prior surgery or instrumentation
- Etiology related to immunologic reaction to altered antigen induced by the procedure

Macroscopic

- Hemorrhage, necrosis, and mucosal irregularity

Microscopic

- Areas of granulomatous inflammation, usually focal
- A central zone of fibrinoid necrosis surrounded by a peripheral rim of palisading epithelioid histiocytes
- Chronic inflammatory infiltrate composed of histiocytes, giant cells, lymphocytes, plasma cells, and eosinophils

Malakoplakia

Clinical

- Female predilection, with peak incidence in the fifth decade
- Atypical infection by bacteria (usually Gram-negative bacteria, such as *E. coli*) in patients with lysosomal defects (defects in histiocyte function with impaired lysosome movement and inability of phagosomes to destroy bacteria)
- Symptoms include recurrent fever, hematuria, pyuria, urgency, pain, and weight loss
- Others organs may be involved
- "Malakoplakia" means soft plaque in Greek

Macroscopic

- Multiple small yellow mucosal nodules or plaques, usually in the area of the trigone

Microscopic

- Mixed inflammatory infiltrate in the lamina propria
- Large numbers of epithelioid histiocytes (von Hansemann histiocytes) with abundant granular eosinophilic cytoplasm and intracytoplasmic inclusions (Michaelis-Gutmann bodies, 3–10 μm)
- Concentrically laminated basophilic round to oval calcospherites (Michaelis-Gutmann bodies) may be seen in the stroma freely or as intracytoplasmic inclusions
- PAS +, iron +, and calcium (von Kossa stain) +

Electron Microscopy

- Concentrically laminated structure with a central electron-dense core and radially oriented spicules (hydroxyapatite crystals)

Schistosomiasis

- Endemic in some parts of Africa and Southwest Asian country, especially Egypt
- Graulomatous inflammation and fibrosis of lamina propria or muscular wall
- Identification of schistosomal eggs (100 μm) in the bladder wall is diagnostic

Treatment-Induced Cystitis

Radiation Cystitis

Clinical

- Inflammatory condition (with acute and chronic phases) associated with pelvic radiation treatment
- Highly dose dependent (50% risk if receiving 70 Gy but only 5% risk with 60 Gy)
- Acute phase occurs in <6 months (usually manifests within 6 weeks of treatment); subacute phase occurs from 6 months to 2 years after treatment; chronic phase usually takes 2–5 years to appear

Macroscopic

- Acute phase:
  - Hyperemia/congestion, petechiae
  - Marked edema with thick mucosal folds ("bullous cystitis")
  - Mucosal erosion and ulceration
- Subacute phase:
  - Mucosal erythema, ulceration, edema, and fistulae formation
- Chronic phase:
  - Thin, atrophic mucosa with ulceration

Microscopic

- Acute phase:
  - Epithelial denudation and ulceration
  - Marked cellular atypia with large hyperchromatic, bizarre nuclei
  - Lamina propria edema and congestion
- Subacute phase:
  - Edema and chronic inflammation
  - Mucosal ulceration, variable atrophy, and hyperplasia
- Chronic phase:
  - Some degree of residual epithelial atypia and areas of ulceration
  - Urothelial metaplasia
  - Fibrosis and collagen deposition in the lamina

propria and muscularis propria with scattered atypical fibroblasts
  - Endothelial proliferation, arteriolar hyalinization, subendothelial and medial fibrosis (endarteritis obliterans)

Differential Diagnosis

- Carcinoma *in situ*
  - High nucleocytoplasmic ratio and nuclear membrane irregularity
  - Collagenization and atypical fibroblasts are not seen

BCG-Induced Cystitis (see page 25-4)

Cytoxan-Induced Hemorrhagic Cystitis

Clinical

- Occurs in up to 40% of patients treated with cyclophosphamide (cytoxan)
- Secondary to toxic metabolite acrolein (an aldehyde and oxidizing agent)

Macroscopic

- Mucosal erosion, ulceration, and erythema

Microscopic

- Urothelial denudation and regeneration with reparative changes
- Edema and vascular congestion of lamina propria

Special Variants of Cystitis

Interstitial Cystitis

Clinical

- Uncommon inflammatory process seen in middle-aged women (30–50 years)
- Patients present with dysuria, urgency, frequency, hematuria, or generalized pelvic pain
- Diagnosis is made clinically based on symptoms and cystoscopic examination and after negative testing for bacterial, fungal, or viral pathogens
- Associated with allergic and immunologic disorder (rheumatoid arthritis, systemic lupus erythematosus, or autoimmune thyroiditis)
- Antinuclear antigen test is positive in >50% of cases

Macroscopic

- Scattered petechial hemorrhages
- Wedge-shaped ulcerations (Hunner's ulcers)

Microscopic

- Mucosa may be denuded or ulcerated, with granulation tissue
- Lamina propria shows edema and congestion, with a mononuclear inflammatory infiltrate
- Mononuclear and mast cell infiltrate in the lamina propria and muscularis propria
- Perineural mononuclear infiltrate
- Fibrosis of the lamina propria and muscularis propria

Differential Diagnosis

- Other forms of cystitis, including
  - Tuberculous cystitis
    - Caseating granulomas containing acid-fast bacteria
  - Eosinophilic cystitis
    - Mononuclear and eosinophilic infiltrate in the lamina propria and muscularis

Eosinophilic Cystitis

Clinical

- Inflammatory process found in women and children; seen with allergic disorders and other diseases associated with peripheral eosinophilia
- Uncommonly seen in elderly men with bladder injury or history of transurethral resection
- Symptoms include severe frequency, urgency, dysuria, and hematuria, with periods of remission and exacerbation
- Spontaneous resolution is common

Macroscopic

- Diffuse mucosal edema and erythema or as velvety yellow plaque
- Tumor-like polypoid growths that appear erythematous and may demonstrate ulceration or necrosis

Microscopic

- Mononuclear and eosinophilic infiltrate in the lamina propria and muscularis
- Early disease is characterized by marked edema, congestion, and a mixed mononuclear and eosinophilic infiltrate
- In severe cases, muscle necrosis may be seen
- As the disease progresses, the inflammatory infiltrate tends to subside and varying degrees of fibrosis may be seen in the lamina propria and muscularis

Differential Diagnosis

- Other forms of cystitis, including:
  - Tuberculous cystitis:
    - Caseating granulomas containing acid-fast bacteria
  - Follicular cystitis:
    - Subepithelial lymphoid follicles with germinal centers
  - Interstitial cystitis:
    - Mononuclear and mast cell infiltrate in the lamina propria and muscularis

BENIGN LESIONS AND MIMICS OF CANCER

Hyperplasia

Flat Urothelial Hyperplasia

- Thickened benign urothelium (>7 cell layers) without cytologic atypia
- Often associated with inflammatory condition or urothelial neoplasm

Papillary Urothelial Hyperplasia

- Undulating pseudopapillary proliferation of urothelium without cytologic atypia
- No requirement of cell thickness for diagnosis
- Lacks well-developed fibrovascular cores
- Considered as a precursor to low-grade papillary urothelial carcinoma by some investigators

Metaplasia

Squamous Metaplasia

Clinical

- More commonly seen in men (4x higher incidence than in women)
- Non-keratinizing squamous metaplasia of the trigone in women is a normal finding secondary to estrogen stimulation
- Benign metaplasia of the bladder epithelium, usually in the setting of chronic inflammation, but may be seen in normal bladder
- Associated conditions include:
  - Exstrophy
  - Neurogenic bladder, indwelling catheter
  - Surgery or biopsy
  - Recurrent infection (e.g., schistosomiasis)
  - Calculi
- Non-keratinizing squamous metaplasia is not associated with increased risk of carcinoma
- May interfere with bladder contraction and dilation if extensive and produce renal colic with renal pelvic involvement

Macroscopic

- May appear as multiple small nodular/papular mucosal lesions, or as dull white plaques
- Trigone is the region most commonly affected
- Renal pelvic involvement may produce filling defect on excretory urogram

Microscopic

- Mature keratinizing or nonkeratinizing squamous epithelium

Nephrogenic Metaplasia

Clinical

- Usually occurs in middle-aged men (M:F = 2:1, mean age = 41 years)
- Occurs in the setting of long-standing chronic irritation
- 20% of cases occur in children and adolescents

Macroscopic

- Papillary or polypoid small solitary yellow nodules (usually <1 cm)
- Erythematous irregular mucosa
- Predilection for trigone

Microscopic

- Well-circumscribed proliferation of orderly small compact tubules, cysts, and delicate filiform papillae lined by columnar or cuboidal hobnail cells
- Cells have clear to eosinophilic cytoplasm and uniform nuclei
- Inconspicuous mitotic figures
- Intracytoplasmic vacuoles (glycogen +) may be seen, imparting a signet ring cell appearance
- Tubules have thickened PAS + basement membrane and may contain eosinophilic PAS + secretions
- Chronic inflammatory infiltrate in the lamina propria
- Often associated with squamous metaplasia, cystitis cystica, and cystitis glandularis

Immunohistochemistry

- Cytokeratin +, EMA +, CEA –

Differential Diagnosis

- Clear cell adenocarcinoma:
  - Usually occurs in elderly women
  - Not confined to the lamina propria
  - Infiltrative rather than well-circumscribed growth
  - Cytologic atypia and frequent mitotic figures
  - Cytokeratin +, EMA +, CEA ±
- Urothelial carcinoma with tubulo-glandular pattern:
  - Tubules lined by multiple layers of urothelial cells rather than single cell layer lining
  - Cytologic atypia, infiltrative growth, and mitotic figures
  - Lacks prominent basement membrane and architectural heterogeneity

Intestinal Metaplasia (Glandular Metaplasia)

Clinical

- Occurs in the setting of long-standing chronic irritation
- Little or no malignant potential

Microscopic

- Glands lined by mucin-producing colonic-type columnar goblet cells
- Paneth cell differentiation may be seen
- Inflammatory background

von Brunn's Nests

- Occur in ~85% of autopsy patients
- Represent a normal variant of bladder mucosa
- Solid nests of urothelium project into the lamina propria
- May contain luminal eosinophilic secretions

Cystitis Cystica

- May appear as small (1–5 μm) yellow cysts in the lamina propria
- Unilocular cysts lined by single or multiple layers of cuboidal urothelial cells
- Acute and chronic inflammation

Florid Cystitis Glandularis

Clinical

- Usually an incidental finding
- Patients may present with irritative obstructive symptoms or hematuria
- No malignant potential

Macroscopic

- Nodular or polypoid lesion, with predilection for the trigone and bladder neck

Microscopic

- Involvement of von Brunn's nest by glandular metaplasia
- Exuberant proliferation of glands lined by columnar cells with or without goblet cells (intestinal metaplasia)
- Lesions are confined to the lamina propria
- Lacks significant cytologic atypia
- Focal extravasation of mucin into the stroma may be seen
- Overlying mucosa may be atrophic, normal, or hyperplastic
- Edema and inflammation in the lamina propria

Differential Diagnosis

- Endocervicosis:
  - Muscularis propria is usually involved
  - More pronounced stromal inflammatory response
- Mullerianosis:
  - Involves the muscularis propria and lamina propria
  - The presence of tubal type epithelium with ciliated cells
  - Lacks identifiable urothelial cells
- Adenocarcinoma (colloid adenocarcinoma):
  - Cytologic atypia and mucin lakes
  - Infiltrative growth and invasion into muscularis propria

Endocervicosis

- Occurs in women of reproductive age
- Predilection for posterior wall or posterior dome
- Proliferation of endocervical-type glands, which are often cystically dilated and display reactive changes
- Lacks significant cytologic atypia
- Usually involves muscularis propria
- Extravasated mucin is associated with stromal edema, fibrosis, and prominent inflammatory response
- May be associated with endometriotic stroma

Mullerianosis

- Occurs in women of reproductive age (37–46 years)
- Located in the posterior wall of the bladder
- Characterized by the presence of at least two of three components: endosalpingiosis, endocervicosis, and endometriosis (triad of endometrial glands, stroma, and hemosiderin-laden histiocytes)
- Involves the lamina propria and muscularis propria
- Proliferation of tubules and cysts lined by endocervical-type epithelium or tubal epithelium (ciliated cells, peg cells, and intercalated cells)

Proliferative Papillary Cystitis (Papillary-Polypoid Cystitis)

- See previous discussion (page 25-4)

Diverticulosis

Clinical

- Acquired outpocketing of the mucosa through the muscularis propria, usually due to the increased pressure associated with bladder outlet obstruction (most commonly prostatic hyperplasia)
- Usually occurs in elderly patients, M>F
- The diverticuli may give rise to calculi or tumor

Macroscopic

- Pockets of bladder mucosa projecting into (and sometimes through) the muscularis propria
- Usually located in the posterior wall, the dome, and

the region of the urachus
- ♦ May contain calculi

Microscopic
- ♦ Lining is usually urothelial
- ♦ Varying degree of inflammation and squamous metaplasia may be seen
- ♦ Associated tumor is usually urothelial carcinoma, but adenocarcinoma or squamous cell carcinoma may be seen

Post-Operative Spindle Cell Nodule

Clinical
- ♦ Post-operative reactive proliferation mimicking cancer
- ♦ A rare sequelae of bladder or prostate surgery, especially transurethral resection
- ♦ Usually presents weeks to months after surgery, either during follow-up, or due to hematuria or obstruction

Macroscopic
- ♦ Polypoid or nodular growth, typically in the same area as the previous surgery
- ♦ Small lesion

Microscopic
- ♦ Highly cellular spindle cell neoplasm mimicking sarcoma
- ♦ Cells are loosely arranged in a myxoid vascular stroma
- ♦ The tumor edge may have a pseudoinfiltrative appearance
- ♦ Mitotic figures are numerous, but not atypical
- ♦ Lacks significant cytologic atypia
- ♦ A significant mononuclear inflammatory infiltrate is usually present

Immunohistochemistry
- ♦ Cytokeratin –, smooth muscle actin ±, vimentin –

Differential Diagnosis
- ♦ Sarcoma (leiomyosarcoma, fibrosarcoma)
  - – Sarcoma will show compact, dense cellularity as well as cytologic atypia, atypical mitotic figures, and tumor necrosis
  - – Clinical history (documentation of surgery or other intervention in the last 6–8 weeks) is helpful in determining the diagnosis
- ♦ Sarcomatoid carcinoma
  - – Cytokeratin +, biphasic tumor with identifiable epithelial elements, cytologic abnormalities

Inflammatory Myofibroblastic Tumor

Clinical
- ♦ Reactive proliferative process in children and adults
- ♦ May recur; complete excision is recommended
- ♦ Usually occurs in young adults (mean age = 28 years), M:F = 1:2

Macroscopic
- ♦ Nodular or polypoid exophytic mass, usually 2–5 cm in size

Microscopic
- ♦ Loosely arranged spindle cells in an edematous myxoid vascular stroma
- ♦ Spindle cells may demonstrate some mild atypia and scattered mitotic figures
- ♦ Edges may be infiltrative
- ♦ Extravasation of red blood cells and focal hemorrhage
- ♦ Often associated with mononuclear inflammatory infiltrate

Differential Diagnosis
- ♦ Sarcoma (myxoid fibrosarcoma or myxoid leiomyosarcoma):
  - – Marked cytologic abnormalities with frequent mitotic figures, including atypical forms
  - – More diffuse infiltrative growth
  - – Areas of tumor necrosis
- ♦ Sarcomatoid carcinoma:
  - – Cytokeratin +, biphasic tumor with identifiable epithelial elements, cytologic abnormalities
  - – More common in elderly men

Urethral Polyp

Inflammatory Polyp
- ♦ Composed of inflamed and vascular stroma lined by normal or hyperplastic urothelium

Urethral Caruncle

Clinical
- ♦ Usually occurs in postmenopausal women (mean age = 56 years)
- ♦ Typically presents as red painful mass at the external ureteral meatus
- ♦ Etiology uncertain
- ♦ Asymptomatic or presents with hematuria, dysuria, and pain

Macroscopic
- ♦ Nodular or pedunculated erythematous lesion in the posterior or lateral distal urethral wall

Microscopic
- ♦ Exuberant proliferation of fibroblasts and endothelial

cells in an inflammatory background, similar to granulation tissue
- Lacks significant cytologic atypia
- Mitotic figures inconspicuous
- Atypical stromal cells may be seen (cytokeratin –)
- Urothelium may show hyperplasia, metaplasia, or be denuded

Differential Diagnosis
- Carcinosarcoma:
  - Cytokeratin +, biphasic tumor, cytologic abnormalities, invasion

Fibroepithelial Polyp

Clinical
- Occurs in young adult men
- Presents with hematuria and intermittent flank pain

Macroscopic
- Polyp in the region of verumontanum or posterior urethra
- Also occurs in proximal ureter (left >right)

Microscopic
- Polypoid projection of edematous vascular stroma with overlying atrophic or hyperplasic urethelium
- Chronic inflammatory infiltrate

Ectopic Prostatic Tissue

Clinical
- Occurs in adolescents or young adults
- Presents with hematuria or irritative symptoms

Macroscopic
- Located in posterior portion of prostatic urethra

Microscopic
- Benign prostatic glands with overlying intact urothelium

Nephrogenic Metaplasia
- Described elsewhere (page 25-7)

Proliferative Papillary Urethritis
- See proliferative papillary cystitis (page 25-4)

Pyogenic Granuloma

Urothelial Papilloma
- Described elsewhere (page 25-10)

Inverted Papilloma
- Described elsewhere (page 25-10)

Condyloma Acuminata

NEOPLASMS OF THE BLADDER

Benign
Urothelial Neoplasms

Urothelial Papilloma

Clinical
- Rare benign urothelial neoplasm
- Accounts for 1% to 2% of papillary urothelial neoplasms
- Usually occurs in young adults (<50 years old)
- May present with painless hematuria
- Post-treatment recurrence is uncommon

Diagnostic Criteria
- Patient age <50 years
- Small solitary lesion (<2 cm)
- The urothelium lining the papillae is normal in thickness (<7 cell layers)
- Minimal or no cytologic atypia

Macroscopic
- Exophytic solitary papillary small lesion (<2 cm)

Microscopic
- Cytologically and architecturally normal urothelium covering delicate fibrovascular stalks
- <7 layers in thickness
- Normal polarity retained
- Lacks mitotic figures
- Lacks cytologic atypia

Differential Diagnosis
- Grade 1 urothelial carcinoma:
  - Thickened urothelium (>7 cell layers) with some degree of cytologic atypia

Inverted Papilloma

Clinical
- Rare benign urothelial neoplasm
- Occurs in elderly patients (60–70 years), with male predominance (M:F = 6:1)

- Presents with hematuria and irritative symptoms
- No recurrence after complete excision

Macroscopic

- Solitary, small (1–3 cm), smooth, dome-shaped, pedunculated, or polypoid lesions
- Usually located in the region of the trigone, as well as bladder neck, ureteral orifice, and posterior urethra

Microscopic

- Anastomosing cords, columns, and trabeculae of invaginated urothelium separated by thin fibrovascular septae
- Peripheral palisading of basaloid cells and preservation of superficial cells
- Prominent thickened basement membrane
- Lacks exophytic growth, fibrovascular cores, or infiltrative borders
- Areas of glandular or squamous differentiation and microcyst formation may be seen in the central areas of solid nests
- Minimal cytologic atypia and inconspicuous mitotic figures
- The overlying mucosa is intact and covered by a normal, hyperplastic, or attenuated urothelium.

Differential Diagnosis

- Low-grade urothelial carcinoma:
  - Cytologic atypia, mitotic figures, and infiltrative growth
- Inverted variant of urothelial carcinoma:
  - Thicker and more irregular column with loss of polarity
  - Lacks peripheral palisading of basaloid cells
  - Cytologic atypia and invariable mitotic figures
  - Extensive keratinization rare in inverted papilloma

Flat Neoplastic Urothelial Lesions: Putative Precursors of Urothelial Carcinoma

Urothelial Atypia of Unknown Significance

- A diagnostic category encompassing a spectrum of histologic abnormalities that may be attributed to reactive or inflammatory atypia alone, but fall below the threshold for the diagnosis of dysplasia
- No unfavorable clinical outcome

Urothelial Dysplasia

Clinical

- Mean age = 60 years, with male predominance (M:F = 3:1)
- Primary dysplasia is rare, and is a strong risk factor for the development of urothelial carcinoma *in situ* and invasive cancer
- Usually associated with concurrent or prior history of urothelial carcinoma; a risk factor for recurrence and progression
- Presents with irritative obstructive symptoms and/or hematuria

Macroscopic

- Non-specific findings, erythematous or normal

Microscopic

- The term dysplasia is used to encompass previously designated mild and moderate dysplasia and does not include severe dysplasia (see carcinoma in situ [CIS])
- Abnormal architectural and cytologic changes fall short of the diagnostic criteria for an unequivocal diagnosis of CIS/severe dysplasia
- Altered polarity with preservation of superficial cells and cytoplasmic clearing
- Cells vary in size and shape
- Cells with irregular granular chromatin, irregular nuclear membranes, nuclear crowding, and hyperchromasia
- The long axes of nuclei are parallel to the basement membrane
- Lacks cytoplasmic vacuoles, prominent nucleoli, or atypical mitotic figures

Urothelial Carcinoma In Situ *(CIS)*

Clinical

- Occurs in elderly men (60–70 years old), with male predilection (M:F = 10:1)
- Usually associated with concurrent or prior history of urothelial carcinoma
- Presents with irritative obstructive symptoms and/or hematuria
- May masquerade clinically as interstitial cystitis

Macroscopic

- Nonspecifc velvety erythematous lesion with granular or cobblestone appearance
- Often occurs in the regions of trigone and base of the bladder
- Multifocal

Microscopic

- Full thickness involvement is not a prerequisite for diagnosis
- The cytologic spectrum includes previously designated severe dysplasia (urothelial CIS and severe dysplasia are indistinguishable histologically)
- Always high grade (grading unnecessary)
- Disorderly proliferation of malignant urothelial cells

- Loss of polarity and cellular cohesion
- High N/C ratio, nuclear pleomorphism, hyperchromasia, irregular nuclear contours, coarsely granular chromatin, prominent nucleoli, and mitotic figures
- Small cell variant has a hyperchromatic nuclei and inconspicuous nucleoli
- Urothelium is often denuded
- Pagetoid spread and von Brunn's nest involvement may be seen
- Micropapillary variant shows pseudopapillary (without fibrovascular core) projections into the lumenal surface

Papillary Urothelial Tumors

Clinical

- Most common bladder tumor (90%)
- Occurs in older adults (median age = 65 years); rare before age 50
- More common in men (M:F = 3:1)
- Presents with hematuria and irritative obstructive symptoms
- Risk factors include:
  - Smoking (four-fold higher risk)
  - Occupational exposure to certain organic compounds, especially benzadine and aromatic amines (up to 50-fold higher risk)
  - Cyclophosphamide treatment (estimated 10% absolute risk for treated patients)
  - Radiation (up to four-fold higher risk)
- Some tumors are readily amenable to transurethral resection, although there is a significant risk of recurrence
- The following are considered unfavorable prognostic factors:
  - Deletion of surface blood group antigen (ABO, H, Lewis)
  - Alteration of Thomser-Friedenreich (T) antigen
  - Marker chromosome (ring or A-1 chromosome)
  - Aneuploidy
- Cytogenetic abnormalities:
  - Chromosome 9 and 17p deletion
  - p53 mutation
  - Trisomy 7
  - Structural anomalies of chromosomes 1 and 11

Reporting of Biopsy Specimens

- Biopsy site
- Histopathologic type of carcinoma
- Grade (low vs. high grade, see grading of papillary urothelial carcinoma)
- Papillary vs. nonpapillary
- Presence or absence of muscularis propria (detrusor muscle)
- Invasion, including depth of invasion (lamina propria vs. muscularis propria) and extent (focal vs. extensive):
  - Muscularis mucosa is variable, and is optional for reporting
  - Inner and outer half of muscularis propria invasion cannot be reliably discerned in biopsy specimens; substaging is not recommended
  - The term "superficial (or deep) invasion" should be discouraged (imprecise)
- Vascular invasion
- Presence or absence of urothelial dysplasia and carcinoma *in situ*
- Associated conditions (e.g., nephrogenic metaplasia)
- Ancillary studies (e.g., DNA ploidy, p53 status, chromosome markers)

Reporting of Cystectomy Specimens

- Histopathologic type of carcinoma
- Grade see grading of papillary urothelial carcinoma)
- Papillary vs. nonpapillary
- Location of cancer
- Multifocality
- Invasion, including depth of invasion:
  - Lamina propria invasion, focal vs. extensive
  - Muscularis propria invasion, inner half vs. outer half
- Surgical margins:
  - Urethral margins
  - Ureteral margins
  - Perivesical soft tissue margins
- Perivesical soft tissue involvement
- Vascular invasion
- Presence or absence of urothelial dysplasia and carcinoma *in situ*
- Lymph node status:
  - Anatomic sites
  - Number of nodes sampled
  - Number of positive nodes
  - Largest dimension of positive nodes
- Involvement of adjacent organs:
  - Prostate:
    - Noninvasive urothelial carcinoma of the prostatic urethra
    - Invasive urothelial carcinoma
  - Vagina and uterus
- Associated conditions (e.g., cystitis glandularis)

- ♦ Ancillary studies (e.g., DNA ploidy, p53 status, chromosome markers)
- ♦ Pathologic stage

Macroscopic

- ♦ Single or multiple exophytic papillary masses

Microscopic

- ♦ Exophytic growth pattern with thickened urothelium (>7 cell layers)
- ♦ Papillae with delicate fibrovascular cores
- ♦ Cells may appear nearly normal or show varying degrees of nuclear atypia (nuclear hyperchromasia, crowding, enlargement, pleomorphism, irregular contour, coarse granular chromatin and prominent nucleoli) (see Grading)
- ♦ Foci of squamous or glandular differentiation (10% of cases, more common in high-grade carcinoma)
- ♦ Small to medium-sized tubules may be seen in otherwise typical urothelial carcinoma (tubulo-glandular pattern)
- ♦ Plasmacytoid changes of urothelial cells have been reported

Grading

- ♦ According to the 1973 WHO classification of urothelial lesions of the urinary bladder
- ♦ Grading should be based on the worst area (highest grade) of the tumor:
  - – Grade 1
    - • Designated as papillary urothelial neoplasm of low malignant potential in the 1998 ISUP/WHO classification
    - • Thickened urothelium with normal architectural arrangement of cells
    - • Well-formed papillae with fibrovascular cores
    - • Superficial cells intact with preservation of cell polarity
    - • Slight nuclear enlargement, crowding, hyperchromasia, minimal nuclear pleomorphism
    - • Lacks mitotic figures, cytoplasmic vacuoles, or prominent nucleoli
    - • Diploid tumor, with absence of marker chromosome
    - • Very low risk for invasion and metastasis
    - • Increases risk for developing recurrent or new papillary urothelial carcinoma
  - – Grade 2
    - • Designated as low grade papillary urothelial carcinoma in the 1998 ISUP/WHO classification
    - • Some degree of architectural irregularity and discohesion
    - • Disorderly maturation with variable loss of superficial cells
    - • Increased nuclear atypia and mitotic figures
    - • Loss of cytoplasmic homogeneity and clearing

    Grade 3:
    - • Designated as high grade urothelial carcinoma in the 1998 ISUP/WHO classification
    - • Loss of normal architectural arrangement of cells
    - • Marked nuclear abnormalities with increased numbers of atypical mitotic figures
    - • Aneuploid tumor with marker chromosome (ring or A1)
    - • Loss of surface blood group antigen

Histologic Variants

- ♦ Micropapillary variant:
  - – M:F = 5:1; mean age = 67 years
  - – Associated with high-stage cancer and poor prognosis
  - – Require >50% of the tumor show a micropapillary pattern for diagnosis
  - – Micropapillary growth with delicate filiform processes or small papillary cell clusters, resembling serous papillary carcinoma of female genital tract
  - – Retraction artifact with "halos"
  - – High nuclear grade
- ♦ Nested variant:
  - – Highly aggressive
  - – Irregularly distributed and compact nests of atypical cells in the lamina propria, mimicking von Brunn's nests
  - – Infiltrative growth
  - – Deep portions of the tumor often show typical urothelial carcinoma
  - – Often lacks intervening stroma (in contrast to von Brunn's nests)
  - – Cells have nuclear pleomorphism and prominent nucleoli
  - – Inconspicuous mitotic figures
- ♦ Microcystic variant (microglandular variant):
  - – Microcystic change in typical urothelial carcinoma with eosinophilic secretions, necrotic debris, or mucin
  - – Multiple small cystic spaces lined by atypical urothelial cells
- ♦ Inverted variant:
  - – Endophytic growth with anastomosing cords and trebeculae of urothelial cells
  - – Thick and irregular column with loss of polarity
  - – Lacks peripheral palisading of basaloid cells in

contrast to inverted papilloma
  - Cytologic atypia and invariable mitotic figures
  - Foci of keratinization
- Lymphoepithelioma-like carcinoma:
  - *Clinical*
    - Occurs in elderly patients (mean age = 69 years), M:F = 3:1
    - Presents with hematuria
    - Some are related to Epstein-Barr viral infection
    - Responds well to chemotherapy
  - *Macroscopic*
    - Infiltrating fungating mass in the dome, posterior wall, or trigone
  - *Microscopic*
    - Syncytial sheets and nests of large round to polygonal cells with abundant basophilic to clear cytoplasm and indistinct cell borders (cytokeratin +)
    - Enlarged nuclei with nuclear pleomorphism, irregular nuclear membranes, coarse granular chromatin, and large prominent nucleoli
    - Heavy inflammatory infiltrate composed predominantly of lymphocytes, histiocytes, and plasma cells

Immunohistochemistry

- Cytokeratin +

- Urothelial carcinoma with syncytiotrophoblasts:
  - The presence of syncytiotrophoblasts may be associated with a poor prognosis
  - The prognostic significance of human chorionic gonadotropin (hCG) immunoreactivity is uncertain
- Urothelial carcinoma with psuedosarcomatous stroma:
  - Atypical spindle stromal cells with abundant eosinophilic cytoplasm and bizarre hyperchromatic degenerative nuclei
  - Inconspicuous nucleoli
  - Cytokeratin –, EMA –, CEA –, vimentin +, actin +
- Urothelial carcinoma with stromal osseous or cartilaginous metaplasia:
  - Lacks cytologic atypia
- Urothelial carcinoma with osteoclast-type giant cells:
  - Cytokeratin – (giant cell carcinoma: cytokeratin +)

Immunohistochemistry (See Table 25-1 and 25-2)

Differential Diagnosis

- Urothelial papilloma:
  - The urothelium lining the papillae are normal in thickness (<7 cell layers)
  - Minimal or no cytologic atypia
  - Small solitary lesion (<2 cm)
  - Patient age <50 years
  - Blunt rather than finger-like papillae
  - Multiple layers of umbrella cells are often present.
- Inverted papilloma:
  - Well-circumscribed, confined within the lamina propria, with muscularis propria involvement
  - Orderly endophytic growth of anastomosing cords and trabeculae of benign-looking urothelial cells with an intact urothelium on the luminal surface
  - Lacks central fibrovascular cores
  - Peripheral palisading of basaloid cells
  - The arborizing invaginations of urothelium are in continuity with the overlying mucosa.
  - Lacks cytologic atypia; occasional squamous differentiation
- Nephrogenic metaplasia:
  - Well-circumscribed proliferation of small tubules with intervening stroma, single cell layer
  - Confined to superficial lamina propria in an inflammatory stroma
  - Lacks significant cytologic atypia
- Proliferative papillary cystitis (polypoid-papillary cystitis):
  - Broad papillae with prominent inflammation and edema of the lamina propria
  - Lacks cytologic atypia
  - History of indwelling catheter or vesical fistula

Non-Papillary Urothelial Carcinoma

Clinical

- Usually high-grade malignant urothelial neoplasm
- Risk factors similar to that of papillary carcinoma

Macroscopic

- Appears as a nodular or ulcerative mucosal lesion with infiltration of the tumor down toward the muscularis

Microscopic

- Islands and trabeculae of tumor cells infiltrating into the lamina propria and muscularis propria
- Large round cells with hyperchromatic, pleomorphic irregular nuclei
- Cells with abundant eosinophilic or clear cytoplasm
- Mitotic figures are numerous
- Areas of squamous or glandular differentiation may be seen in up to 50% of casess

Grading

- See papillary urothelial carcinoma

Table 25-1. Immunohistochemical Profiles of Spindle Cell Lesions of the Bladder

	CK	*SMA/MSA/Desmin*	*EMA*	*Vimentin*
Post-operative spindle cell nodule	–/+	+/–	–	+
Inflammatory myofibroblastic tumor	–/+	+/–	–	+
Malakoplakia and caruncle	–	–	–	+
Sarcomatoid carcinoma	+	+	+	+
Leiomyosarcoma	–	+	–	+
Lymphoepithelioma-like carcinoma	+	–	+	+

Note. CK = cytokeratin; SMA = smooth muscle actin; MSA = muscle-specific actin; EMA = epithelial membrane antigen.

Squamous Cell Carcinoma

Clinical

- Represents <5% of bladder carcinomas in Western countries
- M=F, often presents with advanced cancer stage
- Grading is of little prognostic significance
- Associated with infection by *Schistosomiasis haematobium*, and, consequently, represents >70% of bladder carcinomas in endemic countries
- Schistosomiasis-associated squamous cell carcinoma may have better prognosis than nonschistosomal counterpart
- Other risk factors include:
  - Recurrent bladder infection
  - Diverticuli
  - Calculi (vesical lithiasis)
  - Indwelling catheter in patient with nonfunctioning bladder
  - History of urethral stricture
  - Renal transplantation

Macroscopic

- Exophytic or infiltrative ulcerative nodular, white-tan mass, solitary
- Frequently shows multiple small areas of necrosis

Microscopic

- Infiltrating tongues of large polygonal squamous cells with distinct cell borders, intercellular bridges, and abundant eosinophilic cytoplasm
- Dyskeratotic cells with nuclear pleomorphism, hyperchromasia, and coarsely granular chromatin
- Frequent mitotic figures and areas of necrosis
- Well-differentiated neoplasms may demonstrate keratin pearls
- Associated with keratinizing squamous metaplasia

Variants

- Verrucous carcinoma

Differential Diagnosis

- Urothelial carcinoma:
  - Non-papillary urothelial carcinomas may show areas of squamous differentiation
  - Careful sampling of the tumor will usually show areas of typical urothelial cell differentiation
  - In populations with low incidence of squamous cell carcinoma of the bladder (i.e., Western countries), sample tumor carefully for evidence of urothelial features
  - The findings of squamous metaplasia or squamous dysplasia of the bladder epithelium support the diagnosis of squamous cell carcinoma

Adenocarcinoma

Clinical

- Uncommon malignant glandular neoplasm, which accounts for approximately 1% to 2 % of bladder cancer
- M:F = 2:1, elderly patients (mean age = 58 years)
- May arise from urachul elements or from metaplastic urothelium, which usually occurs in middle-aged patients (mean age = 50 years)
- No prognostic difference between urachal and non-urachal adenocarcinoma
- Association with exstrophy, patent urachus, schistosomiasis, bladder augmentation, or neurogenic bladder has been documented
- Presenting symptoms similar to other bladder carcinomas (hematuria and irritative symptoms) but also demonstrates mucosuria in up to 25% of cases
- Advanced cancer stage at presentation
- Urachal adenocarcinoma:
  - Exclusion of adenocarcinoma elsewhere

  - Located in the dome and anterior wall, involving muscularis propria
  - Intact overlying normal mucosa or ulcerated urothelium with sharp demarcation from the underlying tumor
  - Usually occurs in younger patients (M >F, mean age = 50 years)
  - May extend toward the umbilicus in the space of Retzius
  - Treatment: partial cystectomy with en bloc resection of entire length of urachal-median umbilical ligament, including umbilicus
- Non-urachal adenocarcinoma:
  - May be found anywhere in the bladder with a predilection for trigone and lateral wall
  - Grossly, exophytic papillary growth or infiltrative fungating mass

Macroscopic

- Bulging intramural infiltrative or polypoid masses

Variants

- Mucinous (colloid) adenocarcinoma:
  - Island of tumor cells suspended in mucinous lake
  - More commonly seen in tumors of urachal origin
- Signet ring cell carcinoma:
  - Worst prognosis; >50% of patients died of cancer within 1 year of diagnosis
  - Composed of signet ring cells with intracytoplasmic mucin
  - Infiltrative growth with prominent desmoplasia
- Papillary adenocarcinoma:
  - Composed of tall columnar cell lining papillae with variable mucin production

Differential Diagnosis

- Villous adenoma:
  - Histologically identical to villous adenoma of the colon
  - Nuclear crowding, overlapping, and atypia, but no invasion
- Nephrogenic metaplasia:
  - Well-circumscribed proliferation of compact tubules
  - Confined to superficial lamina propria in an inflammatory stroma
  - Lacks significant cytologic atypia
- Cystitis glandularis:
  - Often co-exists with von Brunn's nests and cystitis cystica
  - Well-circumscribed and confined to the lamina propria
  - Lacks cytologic atypia
- Mullerianosis:
  - Occurs in women of reproductive age (37–46 years)
  - Small lesion, located in the posterior wall of the bladder
  - Proliferation of tubules and cysts lined by endocervical-type epithelium and tubal epithelium (ciliated cells, peg cells, and intercalated cells)
  - Lack cytologic atypia and prominent mucin extravasation

Clear Cell Carcinoma (Mesonephric Carcinoma)

Clinical

- Often occurs in older patients (>35 years, mean = 58 years), with female predilection
- More commonly seen in the urethra, especially in diverticula
- Unknown histogenesis, possibly Müllerian origin
- Aggressive course

Macroscopic

- Papillary or sessile infiltrative mass in trigone and neck

Microscopic

- Infiltrative growth of cysts, trabeculae, fine papillae, and tubules lined by clear cells with hobnail appearance
- Tubules contain eosinophilic secretions.
- Cells have moderate amount of clear to eosinophilic cytoplasm (glycogen +)
- Mitotic figures are frequent

Immunohistochemistry

- Cytokeratin +, EMA+, CEA ±

Differential Diagnosis

- Nephrogenic adenoma:
  - Occurs in younger patients with male predominance
  - Associated with predisposing factors such as long-standing irritative events
  - Small, well-circumscribed, and confined to the lamina propria
  - Lacks mitotic figures or necrosis
  - Cytokeratin +, EMA +, CEA –

Sarcomatoid Carcinoma (Metaplastic Carcinoma; Carcinosarcoma With Homologous Elements)

Clinical

- Occurs in elderly patients (mean age = 67 years), M:F = 4:1

- Highly aggressive, mean survival = 10 months
- No prognostic difference in comparison to carcinosarcoma with heterologous elements
- Pathologic stage is the main predictor of survival
- Presents with hematuria and irritative symptoms

Macroscopic

- Polypoid or nodular mass

Microscopic

- Diffuse infiltration of malignant spindle cells
- Urothelial carcinoma is most commonly recognized epithelial component, followed by squamous cell carcinoma
- Necrosis and hemorrhage

Immunohistochemistry

- Cytokeratin +

Small Cell Carcinoma

Clinical

- Occurs in elderly men, highly aggressive
- Accounts for 0.5% of bladder cancer
- Often (50%) associated with invasive urothelial carcinoma or CIS
- Pure form occurs in ~50% of cases
- May present with paraneoplastic syndrome (ectopic ACTH production-Cushing syndrome, hypercalcemia, and hypophosphatemia)

Macroscopic

- Infiltrative ulcerative fungating intramucosal mass

Microscopic

- Sheets and cords of small cells with high N/C ratio, nuclear hyperchromia, and inconspicuous nucleoli
- Tumor necrosis and crush artifact

Immunohistochemistry

- Neuroendocrine markers are positive, with dot-like cytokeratin positivity

Villous Adenoma

Clinical

- Glandular epithelial neoplasm
- Often associated with urachal adenocarcinoma, but may be seen elsewhere in the bladder

Macroscopic

- Exophytic papillary or polypoid tumor

Microscopic

- Histologically identical to villous adenoma of the colon
- Columnar mucinous cells and goblet cells lining delicate fibrovascular stalks
- Nuclear stratification, crowding, and nuclear hyperchromasia

Differential Diagnosis

- Adenocarcinoma:
  - Significant nuclear atypia, numerous mitotic figures, and invasion

SOFT TISSUE TUMORS

Benign

Leiomyoma

- Occurs in adults, M:F = 1:2
- Presents with irritative obstructive symptoms
- Grossly, polypoid, or pedunculated submucosal mass
- Well-circumscribed, lacks significant cytologic atypia
- Inconspicuous mitotic figures

Hemangioma

- Often occurs in young adults (<30 years) with slight male predominance
- Presents with gross hematuria and obstructive symptoms
- Small, well-circumscribed lesion composed of dilated vascular channels

Malignant

Leiomyosarcoma

Clinical

- Most common sarcoma of the bladder
- M>F; elderly patients (60–70 years old)

Macroscopic

- Large bulging polypoid mass in the dome and lateral wall
- Hemorrhage and necrosis

Microscopic

- Interlacing fascicles of spindle cells with blunt-ended nuclei
- Deeply infiltrative growth pattern with destructive muscle invasion

Table 25-2. Common Patterns of Cytokeration 7 and 20 Immunostaining in Various Cancers

	CK7	*CK 20*
Urothelial carcinoma*	+	+
Prostatic adenocarcinoma	–	–
Clear cell renal cell carcinoma	–	–
Ovarian serous and endometrioid adenocarcinoma	+	–
Ovarian mucinous tumors*	+	+
Uterine endometrial adenocarcinoma	+	–
Breast ductal and lobular adenocarcinoma	+	–
Breast colloid adenocarcinoma	+	–
Colorectal and appendiceal adenocarcinoma**	–	+
Gastric adenocarcinoma	±	+
Pancreatic adenocarcinoma*	+	+
Hepatocellular adenocarcinoma	–	–
Small cell carcinoma	–	–
Lung adenocarcinoma	+	–
Lung squamous cell and neuroendocrine carcinoma	–	–
Mesothelioma	+	–

** Common cytokeratin 7+/cytokeratin 20+ tumors; **Cytokeratin 7-/cytokeratin 20+ pattern is uncommon in other tumors.*

- Cytologic atypia, mitotic figures, hemorrhage, and necrosis
- Inflammatory myxoid background with fine vasculature may be seen
- Smooth muscle differentiation rather than myofibroblastic differentiation

Immunohistochemistry (See Table 25-1)

Differential Diagnosis

- Inflammatory myofibroblastic tumor:
  - Small lesion with circumscribed margin
  - Lacks significant cytologic atypia
  - Lacks necrosis
  - More pronounced inflammatory response

Rhabdomyosarcoma

Clinical

- Occurs predominantly in infants and children, with male predominance
- 20% of childhood embryonal rhabdomysarcoma occur in the genitourinary system, and 25% of these occur in the bladder

Macroscopic

- Multiple broad-based bulging polypoid grape-like masses
- Predilection for trigone and prostatic urethra

Microscopic

- Sheets and cords of primitive small cells with high N/C ratio, nuclear hyperchromasia
- Variable rhabdomyoblasts with or without cross-striations
- The cambium layer of rhabdomyoblasts beneath the surface in the botryoid variant

Immunohistochemistry

- Desmin +, muscle specific actin +, myoglobin +, LCA –

Carcinosarcoma

Clinical

- Occurs in elderly patients (mean age = 66 years), M:F = 2:1

- Highly aggressive, mean survival = 17 months
- Pathologic stage is the main predictor of survival.
- Presents with hematuria and irritative symptoms

Macroscopic

- Polypoid or nodular mass

Microscopic

- Biphasic tumors composed of carcinoma and distinct heterologous nonepithelial sarcomatous components
- Infiltrative sheets of anaplastic spindle cells and identifiable epithelial components merge imperceptibly
- Urothelial carcinoma is the most commonly recognized epithelial component, followed by squamous cell carcinoma
- Heterologous elements (bone, cartilage, or skeletal muscle)
- The most common sarcomatous elements are chondrosarcoma, leiomyosarcoma, and malignant fibrous histiocytoma
- Necrosis and hemorrhage

Immunohistochemistry

- Cytokeratin + (in the epithelial component)

MISCELLANEOUS

Lymphoma (also see chapter 7)

Clinical

- Female predominance in primary lymphoma (M:F = 1:5, mean age = 56 years); slight male predominance in secondary lymphoma (mean age = 50 years)
- Presents with hematuria and irritative symptoms
- Median survival of primary lymphoma is 9 years and secondary lymphoma is 6 months
- Criteria for the diagnosis of primary bladder lymphoma:
  - Presenting symptoms related to bladder involvement
  - No involvement of adjacent tissue
  - Absence of involvement of liver, spleen, lymph node, peripheral blood, and bone marrow within 6 months of the diagnosis
  - The dome and the trigone are the most common sites involved

Microscopic

- Low-grade lymphoma of the muscosa-associated lymphoid tissue (MALT) type is the most frequent type of primary bladder lymphoma
- Diffuse large cell lymphoma is the most common type of secondary lymphoma
- The histology of the MALT-type lymphoma is similar to those from other sites, and is characterized by centrocyte-like cells with irregular nuclear contours, clumped chromatin, and abundant pale to clear cytoplasm

Paraganglioma (Pheochromocytoma)

- Slight female predominance (M:F = 1:1.4); usually occurs in young patients (<50 years)
- >80% of cases are functional
- May present with hematuria and hypertension during voiding, cystoscopic examination, and biopsy
- Small (<3cm), dome-shaped nodules covered by normal mucosa, usually located in the trigone or dome
- Histologically similar to paraganglioma of other body sites, with intact urothelium

TNM CLASSIFICATION OF BLADDER CANCER (1997 REVISION)

- T: Primary tumor
  - T0: no primary cancer
  - Tis: carcinoma in situ
  - Ta: non-invasive papillary carcinoma
  - T1: tumor invades the lamina propria
  - T2a: tumor invades the inner half of muscularis propria
  - T2b: tumor invades the outer half of muscularis propria
  - T3a: tumor invades perivesival tissue microscopically
  - T3b: tumor invades perivesival tissue macroscopically (extravesical mass)
  - T4a: tumor invades prostate, uterus or vagina
  - T4b: tumor invades pelvic wall or abdominal wall
- N: Regional lymph nodes
  - N1: single regional lymph node metastasis, < 2 cm in greatest dimension
  - N2: single positive node, 2-5 cm in greatest dimen-

sion, or multiple positive nodes < 5cm
- N3: any positive node > 5 cm in greatest dimension

- M: Distant metastasis
  - M0: no distant metastasis
  - M1: distant metastasis

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Chapter 26

Testis, Penis, and Paratesticular Region

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Table of Contents

NON-NEOPLASTIC DISEASES OF TESTIS

Congenital Abnormalities

Cryptorchidism

Clinical

- Condition in which one or both testes fail to descend into the scrotum—they may be found in the inguinal canal or the upper scrotum, or within the abdomen
- Bilateral in 18% of patients; reveals a family history in 14%
- Cause unknown:
  - May be related to hormonal abnormalities, mechanical impairment to descent, or unidentified intrinsic abnormalities in the testis
- Complications include infertility and the development of germ cell tumors:
  - Infertility most frequent complication; 9% of infertile males have cryptorchid testes:
    - Only 16% to 25% of patients with bilateral cryptorchid testes are fertile
    - Improves to 25% to 81% if only one testicle undescended
    - Orchidopexy (surgical procedure that places the testicle in the scrotum) must be performed before 4 years to maintain fertility in the undescended testicle
- Germ cell tumors are 4 to 10 times more likely in cryptorchid testis:
  - Orchidopexy does not decrease the risk of a germ cell tumor, but allows for regular testicular exam
- Other complications include torsion and infarction

Macroscopic

- Dependent on age at removal of testicle or orchiopexy
- May be of normal size or small

Microscopic

- Histologic appearance of cryptorchid testis varies with age, testicular position, and prior hormonal therapy (human chorionic gonadotropin or gonadotropin releasing hormone [GnRH] is sometimes used as a hormonal means to bring the testicle into the scrotum)
- Prepurbertal testis may have fewer germinal cells than normal
- Following puberty, changes become more pronounced:
  - Tunica propria thickening
  - Reduced tubular diameter
  - Tubular sclerosis
  - Interstitial fibrosis
  - More prominent Leydig cell clusters

Anorchidism

Clinical

- Absence of both testicles
- Rare condition
- Unilateral in 1 in 5,000 males; bilateral in 1 in 20,000 males
- Gonad may disappear due to multiple causes, including intrinsic gonadal disorder, infection, trauma, torsion, or atrophy resulting from the overproduction of androgens
- Clinical distinction from cryptorchidism is critical

Macroscopic

- No testis is usually identified by a urologist on exploration
- If vas deferens is identified, then an ipsilateral testicle had to exist during gestation
- Epididymis or vas may be all that remains

Polyorchidism

Clinical

- Presence of more than two testicles
- Extremely unusual
- Fewer than 80 reported cases
- Patients present with a scrotal mass that may be confused with a testicular tumor

Macroscopic

- Extra testis may have its own epididymis and a vas deferens that joins other vas distally, or testis may share a common epididymis with another testicle

Microscopic

- Histology of testicle may be normal, or there may be hypospermatogenesis
- Spermatogenic function of the extra testis varies

Adrenal Cortical Rests

Clinical

- Usually an incidental finding of adrenal cortical tissue in the testis, or adjacent spermatic cord or epididymis
- Identified in 4% to 15% of individuals
- Not clinically significant

Macroscopic

- Encapsulated nodules of adrenal cortical tissue usually in spermatic cord, epididymis, rete testis, or tunica albuginea, and rarely within testicle
- Usually <1 cm in size; most only a few millimeters

Microscopic

- Adrenocortical tissue that usually exhibits normal zonation of adrenal tissue seen in cortex
- Adrenal medullary tissue not present

Splenic-Gonadal Fusion

Clinical

- Fusion of spleen and gonad, with a strong male predilection
- Two forms:
  - Continuous:
    - Has cord connecting the splenic tissue to the testicle
  - Discontinuous:
    - No cord
- Approximately one-third of patients with continuous form have severe congenital defects in extremities
- Patients present with a scrotal or inguinal mass

Macroscopic

- Splenic tissue attached to testicle; typically a discrete mass:
  - May be as large as 12 cm
- Small aggregates of splenic tissue may be found along the length of the cord or the entire cord may be composed of splenic tissue
- Grossly, tissue looks identical to spleen

Microscopic

- Splenic tissue looks like normal spleen histologically

Acquired Abnormalities

Testicular Torsion

Clinical

- Describes twisting of the spermatic cord, usually within tunica vaginalis; twisting causes venous obstruction:
  - Testicle becomes hemorrhagic
  - Eventually, arterial flow is interrupted and infarction occurs
- Predisposing conditions include:
  - Absence of scrotal ligaments
  - Shortened attachment of peritoneal ligaments
  - Incomplete descent
  - Testicular atrophy
- Usually young adults:
  - Present with marked testicular pain
  - May develop after physical activity
- Prompt intervention is necessary to prevent infarction:
  - Detorsion should be performed within 6–8 hours of torsion to prevent loss of testicle
  - Infarction is almost certain if torsion is not corrected within 24 hours
- Detorsion may be attempted manually, but it may require surgical intervention (orchidopexy)
- Diagnosis is usually evident by history and exam, but Doppler studies or nuclear-based perfusion scans may be useful to show decreased blood flow in torsion (vs. increased blood flow in epididymitis/inflammatory conditions)

Macroscopic

- Gross exam of testicle reveals a swollen blood-filled testicle

Microscopic

- Up to 6 hours after torsion, testis shows venous congestion and interstitial hemorrhage
- At 9 hours, PMNs are marginating from capillaries and severe interstitial hemorrhage present
- After 1 to 2 days, hemorrhagic infarction develops

Varicocoele

Clinical

- Results from abnormal dilatation and tortuosity to veins of pampiniform plexus of spermatic cord:
  - Thought to be result of insufficient venous valves
- Primarily involves the left side (90%) of cases, or may be bilateral (10%)
- Varicocoele associated with infertility:
  - Number of hypotheses present regarding the cause of infertility:
    - Endocrinologic insufficiency
    - Venous stasis, resulting in a buildup of toxic metabolites and decreased oxygenation
    - Increased temperature
- Ligation of left spermatic vein may correct varicocoele and fertility:
  - Fertility returns in up to 55% of patients undergoing ligation

Macroscopic

- Tortuous and dilated veins of pampiniform plexus
- Rarely seen by pathologist

Microscopic

- Fibrosis of spermatic vein present:
  - Testicular biopsy shows decreased spermatogenesis with germ cell sloughing and Leydig cell hyperplasia
- Histologic changes may revert to normal after spermatic vein ligation

Infections and Inflammatory Conditions of Testis and Epididymis

Viral Orchidoepididymitis

Clinical

- Most common virus involved in viral orchidoepididymitis is mumps; also Coxsackie B (second most common), influenza, EBV, echovirus, adenovirus, varicella, vaccinia, rubella, dengue, and others
- May occasionally cause viral orchitis
- AIDS may involve the testicle and is characterized by a lymphocytic infiltrate
- Usually occurs as a complication of up to 35% of adult mumps
- Infrequent in children
- Bilateral in 25% of cases
- Blateral involvement usually leads to infertility
- Men with unilateral involvement usually maintain fertility
- Testicular involvement typically becomes apparent 4 –6 days after parotid involvement

Macroscopic

- Early, testis may appear normal
- If involvement is severe, atrophic changes develop

Microscopic

- Changes are multifocal and characterized by acute inflammation of seminiferous tubules and interstitium
- Loss of germ cells; ultimately, tubular sclerosis and interstitial fibrosis develop

Bacterial Orchidoepididymitis

Clinical

- Usually due to a spread from bacterial epididymitis resulting in orchidoepididymitis
- May also occur from seeding from other sites via lymphatics or blood
- Most common bacterium involved is *Escherichia coli*
- Other organisms causing acute and chronic bacterial orchitis include *Klebsiella sp.*, streptococci, staphylococci, pneumococci, *Salmonella enteritidis*, and *Actinomyces israeli*
- Brucellosis involves the testicle and epididymis in 20% of all cases
- Brucellosis is characterized by a testicular mass with constitutional symptoms (undulating fever, malaise, headache, and sweats)
- Complications include an abscess with involvement of the scrotum and scrotal sinus formation
- May also be caused by chlamydia trachomatis and neisseria gonorrhea

Macroscopic

- Swollen testicle
- Abscess formation may be present

Microscopic

- Polymorphonuclear leukocyte inflammatory infiltrate involving interstitium and seminiferous tubules
- In advanced cases, abscesses develop
- In brucellosis, an infiltrate of lymphocytes and histiocytes with occasional granulomas present

Granulomatous Orchidoepididymitis

Mycobacterial Orchidoepididymitis

Clinical

- Testicular involvement by mycobacterium tuberculosis is always secondary to infection elsewhere in the body
- In adults, tuberculous orchitis typically occurs as an ascending infection from other sites in the genitourinary tract
- Renal tuberculosis results in bladder and prostatic involvement, with subsequent spread to the epididymis and testicle
- Most patients are adults
- In children, involvement usually occurs by hematogenous spread from the lung
- Patients may have constitutional symptoms but usually present with only testicular swelling and pain

Macroscopic

- Testicle may be enlarged with multiple soft nodular white caseating granulomas that typically are a few millimeters in size
- Fistulae may extend to the scrotum

Microscopic

- Necrotizing and non-necrotizing granulomatous inflammation present
- Granulomas consist of histiocytes, giant cells, and lymphocytes in a fibrotic stroma that surrounds necrotic material
- Inflammatory process is destructive of testicular parenchyma

Fungal Orchidoepididymitis

Clinical

- Rare
- Fungal organisms that can cause orchitis include *Blastomyces hominis*, *Coccidioidomyces immitis*, *Histoplasma capsulatum*, *Cryptococcus neoformans*, and *Trichophyton mentagraphytes*
- Fungal infections involving the genitourinary tract may occur in immunocompromised patients

Macroscopic

- Necrotic granulomas and abscesses are present

Microscopic

- Histologic features are identical to those of fungal infections occurring elsewhere in the body
- Necrotizing and non-necrotizing granulomas and neutrophilic microabscesses are present
- Organisms may be identified using special stains, such as methenamine silver or periodic acid-Schiff stains

Syphilitic Orchidoepididymitis

Clinical

- Congenital and acquired forms occur
- In congenital syphilis, testicular enlargement is present at birth. In the acquired form, the testes are involved in tertiary syphilis

Macroscopic

- In infants, the testes are enlarged; over time, the testes become fibrotic and small
- In adults, the testes are soft, yellow, and necrotic. Gummas may be present

Microscopic

- The testes involved by congenital syphilis exhibit interstitial inflammation with abundant plasma cells
- Arteries show obliterative endarteritis; inflammation destructive; over time, the testes become fibrotic
- Acquired (or tertiary) syphilis has two histologic patterns: interstitial orchitis and gummatous orchitis:
  - Interstitial orchitis is identical to that seen in congenital syphilis, and ultimately leads to small fibrotic testes
  - Gummatous orchitis is characterized by coagulative necrosis with a peripheral zone of fibrous tissue containing lymphocytes, plasma cells, and occasional giant cells
  - Both gummas and interstitial orchitis may occur in the same testicle. Spirochetes may be seen with special silver stains (Warthin-Starry, Dieterle)

Leprosy

Clinical

- Very rare in the United States, but seen in other parts of the world
- May be a cause of infertility
- The testes are frequently involved because lower temperature within the scrotum facilitates the growth of bacillus

Macroscopic

- Gross appearance of testes is dependent on the stage of infection
- Early, testes may look normal
- In latter stages, testes are small and fibrotic

Microscopic

- Three phases of testicular leprosy:
  - Early: a vascular phase characterized by lepra cells containing numerous organisms within blood vessel walls and testicular interstitium
  - Followed by: an interstitial phase with obliterative endarteritis, interstitial fibrosis, and lepra cells
  - Finally: an obliterative phase characterized by a loss of testicular parenchyma and replacement by fibrous tissue

Sarcoidosis

Clinical

- Systemic granulomatous disease of unknown cause
- Genitourinary system is involved in 0.2% of all cases
- Only a few cases involving the testes have been reported
- Testicular sarcoid tends to be unilateral

Macroscopic

- Small nodules may be present

Microscopic

- Non-necrotizing granulomas are present, identical to sarcoid granulomas elsewhere in the body
- Histologically, must exclude a granulomatous reaction due to seminoma, mycobacterial infection, or idiopathic granulomatous orchitis

Malakoplakia

Clinical

- Unusual form of a bacterial infection that most commonly affects middle-aged females
- Patients have a defect in the capacity of their mononuclear cells to kill phagocytized bacteria. Inflammation is histiocytic and forms masses
- Infection is due to coliform bacteria such as *E. coli* (most common), *Proteus vulgaris*, *Klebsiella pneumonia*, and others
- Initially described in bladder and subsequently described in many other organs:
  - The testes are involved in 12% of cases of genitourinary malakoplakia

Macroscopic

- The testes are enlarged, with yellow, soft parenchyma

Microscopic

- Accumulation of histiocytes with abundant, foamy, slightly granular cytoplasm

- Some of the histiocytes contain Michaelis-Gutmann bodies that are intracytoplasmic calcific concretions with target-like appearance
- Causes tubular destruction

Idiopathic Granulomatous Orchitis

Clinical

- Clinically and pathologically defined idiopathic granulomatous inflammatory disorder of older males
- Hypotheses for etiology include infection or autoimmune orchitis
- Presents as a unilateral tender testicular mass mimicking a tumor
- Rare cases have been bilateral; 66% of patients that have symptoms have a urinary tract infection

Macroscopic

- Testis is enlarged and nodular, with white to yellow homogenous parenchyma with areas of necrosis
- Grossly, resembles lymphoma, a leukemic infiltrate, or malakoplakia

Microscopic

- Inflammation may primarily involve tubules (tubular orchitis) or interstitium (interstitial orchitis):
  - In tubular orchitis, inflammatory cells (plasma cells and lymphocytes) ring seminiferous tubules, and there is a loss of germ cells: giant cells may be present within tubules; inflammation is associated with vascular thrombosis and vasculitis
  - In interstitial orchitis, inflammation is interstitial
  - In both forms, a loss of tubules and fibrosis occur as a result of inflammation

Infertility

Pretesticular Causes

- Hypopituitarism:
  - Prepubertal onset
  - Postpubertal onset
- Estrogen excess:
  - Endogenous:
    - Estrogen-producing tumor (of adrenal cortex)
    - Cirrhosis
  - Exogenous
- Androgen excess:
  - Endogenous:
    - Adrenogenital syndrome
    - Androgen-producing tumor
  - Exogenous
- Glucocorticoid excess:
  - Endogenous:
    - Cushing's syndrome
  - Exogenous:
    - Steroid therapy
- Hypothyroidism
- Diabetes mellitus

Testicular Causes

- Maturation arrest
- Hypospermatogenesis (germ cell hypoplasia)
- Sertoli cell-only syndrome (germ cell aplasia)
- Klinefelter's syndrome (sclerosing tubular degeneration)
- Other karyotypic abnormalities
- Cryptorchidism
- Radiation
- Chemotherapy
- Infection (mumps orchitis)
- Occupation exposures (lead, carbon disulfide, others)

Posttesticular Causes

- Obstruction of ducts leading away from testes (excurrent duct obstruction):
  - Congenital:
    - Atresia of vas deferens or epididymis
  - Acquired:
    - Infection:
      - Gonorrheal epididymitis
      - Tuberculous epididyitis
      - Others
    - Vas ligation:
      - Vasectomy
      - Iatrogenic

Testicular Causes of Infertility

Maturation Arrest

Clinical

- Most common cause of testicular infertility
- Spermatogenesis stops at some stage of maturation (usually at the formation of primary spermatocytes or spermatids) that varies from patient to patient
- Patients are potent, with normal secondary sexual characteristic, but they are oligospermic or azoospermic
- Exposure to toxins and postpubertal gonadotropin deficiency can result in a similar pattern
- Usually idiopathic

Macroscopic

- No alterations are evident

Microscopic

- Maturation of spermatogonia stops at one stage
- In some patients with oligospermia, may be incomplete maturation arrest with the production of some late spermatids
- No other changes are usually present

Hypospermatogenesis

Clinical

- Second most common cause of testicular infertility
- Patients are potent and have normal secondary sexual characteristics but are oligospermic
- Germ cells and developing forms are present in normal proportions, but overall numbers are markedly decreased
- Usually idiopathic, but can be related to exposure to toxins, excess heat, varicocele, or hypothyroidism

Macroscopic

- No alterations are evident

Microscopic

- Proportional hypoplasia of all germ cells, resulting in overall thinning of the germinal epithelium
- No other changes are usually present

Sertoli Cell-Only Syndrome (Absence/Aplasia of Germ Cells)

Clinical

- Patients are potent, with normal secondary sexual characteristics, but azoospermic
- Follicle-stimulating hormone levels are always high as a result of absent spermatogenesis
- Idiopathic but alkylating agents and radiation can cause similar changes, and these may be reversible

Macroscopic

- No alterations are usually present, although occasionally, the testes are smaller than normal

Microscopic

- Seminiferarous tubules show a moderate decrease in diameter and are devoid of germ cells
- Only Sertoli cells remain
- In some cases, some tubules show spermatogenesis and diagnosis germinal-cell aplasia with focal spermatogenesis
- Cause unknown

Klinefelter's Syndrome

Clinical

- Result of an abnormal number of X chromosomes and primary gonadal insufficiency
- Affects approximately 1 in 1,000 newborns
- Most common phenotype is 47XXY
- Males have a eunuchoid phenotype with tall stature, incomplete virilization (poorly developed secondary sex characteristics), gynecomastia, and mental retardation; phenotypic and testicular changes become evident at puberty

Macroscopic

- The testes are usually small and firm (<2.5 cm in greatest dimension)

Microscopic

- The testes show progressive failure of spermatogenesis with a loss of germ cells and Sertoli cells
- Tunica of tubules thickens and eventually all that remains are hyalinized empty tubules
- Leydig cell clusters become more prominent
- Debate over whether this represents Leydig cell hyperplasia or prominence of Leydig cells as a result of testicular volume loss

Posttesticular Causes of Infertility

Excurrent Duct Obstruction

Clinical

- Occurs in approximately 10% of biopsied infertile patients
- Patients have azoospermia, normal-sized testicles, and normal spermatogenesis on a testicular biopsy
- Obstruction can be the result of congenital atresia of vas deferens, epididymis, or cystic fibrosis, or acquired by infection or surgical ligation (vasectomy)

Macroscopic

- No alterations in testes

Microscopic

- Spermatogenesis is normal for many years following obstruction. Epididymis has ability to store, and phagocytize sperm and sperm products at a rate that matches sperm production
- Testicular biopsy at time of vasovasostomy (reversal of vasectomy) shows active spermatogenesis with germinal cell disorganization and sloughing, variable amounts of tunica propria thickening, occasional interstitial fibrosis, and sperm granulomata
- Can have impaired sperm motility

NEOPLASMS OF TESTIS (SEE TABLE 26-1.)

Germ Cell Tumors

Cell of Origin

- Precursor of invasive germ cell tumors is intratubular germ cell neoplasia, unclassified type (IGCNU)
- Hypothesized that seminomas arise from IGCNU, and non-seminomatous germ cell tumors arise from seminoma or from IGCNU
- IGCNU does not give rise to spermatocytic seminoma
- Seminoma cells and IGCNU are identical morphologically, and share many other features, including karyotypic abnormalities, DNA content, ultrastructural changes, and immunohistochemical profiles, including + staining with antibodies to placental alkaline phosphatase

Risk of Germ Cell Tumors

- Certain conditions increase the risk of germ cell tumors in men:
  - Cryptorchidism, history of a prior testicular tumor, first degree relative with a germ cell tumor, gonadal dysgenesis, and androgen insensitivity syndrome

Ancillary Stains

See Table 26-2

Staging

- Numerous staging systems for testicular germ cell tumors (see end of chapter)
- Extratesticular extension is present in 16% of cases and occurs at the hilum in 91% of these. The hilum should be sampled in all orchiectomies with tumor

Treatment

Seminoma

- Stage I tumors and nonbulky Stage II tumors are treated by radical orchiectomy and radiation to ipsilateral paraaortic and pelvic lymph nodes
- Some patients with a Stage I tumor are treated by radical orchiectomy alone
- Cure rate is 95% for Stage I tumors and approaches 90% for Stage II tumors
- In patients with bulky Stage II seminoma and advanced stages, orchiectomy, radiation, and chemotherapy are performed, with survival rates of 80%

Non-Seminomatous Germ Cell Tumors

- Stage I:
  - Option A: Radical orchiectomy and retroperitoneal lymph node dissection:
    - Cure rate = 90% to 95%
    - Relapse rate = 5% to 10%
  - Option B: Radical orchiectomy and surveillance:
    - Cure rate = 60% to 70%
    - Relapse rate = 30% to 40%
- Stage II:

Table 26-1. Overview of Testicular Neoplasia

Germ Cell Tumors
Intratubular germ cell neoplasia
Seminoma:
  Classic type
  Spermatocytic type
Non-seminomatous germ cell tumors:
  Embryonal carcinoma
  Yolk sac tumor (endodermal sinus tumor)
  Teratoma
    Immature
    Mature
    Teratoma with overtly malignant component
    Monodermal types
      Carcinoid
      Primitive neuroectodermal tumor
Choriocarcinoma
Mixed germ cell tumor
Sex Cord-Stromal Tumors
Leydig cell tumor
Sertoli cell tumor:
  Typical type
  Sclerosing type
  Large-cell calcifying type
Granulosa cell tumor:
  Juvenile
  Adult
Unclassified type
Mixed type
Mixed Sex Cord-Stromal Tumor and Germ Cell Tumor
Gonadoblastoma
Hematopoietic Tumors
Lymphoma
Plasmacytoma
Leukemia
Metastases

Table 26-2. Immunohistochemical Profiles of Testicular Germ Cell Tumors

Tumor	*Cytokeratin*	*Vimentin*	*PLAP*	*AFP*	*hCG*	*CD30*	*PAS*	*EMA*
Seminoma	–/+*	+	+	–	±	±	+	–
Spertomatocytic seminoma	–	–	–	–	–	–	–	–
Embryonal carcinoma	+	–	+	±	±	+	–	–
Yolk sac tumor	+	+	+	+	–	–	+	–
Teratoma	+	+	±	±	±	–	–	±
Choriocarcinoma	+	–	±	±	+	–	–	+

PLAP = Placental alkaline phosphatase; AFP = alpha-fetoprotein; hCG= human chorionic gonadotropin; PAS = periodic acid-Schiff without diastase; EMA = epithelial membrane antigen
**Wide spectrum cytokeratin is focally positive in 36% of cases (Cheville et al., 2000).*

  - Non-bulky:
    - Orchiectomy, lymph node dissection, and chemotherapy
    - Cure rate = 90%
  - Bulky:
    - Orchiectomy, chemotherapy, and resection of residual masses
    - Cure rate = 70% to 80%
- ♦ In Stage I tumors, a large percentage of embryonal carcinoma (>40%), lymphovascular invasion, and presence of choriocarcinoma are features that put the patient at an increased risk of relapse

Intratubular Germ Cell Neoplasia (IGCNU)

Clinical

- ♦ Intratubular germ cell neoplasia is a putative precursor (in situ) lesion for invasive germ cell tumors
- ♦ IGCNU is identified in almost all testis with invasive germ cell tumors, except testis with spermatocytic seminoma
- ♦ Most patients (>70%) with IGCNU develop an invasive germ cell tumor within 7 years
- ♦ Involvement is patchy, and 40% of cases are bilateral
- ♦ Two 3 mm testicular biopsies will identify the majority of patients with IGCNU
- ♦ IGCNU is identified in 1% of all testicular biopsies performed for infertility
- ♦ Treatment is orchiectomy in unilateral cases and bilateral orchiectomy or radiation in bilateral cases

Macroscopic

- ♦ No alterations

Microscopic

- ♦ Seminiferous tubules contain seminoma cells that are large with oval nuclei, prominent nucleoli, and clear cytoplasm
- ♦ Cells are confined to basilar aspect of tubules
- ♦ Spermatogenesis is absent in involved tubules

Immunohistochemistry

- ♦ IGCNU is uniformly + with stains for placental alkaline phosphatase (PLAP) in a cytoplasmic membranous staining pattern
- ♦ Only rarely are spermatocytes PLAP + and spermatogonia are PLAP –

Cytogenetics

- ♦ DNA content triploid or hypotetraploid
- ♦ Contains isochromosome 12p

Classic Seminoma

Clinical

- ♦ Most common germ cell tumor, accounting for 50% of all germ cell tumors
- ♦ Mean age at diagnosis is 40 years
- ♦ Very rare in children
- ♦ Patients present with a painless testicular mass, but up to 15% may have a normal exam
- ♦ 30% have metastases at presentation, but only 3% have symptoms related to metastases
- ♦ Serum alpha-fetoprotein is normal
- ♦ Beta human chorionic gonadotrophin is elevated in 10% to 20% of patients with Stage I seminoma

Macroscopic

- ♦ Characterized by a circumscribed lobular gray-white fleshy tumor that can have areas of necrosis and hemorrhage

Microscopic

- Cells have round to oval nuclei with one to several nucleoli and clear to slightly eosinophilic cytoplasm
- Cell borders are well-defined
- Arranged in solid sheets interrupted by fibrous septa
- Lymphoid infiltrate is present within septa
- Interstitial growth with preservation of tubules can occur at the periphery of the tumor
- Cord-like and tubular growth patterns can predominate in rare cases
- Granulomatous infiltrate present in 50% of all cases
- Anaplastic seminomas were defined as seminomas with increased mitotic activity. These behave no differently than other seminomas, and the use of the term "anaplastic" has been discontinued
- Syncytiotrophoblastic cells are present in up to 20% of all cases

Immunohistochemistry (see Table 26-2)

- Cells are PLAP +, identical to IGCNU
- Contains cytokeratins, although only 36% of cases are positive and reactivity is almost always confined to <10% of it in paraffin-embedded sections (Cheville et al., 2000)
- EMA –

Spermatocytic Seminoma

Clinical

- Unique tumor with distinct morphological and clinical features
- Occurs only in testis and represents up to 2% of germ cell tumors
- Patients are in their 50's and present with a testicular mass
- Very rarely metastasize
- Usually cured by orchiectomy
- Unusual cases: may be associated with sarcoma:
  - Either rhabdomyosarcoma or undifferentiated sarcoma
  - Aggressive lethal neoplasms

Macroscopic

- Tumors are multinodular and have a yellow edematous appearance
- Hemorrhage and cystic change can be present

Microscopic

- Characterized by a polymorphous cell population composed of small cells to multinucleate giant cells
- Cells are arranged in sheets and microcysts are present
- Nests and pseudoglandular structures are also identified
- Mitotic figures may be numerous
- Lymphoid and granulomatous infiltrate are absent

Immunohistochemistry

- Cells are PLAP –, vimentin –, muscle marker –, cytokeratin –, alpha-fetoprotein –, human chorionic gonadotropin –, EMA –, and CEA –

Electron Microscopy

- EM features are similar to those of leptotene stage spermatocytes

Embryonal Carcinoma

Clinical

- Second most common germ cell tumor, comprising approximately 20% of all cases
- Present in the majority of mixed germ cell tumors
- Most men present in their 20s to 30s with a testicular mass
- Very rare in children and older men
- More than two-thirds of patients have metastases, but only 10% of patients have symptoms related to metastases
- Serum AFP is normal, and beta hCG is elevated in 60% of cases

Macroscopic

- Fleshy gray-white tumor with prominent necrosis and hemorrhage

Microscopic

- Cells of embryonal carcinoma are large, with vesicular nuclei, prominent nucleoli, and indistinct cell borders
- Tumor cells are arranged in sheets, cords, and glandular structures
- Necrosis and hemorrhage may be prominent
- May be intimately admixed with a yolk sac tumor

Immunohistochemistry (see Table 26-2)

- Tumor cells are PLAP +, cytokeratin +, and EMA –, and may be CD30 +

Yolk Sac Tumor (Endodermal Sinus Tumor)

Clinical

- Most common germ cell tumor (and most common testicular tumor) in children, where it occurs in its pure form
- In children, majority of cases are diagnosed before 24 months
- In adults, it is unusual in pure form, but is found in approximately 50% of mixed germ cell tumors
- Both children and adults have elevated serum AFP
- In children, orchiectomy alone results in a cure rate of 90%

- Most adults and children present with a testicular mass

Macroscopic

- White to tan masses, with myxoid and cystic change

Microscopic

- Many histologic patterns:
  - Endodermal sinus pattern
  - Reticular
  - Solid
  - Papillary
  - Microcystic (most common)
  - Macrocystic
  - Alveolar
  - Myxomatous
  - Sarcomatoid
  - Polyvesicular-vitelline
  - Hepatoid
  - Parietal
- Deposition of basement membrane material, and Schiller-Duval bodies (central vessel rimmed by loose connective tissue that in turn is lined by malignant epithelium, all within a cystic space), are characteristic

Immunohistochemistry (see Table 26-2)

- AFP + (focal or patchy), cytokeratin +, PLAP variable, EMA –, CD 30 –

Teratoma

Clinical

- In children, second most common germ cell tumor
- Occurs in its pure form with a mean age of diagnosis at 20 months
- In children, metastases do not occur
- In adults, occurs as a component of a mixed germ cell tumor and is identified in >50% of mixed tumors
- In adults, teratoma is treated like a nonseminomatous germ cell tumor
- In adults, metastases occur, even in pure teratomas
- Adults and children present with a testicular mass

Macroscopic

- In mixed germ cell tumors, teratomatous component is solid and can contain multiple small cysts

Microscopic

- Composed of somatic-type tissues that can include enteric-type glands, respiratory epithelium, cartilage, muscle, squamous epithelium, and others
- Mature teratomas are composed of mature tissues, although this may show atypia
- Immature teratomas contain immature neuroepithelium; blastema or cellular stroma significance of immature elements not clear (unlike immature teratoma of ovary)
- Can give rise to carcinoma, such as adenocarcinoma and squamous cell carcinoma, or sarcoma, such as rhabdomyosarcoma, Wilm's-like tumor, or primitive neuroectodermal tumor (PNET)
- Clinical significance of development of sarcoma or carcinoma not known
- Two monodermal forms: carcinoid tumor and PNET:
  - Carcinoid tumors can be associated with other teratomatous elements (15% of cases)
    - Have a good prognosis, with 10% to 14% developing metastases
    - Carcinoid syndrome occurs rarely
  - PNET result from overgrowth of immature elements in a teratoma
    - Highly malignant

Choriocarcinoma

Clinical

- Pure choriocarcinoma is very unusual (<1% of germ cell tumors) and is a component of 15% of mixed germ cell tumors
- Many patients present with symptoms related to metastases to the brain or lungs
- Serum beta-hCG elevated
- Children do not develop choriocarcinoma
- Patients have a poorer prognosis, but the tumor is sensitive to chemotherapy

Macroscopic

- Hemorrhagic and necrotic

Microscopic

- Contains multinucleated syncytiotrophoblastic cells and mononuclear cytotrophoblast or intermediate trophoblast:
  - Both elements need to be present for diagnosis of choriocarcinoma

Immunohistochemistry (see Table 26-2)

- hCG +, can be PLAP +, cytokeratin +, CEA +, human placental lactogen +

Mixed Germ Cell Tumor

Clinical

- Composed of two or more germ cell tumor types
- Comprise 33% of all germ cell tumors

Sex Cord-Stromal Tumors

Leydig Cell Tumor

Clinical

- Normal Leydig cells produce testosterone and are located in the interstitium of the testis
- Leydig cell tumors comprise 3% to 5% of testicular neoplasms
- Leydig cell tumors occur in both adults (majority: 80%) and children
- Children present with endocrinologic symptoms (virilization, gynecomastia) and adults present with a testicular mass and some (10% to 30%) have gynecomastia
- In children, are benign
- In adults, 10% are malignant
- Benign tumors are treated by orchiectomy; malignant tumors by orchiectomy and retroperitoneal lymph node dissection

Macroscopic

- Leydig cells are light brown, solid, and lobulated
- Malignant tumors tend to be larger (>5 cm) than benign tumors. Necrosis can be seen in malignant tumors

Microscopic

- Leydig cells vary in size but usually have round nuclei, single prominent nucleoli, and abundant eosinophilic cytoplasm
- Spindled cells and cells with abundant clear cytoplasm can be present
- Crystals of Reinke are present in 40% to 70% of cases, and lipofucsin can be abundant in some cases
- Malignant features include large size (>5 cm), increased mitotic activity (>5/10 hpf), necrosis, angiolymphatic invasion, and invasion of surrounding structures, such as tunica, epididymis, and spermatic cord
- Can be difficult to predict malignant behavior from histologic features

Immunohistochemistry

- Inhibin +, and show variable positivity with cytokeratins, S-100, chromogranin, synaptophysin, and estrogen and progesterone receptors

Sertoli Cell Tumor, Typical Type

Clinical

- Sertoli cells are located within seminiferous tubules, and they help support spermatogenesis
- Account for <1% of testicular tumors
- Occur both in children (15% of cases) and in middle-aged adults, and can be malignant (10% of cases) in both
- Patients present with a testicular mass, and estrogen production by the tumor can result in gynecomastia and impotence
- Treatment is orchiectomy
- Proliferation of Sertoli cells may be seen in androgen insensitivity syndrome (Sertoli cell adenoma) and cryptorchid testis (Sertoli cell nodule or Pick's adenoma)

Macroscopic

- Tumors are well-circumscribed, solid yellow, white to gray masses
- Large size and necrosis are worrisome features for malignancy

Microscopic

- Typically composed of solid tubules containing Sertoli cells
- Tubules can contain lumina
- Cells may also be arranged in cords, solid nests, and solid sheets
- Can be difficult to determine malignant behavior
- Features worrisome for malignancy are identical to those seen in Leydig cell tumors

Immunohistochemistry

- Inhibin + and can be + with synaptophysin, chromogranin, S-100, and cytokeratin

Electron Microscopy

- Charcot-Bottcher filaments (perinuclear aggregates of intermediate filaments) are pathognomonic of Sertoli cells or Sertoli cell differentiation

Sclerosing Sertoli Cell Tumor

Clinical

- Rare variant of a Sertoli cell tumor
- Patients present with a testicular mass and without endocrinologic symptoms
- No malignant cases have been reported

Macroscopic

- Similar to a typical Sertoli cell tumor

Microscopic

- Cords, nests, and tubules of Sertoli cells are present within a fibrotic stroma

Large-Cell Calcifying Sertoli Cell Tumor

Clinical

- Rare variant of a Sertoli cell tumor
- Patients are young, with age at diagnosis ranging from 16 to 37 years

- Occur as part of Carney complex and in patients with Peutz-Jeghers syndrome:
  - In this setting, tend to be multifocal
- Malignant tumors (17% of cases) occur, and usually are sporadic type (only one malignant tumor has been reported associated with Carney's syndrome)

Macroscopic

- Benign tumors are small (usually < 2 cm) yellow, tan, or white nodules confined to the testicle
- Malignant tumors are larger and may have areas of necrosis

Microscopic

- Neoplastic cells are arranged in sheets, small nests, and cords, and are present in a myxoid to fibrous stroma
- Dystrophic calcifications, including psammomatous calcifications, are present
- Malignant tumors are large and exhibit extratesticular spread, increased mitotic activity, necrosis, and angiolymphatic invasion

Immunohistochemistry

- S-100 +, EMA –, and cytokeratin variable (usually negative to weak staining)

Electron Microscopy

- Charcot-Bottcher filaments are absent or rarely present

Granulosa Cell Tumor, Adult Type

Clinical

- Much less common than in the adult female ovary
- Average age = 42 years
- Often (20%) associated with gynecomastia
- Four patients had metastasis and two died

Macroscopic

- Lobulated, firm and uniformly yellow-gray mass

Microscopic

- Microfollicular with a few larger cysts
- Call-Exner bodies may be seen
- Cells have scant cytoplasm and angular nuclei
- May have nuclear grooves

Granulosa Cell Tumor, Juvenile Type

Clinical

- Rare sex cord-stromal tumor that occurs in males in first few months of life
- May occur in setting of gonadal dysgenesis
- Infants present with a testicular mass
- No malignant cases have been reported
- May be of Sertoli cell origin (debated)

Macroscopic

- Tumors are small and solid and contain multiple small cysts

Microscopic

- Sheets of spindle cells with abundant cytoplasm intermixed with follicle-like cystic spaces
- Hyalinized collagenous stroma is also a feature in cellular areas

Mixed Germ Cell and Sex Cord-Stromal Tumor

Gonadoblastoma

Clinical

- Composed of a mixture of seminoma cells and Sertoli cells
- Occur in dysgenetic gonads in patients with intersex syndrome (80% phenotypically female; 20% phenotypically male)
- May have ambiguous genitalia
- Patient karyotype 46XY or 45X/46XY most commonly
- Invasive germ cell tumors, usually seminoma, arise in gonadoblastoma
- Treatment is the removal of gonads

Macroscopic

- Solid yellow to tan tumors in dysgenetic gonads; in males, testes are cryptorchid, and contain female components (involution of müllerian structures does not occur)

Microscopic

- Tumor composed of an admixture of seminoma cells and sex cord-stromal (Sertoli) cells
- Tumor cells form nests with central germ cells and peripheral stromal cells
- Globules of eosinophilic basement membrane material with peripheral palisading stromal cells may be present in nests

Hematopoietic Neoplasms

Lymphoma and Plasmacytoma (see chapter 7)

Clinical

- Lymphoma most often result of secondary spread; occasionally, primary lymphoma may occur
- Plasmacytoma also occurs in testes, and is also usually due to secondary spread in a patient with multiple myeloma
- Most men are in their 60s
- Involvement is bilateral in 20% of all cases
- Survival is stage-dependent

Macroscopic

- White to tan fleshy tumor

Microscopic

- In adults, most lymphomas are diffuse large cell types with a B-cell phenotype
- May have immunoblastic features
- In children, small non-cleaved lymphoma is most common
- Has an interstitial growth pattern with sparing of seminiferous tubules
- Plasmacytomas are composed of mature plasma cells that vary in their amount of atypia

Leukemia (see chapter 8)

Clinical

- Testes are a sanctuary site for leukemia, especially for acute lymphoblastic leukemia
- Testicular biopsies may be + for leukemia when patient is in remission

Macroscopic

- Testes may be normal to enlarged, with a mass

Microscopic

- Leukemia has an interstitial growth, like a lymphoma
- Morphologic features are dependent on the type of leukemia

NEOPLASMS OF PARATESTICULAR REGION

Adenomatoid Tumor

Clinical

- Nodule that typically involves epididymis; may also be identified in tunica albuginea and spermatic cord
- Benign lesion cured by complete excision
- Unknown origin

Macroscopic

- Nodule involving epididymis, spermatic cord, or tunica
- May extend into rete testis and testis

Microscopic

- Nests and tubules of epithelioid cells present within a fibrous or fibromuscular stroma
- Epithelioid cells have bland nuclear features
- Cells may be flattened and have an endothelial appearance

Immunohistochemistry

- Epithelioid cells strongly keratin +

Benign Papillary Mesothelioma

Clinical

- Occurs in young men who present with hydocoele sac
- Benign lesion cured by hydrocoelectomy

Macroscopic

- Papillary excrescences present within a hydrocoele sac

Microscopic

- Papillae lined by bland cells with large nuclei and nucleoli
- Cytoplasm is clear to eosinophilic

Malignant Mesothelioma

Clinical

- Rare malignant lesion of testicular mesothelium of tunica vaginalis; rarely involves epididymis or spermatic cord
- May be seen in men with asbestos exposure, suggesting a relationship with asbestos exposure similar to pleural and peritoneal mesothelioma
- Patients present with mass, hydrocoele, or hernia sac
- Treatment is radical orchiectomy with high resection of spermatic cord
- 50% survival long-term

Macroscopic

- Solid and cystic masses line hydrocoele sac; necrosis may be present in larger masses

Microscopic

- Identical to mesotheliomas at other locations with spindle cell, epithelial (75% of cases), and biphasic types (also see chapter 17 and 20)

Immunohistochemistry (also see Table 17-3)

- Cytokeratin +, CEA –

Fibrous Pseudotumor

Clinical

- Benign fibrous lesion of tunica, epididymis, or spermatic cord
- Also known as inflammatory pseudotumor and nodular fibrous periorchitis
- Patients present with a testicular mass mimicking a neoplasm; wide range of patient ages

- Patients may also have a hydrocoele

Macroscopic

- Nodular or diffuse thickening of tunica, spermatic cord, or epididymis

Microscopic

- Appearance similar to inflammatory pseudotumors of other sites
- Active inflammation in a loose stroma to densely collagenized fibrous tissue

Tumors Homologous to Ovarian Tumors

- Tumors that appear of Mullerian origin or homologous with ovarian epithelial neoplasms occur in paratesticular region
- Include mucinous and serous cystadenoma, borderline tumors, and cystadenocarcinoma

Sarcoma

Rhabdomyosarcoma

Clinical

- May arise in tunica, spermatic cord, or epididymis
- Patients present with large scrotal mass
- Occurs at any age, but is most common sarcoma of paratesticular region in children
- Most tumors occur before the age of 10
- Effective therapy (radical orchiectomy, radiation and chemotherapy) has resulted in survivals in excess of 80% of cases

Macroscopic

- Large gray-white masses in scrotum; site of origin is often impossible to locate

Microscopic

- Embryonal rhabdomyosarcoma is the most common type seen in the paratesticular region
- Spindled types may occur, as well as alveolar, pleomorphic, and botryoid types

Liposarcoma

- Most common paratesticular sarcoma in adults
- Most often well-differentiated (sclerosing), but may show dedifferentiation
- In high-grade sarcomas, areas of well-differentiated liposarcoma should be sought with thorough sampling
- Treated by radical orchiectomy
- 23% develop recurrence after surgery; 10% develop metastases

Leiomyosarcoma

- Occurs in adults, and most often involves spermatic cord
- Treated by radical orchiectomy
- Long-term survival is obtained in 67%

NON-NEOPLASTIC DISEASES OF PENIS

Congenital Abnormalities

Epispadias

Clinical

- Urethra opens on the dorsal aspect of the penis
- Occurs in 1 in 117,000 male births
- Associated with other abnormalities, including cryptorchidism, renal agenesis, ectopic kidney, and bladder exstrophy
- Urethral opening may be constricted, and the location may impair normal ejaculation and subsequent insemination, resulting in infertility

Hypospadias

Clinical

- Urethra opens on the ventral surface of the penis (usually on glans) or the perineum
- May be associated with chordee (chordee is bending of the penis, and it is congenital in hypospadias, and is a result of maldeveloped fascia distally)
- Occurs in 1 in 300 male births
- Associated with other GU congenital abnormalities and blocked ejaculation, like epispadias

Other Abnormalities

Aphalia

- Absence of penis (penile agenesis)
- Normal scrotum is present, but no penile shaft
- Genital tubercle does not develop
- Occurs in 1 in 10,000,000 male births
- Associated with cryptorchidism, imperforate anus, renal agenesis and other renal malformations, and musculoskeletal and cardiopulmonary defects

Micropenis

- Small penis < 2 or more standard deviations below mean
- Causes include idiopathic, hypogonadotropic hypogonadism, and hypergonadotropic hypogonadism

Diphallus

- Double penis
- Associated with other congenital anomalies, including hypospadias, renal agenesis, imperforate anus, heart defects, and others

Inflammatory Conditions

Balanoposthitis and Balanitis

Clinical

- Inflammation of glans penis and prepuce (balanoposthitis) and glans penis (balanitis)
- Occurs in uncircumcised men who fail to keep foreskin clean
- Debris accumulates (smegma) and becomes infected by a variety of organisms, including staphylococci, streptococci, coliforms, or gonococci
- Collection of infected smegma results in inflammation
- May lead to scarring and phimosis (inability to retract foreskin over glans penis)

Phimosis and Paraphimosis

Clinical

- Phimosis is the inability to retract the foreskin over the glans penis; paraphimosis is a persistently retracted foreskin
- Phimosis and paraphimosis are most commonly the result of balanitis or balanoposthitis, but may be congenital due to abnormalities of the foreskin
- Phimosis prevents the ability to clean the foreskin
- Treatment of both conditions is circumcision

Balanitis Xerotica Obliterans (Lichen Sclerosus et Atrophicus)

Clinical

- Idiopathic atrophic condition of genital and perianal skin
- May be autoimmune in origin
- Similar changes may be seen in foreskins removed for phimosis
- Occurs in older males
- Asymptomatic
- Treatment is circumcision, topical steroids, and laser therapy
- Cases have been associated with squamous cell carcinoma

Macroscopic

- Well-circumscribed white patch that usually involves glans penis; may also involve prepuce, shaft of penis, and urethral meatus

Microscopic

- Atrophic epidermis (thin epidermis with loss of rete and dermal adnexal structures) with hyperkeratosis and fibrosis (hyalinization) of dermis
- Sparse chronic inflammatory cell infiltrate

Peyronie's Disease

Clinical

- Form of fibromatosis involving penis
- Bending of penis during erection
- Causes painful erection
- Palpable plaque(s) may be present on the dorsal surface of the penis
- Associations have been made with urethritis, trauma during intercourse, and urethral instrumentation

Macroscopic

- Single or multiple plaques are present on the dorsal surface of the penis

Microscopic

- Fibrosis of tunica albuginea forming fibrous plaques; may calcify and ossify

Priapism

Clinical

- Persistent erection that becomes painful from ischemia
- Multiple causes, including drugs (oral, intravenous, and intracavernous), sickle cell anemia, leukemic and other malignant infiltrates (rare cause), trauma, neurologic disorders, and others
- May be idiopathic

Infections

Syphilis

Clinical

- Caused by spirochete *Treponema pallidum*
- Three stages: primary, secondary, and tertiary:
  - Primary syphilis:
    - Characterized by a reddened papule on glans penis, prepuce, or shaft that ulcerates to form characteristic chancre:
      - In 10% of cases, chancre may not be on the genitals
    - Chancre is a well-circumscribed clean-based ulcer with an indurated base
    - Lymphadenopathy is present
    - Ulcer heals in 6–8 weeks
  - Secondary syphilis:
    - Characterized by maculopapular rash; involves

skin and mucosal surfaces, and is associated with generalized lymphadenopathy
    - May also be manifest by an elevated broad-based plaque on genital region (condyloma lata)
- Tertiary syphilis:
    - Now very rare
    - Characterized by gummas that are nodules formed of granulomas that may be necrotic
    - Most commonly involves cardiovascular system (80% of cases) and CNS (10% of cases)
    - Cured with antibiotics in primary stage

Microscopic

- Histologic features of chancre include ulceration of epidermis, with underlying dermis containing an infiltrate of plasma cells and lymphocytes
- Inflammation may be perivascular and endothelial proliferation may be pronounced
- Lymph nodes exhibit follicular hyperplasia and a paracortical plasmacytosis
- Capsule is thickened
- These findings are not specific for syphilis
- Spirochetes may be seen in chancre, and lymph nodes with dark field microscopy or special stains (Warthin-Starry)
- Skin changes in secondary syphilis are non-specific
- Dark-field microscopy may show spirochetes
- Gummas in tertiary syphilis are granulomatous with or without necrosis

Gonorrhea

Clinical

- Caused by pyogenic Gram-negative, diplococci *Neisseria gonorrhoea*
- Sexually transmitted
- Causes urethritis with suppurative discharge and dysuria
- If untreated, may spread to posterior urethra, prostate, and epididymis
- Urethral stricture is a complication
- Untreated males may be silent carriers of gonococci
- Treated with antibiotics

Microscopic

- Neutrophilic infiltrate is present within urethra, may ulcerate
- Gonococci seen within neutrophils on smears of urethral swabs
- Abscess formation may occur in prolonged cases

Herpes Simplex Virus Infection

Clinical

- Sexually transmitted disease caused by herpes simplex virus Type II
- Initial episode of infection is most pronounced, with systemic symptoms (headache, fever, and malaise) and genital lesions
- Multiple vesicles develop and become pustules that eventually rupture to form ulcers
- Recurrent episodes are less severe and consist of genital lesions
- Antivirals, such as acyclovir, will decrease the severity and duration of lesions but will not eliminate the virus or recurrent infections

Microscopic

- Vesicles caused by acantholysis
- Neutrophilic infiltrate and ulceration present
- Viral inclusions are typically seen within epidermal cells and are characterized by intranuclear acidophilic and ground-glass inclusions
- Cell fusion results in giant cells; nuclei of giant cells contain inclusions
- Tzank preparation (examination of vesicle fluid or smear of ulcer and staining with Wright-Giemsa, toluidine blue, or Papanicolaou stains) reveals cells with diagnostic inclusions

Granuloma Inguinale

Clinical

- Caused by Gram-negative facultative intracellular bacillus, *Calymmatobacterium granulomatis*
- Organism is difficult to culture
- Unusual in United States; most frequent in Asia (India and New Guinea) and the Caribbean
- Infections involve penis, perineum, and vulva (males more frequently affected than females)
- Papules develop that ulcerate; ulcers are painless
- Cured with antibiotics

Microscopic

- Epidermal ulceration associated with epidermal hyperplasia is present
- Donovan bodies characteristic and 50 micron dark inclusions within cytoplasmic vacuoles of macrophages
- Donovan bodies seen best with Giemsa or silver stains

Lymphogranuloma Venereum

Clinical

- Venereally transmitted infection caused by L-1, L-2, and L-3 serotypes of chlamydia trachomatis
- Culture is diagnostic

- Three stages:
  - Primary genital stage characterized by a small epidermal vesicle or papule that ulcerates and heals spontaneously
  - Followed by painful lymph node involvement:
    - Lymph nodes become matted together and fluctuant (bubo formation)
  - Rare third stage with ulcers, fistulas, and strictures

Microscopic

- Histologic features of genital cutaneous lesion are nonspecific
- Lymph nodes show stellate microabscesses identical to cat-scratch disease
- Abscesses may enlarge and rupture to the skin surface
- Chlamydial inclusions may be identified by immunofluorescence techniques
- Third stage is characterized by fibrosis and chronic inflammation

Chancroid (Soft Chancre)

Clinical

- Caused by sexually transmitted gram-negative, anaerobic *Hemophilus ducreyi*
- Painful ulcers and lymphadenopathy develop
- Uncommon in United States, but increasing in frequency; more common in Asia, parts of Africa, and the Caribbean

Microscopic

- Soft chancre consists of three zones:
  - Ulcer surface (fibrin, neutrophils, debris)
  - Overlies zone of vascular proliferation:
    - Thrombosed vessels may be present
  - Deep aspect of lesion is infiltrated by plasma cells and lymphocytes
- Organisms can be identified in tissues (best on smears) with Giemsa, Gram, or methylene blue stains
- Lymph nodes may enlarge with bubo formation

NEOPLASMS OF PENIS

Condyloma Acuminata

Clinical

- Caused by sexually transmitted human papilloma virus (HPV)
- Affects young sexually active males
- HPV types 6, 11, 16, 18, 31, and 33 cause condylomata
- Types 16, 18, 31, and 33 are most frequently associated with dysplastic changes
- Treated with podophyllin and laser therapy

Macroscopic

- Condyloma warty papillary growths

Microscopic

- Condylomata papillary with acanthotic parakeratotic (retention of nuclei in superficial epidermis) and hyperkeratotic squamous epithelium
- Koilocytotic change (irregular "boxcar" nuclei, multinucleation, perinuclear halos) is usually minimal (unlike cervix)

Erythroplasia of Queyrat and Bowen's Disease

Clinical

- Erythroplasia of Queyrat (EQ) and Bowen's disease (carcinoma *in situ*) preneoplastic; approximately 10% of patients with these diseases go on to develop invasive squamous cell carcinoma
- EQ affects glans penis and prepuce, and is a red plaque
- Bowen's disease affects penile shaft and scrotum and is a scaly gray-white plaque

Microscopic

- EQ and Bowen's disease are identical histologically
- Entire thickness of epidermis is composed of cells with marked nuclear atypia identical to squamous cell carcinoma
- Failure of maturation
- Basement membrane is intact

Bowenoid Papulosis

Clinical

- Affects younger men than EQ and Bowen's disease
- Tends to be multifocal and involves penile shaft
- HPV Type 16 is identified in 80% of all cases
- Red-brown verrucoid papules that spontaneously regress
- Not associated with the development of squamous cell carcinoma

Microscopic

- Resembles EQ and Bowen's disease, but does exhibit some maturation

Squamous Cell Carcinoma

Clinical

- Affects 1 in 100,000 U.S. men; 1% of all male cancer in the United States
- More frequent in areas without circumcision; 12% of cancers in men in some locations
- Vast majority of cancers affecting penis are squamous cell carcinoma
- Uncircumcised men with phimosis (poor hygiene) affected; smegma has an important role in the development of squamous cell carcinoma
- Circumcision is protective
- HPV types 16 and 18 are identified in 50% of cancers
- Approximately 40% of patients have nodal metastases at presentation; hematogenous or distant metastases are rare at presentation

Macroscopic

- Glans penis and inner surface of prepuce are most frequently involved (70% of cases)
- Tumors can be fungating or flat and infiltrative

Microscopic

- Well-differentiated keratinizing squamous cell carcinoma is most common
- Variants of squamous cell carcinoma:
  - Verrucous carcinoma:
    - Accounts for approximately 10% of cases of squamous cell carcinoma
    - Typically a large warty neoplasm that has minimal cytologic atypia, rare mitotic figures, and a pushing deep margin
    - Cured by resection, and does not metastasize
    - Frequently recurs if inadequately excised
  - Sarcomatoid (spindle cell) squamous cell carcinoma:
    - Very rare, poorly differentiated tumor

TNM CLASSIFICATION OF TESTICULAR AND PENILE TUMORS (1997 REVISION)

Testis

- Tx: Unknown status of testis
- T0: No apparent primary (includes scars)
- Tis: Intratubular neoplasia; no invasion
- T1: Tumor confined to testicle
- T2: Tumor extending through the tunica albuginea with involvement of tunica vaginalis or the presence of angiolymphatic invasion
- T3: Spermatic cord involvement
- T4: Scrotal involvement
- Nx: Nodal status unknown
- N1: Single lymph node involved, <2 cm
- N2: Single node, 2–5 cm or multiple nodes <5 cm
- N3: Any nodes >5 cm
- Mx: Status of metastases unkown
- M0: No distant metastases
- M1: Distant metastases

Penis

- Primary Tumor (T)
  - TX: Primary tumor
  - T0: No evidence of primary tumor
  - Tis: Carcinoma in situ
  - T1: Tunor invades into subepithelial connective tissue
  - T2: Tumor invades corpus spongiosum or cavernosum
  - T3: Tumor invades into urethra or prostate
  - T4: Tumor invades adjacent structures
- Regional Lymph Nodes (N)
  - NX: Regional lymph nodes cannot be assessed
  - N0: No regional lymph node metastases
  - N1: Metastasis in a single superficial lymph node
  - N2: Metastasis in multiple or bilateral superficial inguinal lymph nodes
  - N3: Metastasis in deep inguinal or pelvic lymph nodes, unilateral or bilateral
- Distant Metastasis (M)
  - MX: presence of distant metastasis cannot be assessed
  - M0: no distant metastases
  - M1: distant metastases

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Chapter 27

Esophagus and Stomach

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ESOPHAGUS

Non-Neoplastic Anomalies

Webs and Rings

Clinical

- Primary symptom is dysphagia
- May be associated with Plummer-Vinson syndrome (triad of glossitis, esophageal webs, and iron-deficiency anemia)

Atresia

Clinical

- See Table 27-1
- Newborns present in the first few days of life with regurgitation, choking, aspiration, and cyanosis
- Complete atresia is rare (1:30,000 live births)
- Atresia with tracheo-esophageal fistula is more common (1:800–1,500 live births)

Table 27-1. Types of Atresia

Type	*Macroscopic Description*
Type I	Upper blind pouch connects to the pharynx, lower pouch connects to the stomach
Type II	Proximal and distal portions of the esophagus are completely separate, the upper part connects to the trachea (rare)
Type III	Lower pouch connects with the trachea or mainstem bronchus (most common)
Type IV	Both upper and lower esophageal

Achalasia

Clinical

- An idiopathic disorder of motility
- Occurs when the lower sphincter fails to relax and the esophagus cannot undergo peristalsis
- Adults (occasionally children)
- Reversible if diagnosed early
- Risk of carcinoma if untreated

Macroscopic

- Dilated esophagus
- Distal fibrosis, stenosis, and ulceration

Microscopic

- Acanthosis
- Ductal dilatation with rare cyst formation (intramural diverticulosis and esophagitis cystica)
- Loss of myenteric nerves
- Hypertrophy of all muscle layers
- Chronic inflammation with germinal centers

Glycogen Acanthosis

Clinical

- Common (found in 15–30% of individuals)
- Asymptomatic
- Distal esophagus
- Endoscopic differential includes candidiasis and exudate

Macroscopic

- Uniform, round-oval white plaques
- Size <3 mm
- Longitudinal orientation
- Single or multiple (cobblestone appearance)

Microscopic

- Epithelial hyperplasia
- Glycogenization of superficial cells

Cysts

Clinical

- See Table 27-2
- Majority are asymptomatic but may present with dysphagia and cough
- Appear in childhood or adulthood

Macroscopic

- Dilatation generally in the wall of the esophagus

Diverticulae

- See Table 27-3

Heterotopic Gastric Glands

Clinical

- Rare (prevalence approximately 4%)
- Predominantly submucosal
- Occur anywhere along the esophagus
- Usually asymptomatic

Macroscopic

- Circular, with sharply demarcated borders
- Flat
- Orange-red

Table 27-2. Types of Cysts

Type	*Location*	*Etiology*
Zenker's	Upper third	Weakness in the muscle wall
Traction	Lower third	Caused by attachment of inflamed lymph nodes
Epiphrenic	Immediately superior to the diaphragm	Unknown

Microscopic

- Antral-pyloric glands or clusters of Brunner-type glands or fundic glands
- Inflammation with reactive fibrosis and thin muscular bundles
- Cystic pits or cystic glands may be present

Differential Diagnosis

- Adenocarcinoma:
  - Infiltrative
  - Cytologically malignant

Esophagitis, Nonreflux

Chemical

Clinical

- Together with foreign body aspiration represents the third most common cause of pediatric death
- Signs and symptoms include nausea, vomiting, dysphagia, refusal to drink, abdominal pain, increased salivation, and oropharyngeal burns
- Etiologic agents include alkali (lye), acid, and medication (doxycycline, tetracycline, aspirin, NSAIDs, emperonium bromide, quinidine, slow release KCl).
- Occurs most commonly at narrow sites (level of aortic arch)
- Radiography reveals mediastinitis, pneumonitis, pleural effusion, and perforation
- Primary sequela is stricture formation

Macroscopic

- Nodules, plaques, ulcers, or abnormal folds

Differential Diagnosis

- Infectious esophagitis (candida, herpes)
  - Gomori methenamine silver (GMS) for fungal organisms
  - Cytopathic effect
- Barrett's esophagus:
  - Distal location

Table 27-3. Types of Diverticulae

Type	*Macroscopic Description*
Bronchogenic	Ciliated columnar (respiratory epithelium lining; wall with smooth muscle, mucous glands, cartilage)
Esophageal	Stratified squamous lining; wall with muscularis mucosa, submucosal glands
Duplication	Squamous, gastric (fundic), ciliated columnar or small intestinal epithelial wall with muscularis mucosa, submucosa, and muscularis propria

Radiation

Clinical

- Second most tolerant gastrointestinal (GI) organ to radiation (rectum is first)
- Primary symptom is retrosternal burning
- Significant sequelae are fistula and stricture, with luminal narrowing

Macroscopic

- Erythema
- Mucosal exudate
- Ulceration
- Necrosis
- Telangiectasia

Microscopic

- Degenerative changes
- Decreased mitotic activity
- Epithelial sloughing
- Necrotic lamina propria
- Inflammatory infiltrate
- Fibrosis

Infectious

Candida albicans

Clinical

- Prevalence unknown (many asymptomatic)
- High risk in patients with leukemia, lymphoma, and AIDS, but can be seen in any patient on broad-spectrum antibiotics, H2 receptor antagonists, proton pump inhibitors, or corticosteroids
- Symptoms include dysphagia, odynophagia, and retrosternal pain
- Radiography shows multiple, longitudinal plaques with submucosal edema

- Complications include intramural pseudodiverticulosis and constriction
- Most accurately diagnosed with endoscopic brushing and biopsy

Macroscopic

- Multiple yellow-white plaques
- Plaques are focal and discrete or confluent
- Erythematous, edematous base

Microscopic

- Hyphal forms with an abundance of yeast that adhere to the epithelium

Differential Diagnosis

- Aspergillosis:
  - Refractory to candida therapy
  - Culture

Herpes Simplex Virus (HSV)

Clinical

- 100% of adults show serologic evidence of a previous infection
- Shedding of viable virus seen in 2% of adults
- Frequently preceded by 3–7 days of upper respiratory infection with fever, sore throat, and myalgia
- Symptoms include odynophagia, nausea, vomiting, hematemesis, and fever
- Transmitted through direct contact
- Esophagus is the organ most commonly involved in immunodeficient patients
- Risk factors for infection include malignancy, radiotherapy, and immunosuppression
- Diagnosis is based on identifying HSV by histology, cytology, and culture

Macroscopic

- Variable and nonspecific

Microscopic

- Epithelial ulceration
- Ground glass nuclei (intranuclear inclusions) at edge of ulcer
- Acantholysis
- Multinucleated cells

Cytomegalovirus

Clinical

- Most frequently seen in post-transplant (60–70%) and AIDS patients
- Asymptomatic or mild mononucleosis-like syndrome
- Symptoms include nausea, vomiting, GI bleeding, and fever
- Diagnosis is based on a + culture (blood, throat, stool, urine)

Macroscopic

- Ulcerations, erosions
- Mucosal hemorrhage

Microscopic

- Cells with abundant cytoplasm
- Nuclear enlargement, hyperchromasia
- Associated granulation tissue

Immunohistochemistry and In Situ Hybridization

- CMV +

Esophagitis, Reflux

Clinical

- Presents with regurgitation, heartburn, pain, and dysphagia
- Pathogenesis unknown, but thought to result from vagal nerve dysfunction
- Associated with hiatal hernia, scleroderma, and Zollinger-Ellison syndrome
- Clinical correlation imperative
- Endoscopic findings include erosions and ulcerations

Macroscopic

- Hyperemia
- Superficial ulceration

Microscopic

- Epithelial hyperplasia with neutrophilic and eosinophilic infiltrates
- Epithelial damage (edema, necrosis)
- Balloon cells (round, swollen squamous cells with pale-staining cytoplasm due to loss or dilution of glycogen)
- Basal cell proliferation (>15% of the total epithelial thickness)
- Heightened papillae (>67% of the epithelial thickness)
- Dilatation and congestion of capillaries in the lamina propria
- Erosion, ulceration

Varices

Clinical

- Occurs with portal vein pressure >12 mm Hg
- Etiology, see Table 27-4

Macroscopic

- Prominently congested blood vessels in the mucosa
- Short, bright red, curved streaks on the surface of the varices

Table 27-4. Etiology of Varices

Cirrhotic	*Non-cirrhotic*
Alcohol	AV fistula
Hepatitis	Splenomegaly
	Splenic/portal vein thrombosis
	Idiopathic portal hypertension
	Toxins
	Schistosomiasis
	Malignancy
	Sarcoidosis
	Nodular regenerative hyperplasia
	Focal nodular hyperplasia
	Hepatic vein thrombosis
	Veno-occlusive disease
	Right-sided heart disease

Metaplasia

Barrett's Metaplasia

Clinical

- Usually adults (white males), occasionally children (cystic fibrosis patients and following chemotherapy)
- Etiology unknown, but perhaps genetic predisposition with ulcerative changes from reflux
- Diagnosis suspected with barium swallow, manometry, and pH monitoring
- Diagnosis confirmed with endoscopic exam and biopsy
- A risk factor for stricture formation, hemorrhage, dysplasia, and carcinoma
- A premalignant condition
- Cytogenetic abnormalities result in p53 overexpression, c-erbB-2 oncoprotein expression, and epidermal growth factor receptor gene amplification.

Macroscopic

- Flat, smooth, glistening, salmon-pink

Microscopic

- Specialized columnar epithelium (intestinal metaplasia) with underlying submucosal glands (most common)
- Atrophic, fundic epithelium with parietal and chief cells
- Cardiac or junctional epithelium with mucous glands
- Dysplasia, see Table 27-5

Table 27-5. Microscopic Features of Dysplasia in Barrett's

Low-grade dysplasia	*High-grade dysplasia*
Regular glands	Marked pleomorphism
Moderate hyperchromasia	Marked hyperchromasia
Crowded, elongated nuclei	Disordered nuclei
	Depleted mucous glands
	Absence of mature goblet cells

Differential Diagnosis

- Reactive hyperplasia:
  - Regular glands, mild hyperchromasia, crowded basally oriented nuclei

Sebaceous Gland Metaplasia

Clinical

- Rare (prevalence approximately 2%)
- Occurs at all levels of the esophagus
- Multifocal involvement
- Accepted as a metaplasia, but possibly heterotopic tissue

Microscopic

- Sebaceous glands in the lamina propria
- Lymphocytic infiltrate

Neoplastic—Epithelial

Squamous Papilloma (Fibroepithelial Polyp)

Clinical

- M:F = 2:1
- Average age = 45–50 years
- Average size <5 mm
- May result from chronic irritation
- Human papilloma virus (HPV) recently implicated in the pathogenesis
- Asymptomatic (incidentally found during endoscopy)

Macroscopic

- Middle and lower thirds of the esophagus
- Mostly solitary (10–15% multiple)
- Irregular, polypoid lesion
- Sessile or partly pedunculated
- White-pink
- Soft

Microscopic

- Fronds of hyperplastic squamous mucosa covering spires of lamina propria
- Occasional koilocytotic change
- Occasional proliferative change (basal cell hyperplasia, cellular crowding, increased mitotic activity, mild hyperchromasia, mild pleomorphism)

Squamous Cell Carcinoma

Clinical

- Most common neoplasm of the esophagus
- M:F = 3–4:1
- Average age = 50–60 years
- Increased incidence in African-Americans and Asian-Americans
- Risks include smoking, alcohol, achalasia, Plummer-Vinson syndrome, diverticulae, celiac sprue, irradiation, lye strictures, Barrett's metaplasia, and HPV
- Primary symptom is dysphagia (with advanced disease)
- Suggested etiology is HPV (identified in up to 60% of the cases), especially types 16 and 18
- Diagnosed by endoscopic biopsy and cytologic brushing (99% diagnostic yield when combined)
- Poor prognosis, with a median survival of 1 year after diagnosis
- Factors associated with an unfavorable prognosis include male sex, ≥ 2 + lymph nodes, + surgical margins
- Abnormalites of p53, cyclin D1, and/or epidermal growth factor receptor contribute to the pathogenesis

Macroscopic

- Most common sites are middle and lower thirds of the esophagus
- Multicentric in up to 26% of patients
- Gray-white
- Circumferential mass
- May be fungating, ulcerative, or infiltrative
- Sharply demarcated margins

Microscopic

- Invasive (pushing and budding)
- Generally little desmoplasia
- Variable mitotic rate
- Variable pleomorphism (most are well or moderately differentiated)
- Keratin production
- Submucosal spread up to 5 cm beyond grossly visible margins
- Vascular invasion in 75% of cases

Precursor/Related Lesions

- Carcinoma in situ (CIS)
  - Found at the periphery of 30% of invasive cancers
- Superficial spreading carcinoma:
  - Exhibits lateral mucosal spread only
- Superficial (microinvasive) carcinoma:
  - Does not extend beyond the submucosa
- Intramucosal carcinoma:
  - Does not extend beyond the lamina propria

Variants

- Carcinosarcoma (spindle cell carcinoma, polypoid carcinoma):
  - Polypoid mass with a short, thick stalk
  - Smooth or knobby surface
  - Superficial erosions
  - Biphasic histology with both sarcomatous and carcinomatous elements
  - Edematous, undifferentiated stroma
  - 10% with stromal differentiation toward bone, cartilage, and skeletal muscle
  - Keratin and vimentin +, actin and desmin ±
- Basaloid Squamous Carcinoma:
  - Large, basaloid cells
  - High-grade cytology
  - High mitotic rate
  - Cells form cords, tubules, and solid nests
  - Necrosis
  - Peripheral palisading
  - Squamous differentiation frequently present
- Adenoid Cystic Carcinoma:
  - Uniform basaloid cells with small nuclei
  - Rare mitoses
  - Cells grow in cords, tubules, and solid or fenestrated nests
  - Hyaline stroma (abundant basement membrane) associated with cells
- Verrucous Carcinoma:
  - Polypoid
  - Spires of well-differentiated squamous epithelium
  - Minimal cytologic atypia
  - Invasive border is blunt and pushing
  - Hyperkeratosis

Adenocarcinoma

Clinical

- M:F = 3–7:1
- Average age = 55–60 years

- More common in the Caucasian population (80% of patients)
- Represents 30–35% of all esophageal carcinomas (Second most common esophageal neoplasm)
- Increased incidence over the past decade
- Asymptomatic or symptoms of reflux
- Can arise in Barrett's metaplasia, esophageal glands, and heterotopic gastric mucosa
- Up to 40 fold risk in Barrett's population
- Poor prognosis (14.5% 5-year survival)

Macroscopic

- Most common (80%) in the lower third of the esophagus
- Size ranges from a few millimeters to 10 cm
- Varies from slight mucosal irregularities or plaques to large masses
- Typically flat and ulcerated (70%)
- May be polypoid and fungating (30%)

Microscopic

- Barrett's metaplasia may be present
- Most are well to moderately differentiated
- Infiltration with desmoplastic stromal response
- Nuclear hyperchromasia and pleomorphism
- Increased mitotic rate

Differential Diagnosis

- High-grade dysplasia:
  - Lack of invasion (no small, distorted glands in the lamina propria; no closely packed glands, fenestrations, or single cells or small clusters)

Adenosquamous Carcinoma

Clinical

- Rare
- Very aggressive
- Represents either squamous differentiation in adenocarcinoma or glandular metaplasia in squamous carcinoma

Differential Diagnosis

- Mucoepidermoid carcinoma:
  - Islands of squamous carcinoma with mucous-secreting cells rather than distinct elements

Small Cell Carcinoma

Clinical

- M:F = 2:1
- Average age = 50–60 years
- Presentation is usually at an advanced stage
- Risk factors include smoking and achalasia
- Symptoms include severe weight loss, dysphagia, and chest pain
- Poor prognosis with average survival <6 months

Macroscopic

- Most common in the distal half of the esophagus
- Size ranges from 4–14 cm
- Polypoid, fungating mass or stenotic lesion with ulceration

Microscopic

- Solid sheets, nests, or ribbons of cells
- Diffuse infiltration with a streaming pattern
- Rosettes containing mucin
- Cells are round-oval, hyperchromatic
- Scant cytoplasm
- Frequent mitotic figures
- Nuclear molding

Electron Microscopy

- Dense neurosecretory core granules

Immunohistochemistry

- Keratin and epithelial membrane antigen (EMA) +
- Neuron-specific enolase (NSE) and chromogranin +

Differential Diagnosis

- Poorly differentiated squamous cell carcinoma:
  - Neuroendocrine marker –
  - Dense core granules absent
  - Tonofilaments or desmosomes present
  - Intercellular bridges present

Neoplastic—Mesenchymal

Leiomyoma

Clinical

- M:F = 2:1
- Average age = 45–50 years
- Most common stromal tumor in the esophagus
- Most arise from the inner circular layer of the muscularis propria
- If large, patient becomes symptomatic (dysphagia, chest pain)
- Difficult to see endoscopically
- Radiography reveals a well-defined intramural mass

Macroscopic

- 90% in the lower and middle thirds
- Most are a few millimeters in size
- Most are sessile; few can be polypoid
- Generally single; may be multiple

- Well-circumscribed
- Pale pink-white
- Lobulated, with a whorled cut surface
- Firm

Microscopic

- Fascicles and whorls of mature smooth muscle cells
- Cells typically hypertrophic
- No/low mitotic rate
- Hyalinization is common
- No atypia
- No necrosis

Granular Cell Tumor

Clinical

- Second most common stromal tumor in the esophagus
- M > F
- African-Americans > Caucasians
- Average age = 40–50 years
- Usually asymptomatic
- Endoscopic features (sessile, yellow-white, firm, intact epithelium) can be strongly suggestive
- Prognosis generally good, although a few malignant cases have been reported (size >4 cm, increased pleomorphism, and mitotic activity)

Macroscopic

- Size <2 cm
- Most common site is the lower esophagus (60% of tumors)

Microscopic

- Superficial lesion
- Plump, spindled, or epithelioid cells
- Small, eccentric nuclei
- Abundant cytoplasm with coarse red granules
- Cells arranged in short fascicles or nests

Fibrovascular Polyp

Clinical

- M:F = 3:1
- Exhibits rapid growth
- Symptoms range from dysphagia to a fleshy mass
- Risk of fragmentation with subsequent asphyxiation
- Radiographic findings include a long, smooth, mobile, intraluminal mass
- Local excision is curative

Macroscopic

- 80% are located in the proximal third of the esophagus
- Pedunculated
- Long, slender shape
- Soft
- Tan-pink
- Rare mucosal ulcerations

Microscopic

- Fibrous connective tissue covered by hyperplastic squamous mucosa
- Stromal edema with myxoid change
- Numerous, dilated blood vessels
- Inflammatory infiltrate (lymphocytes, plasma cells, mast cells)
- Scattered lobules of adipose tissue

Neoplastic—Miscellaneous Tumors

Malignant Lymphoma/Plasmacytoma

Clinical

- Most involve the esophagus secondarily
- Rare primary cases
- Symptoms mimic those seen in carcinoma

Macroscopic

- Polypoid
- Proximal dilatation
- Ulcers, strictures, linear rugae

Microscopic

- Most are large cell or immunoblastic B-cell

Malignant Melanoma

Clinical

- Extremely rare (<0.5% of all primary esophageal tumors)
- M:F = 2:1
- Average age = 55–60 years
- Symptoms include dysphagia, pain, and weight loss
- Average 5-year survival is 2%

Macroscopic

- Variable size (up to 17 cm)
- Polypoid
- Ulcerated, pigmented mucosa

Microscopic

- Large, atypical melanocytes with clear cytoplasm
- Nucleus typically hyperchromatic and bizarre
- Melanin granules
- Pagetoid spread
- Epithelioid or spindled invasive component
- Prominent eosinophilic nuclei

Table 27-6. TNM Classification of Esophageal Tumors

T1	Tumor limited to mucosa/submucosa
T2	Tumor involving the muscularis propria
T3	Involvement of adventitia, no extra-esophageal structures
T4	Extension into extraesophageal structures (fat, tissue, heart, trachea, aorta, etc.)
N0	No nodal involvement
N1	Regional nodes involved
	Cervical esophagus: cervical, supra-clavicular lymph nodes
	Thoracic esophagus: mediastinal, paragastric lymph nodes
M0	No distant metastases
M1	Distant metastases, including distant lymph nodes

Table 27-7. Group Staging Criteria

Stage I	T1	N0	M0
Stage IIA	T2-3	N0	M0
Stage IIB	T1-2	N1	M0
Stage III	T3	N1	M0
	T4	any N	M0
Stage IV	any T	any N	M1

Electron Microscopy

- Melanosomes present

Immunohistochemistry

- S-100 protein and HMB45 +

Differential Diagnosis

- Carcinoma:
  - Epithelioid appearance
  - Signet ring cells possibly present
  - Keratin +
  - S-100 protein, LCA, and HMB45 –
- Lymphoma:
  - LCA +
  - Keratin, S-100 protein, and HMB45 –
- Sarcoma:
  - Spindled (desmoplastic) appearance
  - Keratin, LCA, and HMB45 –

Metastases

Clinical

- Most common are lung, breast, and melanoma
- Clinical information is crucial in order to rule out a primary lesion

Staging Esophageal Malignancies

- See Table 27-6 and 27-7

STOMACH

Non-Neoplastic—Anomalies

Hypertrophic Pyloric Stenosis

Clinical

- One of the most common congenital anomalies
- M > F
- Average age of onset is 3–12 weeks (rare in adults)
- Etiology unknown

Macroscopic

- Thickened pyloric muscle

Diverticula

Clinical

- Most common in the cardia
- Due to anatomic weakness

Heterotopic Pancreas

Clinical

- Discovered incidentally or presents as a mass
- Located in the antrum (60% of cases) or pylorus (25%)
- Most (85%) are in the submucosa

Macroscopic

- Hemispheric mass or symmetric cylindric projection
- Cut surface resembles normal pancreas
- Occasional cysts seen

Microscopic

- Typical pancreatic acini and ducts
- 33% with islets

Non-Neoplastic—Hyperplasias and Polyps

Hyperplastic Polyp

Clinical

- Accounts for 75% of gastric polyps
- Tends to occur in patients with hypochlorhydria, hypergastrinemia, or decreased pepsinogen I

Macroscopic

- Small
- Single or multiple (random distribution)
- Smooth to slightly lobulated

Microscopic

- Elongated, tortuous, dilated foveolae
- Deep fundic glands
- Edematous stroma with rare atypical reactive cells
- Patchy fibrosis
- Inflammatory infiltrate
- Scattered bundles of smooth muscle
- Minimal or no epithelial atypia

Fundic Gland Polyp (Fundic Gland Hyperplasia)

Macroscopic

- Small (2–3 mm)
- Polypoid

Microscopic

- Cysts lined by fundic epithelium
- Shortened foveolae

Polyposis Syndromes

- See Table 27-8

Inflammatory Fibroid Polyp

Clinical

- Associated with hypochlorhydria or achlorhydria
- Antral location
- Radiography reveals a sessile or pedunculated mass.
- Treatment is endoscopic excision

Macroscopic

- Elevated or sessile

Microscopic

- Whorl-like proliferation of vascular and fibroblastic elements
- Inflammatory infiltrate, especially eosinophils

Electron Microscopy

- Myofibrils identified

Immunohistochemistry

- Spindle component vimentin +, actin ±, histiocytic markers ±

Hyperplastic Gastropathy (Menetrier's Disease)

Clinical

- Associated with hypo- or achlorhydria and hypoproteinemia
- Typically adults (patients with chronic and severe disease)
- Rare in children (self-limited disease)
- Located along the greater curvature
- No antral involvement
- Radiographically similar to lymphoma and carcinoma

Macroscopic

- Hypertrophic rugae
- Abrupt transition from normal to diseased mucosa

Microscopic

- Tortuous, dilated, hyperplastic foveolae
- Reduced glandular component
- Inflamed, edematous stroma

Zollinger-Ellison Syndrome

Clinical

- Part of multiple endocrine neoplasia (MEN) complex
- Radiographically similar to hyperplastic gastropathy

Macroscopic

- Similar to hyperplastic gastropathy

Microscopic

- Glandular hyperplasia

Gastritis

Chronic

Clinical

- See Table 27-9

Microscopic

- See Tables 27-9 and 27-10

Differential Diagnosis

- See Table 27-9

Histochemistry

- Giemsa, Warthin-Starry, Steiner silver stains for *H. pylori*

Other Forms

- See Table 27-11

Table 27-8. Polyposis Syndromes

Syndrome	*Microscopic*	*Associated Tumor*
Gardners (familial colonic polyposis)	Adenomatous, hyperplastic or fundic gland polyps	Adenocarcinoma, carcinoid
Peutz-Jeghers	Hamartomatous polyp +/- adenomatous component	Adenocarcinoma
Cronkhite-Canada (generalized juvenile polyposis)	Gastric retention polyps	Adenocarcinoma
Cowdens (multiple hamartoma syndrome)	Small, sessile, hyperplastic polyps	

Table 27-9. Types of Chronic Gastritis

Type	*Chronic fundic gastritis (type A)*	*Chronic antral gastritis (type B)*	*Post gastrectomy gastritis*
Clinical	Older patient, megaloblastic anemia	Abdominal pain, vomiting, bleeding	Upper abdominal burning, pain, hemorrhage
Affected area	Fundus, corpus (late spread to antrum)	Antrum	Corpus (adjacent to the anastomotic site)
Etiology	Immunologic injury	Bacteria (H. pylori)	Reflux of bile salts
Associations	Thyroiditis, hypothyroid, diabetes, Sjögrens, myasthenia gravis	MALT type lymphoma (regression with Rx)	Localized gastritis, cystica profunda
Histology	Inflammation, foveolar hyperplasia	Ulcer, atrophy, intestinal metaplasia, H. pylori in surface mucus and lumina of pits	Edema, foveolar hyperplasia, minimal inflammation, atrophy (late)
Differential Dx	Carcinoma, lymphoma, hyperplastic gastropathy	Acute toxic gastritis, chronic peptic ulcer	Recurrent peptic ulcer

Gastric Ulcer

Acute

Clinical

- Usually associated with sepsis, injection (cytomegalo-virus [CMV], Candida, tuberculosis [TB], syphilis), surgery/ trauma, central nervous system (CNS) injury or disease (Cushing's disease), extensive burns (Curling's ulcer), use of drugs (aspirin, steroid), or after radiation therapy
- If superficial, involving mucosa only (erosion), can heal completely
- If deep, fibrosis replaces muscle and perforation may occur

Microscopic

- Marked epithelial atypia

Chronic

Clinical

- M > F
- Average age = 50 years
- Cardinal symptom is nocturnal epigastric pain
- Associated with achlorhydria
- 95% along the lesser curvature
- 95% accuracy with endoscopic and 70% accuracy with radiographic diagnosis
- Questionable risk of malignancy

Macroscopic

- 5% multiple
- Sharp delineation

Table 27-10. Stages of Chronic Gastritis

Stage	*Microscopic Description*
Chronic superficial gastritis	Inflammation limited to foveolae; no glandular atrophy; epithelial changes, including decreased cytoplasmic mucin, nuclear/nucleolar enlargement, and mitotic activity
Chronic atrophic gastritis*	Extensive inflammation; glandular atrophy (glands more widely spaced)
Gastric atrophy	Thin mucosa; no inflammatory changes; cystically dilated glands

** Note: risk of gastric carcinoma*

- Oval, round, or linear
- Overhanging proximal and sloping distal borders
- Fibrous replacement of muscle wall
- Subserosal fibrosis
- Reactive lymph node hyperplasia

Microscopic

- Four layers (purulent exudate, fibrinoid necrosis, granulation tissue, fibrosis)
- Thickened blood vessels
- Hypertrophied nerve bundles
- Intestinal metaplasia, with evidence of epithelial regeneration
- *Helicobacter pylori* may be seen

Differential Diagnosis

- Ulcerated carcinoma:
  - Invasion with desmoplastic response
  - Marked cytologic atypia

Neoplastic—Epithelial

Polyp

Clinical

- May undergo malignant transformation similar to colorectal counterpart
- Usually antral
- Three types:
  - Tubular adenoma
  - Tubulovillous adenoma
  - Villous adenoma

Macroscopic

- Sessile or pedunculated

Microscopic

- Hyperchromatic, crowded nuclei
- Nuclear pleomorphism
- Architectural atypia
- Increased mitotic rate

Adenocarcinoma

Clinical

- Average age >50 years
- Arises from the basal cells of the foveolae in a background of chronic atrophic gastritis with intestinal metaplasia
- Associated with hypochlorhydria in 85–90% of cases
- Factors implicated in the pathogenesis include *H. pylori,* gastric polyp, hyperplastic gastropathy, gastric ulcer, and Epstein-Barr virus
- Location variable
- Types:
  - Intestinal (53% of cases) arises from metaplastic epithelium
  - Diffuse (33%) (linitis plastica, signet ring carcinoma) arises from prepyloric region and results in a thick, rigid organ with pyloric obstruction
  - Mixed (14%)
- Symptoms include anemia, weight loss, and dyspepsia
- Diagnosis is based on radiography, endoscopic biopsy
- Local extension to duodenum, esophagus, omentum, colon, pancreas, and spleen
- Metastases to lymph nodes, liver, peritoneum, lung, adrenal gland, ovary (Krukenberg tumor), uterus, cervix
- Poor prognosis (overall survival rate is 4–13%)
- Unfavorable prognostic factors include young age, proximal location, deep invasion, diffuse infiltration, large size, lack of inflammatory reaction, perineural invasion, + surgical margins, increased number of + lymph nodes, and overexpression of c-erbB-2 protein and/or p53

Macroscopic

- Multiple in 5% of cases
- Varies from fungating and exophytic to flat, ulcerated and deeply invasive
- Fleshy, fibrous, or gelatinous (depending on amount of mucin present, extent of desmoplastic response) in intestinal type
- Submucosal fibrosis, mucosal ulceration, muscular hypertrophy, and subserosal thickening in diffuse type

Table 27-11. Miscellaneous Types of Gastritis

Type	*Etiology*	*Histology*
Acute	Alcohol, aspirin, bile reflux	Fresh hemorrhage, hyperemia, necrosis, neutrophils
Hemorrhagic	Alcohol, aspirin, stress, portal hypertension	Chronic changes, with hemorrhage in lamina propria
Allergic	Allergen	Eosinophils in lamina propria
Diffuse eosinophilic	Allergen, collagen vascular disease	Eosinophilia, edema, necrotizing angiitis
Granulomatous	TB, mycosis, sarcoidosis, Crohns	Caseating or noncaseating granulomas
Infectious	CMV, Norwalk, Cryptococcus, syphilis	Nonspecific

Microscopic

- Glandular to solid growth of columnar, mucous-secreting cells (intestinal type)
- Growth of individual signet ring cells, marked desmoplasia, and inflammation (diffuse type)
- May have prominent tubular or papillary growth
- May have abundant mucin, resulting in mucous lakes with fragments of glands

Cytochemistry

- Mucicarmine and PAS +
- PASD +

Immunohistochemistry

- CEA and Keratin +

Precursor/Related Lesions

- Dysplasia:
  - Must be distinguished from simple or atypical regenerative hyperplasia
  - Increased nuclear to cytoplasmic ratio
  - Nuclear pseudostratification
  - Reduced or absent mucous secretion
  - Frequent mitotic figures
  - Cellular crowding
  - Glandular complexity
  - Depending on severity, divided into mild, moderate, or severe
- CIS:
  - Equivalent to high-grade dysplasia
  - Intact basement membrane
- Intramucosal carcinoma:
  - Basement membrane not intact
  - Dysplastic glands/cells within the lamina propria but confined to the submucosa (no extension beyond the muscularis externa)
  - Also referred to as superficial spreading or microinvasive carcinoma

Differential Diagnosis

- Degenerative changes and granulation tissue in an ulcer or erosion:
  - Maturation toward the surface
  - Regular arrangement of glands
  - Decreased mucin
  - Low columnar cells
  - Vesicular nuclei
  - Small, regular nucleoli
- Lymphoma:
  - No mucin production
  - Leukocyte common antigen +
  - Keratin –, CEA –
- Metastatic carcinoma (breast, lung, melanoma):
  - Multicentric
  - Lack of metaplastic or dysplastic mucosal change
  - Serosal location
  - Marked desmoplastic response
  - Melanoma S-100 protein and HMB45 +
- Carcinoid:
  - Dense core granules present by electron microscopy (EM)
- Granular cell tumors:
  - Submucosal location
  - May be multiple
  - Small benign-appearing nuclei
  - No mitotic figures

  - Granular eosinophilic cytoplasm
  - Mucin –, Cytokeratin –
  - S-100 protein +
- Reactive changes (erosion, ulceration):
  - Granulation tissue present
  - Less frequent mitotic figures
  - Inflammatory background

Variants

- Medullary carcinoma (lymphoepithelioma-like carcinoma):
  - Undifferentiated carcinoma with lymphoid stroma
  - Gray-white, glistening, grossly like lymphoma
  - Widely separated nests of tumor cells (trabeculae, alveoli, tubules)
  - Dense infiltrate of lymphocytes, plasma cells, neutrophils, and eosinophils
  - Lymphoid follicles
  - Small, polygonal cells
  - Clear to eosinophilic cytoplasm
  - Vesicular nuclei
  - Small nucleoli
  - Scant mitotic figures
  - Most are EBV +
- Parietal cell carcinoma:
  - Solid sheets of polygonal cells resembling lymphoma
  - Abundant eosinophilic cytoplasm
  - Abundant mitochondria, tubulovesicles, and intracellular canaliculi by EM
- Hepatoid adenocarcinoma:
  - Mixture of adenocarcinoma and mature, neoplastic hepatocytes
  - Bile production
  - Vascular invasion
  - Abundant cytoplasmic glycogen and hyaline globules
  - Alpha-fetoprotein, alpha-1-antitrypsin, and albumin +
- Mucinous carcinoma:
  - Fragments of glands
  - Abundant extracellular mucin
- Adenosquamous carcinoma:
  - Extensive squamous differentiation
  - Variable amount of glandular component
- Adenocarcinoma with neuroendocrine features:
  - Includes adenocarcinoma admixed with carcinoid tumor, atypical carcinoid, neuroendocrine carcinoma, and small cell carcinoma

Neoplastic—Mesenchymal

Gastrointestinal Stromal Tumor (GIST)

Clinical

- Adults in 5th to 7th decade
- Rare cases in children (generally malignant)
- Symptoms include abdominal pain and melena
- Associated with HIV (EBV+), von Recklinghausen's disease, and Carney's syndrome (a genetically determined complex consisting of cardiac, eyelid, and cutaneous myxomas; cutaneous and labial lentiginosis; myxoid mammary fibroadenomas; adrenocortical nodular dysplasia associated with Cushing's syndrome; and large cell calcifying Sertoli cell tumor of the testis)
- Most common site is the fundus
- Metastases, when they occur, are to the liver, peritoneum, and lungs
- Unfavorable prognostic factors include large size, invasion, and high microscopic grade
- Submucosal (60% of cases), subserosal (30%), and intramural (10%) location
- Malignancy associated with large tumor size, high mitotic rate, and increased cellularity
- Poor prognosis possibly associated with infiltrative margins, necrosis, nuclear DNA content, and cell proliferation

Macroscopic

- Firm
- Central ulceration
- Circumscribed
- Smooth, lobulated, flat cut surface with foci of hemorrhage and necrosis

Microscopic

- Variable, including smooth muscle differentiation, including epithelioid, neural differentiation, smooth muscle and neural differentiation (rare), and undifferentiated (rare)

Immunohistochemistry

- Depending on differentiation, can be desmin, actin, NSE, S-100 protein, PGP 9.5, and CD34 +

Electron Microscopy

- Depending on differentiation, can exhibit structures resembling axons, neurotubules, and neurosecretory granules

Leiomyoma

Clinical

- Most common in the cardia
- Most are small and asymptomatic

Macroscopic

- Well-circumscribed, non-encapsulated, and firm
- Whorled, bulging cut surface

Microscopic

- Mature, hypertrophic smooth muscle cells
- Whorled, fascicular arrangement

Lymphoid Neoplasms (see Chapter 7)

Low-Grade Lymphoma

Clinical

- Average age >50 years
- Insidious onset
- Symptoms simulate gastritis or peptic ulcer
- Located in the antrum
- Frequently multicentric

Macroscopic

- Fish-flesh appearance

Microscopic

- Variable, depending on type:
  - MALT:
    - Monomorphic population of small, centrocyte-like cells
    - Lymphoepithelial lesions
    - Large follicles with reactive germinal centers
    - Dutcher bodies
    - Invasion
  - Follicular:
    - Monomorphic population of small, cleaved cells
    - Follicular growth pattern
    - Invasion

Differential Diagnosis

- Pseudolymphoma:
  - Ulceration and erosion present
  - Extensive fibrosis
  - Reactive germinal centers
  - Blood vessel proliferation
  - Absence of lymphoepithelial lesions, cytologic atypia, Dutcher bodies, and invasion
  - Mixed population of lymphoid cells
  - Polyclonality demonstrated by flow cytometry and immunohistochemistry
- Plasma Cell Granuloma:
  - Mature plasma cells
  - Mixed population of inflammatory cells
  - Fibrosis
  - Polyclonality demonstrated by immunohisto-chemistry

High-Grade Lymphoma

Clinical

- Average age >50 years
- Can present with large palpable mass or patient may be asymptomatic
- Antral location
- 5-year survival rate = 60%
- Most important prognostic factor is stage
- Favorable prognostic factors include small tumor size, superficial invasion, and negative lymph nodes

Macroscopic

- Lobulated or polypoid
- Ulceration, superficial or deep
- Fish-flesh appearance

Microscopic

- Monomorphic population of large, noncleaved cells
- Vesicular nucleus ± prominent nucleoli
- Increased mitotic rate
- Invasion

Differential Diagnosis

- Undifferentiated carcinoma:
  - Continuous with epithelium
  - Acinar, syncytial, confluent, cohesive growth
  - Disrupted muscularis mucosa
  - Mucin
  - Keratin and CEA +
  - LCA –

Neoplastic—Miscellaneous Tumors

Carcinoid

Macroscopic

- Small, sharply circumscribed, flattened mucosa

Microscopic

- Microglandular, trabecular, insular growth
- Regular, normochromatic nuclei
- Few mitotic figures
- Proliferation of blood vessels
- No necrosis

Cytochemistry

- Focally mucin +

Immunohistochemistry

- NSE, chromogranin, and keratin +

Electron Microscopy

- Dense core secretory granules present

Table 27-12. TNM Classification of Gastric Tumors

Tis	Limited to mucosa, no penetration through basement membrane
T1	Limited to mucosa or submucosa
T2	To or into but not through serosa (subserosa)
T3	Through serosa without invasion of adjacent tissue
T4a	Involvement of immediately adjacent structures
T4b	Direct extension to liver, diaphragm, pancreas, abdominal wall, adrenals, kidney, retroperitoneum, small bowel, or extraluminal extension to esophagus or duodenum
N0	No nodal involvement
N1	Perigastric nodes along both curvatures, within 3 cm of tumor
N2	Other regional nodes involved, resectable
N3	Other intraabdominal nodes involved
M0	No distant metastases
M1	Distant metastases

Subtypes

- Enterochromaffin-like neoplasm:
  - More common
  - Multiple
  - Polypoid

Table 27-13. Group Staging Criteria

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2-3	N0	M0
Stage III	T1-3	N1-2	M0
	T4a	N0-2	M0
Stage IV	T1-4a	N3	M0
	T4b	Any N	M0
	Any T	Any N	M1

  - Fundic location
  - Accompanied by smooth muscle proliferation
  - Associated with atrophic gastritis with intestinal metaplasia and Zollinger-Ellison syndrome
- G-cell neoplasm:
  - Solitary
  - Antral location
  - Gastrin +

Glomus Tumor

Microscopic

- Clear epithelioid cells
- Dilated blood vessels

Electron Microscopy

- Abundant myofilaments

Staging Gastric Malignancies

- See Table 27-12 and 27-13

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Chapter 28

Small Intestine, Appendix, and Colon

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Table of Contents

INFLAMMATORY AND MALABSORPTIVE DISORDER

Specific Inflammatory Disease

Infectious Enteritis

Clinical

- Viral > bacterial > parasitic
- Acute onset of diarrhea, usually resolves within days
- Some patients may develop a chronic malabsorptive syndrome specific to one or various test substances
- In children, transient intolerance to cow's milk or gluten; disaccharidase deficiency may occur

Macroscopic

- Normal to mildly erythematous mucosa

Microscopic

- Intraepithelial lymphocytic infiltrate
- Mild villous blunting
- Focal active inflammation may occur

Acute Infectious Enterocolitis

Clinical

- Acute onset of abdominal pain, diarrhea, and bloody diarrhea
- Symptoms are short-lived or self-limited
- Stool culture often –
- Common pathogens: *Campylobacter, Salmonella, Shigella, Yersinia,* and *E. coli*

Macroscopic

- Patchy, extremely variable mucosal erythema, inflammation, and erosion

Microscopic

- Extremely variable
- Mild mucosal edema, congestion, and nonspecific chronic inflammation
- Neutrophilic infiltrate of superficial lamina propia (LP) and crypt
- No chronic mucosal architectural damage

Specific Bacterial Infection

Vibrios

- Unremarkable histology
- Increased mononuclear cell in LP of small intestine
- Irregular widening of intercellular spaces and junctional complexes on electron microscopy

Shigellosis

- Almost always involves rectosigmoid with variable proximal extension
- Small percentage involves cecum and the terminal ileum
- Indistinguishable from other enteric infections
- Purulent LP in severe disease, with cryptitis, crypt abscess, and pseudomembrane
- May resolve to an atrophic mucosa, mimicking inactive ulcerative colitis

Salmonellosis

- The most common foodborne pathogens causing outbreaks
- Many serotypes
- Erythematous, friable mucosa, preferentially in proximal colon
- Rectum also frequently involved
- Indistinguishable from other enteric infections

Campylobacter Enterocolitis

- Numerous species
- Fecal-oral transmission in contaminated water, or sexually transmitted
- Rectal involvement with variable proximal extension, mimicking ulcerative colitis endoscopically
- Some patients may have focal and segmental diseases mimicking Crohn's disease
- Frequent aphthoid ulcer
- Indistinguishable from other enteric infections

Yersiniosis

- Two species:
  - *Y. pseudotuberculosis* and *Y. enterocolitica*
- Cause acute terminal ileitis
- Markedly thickened terminal ileum with enlarged mesenteric lymph nodes
- Necrotizing granulomas with central necrosis, neutrophilic infiltrate, and peripheral palisading histiocytes in the background of dense lymphocytic infiltration

Pseudomembranous Colitis

- Most common in hospitals and nursing homes
- *C. difficile* in 15–20%, occasionally others (verotoxin-producing *E. coli*); unknown cause in most of the remaining cases
- Cramping, abdominal pain, profuse diarrhea, and fever a few days or up to 8 weeks after use of antibiotics
- Affects entire colon, but most severe in the distal colorectum
- Pinpoint or plaque-like smooth, shiny lesions in milder cases
- Diffuse pseudomembrane in severe cases

- Mushroom or volcano-like exudate of neutrophils and mucin from superficial crypt lumen with intact basal crypt
- Diffuse lamina propria neutrophilic infiltration

Enterohemorrhagic E. coli (O157:H7)

- 2.5% of all acute diarrhea, but 15–36% of all acute bloody diarrhea
- Food (hamburger) outbreaks
- Diffuse friable mucosa with patchy hemorrhagic erosion
- Similar to other infectious colitis with features mimicking acute ischemia

Whipple's Disease

Clinical

- Rare, systemic infectious disease
- Caused by *Tropheryma whippelli*
- M > F
- Fever, weight loss, arthritis, diarrhea, and central nervous system (CNS) symptoms

Macroscopic

- Primarily involves the jejunum
- Edematous and thickened intestinal wall with enlarged mesenteric lymph nodes
- Club-shaped villi show white-yellow appearance

Microscopic

- Marked villous blunting
- Foamy macrophages in LP
- Rod-like intracellular organisms strongly + on periodic acid-Schiff (PAS) with diastase stain
- Polymerase chain reaction (PCR) specifically identifies the bacterial genome

Celiac Disease

Clinical

- Incidence of 0.05–0.5% of general population, but may be severely underestimated
- Strong family clustering: 10% prevalence among 1st degree relatives, 30% in human leukocyte antigens (HLA) identical siblings, and 70% in identical twins
- Intestinal epithelial injury caused by dietary wheat gluten (and particularly, its alcohol-soluble fraction, gliadin)
- Variable presentation from minor nutritional deficiencies to more severe steatorrhea, malnutrition, and weight loss
- Bimodal peaks: first 3 years of life and 3rd to 5th decades
- Symptoms appear during the first 3 years of life and persist throughout childhood if left untreated
- Often diminish during adolescence, only to reappear in early adult life
- Circulating antigliadin and antiendomysial antibodies + in > 90% of the untreated patients
- Increased incidence of malignancy (small bowel T cell lymphoma, adenocarcinoma)

Macroscopic

- Most severe in the duodenum and the proximal jejunum
- Ileum is usually spared or minimally affected
- Loss of valvulae resulting in a smooth, tubular appearance of the small intestine
- Scalloped, ridged appearance of mucosa on a close-up view

Microscopic

- Flat duodenal mucosa (villous blunting)
- Numerous surface intraepithelial and intracrypt epithelial T lymphocytes
- Cuboidal or flattened surface epithelium with loss of goblet cells
- Markedly increased epithelial mitosis
- Dense lymphoplasmacytic infiltrate in LP
- In subclinical sprue, partial villous blunting and mild, patchy changes, as mentioned above
- Mucosal architecture restores quickly following a gluten-free diet along with a dramatic improvement of clinical symptoms

Differential Diagnosis

Latent Celiac Sprue

- Usually asymptomatic or carries the diagnosis of dermatitis herpetiformis
- May manifest following an intestinal viral infection or high-gluten diet
- Mild villous blunting of the duodenal mucosa with increased intraepithelial lymphocytes

Refractory Celiac Sprue

- Uncommon, may be *de novo* or initially responsive to a gluten-free diet
- Relapse while on gluten-free diet; only responsive to corticosteroids
- Persistent flat mucosal lesion
- Relentless and progressive malabsorption
- Often culminates in death

Collagenous Sprue

- Rare complication with gloomy prognosis
- Typical flat mucosal lesion with a striking broad band of subepithelial collagen layer

Tropical Sprue Syndrome

- A malabsorptive syndrome associated with small bowel abnormalities
- Occurs in tropical regions in the world
- Unclear pathogenesis, environmental factors? (especially intestinal microbial flora and enterotoxin production)
- Flat mucosal lesion throughout the small intestine
- Responsive to antibiotics, not to a gluten-free diet

Ulcerative Jejunoileitis

- A rare condition in the 6th or 7th decades of life with a poor prognosis
- With or without a history of celiac sprue
- Pathogenesis is unknown; may be associated with intestinal T cell lymphoma, which typically forms the base of the ulceration
- Multiple mucosal ulcers in the jejunoileum
- Flattened intervening mucosa in celiac sprue; of normal height in nonceliac associated lesions
- Patients do not respond to a gluten-free diet

Idiopathic Inflammatory Bowel Disease

Ulcerative Colitis

Clinical

- Incidence of 3.8–13/100,000; F slightly > M; Jews > Caucasians > African Americans
- Most common in 20–50 years of life, with second peak at age 70
- Causes unknown
- 10–20% affected 1st degree relatives

Macroscopic

- Involves the rectum with variable proximal spread in a continuous fashion
- No intervening areas of uninvolved mucosa
- The terminal ileum can be involved in 10–20% of the ulcerative pan-colitis cases
- In active phase:
  - Mucosa appears hyperemic and granular, with inconspicuous or multiple punctate ulcers
  - When severe, the ulcers have "tram-line" like appearance
  - Nonulcerated mucosa often appears polypoid
- In fulminant phase:
  - Toxic megacolon may occur, where the bowel is markedly dilated and thin-walled with diffuse congested and grossly ulcerated mucosa
  - Perforation may also occur
- In quiescent phase:
  - Featureless atrophic mucosa
  - Shortened colon with decreased caliber and thickening of the muscularis propria

Microscopic

- Inflammation exclusively confined to the mucosa in the nonulcerated area
- In active phase:
  - Diffuse cryptitis, crypt abscess, and dense basal lymphoplasmacytic infiltration
  - Marked crypt distortion
  - Paneth cell metaplasia frequent
- In fulminant phase:
  - Indistinguishable from other causes of fulminant colitis, such as ischemic colitis, severe infectious colitis, or Crohn's disease
- In inactive phase:
  - Lack of cryptitis and crypt abscess
  - Marked mucosal architectural abnormalities with crypt distortion; basal lymphoplasmacytosis
  - Paneth cell metaplasia
  - Mucosal atrophy
- Multinucleated giant cells can be seen due to histiocytic response to the ruptured crypts; true noncaseating epithelioid granulomas are not seen

Differential Diagnosis

Crohn's Disease

- Involvement of terminal ileum
- Skip lesions
- Focally intense cryptitis
- Aphthoid lesions
- Epithelioid granulomas

Infectious (Bacterial) Colitis

- Superficial neutrophilic infiltrate
- Preservation of mucosal architecture
- No basal lymphoplasmacytosis

Collagenous Colitis

- Intraepithelial lymphocytosis
- Subepithelial collagen table thickening
- Cuboidal or flat surface epithelium
- Lack of mucosal architectural distortion

Lymphocytic Colitis

- Intraepithelial lymphocytosis
- Cuboidal or flat surface epithelium
- Lack of mucosal architectural distortion

Ischemic Colitis

- Mucosal collapse
- LP neutrophilic infiltrate
- Microcrypts
- Intramucosal hyalinization (fibrosis)

Drug-Induced Colitis and Proctitis

- Lack of active inflammation
- No mucosal architectural distortion
- May have increased epithelial apoptosis
- May also mimic ischemic injury
- Seen with non-steroidal antiinflammatory drugs (NSAID), penicillamine, sulfasalazine, and methyldopa
- Drug history required for the evaluation

Associated Conditions

Ulcerative Colitis-Associated Epithelial Dysplasia

- Incident increases over the duration of the disease
- Risk is highest with ulcerative pan-colitis
- May occur anywhere in the colon as patchy flat or slightly raised mucosal lesions
- Only detected by multiple mucosal biopsies
- Histologically similar to those of colonic adenomas
- Can be very focal and often inconspicuous
- Divided into indefinite, low- and high-grade dysplasia based on both architectural and cytological abnormalities
- If left untreated, most low-grade dysplasia will progress to high-grade dysplasia and invasive adenocarcinoma

Colonic Cancer

- Annual increment of 0.8–1% in risk after 15–20 years of disease
- Preceded by epithelial dysplasia

Crohn's Disease

Clinical

- Incidence of 3–8/100,000, and is increasing
- M:F = 1:1, 1/3 present before age of 20, 1/5 present after age of 50
- Etiology unknown, but strong genetic predisposition; 17–35 times of risk in siblings of patients
- Chronic or nocturnal diarrhea
- Intermittent right lower-quadrant intra-abdominal pain
- Anorexia, weight loss, and fever
- Recurrent oral aphthous ulcerations, perianal fissures, fistulae, or abscesses
- Extra-intestinal manifestations affecting the skin, eyes, and joints
- Complications include small bowel obstruction, malabsorption, salpingitis, fistulae, and perianal abscess formation

Macroscopic

- Inflammation anywhere from mouth to anus
- Most with lesions of small and large intestines:
  - Small intestine only (30–40%)
  - Both small and large intestines (40–50%)
  - Colorectum alone (15–25%)
  - Terminal ileum (90%)
- Colonoscopy:
  - Mucosal cobblestoning, aphthoid or longitudinal ulcers, and strictures
  - Normal intervening mucosa (skip lesions)
- Resected specimen:
  - Markedly thickened bowel wall with luminal narrowing
  - Mucosal cobblestoning, pseudopolyps
  - Fat rapping of the serosal surface
  - Fissures, fistulae, and mesenteric abscesses may also be seen

Microscopic

- Transmural inflammation with multiple lymphoid aggregates
- Noncaseating epithelioid granulomas (in 25–50%)
- Aphthoid and fissuring ulcers
- Focally intense cryptitis, crypt abscess
- Skipped, normal intervening mucosa
- Focal, mild crypt distortion and basal lymphoplasmacytic infiltrates
- Paneth cell metaplasia ±
- Neural hyperplasia, submucosal fibrosis, and hypertrophy of the muscularis mucosae

Differential Diagnosis

Gastrointestinal Tuberculosis (TB)

- Very rare
- Central caseous necrosis
- Travel to or residential history in areas where abdominal TB is common
- A history of contact with TB

Yersinia enterocolitica

- Necrotizing granulomas within the lymphoid follicle of the bowel wall and mesenteric lymph nodes
- Positive *Yersinia* serology with rising antibody titer

Ulcerative Colitis

- See above

Ischemic Enterocolitis

- No epithelioid granulomas
- Usually lacks transmural lymphoid aggregates, neural hyperplasia, or fissuring ulcer
- May be difficult to distinguish a low-grade ischemic colitis in elderly patients from Crohn's; subsequent clinical course may provide better differentiation

Infectious Colitis

- Most common cause of aphthous ulcers of the small and large intestine
- Diffuse superficial neutrophilic infiltrates
- Lacks significant chronic inflammation
- Absence of crypt distortion or basal lymphoplasmacytosis
- No epithelioid granulomas

Diverticular-Disease-Associated Segmental Colitis

- Commonly seen in sigmoid colon
- Diverticula per colonoscopy
- Histologic changes may be very similar to those of Crohn's
- Foreign body type granulomas

Solitary Rectal Ulcer Syndrome/Mucosal Prolapse Change

- Usually seen in the rectum and distal sigmoid
- Polypoid, nodular, or mass-like lesion
- Intramucosal smooth muscle proliferation on histology
- Normal adjacent flat mucosa and proximal colon

Associated Conditions

Crohn's Colitis-Associated Epithelial Dysplasia

- Similar to ulcerative colitis-associated epithelial dysplasia at slightly lower incidence

Malignancy in Crohn's Disease

- Approximately 0.45% of prevalence of malignancy in both small and large intestine
- Most tumors appear to develop in the colon
- Adenocarcinoma is most common type
- Metachronous or synchronous tumors may occur
- May be preceded by detectable epithelial dysplasia

Microscopic Colitis

Lymphocytic Colitis

Clinical

- Affects all ages, M = F
- Unknown etiology
- May be associated with celiac disease
- Prolonged watery diarrhea
- Associated with autoimmune diseases (celiac sprue, arthritis, and thyroiditis)

Macroscopic

- Normal colonoscopic and radiographic examinations of the colorectum

Microscopic

- A marked increase of lymphocytes in the surface and crypt epithelium
- Absence of a thickened subepithelial collagen layer
- Cuboidal and flattened surface epithelium
- Variably increased chronic inflammation in the LP
- No crypt distortion
- Acute cryptitis may be seen

Collagenous Colitis

Clinical

- Affects middle-aged and older women, F:M = 10:1
- Unknown causes
- Protracted watery diarrhea without systemic symptoms

Macroscopic

- Like lymphocytic colitis; normal colonoscopic and radiographic examinations of the colorectum

Microscopic

- Thickened subepithelial collagen layer (usually >10 μm, Normal: 2–3 μm); best viewed by Masson trichrome stain
- More prominent in the proximal colon
- Increased intraepithelial lymphocytes
- Surface epithelial damage
- May have active inflammation

Diversion Colitis

Clinical

- In 90–100% of patients with a history of colostomy or ileostomy for various reasons, including inflammatory bowel disease (IBD)
- Related to the depletion of luminal short-chain-free fatty acids and luminal bacterial stasis
- The inflammation usually persists as long as the mucosa is bypassed

Macroscopic

- Mucosa erythema, friability, edema, and granularity, mimicking ulcerative colitis
- More severe in rectum than in the proximal colon

Microscopic

- Mild to moderate chronic inflammation with mild architectural change

- Cryptitis, crypt abscess, and erosion may be seen
- Prominent mucosal lymphoid hyperplasia
- Occasionally, granulomas
- Mucosal atrophy may be seen

Solitary Rectal Ulcer Syndrome (SRUS)

Clinical

- Affects all age groups, but more common in the young
- Constipation, excessive straining, rectal pain, and mucus discharge

Macroscopic

- Anterior and anterolateral rectum
- Indurated, polypoid lesion, solitary or multiple
- Surface ulceration

Microscopic

- Thickened muscularis mucosae with intramucosal smooth muscle proliferation between the crypts
- Variable acute and chronic inflammation of the LP
- Surface erosion and inflammatory exudate
- Submucosa entrapment of crypts filled with mucin (*colitis cystica profunda*)

Differential Diagnosis

Crohn's Disease

- See above
- Clinical history
- Abnormal proximal colonic biopsies

Malignancy-Induced SRUS/Mucosal Prolapse

- SRUS-like changes in the mucosa overlying a malignant infiltrate located in the submucosa or muscularis propria due to primary tumor or metastasis
- Atypical cells may or may not be seen in the biopsy
- Immunohistochemistry may be required to identify the tumor cells
- Perirectal mass or rectal wall thickening on computed tomography

Radiation Proctitis/Colitis

- See below

Radiation Proctitis/Colitis

Clinical

- History of radiation to pelvic or intraabdominal malignancies
- Most common in rectosigmoid
- Symptoms appear early during therapy or shortly or months to many years after therapy
- Acute phase:
  - Diarrhea, tenesmus, mucoid rectal discharge, and rectal bleeding
- Chronic phase/complications:
  - 10% of the cases
  - Tenesmus, mucoid rectal discharge, which may be bloody
  - Persistent decrease in stool caliber and constipation

Macroscopic

- Focal, limited to the immediate field of irradiation
- Variably dusky and edematous mucosa with a blurred vascular pattern
- Mucosal red friability and ulceration in high dose of radiation
- Multiple mucosal telangiectasis and luminal narrowing with fibrosis

Microscopic

- Acute changes:
  - Last for 1–2 months
  - Edematous lamina propria with fibrinoid vascular necrosis
  - Reactive endothelial and epithelial cells
  - Excess of apoptosis in the basal crypts
  - Neutrophilic infiltration of the LP and crypts
- Late changes:
  - Mucosal atrophy with reduction of crypt epithelium
  - Crypt distortion, Paneth cell metaplasia, fibrosis, and smooth muscle proliferation
  - Intramucosal, dilated telangiectatic blood vessels approaching the luminal surface

Diverticular Disease

Clinical

- Uncommon before age 40; approaching 50% by the 9th decade of life
- Sigmoid most common in the United States; right-sided lesion more common in Asia
- The pathogenesis is multifactorial, including an increase in intraluminal pressure, colonic wall aging and motor dysfunction, and lack of dietary fiber
- Majority are asymptomatic
- Presents with bloating, excessive flatulence, and intermittent abdominal pain
- Fever is associated with inflamed diverticulitis

Macroscopic

- Two rows on either side of the colon between mesenteric and antimesenteric teniae
- <1 cm, lie within the pericolic fat, and especially the appendices epiploicae
- Markedly thickened colon wall

- ♦ Prominent mucosal ridges and intervening saccular dilatations
- ♦ Pericolic abscess formation is common

Microscopic

- ♦ Diverticula are lined by mucosa and submucosa and covered by pericolic connective tissue and serosa
- ♦ Hypertrophied muscularis propria at the neck of diverticula
- ♦ In diverticulitis:
  - – Neutrophilic infiltration of the crypts, LP, and surrounding pericolic fat
  - – Prominent chronic inflammation and fibrosis
  - – Foreign body giant cells

VASCULAR LESIONS

Acute Intestinal Ischemia

Clinical

Occlusive Causes

- ♦ Arterial thrombosis and embolism:
  - – Most common cause of acute small intestinal ischemia
  - – Frequently superimposed on severe superior mesenteric artery (SMA) atherosclerosis
  - – Sources of emboli include ischemic heart disease, spontaneous or procedure-related cholesterol emboli, and iatrogenic embolization by "Gelfoam"
- ♦ Atherosclerosis:
  - – Most common mesenteric vascular disease, but rarely the cause of acute ischemia by itself
  - – Usual cause of chronic ischemia
- ♦ Arteritis:
  - – Usually as part of a systemic disorder
  - – Examples include polyarteris nodosa (PAN), rheumatoid arteritis, systemic lupus erythematosus (SLE), and Takayashu's disease
- ♦ Small vessel disease:
  - – Henoch-Schonlein purpura, leukocytoclastic vasculitis, and disseminated intravascular coagulation (DIC)
- ♦ Mesenteric venous thrombosis:
  - – Rare, less than 10% of the causes
  - – Associated with portal hypertension, hypercoagulable state, abdominal surgery or trauma, and intra-abdominal sepsis
- ♦ Mechanical obstruction:
  - – Volvulus, strangulation, and intussusception
- ♦ Others:
  - – Dissecting aneurysm involving SMA
  - – Arteriopathies with intimal hypertrophy in systemic hypertension
  - – Irradiation injury or fibro-elastosis adjacent to carcinoid tumors

Nonocclusive Causes

- ♦ Account for 25–50% of all cases
- ♦ A consequence of vasoconstriction in response to decreased cardiac output, hypotension, hypovolemia, dehydration, or drugs (digitalis, cocaine), frequently with underlying arterial atherosclerosis

Macroscopic and Microscopic (Acute Intestinal Ischemia)

- ♦ See Table 28-1

Chronic Ischemic Injury

Clinical

- ♦ A consequence of acute mural infarct or chronic mesenteric insufficiency
- ♦ SMA atherosclerotic narrowing is the most common cause.
- ♦ Others include aortic aneurysm and congenital anomalies of SMA
- ♦ Usually manifests as abdominal pain
- ♦ Poor correlation with angiographic studies

Macroscopic

- ♦ Segmental chronic ulcers with excessive fibrosis and stricture

Microscopic

- ♦ Ulcer bed with inflamed granulation tissue, excessive fibrosis, hemosiderin-laden macrophages, and fibrous replacement of the muscle layers
- ♦ Regenerative epithelial hyperplasia at the margins
- ♦ Chronic inflammation at the periphery of the ulcer
- ♦ Mucosa away from the ulcers is usually normal

Differential Diagnosis

Crohn's Disease

- ♦ Mucosal inflammation away from the ulcer
- ♦ Dense, aggregated inflammation extends to the serosa
- ♦ Presence of granulomas

Drug-Induced Ulcers

Table 28-1. Acute Ischemic Injury of the GI Tract

Stage of injury	*Gross*	*Histology*	*Prognosis*
Mucosal necrosis	Mucosal congestion and erythema	Disintegration of surface and crypt epithelium	Usually reversible
	Small shallow ulcers	Interstitial hemorrhage, edema, and neutrophilic infiltrate	
		Mucosal outline usually preserved	
Mural necrosis	Marked mucosal congestion, hemorrhage, and ulcers	Mucosal and submucosal necrosis and hemorrhage	Progress to transmural necrosis
	Serosal congestion	Eosinophilic necrosis of the inner smooth muscle layer	May heal with interruption of muscularis and
		Neutrophilic infiltrate	submucosal scar, which may lead to stricture
Transmural necrosis	Gangrenous, flaccid, dilated, and serosal fibrinous exudate	Smooth muscle necrosis with marked edema and neutrophilic infiltrate	Perforation
	May have perforation	Marked congestion involving subserosa	Surgery is always indicated; if massive, may not survive

- Morphologically very similar
- History of medication
- Lack of hypotensive and vascular diseases

Special Forms

Ischemic Colitis

- More common in 6th and 7th decades
- Torsion or hernia strangulation are uncommon causes due to the location of the large intestine being primarily retroperitoneal
- More prone to primary vascular causes of ischemia
- Inferior mesenteric artery (IMA) is less prone to embolization than the SMA
- Acute fulminant disease with progression to transmural necrosis is rare
- Complete resolution of symptoms within 4 weeks in 50% of patients; 5–12% recurrence rate
- Splenic flexure (watershed area) is the most common site of ischemia
- Chronic ischemia may lead to progressive stenosis and obstruction

Small Intestinal Ischemia

- SMA embolism is the most common cause (40–50%), followed by nonocclusive mesenteric ischemia and SMA thrombosis (5–10%)
- Most common in elderly with underlying cardiovascular disease
- Frequently presents with an acute onset of abdominal pain
- Small intestine is prone to torsion or hernia strangulation, which may also lead to segmental ischemia

Angiodysplasia

Clinical

- Vast majority occurs in the right colon, occasionally in the small intestine
- Presents with chronic intestinal bleed, anemia, and weight loss
- Three types:
  - Type I: most common, >55 years of age, usually in the right colon
  - Type II: mean age of 29, usually in the stomach and proximal small bowel
  - Type III: with family history and punctate telangiectatic lesions in gastrointestinal (GI) tract, oral mucosa, and skin

Macroscopic

- Under colonoscopy, the lesion appears as one or more sharply delineated red and flat or slightly raised mucosa with scalloped edges and a prominent draining vein

Microscopic

- Dilated, tortuous submucosal veins with distended branches piercing through the muscularis mucosae, connecting with dilated capillaries between the crypts in the lamina propria
- Later, the entire mucosa may be filled with a large number of ectatic small vessels

Table 28-2. Types of Vasculitis Affecting the GI Tract

Type of Vasculitis	*Type of Vessel Affected*	*Fibrinoid Necrosis*	*Thrombi*	*Histological Pattern*
Polyarteritis nodosa	Medium arteries, arterioles, large arteries	Very common, often segmental	Uncommon	Mixed acute and chronic necrotizing inflammation May be focal and segmental
Phlebitis	Medium veins, venules, large veins	Uncommon	Uncommon	Lymphocytic infiltrate of veins with sparing of artery
Churg-Strauss angiitis	Medium veins and arteries, arterioles and venules, large veins and arteries (less common)	Common	Uncommon	Extravascular granuloma with eosinophilic microabscess
Small-vessel vasculitis	Arterioles, venules	Common	Uncommon	Lymphocytic cuffing Numerous nuclear dust

- The surface mucosa may show erosion and acute and chronic inflammation

Vasculitis

Clinical

- As a part of systemic vasculitis with GI tract involvement or an isolated vasculitis affecting only the GI tract (serum autoantibodies frequently –)
- The frequency of GI tract involvement by a systemic vasculitis:
  - 25% in polyarteritis nodosa
  - 25% in rheumatoid arthritis
  - 2% in SLE
  - Very high frequency in Henoch-Schonlein purpura
- Organ involvement varies among the types of vasculitis:
  - Polyarteritis often affects the small intestine
  - Phlebitis usually involves the colon

Macroscopic

- A spectrum of ischemic bowel disease may occur
- Solitary or multiple ulcers, mucosal or transmural necrosis
- Short or long segment of involvement
- Stricture may follow recovery of transmural ischemic necrosis
- Unremarkable mesenteric vessels grossly
- A histological examination is required to diagnose vasculitis

Microscopic

- All vasculitides, regardless of systemic or localized forms, demonstrate similar histological changes
- Specific types of vasculitis can only be distinguished by microscopic examinations (Table 28-2)

Scleroderma

Clinical

- A progressive systemic sclerosis involving multiple organs that include skin, cardiovascular system, and GI tract
- Changes in medium and small arteries are common and are thought to be the basis of tissue damage
- Visceral involvement by the disease may precede or occur in the absence of skin changes
- Within the GI tract, the esophagus is by far the most frequently affected organ

Macroscopic

- Rigid, fibrotic, and often dilated intestinal tract
- Mucosal inflammation is often seen due to bacterial stasis
- Large diverticula have also been reported

Microscopic

- Atrophy of muscularis propria with disappearance of circular muscle coat
- Fibrous replacement of inner circular muscle coat
- Medium- and small-sized arteries show concentric intimal thickening, medial fibrosis, and fibrin deposition
- Mucosa may show nonspecific chronic or active inflammation

APPENDIX

Inflammatory Lesions

Acute Appendicitis

Clinical

- Definitive causes unknown, but most likely secondary to luminal obstruction in the form of fecalith, or less commonly, a gallstone, tumor, or worms, which results in ischemic injury
- Usually presents with acute onset of right lower quadrant pain with chills and fever

Macroscopic

- Usually swooned appendix with congested, often purulent serosal surface
- Reddened mucosa on cut surface
- Often with luminal pus
- Gangrenous necrosis of the muscular wall in advanced cases
- With or without perforation

Microscopic

- Neutrophilic infiltrate of the mucosa and the muscularis propria; the latter is generally required the diagnosis
- Acute inflammation may be focal

Differential Diagnosis

Yersinia Enterocolitis

- Usually shows prominent lymphoid aggregate with central zone necrotizing granuloma

Parasitic Infection

- The appendix may be involved and include enterobius vermicularis, amebiasis, and schistosomiasis.

Crohn's Disease

- Lymphoplasmacytic transmural inflammation with lymphoid aggregates
- Mural thickening
- Occasional granulomas

Ischemia

- May be involved in ischemic injury of the right colon

Tumors

Noncarcinoid Tumors

Clinical

- Uncommon, with overall incidence of 1–2% of the resected appendiceal specimens
- Adenocarcinoma is even more rare and accounts for 0.3% incidence
- Rarely diagnosed pre- or intra-operatively
- May initially present with ovarian tumors (Krukenberg tumors)
- The terminology of mucocele and pseudomyxoma peritonei does not truly reflect the underlying pathology
- May be an incidental finding after appendectomy for acute appendicitis

Macroscopic

- May be normal appearance
- May show inflammatory changes
- May be enlarged, and sometimes filled with mucus (mucocele)
- With rupture, mucinous material may be present on the serosal surface and mesoappendix
- Mucous globes may also be seen in the peritoneal cavity (mucinous peritoneal implants)
- May have identifiable tumor

Microscopic

- Adenoma:
  - Identical to the colonic counterpart
  - More often tubulovillous adenoma
- Hyperplastic polyps:
  - Identical to the colonic counterpart
- Mixed adenoma and hyperplastic polyp:
  - Identical to the colonic counterpart
- Adenocarcinoma:
  - Identical to the colonic counterpart
  - Often mucinous type
  - May be + for both CK7 and CK20
  - Malignant pseudomyxoma peritonei frequently occur
- Soft tissue tumors:
  - Mostly leiomyoma and neuroma
- Lymphoma:
  - Very rare
- Carcinoid tumors:
  - See intestinal neoplasms (page 28-15)

INTESTINAL POLYPS

Polyps

Developmental Polyps—Hamartomatous Polyp, Peutz-Jeghers Type

Clinical

- An autosomal dominant trait with variable penetrance
- Most common manifestation of Peutz-Jeghers syndrome
- Polyp itself has no or very low malignant potential, but epithelial dysplasia can occur
- Increased GI tract malignancy, 2–3% in western countries and up to 17% in Japanese series
- Increased extraintestinal benign and malignant tumors, especially ovarian sex cord tumors and adenoma malignum of the endocervix

Macroscopic

- GI tract polyps, usually <100
- Most common in small bowel, but can occur in the stomach and colon
- Large, lobulated mass, sessile or peduculated; may cause obstruction and intussusception

Microscopic

- Mucosal components in fairly normal proportion, typical of their site of origin, arranged on a complex branching of muscularis propria
- May have surface erosion and active chronic inflammation
- Epithelial dysplasia may occur on the surface

Differential Diagnosis

Juvenile Polyp

- See below

Developmental Polyps—Hamartomatous Polyp, Juvenile Type

Clinical

- Appear in 1st and 2nd decade of life with the peak incidence at 4–5 years of age
- As isolated cases or as juvenile polyposis (JP) syndrome
- JP is defined as:
  - More than 5 juvenile polyps of the colorectum and/or
  - Juvenile polyps throughout the GI tract and /or
  - Any number of juvenile polyps with a family history of JP
- An autosomal dominant trait with high penetrance is seen in one-third of JP patients; new mutations may occur in nonfamilial cases
- Favor colorectum, usually presents with small amount of bright red blood during defecation
- Less frequently, severe bleed, anemia, intussusception, failure to thrive, and rectal prolapse
- Most lesions, if undetected, regress before adolescence
- Unusually high incidence of allergic symptoms such as asthma and hay fever
- The usual solitary juvenile polyps have no increased risk for malignancy
- JP patients have shown an increased incidence of GI cancer (>10%)

Macroscopic

- A few solitary (in nonpolyposis cases) or multiple (usually 50–200 in JP of both familiar and nonfamilial cases) pedunculated polyps (in 90%) of 0.1 cm–5 cm, frequently in colorectum
- Usually with a smooth rounded surface and may be diffusely ulcerated, and numerous mucus-filled cysts on cut surface

Microscopic

- Expanded edematous LP permeated with inflammatory cells frequently including eosinophils
- The lamina propria may contain rare thin strips of smooth muscle (vascular in origin, not muscularis mucosae) and may become collagenous in older lesions
- Grotesquely distorted or dilated crypts lined by normal colonic-type goblet and absorptive cells that may show regenerative and hyperplastic features
- Some crypts may be large and filled with mucin
- May contain adenomatous (dysplastic) foci or true adenomas site by site with all grades of dysplasia

Differential Diagnosis

Peutz-Jeghers Polyp

- See above

Inflammatory Polyp

- See below

Inflammatory Pseudopolyps

Clinical

- As a result of colonic inflammatory condition
- Commonly seen in ulcerative colitis and Crohn's disease
- Rare in infectious colitis
- Polyp itself has no intrinsic malignant potential

Macroscopic

- Usually multiple
- Polypoid mucosal projections with varying length of stalk
- Abnormal surrounding mucosa that may be diffusely ulcerated

Microscopic

- Polypoid mucosal lesions composed of distorted, dilated, and branched crypts surrounded by inflammatory granulation tissue that usually contains bundles of smooth muscle
- Cryptitis or crypt abscess is commonly seen:
  - Some crypts may show regenerative changes
  - Some may be composed entirely of granulation tissue
  - Some may be composed of relatively normal looking residual mucosa among an ulcer bed
- Adjacent or distant colonic mucosa shows underlying disease if associated with IBD

Differential Diagnosis

Juvenile Polyps

- See above

Hyperplastic Polyps

Clinical

- The most common colonic polyps (10 times that of colonic adenomas)
- Caused by delayed surface epithelial loss and normal basal crypt production
- Asymptomatic; increasing incidence with age
- No clear association with IBD or neoplasms
- Generally not considered as a neoplastic process, but limited recent studies show a low frequency of K-ras mutation, especially in patients with diffuse hyperplastic polyposis, which is a rare nonhereditary condition

Macroscopic

- Occur only in the colorectum and appendix
- Frequently multiple rounded to oval mucosal elevations or plaques
- Usually 1–3 mm, but rarely, may reach 1 cm

Microscopic

- Localized mucosal expansion (both crypts and lamina propria)
- Mature columnar and goblet cells piling up along the crypt, which creates a serrated surface
- Frequently thickened subepithelial basement membrane
- Occasional crypt epithelial neutrophilic infiltration
- May occasionally superimpose on an adenoma (mixed adenoma and hyperplastic polyp)

Neoplastic Polyps—Adenomas

Clinical

- Second most common GI tract polyps
- A precancerous lesion
- Affecting 30% or more individuals after 40 years of age with the peak incidence in 6th and 7th decade of life
- The vast majority are sporadic and are therefore nonfamilial nor associated with familiar adenomatous polyposis (FAP) syndrome
- Most adenomas remain asymptomatic and are only found through a routine colonoscopy examination
- Those located in the rectosigmoid colon may be traumatized and bleed
- Multiple factors are associated with the development of cancer in adenomas; in general, they are related to the size and number of adenomas, the duration and family history of colorectal cancer, and additional molecular alterations that may have occurred in the tumor epithelium
- The adenoma-carcinoma sequence is usually associated with a series of predictable genetic changes
- Overall 21–41% recurrent rate after polypectomy
- Incomplete removal is common in villous and sessile adenomas

Macroscopic

- Pedunculated, sessile, or carpet-like mucosal lesions with multi-lobulated, friable outer surface and homogeneous cut surface
- Tubular adenomas predominate and usually measure >1 cm
- Villous adenomas or tubulovillous adenomas are usually larger and sessile, and they are more likely to be located in the cecum and rectosigmoid

Microscopic

- Adenomas are classified according to their architecture:
  - Tubular adenoma: tube-like crypts
  - Villous adenoma: finger-like crypts
  - Tubulovillous adenoma: both tubule and finger-like features
- The adenomatous crypts are populated by tall columnar cells with enlarged, elongated, and hyperchromatic nuclei arranged in a pseudostratified pattern, usually along the basement membrane
- Variably decreased epithelial mucus content, but occasionally abundant mucus production
- May contain dystrophic goblet cells, endocrine cells, Paneth cells, or even squamous cells
- LP contains the usual types of inflammatory cells and immature fibroblasts

- Sharp transition between adenomas and normal adjacent crypts
- If pedunculated, the stalk is usually composed of normal mucosa with abrupt transition to the adenomatous epithelium

Special Considerations

Serrated Adenoma

- Adenoma with nuclear features of adenoma but architectural features of hyperplastic polyp

Mixed Hyperplastic and Adenomatous Polyp

- Polyp with both well-defined adenomatous and hyperplastic components in the same tumor in a variable proportion

Adenoma with High-Grade Dysplasia

- Adenomas with complex and cribriform architecture and enlarged, rounded nuclei containing vesicular nuclear chromatin and prominent nucleolus
- The nuclei usually reach the luminal surface of the crypt
- Usually occurs focally or multifocally in a large adenoma
- May be associated with invasive adenocarcinoma if mass lesions are present
- By definition, the lesion is confined entirely within the lamina propria (LP)
- Should only be diagnosed when there is no invasion of the submucosa
- It carries no metastatic potential if completely excised; therefore, it is now accepted terminology to replace carcinoma in situ, a once very popular name
- It should be differentiated from polypoid adenocarcinoma (see below)

Adenoma with Pseudocarcinomatous Invasion

- Adenomatous gland misplacement in the submucosa, therefore mimicking submucosal invasion by carcinoma
- Usually due to ulceration and healing fibrosis of the adenoma caused by trauma; therefore, more common in the rectosigmoid colon
- Key diagnostic features include a lack of cytological atypia of cancer and a lack of desmoplasia of the surrounding stroma
- Submucosa occasionally may contain hemosiderin pigment

Adenoma versus Dysplasia Complicating IBD

- The two lesions may be identical and are impossible to distinguish with certainty on biopsy specimens
- However, true dysplasia associated with IBD tends to be a flat, locally diffuse lesion
- Clinical history and histological evidence of IBD of the nonadenomatous colonic mucosa are the key factors for the distinction
- The patient age is also helpful, as most sporadic adenomas occur after 40 years of age

Polypoid Adenocarcinoma

- Polypoid colonic adenocarcinoma almost entirely composed of carcinomatous epithelium
- Usually associated with intramucosal or submucosal invasion
- It has a metastatic potential, and therefore cannot be cured by polypectomy

Familiar Adenomatous Polyposis (FAP)

- One of the two best understood inherited predispositions to colorectal cancer (see chapter 2)
- Caused by germ-line mutations of the *APC* (*adenomatous polyposis coli*) gene, located on 5q21, which in >95% of the cases results in truncations of the encoded protein
- An overall incidence of 1 in every 10,000 births
- Two-thirds inherit the disease as an autosomal dominant trait, and one-third have no family history and therefore represent new mutation
- The majority of colorectal cancers do not have a well-recognized inherited component and are therefore are classified as sporadic in nature
- Average of onset of polyposis is 25 years of age
- Generally becoming symptomatic at 33 and most commonly diagnosed at 36
- Molecular test detects patients at a much younger age.
- Polyps, usually <1 cm, are evenly distributed through all segments of the large intestine, with the rectum being espared only occasionally
- Minimal 100 polyps for diagnosis (although it is no longer absolute if APC gene testing is positive, it usually exceeds 1,000
- Adenocarcinoma inevitably develops in all patients if left unattended, usually during the 3rd decade of life
- The number of carcinomas rarely exceeds three
- Early carcinomas are usually found in those polyps > 1 cm
- Histologically, FAP adenomas are similar to those of sporadic tubular adenomas.
- Microadenomas are more characteristic of the lesion.
- Extracolonic manifestations:
  - Periampullary, jejunal, ileal, and rarely gastric adenomas with an overall incidence of upper GI tract carcinoma of 4.5%
  - Desmoid tumor (Gardener's syndrome)
  - Turcot's syndrome

MALIGNANT TUMORS

Adenocarcinoma

Clinical

- The most common malignant tumors of the large intestine; account for 98% of all large intestinal cancers
- Approximately 160,000 new cases and 60,000 deaths each year, which accounts for 15% of all cancer-related death
- Peak incidence in 60–70 years of age; 20% occur under the age of 50
- If seen in younger patients, predispositions such as ulcerative colitis, FAP, or hereditary non-polyposis colorectal carcinoma (HNPCC) should be suspected
- Majority are sporadic in nature; HNPCC- and FAP-associated carcinomas account for 5–15% and 1% of all colorectal cancers, respectively
- Rare in the small intestine, accounts for <1% of all GI tract malignancies
- Within the small bowel, the tumor favors the duodenum, including ampulla vater, which leads to cramping abdominal pain, nausea, vomiting, and weight loss
- Most of the cancers are located in the rectosigmoid region. The incidence of right-sided tumor is rising
- Prognosis correlates best with tumor staging (see TMN classification of colorectal Adenocarcinoma)

Macroscopic

- Polypoid type:
  - Exophytic intraluminal mass
  - More common in the cecum and the right colon
  - Likely to arise in an adenoma
- Fungating type:
  - Polypoid type with prominent ulceration
- Ulcerative type:
  - Invades deeply into the colonic wall with ulcerative surface
- Infiltrative type:
  - Invades intestinal wall diffusely and often circumferentially, without forming a nodular mass

Microscopic

- Most are well to moderately differentiated gland-forming adenocarcinoma
- Well-differentiated type:
  - >75% of the tumor contains glands
- Moderately differentiated type:
  - >25% of the tumor contains solid sheets of tumor cells
- Poorly differentiated type:
  - >75% of the tumor is solid sheets

Specific Variants

Mucinous Type

- >50% of the tumor appears mucinous

Colloid Type

- Large extracellular mucinous pools with floating tumor cells
- Tumor cells may not be abundant and often show signet ring features

Signet Ring Cell Type

- Solid sheets of tumor cells with prominent intracellular mucin
- Rare, and are often seen in IBD-associated cancers

Mixed Carcinoid-Adenocarcinoma Type

- Typically affects the appendix, but arises in the colon as well
- Mucous tumor cells arranged in nests or trabeculae with admixed endocrine or Paneth cells
- Highly aggressive
- Often presents with intraabdominal metastasis such as bilateral ovaries

Small-Cell Carcinoma

- Rare, highly aggressive, favors right colon and rectum
- Mean age of 63
- Grossly indistinguishable from ordinary types
- Histological features are similar to those of oat cell carcinoma of the lung

Adenosquamous Type

- Rare (0.05% of colorectal cancers)
- Aggressive tumors with poorer prognosis
- Most occur in the rectosigmoid as fungating masses
- Histologically, the cancer contains both adeno- and squamous carcinoma of varying proportion
- Differs from adenocarcinoma, containing occasional metaplastic squamous cells, seen in approximately 5% of the cases

Carcinoid Tumors

Clinical

- Biologically malignant, slow growing, locally infiltrative with the potential for metastasis
- Account for 2% of all malignant GI tract tumors
- Approximately 50% found in the small intestine, 34%

Table 28-3. Metastatic Potential of Carcinoid Tumor of the GI Tract

Site and Size	*Metastasis*
Stomach	
<1.8 cm	15%
>5 cm	80%
Appendix	
<2 cm	Almost never
>2 cm	31%
Small bowel and colorectum	
<1 cm	22%
>1 cm	58%

in the appendix, and the remaining in the colorectum and stomach

- Carcinoid syndrome occurs in a minority of cases, most of which are ileal in origin, with liver metastasis
- The term of neuroendocrine cell carcinoma should only be used when there is distant metastasis by the tumor
- Metastatic potential is related to the site and the size of the tumor (Table 28-3)

Macroscopic

- Duodenal carcinoids:
  - Usually small polypoid lesions up to a few millimeters in size
  - Covered by intact mucosa
- Small intestinal carcinoids (other than duodenum):
  - Usually <2 cm
  - Indurated, yellowish nodules lie predominantly in the submucosa
  - Attenuated, rarely ulcerated overlying mucosa
  - Multiple tumors in up to 40% of the cases
  - When tumor invades the deep muscle coat and serosa, it often produces dense fibrosis, which causes kinking of the bowel wall and peritoneal adhesions
- Appendiceal carcinoids:
  - Usually small, <1 cm
  - Round nodule located in the tip, forming solid, bulbous swelling and causing luminal obliteration
  - Often discovered incidentally
  - Rarely, patients present with acute appendicitis or mucocele
- Colorectal carcinoids:
  - Vast majority occur in the rectum
  - Solitary, occasionally multiple, small, rubbery, polypoid nodules
  - Attenuated, sometimes friable overlying mucosa
  - Cecal and proximal colonic tumors tend to be large and bulky

Microscopic

- Duodenal carcinoids:
  - Tumor cells arrange in trabecular or ribbon patterns with occasional rosette formation
  - May contain gastrin, somatostatin, substance P, serotonin, or glucagon, or may be multi-hormonal
- Carcinoids of the small intestine (excluding duodenum):
  - Monotonous appearing tumor cells
  - Centrally located nuclei, stippled nuclear chromatin, and small nucleoli
  - Indistinct cytoplasmic borders
  - Tumor forms insular (solid sheets of tumor cells with peripheral palisading) and/or trabecular, anastomosing ribbon-like cords in a vascularized stroma
  - Many produce serotonin and other hormones
- Appendiceal carcinoids:
  - Similar to that of small intestinal carcinoids
  - Contain serotonin
  - Often show intimate association with nerve fibers
  - Often show diffuse muscularis invasion
  - Lymphatic permeation is also common
  - Malignancy is exceedingly rare, even with muscular and lymphatic invasion
  - Malignancy best correlates with tumor size
- Tubular carcinoids:
  - Almost entirely composed of tubular structures and trabeculae containing primarily endocrine cells with a few goblet cells
  - Diffusely infiltrative among the smooth muscles of the muscularis
  - Lack cytological atypia
  - Mitotically inactive (0–2 mitosis/10hpf)
  - Share the same biological behavior with typical appendiceal carcinoids
- Goblet cell carcinoids:
  - Tubular structures containing variable number of goblet lining cells + on mucin stains
  - Diffusely infiltrative among the smooth muscles of the muscularis
  - Usually without cytological atypia
  - Mitosis in average 1/10 high power fields (HPF)
- Colorectal carcinoids:
  - Most tumors show trabecular with mixed alveolar patterns

Table 28-4. Gastrointestinal Stromal Tumor

Characteristics of tumor	*Likely benign*	*Likely malignant*
Location	Esophagus, 2/3 of stomach	Small and large intestines
Size	< 3 cm (< 5 cm in stomach)	> 3 cm (> 5 cm in stomach)
Invasion of mucosa or adjacent organ	No	Yes
Parenchymal necrosis (excluding surface erosion)	No	Yes
Mitotic figures	< 5/50 HPF	> 10/50 HPF

- Many are multi-hormonal by immunohistochemistry, but rarely are they functional
- Therefore, carcinoid syndrome is rare

Immunohistochemistry

- \+ for chromogranin, synaptophysin, neuron-specific enolase (NSE), and cytokeratin
- Goblet carcinoids may also express carcinoembryonic antigen (CEA)

Differential Diagnosis

- Mixed carcinoid-adenocarcinoma
  - Usually affects the appendix, and occasionally the colon and stomach
  - Mucous tumor cells arranged in nests, glands, trabeculae, or single signet ring cells with admixed endocrine or Paneth cells
  - Prominent cytological atypia with high mitotic count (average 10/10 HPF)
  - Scattered chromogranin reactivity
  - Highly aggressive
  - Often presents with intraabdominal metastasis such as bilateral ovaries

Gastrointestinsal Stromal Tumor (GIST)

Clinical

- Patients usually present during 4th and 7th decades of life
- Affect male and female equally
- 2/3 occur in the stomach, 25% in the small intestine, and small numbers in the rectosigmoid; very rarely seen in the proximal colon
- Typical presentation includes obstruction, intra-abdominal mass, bleeding, and weight loss

Macroscopic

- Usually single intramural mass
- Expands the wall, or in large tumors, outside the wall, with a narrow attachment to the muscularis propria
- Cut sections show circumscribed, expansile masses with flat, granular surface
- May contain hemorrhage, cystic changes or necrosis

Microscopic

- Spindle cell with elongated nuclei, often arranged in bundles with palisading reassembling those of either leiomyoma or schwannoma
- Some may also contain epithelioid cells that are usually rounded with abundant cytoplasm, admixed with spindle cells
- Stroma may be hyalinized, fibrotic, myxoid, or necrotic
- Evaluation for malignancy is difficult, often requires extensive sampling

Immunohistochemistry

- C-kit: ++++; CD34: +++ to ++++; S-100: ±; smooth muscle actin (SMA): ±, Cytokeratin ±

Benign or Malignant

- Malignant potential of GIST is largely determined by the tumor location, the size, the presence or absence of tumor necrosis and invasion, and finally, mitotic activity
- Table 28-4 may be helpful in making such distinction

Differential Diagnosis

- Leiomyoma:
  - Usually located in the esophagus
  - If occurs in the small and large intestine, often as a small submucosal polypoid mass
  - \+ for SMA, but – for C-kit, CD34, or S-100
- Schwannoma:
  - Almost always occurs in the stomach
  - Can be cystic, and usually associated with lymphoplasmacytic infiltrate
  - \+ for S-100, but – for SMA, C-kit, or CD34
- Gastrointestinal autonomic nerve tumors (GANT):
  - Rare, have only been described in the stomach and small intestine

  - Ovoid tumor cells with cytoplasmic clearing, resembling epithelioid GIST
  - Usually + for synaptophysin and NSE, – for S-100, CD34, or C-kit
  - Criteria for malignancy are similar to those of GIST
- Mesenteric fibromatosis:
  - The bulk of the tumor is usually in the serosa or the mesentery
  - Often invades the muscularis
  - Spindle tumor cells, but less cellular than GIST
  - Lack nuclear pleomorphism
  - Stroma tends to be myxoid

Gastrointestinal Lymphoma

General Features

- Almost exclusively of non-Hodgkin's type
- Constitute 4–18% of all non-Hodgkin's lymphoma (NHL) and 1–2% of all GI tract malignancies
- May be secondarily involved by systemic non-Hodgkin's lymphoma
- Up to 40% arise as primary GI tract lymphoma, which is defined, as the main bulk of tumor is limited in the GI tract with or without the involvement of contiguous lymph nodes
- Usually arise as sporadic neoplasms (B cell MALTomas)
- Also occur in certain patient populations:
  - Sprue-associated lymphoma (T cell in origin)
  - Mediterranean lymphoma (alpha heavy chain disease)
  - HIV or organ transplantation associated lymphoma (B large cell lymphoma)
- Usually affects adults, with equal sex distribution
- May arise anywhere in the GI tract:
  - Stomach: 50–60%
  - Small intestine: 25–30%
  - Proximal colon: 10–15%
  - Distal colorectum: Up to 10%
- Any lymphoma may occur as a primary tumor of the GI tract
- Most, however, are distinct entities that do not arise in peripheral lymph nodes, and do not form a part of any current lymphoma classification, as is listed in Table 28-5
- Unlike nodal low-grade B cell lymphoma, low-grade mucosa-associated lymphoid tissue (MALT) lymphoma of the GI tract is usually confined to the site of origin at presentation; the prognosis is more favorable than the equivalent nodal disease

Table 28-5. Lymphomas of the GI Tract

B cell

Lymphomas of mucosa-associated lymphoid tissue (MALT)

Low-grade B cell lymphoma of MALT

High-grade B cell lymphoma of MALT with/without a low-grade component

Mantle cell lymphoma (lymphomatous polyposis)

Burkitt's or Burkitt's-like lymphoma

Other types (corresponding to peripheral lymph node equivalents)

T cell

Sprue-associated T cell lymphoma

Specific Types (also see chapter 7)

B Cell Lymphoma of MALT

Clinical

- The majority arise in the small intestine of any part as a single lesion
- Colorectal involvement are distinctly rare
- More common in the elderly
- Presents with melena or obstruction
- Mesenteric lymph node involvement is common
- Extra-abdominal spread is unusual at presentation
- Prognosis is not as favorable for tumors arising in the lower GI tract

Macroscopic

- Most are grossly single lesions, although can be multifocal microscopically
- Poorly-defined, fleshy, thickened bowel wall with extensive mucosal ulceration
- Mesenteric lymph nodes may be enlarged

Microscopic

- Heavy intramucosal lymphoid infiltrate that usually forms the base of a mucosal ulceration
- Lymphoepithelial lesions
- Small to medium size lymphocytes with irregular nuclei and moderate amount of cytoplasm (centrocyte-like [CCL] cells) infiltrates around reactive, nonneoplastic follicles (Peyer's patch marginal zone), spreading diffusely into the surrounding mucosa
- Small number of transformed blasts and plasma cell differentiation are characteristic
- Tumor cells invade nonneoplastic follicles in several different ways

  - Total replacement
  - Partial replacement
  - Striking and uniform blastic transformation
  - Plasma cell differentiation
- High-grade MALT lymphoma is more common, compared to gastric counterpart
- It is characterized by confluent clusters of transformed cells outside of the colonized follicles
- Small foci of tumor are often present at remote distances from the main tumor mass

Immunohistochemistry

- CD20 +, CD5 –, CD10 –, CD43 usually –
- Monoclonal plasma cells

Mantel Cell Lymphoma (Lymphomatous Polyposis)

Clinical

- Affects patients >50 years of age
- Abdominal pain and melena
- Involves any part of the GI tract, but the most predominant mass is usually seen in the ileocecal region
- Tend to disseminate early to lymph nodes, liver, spleen, and bone marrow

Macroscopic

- Multiple fleshy mucosal polyps ranging from 0.5–2 cm, or even larger
- Mesenteric lymph nodes often involved

Microscopic

- Intramucosal lymphoid aggregates, single or multiple
- Entrapped, reactive follicular centers in the lymphomatous infiltrate
- Follicular centers may be entirely replaced
- Lymphomatous infiltrate selectively replaces the mantle zones

Immunohistochemistry

- CD5 +, CD20 +, CD10 – CD43+, bcl-1 +

Burkitt's and Burkitt-Like Lymphomas

Clinical

- Two forms:
  - Endemic Burkitt's lymphoma
  - Sporadic Burkitt's lymphoma
- Patients are usually young; present with abdominal pain and obstructive symptoms
- Epstein-Barr virus (EBV) genomes are found in all cases of endemic form, but in only 1/3 of the sporadic form
- t(8,14) in 80% of the cases

Macroscopic

- Favor ileocecal region
- Localized obstructing masses or huge masses involving long segments of intestine
- Mesenteric lymph node and retroperitoneal involvement are common

Microscopic

- Effacement of mucosa by sheets of monomorphic blasts interspersed with macrophages give a characteristic "starry sky" appearance
- The blasts are small, noncleaved cells with granular nuclear chromatin, 3–4 nucleoli, and a well-defined ring of deeply basophilic cytoplasm
- Lymphoepithelial lesions are rare

Immunohistochemistry

- CD10 +

Sprue-Associated T Cell Lymphoma

Clinical

- Median age of 60, rare under the age of 30, with slight male predominance
- Most patients have a history of abdominal pain and weight loss for a few months or a few years
- Some patients have a remote history of malabsorption
- Not infrequently, patients present with an acute emergency with GI tract perforation, obstruction, and hemorrhage

Macroscopic

- Most common in the jejunum
- Frequently multiple, circumferential ulcers without forming large tumor masses
- Mesenteric lymph nodes are usually enlarged, due both to tumor involvement and to reactive changes

Microscopic

- Mucosal ulceration is common, with dense lymphocytic infiltration forming the base of the ulcer
- Adjacent, nonulcerated mucosa shows extensive villous atrophy with prominent intra-epithelial T lymphocytes
- Highly pleomorphic T lymphocytes with bizarre, multinucleated forms

Immunohistochemistry

- CD3 +, CD20 –

TNM CLASSIFICATION OF COLORECTAL ADENOCARCINOMA

- T: Primary Tumor
  - Tis: carcinoma in situ
  - T1: lamina propria or submucosal invasion
  - T2: muscularis propria invasion
  - T3: subserosa or pericolic tissue invasion (mesentery in small bowel)
  - T4: adjacent organ invasion and/or perforates visceral peritoneum
- N: Regional lymph nodes
  - N0: no nodal metastasis
  - N1: 1–3 positive nodes
  - N2: ≥ 4 positive nodes
- M: Distant metastasis
  - M0: no distant metastasis
  - M1: distant metastasis

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Chapter 29

Pancreas

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NONNEOPLASTIC LESIONS

Pancreatitis

Clinical

- Common clinical disease, uncommonly biopsied or resected
- Risk factors:
  - Majority due to cholelithiasis or alcoholism, but can be due to multiple causes resulting in duct obstruction, acinar cell injury, or derangement of intracellular pancreatic enzyme transport
  - Acute pancreatitis often becomes chronic due to scarring-local obstruction-relapse cycle

Macroscopic

- Early pancreatitis unevenly affects the pancreas, with the affected regions being enlarged and firm; these regions may contain calculi
- Advanced chronic pancreatitis shows the entire pancreas to be firm and sclerotic, with overall diminution of gland size; ducts show irregular dilatations and distortions with numerous calculi identified
- Chronic pancreatitis may be associated with fluid-filled pseudocysts

Microscopic

- Active disease will show areas of enzymatic fat necrosis
- Severe perilobular and intralobular fibrosis associated with ductal scarring:
  - Ductular (small duct ramifications) proliferation may simulate adenocarcinoma given the dense scarring
- Islet clusters are retained and may become a prominent feature in the remaining parenchyma; however, they are not tumefactive

Differential Diagnosis

- Ductal adenocarcinoma:
  - Ill-defined firm mass in the head of pancreas with remaining pancreas uninvolved
  - Neoplastic duct-like structures and glands embedded in fibrous tissue display significantly dysmorphic architectural features and/or cytologic atypia
  - Frank invasion into fatty tissue or perineural invasion is helpful
  - Difficult differential diagnosis on needle biopsy
- Islet cell tumor:
  - Single or few significant masses with loss of islet architecture
- Intraductal papillary mucinous tumor:
  - Significant epithelial proliferation within ducts; uniformly accompanied by chronic pancreatitis

Nesidioblastosis

Clinical

- Hyperfunctioning beta islet cells with associated hyperinsulinemic syndrome predominantly in infants; associated with persistent neonatal hyperinsulinemic hypoglycemia (PNHH)
- Rare syndrome, mostly sporadic in diabetic infants born to diabetic mothers
- Rare familial disease has been mapped to chromosome 11p14-15.1

Macroscopic

- Typically undetectable at macroscopic level

Microscopic

- Multifocal confluent islet cell clusters (typically 1–3 mm) within fibrous cords, with rims of acinar cells; large polypoid nuclei may be seen; the exocrine pancreas is normal

Immunohistochemistry

- Insulin-secreting cells comprise 70% to 90% of islets (normal in neonates = 50%) and almost all of the periductal islet cells
- Glucagon, somatostatin, and PP cells are also identified in the islets in normal numbers

Electron Microscopy

- B cells show active protein synthesis with well-developed endoplasmic reticulum and prominent Golgi complexes

Differential Diagnosis

- Nesidioblastosis/persistent neonatal hyperinsulinemic hypoglycemia is predominately a clinicopathologic correlate

Pseudocyst

Clinical

- Common complication of chronic pancreatitis
- Most frequently seen in alcoholic males
- Represents the most common type of pancreatic cyst

Macroscopic

- 3–10 cm unilocular cyst filled with necrotic fluid, located adjacent to the pancreas

Microscopic

- Cyst wall is dense fibrous tissue with granulation tissue lining inner surface

- No epithelial lining, by definition

Differential Diagnosis

- Mucinous cystic neoplasm-epithelial lining
- Other congenital cysts-epithelial lining

Lymphoepithelial Cyst

Clinical

- Uncommon
- Described only in men, age 36–73 years

Macroscopic

- Cyst well-demarcated from pancreatic tissue, thin-walled unilocular, filled with gray-white pasty material; "dermoid cyst" of the pancreas

Microscopic

- Cyst lined by mature keratinizing squamous epithelium with surrounding lymphoid tissue and occasional germinal centers; no adnexal or mesenchymal tissue is present

Differential Diagnosis

- Cystic teratoma:
  - Extremely rare in pancreas and associated with adnexal or mesenchymal tissue in wall of cyst

Miscellaneous Pancreatic Changes

Congenital Cyst

- Rare congenital cysts lined by serous (cysgenetic cyst) or respiratory (ciliated foregut cyst) epithelium; no cytologic atypia or malignant risk

Cystic Fibrosis

- Pancreatic involvement in 80% to 90% of patients; associated with accumulation of mucous in ducts and dilatation of exocrine glands:
  - In advanced cases, complete plugging of ducts with atrophy of exocrine glands and fibrosis
  - Associated with similar mucous plugging in other organs, particularly the lungs

Diabetes Mellitus

- Pancreatic involvement is not always seen, but when identified, is associated with reduction or proliferation in the size and number of islets, presence of fibrosis, islet amyloid deposition, and/or mild leukocytic infiltrates

CHILDHOOD NEOPLASMS (SEE TABLES 29-1 AND 29-2)

Pancreatoblastoma

Clinical

- Extremely rare neoplasm (<35 patients described), but still relatively common among childhood pancreatic neoplasms
- M:F = 2:1; two-thirds described in Asians, one-third in Caucasians; mean age = 4 years; 7 adult cases described
- One-fourth to one-third of patients demonstrate elevated alpha fetoprotein levels
- Occasionally associated with Beckwith-Wiedemann syndrome
- 5-year survival = 25%

Macroscopic

- Well-demarcated, solitary, solid, multilobulated, encapsulated tumor; yellow-tan cut surface
- Typical size = 7–18 cm

Microscopic

- The architecture features lobules, nests, and acini; a dense fibrous stroma can be present
- Cytology is that of columnar/cuboidal epithelial cells with prominent eosinophilic cytoplasm and round to oval nuclei
  - Squamous cell nests with basophilic to clear cytoplasm and occasional keratin pearls are also seen
  - Occasional necrotic foci and mitotic figures are present

Immunohistochemistry

- The majority of cells are positive for acinar cell antigens, including keratin, lipase, trypsin, chymotrypsin, and alpha-1-antitrypsin
- Squamous cells are negative for pancreatic enzymes or endocrine markers
- Occasional chromogranin-positive endocrine cells can be noted; some tumors AFP +

Differential Diagnosis

- Acinar cell carcinoma:
  - Absence of squamoid nests
- Islet cell tumors:
  - Diffusely positive for synaptophysin and chromogranin and negative for alpha fetoprotein

- Solid pseudopapillary tumors:
  - Predilection for females >9 years of age; distinct histologic pattern of solid areas intermixed with pseudopapillary structures

Islet Cell Tumor

Clinical

- Uncommon tumor in children
- See Section in Adult Neoplasms (malignant) for in-depth discussion of this neoplasm

Solid-Pseudopapillary Tumor (Solid-Cystic Tumor, Papillary-Cystic Tumor, Solid and Papillary Epithelial Neoplasms)

Clinical

- Rare pediatric tumor; predominantly adolescent/young adult females; mean age = 35 years
- Surgical removal = 95% cure rate
- See section on Adult Neoplasms (malignant) for in-depth discussion of this neoplasm

Acinar Cell Carcinoma

Clinical

- Rare pediatric tumor; predominantly in adults (average age = 60)
- See section on Adult Neoplasms (malignant) for in-depth discussion of this neoplasm

Table 29-1. Immunohistochemical Profiles of Adult Pancreatic Neoplasms

	Keratin	*Synaptophysin/Chromogranin*	*Tryptase lipase*
Ductal origin -IPMT -Ductal AdCA	+	–	–
Islet cell origin -Endocrine tumors	+	+	–
Acinar/unknown origin	+	–	+

Note: IPMT = intraductal papillary-mucinous tumor; AdCA = adenocarcinoma

Table 29-2. Distribution of Pancreatic Neoplasms

Diagnosis	*All ages*	*Age <40*	*Childhood*
Ductal adenocarcinoma	90%	10%	—
Islet cell tumor	2%	50%	rare
Solid pseudopapillary tumor	1%	30%	rare
Mucinous cystic tumor	2%	2%	—
Serous cystadenoma	1%	2%	—
IPMT	1%	2%	—
Acinar cell carcinoma	1%	2%	rare
Pancreatoblastoma	<1%	2%	rare
Miscellaneous	1%	—	—

Note: IPMT = intraductal papillary-mucinous tumor

ADULT NEOPLASMS, BENIGN

Serous Cystadenoma (Microcystic Adenoma)

Clinical

- 1% to 2% of pancreatic tumors, M:F = 1:3; mean age = 66 years (range 34–91)
- Rarely associated with von Hippel-Lindau syndrome
- One-third are incidental findings, two-thirds are symptomatic

Macroscopic

- Well-demarcated solitary multilocular cystic lesion with central stellate scar
- Typical overall size = 4–10 cm
- Numerous tiny cysts with few larger spaces results in sponge-like appearance

Microscopic

- Cysts uniformly lined by simple low cuboidal epithelium
- Low nuclear:cytoplasmic ratio, clear cytoplasm, no atypia

Immunohistochemistry

- Keratin +
- Essentially never needed

Variant

- Occasionally few or single larger cystic space(s) with typical epithelial lining (oligocystic or microcystic)

Differential Diagnosis

- Serous cystadenocarcinoma:
  - Extremely rare neoplastic transformation of serous cystadenoma (four case reports)
  - Rare multifocal occurrence of benign tumors has also been observed
- Mucinous cystic neoplasm:
  - Unilocular/oligolocular lesions with viscous mucin; columnar epithelium positive for mucin and CEA
- Lymphoepithelial cyst:
  - Unilocular cyst filled with keratinaceous material lined by keratinizing squamous epithelium supported by lymphoid stroma

Mucinous Cystadenoma

Clinical

- 1% to 2% of pancreatic neoplasms
- Almost exclusively in females ages 40–60 presenting with nonspecific GI symptoms
- Diagnosis should be made with caution after extensive sampling to exclude cystadenocarcinoma

Macroscopic

- Well-circumscribed solitary lesion in pancreatic body or tail
- Generally unilocular containing mucinous/hemorrhagic material

Microscopic

- Cysts lined by simple (single layer) tall columnar epithelium with marked intracellular mucin and minimal or no atypia; occasional goblet cells admixed
- In a significant subset, the subepithelial stroma is cellular, with deeper hyalinized layer resembling ovarian stroma

Immunohistochemistry

- Keratin, EMA, and CEA +; vimentin, chromogranin, and NSE –

Differential Diagnosis

- Mucinous cystadenocarcinoma:
  - Malignant counterpart of mucinous cystadenoma with the columnar epithelial cells demonstrating architectural irregularities or significant cytologic atypia
  - Extensive sampling of the tumor must be performed as malignant areas may be present in otherwise benign-appearing tumors
- Pseudocyst:
  - 70% to 90% of all pancreatic cystic lesions; lack epithelial lining
- Intraductal papillary mucinous tumor:
  - Associated with cystic dilatation of the main pancreatic duct/branches; intraductal papillary growth of mucin-producing columnar cells, often without cyst formation
- Serous cystadenoma:
  - Polycystic lesion with central stellate scar lined by low cuboidal epithelial cells without mucin production

ADULT NEOPLASMS, MALIGNANT (SEE TABLES 29-1 AND 29-2)

Ductal Adenocarcinoma

Clinical

- 85% to 90% of all pancreatic tumors; fifth leading cause of cancer death in the United States; M:F = 1.5:1, African American:Caucasian = 2:1; usually ages 60–80, 10% of patients less than 40 years old
- Associated with abdominal pain, weight loss, and painless jaundice; rarely familial
- Untreated mean survival is 3 months; with surgical treatment, survival is 10–20 months; 5-year survival = 3.5%
- K-ras oncogene point mutations in codon 12 have been described in 80% of ductal adenocarcinomas and p53 mutations are identified in 50% of ductal adenocarcinomas, although clinical utility remains to be ascertained

Macroscopic

- 60% to 70% occur in head of pancreas, 5% to 10% in body, 10% to 15% in tail, 10% to 15% in multiple regions
- Firm yellow-white mass with ill-defined margins; associated with duct obstruction/destruction and upstream dilation
- Typical size = 3 cm
- Majority demonstrate extrapancreatic extension/metastases

Microscopic

- Typically, moderately to well-differentiated malignant glandular structures with prominent desmoplastic stromal reaction (often comprising the vast majority of the tumor)
- Duct arrangement disregards the normal lobular architecture and displays ruptured and incomplete gland formation
- The neoplastic cells are cuboidal to columnar, with variable mucin production and nuclear atypia
- Mitotic figures are infrequent in typical well-differentiated cases
- Perineural invasion and extrapancreatic extension is very common

Immunohistochemistry

- Positive for keratin, CEA, and CEA125; negative for vimentin, synaptophysin, and chromogranin
- Seldom necessary

Variants

- Undifferentiated (anaplastic) carcinoma:
  - Occasional undifferentiated cases contain osteoclast-like giant cells, which are most likely nonneoplastic (See Osteoclast-like giant cell tumor) and
- Sarcomatoid carcinoma (carcinosarcoma)
- Adenosquamous carcinoma
- Signet ring cell type carcinoma
- Small cell carcinoma
- Mixed ductal-endocrine carcinoma

All variants have poor prognosis

Differential Diagnosis (see Tables 29-1 and 29-2)

- Chronic pancreatitis:
  - Preserved lobular architecture despite loss of exocrine cells and presence of fibrosis and ductular proliferation
  - Lack of cytologic atypia or irregularly infiltrating glands; difficult practical problem on needle biopsy
- Ampullary carcinoma/common bile duct carcinoma:
  - Both tumors share microscopic features with ductal adenocarcinoma
    - Distinguished by careful assessment of macroscopic and microscopic localization of the tumor
- Intraductal papillary-mucinous tumor:
  - Neoplastic proliferation is confined to the ductal system; when invasion occurs, it is typically ordinary ductal-type adenocarcinoma
- Acinar cell carcinoma:
  - Acinar architecture; much less desmoplasia; granular cytoplasmic PAS-D +; mucin –
- Islet cell tumors:
  - Trabecular or microglandular patterns without mucin production; less desmoplastic; expresses chromogranin and synaptophysin
- Pancreatoblastoma:
  - Rare childhood tumor with acinar cell differentiation and squamoid nests

Intraductal Papillary-Mucinous Tumor (IPMT)

Clinical

- At least 1% of pancreatic neoplasms; M:F = 3:2, age peak is sixth decade
- Present with symptoms of pancreatitis
- Good prognosis due to relatively low frequency of invasion

Macroscopic

- Single or multiple dilated ducts containing intraductal papillary proliferations and abundant mucin
- The associated chronic pancreatitis results in a firm

nodular pancreas

- The majority occur in the head of the pancreas, with prominent dilated proximal ducts, although it is not uncommon to have involvement of the entire gland

Microscopic

- Marked mucin overexpression expanding ducts
- Epithelial proliferation is variable within a given case with flat normal-appearing areas, nondysplastic proliferations, flat dysplasia, and multifocal villous dysplasia analogous to colonic villous adenomas
- 10% to 20% show invasion into underlying parenchyma, which resembles ductal adenocarcinoma

Immunohistochemistry

- Positive for cytokeratin and CEA
- Typically not needed

Differential Diagnosis

- Mucinous cystic tumor:
  - Large unilocular circumscribed cyst separate from the duct system; connection with duct system and multifocality suggests IPMT
- Ductal adenocarcinoma:
  - Tumor with intraductal spread; must be differentiated from IPMT with invasion
  - IPMT appears to be a precursor lesion to some cases of ductal adenocarcinoma
- Chronic pancreatitis with ductal papillary hyperplasia:
  - Nonneoplastic pancreatic duct change in obstructed ducts; no dysplastic changes and much less mucin

Mucinous Cystadenocarcinoma

Clinical

- <1% of all pancreatic neoplasms
- M:F = 2:1, peak age fifth decade, men usually older
- Most cases probably progress from mucinous cystaenoma

Macroscopic

- Most associated with areas of benign mucinous cystadenomas
- 80% occur in pancreas body or tail
- May show obvious invasion into peripancreatic tissues or adjacent organs

Microscopic

- Tall columnar epithelial cells with intracellular mucin; severe dysplasia may be focal
- Severe nuclear atypia, frequent mitotic figures, and numerous irregular papillary structures with atypical glands invading stroma
- Invasive component usually resembles ductal adenocarcinoma, but may show dedifferentiation; underlying ovarian-type stroma may be present

Immunohistochemistry

- Positive for cytokeratin and CEA

Differential Diagnosis

- Mucinous cystadenoma:
  - Benign columnar epithelial cells with mucin production must be well sampled to rule out malignant transformation to mucinous cystadenocarcinoma
- Pseudocyst:
  - Lack of epithelial lining, ovarian-type stroma, and mucoid contents
- Intraductal papillary-mucinous tumor:
  - Cystic dilation of main pancreatic duct and branches, with papillary growth of mucin-producing cells; no ovarian-type stroma

Acinar Cell Carcinoma

Clinical

- Uncommon neoplasm (< 1% of exocrine pancreatic tumors)
- M:F = 2:1; rare in children; predominantly in adults (average age = 60)
- Associated with polyarthralgia-polyarthritis and disseminated subcutaneous fat necrosis syndrome in 10% of patients due to elevated lipase/trypsin production by the tumor
- >50% with metastasis at diagnosis
- 5% 5-year survival

Macroscopic

- Well-circumscribed nodular soft yellow-tan mass with fibrous bands and frequent necrosis
- Typical size = 10 cm

Microscopic

- The architecture consists of tightly-packed acini simulating cribriforming; variable fibrosis
- The neoplastic cells exhibit hypergranular cytoplasm (zymogen granules) and round uniform nuclei with distinct nucleoli; mitotic figures are rare

Immunohistochemistry

- Cytoplasmic granules are PAS +, diastase resistant
- Trypsin, lipase, keratin and alpha-1-antitrypsin are +; mucin stains –

Variant

- Mixed acinar/endocrine type

Differential Diagnosis

- Islet cell tumor:
  - Acinar differentiation may be present, but architec-

ture is more variegated; synaptophysin and chromogranin +; PAS-D, lipase, and trypsin –

- Solid pseudopapillary tumor:
  - Nearly exclusive occurrence in young females; solid and pseudopapillary histologic pattern with distinctly myxoid fibrovascular stroma and monomorphic epithelioid cytology
- Pancreatoblastoma:
  - Acinar pattern present, but accompanied by significant solid and squamous areas and neoplastic stroma; may be difficult to distinguish in children
- Ductal adenocarcinoma:
  - Firm ill-demarcated tumor; duct-like glands lined by cuboidal cells, embedded in fibrous stroma

Islet Cell Tumor

Clinical

- May be hormonally active (50%) or present as mass without hormone production (50%)
- May be associated with MEN-1:
  - MEN-1 related islet cell tumors tend to be multiple and less aggressive (see chapter 2)
- Islet cell tumors should all be considered neuroendocrine carcinomas with unpredictable malignant potential; metastasis are usually to liver

Macroscopic

- Generally well-circumscribed with partial to complete encapsulation; tan, soft cut surface; occasionally cystic
- Larger tumors (>6 cm) can rarely show gross invasion into peripancreatic tissues
- Hormonally active tumors (gastrinoma, insulinoma) can be quite small (<1 cm) at presentation

Microscopic

- Architectural patterns are numerous, including solid, gyriform (ribbon-like), acinar, and glandular
- Cytology tends to be uniform and low grade, with moderate nuclear:cytoplasmic ratio and evenly distributed stippled chromatin in round nuclei without macronucleoli:
  - Histologically indistinguishable from carcinoid
- Histologic features are not predictive of behavior

Immunohistochemistry

- Chromogranin, synaptophysin +
- Various hormone immunostains may be positive singly, in combination with, or entirely negative, including insulin, glucagon, vasoactive intestinal peptide (VIP), somatostatin, and gastrin
- Immunohistochemical evidence of hormone production may not correlate with clinical syndrome, and will often focally demonstrate multiple hormones
- Insulinomas tend to be benign (90%), but hormone production does not otherwise predict outcome

Electron Microscopy

- Prominent secretory granules are identified; certain hormones (insulin) show specific granule features

Differential Diagnosis

- Chronic pancreatitis:
  - Exocrine atrophy with marked fibrosis and secondary islet aggregation diffusely involving the pancreas
  - Discrete nodules of islet aggregation are not seen
- Acinar carcinoma:
  - Uniform acinar architecture; negative for chromogranin and synaptophysin; PAS-D +
- Solid pseudopapillary tumor:
  - Difficult differential diagnosis; more uniformly papillary and cystic with typical myxoid fibrovascular cores; usually chromogranin and synaptophysin –

Solid-Pseudopapillary Tumor

Clinical

- Uncommon neoplasm; 1% to 2% of all exocrine pancreatic tumors
- Predominantly adolescent/young adult females; mean age = 35 years; rare pediatric tumor
- Surgical removal = 95% cure rate

Macroscopic

- Well-demarcated, solitary, encapsulated tumor
- Cut surface shows lobulated light brown zones admixed with hemorrhage, necrosis, and cystic spaces
- Typical size = 8–10 cm

Microscopic

- The architecture is variegated with both solid and pseudopapillary areas of necrosis and cystic degeneration; several cell layers line myxoid fibrovascular cores
- Cells are cuboidal with eosinophilic to clear cytoplasm and round to oval nuclei; solid areas contain large tumor cells with foamy cytoplasm; overt invasion or significant mitotic activity is rare

Differential Diagnosis

- Islet cell tumor:
  - Lacks widespread hemorrhagic/necrotic changes or pseudopapillary pattern; positive for synaptophysin and chromogranin
  - Islet cell neoplasm may become cystic
- Acinar cell carcinoma:

- Poorly demarcated with nodular cut surface; lacks pseudopapillary changes; positive for trypsin and lipase; more frequent in men than women

♦ Pancreatoblastoma:

– Lacks pseudopapillary pattern; displays acinar architecture

Osteoclast-Like Giant Cell Tumor

Clinical

♦ Very rare tumor (21 cases described); wide age range, 32–82 years of age

♦ Presenting symptoms are abdominal pain, weight loss, palpable mass, and jaundice

♦ Subtype of ductal adenocarcinoma

Macroscopic

♦ Most in head of pancreas

♦ Typically large mass (5–8 cm)

♦ Firm, lobulated, white-yellow color with frequent extrapancreatic extension

Microscopic

♦ Often admixed with ductal adenocarcinoma

♦ Two cell populations:

- Pleomorphic malignant cells are large, spindled, or ovoid with high nuclear:cytoplasmic ratio with prominent nucleolus; mitoses are abundant
- Intermixed is second population of benign multinucleated osteoclast-like giant cells that lack mitotic figures

Immunohistochemistry

♦ Pleomorphic malignant cells are keratin +; multinucleate osteoclast-like cells are often keratin –

Differential Diagnosis

♦ Sarcoma:

- Lacks keratin expression; usually lacks osteoclast-like giant cells; extremely rare in pancreas

Miscellaneous Tumors

Malignant Lymphoma

♦ Secondary involvement by advanced hematopoietic malignancies is not uncommon

♦ Primary lymphomas are extremely rare, usually presenting as large nodular masses in the head of the pancreas

♦ These tumors must be distinguished from large undifferentiated carcinomas

Sarcoma

♦ Case reports exist for rare occurrences of primary soft tissue sarcomas occurring in the pancreas

♦ Metastatic sarcoma and variants of primary pancreatic epithelial tumors must be excluded

Metastases

♦ Metastatic tumors can involve the pancreas either by direct extension or by hematogenous spread

- Direct extension occurs mainly from gastrointestinal or biliary tract adenocarcinomas:
  - Gross and microscopic examination of these tumors is needed to exclude a primary pancreatic neoplasm
- The most frequent hematologic metastases occur from kidney, breast, lung, and melanoma
- Secondary involvement of the pancreas by metastic tumors is rarely clinically evident

TNM CLASSIFICATION OF PANCREATIC TUMORS (1997 REVISION)

♦ T: Primary tumor

- Tx: primary tumor cannot be assessed
- T0: no evidence of primary tumor
- Tis: carcinoma in situ
- T1: tumor limited to the pancreas, ≤ 2 cm in greatest dimension
- T2: tumor limited to the pancreas, > 2 cm in greatest dimension
- T3: tumor extends directly into any of the following: duodenum, bile duct (including ampulla of Vater), peripancreatic tissues (including retroperitoneal fat, mesentery, mesocolon, greater and lesser omentum, and peritoneum)
- T4: tumor extends directly into any of the following: stomach, spleen, colon, adjacent blood vessels (portal vein, celiac artery, superior mesenteric, and common hepatic vessels)

♦ N: Regional lymph nodes

- Nx: regional lymph nodes cannot be assessed
- N0: no regional lymph node metastasis
- N1: regional lymph node metastasis
- N1a: metastasis in a single regional lymph node
- N1b: metastasis in multiple regional lymph nodes

♦ M: Distant metastasis

- Mx: distant metastasis cannot be assessed
- M0: no distant metastasis
- M1: distant metastasis

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Chapter 30

Non-Neoplastic Hepatobiliary Disease

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Table of Contents

VIRAL HEPATITIS

Grading and Staging of Viral Hepatitis

- Grade reflects the degree of inflammatory activity:
  - Old terms are chronic persistent hepatitis, chronic active hepatitis, and chronic lobular hepatitis; these terms have become obsolete
  - Main determinants of grade are degree of lobular hepatocellular necrosis and degree of periportal lymphocytic piecemeal necrosis ("interface hepatitis")
  - Histological activity index of Knodell et al. is widely used in clinical trials and assesses grade and stage by adding numerical values for periportal and lobular necrosis, portal inflammation, and fibrosis
  - Simplified schemes exist and are more appropriate in daily patient care settings, using semiquantitative numeric values
  - Most practical is a grading system using "none, minimal, mild, moderate, and severe" as descriptive terms
  - Both chronic hepatitis B and C are amenable to grading, with hepatitis B showing much greater range of disease activity than hepatitis C
- Stage refers to the degree of fibrosis, presumably subsequent to prior necroinflammatory insults
  - Staging requires appropriate stains (Masson's trichrome)
  - Detailed staging systems have been proposed, but most practical is
    - Fibrosis restricted to portal tracts (stage 1)
    - Periportal fibrosis and rare portal-portal septa (stage 2)
    - Numerous septa leading to architectural distortion (stage 3)
    - Bridging fibrosis with nodular regeneration (stage 4); stage 4 represents cirrhosis

Hepatitis A

Clinical

- Picornavirus (non-enveloped ssRNA) icosahedral, 27 nm; not directly cytopathic
- 1-month incubation period, antibodies appear 2 weeks later; IgG indicates exposure in the past, IgM is marker for acute infection; may persist for 1 year
- Most cases anicteric, self-limited illness
- Fatalities in <0.5%; no chronic carrier state
- Interferon treatment in selected cases of fulminant hepatitis A

Microscopic

- Inflammation is lymphocytic, involving portal, periportal, and lobular areas
- Variable cholestasis

Differential Diagnosis

- Hepatitis E
- Drug-induced hepatitis
- Autoimmune hepatitis

Hepatitis B

Clinical

- One of the most common viral diseases; endemic in the developing world
- Enveloped (42 nm) "Dane particle," hexagonal inner core with circular dsDNA genome
- Not directly cytopathic; injury due to inflammation after integration into host cell
- Present in blood near the end of the incubation period; transmission by blood or sexual contacts
- Most cases are subclinical, 10% with fulminant hepatitis or chronic disease; host factors are probably the most important determinant of the individual clinical course
- Increased risk for hepatocellular carcinoma
- HBsAg appears first, followed shortly by HBeAg, which disappears with the arrival of IgM anti-HBc (beginning of symptoms) and later anti-HBe; HBsAg lost after approximately 2 months; 1–4 month "window period" before anti-HBs develops
- Persistence of HBeAg indicates persistent infection and likely progression to chronic hepatitis
- Active immunization is successful in preventing the disease; a "therapeutic" vaccine for chronic hepatitis B patients is in development

Microscopic (Acute Hepatitis B)

- Lobular predominant inflammation with highly varying degrees of degeneration (hepatocellular ballooning, necrosis) and regenerative changes
- Lymphocytosis very uncommon; portal tracts rarely affected
- No ground glass hepatocytes (cytoplasmic aggregates of excess HBsAg admixed with smooth endoplasmatic reticulin, which distend the cytoplasm and displace the nucleus peripherally)

Microscopic (Chronic Hepatitis B)

- Varying degrees of portal/periportal inflammation, predominantly lymphocytic; piecemeal necrosis is typical
- Varying degrees of fibrosis (stage)
- Varying degrees of hepatocellular disarray, necrosis, and cytoplasmic swelling (grade)

- Steatosis uncommon
- Frequently associated with scattered ground glass hepatocytes
- Grading is useful and may predict the likelihood of progression to cirrhosis, dying from disease, and responding to therapy; however, the histologic grade is inter-related with replication status and host response:
  - Grading may not be useful in a patient with non-replicating disease
- Staging for prognostic purposes, prediction of therapy response to alpha interferon, confirmation of cirrhosis, and monitoring of disease progression

Special Studies

- HBsAg and HBcAg are immunohistochemically – in acute hepatitis B and may be + in chronic hepatitis B
- Membranous HbsAg + (indirect evidence of active viral replication)
- Cytoplasmic HbsAg + (associated with or without core formation)
- Nuclear HbcAg + (indicative of active viral replication); when cytoplasmic HBcAg is also demonstrable, even greater degree of viral replication likely

Differential Diagnosis

- Other viral hepatitis
- Drug-induced hepatitis
- Autoimmune hepatitis

Hepatitis C

Clinical

- Enveloped ssRNA flavivirus, directly cytopathic; major cause for post-transfusion (before 1991) and "sporadic" non-A, non-B hepatitis; large cumulative medical burden with high costs per case
- Prevalence from 0.5% (Great Britain) to 40% (Cameroon)
- Six genotypes with 40 subtypes exist:
  - An individual patient may harbor several subtypes (quasispecies)
  - Genotypes 1a, 1b, 2a, 2b, and 3a are common in Western Europe and the United States
  - Genotype 4 is common in Africa and the Middle Easts
- Incubation time is 6–7 weeks; acute infection goes unrecognized in 90%; 90% of infected individuals carry the virus indefinitely
- Relatively indolent course over many years; more severe cases with certain virus genotypes; presence of cirrhosis often underestimated clinically
- Major complications include significant fatigue (50% at 10 years), cirrhosis (25% at 20 years), and hepatocellular carcinoma (5% at 30 years); HCV infection is the leading cause for liver transplantation
- Diagnosis by enzyme immunoassay; confirmation by recombinant immunoblot assay
- Interferon alpha is the only established treatment, but only about 25% of infected individuals benefit; genotype 1b responds less well; liver transplantation for end-stage liver disease
- Recurrence after liver transplantation, but less rapid progression compared to hepatitis B recurrence
- Vaccines are difficult to develop and currently are not available

Microscopic (Acute Hepatitis C)

- Lobular hepatitis similar to hepatitis A or B, but bridging necrosis is rare
- Significant portal inflammation and lymphoid aggregates are common
- Overall picture is similar to chronic hepatitis C; however, fibrosis is absent

Microscopic (Chronic Hepatitis C)

- Prominent portal and periportal inflammation with lymphoid infiltrates; lymphoid aggregates/follicles in 50%
- Some lymphocytic bile duct damage without ductopenia is common.
- Lymphocytic piecemeal necrosis (interface hepatitis), lobular inflammation, and hepatocellular necrosis define disease activity (grade); these changes are common, but usually mild
- Macrovesicular steatosis, generally mild and non-zonal, is typical
- Increase in sinusoidal lymphocytes and macrophages ("string of beads") is common
- Grading continues to be important in assessing disease activity because other reliable surrogate markers are not available:
  - Grading also plays a role in prognosis assessment and the predication of response to alpha interferon
- Staging predicts time to development of cirrhosis, response to medical therapy, rate of disease progression in untreated patients, and efficacy of therapy

Special Studies

- Immunohistochemical and/or in situ identification of HCV are technically possible but remain challenging; no diagnostic role in the non-transplant setting
- HCV RNA levels and HCV genotype can help predict response to alpha interferon

Differential Diagnosis

- Other viral hepatitis
- Steatohepatitis of other causes

- Drug-induced hepatitis
- Autoimmune hepatitis

Hepatitis D

- Very small RNA virus contained in hepatitis B virus protein envelope (HBs antigen), which is needed for entry into hepatocytes; requires the presence of HBV to replicate
- Worldwide distribution, with significant geographic variation; highest in South America; accounts for 5% of hepatitis B carriers
- HDV infection as coinfection at the time of HBV acquisition or as superinfection of chronic hepatitis B; wide range of clinical course
- Microscopic features in the range of those observed in hepatitis B; microvesicular steatosis and numerous acidophil bodies are prominent
- Increases the severity of acute and chronic HBV infection and decreases the risk of becoming an HBV carrier
- Sexual and vertical transmission less common than in hepatitis B
- Detection by serologic testing or RT-PCR (method of choice); treatment with interferon is of uncertain benefit; prevention relies on hepatitis B prevention
- Liver transplantation is a valid treatment option; risk of allograft re-infection is much less than in typical hepatitis B case

Hepatitis E

Clinical

- RNA virus (calicivirus), endemic and/or epidemic in the developing world
- Transmission by fecal-oral route (contaminated water)
- Clinically indistinguishable from hepatitis A; incubation period is 2–9 weeks; commonly produces cholestasis
- Microscopically resembles hepatitis A
- Mild clinical course with resolution in a few weeks, however, high mortality in pregnancy (20%)
- Detection by serologic testing or by PCR; no specific treatment
- Prevention by prudent travel hygiene and sanitation

Hepatitis F

- Hepatitis F virus has been described in only a few cases from France, with subsequent experimental transmission to primates
- Virology, epidemiology, hepatotropicity, and clinical significance are quite uncertain at this point

Hepatitis G

- Also known as GBV-C
- Role as a true hepatitis virus uncertain
- Flavivirus, distant relative of HCV
- Currently identifiable only with PCR, indicating current infection; immunoassay is in development; once antibodies are formed, HGV RNA is no longer present
- Nature, prevalence, risk factors, and preventive measures are unclear at this point
- Transmission is through blood transfusions, mother to child, and intravenous drug users
- Two percent of healthy blood donors test positive for HGV RNA
- Co-infection with HBV or HCV is common, but no worsening of hepatitis B or C
- HGV may be a "virus looking for a disease"; likely does not cause acute hepatitis, but may be a co-factor in chronic hepatitis in certain risk groups

Human Immunodeficiency Virus Infection and AIDS

Clinical

- Majority of patients with AIDS reveal liver function abnormalities, secondary to associated infections, neoplasms, and drug toxicity
- Prognosis related to AIDS stage
- Coinfection with hepatitis B and C is common.

Microscopic

- Lymphocytic depletion in portal tracts in 50% of all cases
- Kupffer cells are main hepatic target for HIV.
- Changes secondary to opportunistic infections (granulomas, multimicrobial AIDS cholangiopathy)
- Kaposi's sarcoma, lymphoma

Special Stains

- Acid-fast bacilli (*M. tuberculosis, avium-intracellulare*)
- Methenamine silver (fungal organisms)

Differential Diagnosis

- Other immunocompromising conditions

Epstein-Barr Virus Infection

Clinical

- Causes infectious mononucleosis; U.S. incidence twice that of acute viral hepatitis
- Five-week incubation period; 50% of cases clinically asymptomatic
- Liver involvement in 90% (elevated LFTs), jaundice only in 5%
- Immunocompromised patients may show signs of infection for years, no permanent liver damage

Microscopic

- Portal tract expansion by marked lymphoid infiltration; some lymphocytes are large and atypical, with circulating atypical lymphocytes in sinusoids (Indian file)
- Cord-sinus pattern is intact, only minimal hepatocellular changes; no fibrosis

Special Studies

- "Monospot" test is sensitive and specific
- EBV-specific antibodies confirm diagnosis

Differential Diagnosis

- Acute viral hepatitis
- CMV hepatitis
- Drug-induced hepatitis
- Lymphocytic leukemia

Cytomegalovirus Infection

Clinical

- Latent infection with subsequent reactivation in immunosuppression
- May be acquired from blood transfusions or congenital infection; multiorgan damage
- Clinically mild and self-limiting; rare cases of fatal liver failure in immunocompromised individuals

Microscopic

- Large intranuclear amphophilic inclusions with surrounding halo (owl's eye) are diagnostic, but generally only seen in immunocompromised individuals
- Mimics infectious mononucleosis when present in immunocompetent individuals
- Neonatal form with portal fibrosis, giant cells, and cholangitis

Special Studies

- CMV-specific serum antibodies

Immunohistochemistry

- CMV antigen as nuclear staining pattern in hepatocytes and bile duct epithelium

Differential Diagnosis

- Acute viral hepatitis
- EBV hepatitis
- Drug-induced hepatitis
- Lymphocytic leukemia

Herpes Simplex Virus Infection

Clinical

- Immunocompromised patients only
- Type 1 oral, type 2 genital; both may involve the liver
- Marked elevation of LFTs; disseminated intravascular coagulation common
- 90% fatality with symptomatic hepatic necrosis

Microscopic

- Coagulative necrosis and hemorrhage in large areas; no zonal distribution
- Two types of intranuclear inclusions: Cowdry A and B, only in hepatocytes

Special Studies

- Feulgen reaction: nuclear staining + with Cowdry B, – with Cowdry A
- HSV-genome sequencing after PCR-amplification distinguishes type 1 and 2

Immunohistochemistry

- Herpes virus (type 1 and 2 antigen not distinguishable)

Differential Diagnosis

- *Varicella-zoster*
- *Vaccinia*
- Eclampsia

NONVIRAL INFECTIONS

Bacterial Infection

Pyogenic Bacterial Infection

Clinical

- Pyogenic abscesses from trauma, septicemia, and direct extension from other foci
- Malaise, pain, fever, hepatomegaly
- Treatment with antibiotics, aspiration, and culture for diagnosis
- Prognosis related to underlying condition

Microscopic

- Acute and chronic portal inflammation with cholestasis and microabscesses in parenchyma
- Liver cell necrosis, parenchymal inflammation with increased sinusoidal neutrophils

Special Stains

- Gram
- PAS (*Entamoeba histolytica*)

Differential Diagnosis

- Acute viral hepatitis
- Extrahepatic biliary obstruction
- Amebic abscess

Brucellosis

Clinical

- *Brucella* (gram-coccobacillus), contraction by close contact with infected animals
- Fever, chills, hepatosplenomegaly, lymphadenopathy
- Diagnosis by culture from tissue (bone marrow); 5% fatality rate if untreated

Microscopic

- Granulomatous hepatitis with Kupffer cell hyperplasia
- Rarely microabscesses

Special Studies

- Tissue culture for diagnosis

Differential Diagnosis

- Typhoid fever
- Tularemia
- Drug-induced granulomatous changes
- Acid-fast bacilli or fungal organisms

Salmonellosis

Clinical

- *S. typhi/paratyphi/typhimurium*—food poisoning
- Hepatomegaly in 30%; jaundice infrequent
- Diagnosis by culture (blood, stool)
- 15% mortality if untreated; biliary tract disease as complication
- Chronic carrier state in 3%; gallbladder is reservoir for organisms

Microscopic

- Marked Kupffer cell hypertrophy and hyperplasia
- "Typhoid nodules" (focal necrosis and inflammatory aggregates) randomly seen in parenchyma
- Portal inflammation

Special Studies

- Culture for diagnosis, Gram-organisms in Kupffer cells

Differential Diagnosis

- Brucellosis
- Reticuloendothelial neoplasms

Recurrent Pyogenic Cholangiohepatitis

Clinical

- Frequently seen in the Far East; pathogenesis uncertain
- Clonorchis sinensis is present in 50%; biliary cultures are positive for enteric bacteria
- Recurrent symptoms of acute cholangitis
- Biliary calculi and sludge are present; left lobe is predominantly affected
- Complications include pancreatitis, liver abscess, fistulas, septicemia, cholangiocarcinoma, and portal vein thrombosis
- Prognosis related to complications

Microscopic

- Intrahepatic duct dilatation with surrounding inflammation and abscess formation
- Cholestasis, fibrosis, intrahepatic calculi, sludge

Differential Diagnosis

- Extrahepatic obstruction
- Primary sclerosing cholangitis
- Caroli's disease

Syphilis

Clinical

- Treponema pallidum—liver involvement in three stages; consequences of tertiary disease determine prognosis:
  - Congenital syphilis (liver disease years after birth)
  - Secondary syphilis (10% of infected patients, nonspecific liver disease)
  - Tertiary syphilis (Hepar lobatum— deeply scarred liver secondary to fibrosed gumma

Microscopic

- Congenital: Severe portal and interstitial fibrosis with focal necrosis; no regeneration
- Secondary: Scattered epithelioid granulomas and small vessel vasculitis typical
- Tertiary: Gumma formation and obliterative endarteritis, dense scar formation, and amyloid deposition

Special Studies

- Darkfield microscopy
- Immunohistochemistry
- Silver stain (congenital, some secondary stage cases)

Differential Diagnosis

- Neonatal giant cell hepatitis
- Brucellosis/salmonellosis
- Drug-induced granulomatous hepatitis

Mycobacterium Infection

Tuberculosis

Clinical

- Hepatic involvement in 25% (chronic forms), 70% (acute primary pulmonary disease) to 95% (miliary tuberculosis)

- High index of suspicion because necrotizing granulomas, stained organisms, or positive culture are rather uncommon on liver biopsy
- Non-specific liver disease at presentation; severe hepatic dysfunction is rare; liver disease is almost never responsible for mortality

Microscopic

- Well-defined portal and parenchymal epithelioid granulomas with Langerhans' giant cells
- Necrotizing granulomas rare, seen with active organism growth
- Macrovesicular steatosis

Special Studies

- Acid-fast stain (commonly negative though)

Differential Diagnosis

- Sarcoidosis
- Other granulomatous reactions

Mycobacterium-avium intracellulare *(MAI) Infection*

Clinical

- Slowly growing nontuberculous organism; disseminated infection in immunocompromised individuals
- Hepatic involvement in 50%, with non-specific liver disease
- Treatment response in AIDS and other immunocompromised patients dismal

Microscopic

- Less circumscribed, usually non-necrotizing granulomas in portal tracts and parenchyma, with foamy histiocytes in immunocompromised patients
- No zonal distribution of granulomas

Special Studies

- PAS
- Acid-fast stain

Differential Diagnosis

- Tuberculosis
- Gaucher's disease
- Histiocytosis X
- Neoplasms

Leprosy

Clinical

- *M. leprae*, an estimated 20 million people infected (tropical climate); hepatic granulomas in >50%
- Systemic amyloidosis is a frequent complication
- Difficult to eradicate; morbidity from nerve destruction

Microscopic

- Tuberculoid type (granulomas), lepromatous type (granulomas and foamy histiocytes), intermediate types
- Portal inflammation

Special Studies

- Acid-fast (lepromatous type)
- Silver stains (non-viable organisms)

Differential Diagnosis

- Sarcoidosis
- Tuberculosis

Rickettsial Infection

Clinical

- Coxiella burnetti (Q fever) and R. rickettsii (Rocky Mountain spotted fever)
- Liver involvement in 85%; antibiotics curative

Microscopic

- Granulomatous hepatitis with focal necrosis; fibrin ring around fat vacuoles (fibrin ring granulomas)
- Portal inflammation and macrovesicular steatosis
- Prominent Kupffer cell hyperplasia

Differential Diagnosis

- Bacterial infections
- Lymphomas
- EBV infection

Fungal Infection

Histoplasmosis

Clinical

- Histoplasma capsulatum, highly endemic in Ohio and Mississippi River Valleys and in South America
- Birds are main carriers; asymptomatic infection in 90%
- Immunocompromised individuals with disseminated disease and liver involvement
- Mortality is high in untreated symptomatic disease

Microscopic

- Parenchymal granulomas, some necrotizing, often calcified in late stages
- Organisms (2–5 mm with crescent appearance) in Kupffer cells and histiocytes
- Abundant organisms and scant granulomas in immunocompromised patients

Special Studies

- PAS
- Silver stain

Differential Diagnosis

- Tuberculosis
- Sarcoidosis
- Leishmaniasis

Coccidioidomycoses

Clinical

- Coccidiodes immitis, endemic in southwestern United States and South America
- Usually benign, self-limited pulmonary infection
- Immunocompromised individuals with disseminated disease and liver involvement
- Mortality high in untreated symptomatic disease

Microscopic

- Epithelioid granulomas with multinucleated giant cells containing the organisms (20–200 mm spherules with 2 mm wall); no calcifications seen
- Portal inflammation

Special Studies

- PAS
- Silver stain

Differential Diagnosis

- Tuberculosis
- Sarcoidosis
- Blastomycosis

Parasite Infection

Amebic Abscess

Clinical

- Access of Entamoeba histolytica into the portal system from the intestine
- Usually single abscess, 8–12 cm diameter
- Gradual clinical onset with fever and pain; amebic serology is positive
- Responds to treatment; complications include dissemination or rupture

Macroscopic

- Abscess (cyst) formation with fibrous capsule

Microscopic

- Only minimal inflammatory reaction in cyst and wall
- Trophozoites identifiable at periphery (round to oval, 20–60 mm, spherical nuclei and eosinophilic cytoplasm, phagocytosed red blood cells)

Special Studies

- Immunostaining possible
- PAS

Differential Diagnosis

- Pyogenic abscess
- Necrotic tumor mass

Malaria

Clinical

- *Plasmodium* species, 100 million cases per year worldwide
- Liver involvement by adherence to liver venules and ischemic necrosis
- Liver forms of the organism responsible for late relapses
- Malaria symptoms plus hepatosplenomegaly; jaundice possible
- Increased mortality with *P. falciparum* species

Microscopic

- Dark pigment (hemozoin) in Kupffer cells
- Perivenular necrosis
- Sinusoidal congestion with parasite-filled Kupffer cells and red blood cells

Special Studies

- Prussian blue; hemozoin is –
- Immunostaining for the organism possible

Differential Diagnosis

- Disorders with hemosiderin deposition in Kupffer cells
- Schistosomiasis
- EBV infection

Hydatid Cyst

Clinical

- Echinococcus species, transmitted by dog feces
- Usually single cyst, slowly enlarging (up to 25 cm), often palpable
- Complications include biliary obstruction, cholangitis, superinfection, and anaphylaxis
- Prognosis usually good, if treated (surgical resection and/or parasiticidal drugs)

Macroscopic

- Unilocular or multilocular, endogenous (E. granulosus) or exogenous (E. multiloculare) daughter cyst formation
- Calcifications common

Microscopic

- Cyst wall with thin inner germinal layer and outer layer of dense hyalinized/calcified tissue with surrounding inflammation
- Scolices present within the cyst

Differential Diagnosis

- Amebic abscess

Clonorchiasis

Clinical

- Clonorchis sinensis, common infection in the Far East, humans as definitive host; parasite rests in major intrahepatic ducts
- Usually asymptomatic; severe infections cause recurrent pyogenic cholangitis with typical symptoms
- Complications include duct obstruction, cholangitis, and cholangiocarcinoma; prognosis with treatment good

Macroscopic

- Hepatomegaly with grey and pale blue subcapsular cysts (dilated ducts with parasites)

Microscopic

- Organism in bile ducts
- Proliferation of small glands around affected bile ducts
- Ductular proliferation in portal tracts

Differential Diagnosis

- Mechanical duct obstruction
- Recurrent pyogenic cholangiohepatitis

Schistosomiasis

Clinical

- Schistosoma species, infection through skin in infested waters; liver disease by S. mansoni and S. japonicum
- Mortality due to portal hypertension in chronic disease (granulomatous reaction to organism eggs in portal circulation)

Microscopic

- Granulomatous portal inflammation surrounding parasite eggs
- Variable degrees of lamellar fibrosis (pipe-stem lesion)

Special Studies

- Acid-fast +

Differential Diagnosis

- Granulomatous lesions of other etiologies
- Portal fibrosis

DRUGS AND TOXINS

General Features

- Drugs and other chemical toxins account for <5% of cases of jaundice, hepatitis, or chronic liver disease, but are an important cause of more severe types of hepatic injury
- Drugs produce an array of hepatic lesions that mimic all known hepatobiliary diseases and pose a diagnostic challenge for clinicians and pathologists
- Diagnosis is circumstantial, with positive rechallenge being the only factor that unequivocally implicates a particular agent after consideration of the temporal relationships between drug ingestion and liver disease and exclusion of other hepatobiliary disorders
- Liver biopsy can lend support to the diagnosis; early detection is critical
- Protocol screening of patients with liver function tests and/or biopsy is recommended for certain drugs, but efficiency and cost-effectiveness are mostly unknown and controversial

Pure Hepatocellular Necrosis

Common Example: Acetaminophen

- Large dose (>10g) results in liver cell necrosis with rapid development of liver failure; typically suicidal
- N-acetylcysteine (repletes glutathione) administration up to 10 hours after ingestion prevents catastrophic outcome; transplantation is life-saving, but controversial
- Coagulative-type necrosis, perivenular; uniform liver involvement
- Marked midzonal and portal regeneration after 1 week

Other Drugs

- Periportal (zone 1): Ferrous sulfate, phosphorus
- Midzonal (zone 2): Beryllium, dioxane, disulfiram, sulfasalazine, indomethacin
- Perivenular (zone 3): Aflatoxin B1, chloroform, carbon tetrachloride, halogenated hydrocarbons, phalloidin, other alkaloids
- Diffuse: Trinitrotoluene, tetrachlorethane, piroxicam, cimetidine, carbamazepine

Acute Hepatitis

Common Example: Isoniazid

- Incidence of acute hepatitis and abnormal liver function tests in patients over 35 years of age is 3% and 30%, respectively; 10% of symptomatic patients die of

hepatic failure; overall mortality is 0.1%

- Subacute hepatic injury or overt hepatic injury 2–11 months after treatment initiation
- Drug withdrawal resolves the problem in 70% of all cases; supportive treatment, liver transplantation
- Diffuse hydropic change, focal necroses, and periportal inflammation

Common Example: Phenytoin

- Incidence of acute hepatitis is 1%; hepatotoxicity is caused by hypersensitivity
- Clinical presentation like viral hepatitis plus rash and eosinophilia
- Prompt reproducibility upon rechallenge; excellent prognosis
- Features resembling viral hepatitis and EBV infection with "Indian filing" of sinusoidal lymphocytes

Common Example: Halothane

- Incidence of acute hepatitis is 1:9,000; mortality rate is 1:40,000
- Clinical symptoms after 1–14 days of exposure; abrupt onset; jaundice
- Re-exposure triggers a more severe response
- Supportive treatment or liver transplantation
- Similar features as phenytoin and isoniazid, plus perivenular stromal collapse after repeated exposure

Other Drugs

- Alpha-methyldopa, diclofenac, tetracyclins, indomethacin, nitrofurantoin, phenylbutazone, rifampin, sulfasalazine

Chronic Hepatitis

Common Example: Nitrofurantoin

- Latent period is >6 months, probable autoimmune etiology (ANA +, SMA +)
- Jaundice, fatigue, fever
- Drug withdrawal results in resolution
- Periportal inflammation, diffuse liver cell necrosis, portal fibrosis, hydropic change, cholestasis

Other Drugs

- Alpha-methyldopa, aspirin, chlorpromazine, diclofenac, tetracyclins, disulfiram, isoniazid, methotrexate, propylthiouracil, sulfonamides

Cholestasis and Duct Injury

Common Example: Oral Contraceptives

- Overall incidence 1:10,000 users, symptomatic within 1–6 months
- Gradual onset of hepatitis/cholestasis symptoms
- Cessation of the drug induces remission
- Hepatocellular cholestasis, perivenular dilated canaliculi
- Other hepatic structures relatively normal

Other Drugs

- Pure cholestasis: Anabolic steroids
- Cholestatic hepatitis: Azathioprine, chlorpromazine, cimetidine, erythromycin, 6-mercaptopurine, flucloxacillin, nitrofurantoin, penicillin, sulfonamides, tamoxifen, verapamil
- Acute cholangitis: Allopurinol, chlorpromazine, hydralazine
- Biliary cirrhosis: Ajmaline, chlorpromazine, methyl testosterone, sulfonylurea, tolbutamide

Fibrosis

Common Example: Methotrexate

- Liver cell injury is dose-dependent (cumulative dose >2–4g) and "predictable"
- Insidious onset of hepatosplenomegaly and ascites
- Surveillance liver biopsies recommended in long-term treatment
- Portal fibrosis and sinusoidal collagen deposition
- Prominent diffuse hepatocellular disarray and dysplasia

Other Drugs

- Aflatoxin, copper, disulfiram, alpha-methyldopa, isoniazid

Steatosis

Macrovesicular

- Bleomycin, L-asparaginase, methotrexate, steroids, cisplatin, sulfasalazine, warfarin, indomethacin, tamoxifen

Microvesicular

- Aflatoxin, aspirin, phalloidin, tetracycline, valproic acid

Vascular Abnormalities

Peliosis-like Lesions

- Anabolic steroids, phalloidin, vitamin A

Sinusoidal Dilatation

- Oral contraceptives

Veno-Occlusive Disease

- Aflatoxin, azathioprine, busulfan, mitomycin C, oral contraceptives, tamoxifen, vinyl chloride, vitamin A

Vasculitis

- Allopurinol, chlorthiazide, penicillin, phenylbutazone, phenytoin, sulfonamides

Granulomas

- Non-necrotizing epithelioid or inflammatory types possible
- Usually random distribution
- May be associated with mild non-specific inflammatory changes
- Common examples include allopurinol, alpha-methyldopa, carbamazepine, hydralazine, penicillin, phenylbutazone, phenytoin, quinidine, and sulfonamides

Neoplasms

Liver Cell Adenoma

- Anabolic steroids
- Oral contraceptives controversial

Hepatocellular Carcinoma

- Aflatoxin, anabolic steroids, mycotoxins, thorotrast, vinyl chloride

Cholangiocarcinoma

- Thorotrast, vinyl chloride

Angiosarcoma

- Anabolic steroids, copper sulfate, diethylstilbestrol, thorotrast, vinyl chloride

STEATOHEPATITIC LIVER DISEASE

Acute Alcoholic Liver Disease

Steatosis Hepatis

Clinical

- Most common hepatic abnormality in alcoholics (>90%); may occur in many other clinical conditions (see differential diagnosis)
- Degree of steatosis somewhat proportional to alcohol intake and dietary protein
- Hepatomegaly as the only clinical sign, demonstrable by ultrasound and CT; steatosis may appear focal
- Asymptomatic if steatosis only; completely reversible in 8 weeks if abstinent from alcohol

Microscopic

- Macrovesicular steatosis, more prominent perivenular
- Parenchymal lipogranulomas
- No significant inflammation

Differential Diagnosis

- Obesity
- Diabetes mellitus
- Jejunoileal bypass
- Drugs
- Malnutrition

Steatohepatitis

Clinical

- Chronic alcohol consumption; similar histology can be seen in non-alcoholics (non-alcoholic steatohepatitis, aka "NASH") in generally milder form clinically and histologically
- Wide range of possible presenting symptoms, including nausea, vomiting, hepatomegaly, fever, jaundice, ascites, and hepatic encephalopathy
- Occurs usually after several years of heavy drinking; one-third of patients have significant fibrosis/cirrhosis at presentation
- Cessation of alcohol intake and supportive treatment as the only therapeutic option; worsening of clinical symptoms 2–4 weeks after abstinence possible
- High mortality or definite progression to cirrhosis if drinking problem continues

Microscopic

- Variable macrovesicular steatosis, may be marked
- Hydropic change of hepatocytes, most prominent perivenular
- Neutrophilic infiltrate around damaged hepatocytes
- Amorphous, eosinophilic material in many affected hepatocytes (Mallory bodies)
- Varying degrees of fibrosis, usually perivenular; later stages also bridging
- Cholestasis possible
- Histologic variants include alcoholic foamy degeneration and acute sclerosing hyaline necrosis

Special Studies

- Masson's trichrome
- PAS diastase

Differential Diagnosis

- Wide range of differential diagnoses (see steatosis hepatis)
- Search for other etiologies after exclusion of alcohol

Chronic Alcoholic Liver Disease

Progressive Perivenular Fibrosis

Clinical

- Precirrhotic stage of chronic alcoholic liver disease
- Differs from the "usual" perivenular fibrosis in alcoholics by denseness and degree of perivenular fibrosis and by absence of regenerative nodules
- Patients present with jaundice and ascites, which is resistant to diuretics
- Uniform liver involvement with severe venous outflow obstruction, subsequent clinical features of portal hypertension, and concomitant cirrhosis
- Treatment and prognosis similar to cirrhosis

Microscopic

- Dense sclerosis of perivenular zones
- Only minimal portal fibrosis
- Minimal or absent regeneration

Special Studies

- Masson's trichrome

Cirrhosis

Clinical

- Initial presentation in 40% of cases of alcohol-induced liver disease
- Several years of heavy drinking required; only a subset of chronic drinkers develop cirrhosis; dietary factors may play a role (protein)
- Women have a much lower threshold
- Active drinker has micronodular cirrhosis (nodules between 1–4 mm in size); with abstinence, the regenerative nodules become larger
- Laboratory tests and symptoms may be normal unless acute liver disease or decompensation is present
- Hepatomegaly in early stages; later, atrophic livers predominate
- Hepatocellular carcinoma in 5% to 10%
- Management similar to cirrhosis from other causes; abstinence does not influence survival in the cirrhotic stage; however, it is required for consideration of liver transplantation
- One-year survival after onset of gastrointestinal hemorrhage or ascites = 30% to 50%; 5-year survival after portacaval shunting = 25%; transplantation is curative

Microscopic

- Increasing fibrosis (portal and perivenular, septal, bridging) determines stage with increasing thickness of fibrous septa
- Regenerative nodules of hepatocytes
- Varying degrees of inflammation and steatosis, cholestasis possible

Special Studies

- Masson's trichrome

Differential Diagnosis

- Cirrhosis of other etiologies

Total Parenteral Nutrition

Clinical

- Steatosis due to imbalances in lipoprotein and fatty acid synthesis with subsequent cholestasis
- Jaundice develops after 4–40 days of total parenteral nutrition, resolves with normal oral food intake; cirrhosis in long-standing total parenteral nutrition possible
- Gallstones and sludge develop frequently
- Disease mechanism in neonates and infants more complex; 2% mortality from liver failure

Microscopic

- Variable degrees of macrovesicular steatosis
- Perivenular cholestasis and portal bile duct proliferation
- Giant cell transformation of hepatocytes in the neonate

Differential Diagnosis

- Extrahepatic biliary atresia
- Choledochal cyst
- Neonatal giant cell hepatitis

Non-Alcoholic Steatohepatitic Liver Disease

Jejunoileal Bypass

Clinical

- Procedure done for morbid obesity, 5% will develop hepatic failure months after surgery, with high mortality unless normal anatomy is restored
- Significant fibrosis and cirrhosis in 7% within 1–2 years

Microscopic

- Acute: significant macrovesicular steatosis, perivenular collagen deposition in sinusoids, with liver cell necrosis
- Chronic: well-circumscribed regenerative nodules with fibrosis/cirrhosis; no significant inflammation

Special Studies

- Masson's trichrome

Differential Diagnosis

- Drugs
- Obesity
- Diabetes mellitus

- Acute alcohol-induced liver disease

Obesity and Diabetes Mellitus

Clinical

- Liver function test abnormalities in 35% of patients with diabetes mellitus
- Typically overweight women, even in the absence of diabetes mellitus
- Cirrhosis more frequent in diabetics; weight loss as therapy

Microscopic

- Significant diffuse macrovesicular steatosis
- Glycogenated nuclei more commonly in the diabetic
- Minimal inflammatory changes, mild portal bile duct proliferation
- Micronodular cirrhosis in chronic cases

Special Studies

- Masson's trichrome

Differential Diagnosis

- Jejunoileal bypass
- Acute alcohol-induced liver disease

Acute Fatty Liver of Pregnancy

Clinical

- Young women in their first pregnancy, third trimester
- Rare disorder (<1:10,000 deliveries), etiology unknown
- Non-specific symptoms followed by jaundice
- Supportive treatment with termination of pregnancy; good prognosis with early recognition; overall mortality = 10% to 20%

Microscopic

- Marked microvesicular steatosis, less prominent periportal
- Minimal inflammation and necrosis

Special Studies

- Fat stains

Differential Diagnosis

- Drugs
- Alcohol-induced foamy degeneration
- Reye's syndrome

VASCULAR DISORDERS

Hepatic Venous Outflow Obstruction

Congestive Heart Failure

Clinical

- Serum LFTs usually mildly elevated or normal; jaundice almost never seen
- Chronic right-sided heart failure may cause phlebosclerosis
- "Cardiac cirrhosis" (long-standing congestion) takes years to develop; no regenerative nodules seen
- Treatment of heart disorder resolves liver disease; mortality due to cardiac complications

Microscopic

- Acute: perivenular sinusoidal dilatation and congestion
- Chronic: perivenular sinusoidal dilatation, collagen deposition, and adjacent liver cell atrophy; bridging fibrosis (reversed lobulation) with macronodular cirrhosis in long-standing conditions

Special Studies

- Masson's trichrome

Differential Diagnosis

- Budd-Chiari syndrome
- Cirrhosis, non-cardiac

Budd-Chiari Syndrome

Clinical

- Hepatic venous outflow obstruction
- Causes include membranous obstruction of large hepatic veins (South Africa, Japan, India) and fibrous obliteration of major hepatic veins (Western countries), malignancy, trauma, infection, and radiation
- Clinical presentation with symptoms of acute to chronic liver failure; laboratory tests similar to cirrhosis
- Outcome and complications similar to cryptogenic cirrhosis (chronic forms), acute Budd-Chiari syndrome with poor prognosis

Microscopic

- Acute: severe perivenular dilatation, congestion and hemorrhage, anoxic damage, and red blood cell trabecular lesion
- Chronic: perivenular fibrosis with sinusoidal collagen deposition and bridging fibrosis

Special Studies

- Masson's trichrome

Differential Diagnosis

- Cardiac congestion
- Drug effect
- Cirrhosis

Veno-Occlusive Disease

Clinical

- Acute (hepatic failure) and chronic (insidious liver disease) presentations
- Direct hepatic vein endothelial damage with fibrin deposition
- Causes include radiation, chemotherapy, graft-versus-host disease in bone marrow transplantation, and alcoholic liver disease
- Endemic in the West Indies (tea with toxic alkaloids)
- Symptomatic treatment as in chronic liver disease, liver transplantation

Microscopic

- Acute: fibrous obliteration of terminal hepatic venules, sinusoidal congestion, and dilatation
- Chronic: perivenular bridging fibrosis, sinusoidal congestion, no changes in larger hepatic veins

Special Studies

- Masson's trichrome

Differential Diagnosis

- Budd-Chiari syndrome
- Right-sided heart failure

Hypotensive Anoxia

Clinical

- Hepatic arterial blood flow directly related to cardiac output; only severe hypotension leads to extensive liver cell necrosis; usually varying degrees of mild ischemic necrosis throughout the liver; rarely significant hepatic dysfunction
- Full recovery from a single hypotensive episode; prognosis related to underlying problem

Microscopic

- Liver cell coagulative necrosis, prominent in perivenular zones, later perivenular collapse

Special Studies

- Reticulin

Differential Diagnosis

- Drug-induced liver injury
- Viral hepatitis

Inflammatory Vascular Lesions

Pylephlebitis

Clinical

- Portal vein inflammation secondary to intra-abdominal suppurative infection (appendiceal, diverticular, or pelvic abscess)
- High mortality if infection cannot be eradicated; hepatic abscesses common complication

Microscopic

- Periportal neutrophilic infiltrate and vasculitis, thrombosis, microabscesses

Differential Diagnosis

- Acute cholangitis
- Neoplasm-related thrombosis
- Graft rejection following liver transplantation

Polyarteritis

Clinical

- Necrotizing vasculitis of small arteries, immune-mediated
- Hepatic involvement (60% of all cases) may be symptomatic.
- Thrombosis with infarction and aneurysms as complications
- Immunosuppression and plasmapheresis are therapeutic options

Microscopic

- Fibrinoid necrosis of arteries with mixed inflammatory infiltrate
- Secondary thrombosis

Differential Diagnosis

- Infarction from other causes
- Pylephlebitis

Miscellaneous Vascular Disorders

Peliosis Hepatis

- See chapter 31

Hereditary Hemorrhagic Telangiectasia (Osler-Weber-Rendu Disease)

Clinical

- Autosomal dominant disorder, capillary arterio-venous malformations
- Number of lesions increases with age; liver involvement usually not symptomatic

Microscopic

- Dilated and enlarged portal vessels and arterio-venous malformations

- Variable degrees of fibrosis

Differential Diagnosis

- Idiopathic portal hypertension
- Primary biliary cirrhosis
- Cirrhosis of other etiology

Idiopathic Portal Hypertension (Non-Cirrhotic Portal Fibrosis)

Clinical

- Rare in Western countries; common in India and Japan
- Primary vascular disease, insidious onset with non-specific laboratory findings
- Portal hypertension with typical complications and symptomatic treatment
- Prognosis better than in cirrhosis

Microscopic

- Portal fibrosis, increased dilated vessels, no inflammatory changes, no bile duct anomalies
- No consistent portal-venous fibrosis pattern

Differential Diagnosis

- Osler-Weber-Rendu disease
- Primary biliary cirrhosis
- Drugs/toxins
- Alcohol-induced liver disease

CHOLESTASIS AND BILIARY TRACT DISORDERS

Acute Mechanical Duct Obstruction

Clinical

- Common causes include choledocholithiasis, neoplasms, acute pancreatitis, postoperative iatrogenic duct stricture, and abdominal trauma
- Clinical presentation with Charcot triad (pain, fever, jaundice), due to secondary cholangitis
- Relief of obstruction and antibiotics, otherwise development of chronic stages

Microscopic

- Acute cholangitis with perivenular cholestasis
- Periductal edema with neutrophilic infiltrate
- Dilatation and proliferation of interlobular ducts
- Hepatocellular necrosis and microabscesses
- Bile lakes (leakage from damaged interlobar ducts) and bile infarcts (toxic effect of bile to hepatocytes) are diagnostic, but not readily seen on biopsy

Differential Diagnosis

- Acute alcoholic liver disease
- Pylephlebitis
- Toxic shock syndrome
- Septicemia
- Primary sclerosing cholangitis, non-cirrhotic stage

Chronic Mechanical Duct Obstruction

Clinical

- Common causes include chronic pancreatitis, neoplasms, parasitic infection, extrahepatic biliary atresia, and chronic stages of acute etiologies
- Partial chronic obstruction commonly results in abscess formation and septicemia
- Recurrent cholangitic episodes with fibrosis/cirrhosis
- Interval to biliary cirrhosis is 4–7 years (common duct stricture or choledocholithiasis), 6 months in neonates with extrahepatic biliary atresia
- Cirrhotic patients are usually asymptomatic; no hepatocellular carcinoma risk
- Relief of obstruction reverses liver changes in non-cirrhotic patients

Microscopic

- Secondary biliary fibrosis/cirrhosis
- Thickening of arterioles
- Bile ducts are proliferating, later decreased or absent
- Cholestasis, acute cholangitis, bile lakes, and bile infarcts are sometimes seen, but are not as common as in acute obstruction

Differential Diagnosis

- Primary biliary cirrhosis
- Primary sclerosing cholangitis
- Drug-induced reactions

Primary Biliary Cirrhosis

Clinical

- Chronic progressive bile duct destruction leading to biliary cirrhosis; no definite drug treatment
- Prevalence of 20–240 cases per million population; rarely in Africa or India
- Pathogenesis unknown; *E. coli* and mycobacteria implicated
- Presentation with pruritus (50%), fatigue and pain

(25%), and hepatic decompensation (25%); portal hypertension may develop before onset of cirrhosis; cholestatic liver function tests positive

- Commonly associated is sicca syndrome, also thyroid disease, arthralgia, sclerodactyly, and Raynaud's disease; only weak HLA association (DR8)
- Increased serum immunoglobulins, many autoantibodies
- Anti-mitochondrial autoantibodies (E2-subtype) are specific and are found in 96% of all cases
- Mayo prognostic index is most widely used (serum bilirubin, albumin, age, edema, and prothrombin time); median survival time from diagnosis = 3–10 years (stage-dependent)
- Symptomatic treatment for pruritus, lethargy, and osteopenia; ursodeoxycholic acid slows development of cirrhosis; liver transplantation life-saving

Microscopic

- Non-suppurative destructive, granulomatous cholangitis and lymphocytic cholangitis
- Duct loss (ductopenia) in later stages
- Quiescent lobules with variable sinusoidal lymphocytosis
- Pseudoxanthomatous swelling, copper deposition, and Mallory's hyaline in periportal hepatocytes in later stages, reflecting bile acid (cholate) stasis
- Four stages:
  - Portal fibrosis
  - Periportal inflammation and fibrosis
  - Septal fibrosis
  - Cirrhosis
- Recurrence in the allograft is increasingly recognized; associated with degree of immunosuppression and characterized by granulomatous cholangitis and AMA-deposition in biliary epithelium

Differential Diagnosis

- Sarcoidosis
- Graft-versus-host disease
- Chronic hepatitis C
- Primary sclerosing cholangitis

Primary Sclerosing Cholangitis

Clinical

- Slowly progressive (10–15 years) cholestatic disease with resulting biliary cirrhosis; prevalence is 2–7 per 100,000 population
- Etiology unknown; implicated factors include chronic portal bacteremia, toxic bile acid metabolites, chronic viral infections, and ischemic vascular changes
- Male predominance (75%); average age at diagnosis = 40 years
- Typically associated with inflammatory bowel disease (70%); usually chronic ulcerative colitis
- Associated with HLA B8/DR3 haplotype; antineutrophil nuclear and cytoplasmic antibodies (ANCA) are usually +
- Presentation with one or more of progressive fatigue, pruritus, or jaundice in 75%, cholestatic liver function tests
- Diagnosis with liver biopsy and cholangiogram via ERCP (beaded appearance)
- Median survival time from diagnosis = 9–11 years; no association with bowel disease stage
- D-penicillamine, methotrexate, ursodeoxycholic acid, steroids, and other immunosuppressants have not shown definite beneficial treatment effects
- Complications include fat-soluble vitamin deficiencies, metabolic bone disease, recurrent bacterial cholangitis (frequent), cholelithiasis (30%), bile duct strictures (20%), and cholangiocarcinoma (10% to 15%)
- Liver transplantation treatment of choice; fourth leading cause for liver transplantation in the United States; liver transplantation for diagnosed cholangiocarcinoma experimental
- Recurrent primary sclerosing cholangitis in approximately 8% at 3–5 years after transplantation

Microscopic

- Liver biopsy rarely definitive
- Periductal fibrosis and inflammation, ductular proliferation, biliary ductopenia
- Fibrous obliterative cholangitis ("onion-skin appearance") diagnostic, but rarely present in biopsy specimens
- Four stages:
  - Portal fibrosis
  - Periportal inflammation and fibrosis
  - Septal fibrosis
  - Cirrhosis

Differential Diagnosis

- Sarcoidosis
- Graft-versus-host disease
- Chronic hepatitis C
- Primary biliary cirrhosis
- Alcohol-, drug-, and autoimmune-induced hepatitis

Intrahepatic Cholestasis

Postoperative Cholestasis

Clinical

- Benign, infrequent surgical complication (0.2% of elective procedures); more common after cardiac surgery

- Occurs 1–2 days after prolonged surgical procedures, secondary to bilirubin overload (hemolysis, transfusions) and temporary decrease in liver function
- Prognosis related to surgical complications

Microscopic

- Cholestasis within perivenular hepatocytes and dilated canaliculi
- Minimal inflammation only, bile ducts normal in number; no fibrosis

Differential Diagnosis

- Drugs
- Septicemia
- Early acute duct obstruction
- Intrahepatic cholestasis of pregnancy
- Benign recurrent intrahepatic cholestasis

Intrahepatic Cholestasis of Pregnancy

Clinical

- Third trimester, 2% to 5% of all pregnancies; higher prevalence in Chile and Sweden
- Mild jaundice, disappears after delivery; recurrence in 50% of subsequent pregnancies
- Etiology might be secondary to liver dysfunction from gonadal and placental hormones
- No consequences (other than pruritus) for the mother; increased risk of fetal distress and stillbirth
- Apparent interplay between genetic predisposition and exogenous factor(s) (e.g., selenium deficiency)
- Ursodeoxycholic acid improves maternal pruritus and fetal prognosis

Microscopic

- Cholestasis within perivenular hepatocytes and dilated canaliculi
- Minimal inflammation only, bile ducts normal in number; no fibrosis
- Giant cell transformation of hepatocytes possible

Differential Diagnosis

- Drugs
- Septicemia
- Early acute duct obstruction
- Postoperative cholestasis
- Benign recurrent intrahepatic cholestasis

Benign Recurrent Intrahepatic Cholestasis

Clinical

- Recurrent events of pruritus and jaundice throughout life; begins in childhood
- Intervals (months to years) of entirely normal liver function between bouts
- Might represent immunological dysfunction triggered by environmental agent
- No adverse long-term outcome

Microscopic

- Cholestasis within perivenular hepatocytes and dilated canaliculi
- Minimal inflammation only, bile ducts normal in number; no fibrosis

Differential Diagnosis

- Drugs
- Septicemia
- Early acute duct obstruction
- Intrahepatic cholestasis of pregnancy
- Postoperative cholestasis

Extrahepatic Biliary Atresia

Clinical

- Probably in utero acquired disorder (viral infection?); incidence is 1:15,000 births
- Usually complete involvement of extrahepatic duct system; minority of cases have partial atresia or hypoplasia
- Jaundice develops 1–2 weeks after birth; dark urine, acholic feces, hepatomegaly
- Mortality is 50% in 1 year if untreated; biliary cirrhosis develops rapidly
- Roux-en-Y anastomosis in partially obstructed cases; most patients require Kasai procedure (hepatoportoenterostomy) with at least temporary benefit; liver transplantation is definite treatment if surgery does not improve bile flow significantly

Microscopic

- Marked dilatation and proliferation of interlobar bile ducts and cholangioles
- Prominent perivenular cholestasis, portal acute and chronic inflammation
- Portal fibrosis of varying stages; secondary biliary cirrhosis in late stages
- Multinucleated giant cell transformation of hepatocytes

Differential Diagnosis

- Choledochal cyst
- Neonatal giant cell hepatitis

Intrahepatic Biliary Atresia

Paucity of Ducts Syndrome

Clinical

- Isolated forms or associated with other syndromes or malformations
- 20% of cases of neonatal cholestasis
- Jaundice and severe pruritus within the first 3 months
- Non-syndromatic cases develop cirrhosis within the first decade of life; syndromatic cases show only fibrosis
- Liver transplantation as definitive treatment, depending on the overall situation

Microscopic

- Portal tracts with decreased to absent interlobular bile ducts and ductular proliferation
- Intralobular cholestasis, most prominent perivenular
- Mild chronic portal inflammation, not directed toward bile ducts
- Mild fibrosis in most cases; cirrhosis only in non-syndromatic cases

Differential Diagnosis

- Alpha-1-antitrypsin deficiency
- Neonatal giant cell hepatitis
- Extrahepatic biliary atresia
- Intrahepatic familial cholestasis (Byler's syndrome)

Intrahepatic Familial Cholestasis (Byler's Syndrome)

Clinical

- Autosomal recessive, possible defect in bile acid transport mechanisms
- Presents with diarrhea and foul-smelling stools, progression to jaundice within 1 year
- Poor prognosis, death from hepatic failure and portal hypertension within 10 years
- Liver transplantation

Microscopic

- Normal portal tracts with duct proliferation in early stages
- Paucity of ducts and biliary fibrosis/cirrhosis in later stages
- Giant cell transformation is rare

Differential Diagnosis

- Alpha-1-antitrypsin deficiency
- Neonatal giant cell hepatitis
- Extrahepatic biliary atresia
- Paucity of ducts syndrome

Bile Duct Dilatation

Choledochal Cyst (Extrahepatic)

Clinical

- Exposure to pancreatic enzymes (reflux) damages bile duct, subsequent expansion and cyst formation; often associated with other duct anomalies; female predominance
- May present at any age, 20% within the first year of life; adults present with mild obstructive jaundice, children with progressive biliary disease
- Increased incidence of cholangiocarcinoma
- Surgical therapy with complete resection and hepaticojejunostomy

Macroscopic

- Cysts vary in size, may contain up to 5 liters of bile
- Saccular or fusiform shapes possible

Microscopic

- Fibrotic cyst wall with chronic inflammation and sometimes abundant mucinous glands
- Secondary cholestasis with duct proliferation, cholangitis, and biliary cirrhosis in long-standing cases

Differential Diagnosis

- Recurrent pyogenic cholangiohepatitis
- Extrahepatic biliary atresia

Caroli's Syndrome (Intrahepatic)

Clinical

- Diffuse or multifocal segmental dilatation of ducts with interspersed normal areas
- Often associated with other duct anomalies; may present at any age, predominantly adolescents
- Hepatomegaly and jaundice, progressive biliary disease with cirrhosis
- Increased incidence of cholangiocarcinoma
- Surgical therapy with complete resection of affected segments or liver transplantation in severe cases

Microscopic

- Dilated ducts with columnar or cuboidal epithelium
- Portal fibrosis of varying degrees with superimposed acute inflammation and microabscesses
- Lobular cholestasis

Differential Diagnosis

- Recurrent pyogenic cholangiohepatitis
- Extrahepatic biliary atresia

DEVELOPMENTAL, HEREDITARY, AND METABOLIC LIVER DISEASE

Cystic Liver Disease

Solitary Unilocular Cyst

Clinical

- Congenital and developmental forms; may arise from aberrant bile ducts
- Usually asymptomatic, incidental finding; rarely rupture or compression symptoms
- Surgical excision if symptomatic

Macroscopic

- Well-circumscribed
- Usually small; may contain several liters of fluid

Microscopic

- Cyst wall lined by flat or cuboidal epithelium
- Well-demarcated from hepatic parenchyma by collagen capsule; contains serous or mucinous fluid

Differential Diagnosis

- Caroli's syndrome
- Cystadenoma

Infantile Polycystic Disease

Clinical

- Early presentation with portal hypertension
- Increasing microcystic changes
- Death from associated chronic renal failure and hypertension

Microscopic

- Dilated, anastomosing, and proliferating bile ducts and prominent vascular channels; true cyst formation is uncommon
- Biliary channels extend into lobules
- Portal fibrosis

Differential Diagnosis

- von Meyenburg complexes
- Congenital hepatic fibrosis

Adult Polycystic Disease

Clinical

- Rare, autosomal dominant disorder (0.1% incidence); female predominance
- Associated with adult polycystic renal disease in 50%
- Typically asymptomatic; rarely rupture or compression symptoms; treatment usually not necessary

Macroscopic

- Variable, diffuse liver involvement, with cyst sizes of 1 mm to several centimeters
- Clear to yellow cyst fluid

Microscopic

- Cyst wall lined by flat or cuboidal epithelium
- Less well-defined fibrous walls with mild chronic inflammation

Differential Diagnosis

- von Meyenburg complexes
- Congenital hepatic fibrosis

Congenital Hepatic Fibrosis

Clinical

- Rare autosomal recessive disorder, part of the cystic disease complex; associated renal cystic disease in 50%
- Adolescents present with complications of portal hypertension; shunt procedures often helpful
- Death from esophageal varices bleeding or renal failure; not hepatic failure

Microscopic

- Marked portal fibrosis with dilated anastomosing bile duct structures that communicate with the regular biliary tree
- No regenerative nodules; no lobular inflammation

Differential Diagnosis

- Bile duct adenoma
- von Meyenburg complexes
- Cholangiocarcinoma
- Metastatic adenocarcinoma

Cystic Fibrosis

Clinical

- Autosomal recessive disorder, incidence = 1:2,000 births; carrier frequency is 5%
- Liver disease due to viscous mucus production with bile duct plugging, cholestasis, and biliary fibrosis
- 10% develop cirrhosis by age 25, microgallbladder in 20%
- Death from pulmonary complications

Microscopic

- Focal biliary fibrosis with periportal steatosis and cholestasis
- Proliferation and dilatation of cholangioles with intraluminal eosinophilic excretions

Differential Diagnosis

- Extrahepatic biliary obstruction

Alpha-1-Antitrypsin Deficiency

Clinical

- Normal alpha-1-antitrypsin (acute phase glycoprotein) inhibits neutrophilic proteases
- Common type of alpha-1-antitrypsin deficiency (PiZZ) due to a point mutation (Glu342Lys) in the alpha-1-antitrypsin gene, resulting in accumulation of the abnormal protein in the endoplasmatic reticulum of hepatocytes (typical globules seen microscopically); mechanisms of liver damage unclear
- Phenotypes are PiMM (normal), PiZZ (homozygote), and PiMZ (heterozygote); other rare phenotypes exist
- Most common cause for liver disease in children, often ductopenic, affecting 1 in 1,700 life births; only a subgroup develops clinically significant liver disease (10% of homozygotes)
- Clinical presentation as early as neonates, with jaundice, hepatosplenomegaly, and ductopenia, but can occur at any age, with adults presenting as (non-ductopenic) cirrhosis; increased risk for cirrhosis and hepatocellular carcinoma
- Diagnosis by phenotyping of alpha-1-antitrypsin in the serum
- Risk or predisposition of heterozygotes (MZ-phenotype) to liver injury is less than that of the ZZ-phenotype, but likely an uncommon cause of cirrhosis and a potentiator of fibrosis when co-existing with other liver disease(s)
- Treatment includes avoidance of smoking (potentiates associated pulmonary disease), supportive and symptomatic measures for liver disease management, and liver transplantation

Microscopic

- Periportal hepatocytes with abundant round eosinophilic cytoplasmic inclusions
- Mixed micro-and macronodular cirrhosis (adults); biliary cirrhosis in children
- Smaller, less numerous cytoplasmic inclusions in the heterozygote
- Associated giant cell transformation of hepatocytes in children
- Initial bile duct proliferation; later stages show paucity of ducts in children
- Only mild portal mononuclear inflammatory infiltrate

Special Studies

- PAS with diastase +
- Alpha-1-antitrypsin immunohistochemistry

Differential Diagnosis

- Giant cell hepatitis
- Extrahepatic biliary atresia
- Paucity of ducts syndrome
- Drug- and alcohol-induced liver disease

Hereditary Hyperbilirubinemias

Dubin-Johnson Syndrome

Clinical

- Autosomal recessive disorder with inability to secrete conjugated bilirubin in canaliculi
- Chronic intermittent episodes of jaundice, precipitated by stress, trauma, infection, or pregnancy
- No specific therapy; avoidance of precipitating factors, phenobarbital

Microscopic

- Granular, dark brown pigment in hepatocytes, more prominent around canaliculi and perivenular
- Portal tracts normal, no inflammation

Differential Diagnosis

- Drugs
- Lipofuscin in the elderly

Other Hereditary Hyperbilirubinemias

Clinical

- Crigler-Najjar syndrome:
  - Inability to conjugate bilirubin, glucuronyltransferase deficiency (complete or partial), unconjugated bilirubin increased
  - Presentation as neonate; death within 2 years (complete deficiency); life expectancy = 40–50 years (partial deficiency)
- Gilbert's syndrome:
  - Inability to conjugate bilirubin, transglucuronidation deficiency, unconjugated bilirubin increased
  - Presentation from neonates to adolescents; jaundice precipitated by stress, alcohol, infection, or trauma; normal life expectancy
- Rotor's syndrome:
  - Inability to secrete conjugated bilirubin, conjugated and unconjugated bilirubin increased
  - Presentation in childhood; fluctuation of jaundice; normal life expectancy

Microscopic

- Overall, the hepatic morphology is not distinctive
- Occasional bile plugs (Crigler-Najjar syndrome)
- Rarely increase in pigment (Gilbert's syndrome)

Genetic Hemochromatosis

Clinical

- Incidence = 1–2:1,000; male predominance; needs to be distinguished from other (secondary) iron overload conditions
- Failure to regulate iron absorption, resulting in severe iron overload; exact mechanism still unknown
- Associated with two missense mutations (Cys282Tyr and His63Asp) in the HFE gene on chromosome 6p21.3 coding for an MHC class I-like molecule
- Homozygosity for Cys282Tyr in 80% to 90% of patients with typical hemochromatosis
- Compound heterozygotes (Cys282Tyr and His63Asp) comprise 5%; 5% to 10% of patients are wild-type for both loci, suggesting yet another genotype
- Presentation with signs of liver damage, abdominal pain, skin pigmentation, diabetes, and cardiomegaly (25%) or asymptomatic until late (75%)
- Many patients identified through abnormal serum iron studies; sensitivity and specificity of iron laboratory studies rather low
- Liver biopsy to establish diagnosis; hepatic iron index (hepatic iron contents in mmol/g dry weight divided by age) >1.9 typically associated with homozygous hemochromatosis, although exceptions exist (exogenous iron overload, cirrhosis in particular)
- PCR-based diagnosis of Cys282Tyr and/or His63Asp highly specific
- Family screening recommended; treatment of choice is multiple phlebotomy until development of iron-limited hematopoiesis, then maintenance phlebotomy as required

Microscopic

- Extensive hemosiderin pigment (iron) deposition in cytoplasm of periportal hepatocytes (early) and eventually all hepatocytes (late)
- Subsequent portal fibrosis and cirrhosis
- Kupffer cell hyperplasia
- Only mild inflammation

Special Studies

- Prussian blue
- Masson's trichrome

Differential Diagnosis

- Hemosiderosis from other etiologies
- Alcohol-induced liver disease

Copper Storage Disorders

Wilson's Disease

Clinical

- Autosomal recessive disorder of copper metabolism with highly variable presentation
- Incidence of 2:100,000; carrier frequency 1/100
- Altered gene is on chromosome 13q, codes for a copper-transporting adenosine triphosphatase
- Hepatic copper accumulation causes hepatocellular necrosis, periportal inflammation, and fibrosis/cirrhosis; patients present at various stages of chronic liver disease
- Acute episodes (sudden copper release into circulation) associated with hemolysis
- Later stages develop corneal and brain deposits of copper with severe neurologic deficits; liver damage presents usually before neurologic deficit; early diagnosis is crucial
- Presence of Kayser-Fleischer rings (cornea) and low serum ceruloplasmin is sufficient for diagnosis
- High index of suspicion; after exclusion of other liver diseases, measurement of hepatic copper contents is mandatory in patients with liver biopsy (+ if >250mg/g dry weight)
- Treatment is D-penicillamine and/or zinc; death in untreated cases; liver transplantation should be offered

Microscopic

- Non-specific inflammatory changes of variable degrees in early stages; copper is variably demonstrable and is predominantly periportal but may be inapparent by special stains
- Later stages show micro- and macronodular cirrhosis, steatosis, cholestasis, and hepatocellular copper deposits
- Liver cell nuclei with significant anisocytosis

Special Studies

- Rhodanine-stain (copper, red)
- Orcein (copper binding protein, black-brown)

Differential Diagnosis

- All major chronic liver diseases
- Drugs (chlorpromazine)
- Indian childhood cirrhosis

Indian Childhood Cirrhosis

Clinical

- Hepatic disorder of predominantly Indian children with familial predisposition; rare case reports of patients in the United States
- Yet unidentified defect in copper metabolism with copper deposition in the liver
- Exogenous causes with underlying predisposition debated
- Clinical presentation as young children (1–5 years) with gradual progression to micronodular cirrhosis
- Alpha-fetoprotein levels elevated from birth
- Death within 1–2 years of diagnosis, if untreated
- Early initiation of penicillamine treatment offers regression of hepatic disease

Microscopic

- Extensive fibrosis/cirrhosis with Mallory bodies in hepatocytes
- Mild portal mononuclear inflammatory infiltrate
- No prominent giant cell transformation of hepatocytes
- Increased copper and copper-binding protein

Differential Diagnosis

- Metabolic defects with fibrosis/cirrhosis
- Alpha-1-antitrypsin deficiency

Amyloidosis

Clinical

- Systemic amyloidosis in 0.5% at autopsy; 50% liver involvement
- Primary (familial) amyloidosis is rare; high index of suspicion; liver transplantation may become necessary
- Secondary amyloidosis frequently related to systemic diseases (multiple myeloma, connective tissue diseases, infections)
- Hepatomegaly, rarely severe liver problems
- Underlying diseases determine the prognosis

Microscopic

- Perireticular and pericollagenous (portal tract, vessel wall) deposits of amorphous eosinophilic material; globular amyloid in rare cases
- Occasionally cholestasis, no fibrosis

Special Studies

- Congo red +
- Immunohistochemistry with antibodies for specific subtypes (AL kappa, lambda, AA, transthyretin, beta-2 microglobulin)

Differential Diagnosis

- Collagen or fibrin depositions
- Intracellular inclusions

Porphyrias

Porphyria Cutanea Tarda

Clinical

- Uroporphyrinogen decarboxylase deficiency, autosomal dominant inheritance
- Incidence = 5:100,000, manifests after the age of 35
- Associated with chronic alcoholic liver disease in 90% of all cases; liver involvement manifests late, usually cirrhosis present
- Overall prognosis is good

Microscopic

- Massive uroporphyrin deposits in hepatocytes, causing prominent red autofluorescence on frozen sections and birefringent cytoplasmic inclusions
- Macrovesicular steatosis, cirrhosis in 20%, increased iron

Special Studies

- Prussian blue

Differential Diagnosis

- Iron overload
- Chronic alcoholic liver disease
- Diabetes mellitus
- Other porphyrias

Erythropoietic Protoporphyria

Clinical

- Deficiency in ferrochelatase
- Liver involvement with cirrhosis is rare

Microscopic

- Dark brown pigment in almost all liver elements
- Orange-red autofluorescence on frozen sections and birefringent cytoplasmic inclusions
- Fibrosis/cirrhosis possible; varying degrees of chronic inflammation with focal necrosis

Differential Diagnosis

- Iron overload
- Other porphyrias

Sickle Cell Anemia

Clinical

- Liver involvement in 2%, typically anoxic-type necrosis due to sickling of RBC's in the homozygote
- Hyperbilirubinemia predominantly due to hemolysis, gallstones in 50% of all cases
- Overall prognosis not liver-related

Microscopic

- Sickling of RBS's with fibrin deposition in dilated sinusoids, most prominent perivenular; focal necroses and hemosiderin deposits
- Extramedullary hematopoiesis in 50% of all cases, secondary to hemolytic anemia

Differential Diagnosis

- Disseminated intravascular coagulation
- Passive congestion
- Acute viral hepatitis

Other Storage Disorders

- Glucocerebrosidoses (e.g., Gaucher's and Niemann-Pick; marked Kupffer cell hypertrophy with foamy

changes)
- Glycogen storage diseases (e.g., von Gierke's and Pompe's; cytoplasmic glycogen deposits, fibrosis/cirrhosis in types III and IV)
- Mucopolysaccharidoses (e.g., Hurler's; small lipid droplets in liver cells, Kupffer and Ito cells, fibrosis)
- Lipid and cholesterol storage disorders (small fat droplets in hepatocytes, foamy macrophages with cholesterol deposits)
- Glycosphingolipidoses (e.g., Fabry's; hypertrophy of portal macrophages, Kupffer cells)
- Gangliosidoses (e.g., Tay-Sachs; laminated inclusions in hepatocytes only by electron microscopy)

MISCELLANEOUS CONDITIONS

Autoimmune Hepatitis

Clinical
- Younger to middle-aged females predominantly affected; clinical presentation often with jaundice and hepatosplenomegaly
- Immunologic diseases are present in half of all cases; serum IgG is usually elevated
- Autoantibodies are present, including ANA (nuclear components), SMA (smooth muscle); LKM (liver kidney microsomal), LMA (liver membrane), LSP (liver-specific lipoprotein). These autoantibodies are sensitive, but not specific markers
- AMA (antimitochondrial antibodies) are not seen, as opposed to findings in primary biliary cirrhosis
- May overlap with other chronic liver diseases
- Treatment is with corticosteroids; many cases present with fibrosis or early cirrhosis
- Prognosis is good in responding patients; liver transplantation for unresponsive cases

Microscopic
- Portal inflammation with prominent plasma cells
- Lymphocytic piecemeal necrosis during active disease
- Varying degrees of portal fibrosis or cirrhosis
- Irregular distribution of lobular inflammation and hepatocellular necrosis of variable severity
- Minimal inflammation in treated or spontaneously inactive cases

Special Studies
- Serum autoantibody assays

Differential Diagnosis
- Viral hepatitis
- Drug-related liver disease

Granulomatous Liver Disease

General Features
- Granulomas are present in approximately 5% of all liver biopsy specimens
- Causes include systemic disease (70%), primary liver diseases (5%), and unknown etiologies (25%)
- Tuberculosis and sarcoidosis are the most common causes worldwide
- Associated conditions: infections, hypersensitivity reactions to drugs, neoplasms, foreign body material in iv-drug users, and primary biliary cirrhosis
- Two major morphologic types:
  - Inflammatory, poorly defined (CMV-infection, drugs)
  - Epithelioid, well-demarcated (tuberculosis, sarcoidosis)
- Other types include lipogranulomas and fibrin ring granulomas

Sarcoidosis

Clinical
- Liver involvement in 60% to 90% of all cases; clinically significant liver problems are rare
- Variable number of granulomas in early stages; fibrosis and rarely total resolution in later stages
- Minority of cases progress to portal hypertension due to portal granulomas and fibrosis
- Prognosis is generally good; pulmonary fibrosis determines clinical outcome

Microscopic
- Non-necrotizing epithelioid granulomas, most prominent portal/periportal
- Intersegmentation of granulomas by fibrous septae possible and typical
- Multinucleated giant cells rather uncommon
- Cytoplasmic inclusions (Asteroid bodies) and varying degrees of portal fibrosis

Special Studies
- Masson's trichrome
- Acid-fast
- Methenamine silver

Differential Diagnosis

- Granulomas of other causes
- Viral hepatitis
- Primary biliary cirrhosis

Inflammatory Bowel Disease

- 50% of patients with chronic ulcerative colitis or Crohn's disease exhibit hepatic dysfunction of varying degrees; 5% develop clinically significant liver disease, most often primary sclerosing cholangitis
- Non-specific reactive changes with mild elevations in serum LFTs and asymptomatic clinical course represent the majority of cases
- Primary sclerosing cholangitis (5%) with cirrhosis (1%) and cholangiocarcinoma (1%) are relatively common complications of chronic ulcerative colitis.
- Chronic hepatitis C and autoimmune hepatitis in 1% to 2% of all cases
- Colon resection for inflamatory bowel disease does not influence the course of primary sclerosing cholangitis

Neonatal Giant Cell Hepatitis

Clinical

- Non-specific reaction pattern with conjugated hyperbilirubinemia, normal biliary tree, chronic inflammation, and syncytial giant cell transformation of hepatocytes by cell fusion and/or mitotic inhibition
- Most common associated disorder is alpha-1-antitrypsin deficiency; other metabolic, biliary, or infectious etiologies; half of all cases have no known cause
- Overall prognosis variable; underlying liver disease (if known) determines clinical cause and outcome

Microscopic

- Syncytial giant cell transformation of hepatocytes; typically diffuse distribution with lobular disarray
- Lymphocytic chronic inflammation and normal bile ducts; some cholestasis possible

Special Studies

- Immunostains and/or PAS-diastase to rule out alpha-1-antitrypsin deficiency

Differential Diagnosis

- Extrahepatic biliary atresia
- Intrahepatic biliary atresia
- Alpha-1-antitrypsin deficiency

Reye's Syndrome

Clinical

- Children, usually younger than 5 years
- Acute encephalopathy and diffuse microvesicular steatosis hepatis; other organs also with fatty change; generalized mitochondrial problem is likely
- Often associated with viral upper respiratory tract infection and aspirin exposure
- Supportive treatment, severe liver disease uncommon, responds to aggressive management; 25% mortality

Microscopic

- Uniform distribution of microvesicular steatosis without significant inflammation
- Microvesicular fat also accumulates in proximal tubules of the kidney, in myocardium, and in skeletal muscle
- May lead to zonal or massive hepatic necrosis

Special Studies

- Fat stains
- Electron microscopy shows enlarged pleomorphic mitochondria with swollen matrix

Differential Diagnosis

- Metabolic storage disorders
- Drugs/toxins

Toxemia of Pregnancy

Clinical

- Responsible for 5% of jaundice during pregnancy, usually in third trimester
- Vasospasms and/or disseminated intravascular coagulation as initiating event
- Treatment supportive with termination of pregnancy

Microscopic

- Periportal fibrin deposition along sinusoids
- Hemorrhage and ischemic hepatocellular necrosis
- Fibrin thrombi in portal veins

Liver Transplantation

Indications

- Posthepatitic cirrhosis (chronic hepatitis B and C, autoimmune/drug-induced hepatitis, cryptogenic hepatitis)
- Biliary cirrhosis (PBC, PSC)
- Alcohol-related cirrhosis, if abstinent patient
- Fulminant hepatic failure
- Miscellaneous conditions (storage disorders, genetic enzyme deficiencies, hemochromatosis, Wilson's disease, alpha-1-antitrypsin deficiency, Budd-Chiari syndrome, hepatic malignancies)

Absolute Exclusions

- HIV positivity
- Extrahepatic malignancy
- Septicemia
- Major comorbidity

Relative Exclusions

- Prior extensive abdominal surgery
- Portal vein thrombosis
- High-stage liver cell carcinoma
- Cholangiocarcinoma
- HBeAg positivity in hepatitis B patient

Donor Liver

- Donor must be legally and medically brain-dead, hemodynamically stable, acceptable liver function and infectious disease status, preferably less than 7 days hospitalized and less than 65 years of age; partial hepatectomies from living donors an alternative
- Poor graft function correlated with >30% hepatocellular steatosis, cold preservation time >12 hours, and increasing donor age

Surgical Procedures

- Orthotopic liver transplantation (most common, "typical" procedure)
- Heterotopic (auxiliary) liver transplantation (fulminant hepatic failure, bridging the time to recovery of the patient's native liver; no need for long-term immunosuppression; higher complication rate)
- Split and reduced-size liver transplantation (pediatric patients; increase in graft supply; higher complication rate)
- Living-related liver transplantation (increase in graft supply; very good results in elective settings; risk for donor)

Complications

- Hepatic artery thrombosis (1% to 5%)
- Portal vein thrombosis (2% to 3%)
- Biliary complications (bile leaks, cholangitis, bilomas)
- Bacterial infections (40% to 60%)
- CMV and fungal infections (immunosuppression)
- Allograft rejection and graft-versus-host disease
- Recurrent hepatitis C (often confused with allograft rejection, fairly good prognosis)
- Recurrent hepatitis B (increased risk for graft loss)
- Biliary tract stricture (surgical revision may be required)
- Drug-induced liver injury (post-transplant medications)
- Obesity and diabetes mellitus (20% to 30%)
- Hypercholesterolemia (40%)
- Hypertension (40%)
- Chronic renal failure (10%)

Immunosuppression

- Double drug (prednisone/cyclosporine or tacrolimus) or triple drug (prednisone/cyclosporine or tacrolimus/azathioprine) regimens, sometimes antilymphocyte globulins
- Highly immunosuppressive induction protocols are not necessary
- Late complications common (see above)

Graft and Patient Survival

- 1-year survival is currently 75% to 85%.
- 3-year survival is currently 65% to 75%.
- Early death related to allograft nonfunction or rejection, hepatic artery thrombosis, infection, or multiorgan failure
- Late death related to malignancy or recurrent native disease

Early Graft Failure

- Hypotension and inadequate graft preservation or poor graft characteristics predispose to immediate graft failure
- Biopsy shows marked hydropic changes, vascular thromboses, and severe ischemic necroses without significant inflammatory infiltrates
- Re-transplantation is the only therapy

Acute Rejection

- Usually occurs within the first 2 months after transplantation, typically between days 5 and 15 post-transplant
- Clinical symptoms of acute liver failure
- Adjustments in immunosuppressive therapy usually successful

- Lymphoplasmacytic infiltrate in portal tracts (portal hepatitis), epithelial degeneration of interlobular ducts with inflammatory infiltrate (lymphocytic cholangitis), inflammatory changes in the endothelium ("endotheliitis")

Chronic Rejection

- Often secondary to repeated episodes of acute rejection; may occur years after transplant but usually within first 6 months
- Variable degrees of portal fibrosis with arteriolar thickening due to foamy arteriopathy
- Features of bile duct destruction with paucity of ducts and cholestasis late
- "Vanishing bile duct syndrome" in 5% to 10% (irreversible acute rejection, within 100 days post-transplant) necessitates re-transplantation
- No inflammation unless residual acute rejection
- May result in biliary-type cirrhosis

Graft-Versus-Host Disease

- Occurs after bone marrow transplantation, incidence is up to 70%; jaundice in 50%
- Acute reaction 5–50 days post transplant, chronic GvH disease >100 days post transplant
- Lymphocytic infiltrate in portal tracts and lobules, epithelial degeneration of interlobular ducts (acute); biliary fibrosis and cirrhosis with decreased number of ducts (chronic)
- Veno-occlusive disease (10% to 20%) is more related to chemotherapy and radiation
- Treatment with steroids and immunosuppressants
- Clinical outcome varies with degree of GvH; mortality is 7% to 100%

DISORDERS OF THE GALLBLADDER

Acute Cholecystitis

- Usual cause is cystic duct or Hartmann's pouch occlusion by a gallstone; rarely occlusion by neoplasm; secondary bacterial infection
- Acalculous cholecystitis may occur after polytrauma, burns, or major surgery; may also complicate hemolysis, typhoid fever, brucellosis, or pancreatitis
- Presentation with initial biliary colic, but continuous pain; vomiting, fever; mild jaundice possible; elderly patients may present pain-free and afebrile
- Inflammatory laboratory parameters +; LFTs may be abnormal; ultrasonography diagnostic
- Treatment includes antibiotics and semi-elective cholecystectomy after 2–3 days of medical treatment
- Complications include empyema, gangrene, abscess, and peritonitis

Chronic Cholecystitis and Biliary Colic

- Chronic cholecystitis is due to stones in the gallbladder; poor correlation between clinical features and pathologic findings
- Gallbladder wall is typically thickened; the mucosal surface becomes flattened and may ulcerate; microscopically there is fibrosis and variable chronic inflammatory infiltrate; Rokitansky-Aschoff sinuses (mucosal diverticula) usually present
- Various reactive and hyperplastic mucosal changes frequently develop; several polyps and tumor-like conditions can be seen (see chapter 31)
- Extensive wall calcifications lead to a "porcelain gallbladder"
- Biliary colic episodes are common symptoms with sudden onset of pain (which is not colicky despite its name) after certain meals
- Oral cholecystography and ultrasound are diagnostic; ultrasound is more sensitive (stones 1–3 mm in size identifiable)
- Pain relief in acute attacks, followed by elective cholecystectomy, possibly laparoscopic; mortality rate = 0% to 1%, four times higher if choledocholithotomy is performed

Cholelithiasis

- Most common disorder of the biliary system; gallstones are usually designated as cholesterol stones, mixed stones, or pigment stones
- Continuous spectrum of stone composition:
  - Only 20% are pure cholesterol or pigmented stones
  - 10% to 20% of stones contain enough calcium to be radio-opaque
- Prevalence varies considerably:
  - Rare in Africa and among Eskimos
  - Common in Western countries
  - Very high frequency among American Pima Indians suggests genetic predisposition along with lifestyle factors
  - Incidence is increasing worldwide
- Gallstones become more common with age; females

two to three times more often affected than males; risk factors also include obesity, high calorie diet, and long-term parenteral nutrition

- Pigment stones arise when excess unconjugated bilirubin leads to precipitation of calcium bilirubinate; they are especially common in the Far East, equal frequency in men and women; associated with hemolytic anemia, cirrhosis, and cholangitis; occur also in the absence of known risk factors
- Gallstones are found in most patients with carcinoma of the gallbladder and in 50% of patients with acute pancreatitis
- Dissolution therapy only indicated in patients with small (<1.5 cm), cholesterol-rich stones; chenodeoxycholic acid most widely used; recurrence when therapy is stopped
- Cholecystectomy as definite treatment in symptomatic patients; only 20% of patients with gallstones develop symptoms
- Complications include biliary colic, acute cholecystitis, acute pancreatitis, and biliary obstruction; rarely, gallbladder carcinoma, fistules, or gallstone ileus

Choledocholithiasis

- 10% of patients with cholecystolithiasis, incidence increases with age
- Majority of bile duct stones have migrated from the gallbladder and may increase in size in the bile duct; primary bile duct stones are rarer and typically associated with partial biliary obstruction due to strictures; primary duct stones are usually single, ovoid, soft, and conform to the bile duct
- Secondary hepatic changes dependent on degree of obstruction, time present, and amount of biliary infection
- Episodes of obstructive jaundice or pancreatitis; recurrent symptoms after cholecystectomy; Charcot's triad (pain, obstructive jaundice, fever)
- Ultrasound and/or ERCP for diagnosis
- Complications include acute cholangitis and septicemia
- Treatment of choice is ERCP-based stone extraction or cholecystectomy with bile duct exploration

Post-Cholecystectomy Syndrome

- Describes residual recurrent pain or discomfort in the upper abdomen following cholecystectomy; 30% of patients are affected, 2% to 5% with severe symptoms
- Extrabiliary causes include reflux esophagitis, peptic ulceration, chronic pancreatitis, irritable colon, and functional pain
- Major biliary causes include retained common bile duct stones and biliary stricture
- Debated causes include long cystic duct remnant, papillary stenosis, adhesions, and traumatic neuromas
- Pain typical of organic biliary disease may arise in the absence of demonstrable biliary calculi; pain mechanism poorly understood; dysmotility of gallbladder and sphincter of Oddi suspect
- Treatment includes searching for definable cause, ERCP, cholecystectomy, or sphincterotomy; only 50% of patients benefit from surgical intervention

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Chapter 31

Neoplasms of the Liver and Biliary System

Hagen Blaszyk, MD
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Table of Contents

TUMORS OF THE LIVER AND INTRAHEPATIC BILE DUCTS

Benign Epithelial Tumors

Liver Cell Adenoma

Clinical

- Occurs most commonly in women of reproductive age taking oral contraceptive steroids with a causal link related to dose, duration of use, and patient's age
- Absolute risk of <3 per 100,000 oral contraceptive users per year for women under 30 years of age; may be higher for older women
- Also occurs in adult men and children treated with anabolic/androgenic steroids
- Spontaneous regression after discontinuation of the drug is rare, as are instances of malignant transformation
- Clinical presentation (depending on tumor size) with episodic right upper quadrant pain and discomfort, or with severe abdominal pain, hemorrhage, and shock; overall mortality may approach 20%
- Surgical resection indicated in most cases
- No production of excess alpha-fetoprotein

Macroscopic

- Usually solitary, occasionally pedunculated; can arise anywhere in the liver
- Bulging mass with dilated blood vessels over its surface; up to 30 cm in size
- Cut surface soft, well-demarcated, usually spherical, seldom encapsulated
- Yellow-tan-brown color spectrum; frequent necrosis and hemorrhage
- Not associated with cirrhosis; remaining liver is usually normal

Microscopic

- Made up purely of hepatocytes arranged in plates two to three cells thick, never more; separated by inconspicuous, endothelial-lined sinusoids
- Tumor cells generally larger than hepatocytes with uniform nuclei; cytoplasm may be pale or clear; mitoses are absent or few
- Bile may be present as cytoplasmic droplets or plugs in distended canaliculi
- Often very vascular with large, tortuous arteries and veins
- Fibrous septae without bile ducts; hepatic reticulin framework usually preserved
- Peliosis more common in anabolic/androgenic steroid users
- Rare features are epithelioid and giant cell granulomas, steatohepatitic changes, and extramedullary hematopoiesis

Differential Diagnosis

- Focal nodular hyperplasia
- Well-differentiated hepatocellular carcinoma
- Hepatocellular carcinoma arising in liver cell adenoma

Bile Duct Adenoma

Clinical

- Common (up to 30%) incidental finding at laparotomy or autopsy
- May be mistaken for metastases as their only clinical significance

Macroscopic

- Solitary, small, subcapsular, white, firm; without encapsulation

Microscopic

- Small tubules set in a fibrous stroma with lymphocytes
- Single layer of cuboidal cells; possible mucin secretion; no bile in lumen
- Normal portal tracts often included
- May actually represent peribiliary gland hamartomas

Differential Diagnosis

- Evolving bile duct carcinoma
- Biliary hamartoma (von Meyenburg complexes)
- Mesenchymal hamartoma

Hepatobiliary Cystadenoma

Clinical

- Rare, resembling cystadenomas of the pancreas or ovary
- May arise from ectopic embryonal tissue (gallbladder precursor)
- Middle-aged women; usual presentation with pain and discomfort
- Slow growth; tends to become symptomatic with increasing size
- Surgical resection always indicated, malignant transformation possible

Macroscopic

- Always multilocular, usually >10 cm
- Contains clear to cloudy mucinous fluid
- Inner surface usually smooth, sometimes trabeculated, or with small projections

Microscopic

- Epithelium is mucinous, simple columnar; may become atrophic and cuboidal focally

- ♦ May contain cellular, myofibroblastic stroma in women ("ovarian" type); commonly with cholesterol clefts or calcifications
- ♦ Invasion, indicative of malignant transformation, should be sought through extensive sampling

Differential Diagnosis

- ♦ Developmental cysts
- ♦ Cystadenocarcinoma

Biliary Papillomatosis

Clinical

- ♦ Rare; middle-aged patients
- ♦ Numerous lesions of intra- and extrahepatic bile ducts
- ♦ Clinical course always progressive; high mortality

Macroscopic

- ♦ Dilated major bile ducts with friable papillary excrescences

Microscopic

- ♦ Mucus-secreting columnar epithelial cells with thin fibrovascular stalks
- ♦ Atypia and focal invasion possible

Malignant Epithelial Tumors

Hepatocellular Carcinoma

Clinical

- ♦ Geographic variation in incidence (per 100,000 population and year):
  - – 20–150 in most of Africa and South-East Asia
  - – <5 in Europe, North and South America, and Australia
  - – 5–20 in Japan, North Africa, and Middle East
- ♦ More frequent in men; racial variations in incidence in the same geographic region explained by hepatitis B prevalence
- ♦ Common predisposing factors include:
  - – Chronic liver diseases with cirrhosis as the common denominator
  - – Most important factor is chronic hepatitis B (HBV DNA integration into host genome with subsequent malignant transformation)
  - – Aflatoxin B_1 exposure (molds) with molecular "fingerprint" in the p53 gene (G>T transversion at codon 249)
  - – Rare predisposing factors include type-1 tyrosinemia, familial ataxia-telangiectasia, and hepatic porphyrias
- ♦ Xenobiotics weakly associated with hepatocellular carcinoma include organochloride pesticides, polychlorinated biphenyls, thorotrast, and vinyl chloride
- ♦ Clinical presentation:
  - – Middle-to-early old age patients with long-standing cirrhosis and rapidly developing liver failure (low incidence areas)
  - – Young adults presenting with pain, weight loss, or hemorrhage (high incidence areas)
- ♦ Significantly elevated serum AFP may be diagnostic, but is only moderately sensitive; imaging studies are almost always conclusive
- ♦ Lymph node metastases are common and treatment results are poor
- ♦ Most patients die within months of presentation, although better results are seen with small and incidental tumors

Macroscopic

- ♦ Soft, yellow-green or reddish masses of varying size; three basic patterns encountered (multinodular, solitary massive, or diffuse)
- ♦ For symptomatic individuals, most common is a large mass surrounded by several "satellite" nodules; multinodular appearance may be difficult to distinguish from cirrhosis; diffuse patterns are rare
- ♦ Tumor thrombi in veins are common, as is spontaneous rupture of larger masses

Microscopic

- ♦ Several histologic and cytologic variants are recognized that commonly occur in combinations and are helpful for the pathological diagnosis
- ♦ These variants as well as histologic grade are of little or no clinical or biological significance
- ♦ Microscopic variability gives rise to confusion with cholangiocarcinoma or metastatic lesions. This can largely be avoided by remembering the most frequent architectural characteristic: resemblance to normal liver plates, but plates more than two to three cells thick
- ♦ Major histological patterns include trabecular, pseudoglandular, and solid growth
- ♦ Less common patterns include clear cell, steatohepatitis-like, inflammatory, anaplastic giant cell, and spindling.
- ♦ Common cytological features are hepatocyte-like appearance, prominent nucleoli, slightly more basophilic cytoplasm than normal liver cells, scattered pleomorphic cells with bizarre nuclei, and clear cells
- ♦ Inclusions are common (eosinophilic intranuclear, hyaline cytoplasmic, pale cytoplasmic)
- ♦ Fine-needle aspirations yield a low rate of false +, but a rather high false – rate. Helpful features include "naked nuclei" and intranuclear inclusions

Special Stains

- ♦ Reticulin (outline of sinusoids diminished)
- ♦ PAS (clear cell variant)
- ♦ Mucin (absent in hepatocellular carcinoma)
- ♦ Trichrome (cytoplasmic inclusions)

Immunohistochemistry and In Situ *Hybridization*

- Alphafetoprotein + (in 25%)
- Keratin variable, Mucin –
- Albumin mRNA in situ hybridization +
- Hepatocyte-specific antigen (HSA)+
- Polyclonal CEA and CD10 + (canalicular pattern)

Variants

- Pedunculated hepatocellular carcinoma (better prognosis for surgical reasons)
- Minute (small, encapsulated) hepatocellular carcinoma (15% of all liver cell cancers from South-East Asia) with better prognosis

Differentia Diagnosis

- Liver cell adenoma
- Cholangiocarcinoma
- Metastatic tumors
- Mixed hepatocellular carcinoma and cholangio–carcinoma

Fibrolamellar Carcinoma

Clinical

- Vast majority occur in patients between 18 and 45 years of age; rarely (if ever) in elderly
- Presentation with abdominal pain, malaise, and weight loss; a mass is usually readily palpable
- Patients do not have cirrhosis; hepatitis B infection infrequent
- Frequently localized to the liver at diagnosis; often resectable
- Slow progression; 5-year survival 10% to 50%

Macroscopic

- Well-defined, solitary mass; lobular arrangement with interconnecting fibrous septae or central scar; small satellite nodules possible
- Metastases to regional lymph nodes and lungs in late stages

Microscopic

- Three major criteria: macronucleoli, abundant eosinophilic cytoplasm (abundant mitochondria), and lamellar (plate-like) fibrosis at least focally
- Peripheralized chromatin
- Cytoplasmic globules and "pale bodies" common; bile droplets possible; occasionally fat

Immunohistochemistry and In Situ *Hybridization*

- Polyclonal CEA outlines bile canaliculi
- Usually alphafetoprotein –
- Albumin in situ hybridization usually +

Hepatoblastoma

Clinical

- Children <5 years old; peak incidence in the first 2 years of life; rare cases in adolescents and young adults
- Incidence worldwide identical; nephroblastoma:neuroblastoma:hepatoblastoma = 6:3:1
- $^1/_3$ of patients with congenital anomalies (familial colonic polyposis, nephroblastoma, Down's syndrome, or other malformations)
- Presenting features include failure to thrive, weight loss, and rapidly enlarging upper abdominal mass with markedly elevated serum levels of alphafetoprotein
- Primary treatment is surgical resection, preceded by chemo/radiotherapy (mortality 25%); long-term survival = 15% to 35%
- Poor prognosis in age <1 year, large size, vital structures involved, predominance of small anaplastic cells (uniformly fatal) or macrotrabeculae (chemotherapy resistance)

Macroscopic

- Single, large mass (up to 25 cm)
- Variegated gross appearance, according to histologic components present
- Often necrosis, cystic change, hemorrhage with prominent vascularity and thin capsule
- Remainder of the liver normal

Microscopic

- Epithelial component of several types:
  - Large, polygonal fetal-type cells with oval nuclei, single nucleoli, and granular or clear cytoplasm organized into irregular plates with bile canaliculi and sinusoids
  - Smaller, darkly staining embryonal-type cells with scant cytoplasm, aggregating into cords, ribbons, or rosette-like clusters
  - Anaplastic small cells (small blue cell or neuroblastoma type)
  - Macrotrabecular component (resembles hepatocellular carcinoma)
- First two components are invariably present in varying proportions
- Mesenchymal component with osteoid or undifferentiated spindle cell mesenchyme
- Extramedullary hematopoiesis common; intestinal glands and squamous metaplasia may be seen

Immunohistochemistry and In Situ Hybridization

- Alphafetoprotein + (fetal and embryonal cells), beta-hCG + (giant cells), vimentin + (anaplastic cells), albumin in situ hybridization +, HSA +

Variants

- Teratoid hepatoblastoma (presence of cartilage, striated muscle, neural tissue)

Cholangiocarcinoma

Clinical

- Tumor arises in ducts proximal to the liver hilum
- Associated with liver flukes (*Clonorchis sinensis*: Hong Kong, Canton; *Opisthorchis viverrini*: Thailand), hepatolithiasis, primary sclerosing cholangitis, congenital anomalies, and Thorotrast exposure
- No association with cirrhosis, HBV infection, or mycotoxins
- Patients in fifth and sixth decade present at late stage with pain, weakness, and weight loss
- Serum AFP usually normal, CEA elevated
- Frequently *ras*-mutations (possibility for carcinoma-screening)
- Metastases common (regional lymph nodes, later hematogenous spread)
- Frequently not resectable; prognosis very poor

Macroscopic

- Solitary, sometimes multinodular grey-white, firm mass with predominantly central sclerosis and calcifications; finger-like extensions from main mass (lymphatic spread)
- Characteristically avascular
- Growth into major bile ducts or blood vessels rarely seen

Microscopic

- Well- to moderately differentiated tubular adenocarcinoma in abundant fibrous stroma; PAS or mucin stains +
- Many different architectural growth patterns possible, with no biological or clinical significance
- Remaining liver frequently shows bile duct hyperplasia, atypical hyperplasia, and carcinoma in situ adjacent to the tumor
- Tumors associated with stones, cysts, or anomalies may be squamous
- Distinction from metastases requires demonstration of carcinoma in situ in adjacent ducts; not possible in needle biopsies

Immunohistochemistry

- Mucin +
- Alphafetoprotein –
- EMA +
- CEA + (cytoplasmic pattern)
- Keratin +

Variants

- Hilar adenocarcinoma (Klatskin tumor) with slower growth and better prognosis (arises from the main hepatic duct or lobar branches with early jaundice as presenting symptom)

Differential Diagnosis

- Metastatic adenocarcinoma
- Hepatocellular carcinoma
- Atypical benign bile duct proliferation in hepatolithiasis or malformations

Hepatobiliary Cystadenocarcinoma

Clinical

- Very rare malignant counterpart of bile duct cystadenoma; "borderline" tumors are described
- Majority in middle-aged women; no symptoms until very large
- Usually grows well-defined; surgery often possible with good prognosis

Macroscopic

- Similar to hepatobiliary cystadenoma

Microscopic

- Similar to hepatobiliary cystadenoma, but with invasion
- Significance of high-grade dysplasia and solid intracystic masses independent of invasion unclear

Immunohistochemistry

- Similar to cholangiocarcinoma

Differential Diagnosis

- Hepatobiliary cystadenoma
- Carcinoma arising in developmental cysts

Miscellaneous Malignant Epithelial Tumors

- Mixed hepatocellular carcinoma/cholangiocarcinoma rarely seen
- Adenosquamous or squamous carcinomas in association with stones, cysts, or anomalies
- Mucoepidermoid carcinoma of salivary gland type
- Primary carcinoid tumor
- Neuroendocrine carcinoma

Benign Mesenchymal Tumors

Hemangioma

Clinical

- Most common benign liver tumor; mostly incidental finding in all ages and both sexes
- Usually solitary and <5 cm; remain stable or involute
- "Giant" hemangiomas >10 cm are symptomatic with pain and discomfort

- Resection only if symptoms or rare complications (rupture, thrombocytopenia) occur

Macroscopic

- Subcapsular, flat, circumscribed; may be pedunculated
- Red-blue color
- Usually collapsing upon sectioning
- May show fibrosis and calcification

Microscopic

- Cavernous vascular spaces with flattened endothelium
- Fibrous septae, thrombosis, and calcifications common

Differential Diagnosis

- Peliosis hepatis
- Angiosarcoma
- Hereditary hemorrhagic telangiectasia

Infantile Hemangioendothelioma

Clinical

- Most common mesenchymal liver tumor in infancy (first 6 months of life), often associated with cutaneous hemangiomas
- Presenting features include hepatomegaly, mass, failure to thrive, and high output cardiac failure (A-V shunting in the tumor), complications (rupture, thrombocytopenia) are rare
- Tumor tends to regress gradually over a few months
- Treatment (surgery, embolization, steroids) sometimes required, overall very good prognosis

Macroscopic

- Usually multinodular or diffuse growth
- Spongy, red-brown with scarring

Microscopic

- Intricate maze of vascular channels lined by prominent endothelial cells with variable appearance
- Thrombosis and infarction common
- Small bile ducts present throughout the lesion
- Nuclear atypia, multilayering, and endothelial hypertrophy possible

Differential Diagnosis

- Angiosarcoma
- Hemangioma

Miscellaneous Benign Mesenchymal Tumors

- Lymphangioma/lymphangiomatosis
- Angiomyolipoma
- Lipoma
- Hibernoma
- Leiomyoma
- Granular cell tumor
- Chondroma
- Solitary fibrous tumor
- Hamartoma

Malignant Mesenchymal Tumors

Angiosarcoma

Clinical

- Most common sarcoma arising in the liver (annual incidence 0.25 per million), with peak age incidence sixth and seventh decade
- Strongly associated with exposure to Thorotrast (radioactive contrast medium used in 1920–1955) and vinyl chloride monomer (molecular fingerprint in the p53 gene, similar to aflatoxin); also associated with chronic arsenic exposure
- Clinical presentation with abdominal pain, hemorrhage, jaundice, and coagulopathy
- Death within 6 months of diagnosis; no treatment successful

Macroscopic

- Ill-defined, spongy nodules with hemorrhage; usually throughout the liver at autopsy
- Metastases (regional and distant) in 20%

Microscopic

- Liver changes preceding overt angiosarcoma include sinusoidal dilatation, endothelial hyperplasia, and excess reticulin
- Angiosarcoma with characteristic scaffold-like (tectorial) growth on liver cell plates; the latter atrophy and disappear as the tumor progresses
- Solid masses are rarely seen; typical features are large, cavernous spaces with coarse reticulin pattern
- Pleomorphic, elongated nuclei; scanty cytoplasm; vascular invasion; necrosis; and hemorrhage

Immunohistochemistry

- Factor VIII +, CD31 +, and CD34 +

Differential Diagnosis

- Hemorrhagic liver cell carcinoma
- Vascular leiomyosarcoma
- Diffuse metastatic disease in sinusoids
- Kaposi's sarcoma
- Epithelioid hemangioendothelioma

Epithelioid Hemangioendothelioma

Clinical

- Rare tumor; wide age range (second to eighth decade of life)

- Oral contraceptives may have a weak etiological role in younger women
- Vague clinical presentation with malaise, weight loss, and upper abdominal discomfort
- Surgical resection or liver transplantation possible
- Histology is unreliable to predict clinical outcome
- Prognosis better than angiosarcoma; with a substantial percentage of long-term survivors

Macroscopic

- Solitary or multiple fibrous masses

Microscopic

- Mildly pleomorphic cells with epithelioid appearance infiltrating sinusoids at the periphery of the tumor and replacement of liver parenchyma in cords toward the center of the lesion
- Fairly abundant connective tissue stroma; light blue (vaguely "chondroid" in appearance) or pink with hematoxylin and eosin
- Tumor center is fibrous, hyalinized, and often calcified, with scanty tumor cells
- Tumor cells may have intracytoplasmic vascular lumina (visible as large vacuoles)
- Tumor cells may form papillary tufts within vascular channels or sinusoidal spaces

Immunohistochemistry

- Factor VIII +, CD31 +, and CD34 +
- Keratin may be +

Differential Diagnosis

- Angiosarcoma
- Hemorrhagic hepatocellular carcinoma
- Diffuse metastatic disease in sinusoids
- Cholangiocarcinoma

Undifferentiated Sarcoma

Clinical

- Third most common malignant liver tumor in children
- Age usually 6–10 years; rarely in adults
- Presenting with weight loss and abdominal swelling
- Large, hypodense, avascular mass on imaging
- Prognosis very poor; 5-year survival with aggressive chemotherapy = 15%

Macroscopic

- Soft, globular, large mass, usually in the right lobe
- Cut surface variegated; solid and cystic areas; necrosis and hemorrhage common
- Thin pseudocapsule usually present

Microscopic

- Loosely arranged, spindle-shaped, pleomorphic cells
- Compact areas with more rounded nuclei possible
- Abundant mucopolysaccharide matrix
- Dilated, benign-appearing bile ducts and PAS + diastase-resistant globules characteristic

Immunohistochemistry

- Wide range of mesenchymal differentiation in individual cases
- Vimentin uniformly +, keratin may be focally +

Differential Diagnosis

- Rhabdomyosarcoma
- Metastatic tumors

Embryonal Rhabdomyosarcoma

Clinical

- Children <5 years of age; rarely in adults
- Obstructive jaundice, fever, and weight loss
- Tumor arises from major bile ducts at the hilum
- Treatment and prognosis similar to undifferentiated sarcoma

Macroscopic

- Gelatinous, grape-like (botryoid) masses with biliary epithelium-covered projections into bile duct lumina

Microscopic

- "Cambium" layer of dark, round cells beneath the surface and spindle cells in a loose myxoid stroma elsewhere; numerous mitoses
- "Typical" cross-striated structures seldom seen

Immunohistochemistry

- Actin +, myosin +, myoglobin +, and desmin +

Differential Diagnosis

- Undifferentiated sarcoma

Miscellaneous Malignant Mesenchymal Tumors

- Rare as primary liver tumors, usually in middle and old age
- Presentation in advanced stage
- Wide range of mesenchymal differentiation in individual cases; most common are fibrosarcoma, malignant fibrous histiocytoma, and leiomyosarcoma
- Slow progression, with poor prognosis
- Rule out metastatic lesions

Hematopoietic Neoplasms

Primary Malignant Lymphoma

Clinical

- Wide age range with biphasic age/incidence pattern (children/adolescents and older adults) and male predominance
- Clinical presentation with pain, mass, or hepatomegaly; B-symptoms in 50%
- Some associated with hepatitis B virus infection or AIDS
- Surgical resectability provides good prognosis; aggressive radiochemotherapy offers clinical benefit

Macroscopic

- Mostly solitary or multifocal; some cases with diffuse infiltration pattern
- Fish-flesh appearance on cut section

Microscopic

- All are non-Hodgkin's lymphomas, usually high-grade
- May be of B- or T-cell lineage, the latter typically of the diffuse type
- Destructive nature of the infiltrate and monoclonality best clues for the diagnosis

Differential Diagnosis

- Metastatic carcinoma
- Metastatic malignant melanoma
- Inflammatory pseudotumor
- Chronic hepatitis

Secondary Hematopoietic Neoplasms

- Hodgkin's lymphoma
- Non-Hodgkin's lymphoma
- Leukemias
- Multiple myeloma
- Histiocytosis
- Mast cell disease

Metastases

- Common site for metastases, particularly from lung, breast, and GI tract
- Diffuse infiltrate may resemble primary liver tumor
- Metastases may be missed by needle biopsy; characteristic triad in adjacent liver (proliferating bile ducts, leukocytes, and sinusoidal dilatation) may be helpful clues to sampling error
- Resection beneficial if few isolated lesions

Tumor-like Lesions

Cysts

- Multiple intrahepatic cysts occur in polycystic disease, congenital hepatic fibrosis, and Caroli's disease (see chapter 30), and are developmental in origin
- Solitary, non-neoplastic and non-parasitic cysts rare
- Ciliated hepatic foregut cysts are reported with differentiation toward bronchial structures

Focal Nodular Hyperplasia

Clinical

- Thought to be a vascular malformation with A-V anastomoses and localized overgrowth of all liver constituents
- Occurs in both sexes at all ages, but most commonly in young women
- Incidental finding, rarely symptomatic (pain, palpable mass)
- Occasionally large (up to 15 cm), sometimes pedunculated
- Association with oral contraceptives controversial
- Treatment usually not necessary; surgery only for symptomatic lesions

Macroscopic

- Usually solitary, <5 cm in size
- Well-circumscribed fibrous mass with bulging of the cut surface
- Multiple yellow-brown nodules of liver parenchyma separated by fibrous septae
- Central scar typical

Microscopic

- Central stellate scar with thick-walled vessel that lacks internal elastic lamina; no bile ducts; variable inflammation
- Incomplete septa radiating from central scar; composed of fibrous tissue, variable inflammation, no bile ducts, and often prominent proliferating ductules (cholangioles)
- Regenerative nodules of hepatic parenchyma with occasionally increased glycogen and/or fat; bile, Mallory's hyaline uncommon

Differential Diagnosis

- Liver cell adenoma
- Mesenchymal hamartoma

Nodular Regenerative Hyperplasia

Clinical

- Occurs in both sexes and at all ages
- Associated with a large number of a variety of extrahepatic diseases (usually vascular or circulatory abnormality)
- May be a secondary, non-specific tissue adaptation to uneven distribution of total hepatic blood flow
- Not a preneoplastic condition

- Usually incidental finding; may cause non-cirrhotic portal hypertension or intraperitoneal hemorrhage
- Diagnosis by liver biopsy difficult; most cases seen at autopsy or laparotomy

Macroscopic

- Numerous nodules (0.1–1 cm) throughout the liver
- May spare portions of the liver ("partial nodular transformation")
- Rare cases with large (up to 10 cm) nodules

Microscopic

- Nodules composed of hepatocytes, expansile with distortion, but not effacement of the hepatic architecture
- Plates with two to three liver cells in thickness, with atrophic intervening parenchyma
- No fibrous septae; normal portal structures remain evenly distributed
- Obliterative portal venular changes often seen

Differential Diagnosis

- Liver cell adenoma, if large nodules present

Mesenchymal Hamartomas

Clinical

- Localized abnormality of ductal plate development preceding birth, with subsequent enlargement (fluid accumulation)
- Related to polycystic disease, congenital hepatic fibrosis, and biliary hamartoma
- Almost exclusively in young children (median = 15 months of age)
- Progressive abdominal enlargement as presenting feature; surgical resection curative

Macroscopic

- Large (>1 kg) multicystic mass with soft, smooth surface and gelatinous contents
- Solid areas are fibrous, myxoid, or liver-like

Microscopic

- Haphazard and variable admixture of normal liver structures
- Predominant component is loose, edematous mesenchymal tissue
- Dilated lymphatic channels and blood vessels; randomly scattered bile ducts and hepatocyte nodules

Differential Diagnosis

- Focal nodular hyperplasia
- Liver cell adenoma

Biliary Hamartoma (von Meyenburg Complex)

Clinical

- Often multiple, throughout the liver
- Part of the spectrum of polycystic disease

Macroscopic

- Small (<0.5 cm) whitish nodules

Microscopic

- Small, irregular, occasionally dilated ducts in a fibrous stroma
- May contain bile
- No significant cytologic atypia or mitosis

Differential Diagnosis

- Bile duct adenoma
  - More compressed ducts, less fibrous stroma
  - Lumens may contain mucin (not bile)

Peliosis Hepatis

Clinical

- Often associated with exposure to anabolic steroids and various drugs, as well as in transplant and AIDS patients
- Also seen in liver cell adenomas induced by anabolic steroids
- Similar lesions described in spleen, lungs, and lymph nodes
- Pathogenesis unknown (endothelial cell injury?)
- May present with liver failure, portal hypertension, or severe hemorrhage

Macroscopic

- Multiple, blood-filled spaces throughout the liver
- Size from 1 mm to several cm

Microscopic

- Blood-filled spaces with "capsule" of fibrin/early collagen; may have endothelial lining

Differential Diagnosis

- Bacillary peliosis hepatis ("bacillary angiomatosis") in AIDS

Inflammatory Pseudotumor

Clinical

- Rare lesion, similar to those occurring in multiple other sites of the body
- Usually young adults; several causes proposed, including ascending cholangitis, autoimmune processes, and ischemia; rare cases may be true neoplasms

- Many synonyms (e.g., plasma cell granuloma and inflammatory myofibroblastic tumor), reflecting the wide range of histologic patterns
- Presentation with intermittent fever, pain, and weight loss
- Inflammatory laboratory markers +, alkaline phosphatase elevated
- Almost always mistaken for malignancy by radiography
- Surgery is curative, but not necessary; lesions usually regress after steroid treatment or spontaneously

Macroscopic

- Tumor-like lesion, solitary or multiple, up to 25 cm in size; may invade adjacent structures

Microscopic

- Mixture of chronic inflammatory cells with sclerosis
- Nuclear atypia (reactive)
- Polyclonal plasma cells predominate
- EBV + in some cases

Immunohistochemistry

- Plasma cells are polyclonal for kappa/lambda light chains

Differential Diagnosis

- Malignant lymphoma
- Malignant fibrous histiocytoma

TUMORS OF THE GALLBLADDER AND EXTRAHEPATIC BILE DUCTS

Benign Epithelial Tumors and Lesions

Polyps

- Lymphoid polyps:
  - Benign, sessile, or pedunculated hyperplastic lymphoid lesions covered by normal biliary epithelium
  - 2–4 mm in size
  - Older age group
- Granulation tissue polyps:
  - Contain numerous small vascular channels with inflammatory cells
  - Overlying epithelium typically denuded
  - <1 cm in size
  - Associated with acute and chronic cholecystitis
- Fibrous polyps:
  - Larger in size, detectable by ultrasonography, with abundant edematous connective tissue stroma and only scattered glands/ducts
  - Covered by normal biliary epithelium
- Cholesterol polyps:
  - Small pedunculated yellow structures filled with lipid-laden macrophages and covered by normal gallbladder epithelium
  - Represent 50% of all gallbladder polyps
  - Usually *not* associated with cholesterolosis

Hyperplasia and Metaplasia

- Nodular hyperplasias of pseudopyloric glands:
  - Sessile, small nodules
  - Often seen adjacent to adenomas and carcinomas
  - Tall, mucin-producing cells and Paneth cells
  - Relatively poor demarcation
  - Dysplasia possible
- Intestinal metaplasia:
  - Characterized by replacement of the normal surface epithelium by intestinal-type cells
  - Dysplastic changes seen
  - Process may be focal, segmental, or diffuse
  - May co-exist with adenomas and carcinomas

Papillary Hyperplasia

- Primary papillary hyperplasia:
  - Can be focal, segmental, or diffuse in gallbladder and/or extrahepatic bile ducts
  - Papillary structures
  - No intestinal-type cells, no dysplasia
- Secondary papillary hyperplasia:
  - Typically associated with cholecystitis and cholelithiasis
  - Numerous crowded mucosal folds lined by tall columnar cells with mucin, interspersed goblet- and Paneth cells
- Biliary papillomatosis

Hepatobiliary Cystadenoma

- See page 31-2

Adenoma

- Rare (0.5%) lesions, usually not precancerous
- Occasionally in association with familial polyposis coli or Gardner's syndrome
- Typically incidental findings (gallbladder) may be symptomatic with jaundice, cholangitis, or hemobilia (common bile duct)
- Usually <2 cm in size; sessile or pedunculated; solitary

- Tubular, papillary, or mixed architectural patterns; pyloric-type or colonic mucosa common
- Paneth cells or neuroendocrine elements possible; variable degrees of dysplasia seen
- Differential diagnosis includes adenocarcinoma, biliary cystadenoma, and biliary papillomatosis

Malignant Epithelial Tumors

Carcinoma of the Gallbladder

Clinical

- Fourth most common malignant neoplasm of the GI tract
- Main etiological association with gallstones/chronic inflammation
- Gallstones are present in 80% to 90% of all cases
- Arise from flat dysplasia, not adenoma
- Usually incidental discovery during surgery, but with metastatic spread to lymph nodes and the liver bed in 50% to 70%
- Distant metastases to liver, peritoneum, and lungs
- Curable if confined to the gallbladder, without muscular invasion
- Overall 5-year survival = 5% to 10%

Macroscopic

- Usually diffuse thickening of the gallbladder wall
- Polypoid neoplasms rare

Microscopic

- Typical adenocarcinoma in 85%, usually tubular type
- Commonly associated with hyperplasia, or antral or intestinal metaplasia
- Dysplasia or carcinoma in situ in adjacent mucosa
- Perineural invasion common

Immunohistochemistry

- CEA +, keratin +

Variants

- Intestinal, mucinous, signet ring types
- Clear cell and aggressive oat cell carcinoma
- Adenosquamous and pure squamous cell carcinoma
- Undifferentiated (spindle cell) carcinoma

Differential Diagnosis

- Dysplasia extending into the cystic duct, Luschka's ducts, and Aschoff-Rokitansky sinuses
- Adenoma/cystadenoma
- Adenomyoma

Carcinoma of the Extrahepatic Bile Ducts

Clinical

- Less common than, and different from, gallbladder carcinoma
- Older individuals; cholelithiasis less commonly associated
- Choledochal cysts prone to malignant transformation
- Obstructive jaundice, cholangitis, and hemobilia as presenting symptoms
- Resectability and prognosis poor, with better results for distal lesions
- Metastatic spread to lymph nodes and liver frequent at diagnosis

Macroscopic

- Appearance as diffuse segmental thickening, stricture, or small polyp

Microscopic

- Similar to gallbladder carcinoma
- May be associated with metaplasia, dysplasia, or adenoma

Immunohistochemistry

- Monoclonal CEA + (cytoplasmic)

Differential Diagnosis

- Non-neoplastic fibrous stricture
- Primary sclerosing cholangitis

Miscellaneous Malignant Epithelial Tumors

- Carcinosarcoma/undifferentiated spindle cell carcinoma
- Carcinoid tumor
- Metastatic tumors (breast, stomach, pancreas)

Benign and Malignant Non-Epithelial Tumors

- Granular cell tumor
- Malignant melanoma
- All others are exceedingly rare, including: lipoma, hemangioma, neurofibroma, paraganglioma, leiomyorhabdomyosarcoma, MFH, and malignant lymphoma

Tumor-like Lesions

Adenomyoma

Macroscopic

- Anywhere in the gallbladder or extrahepatic bile ducts
- Localized, segmental, or diffuse

Microscopic

- Branching, ductal, or cystic glandular structures; no dysplasia
- Hyperplastic smooth muscle cell stroma
- Lumina with mucus, bile, or stones
- Granulomatous inflammation with fibrosis around ruptured glands

TNM CLASSIFICATION OF LIVER TUMORS (1997 REVISION)

- T: Primary Tumor
  - Tx: Primary tumor cannot be assessed
  - T0: No evidence of primary tumor
  - T1: Solitary tumor ≤ 2 cm in greatest dimension without vascular invasion
  - T2: Solitary tumor > 2 cm in greatest dimension without vascular invasion

    Or solitry tumor ≤ 2 cm in greatest dimension with vascular invasion

    Or multiple tumors (≤ 2 cm) limited to one lobe without vascular invasion
  - T3: Solitary tumor > 2 cm in greatest dimension with vascular invasion

    Or multiple tumors limited to one lobe with vascular invasion

    Or multiple tumors, any > 2 cm, with or without vascular invasion
  - T4: Multiple tumors in one than one lobe

    Or tumor involves a major branch of the portal or hepatic vein

    Or invasion of adjacent organs other than gallbladder

    Or perforation of the visceral peritoneum
- N: Regional Lymph Nodes
  - Nx: Regional lymph modes cannot be assessed
  - N0: No regional lymph node metastasis
  - N1: Regional lymph node metastasis
- M: Distant Metastasis
  - Mx: Distant metastasis cannot be assessed
  - M0: No distant metastasis
  - M1: Distant metastasis

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Essentials of Anatomic Pathology

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During the past decade the ability of surgical pathologists to reach a definitive diagnosis has been greatly enhanced—but also complicated—by the availability of many new markers and innovative immunohistochemical techniques. In *Essentials of Anatomic Pathology,* a distinguished panel of experts concisely reviews these diagnostic advances in classic pathology to produce a readily accessible guide that helps the practicing pathologist achieve accurate everyday diagnoses. Arranging the important diagnostic features of the most common diseases and tumors by bodily organ, the book provides for each disease the pertinent clinical information, its salient diagnostic features, relevant ancillary data (e.g., immunohistochemical profiles), the main differential diagnoses, and the latest tumor staging information, thus ensuring easy access to all the information essential for case sign-out. Additional chapters afford background reviews of the fundamentals of general anatomic pathology, including diagnostic molecular pathology, diagnostic electron microscopy, human genetic disorders, forensic pathology, cytopathology, and microbiology for surgical pathologists.

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