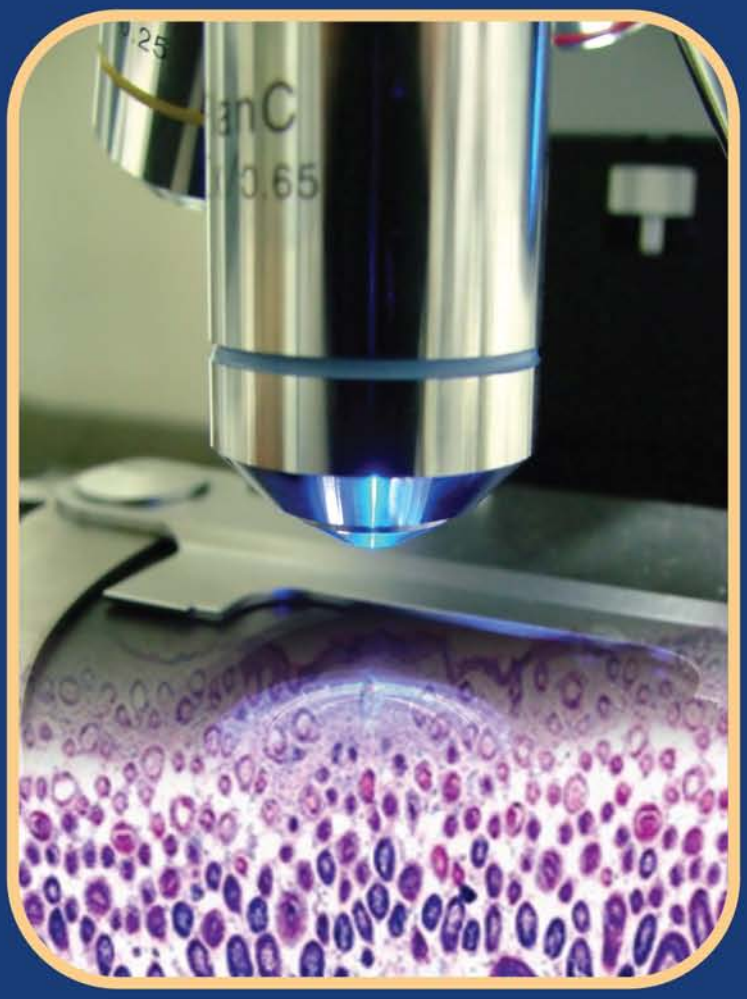
COLOR ATLAS OF DERMATOPATHOLOGY



Edited by

Jane M. Grant-Kels

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DERMATOLOGY: CLINICAL & BASIC SCIENCE SERIES

COLOR ATLAS OF DERMATOPATHOLOGY

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DERMATOLOGY: CLINICAL & BASIC SCIENCE SERIES

COLOR ATLAS OF DERMATOPATHOLOGY

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This book is dedicated to the memory of my Dad,
George H. Grant, D.D.S. who died on June 8, 2006 at noon
and to my husband, Barry D. Kels, M.D., J.D.
They are both gentle yet strong, demonstrate an absolute love of life and family,
and my greatest supporters. In their arms, I have learned what it means to feel safe and secure.
My Dad was the first man in my life that I loved with every ounce of my being
and my husband is my second and last.

I am also indebted to my loving Mother, Charlotte Grant,
who has been my role model for caring, grace and dignity
and to my adored children, Joanna Kels Albright and Captain Charles Grant Kels, USAF.
Their love has enveloped me and my love for them has given me great joy.

Preface

Why one more book on dermatopathology? Certainly there are many outstanding encyclopedic textbooks already written and even recently updated. Why one more atlas? Hopefully you will agree that this book is different. We have tried to pair clinical and histologic photographs to enhance the reader's appreciation for clinical-pathological correlation. In addition, this text is meant to be user friendly whether you are approaching dermatopathology from a background of dermatology or pathology. Herein we hope to share with you our enthusiasm as well as the helpfulness of clinical-pathological as well as pathological-clinical correlation. Ideally after reading through some of our examples, the next time you look through the microscopic oculars at a skin slide, you will ask yourself "how would this lesion look clinically?" Conversely, when you examine a skin lesion or rash in vivo, you will ask yourself "how would this look under the microscope?" Once you ask yourself these questions enough times, it will become automatic and so helpful to you in developing your differential lists, you will be incredulous that you did not always approach dermatopathology and dermatology in this manner.

This book is not meant to be a complete review of all skin diseases. It is meant to try to teach you a different approach to the patient and to the biopsy obtained from a patient's skin. One should always be mindful of the clinical-pathologic corollaries that will help improve your diagnostic acumen. I personally hope that in addition to finding this book educational, you will also have some fun. In the words of A. Bernard Ackerman, dermatopathology is "art in vivo"!

The many authors who have contributed to this volume are the thought leaders in our field. They are scattered geographically but share their continued enjoyment in becoming better dermatopathologists. Some of the authors have been my friends, "classmates," colleagues, and teachers since I began my journey in dermatopathology in 1978! Others are younger and compose the next generation of leaders in dermatopathology. All have brought their enthusiasm to this project for which I am grateful.

I now invite you to "see" skin disease through new oculars! Not only will the journey be fun, but it will make you a better diagnostician whether you treat patients in an office or study slides in a lab.

Jane M. Grant-Kels

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A Philosophy of an Approach to a Slide

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By way of introduction, I would like to review with you my personal approach to a slide. None of the ideas presented herewith are original; they represent a compendium of ideas that have been borrowed from my teachers, especially my first mentor in dermatopathology, Dr. A. Bernard Ackerman, and all of my friends and colleagues I had taken training with and have collaborated with over the years, many of whom are authors of chapters in this book.

Remember, how well you perform as a dermatopathologist is directly correlated to the development of the proper philosophical and intellectual approach to our specialty and each individual slide that crosses the stage of your microscope.

Philosophically:

1. It is important to approach the pathology you see under the microscope from the clinician's point of view. Clinical–pathological correlation is essential. When you gaze on the histologic changes you should be able to imagine how the lesion looked clinically.
2. Know normal anatomy at various anatomic sites and learn to recognize changes that may be normal due to age or exposure to the elements. Once you know normal histology and its variants you will be able to recognize what is abnormal on the slide.
3. Learn to recognize common artifacts of either processing or biopsy technique.
4. The criteria applied to each case must be repeatable and well established.
5. The language of your report must be precise.
6. Be willing to admit when you do not know the diagnosis and appropriately seek the opinion of others.
7. Diseases are dynamic and demonstrate changes that correspond to their chronology or "lives." Learn to recognize the changing histologic features of an acute, fully developed, and resolving lesion.
8. Our knowledge of diseases is also dynamic. Therefore, keep an open mind. Criteria for diagnoses may evolve over the years with increased experience and new staining techniques. Be willing to learn and be open to new ideas.
9. Finally, there is much that is subjective in dermatopathology; mistakes are inevitable. Learn from errors rather than hide from them. Mistakes and malpractice are not synonymous.

Your practical approach to the slide should demonstrate a methodical approach following a checklist of sequential steps (algorithmic method) utilizing pattern analysis. Sign out of slides should be done in a quiet place without distractions. All slides should be initially examined without knowledge of the clinical history. Prior to reviewing the slide under the microscope, examine the slide with the naked eye: make note of how the specimen was grossed and how many pieces of tissue are present to be examined on each slide. Establish the kind of biopsy technique used, that is, shave, punch, curette, or excision. If there are multiple small fragments, circle them to ensure that all pieces of tissue are reviewed.

Once you have placed the slide on your microscope stage (Table 1):

1. Employ scanning magnification. Try to establish the pattern of the infiltrate of cells. Is this an inflammatory or neoplastic infiltrate? Higher magnification should be used later to review cytologic changes.
2. Try to determine the anatomic site of the biopsy. Various anatomic locations have key distinguishing features. Certain diseases favor certain anatomic sites and, therefore, this information will help in clinical–pathological correlation. In addition, some locations may alter the appearance of the pathology. For example, overlapping stasis changes often alters a lesion on the leg of an older adult.
3. Try to determine the approximate age of the patient. Is there solar elastosis suggesting a sun-damaged adult? Are there effete sebaceous glands as would be seen in a young child? Many diseases have a tendency to occur in certain age groups as well as locations.
4. Confirm your impression regarding how the biopsy was obtained.
5. Look at all the sections on the slide.
6. Learn to recognize artifacts so that you do not assign inappropriate import to these changes.
7. Develop a systematic approach to looking at the sections of skin. Some dermatopathologists study the biopsy from top to bottom (stratum corneum → rest of epidermis → dermis → subcutaneous tissue). Others prefer to first determine the pattern of changes in the dermis and then proceed to the epidermis and subsequently to the changes in the subcutis. Although I prefer the latter style, it is irrelevant which technique you use as long as you are methodical, consistent, and systematic in your approach.
8. Apply pattern analysis to help you determine whether a lesion is inflammatory, malformation, deposition, or neoplastic. This seemingly simple step is not always easy. It is not uncommon for neoplasms to be associated with significant inflammation and for inflammatory conditions to mimic a neoplastic process. Therefore, a specific diagnosis cannot always be achieved. However, the system works in most cases and one's

Table 1 Algorithmic Approach to a Slide

Scanning magnification:

1. look at all the sections and pieces of skin present on the slide
2. assess how specimen was obtained—punch, shave, etc.
3. determine anatomic site
4. determine approximate age of patient
5. imagine the clinical appearance of the lesion (CPC)
6. Is the lesion:

Inflammatory	or	Neoplastic
↓		↓
Which of 9 major patterns?		Benign vs. malignant
↓		↓
What is the epidermal pattern?		Epithelial or nonepithelial?
↓		↓
Are there changes in the subcutaneous tissue?		Specific type of cell? or
↓		↓
What types of cells are present in the infiltrate?		Specific type of differentiation?
↓		↓
Obtain clinical information: clinical–pathological correlation		Obtain clinical information: CPC
↓		↓
Specific diagnosis or differential		Specific diagnosis or differential

Table 2 Neoplasms: Benign vs. Malignant

Benign	Malignant
Small	Large
Symmetric	Asymmetric
Well circumscribed	Poorly circumscribed
Smooth margins	Irregular, jagged margins
V-shaped lesions	Not V-shaped lesions
Superficial	Deep
Not usually ulcerated	Tends to ulcerate
Neoplastic cells discretely arranged	Neoplastic cells in sheets
Aggregations uniform in size and shape	Aggregations vary in size and shape
Cells well differentiated	Cells poorly differentiated
Adnexal structures usually preserved	Adnexal structures often absent
Maturation: nuclei of cells at base of lesion smaller than those near the surface	No maturation
No necrosis or necrosis only of single cells	Necrotic cells in aggregate
No neoplastic cells in perineural locations	Neoplastic cells in perineural locations
No neoplastic cells in vessels	Neoplastic cells in vessels
Epithelial cells not in single file between collagen bundles	Epithelial cells in single file between collagen bundles
Peripheral fibrous tissue well-packed	Peripheral fibrous tissue not well-packed
Clefts between well-packed fibrous tissue and normal fibrous tissue	Clefts between neoplastic cells and altered stroma

Source: From Ref. 1.

Table 3 Patterns of Inflammatory Diseases

Ackerman's Original Nine Basic Patterns of Inflammatory Diseases Circa 1978

1. Superficial perivascular dermatitis
2. Superficial and deep perivascular dermatitis
3. Vasculitis
4. Nodular and diffuse dermatitis
5. Intraepidermal vesicular and pustular dermatitis
6. Subepidermal vesicular dermatitis
7. Folliculitis and perifolliculitis
8. Fibrosing dermatitis
9. Panniculitis

Ackerman's New Schema of Eight Basic Patterns of Inflammatory Diseases Circa 2005

1. Perivascular dermatitis (superficial as well as superficial and deep perivascular)
2. Nodular and diffuse dermatitis
3. Vasculitis
4. Vesicular dermatitis (intraepidermal vesicular and/or subepidermal vesicular dermatitis)
5. Pustular dermatitis (intraepidermal and infundibular epidermal pustular dermatitis)
6. Peri-infundibulitis and perifolliculitis
7. Fibrosing dermatitis
8. Panniculitis (predominantly septal or predominantly lobular)

ability to apply the pattern analysis approach improves with experience.

9. If the lesion is neoplastic:
   - The next critical question is whether the lesion is benign or malignant? Architectural pattern is extremely important in making this important distinction. Size, symmetry, and circumscription patterns outweigh cytology. Table 2 presents an overview of features useful in distinguishing benign versus malignant neoplasms (1).
   - Is the lesion epithelial or nonepithelial?
   - What cells are proliferating? Keratinocytes, melanocytes, fibroblasts, muscle cells, nerve cells, sebocytes, ductal cells, lymphocytes, histiocytes, mast cells, and so on.
10. If the lesion is inflammatory, determine the pattern of the inflammatory cells in the dermis and subcutaneous tissue.
   - There are nine major patterns of inflammatory infiltrates (Table 3). Although many more patterns and variations have been described, it is still worthwhile to go back to simple basics and start with the original nine described many years ago.
   - What pattern of change is noted in the epidermis? (spongiosis, interface, psoriasiform hyperplasia, etc.)
   - What types of cells predominate in the infiltrate? (lymphocytes, histiocytes, neutrophils, eosinophils, etc.)

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2

Perivascular Dermatitis

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CONTENTS

This chapter covers diseases that consist of perivascular (and interstitial) infiltrates of inflammatory cells devoid of marked changes in the epidermis. Clinically, these diseases usually present with smooth surfaced macules, patches, papules, and plaques without either the crust, scale, or both. Some of the diseases in this chapter are characterized by infiltrates that include neutrophils (urticaria, erysipelas), others by infiltrates that typically show numerous eosinophils (pruritic urticarial papules and plaques of pregnancy), or plasma cells (erythema migrans), or by infiltrates that are virtually monopolized by lymphocytes (persistent pigmented purpuric dermatitis, viral exanthems, polymorphous light eruption, tumid lupus erythematosus, pernio, erythema figuratum); still others are typified by sparse infiltrates of inflammatory cells accompanied by very subtle, but highly characteristic changes in epidermis or dermis (postinflammatory pigmentary alteration, vitiligo, tinea versicolor, erythrasma).

It should be mentioned that many diseases dealt with in separate chapters of this book may present themselves also as perivascular dermatitis devoid of marked changes in the epidermis at an early or resolving stage. Among those are bullous diseases (e.g., bullous pemphigoid) and vasculitides (e.g., leukocytoclastic vasculitis).

URTICARIA

Synonyms: Nettle rash; hives; wheals.

Clinical Presentation (Fig. 1A):

- Edematous papules and plaques, discrete or confluent
- Localized, regional, or widespread
- Individual lesions disappear in hours
- Lesions are intensely pruritic

Histopathology (Figs. 1B and C):

- Perivascular infiltrate of neutrophils and eosinophils early
- Lymphocytes perivascular, neutrophils, and eosinophils interstitial later
- Sparse perivascular infiltrate of lymphocytes and a few eosinophils in a resolving lesion

Clinicopathologic Correlation:

Clinical Feature	Pathologic Feature
Edematous papules and plaques	Edema located mostly in the reticular dermis (not visualizable in H+E)
Erythema	Dilated vessels

Differential Diagnosis:

Insect Bites	Urticarial Lesions of Bullous Pemphigoid or Pemphigus Vulgaris	Urticarial Lesions of Prurigo Pigmentosa
Wedge-shaped infiltrate of lymphocytes and eosinophils	Bandlike infiltrate housing numerous eosinophils	Superficial perivascular infiltrate of neutrophils mostly
Spongiosis, a spongiotic vesicle sometimes	Eosinophilic spongiosis sometimes	Scattered neutrophils in the epidermis

Pathophysiology:
- Different causes lead to degranulation of mast cells, which attract inflammatory cells and cause vasodilation and edema in the dermis.

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ERYSIPELAS

Synonyms: St. Anthony's fire; *ignis sacer.*

Clinical Presentation (Fig. 2A):
- Sharply demarkated erythematous or purpuric patch or plaque, sometimes covered by vesicles and/or bullae
- Often accompanied by edema, lymphangitis, lymphadenitis, and fever
- Face and lower extremities involved commonly, usually unilateral
- Lesion is painful

Histopathology (Figs. 2B and C):
- Sparse to moderately dense perivascular and interstitial mixed-cell infiltrate of lymphocytes, neutrophils, and few eosinophils
- Erythrocytes extravasated in number
- Widely dilated venules and lymphatics
- Edema of the papillary dermis
- Spongiosis and ballooning of the epidermis sometimes

Clinicopathologic Correlation:

Clinical Feature	Pathologic Feature
Erythema	Dilated vessels
Purpuric color	Extravasated erythrocytes
Vesicles and bullae	Extensive edema of the papillary dermis, and/or spongiosis, and ballooning

Differential Diagnosis:

Urticaria	Zoster Early in the Course of an Eruption
Perivascular and interstitial infiltrate of lymphocytes, neutrophils, and eosinophils	Superficial and deep infiltrate of lymphocytes mostly
No changes in surface epidermis	Ballooning of the epidermis, acantholysis, multinucleated epithelial cells

Pathophysiology:
- Beta-hemolytic streptococcus is responsible most commonly, *Staphylococcus aureus* less commonly.

References:

1. Chartier C, Grosshans E. Erysipelas. Int J Dermatol 1990; 29: 459–467.
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PRURITIC URTICARIAL PAPULES AND PLAQUES OF PREGNANCY

Synonyms: Pruritic urticarial papules and plaques of pregnancy (PUPPP), polymorphic eruption of pregnancy, Bourne's toxemic rash of pregnancy, toxic erythema of pregnancy, nurse's late onset prurigo of pregnancy.

Clinical Presentation (Fig. 3A):
- Urticarial papules and plaques
- Abdomen, buttocks, and thighs especially, often beginning in abdominal striae
- Lesions usually disappear shortly after term
- Lesions are itchy
- Primigravidas late in the third trimester

Histopathology (Figs. 3B–D):
- Superficial perivascular infiltrate of lymphocytes (Fig. 3C)
- Eosinophils scattered interstitially (Fig. 3D)
- Focal spongiosis and parakeratosis sometimes

Clinicopathologic Correlation:

Clinical Feature	Pathologic Feature
Papules and plaques	Sparse perivascular and interstitial infiltrates of inflammatory cells and slight edema in the upper part of the dermis
Erythema	Dilated blood vessels
Subtle scale	Parakeratosis

Differential Diagnosis:

Urticaria	Insect Bites
Perivascular and interstitial infiltrate	Dense, wedge-shaped infiltrates, perivascular and interstitial
Neutrophils and eosinophils	Lymphocytes and eosinophils
No changes in the epidermis	Spongiosis in the center of the lesion

Pathophysiology:
- Unknown

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ERYTHEMA MIGRANS

Synonyms: None.

Clinical Presentation (Fig. 4A):
- Macules, patches, or plaques
- Centrifugal extension with healing in the center leads to formation of annular shapes
- Hemorrhagic or scaly lesions sometimes

Histopathology (Figs. 4B and C):
- Perivascular and sometimes interstitial infiltrate of lymphocytes and plasma cells
- Eosinophils in the vicinity of the "bite" of the tick in an early lesion
- Spongiosis and parakeratosis rarely

Clinicopathologic Correlation:

Clinical Feature	Pathologic Feature
Annular plaque	Perivascular and sometimes interstitial infiltrate
Scale	Parakeratosis

Differential Diagnosis:

Insect Bites	Erythema Figuratum/ Deep Gyrate Erythema	Tumid Lupus Erythematosus
Wedge-shaped infiltrate	Perivascular infiltrate, no involvement of the interstitium	Perivascular and interstitial infiltrate
Numerous eosinophils	Lymphocytes monopolize	Lymphocytes monopolize
Interstitial mucin sometimes	No mucin	Interstitial mucin always

Pathophysiology:
- Erythema migrans is caused by species of *Borrelia burgdorferi* (*Borrelia burgdorferi sensu stricto, Borrelia garinii*, and *Borrelia afzelii*)

References:

1. Afzelius A. Erythema chronicum migrans. Act Derm Venereol 1921; 2:120–125.
2. Berger BW, Clemmensen OJ, Gottlieb GJ. Spirochetes in lesions of erythema chronicum migrans. Am J Dermatopathol 1982; 4: 555–556.

PERSISTENT PIGMENTED PURPURIC DERMATITIS

Synonyms: Pigmented purpuric dermatitis; progressive pigmented prupura.

Clinical Presentation (Fig. 5A):
- Purpuric macules and papules, sometimes scaly
- Symmetrically involving legs and thighs, rarely the trunk and the upper extremities
- Variations include Schamberg's disease (purpuric and pigmented macules), lichenoid purpura of Gougerot-Blum (lichenoid papules), lichen aureus (yellow or brown patches), purpura of Doucas and Kapetanakis (scaly papules), and purpura annularis telangiectodes of Majocchi (annular purpuric macules)

Histopathology (Figs. 5B–E):
- Superficial perivascular and interstitial, sometimes lichenoid, infiltrate of lymphocytes
- Dermoepidermal junction often spared but sometimes lymphocytes scattered in the epidermis accompanied by slight spongiosis and parakeratosis
- Extravasated erythrocytes and/or siderophages in the upper part of the dermis
- Wiry bundles of collagen in the upper part of the dermis, sometimes

Clinicopathologic Correlation:

Clinical Feature	Pathologic Feature
Purpuric macules	Extravasated erythrocytes in the dermis
Yellow or brown macules	Multiple siderophages in the dermis
Lichenoid papules	Bandlike infiltrates of lymphocytes
Scale	Parakeratosis

Differential Diagnosis:

Drug Eruption	Mycosis Fungoides
Perivascular or lichenoid infiltrate	Lichenoid or psoriasiform-lichenoid infiltrate
Eosinophils in the infiltrate	Lymphocytes monopolize
Vacuolar alteration, necrotic keratinocytes	Lymphocytes in the epidermis accompanied by subtle spongiosis
No changes of collagen	Wiry bundles of collagen
Focal parakeratosis	Elongated mounds of parakeratosis

Pathophysiology:
- Unknown, but drugs as well as infectious foci have been claimed to induce the eruption.

Reference:

1. Ackerman AB, Böer A, Bennin B, Gottlieb GJ. Histologic Diagnosis of Inflammatory Skin Diseases. 3rd ed. New York: Ardor Scribendi, 2005.

VIRAL EXANTHEMS

Synonyms: None.

Clinical Presentation (Fig. 6A):
- Exanthem of macules and/or papules
- Sometimes morbilliform (measles), and rubeoliform, (German measles)
- Children, especially
- Variations include erythema infectiosum (appearance of cheeks that have been slapped), roseola/exanthema subitum (discrete, small macules and papules similar to those of rubella)

Histopathology (Figs. 6B and C):
- Sparse perivascular infiltrate of lymphocytes
- Few eosinophils, sometimes
- Extravasate erythrocytes, sometimes

Clinicopathologic Correlation:

Clinical Feature	Pathologic Feature
Red macules and papules	Sparse superficial perivascular infiltrate and vasodilation

Differential Diagnosis:

Drug Eruption	Persistent Pigmented Purpuric Dermatitis
Perivascular or lichenoid infiltrate	Perivascular and interstitial, sometimes lichenoid, infiltrate
Eosinophils in the infiltrate	Lymphocytes, erythrocytes, and siderophages
Vacuolar alteration and necrotic keratinocytes often	No changes in the epidermis or slight spongiosis
No changes of collagen	Wiry bundles of collagen

Pathophysiology:
- Erythema infectiosum is caused by parvovirus B19, roseola is caused by human herpesvirus 6, and other exanthems are caused by other specific viruses.

Reference:
1. Ackerman AB, Böer A, Bennin B, Gottlieb GJ. Histologic Diagnosis of Inflammatory Skin Diseases. 3rd ed. New York: Ardor Scribendi, 2005.

POLYMORPHOUS LIGHT ERUPTION

Synonyms: Polymorphic light eruption; summer prurigo, summer eruption; prurigo aestivalis.

Clinical Presentation (Fig. 7A):
- Scattered edematous papules and plaques
- Sites exposed to sunlight, mostly the face, chest, and arms
- Young women especially
- Variations include actinic prurigo (occurs in Indians of North and South America) and spring eruption of juveniles (vesicles on helices of boys)

Histopathology (Figs. 7B and C):
- Sparse to moderately dense infiltrate of lymphocytes
- Extravasated erythrocytes often
- Marked edema of the papillary dermis
- Spongiosis of variable extent sometimes

Clinicopathologic Correlation:

Clinical Feature	Pathologic Feature
Papules	Perivascular infiltrates of lymphocytes and edema in the papillary dermis
Scale-crust	Parakeratosis above spongiosis

Differential Diagnosis:

Tumid Lupus Erythematosus	Hydroa Vacciniforme
Superficial and deep infiltrate of lymphocytes	Superficial and deep infiltrate of lymphocytes
Abundant mucin in the reticular dermis	No mucin
No edema in the papillary dermis or changes in the epidermis	Edema of the papillary dermis, ballooning and reticular alteration of the epidermis

Pathophysiology:
- Ultraviolet light is the causative agent but the mechanism is not known precisely.

References:
1. Boonstra HE, van Weelden H, Toonstra J, van Vloten WA. Polymorphous light eruption: a clinical, photobiologic, and follow-up study of 110 patients. J Am Acad Dermatol 2000; 42(2 Pt 1):199–207.
2. Mikhail M, Ackerman AB. Actinic prurigo; Hutchinson's summer prurigo, prurigo solare, and hereditary polymorphic light eruption of the American Indians. Dermatopathol Pract 10(3):3, available at www.derm101.com.
3. Stratigos AJ, Antoniou C, Papadakis P, et al. Juvenile spring eruption: clinicopathologic features and phototesting results in 4 cases. J Am Acad Dermatol 2004; 50:S57–S60.

TUMID LUPUS ERYTHEMATOSUS

Synonyms: Lymphocytic infiltration of Jessner and Kanof most likely is tumidus lupus erythematosus.

Clinical Presentation (Fig. 8A):
- Smooth surfaced red macules, papules, and plaques
- Often localized on sun-exposed sites such as the face, chest, and arms

Histopathology (Figs. 8B and C):
- Perivascular and periadnexal infiltrate of lymphocytes, superficial and deep
- Mucin in abundance in the reticular dermis

Clinicopathologic Correlation:

Clinical Feature	Pathologic Feature
Papules and plaques	Superficial and deep infiltrate of lymphocytes and deposits of mucin
Erythema	Dilation of vessels in the dermis
Smooth surface	No changes in the epidermis

Differential Diagnosis:

Polymorphous Light Eruption	Erythema Figuratum/ Deep Gyrate Erythema	Chronic Lymphocytic Leukemia
Infiltrate of normal lymphocytes	Infiltrate of normal lymphocytes, no involvement of the interstitium	Infiltrate of lymphocytes that may have abnormal nuclei
Edema of the papillary dermis	No edema of the papillary dermis	No edema of the papillary dermis
Spongiosis	No changes in the epidermis	No changes in the epidermis

Pathophysiology:
- Lupus erythematosus is considered to be an autoimmune disease but the mechanism precisely is not known; genetic factors, estrogens, and deficiency of complement also seem to play a role in the pathogenesis.
- ANA and anti-ds DNA antibodies are variably present in the serum of patients with tumid lupus erythematosus, and direct immunofluorescence is usually negative.

References:

1. Kuhn A, Sonntag M, Ruzicka T, et al. Histopathologic findings in lupus erythematosus tumidus: review of 80 patients. J Am Acad Dermatol 2003; 48:901–908.
2. Lee SS, Ackerman AB. Lupus dermatitis is an expression of systemic lupus erythematosus. Dermatopathol: Prac & Conc 1997; 3:346–347.

PERNIO

Synonyms: Dermatitis congelationis; chilblains; perniosis; erythema pernio.

Clinical Presentation (Fig. 9A):
- Papules, papulovesicles, nodules, and ulcerations
- Fingers, toes, nose, and ears
- Young persons usually

Histopathology (Figs. 9B and C):
- Superficial and deep perivascular infiltrate of lymphocytes
- Extravasated erythrocytes
- Edema of the papillary dermis
- Lymphocytes at the dermoepidermal junction often
- Thrombi in the lumen and/or fibrin in the wall of vessels sometimes
- Mucin in the reticular dermis

Clinicopathologic Correlation:

Clinical Feature	Pathologic Feature
Edematous papules and nodules	Perivascular infiltrate of lymphocytes, deposits of mucin in the reticular dermis, and edema of the papillary dermis
Papulovesicles	Extensive subepidermal edema

Differential Diagnosis:

Erythema Multiforme	Hydroa Vacciniforme	Polymorphous Light Eruption
Lichenoid infiltrate of lymphocytes	Superficial and deep perivascular infiltrate of lymphocytes	Superficial and deep perivascular infiltrate of lymphocytes
No deposits of mucin in the dermis	No deposits of mucin in the dermis	No deposits of mucin in the dermis
Numerous individual necrotic keratinocytes	Ballooning and reticular alteration	Spongiosis

Pathophysiology:
- Caused by continued exposure to cold, the exact mechanism being opaque
- Sometimes presenting as a variant of lupus erythematosus (i.e., Chilblain lupus)

Reference:

1. Ackerman AB, Böer A, Bennin B, Gottlieb GJ. Histologic Diagnosis of Inflammatory Skin Diseases. 3rd ed. New York: Ardor Scribendi, 2005.

ERYTHEMA FIGURATUM

Synonyms: Deep gyrate erythema; "deep type" of erythema annulare centrifugum of Darier; palpable migratory and arciform erythema; erythema figuratum perstans; figurate erythema.

Clinical Presentation (Fig. 10A):
- Annular, arcuate, polycyclic, and serpentine papules and plaques devoid of scale
- Localized or widespread, trunk and proximal extremities especially
- Adults

Histopathology (Figs. 10B and C):
- Superficial and deep perivascular infiltrate of lymphocytes, the interstitium of the reticular dermis usually being spared
- No increase in mucin in the reticular dermis
- No edema of the papillary dermis
- No changes in the epidermis

Clinicopathologic Correlation:

Clinical Feature	Pathologic Feature
Red papules and plaques	Moderately dense infiltrates of lymphocytes around dilated venules

Differential Diagnosis:

Erythema Migrans	Chronic Lymphocytic Leukemia	Tumid Lupus Erythematosus
Perivascular and sometimes interstitial infiltrate	Dense perivascular infiltrate	Perivascular and interstitial infiltrate
Normal lymphocytes and plasma cells	Lymphocytes may have abnormal nuclei	Normal lymphocytes monopolize
No increase in mucin	No increase in mucin	Abundant mucin in the reticular dermis

Pathophysiology:
- Unknown, but figurate erythema may represent a pattern encountered in a variety of conditions rather than being a distinctive disease.

References:

1. Ackerman AB, Böer A, Bennin B, Gottlieb GJ. Histologic Diagnosis of Inflammatory Skin Diseases. 3rd ed. New York: Ardor Scribendi, 2005.
2. Clark WH, Mihm MC, Reed RJ, Ainsworth AM. The lymphocytic infiltrates of the skin. The lymphocytic infiltrates of the skin. Hum Pathol 1974; 5:25.
3. White JW Jr. Gyrate erythema. Dermatol Clin 1985; 3(1): 129–139.

POSTINFLAMMATORY PIGMENTARY ALTERATION

Synonyms: Postinflammatory pigmentary change.

Clinical Presentation (Fig. 11A):
- Pigmented macules and patches
- Sites of a previous dermatitis
- More prominent in dark-skinned individuals
- Fading gradually over months or years

Histopathology (Figs. 11B and C):
- Little or no infiltrate of lymphocytes around venules of the superficial plexus and along the dermoepidermal junction
- Hints of vacuolar alteration sometimes
- Melanophages in the papillary dermis and in the upper part of the reticular dermis range from few to many
- Papillary dermis thickened sometimes by subtle fibroplasia

Clinicopathologic Correlation:

Clinical Feature	Pathologic Feature
Pigmented macules	Melanophages

Differential Diagnosis:
- Hyperpigmentation in mycosis fungoides (parakeratosis variegata) is accompanied by features typical of mycosis fungoides, that is, lymphocytes are accompanied by scant spongiosis in the epidermis.

Pathophysiology:
- Lymphocytes of an inflammatory process, nearly always of an interface type destroy keratinocytes of the basal layer; melanin comes to be situated in the dermis, where it is ingested by macrophages.

References:

1. Pandya AG, Guevara IL. Disorders of hyperpigmentation. Dermatol Clin 2000; 18(1):91–98, ix.
2. Ruiz-Maldonado R, Orozco-Covarrubias ML. Postinflammatory hypopigmentation and hyperpigmentation. Semin Cutan Med Surg 1997; 16:36–43.

VITILIGO

Synonyms: Achroma vitiligo.

Clinical Presentation (Fig. 12A):
- Depigmented macules and patches
- Localized, segmental, or widespread; often symmetric
- Association, episodically, with alopecia areata, Hashimoto's thyroiditis, diabetes mellitus, Addison's disease, lupus erythematosus, myasthenia gravis, primary biliary cirrhosis, or Vogt-Koyanagi-Harada's syndrome

Histopathology (Figs. 12B and C):
- Sparse superficial perivascular infiltrate of lymphocytes
- Few lymphocytes sprinkled in the lower half of the epidermis sometimes
- Melanocytes at the dermoepidermal junction decreased markedly in number or absent entirely
- Melanin in the epidermis decreased in amount

Clinicopathologic Correlation:

Clinical Feature	Pathologic Feature
Hypopigmented macules	Absence of melanocytes

Differential Diagnosis:

Pityriasis Alba	Hypopigmented Scar
Perivascular dermatitis, lymphocytes monopolize	No or sparse infiltrate, collagen bundles arranged horizontally
Melanocytes present in the epidermis	Melanocytes present in the epidermis

Pathophysiology:
- The disorder is thought to be an autoimmune disease.
- Antimelanocyte antibodies are present in the serum of patients.

References:

1. Gauthier Y, Cario Andre M, Taieb A. A critical appraisal of vitiligo etiologic theories. Is melanocyte loss a melanocytorrhagy? Pigment Cell Res 2003; 16(4):322–332.
2. Gokhale BB, Mehta LN. Histopathology of vitiliginous skin. Int J Dermatol 1983; 22:477–480.
3. Hann SK, Park YK, Lee KG, Choi EH, Im S. Epidermal changes in active vitiligo. J Dermatol 1992; 19:217–222.

TINEA VERSICOLOR

Synonyms: Pityriasis versicolor; dermatomycosis furfuracea.

Clinical Presentation (Fig. 13A):
- Slightly scaly macules and patches
- Hypopigmented in dark-skinned and hyperpigmented in light-skinned persons
- Symmetrical on the trunk, sometimes involving proximal extremities
- Recurrences are the rule

Histopathology (Figs. 13B and C):
- Sparse superficial perivascular infiltrate of lymphocytes
- Short branching septate hyphae and spores in the cornified layer
- Slight hyperkeratosis in basket-weave fashion
- Slight spongiosis and parakeratosis rarely

Clinicopathologic Correlation:

Clinical Feature	Pathologic Feature
Hypopigmented macules	*Malassezia furfur* in the cornified layer produces a sun-protection factor
Hyperpigmented macules	Colored hyphae of *Malassezia furfur* in the cornified layer (visualizable in H + E)
Scale	Orthokeratosis

Differential Diagnosis:
- None

Pathophysiology:
- The cause is *Malassezia furfur* (*Pityrosporum orbiculare*).

References:

1. Aljabre SH, Alzayir AA, Abdulghani M, Osman OO. Pigmentary changes of tinea versicolor in dark-skinned patients. Int J Dermatol 2001; 40(4):273–275.
2. Janaki C, Sentamilselvi G, Janaki VR, Boopalraj JM. Unusual observations in the histology of pityriasis versicolor. Mycopathologia 1997; 139:71–74.

ERYTHRASMA

Synonyms: None

Clinical Presentation (Fig. 14A):
- Solitary patches and subtle red plaques covered by fine scales
- Coral-red fluorescence when exposed to Wood's light
- Intertriginous regions
- Elderly persons of both sexes, especially those with diabetes mellitus
- Recurrences are common

Histopathology (Figs. 14B and C):
- Sparse superficial perivascular infiltrate of lymphocytes
- Slight orthokeratosis
- Blue-staining organisms in the form of delicate rods and filaments in the cornified layer
- Gram stain shows delicate gram-positive rods and filaments in the cornified layer

Clinicopathologic Correlation:

Clinical Feature	Pathologic Feature
Red macules, patches, and subtle plaques	Sparse superficial perivascular infiltrate of lymphocyte
Scale	Orthokeratosis which houses corynebacteria

Differential Diagnosis:

Candidiasis	Tinea Corporis
Pseudohyphae in the cornified layer oriented both vertically and horizontally on all levels of the cornified layer	Hyphae in the lowermost part of the cornified layer, oriented horizontally
Intraepidermal and infundibular pustules often	Intraepidermal and infundibular pustules often
Mixed infiltrate containing neutrophils	Mixed infiltrate containing neutrophils

Pathophysiology:
- Erythrasma is caused by *Corynebacterium minutissimum*, a porphyrin-producing diphtheroid bacillus.

References:

1. Montes LF, Black SH, McBride ME. Bacterial invasion of the stratum corneum in erythrasma. I. Ultrastructural evidence for a keratolytic action exerted by Corynebacterium minutissimum. J Invest Dermatol 1967; 49:474–485.
2. Sindhuphak W, MacDonald E, Smith EB. Erythrasma. Overlooked or misdiagnosed? Int J Dermatol 1985; 24:95–96.

Acknowledgments:
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Photomicrographs 2B and 2C, 6B and 6C are reproduced with permission from Ackerman AB. Interactive Quizzes: CPC. New York: Ardor Scribendi, 2005; available at www.derm101.com.

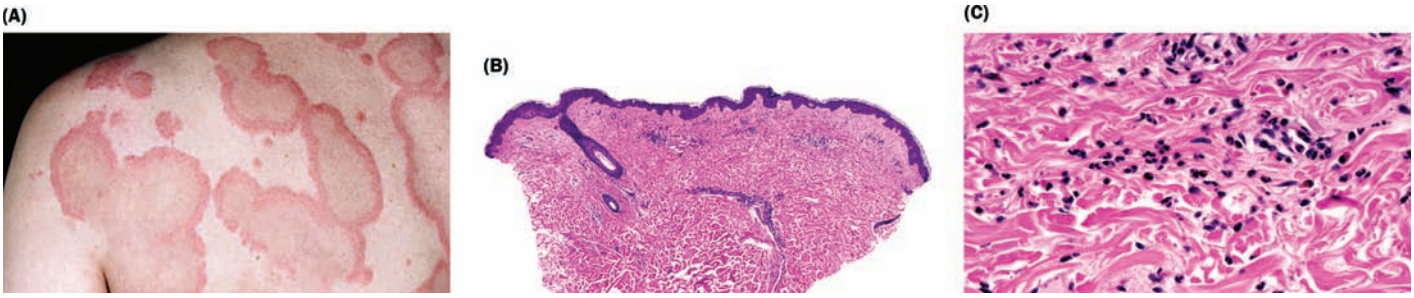

Figure 1 (**A**) Urticae on the trunk. (**B**) Perivascular and interstitial dermatitis without epidermal changes. (**C**) Lymphocytes and eosinophils perivascular and numerous neutrophils interstitial.

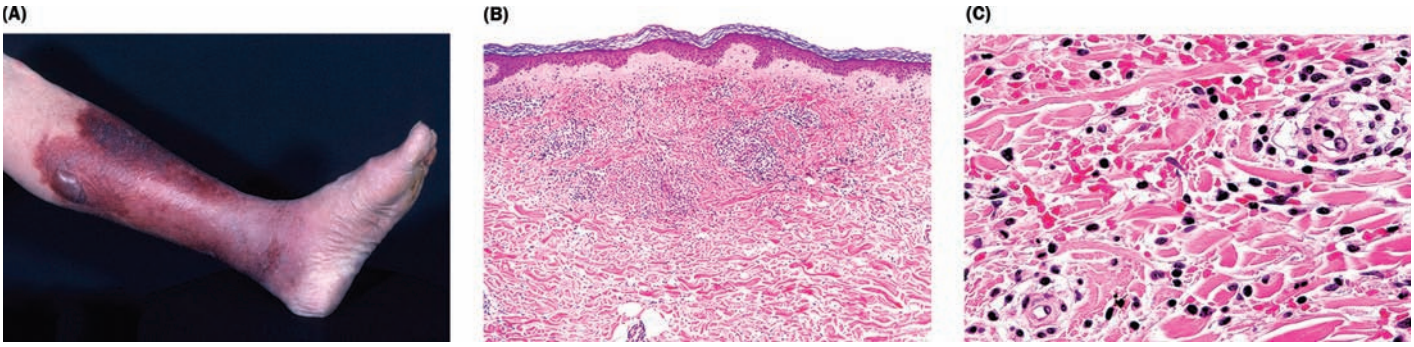

Figure 2 (**A**) Sharply demarcated purpuric erythema on the leg, a bulla is seen in the uppermost part of the lesion. (**B**) Perivascular and interstitial dermatitis without epidermal changes. (**C**) Lymphocytes and neutrophils perivascular and interstitial accompanied by numerous extravasated erythrocytes.

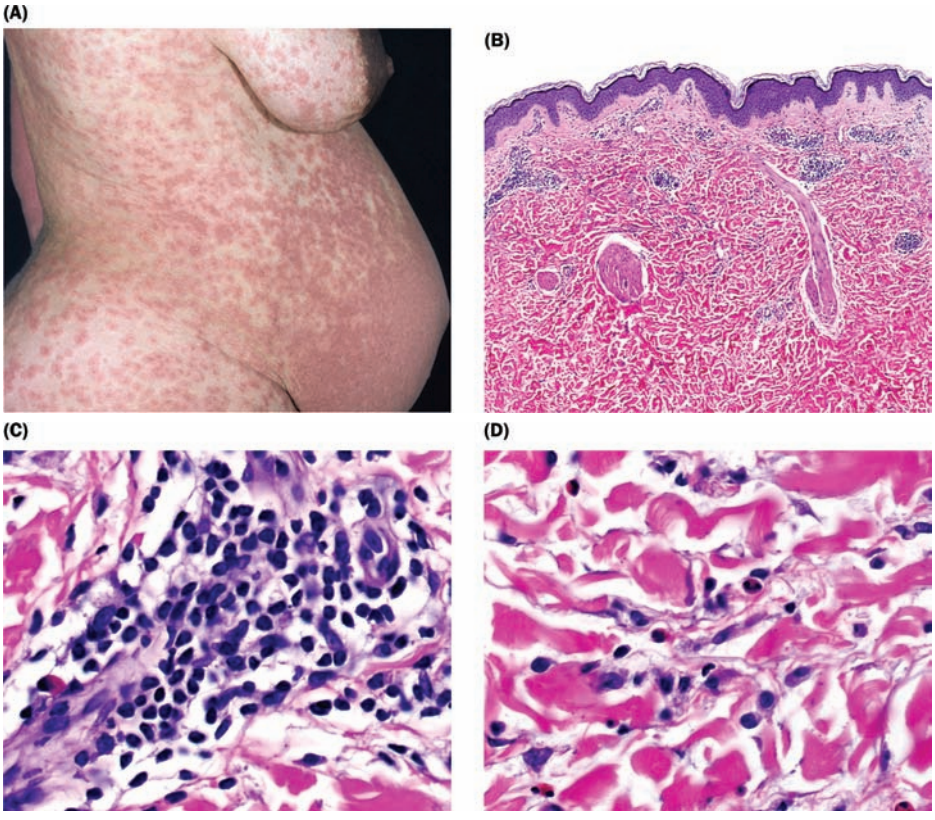

Figure 3 (**A**) Urticarial papules and plaques in a pregnant woman. (**B**) Perivascular and interstitial dermatitis without epidermal changes. (**C**) Lymphocytes and few eosinophils around vessels. (**D**) Eosinophils scattered interstitially. (*Continued*)

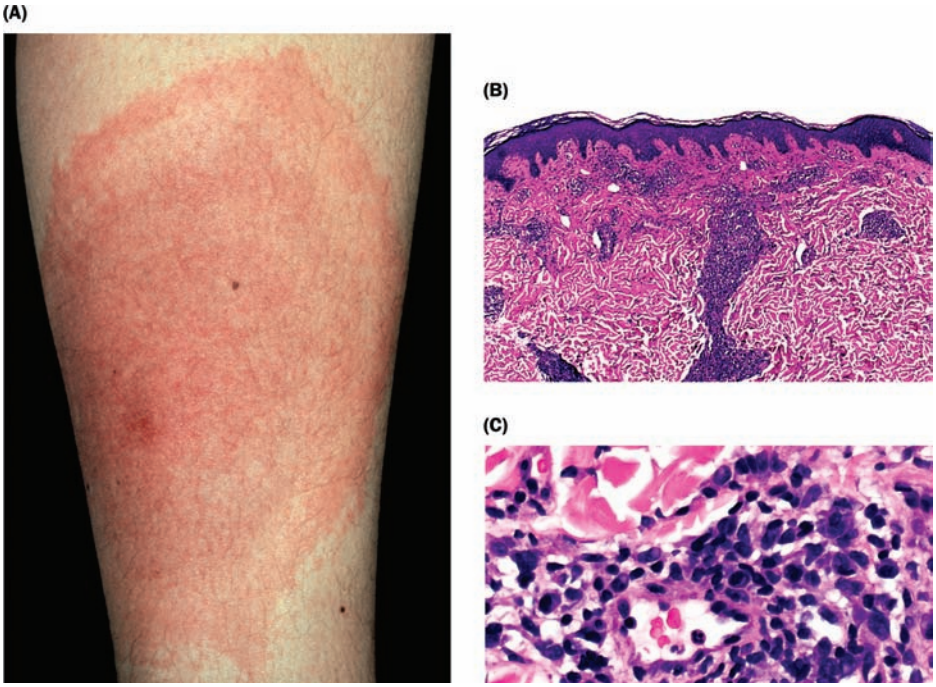

Figure 4 (**A**) Erythematous patch on the thigh with a bright red slightly elevated border and a paler red in the center. (**B**) Perivascular dermatitis without epidermal changes. (**C**) Infiltrate consisting of lymphocytes and plasma cells.

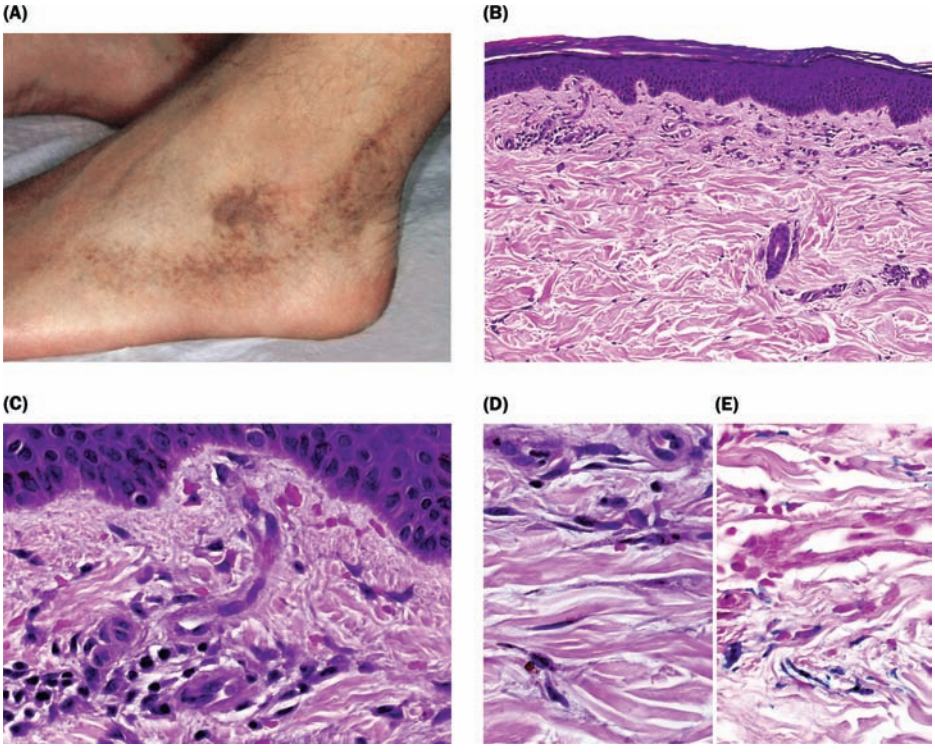

Figure 5 (**A**) Pigmented macules on the ankles. (**B**) Superficial perivascular dermatitis. (**C**) Infiltrate of lymphocytes and extravasated erythrocytes. (**D**,**E**) Hemosiderophages in the dermis are staining blue in an iron stain.

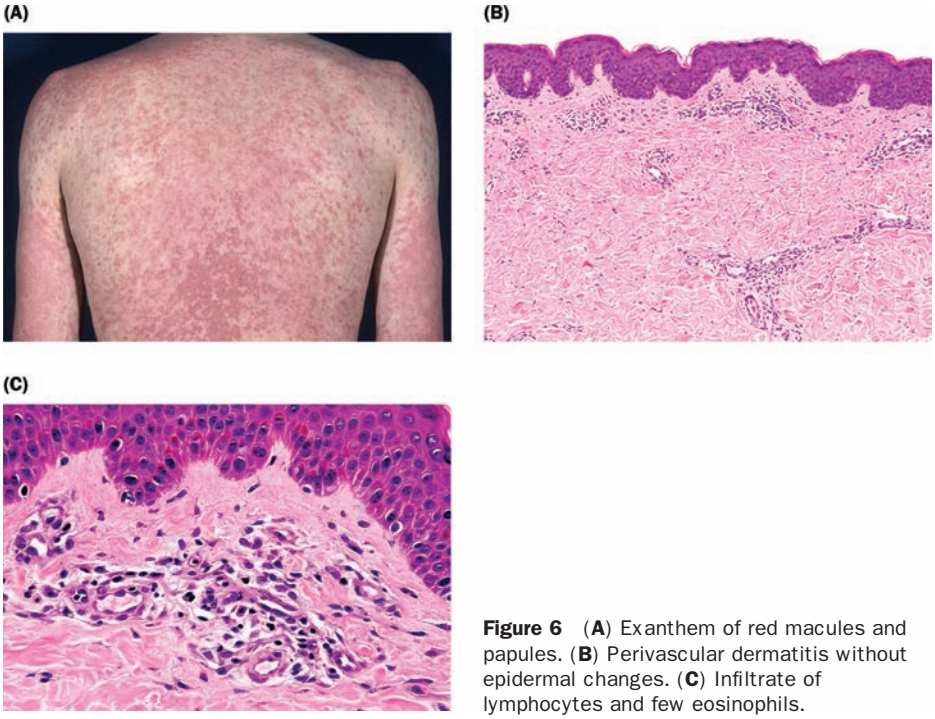

Figure 6 (**A**) Exanthem of red macules and papules. (**B**) Perivascular dermatitis without epidermal changes. (**C**) Infiltrate of lymphocytes and few eosinophils.

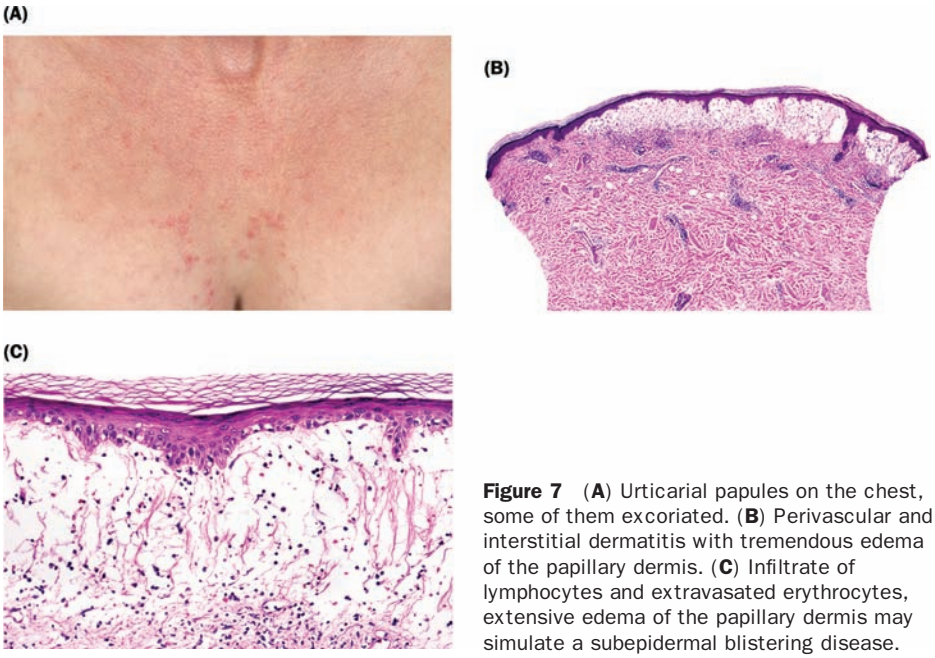

Figure 7 (**A**) Urticarial papules on the chest, some of them excoriated. (**B**) Perivascular and interstitial dermatitis with tremendous edema of the papillary dermis. (**C**) Infiltrate of lymphocytes and extravasated erythrocytes, extensive edema of the papillary dermis may simulate a subepidermal blistering disease.

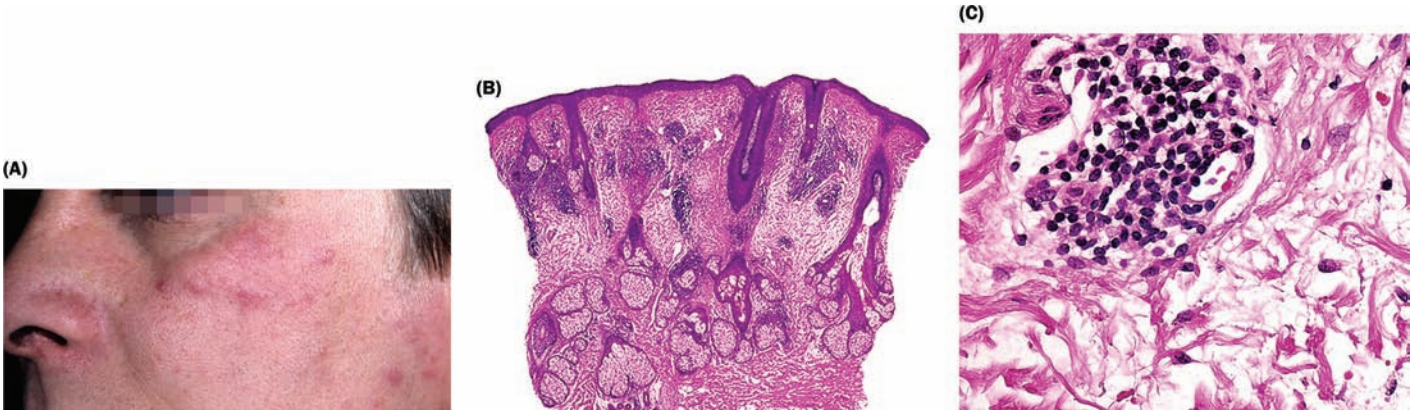

Figure 8 (**A**) Smooth surfaced erythematous papules and plaques on the face. (**B**) Superficial and deep perivascular and periadnexal dermatitis. (**C**) Infiltrates of lymphocytes are accompanied by mucin in abundance in the interstitium.

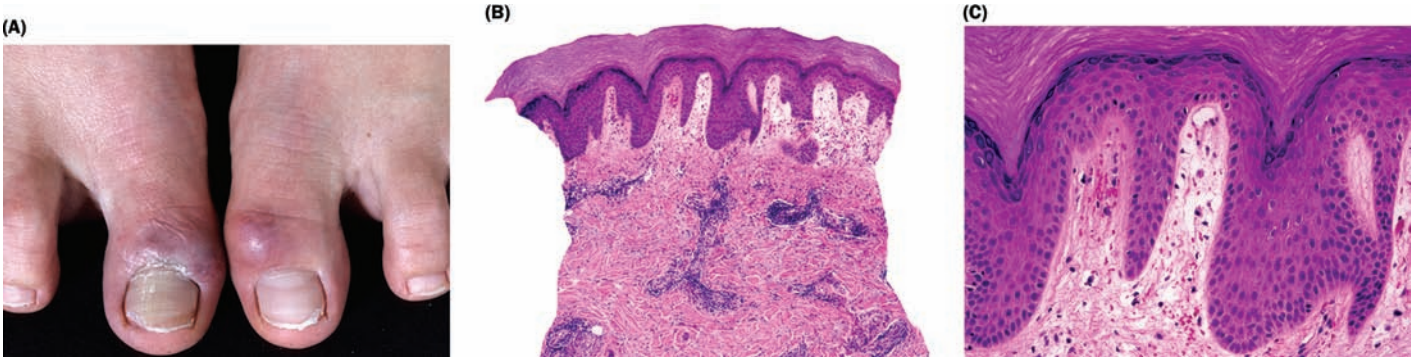

Figure 9 (**A**) Livid papules and nodules on the toes. (**B**) Superficial and deep perivascular infiltrate of lymphocytes. (**C**) Epidermis covered by compact orthokeratosis indicates an acral site of the lesion. Extravasated erythrocytes are housed in an edematous papillary dermis.

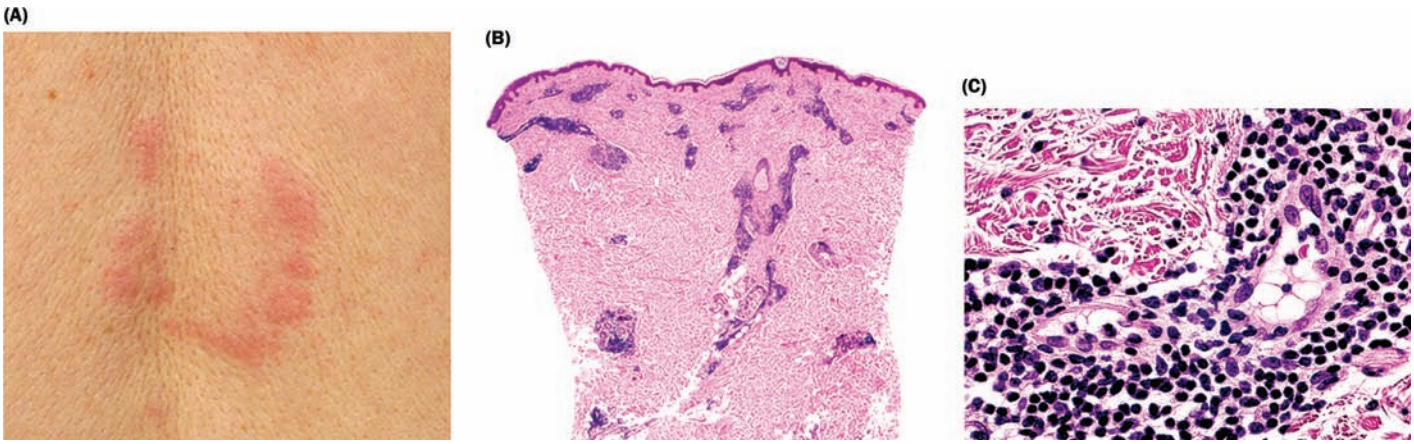

Figure 10 (**A**) Figurate erythematous macules and slightly elevated plaques on the back. (**B**) Strictly perivascular infiltrate. (**C**) Monomorphic lymphocytes monopolize, mucin is not increased in the interstitium.

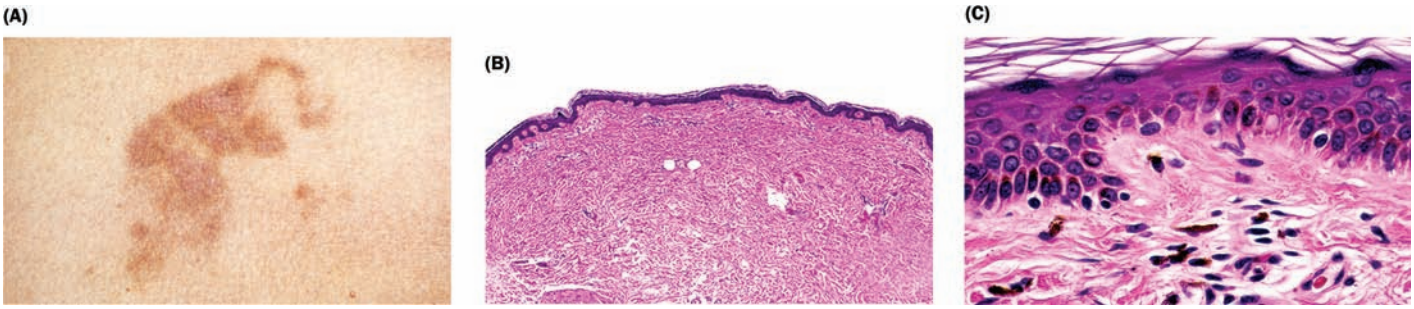

Figure 11 (**A**) This bizarre shaped pigmented macule developed consequent to a phototoxic dermatitis. (**B**) Very subtle infiltrate of lymphocytes in the dermis. (**C**) Numerous melanophages in the papillary dermis.

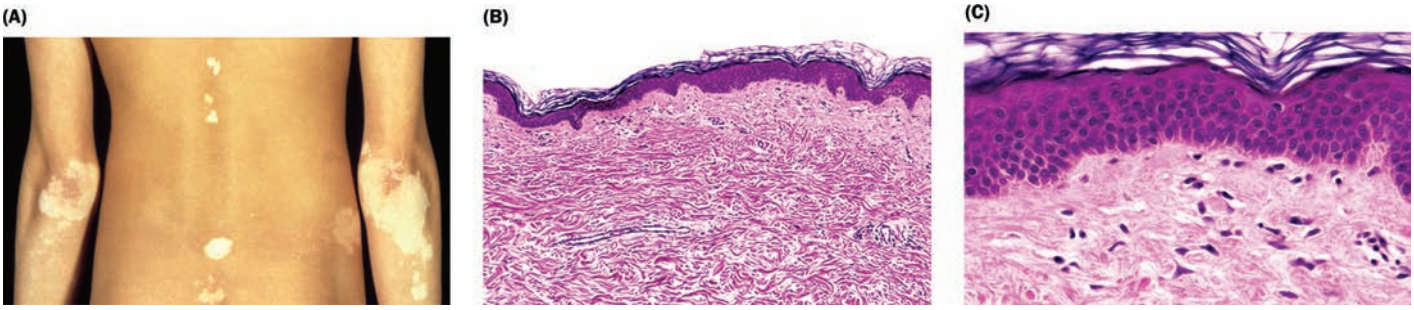

Figure 12 (**A**) Depigmented macules distributed rather symmetrically on trunk and extremities. (**B**) Very subtle infiltrate of lymphocytes in the dermis. (**C**) Melanocytes are lacking from the epidermis.

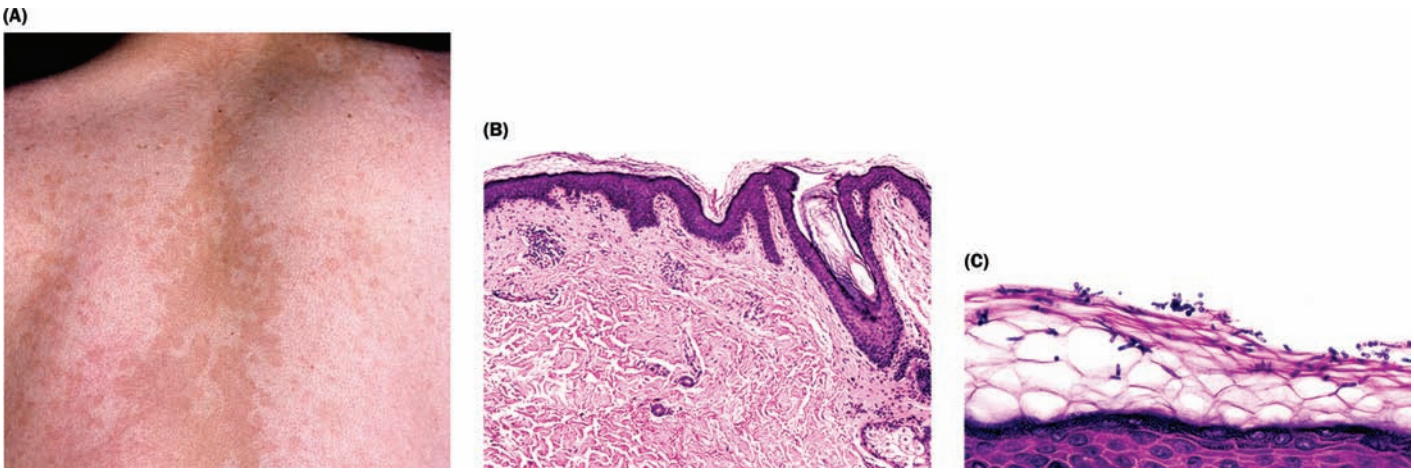

Figure 13 (**A**) Pigmented macules distributed rather symmetrically on trunk. (**B**) Sparse perivascular and interstitial dermatitis consisting of lymphocytes. (**C**) Numerous hyphae and spores in an orthokeratotic cornified layer stain blue in H+E.

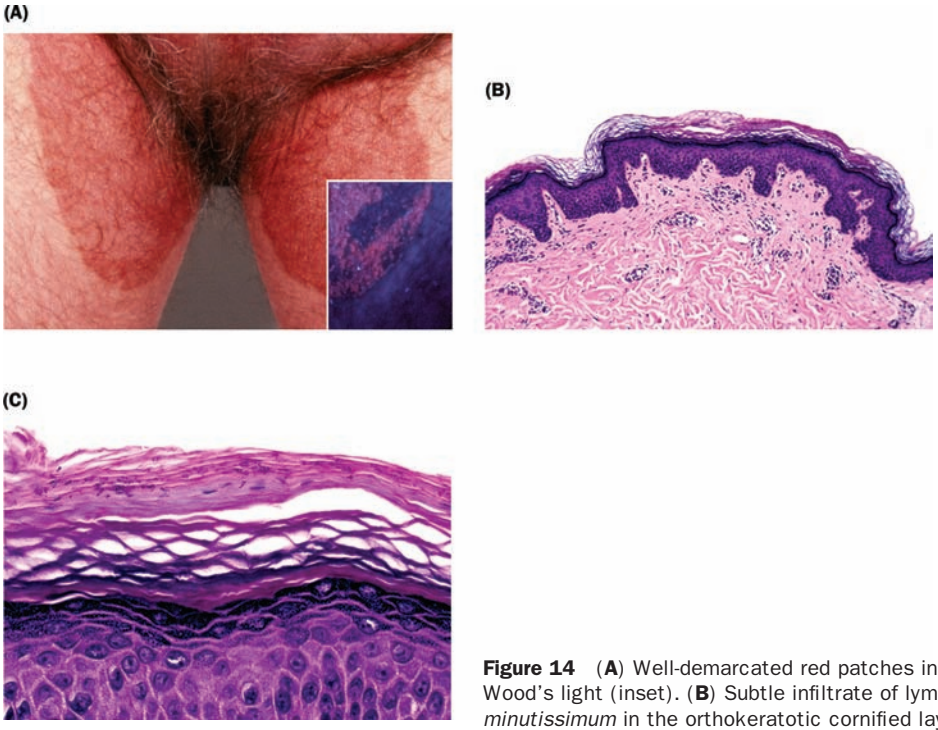

Figure 14 (**A**) Well-demarcated red patches in the groins show coral red fluorescence in Wood's light (inset). (**B**) Subtle infiltrate of lymphocytes in the dermis. (**C**) *Corynebacterium minutissimum* in the orthokeratotic cornified layer stains blue in H+E.

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Interface Dermatitis

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CONTENTS

The phrase "interface dermatitis" refers to those dermatoses in which an inflammatory process occurs along the dermoepidermal junction with injury, and even necrosis, of the basal keratinocytes. Interface dermatitides can be characterized further as being either vacuolar or lichenoid in nature.

VACUOLAR INTERFACE DERMATITIS

Key Features:
- Relatively sparse inflammatory cell infiltrate that obscures the dermoepidermal junction
- Vacuolar alteration of basal keratinocytes ± necrotic keratinocytes
- Infiltrate may be only in the superficial dermis, or in both the superficial and deep dermis

VACUOLAR INTERFACE DERMATITIS—SUPERFICIAL

ERYTHEMA MULTIFORME

Clinical Presentation:

Erythema Multiforme Minor:

Synonym: von Hebra's disease.
- Acute, self-limited, recurrent disease of the skin and mucous membranes, most commonly in response to infection with herpes simplex virus types I and II
- Pleomorphic eruption with erythematous and violaceous macules, papules, urticarial plaques, vesicles and bullae, and targetoid or iris lesions, in which an erythematous patch or urticarial plaque surrounds a central bulla or dusky macule
- Lesions distributed symmetrically with a predilection for the distal extremities

Erythema Multiforme Major:

Synonyms: Stevens-Johnson syndrome; toxic epidermal necrolysis (TEN) spectrum; Lyell's syndrome (eponym for TEN).
- Acute, severe, sometimes fatal systemic disease, with involvement of skin and several mucous membranes, associated with fever; most commonly drug-induced
- Generalized, tender erythema, which quickly progresses to bulla formation with extensive separation of the epidermis in sheets
- Erosive mucosal lesions

Histology:
- Similar for erythema multiforme minor and major
- Vacuolar alteration of the basal keratinocytes, which may progress to frank subepidermal vesiculation (Figs. 1A–C)
- Necrotic keratinocytes that may be individual or confluent; in TEN, there is confluent, full-thickness epidermal necrosis (Fig. 1D)
- Sparse perivascular lymphohistiocytic infiltrate in superficial to mid dermis obscures dermoepidermal junction
- Basket-weave stratum corneum (Figs. 1C and D)

Immunofluorescence:

Direct Immunofluorescence:
- Homogeneous staining for IgM (and sometimes granular staining for C3) of intraepidermal cytoid bodies (fluorescent keratinocytes)
- Granular staining for C3 and fibrinogen along the dermoepidermal junction

Clinicopathologic Correlation:

Clinical Feature	Histopathologic Correlate
Dusky center of target lesion	Necrotic keratinocytes
Vesiculo-bullous lesion	Confluent vacuolar alteration of basal keratinocytes resulting in subepidermal cleft

Differential Diagnosis:

Erythema Multiforme/ Toxic Epidermal Necrolysis	Drug Eruption	Staphylococcal Scalded Skin Syndrome
Subepidermal vesiculation	Vesiculation, when present, is subepidermal	Subcorneal vesiculation
Frozen section of blister roof shows full-thickness epidermal necrosis	—	Frozen section of blister roof shows subcorneal epidermal split
Sparse lymphohistiocytic Infiltrate	Sparse to moderate inflammatory cell infiltrate with eosinophils	—

Pathophysiology:

- Erythema multiforme minor and major are thought to represent a cell-mediated immune response to complexes formed between exogenous antigens (e.g., viral antigens or from reactive metabolites of drugs) and host tissues.
- It is thought that these host cell–antigen complexes lead to
  - release of soluble cytokines by cytotoxic T-lymphocytes (e.g., tumor necrosis factor-α and others), which cause keratinocyte necrosis, and
  - increased expression of keratinocyte Fas ligand (FasL), thereby activating the keratinocyte Fas–FasL pathway and culminating in massive keratinocyte apoptosis

References:

1. Fritsch PO, Sidoroff A. Drug-induced Stevens-Johnson syndrome/toxic epidermal necrolysis. Am J Clin Dermatol 2000; 1(6):349–360.
2. Finan MC, Schroeter AL. Cutaneous immunofluorescence study of erythema multiforme: correlation with light microscopic patterns and etiologic agents. J Am Acad Dermatol 1984; 10(3):497–506.
3. Paul C, Wolkenstein P, Adle H, et al. Apoptosis as a mechanism of keratinocyte death in toxic epidermal necrolysis. Br J Dermatol 1996; 134(4):710–714.

ACUTE GRAFT-VS.-HOST REACTION

Clinical Presentation:

- Systemic syndrome with fever and cutaneous, gastrointestinal, and hepatic manifestations
- Typically develops 7 to 21 days postprocedure as complication of allogeneic hematopoeitic stem-cell transplantation or, rarely, as a congenital disease as a result of maternal lymphocytes establishing themselves in fetal circulation and reacting against the host
- Sudden onset of blanching, erythematous morbilliform eruption that begins acrally, with predilection for the palms, soles, cheeks, and ears
- May eventually become generalized with bulla formation, desquamation and mucous membrane involvement

Histology:

- Sparse lymphocytic infiltrate obscures dermoepidermal junction (Fig. 2A)
- Exocytosis of mononuclear cells into epidermis associated with focal spongiosis (Figs. 2A and B). Classically divided into four histopathologic grades
  - *Lerner Grade I*: Vacuolar alteration of basal keratinocytes
  - *Lerner Grade II*: "Satellite cell necrosis"; individually necrotic keratinocytes within the epidermis with adjacent lymphocytes (Figs. 2A and B)
  - *Lerner Grade III*: Subepidermal cleft formation
  - *Lerner Grade IV*: Complete, full-thickness loss of epidermis

Immunofluorescence:

***Direct Immunofluorescence*:**

- Granular staining for IgM along the dermoepidermal junction

Clinicopathologic Correlation:

Clinical Feature	Histopathologic Correlate
Epidermal desquamation	Confluent vacuolar alteration of basal keratinocytes resulting in subepidermal cleft

Differential Diagnosis:

Acute Graft-vs.-Host Reaction	Erythema Multiforme/Toxic Epidermal
Dyskeratosis of follicular keratinocytes	Follicular involvement less likely

Pathophysiology:

- Donor-derived CD8+ T lymphocytes recognize host cell antigens as foreign
- These T cells react directly to "foreign" antigens bound to major histocompatibility complex (MHC) molecules and, through mediation by a variety of cytokines, including interleukin-2 and interferon-gamma, effect target/host organ necrosis

References:

1. Lerner KG, Kao GF, Storb R, et al. Histopathology of graft-versus-host reaction (GvHR) in human recipients of marrow from HLA-matched sibling donors. Transplant Proc 1974; 6:367.
2. Tsoi MS, Storb R, Jones E, et al. Deposition of IgM and C at the dermoepidermal junction in acute and chronic cutaneous graft-versus-host disease in man. J Immunol 1978; 120:1485.

SYSTEMIC LUPUS ERYTHEMATOSUS

Clinical Presentation:

- Chronic, systemic autoimmune disease with cutaneous, renal, joint involvement, and serositis.
- Patients may also develop neurologic manifestations secondary to circulating anticardiolipin ("lupus anticoagulant") antibodies, which can precipitate thromboembolic events.
- Typical cutaneous manifestations include: "butterfly" malar erythema; photosensitivity; erythematous, scaly plaques between joints on dorsal fingers and on sun-exposed skin; periungual telangiectases and Raynaud's phenomenon.
- Less commonly, lesions may include purpura, bullae, ulcers, discoid lesions, scarring alopecia, and chilblains (perniosis).

Histology:

- Vacuolar alteration of basal keratinocytes (Fig. 3A)
- Perivascular lymphocytic infiltrate with obscuration of the dermoepidermal junction (Fig. 3B)
- Altered basement membrane
- +/− dermal mucin deposition
- Leukocytoclastic vasculitis may be present

Immunofluorescence:

Direct Immunofluorescence:

- Band-like staining pattern for IgG or IgM at dermoepidermal junction of lesional and nonlesional, sun-exposed skin (the so-called "lupus band")

Differential Diagnosis:

Systemic Lupus Erythematosus	Dermatomyositis	Polymorphous Light Eruption
Mucin usually present	Mucin usually abundant	Mucin usually absent

Pathophysiology:

- Deregulated T lymphocytes activate B cells to produce pathogenic autoantibodies and cause immune complex deposition, which result in tissue damage and vascular injury
- The etiology of this immune deregulation is unknown, but ultraviolet light (UVA and UVB), as well as genetic predisposition are thought to have some role in the pathogenesis of systemic lupus erythematosus.
- Some drugs (e.g., procainamide, hydralazine, isoniazid, minocycline, and hydrochlorothiazide) may precipitate a lupus-like syndrome that slowly resolves with discontinuation of the drug.

References:

1. Clark WH, Reed RJ, Mihm MC. Lupus erythematosus. Histopathology of cutaneous lesions. Hum Pathol 1973; 4:157–163.
2. Al-Suwaid AR, Venkataram MN, Bhushnurmath SR. Cutaneous lupus erythematosus: comparison of direct immunofluorescence findings with histopathology. Int J Dermatol 1995; 34:480–482.

DERMATOMYOSITIS

Clinical Presentation:

- Systemic autoimmune disease characterized by dermatitis +/− a nonsuppurative polymyositis. May occur in childhood or adulthood
- Adult dermatomyositis is associated with an increased incidence of malignancy
- Typical cutaneous findings include: violaceous, edematous patches on periorbital skin ("heliotrope" rash), erythematous, slightly scaly or poikilodermatous patches on shoulders ("shawl" sign), violaceous papules on bony prominences (Gottron's papules), periungual telangiectases, and photosensitivity

Histology:

- Epidermal atrophy
- Vacuolar alteration of basal keratinocytes (Fig. 3C)
- Perivascular lymphocytic infiltrate with obscuration of the dermoepidermal junction (Fig. 3C)
- Abundant mucin in the interstitial dermis (Fig. 3D)

Differential Diagnosis:

Dermatomyositis	Systemic Lupus Erythematosus
Negative lupus band test	Positive lupus band test

Pathophysiology:

- Deregulated T lymphocytes activate B cells to produce pathogenic autoantibodies and cause immune complex deposition, which result in cutaneous and muscle damage, and microvascular injury

References:

1. Janis JF, Winklemann RK. Histopathology of the skin in dermatomyositis. Arch Dermatol 1968; 97:640–650.
2. Magro CM, Crowson AN. The immunofluorescent profile of dermatomyositis: a comparative study with lupus erythematosus. J Cutan Pathol 1997; 24(9):543–552.

LICHEN SCLEROSUS AND ATROPHICUS

Clinical Presentation:

- Chronic inflammatory dermatosis, which typically presents as pruritic, ivory-to-white macules coalescing into patches with comedo-like plugs and a wrinkled surface occurring primarily on the anogenital region in middle-aged women.
- Occurs rarely in men and children
- Twenty percent of cases are extragenital
- Genital lesions occasionally are associated with squamous cell carcinoma

Histology:

- Vacuolar alteration of basal keratinocytes
- Edema and/or sclerosis of the superficial dermis (Figs. 4A–C)
- Patchy, lymphocytic infiltrate below the zone of altered collagen (Fig. 4D)
- Thinned epidermis with effacement of the rete ridge pattern (epidermal atrophy)
- Plugged follicular units

Clinicopathologic Correlation:

Clinical Feature	Histopathologic Correlate
Comedo-like plugs	Follicular units plugged with keratin
Wrinkled surface	Thinned epidermis with effacement of rete ridge pattern

Differential Diagnosis:

Lichen Sclerosus and Atrophicus	Morphea/Scleroderma
Vacuolar alteration of basal keratinocytes	No basal vacuolar change
Well-defined lymphocytic infiltrate below zone of altered collagen	Lymphoplasmacytic infiltrate is more dispersed, less well defined
Changes are limited to the superficial-to-mid dermis	Changes may go deep into the subcutis

Pathophysiology:

- The pathogenesis of lichen sclerosus and atrophicus (LS et A) is poorly understood.
- The inflammatory infiltrate is CD8+, CD57+ T lymphocyte-rich, and it has been speculated that the infiltrate and the resulting alterations in the epidermis and dermis are a response to a virus, as yet unidentified.
- There is also speculation that LS et A represents a superficial, localized variant of morphea, and is essentially autoimmune in nature.

References:

1. Barker LP, Gross P. Lichen sclerosus et atrophicus of the female genitalia. Arch Dermatol 1962; 85:362–373.
2. Carlson JA, Grabowski R, Chichester P, et al. Comparative immunophenotypic study of lichen sclerosus. Epidermotropic CD57+ lymphocytes are numerous—implications for pathogenesis. Am J Dermatopathol 2000; 22:7–16.
3. Uitto J, Santa Cruz DJ, Bauer EA, Eisen AZ. Morphea and lichen sclerosus et atrophicus. J Am Acad Dermatol 1980; 3:271–279.

VACUOLAR INTERFACE DERMATITIS—SUPERFICIAL AND DEEP

DISCOID LUPUS ERYTHEMATOSUS

Clinical Presentation:

- Typically presents as sharply demarcated, scaly, erythematous patches with comedo-like plugs on the face, ears, and scalp and associated with a scarring alopecia; less commonly, lesions involve the skin below the neck
- More common in women and blacks
- Five percent progress to, or are associated with, systemic lupus erythematosus

Histology:

- Vacuolar alteration of the basal keratinocytes (Fig. 5B)
- Superficial and deep perivascular and periadnexal infiltrate of lymphocytes (Figs. 5A and C)
- Altered (thickened) basement membrane (Fig. 5D)
- Plugged follicular units
- +/− mucin deposition in the dermis

Immunofluorescence:

Direct Immunofluorescence:

- Fifty percent of cases will show granular deposition of IgG and IgM along the dermoepidermal junction in lesional skin
- Lupus band test is frequently negative (low sensitivity), and may be positive in chronically sun-exposed skin of unaffected individuals (low specificity)

Clinicopathologic Correlation:

Clinical Feature	Histopathologic Correlate
Comedo-like plugs	Follicular units plugged with keratin

Differential Diagnosis:

Discoid Lupus Erythematosus	Lichen Planopilaris
Lymphocytic infiltrate is deeper	Periadnexal lymphocytic infiltrate is more superficial

Pathophysiology:

- Deregulated T lymphocytes activate B cells to produce pathogenic autoantibodies which result in cutaneous damage
- The etiology of this immune deregulation is unknown, but ultraviolet light (UVA and UVB), as well as genetic predisposition are thought to have some role in the pathogenesis of discoid lupus erythematosus

References:

1. Clark WH, Reed RJ, Mihm MC. Lupus erythematosus. Histopathology of cutaneous lesions. Hum Pathol 1973; 4:157–163.
2. Weigand DA. The lupus band test: a reevaluation. J Am Acad Dermatol 1984; 11:230–234.

PITYRIASIS LICHENOIDES AND VARIOLIFORMIS ACUTA

Synonym: Mucha-Habermann disease.

Clinical Presentation:

- Acute eruption on the trunk and extremities typified by recurrent crops of hemorrhagic, erythematous papules or vesiculopustules with central necrosis that heal within several weeks with no scarring or occasionally with varioliform scars.

Histology:

- Vacuolar alteration of the basal keratinocytes (Fig. 6C)
- Superficial and deep lymphocytic infiltrate with obscuration of the dermoepidermal junction (Fig. 6A)
- Neutrophils in the stratum corneum (Fig. 6B)
- Necrotic keratinocytes scattered throughout the epidermis (Fig. 6C)
- Erythrocytes interposed between keratinocytes (Fig. 6C)

Clinicopathologic Correlation:

Clinical Feature	Histopathologic Correlate
Hemorrhagic lesion	Erythrocytes interposed between keratinocytes
Papulonecrotic lesion	Extensive epidermal necrosis

Differential Diagnosis:

Pityriasis Lichenoides and Varioliformis Acuta	Vesicular Insect Bite	Lymphomatoid Papulosis
Eosinophils within dermal infiltrate are rare to absent	Numerous eosinophils within a wedge-shaped dermal infiltrate	Eosinophils may be conspicuous within dermal infiltrate
Atypical lymphocytes, if present, are few in number	—	Large, atypical (CD30+) lymphocytes are conspicuous within dermal infiltrate

Pathophysiology:

- Pityriasis lichenoides and varioliformis acuta is believed to be a benign clonal lymphoproliferative disorder, the etiology of which has not yet been elucidated
- Activated T lymphocytes in the dermis are thought to effect epidermal necrosis through directly cytotoxic immune mechanisms

References:

1. Hood AF, Mark EJ. Histopathologic diagnosis of pityriasis lichenoides et varioliformis acuta and its clinical correlation. Arch Dermatol 1982; 118:478.
2. Dereure O, Levi E, Kadin ME. T-cell clonality in pityriasis lichenoides et varioliformis acuta. A heteroduplex analysis of 20 cases. Arch Dermatol 2000; 136:1483–1486.

FIXED DRUG ERUPTION

Clinical Presentation:

- Typically presents as a circumscribed, round or oval, erythematous-to-dusky patch, which develops within hours of consuming the offending drug
- Recurs at the same site with each subsequent exposure to the offending agent
- Characteristic sites of predilection include the face, lips, buttocks, and genitals
- Upon discontinuation of the offending drug, eruption resolves with hyperpigmentation
- Lesions are usually single but may be multiple or generalized, and a bullous variant exists
- Most commonly implicated drugs: trimethoprim-sulfamethoxazole, phenolphthalein, tetracycline, acetyl salicylic acid, and barbiturates

Histology:

- Vacuolar alteration of basal keratinocytes (Fig. 7A)
- Necrotic keratinocytes along the dermoepidermal junction and at higher levels of the epidermis; sometimes epidermal necrosis becomes confluent (Figs. 7A and B)
- Mixed, superficial and deep perivascular inflammatory cell infiltrate composed of lymphocytes, eosinophils and neutrophils (Fig. 7C)
- Melanophages are frequently present in the upper dermis

Clinicopathologic Correlation:

Clinical Feature	Histopathologic Correlate
Dusky lesion	Extensive necrosis of keratinocytes
Bullous lesion	Confluent vacuolar alteration of basal keratinocytes resulting in subepidermal cleft

Differential Diagnosis:

Fixed Drug Eruption	Erythema Multiforme
Sparse to moderate inflammatory cell infiltrate with eosinophils	Sparse superficial lymphohistiocytic infiltrate; eosinophils usually absent

Pathophysiology:

- The offending drug acts as a hapten which binds to a protein in basal keratinocytes or in melanocytes within the basal layer of the epidermis
- The hapten–host protein complex appears to activate T lymphocytes, thereby inciting a cytotoxic immune reaction that may be antibody-mediated
- The site-specificity and sharp circumscription of the clinical lesions may be due to localized expression on keratinocytes of a cell-adhesion antigen (CD54, ICAM-1) involved in the adherence between keratinocytes and lymphocytes

References:

1. Korkij W, Soltani K. Fixed drug eruption. A brief review. Arch Dermatol 1984; 120:520–524.
2. Smoller BR, Luster AD, Krane JF, et al. Fixed drug eruptions: evidence for a cytokine-mediated process. J Cutan Pathol 1991; 18:13–19.
3. Teraki Y, Moriya N, Shiohara T. Drug-induced expression of intercellular adhesion molecule-1 on lesional keratinocytes in fixed drug eruption. Am J Pathol 1995; 145:550.

LICHENOID INTERFACE DERMATITIS

Key Features:

- Dense, band-like inflammatory cell infiltrate, which obscures the dermoepidermal junction
- Infiltrate may be only in the superficial dermis, or both the superficial and deep dermis

LICHENOID INTERFACE DERMATITIS — SUPERFICIAL

LICHEN PLANUS

Clinical Presentation:

- Chronic dermatosis with skin, hair follicle, and mucous membrane involvement; 10% of cases show involvement of the nail unit, often with pterygium formation
- Presents clinically as pruritic, violaceous, flat-topped, polygonal papules, and plaques
- Sites of predilection include inner aspects of wrists, flexor forearms, anterior thighs and the shins; lichen planopilaris (follicular lichen planus) primarily affects the scalp
- There is a reported association with hepatitis C seropositivity

Histology:
- Compact orthokeratosis (Figs. 8A and B)
- Wedge-shaped hypergranulosis (Fig. 8B)
- Jagged, "saw-tooth" acanthosis of the epidermis (Fig. 8B)
- Band-like, superficial lymphocytic infiltrate which obscures the dermoepidermal junction (Figs. 8A–C)
- Necrotic keratinocytes in the lower one-third of the epidermis (Fig. 8D)
- Civatte bodies: homogeneous, eosinophilic globules (representing apoptotic keratinocytes) in the lower epidermis and in the papillary dermis (Fig. 8D)
  - A.K.A.: colloid bodies: periodic acid Schiff (PAS)-positive, diastase-resistant
- Max-Joseph spaces: small sub-epidermal clefts secondary to damage to basal keratinocytes

Immunofluorescence:

Direct Immunofluorescence:
- Colloid bodies stain positively for complement and immunoglobulins, mainly IgM
- There is an irregular band of staining for fibrin along the basement membrane zone

Pathophysiology:
- Lichen planus is of unknown etiology
- The majority of the inflammatory cell infiltrate consists of activated T lymphocytes, which are likely responsible for a cell-mediated cytotoxic immune reaction against keratinocytes and mucosal epithelial cells

References:

1. Ellis FA. Histopathology of lichen planus based on analysis of one hundred biopsies. J Invest Dermatol 1967; 48:143.
2. Abell E, Presbury DG, Marks R, et al. The diagnostic significance of immunoglobulin and fibrin deposition in lichen planus. Br J Dermatol 1975; 93:17.
3. Buechner SA. T-cell subsets and macrophages in lichen planus. Dermatologica 1984; 169:325.

LICHENOID DRUG ERUPTION

Clinical Presentation:
- Characterized by the development of erythematous-to-violaceous, flat-topped papules, and plaques on the trunk and extremities after ingestion of a drug
- Most commonly implicated drugs are: gold, β-adrenergic antagonists, captopril, penicillamine, and antimalarials
- The eruption clears slowly several weeks after discontinuation of the offending agent.

Histology:
- Focal parakeratosis (Fig. 9B)
- Wedge-shaped hypergranulosis (Fig. 9A)
- Jagged, "saw-tooth" acanthosis of the epidermis (Fig. 9A)
- Band-like, mixed infiltrate including variable numbers of eosinophils obscures the dermoepidermal junction. (Figs. 9B and C)
- Necrotic keratinocytes in all layers of the epidermis (Fig. 9B)
- Melanophages are often present on the papillary dermis

Differential Diagnosis:

Lichen Planus	Lichenoid Drug Eruption
Parakeratosis is not a feature	Parakeratosis is frequently present
Band-like infiltrate is lymphohistiocytic	Band-like infiltrate is mixed and often contains eosinophils
Necrotic keratinocytes are usually limited to the lower one-third of the epidermis	Necrotic keratinocytes are found in all layers of the epidermis

Pathophysiology:
- The offending drug acts as a hapten, which binds to a protein in keratinocytes and activates CD8+ T lymphocytes, thereby inciting a cytotoxic immune reaction against the keratinocytes

References:

1. West AJ, Berger TG, LeBoit PE. A comparative histopathologic study of photodistributed and non-photodistributed lichenoid drug eruptions. J Am Acad Dermatol 1990; 23:689–693.
2. Shiohara T, Mizukawa Y. The immunological basis of lichenoid tissue reaction. Autoimmun Rev 2005; 4(4):236–241.

LICHEN PLANUS-LIKE KERATOSIS

Synonyms: Benign lichenoid keratosis; solitary lichenoid keratosis solitary lichen planus.

Clinical Presentation:
- Present as a solitary, violaceous, slightly scaly papule, or plaque of apparently acute onset, usually on the upper trunk or proximal upper extremities in adults between the ages 40 and 70

Histology:
- Focal-to-prominent parakeratosis (Fig. 10B)
- Wedge-shaped hypergranulosis (Fig. 10A)
- Jagged, "saw-tooth" acanthosis of the epidermis (Fig. 10A)
- Band-like, superficial lymphocytic infiltrate which obscures the dermoepidermal junction (Fig. 10A)
- Necrotic keratinocytes scattered throughout the epidermis
- There may be a residual solar lentigo at the edge of the lesion (Fig. 10C).
- Keratinocytic atypia is minimal or absent

Differential Diagnosis:

Lichen Planus-Like Keratosis	Lichen Planus	Lichenoid Solar Keratosis
Parakeratosis is commonly present and may be prominent	Parakeratosis is not a feature	—
Minimal-to-absent keratinocytic atypia	—	Prominent keratinocytic atypia

Pathophysiology:
- Lichen planus-like keratosis is thought to represent the spontaneous involution of a solar lentigo, large cell acanthoma, or reticulated seborrheic keratosis via a cell-mediated immunologic reaction

References:
1. Laur WE, Posey RE, Waller JD. Lichen planus-like keratosis. A clinicohistopathologic correlation. J Am Acad Dermatol 1981; 4:329–336.
2. Goldenhersh MA, Barnhill RL, Rosenbaum HM, Stenn KS. Documented evolution of a solar lentigo into a solitary lichen planus-like keratosis. J Cutan Pathol 1986: 13:308–311.

LICHENOID PIGMENTED PURPURA

Clinical Presentation:
- Variants: pigmented purpuric lichenoid dermatosis of Gougerot and Blum
  - Clinically presents as symmetric, bilaterally-distributed, purpuric, and flat-topped papules that coalesce into plaques on the lower extremities
- Variants: lichen aureus
  - Clinically presents as unilateral group of macules or papules with a rusty, golden color; sites of predilection are the lower extremities and trunk
- Associated rarely with hepatitis C seropositivity

Histology:
- Band-like, mixed infiltrate does not obscure the dermoepidermal junction (the "noninterface interface" dermatosis) (Fig. 11A)
- The mixed infiltrate includes variable numbers of extravasated erythrocytes and/or hemosiderin-laden macrophages (siderophages) (Figs. 11B and C)
- There may also be hemosiderin pigment deposition in the dermis (Fig. 11C)

Clinicopathologic Correlation:

Clinical Feature	Histopathologic Correlate
Purpuric papules	Extravasated erythrocytes in superficial dermis

Differential Diagnosis:

Pigmented Purpuric Dermatosis	Mycosis Fungoides	Stasis Dermatitis
Hemosiderin pigment is usually present only in superficial to mid dermis	—	Hemosiderin pigment is present in deep dermis
Atypical lymphocytes are not prominent	Atypical lymphocytes are a prominent feature	—
Epidermotropism when present usually does not extend beyond the basal layer	Epidermotropism can extend higher than the basal layer	—
Papillary dermal fibrosis not a feature	Papillary dermal fibrosis is characteristic	

Pathophysiology:
- Increased capillary fragility, possibly related to venous hypertension, is thought to lead to the extravasation of lymphocytes and erythrocytes from the vessels.

References:
1. Rao BK, Igwegbe I, Wiederkehr M, et al. Gougerot-Blum disease as a manifestation of hepatitis C infection. J Cutan Pathol 2000; 27:569.
2. English J. Lichen aureus. J Am Acad Dermatol 1985; 12:377–378.

LICHEN NITIDUS

Clinical Presentation:
- Chronic eruption which typically presents as multiple, grouped, asymptomatic, pinpoint-sized, flesh-colored papules in children and young adult men
- Occurs most commonly on the upper extremities and genitalia

Histology:
- Lymphohistiocytic infiltrate filling the dermal papilla and obscuring the dermoepidermal junction (Fig. 12)
- "Claw-like" hyperplasia of the rete surround the infiltrate (Fig. 12)
- Epithelioid and multinucleated histiocytes may be present, or the infiltrate may be frankly granulomatous (Fig. 12)

Immunofluorescence:
- Direct immunofluorescence is usually negative (in contrast to lichen planus)

Differential Diagnosis:

Lichen Nitidus	Lichen Scrofulosorum
Infiltrate causes widening of dermal papillae	Granulomatous infiltrate does not expand dermal papillae
Neutrophils not usually a feature	There may be neutrophils in the epidermis associated with mild spongiosis

Pathophysiology:
- The etiology of lichen nitidus is unknown
- The relationship between lichen nitidus and lichen planus is controversial

References:
1. Lapins NA, Willoughby C, Helwig EB. Lichen nitidus. A study of forty-three cases. Cutis 1978; 21:634–637.
2. Smoller BR, Flynn TC. Immunohistochemical examination of lichen nitidus suggests that it is not a localized papular variant of lichen planus. J Am Acad Dermatol 1992; 27:232–236.
3. Khopkar U, Joshi R. Distinguishing lichen scrofulosorum from lichen nitidus. Dermatopathol: Practical Concept 1999; 5:44–45.

LICHENOID INTERFACE DERMATITIS — SUPERFICIAL AND DEEP

LICHEN STRIATUS

Clinical Presentation:
- Typically presents as a unilateral, pruritic eruption of Blaschko linearly-arranged, erythematous, slightly scaly papules in children or adolescents
- There is a female predominance
- Sites of predilection are the extremities, neck, and trunk; occasionally, there is nail involvement

Histology:
- Superficial and deep perivascular and periadnexal (often peri-eccrine) inflammatory cell infiltrate (Fig. 13A)
- Band-like lymphohistiocytic infiltrate which obscures the dermoepidermal junction (Fig. 13B)

- Hyperplastic epidermis with spongiosis (Fig. 13B)
- Lymphocytes extend into the epidermis (Fig. 13B)
- There may be mild hyperkeratosis or focal parakeratosis

Differential Diagnosis:

Lichen Striatus	Linear Lichen Planus
Epidermal spongiosis may be present	Spongiosis is not a feature
Inflammatory infiltrate is deep and often periadnexal	Inflammatory infiltrate is limited to superficial dermis
Focal parakeratosis may be present	Parakeratosis is not a feature

Pathophysiology:

- Etiology of lichen striatus is unknown
- Suppressor-cytotoxic CD8+ T lymphocytes effect a cell-mediated cytotoxic immune reaction against keratinocytes

References:

1. Taieb A, el Youbi A, Grosshans E, Maleville J. Lichen striatus. A Blaschko linear acquired inflammatory skin eruption. J Am Acad Dermatol 1991; 25(4):637–642.
2. Gianotti R, Restano L, Grimalt R, et al. Lichen striatus—a chameleon: an histopathological and immunohistological study of forty-one cases. J Cutan Pathol 1995; 22(1):18–22.
3. Tosti A, Peluso AM, Misciali C, Cameli N. Nail lichen striatus: clinical features and long-term follow-up of five patients. J Am Acad Dermatol 1997; 36(6 Pt 1):908–913.

SECONDARY SYPHILIS

Synonym: Lues.

Clinical Presentation:

- Syphilis is an infectious, sexually-transmitted disease, the clinical manifestations of which are protean; secondary syphilis is known as the "great imitator," producing cutaneous lesions of every morphology except pustules
- Secondary syphilis generally presents 2 to 10 weeks after the appearance of the painless ulcer (the chancre of primary syphilis)
- Patients with secondary syphilis show a generalized lymphadenopathy associated with mucocutaneous lesions that may include: a generalized papulosquamous eruption involving the palms and soles; patchy, "moth-eaten" alopecia; "split" papules and condylomata lata at mucocutaneous junctions; mucous patches on buccal or anal mucosa; and hypopigmented patches on the lateral neck—the so-called "necklace of Venus."
- There may also be associated hepatitis, meningitis, colitis, nephritis, arthritis, and so on.

Histology:

- As with the clinical, the histologic presentation is highly variable
- Acanthosis or psoriasiform epidermal hyperplasia (Figs. 14A and B)
- Lymphohistiocytic infiltrate fills the papillary dermis and obscures the dermoepidermal junction (Figs. 14A and B)
- Superficial and deep perivascular inflammatory cell infiltrate
- Plasma cells present in 80% of cases (Fig. 14C)

Differential Diagnosis:

Secondary Syphilis	Psoriasiform/Lichenoid Drug Eruption
Eosinophils do not usually feature in infiltrate	Eosinophils usually prominent in inflammatory infiltrate

Pathophysiology:

- *Treponema pallidum*, a microaerophilic spirochete, usually acquired through sexual contact, penetrates intact mucous membranes or microabrasions in the skin and rapidly enters the lymphatics and blood to cause systemic infection.
- The spirochetes bind to endothelial cells and cause an obliterative endarteritis.
- The plasma cell–rich infiltrates, characteristic of secondary syphilis, reflect a delayed-type hypersensitivity reaction to the treponeme.

References:

1. Hook EW, Marra CM. Acquired syphilis in adults. N Engl J Med 1992; 326:1060.
2. Fitzgerald TJ. The Th1/Th2-like switch in syphilitic infection: is it detrimental? Infect Immun 1992; 60(9):3475–3479.

LYMPHOMATOID PAPULOSIS

Synonym: Macaulay disease.

Clinical Presentation:

- Chronic dermatosis on the trunk and extremities typified by recurrent crops of multiple erythematous papulonodules that become crusted, ulcero-necrotic lesions, and which resolve over several weeks, occasionally with atrophic scars.
- The clinical course is indolent and may wax and wane over decades.
- There is an increased incidence of preexisting, comorbid, or subsequent lymphoproliferative disorders [most commonly Hodgkin's lymphoma and mycosis fungoides (MF)].
- It is reported that 5% to 10% of cases progress to a malignant lymphoproliferative disorder [most commonly anaplastic large cell lymphoma (ALCL), MF, and Hodgkin's lymphoma].

Histology:

- Band-like, mixed dermal infiltrate with obscuration of the dermoepidermal junction.
- Variable numbers of large, atypical lymphocytes may be conspicuous in a background of a mixed dermal inflammatory cell infiltrate, primarily consisting of lymphocytes, histiocytes, eosinophils and/or neutrophils; mitotic figures may be prominent.
- Epidermotropism of predominantly small-to-medium-sized lymphocytes may be present.
- Focal parakeratosis with neutrophils.
- Necrotic keratinocytes and ulceration may be present.

Immunohistochemistry:

- Large, atypical lymphocytes within the dermal infiltrate are CD30+ (Ki-1), CD3+, and CD15−.
- All CD30+ cells are anaplastic lymphoma kinase (ALK)-negative.

Differential Diagnosis:

Lymphomatoid Papulosis	Vesicular Insect Bite	Pityriasis Lichenoides and Varioliformis Acuta
Eosinophils may be conspicuous within dermal infiltrate	Numerous eosinophils within a wedge-shaped dermal infiltrate	Eosinophils within dermal infiltrate are rare to absent
Large, atypical (CD30+) lymphocytes are conspicuous within dermal infiltrate	—	Atypical lymphocytes, if present, are few in number

Pathophysiology:

- Lymphomatoid papulosis is a lymphoproliferative disorder representing a clonal expansion of CD30+ T cells with a common rearrangement in the T-cell receptor(TcR) gene

References:

1. Cabanillas F, Armitage J, Pugh WC, et al. Lymphomatoid papulosis: a T-cell dyscrasia with a propensity to transform into malignant lymphoma. Ann Intern Med 1995; 122(3):210–217.
2. El-Azhary RA, Gibson LE, Kurtin PJ, et al. Lymphomatoid papulosis: a clinical and histopathologic review of 53 cases with leukocyte immunophenotyping, DNA flow cytometry, and T-cell receptor gene rearrangement studies. J Am Acad Dermatol 1994; 30(2 Pt 1):210–218.
3. Gellrich S, Wernicke M, Wilks A, et al. The cell infiltrate in lymphomatoid papulosis comprises a mixture of polyclonal large atypical cells (CD30-positive) and smaller monoclonal T cells (CD30-negative). J Invest Dermatol 2004; 122(3):859–861.
4. Wood GS, Crooks CF, Uluer AZ. Lymphomatoid papulosis and associated cutaneous lymphoproliferative disorders exhibit a common clonal origin. J Invest Dermatol 1995; 105(1):51–55.

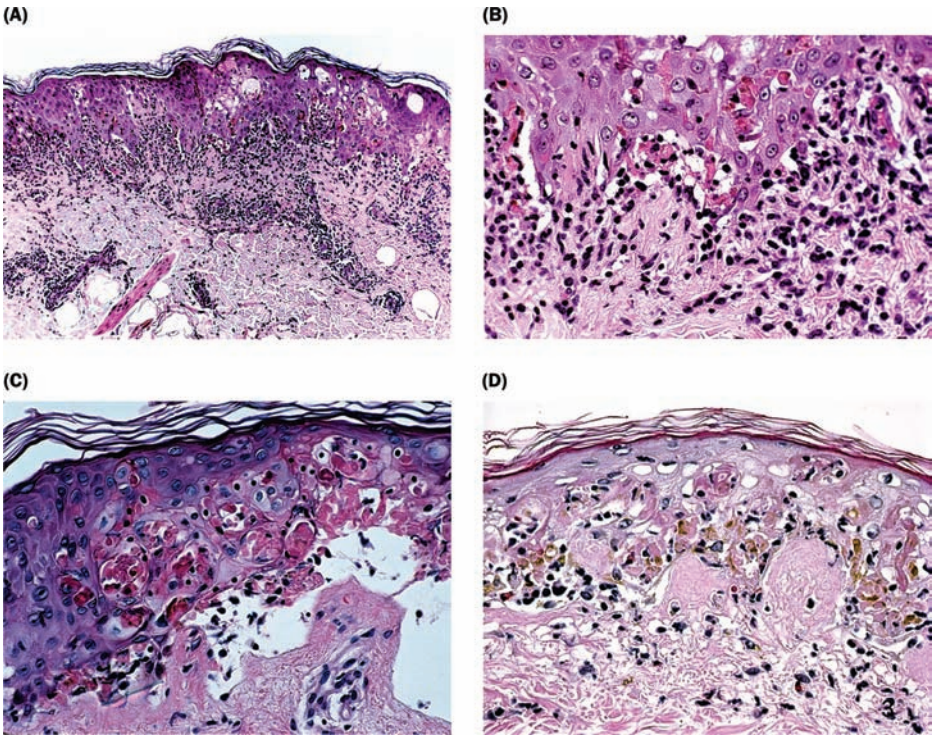

Figure 1 Erythema multiforme minor and major. There is obscuration of the dermoepidermal junction with vacuolar alteration of the basal keratinocytes (**A** and **B**). Necrotic keratinocytes may be individual or confluent (**B**). The process may progress to frank subepidermal vesiculation (**C**). Toxic epidermal necrosis with confluent, full-thickness epidermal necrosis (**D**). Note the preservation of the basket-weave horn.

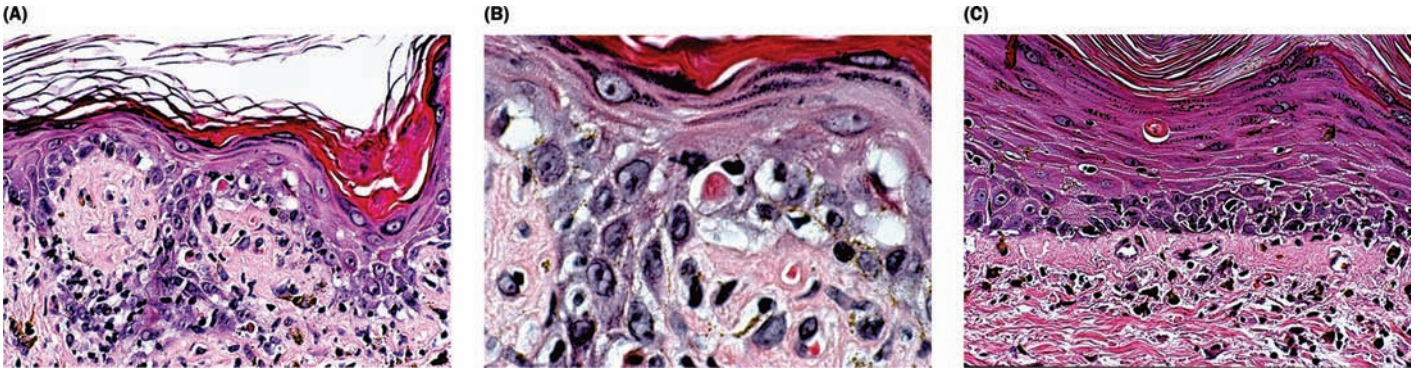

Figure 2 Acute graft versus host reaction (GvHR). There is a sparse lymphocytic infiltrate obscuring the dermoepidermal junction (**A**). Lymphocytes are present in the epidermis (exocytosis) with adjacent individually necrotic keratinocytes (satellite cell necrosis) (**B**). Chronic GvHR. There is acanthosis of the epidermis with hypergranulosis and a patchy band-like lymphocytic infiltrate. The dermis is fibrotic (**C**).

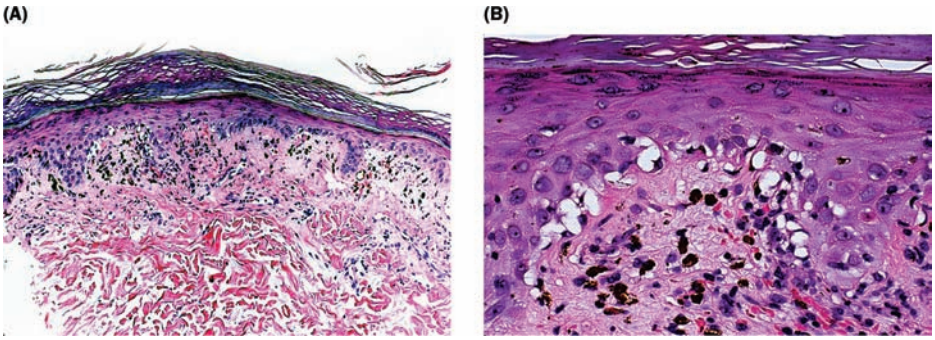

Figure 3 Systemic lupus erythematosus. There is obscuration of the dermoepidermal junction with vacuolar alteration of the basal keratinocytes with a sparse lymphocytic infiltrate (**A** and **B**). Dermatomyositis. This may appear identical to systemic lupus erythematosus. There is a sparse lymphocytic infiltrate with vacuolar alteration of the basal keratinocytes (**C**). Abundant mucin interposed between the dermal collagen bundles (**D**). (*Continued*)

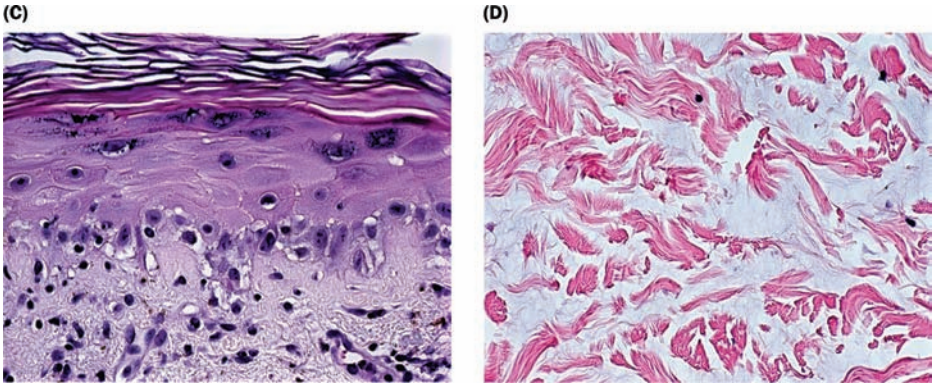

Figure 3 *Continued.*

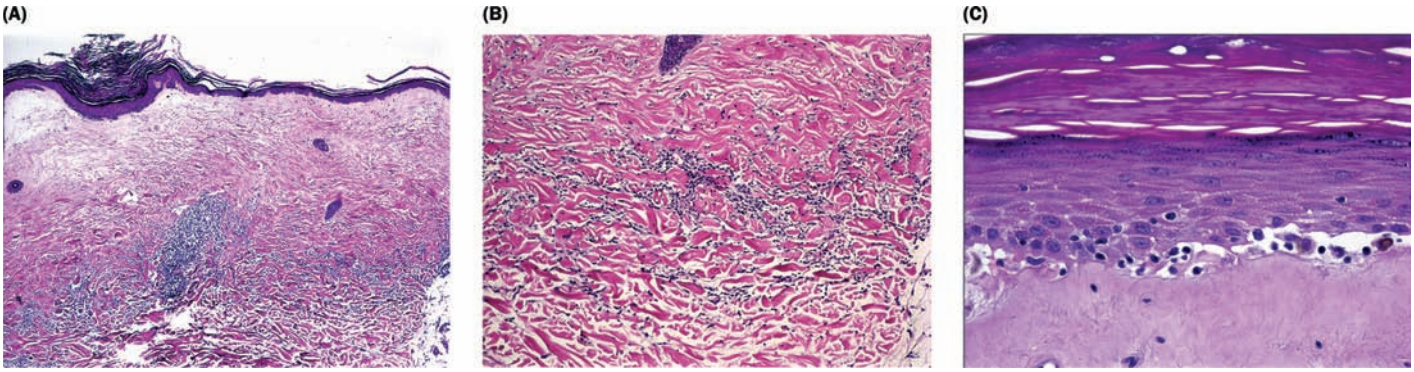

Figure 4 Lichen sclerosus et atrophicus (LS et A), early. There is marked edema of the upper dermis with a patchy, band-like predominantly lymphocytic infiltrate interposed between the altered collagen of the upper dermis and the normal collagen of the lower dermis (**A** and **B**). Fully developed LS et A. There is effacement of the rete ridge pattern of the epidermis with vacuolar alteration of the basal keratinocytes and sclerosis of the dermis (**C**).

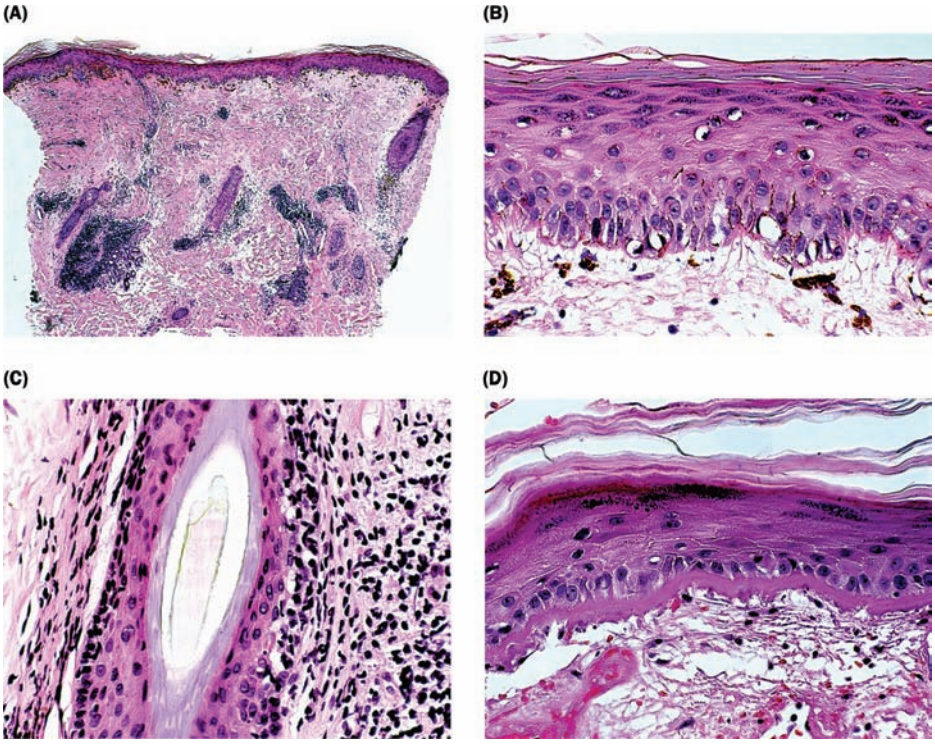

Figure 5 Discoid lupus erythematosus. There is a superficial and deep perivascular and periadnexal lymphocytic infiltrate with vacuolar alteration of the basal keratinocytes (**A** and **B**). A dense lymphocytic infiltrate surrounds the follicular adnexae with obscuration of the epithelial-stromal junction(**C**). Note the marked thickening of the basement membrane (**D**).

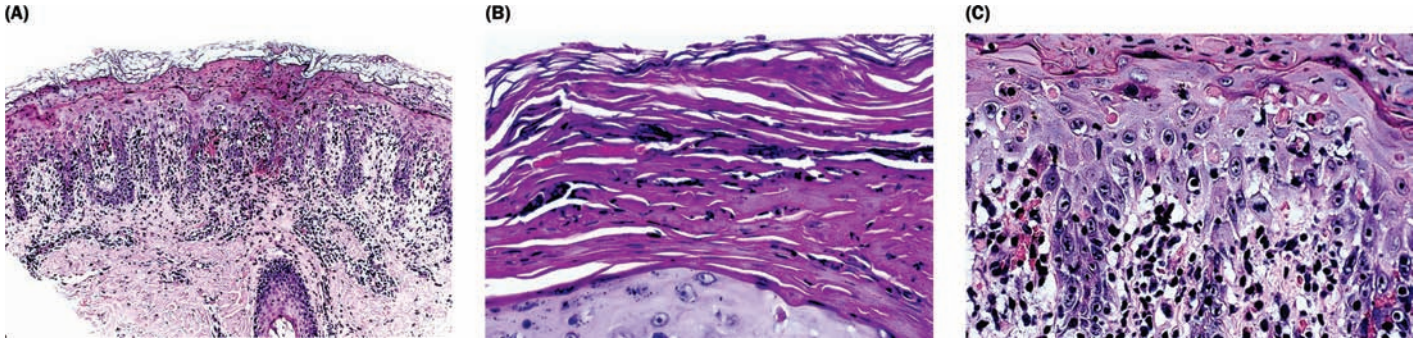

Figure 6 Pityriasis lichenoides et varioliformis acuta (PLEVA). There is a superficial and deep perivascular lymphocytic infiltrate that obscures the dermoepidermal junction (**A**). Neutrophils are in the stratum corneum admixed with degenerated necrotic keratinocytes and parakeratotic corneocytes (**B**). Necrotic keratinocytes are scattered throughout the epidermis and erythrocytes are interposed between the keratinocytes (**C**).

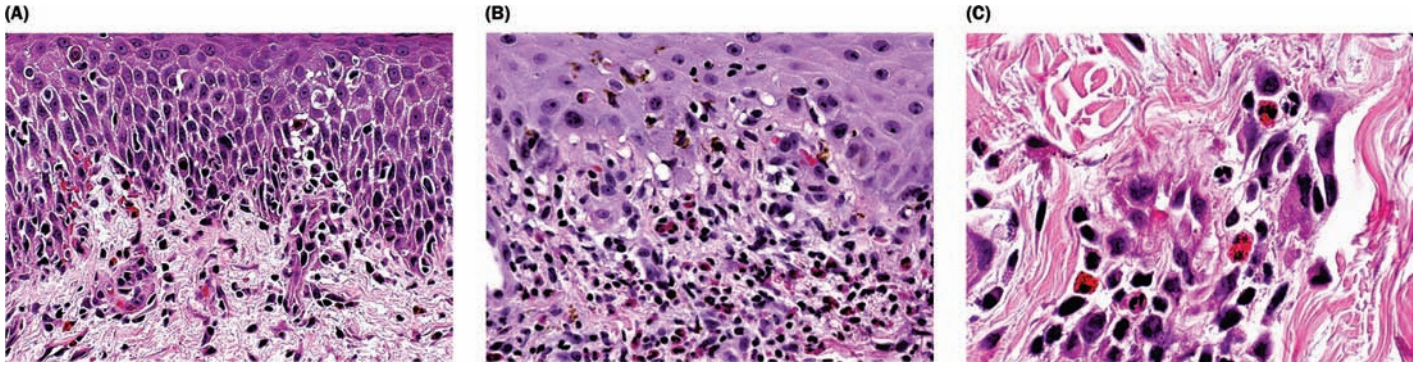

Figure 7 Fixed drug eruption. There is obscuration of the dermoepidermal junction with a mixed inflammatory cell infiltrate composed of lymphocytes numerous eosinophils and neutrophils (**A** and **B**). Necrotic keratinocytes can be identified throughout all levels of the epidermis (**A**) and may tend toward confluence. A mixed perivascular infiltrate can be present in the deep dermis (**C**).

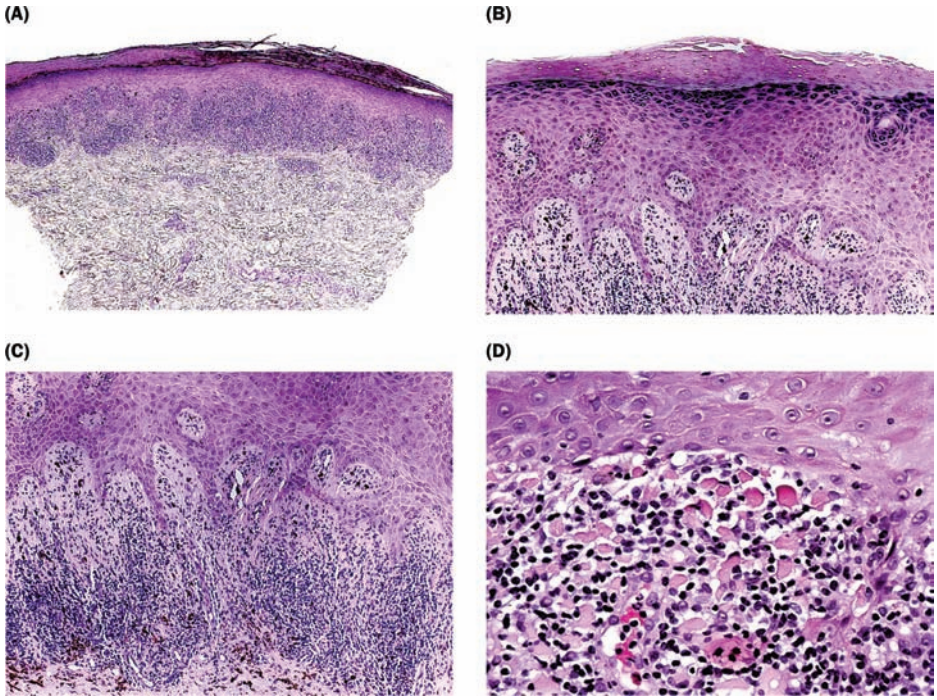

Figure 8 Lichen planus. There is compact orthokeratosis with no parakeratosis, wedge-shaped hypergranulosis, jagged acanthosis of the epidermis, and a band-like lymphocytic infiltrate obscures the dermoepidermal junction (**A**–**C**). Necrotic keratinocytes are in the lower one-third of the epidermis with colloid bodies in the superficial papillary dermis (**D**).

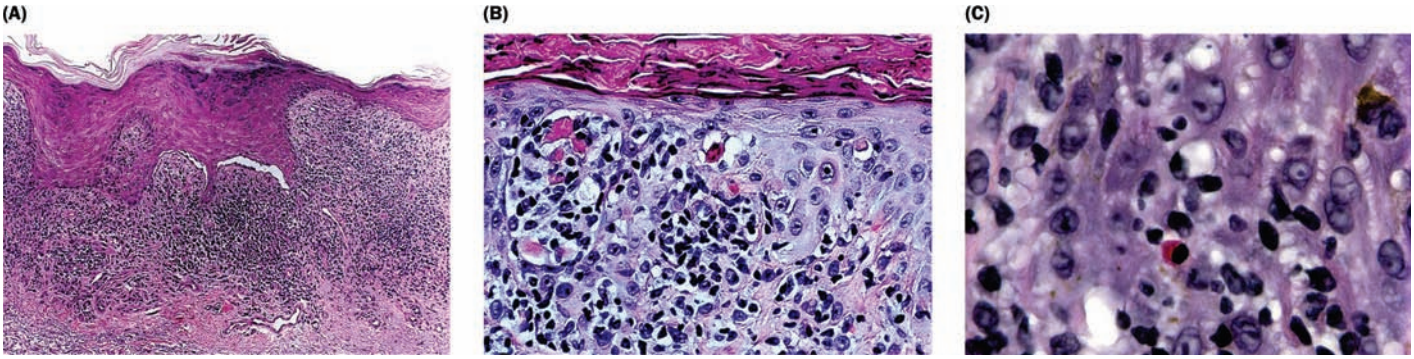

Figure 9 Lichenoid drug eruption. The histologic presentation can be identical to lichen planus (**A**). Differentiating features may include focal pararkeratosis, necrotic keratinocytes in all layers of the epidermis, and eosinophils within the infiltrate (**B** and **C**).

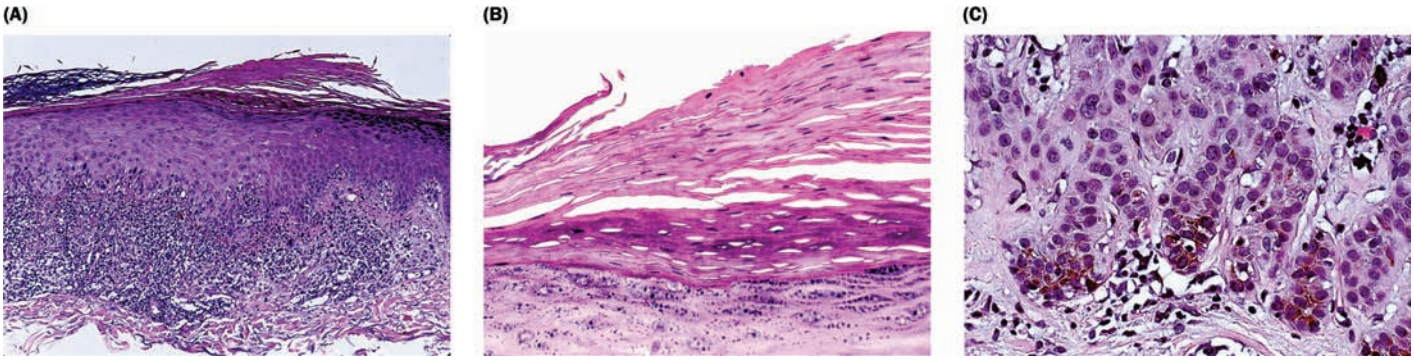

Figure 10 Lichen planus-like keratosis. The histologic presentation can be identical to lichen planus (**A**). Differentiating features may include focal parakeratosis (**B**), and residual solar lentigo at the edge of the lesion (**C**).

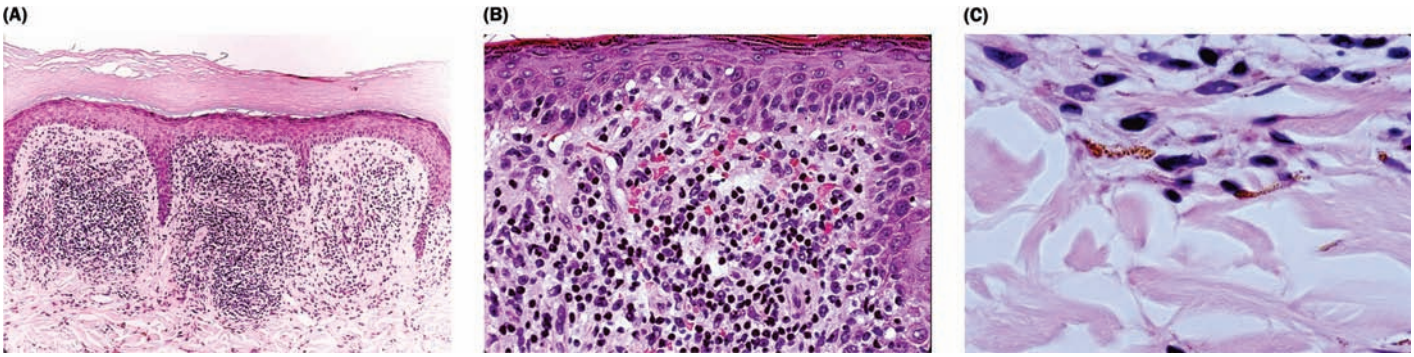

Figure 11 Lichenoid pigmented purpura. There is a band-like lymphocytic infiltrate that does not obscure the dermoepidermal junction (**A**). Extravasated erythrocytes and/or hemosiderin-laden macrophages are a prominent feature (**B** and **C**).

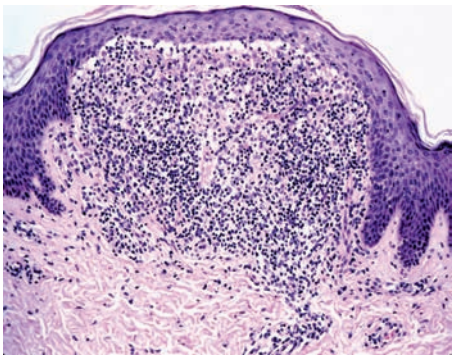

Figure 12 Lichen nitidus. There is a lymphohistiocytic infiltrate filling the papillary dermis with "claw-like" hyperplasia of the surrounding epidermis.

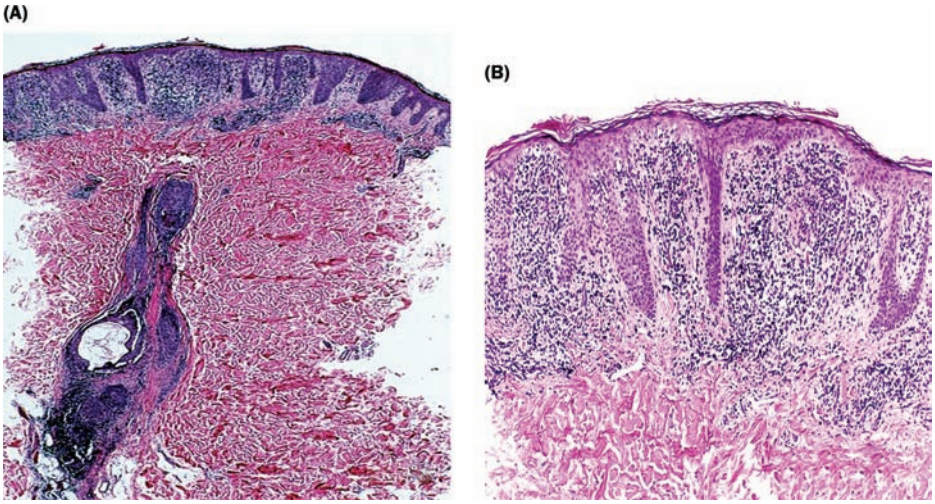

Figure 13 Lichen striatus. There is a superficial and deep perivascular and periadnexal lymphohistiocytic infiltrate with a band-like component that obscures the dermoepidermal junction (**A**). The epidermis is hyperplastic with spongiosis and may show exocytosis of lymphocytes (**B**).

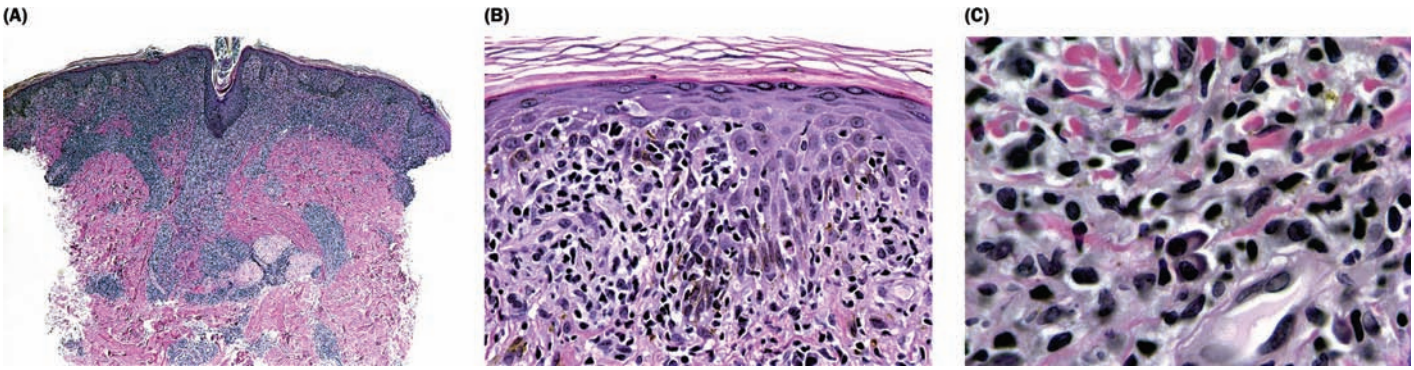

Figure 14 Secondary syphilis. The histologic presentation can be highly variable. The characteristic features include a superficial and deep perivascular and lichenoid lymphohistiocytic infiltrate obscuring the dermoepidermal junction with acanthosis of the epidermis (**A** and **B**). Plasma cells are present in 80% of cases.

4

Psoriasiform and Spongiotic Dermatoses

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CONTENTS

This chapter covers the psoriasiform and spongiotic dermatoses. This group of disorders is among the most common "rashes" seen in the offices of pediatric, family practice, and internal medicine physicians, as well as dermatologists. Clinically, the lesions appear elevated or raised (papular) and scaly (squamous) and are sometimes referred to as papulosquamous eruptions. The spongiotic group includes variable clinical presentations with the common histopathologic finding of spongiosis.

Definitions:

- *Acanthosis*: A histopathologic term describing thickening of the epidermis; may be regular or irregular.
- *Parakeratosis*: A histopathologic term describing the retention of nuclei within the stratum corneum.
- *Periodic acid Schiff (PAS)/Grocott methenamine silver (GMS)*: Special stains to identify fungal organisms.
- *Psoriasiform*: A histopathologic term describing uniform, regular thickening of the epidermis as seen in classic psoriasis; regular acanthosis.
- *Spongiosis*: A histopathologic term describing the separation of individual epidermal keratinocytes by intercellular edema.

PSORIASIFORM DERMATOSES

This group of disorders is characterized by the histologic finding of uniform, regular epidermal acanthosis.

PSORIASIS

Clinical Presentation of Classic Psoriasis:

- Well-demarcated erythematous plaques (Fig. 1A)
- Silver-white micaceous scale
- Symmetric distribution on extensor regions such as elbows, knees, and buttocks, may be diffuse (Fig. 1B)
- Hemorrhagic crusts, pinpoint bleeding when scale is removed (Auspitz sign)
- Scalp lesions common
- Nail changes—pits and "oil" spots (yellow-brown discoloration of the nails that look like oil)

Clinical Presentation of Guttate Variant:

- Acute onset
- Occurs more frequently in children than in adults
- Generalized multiple small thin scaly plaques (Fig. 2A)
- Often associated with precedent upper respiratory, streptococcal, or other infection

Clinical Presentation of Pustular Variant:

Localized:
Pustules on erythematous plaques particularly on palms and soles (Fig. 2B)
- Generalized (von Zumbusch)

Clinical Presentation of Inverse Variant:

- Pink-red plaques in skin folds
- Less scale than classic psoriasis

Clinical Presentation of Erythrodermic Variant:

- Full body red skin

Histology of Classic Psoriasis (Fig. 3A):

- Regular epidermal acanthosis
- Confluent parakeratosis with loss of underlying granular cell layer
- Polymorphonuclear leukocytes admixed with parakeratosis = Munro microabscess
- Clusters of polymorphonuclear leukocytes in superficial epidermis = spongiform pustule (of Kogoj) (Fig. 3B)
- Thin suprapapillary epidermal plates
- Dilated and tortuous capillaries
- Mild lymphocytic inflammation

Histology of Guttate Variant (Fig. 4A):

- Mild epidermal acanthosis with parakeratosis
- Mild spongiosis

Histology of Pustular Variant (Fig. 4B):

- Intraepidermal spongiform pustules
- Subcorneal pustules

Table 1A Histologic Differential Diagnosis: Psoriasis

	Psoriasis	Reiter's	Lichen Simplex Chronicus	Fungal	Clear Cell Acanthoma
Epidermal acanthosis	Yes regular	Yes regular	Yes irregular	Yes variable mild	Yes regular focal
Parakeratosis	++ focal to confluent	++++ confluent	+/− focal	++/− focal to confluent	+ focal over acanthosis
Loss of granular cell layer	Yes	Yes	No	No	Yes
Neutrophils in epidermis	Yes	Yes	No	Yes	Yes diffuse
Parakeratosis with admixed neutrophils	Yes in mounds	Yes in mounds	No	Yes focal to mounds	Yes over acanthosis
Spongiosis	No +Guttate variant	No	No mild	No mild	No mild
Clear/pale epidermal keratinocytes	No	No	No	No	Yes
Periodic acid schiff/ Grocott methenamine silver stain	Negative	Negative	Negative	Positive	Negative

(*Continued*)

Clinicopathologic Correlation:

Clinical Feature	Pathologic Feature
Thick erythematous plaques	Regular psoriasiform epidermal hyperplasia, thinned suprapapillary epidermal plates, dilated capillaries
Silver white scale	Parakeratosis
Hemorrhagic crusts	Shallow epidermal erosions with serum and red blood cells
Auspitz sign	Dilated tortuous papillary dermal blood vessels immediately beneath a thinned suprapapillary plate, which bleed when parakeratotic scale is removed
Thin guttate plaques	Mild epidermal acanthosis, spongiosis
Pustular plaques	Intraepidermal spongiform pustules

Clinical Differential Diagnosis:

Psoriasis	Guttate Psoriasis	Pustular Psoriasis	Erythrodermic Psoriasis
Lichen simplex Chronicus	Lichen simplex Chronicus	Impetigo	Atopic dermatitis
PRP (Pityriasis rubra pilaris)	Pityriasis rosea	Drug reaction	Drug reaction
Reiter's	Secondary syphilis	Reiter's	Mycosis fungoides
Fungal	Fungal	Fungal	

Histologic Differential Diagnosis:

See Tables 1A and B.

Pathophysiology:

- Accelerated epidermal proliferation and angiogenesis
- Abnormal cellular immune disorder (T cell)

Reference:

1. Bowcock AM, Barker JN. Genetics of psoriasis: the potential impact on new therapies. J Am Acad Dermatol 2003; 49(2 suppl):S51–S56.

Table 1B Histologic Differential Diagnosis: Psoriasis

	Pityriasis Rubra Pilaris	Pityriasis Rosea
Epidermal acanthosis	Yes regular mild	No mild
Parakeratosis	++ alternating orthokeratosis and parakeratosis "checkerboard"	+ very focal
Loss of granular layer	Yes focal	No very focal
Neutrophils in epidermis	No	No
Parakeratosis with admixed neutrophils	No	No
Spongiosis	No	Yes mild
Clear/pale epidermal keratinocytes	No	No
Periodic acid Schiff/Grocott methenamine silver stain	Negative	Negative

Table 2A Histologic Differential Diagnosis: Inflammatory Linear Verrucous Epidermal Nevus

	Inflammatory Linear Verrucous Epidermal Nevus	Psoriasis	Lichen Simples Chronicus	Lichen Striatus
Stratum corneum	Hyperkeratotic orthokeratosis alternating with parakeratosis	Hyperkeratotic parakeratosis	Hyperkeratotic orthokeratosis	Orthokeratosis, focal parakeratosis
Granular layer	Increased alternating with decreased	Absent	Increased	Normal
Acanthosis	Regular	Regular	Irregular	Mild
Spongiosis	+/−	−	+/−	++
Neutrophils in epidermis	+/−	++	−	−
Inflammation	Perivascular	Perivascular	Perivascular	Lichenoid

REITER'S DISEASE

Clinical Presentation:
- Psoriasiform skin lesions (5%)
  - Plantar pustular lesions (keratoderma blenorrhagicum)
  - Penile plaques (balanitis circumscriptum)
  - Knees, elbows, scalp, and dorsal hands
- Urethritis
- Arthritis
- Ocular findings
- Oral ulcers

Histology:
- May be indistinguishable from psoriasis
- Markedly thickened parakeratotic stratum corneum

Pathophysiology:
- Greater than eighty percent HLA-B27 positive
- Associated with urogenital or gastrointestinal infection

Reference:
1. Schneider JM, Matthews JH, Graham BS. Reiter's syndrome. Cutis 2003; 71(3):198–200.

PITYRIASIS RUBRA PILARIS

Clinical Presentation (Fig. 5A):
- Adult and juvenile forms
- Diffuse and coalescing scaly plaques on trunk and extremities
- Salmon-pink colored lesions
- Follicular accentuation with perifollicular erythema
- Islands of spared skin
- Palmoplantar keratoderma

Histology (Fig. 5B):
- Mild psoriasiform epidermal hyperplasia
- Thickened suprapapillary epidermal plates
- Stratum corneum with vertical and horizontally oriented alternating ortho and parakeratosis in a "checker board" pattern
- Hyperkeratotic plugged follicular infundibuli

Table 2B Histologic Differential Diagnosis: Inflammatory Linear Verrucous Epidermal Nevus

	Psoriasis	Pityriasis Rubra Pilaris
Epidermal acanthosis	Regular	Regular mild
Parakeratosis	Confluent	Alternating ortho and parakeratosis
Suprapapillary epidermal plates	Thin	Normal to thick
Follicular hyperkeratotoic plugs	No	Yes
Neutrophils in epidermis	Yes	No

Pathophysiology:
- Uncertain but keratinocyte dysfunction and vitamin A may play a role

References:
1. Magro CM, Crowson AN. The clinical and histomorphological features of pityriasis rubra pilaris. A comparative analysis with psoriasis. J Cutan Pathol 1997; 24(7):416–424.
2. Allison DS, El-Azhary RA, Calobrisi SD, Dicken CH. Pityriasis rubra pilaris in children. J Am Acad Dermatol 2002; 47(3): 386–389.

INFLAMMATORY LINEAR VERRUCOUS EPIDERMAL NEVUS

Clinical Presentation:
- Linear to curved, whorled (Blaschkoid) verrucous scaly plaques
- Pruritic
- Lower extremity
- Occurs more frequently in children than in adults
- Can look identical to lichen striatus, but is persistent

Histology:
- Psoriasiform epidermal hyperplasia
- Compact orthkeratotic hyperkeratosis alternating with parakeratosis
- Polymorphonuclear leukocytes in epidermis are rarely seen
- Mild spongiosis

Histologic Differential Diagnosis:
See Tables 2A and B.

Table 3 Histologic Differential Diagnosis: Spongiotic Dermatoses

Pattern	Acute	Subacute	Chronic
Stratum corneum	Orthokeratotic	Parakeratosis and orthokeratosis	Hyperkeratotic orthokeratosis, or parakeratosis
Epidermal acanthosis	None to minimal	Mild to moderate	Moderate to marked
Spongiosis	Mild to marked, usually marked	Mild to moderate	Minimal to absent
Intraepidermal vesicles	Yes	Rare	No
Dermal perivascular inflammation	Eosinophils and lymphocytes	Lymphocytes and sometimes eosinophils	Lymphocytes and rare eosinophils
Dermal fibrosis	No	No	Yes
Clinical prototype	Allergic contact dermatitis	Nummular dermatitis	Lichen simplex chronicus

Pathophysiology:
- Altered keratinocyte differentiation

Reference:
1. Lee SH, Rogers M. Inflammatory linear verrucous epidermal naevi: a review of 23 cases. Australas J Dermatol 2001; 42(4): 252–256.

SPONGIOTIC DERMATOSES

This group of disorders is characterized by the histologic finding of spongiosis. Clinical pathologic correlation is essential as several disease entities may appear indistinguishable histologically and yet be clinically distinct. Many of these disorders present with vesicles or bullae in their early or acute forms. Epidermal spongiosis is one mechanism by which intraepidermal vesicles are formed.

In general, the spongiotic dermatoses can be divided histologically into a spectrum of acute, subacute, and chronic forms (Table 3).

Clinicopathologic Correlation:

Clinical Feature	Pathologic Feature
Vesicle or bulla	Marked epidermal spongiosis
Scale	Orthokeratosis and parakeratosis
Crust	Serum, red blood cells, and debris on surface
Thin plaque	Mild to moderate acanthosis
Thick, lichenified plaques	Marked acanthosis and dermal fibrosis

Acute spongiotic pattern is commonly seen in these clinical entities
- Allergic contact dermatitis
- Irritant contact dermatitis
- Dyshidrotic dermatitis
- Photoallergic dermatitis
- Id reaction
- Incontinentia pigmenti (stage I)
- Miliaria
- Bullous dermatophyte

ALLERGIC CONTACT DERMATITIS

Clinical Presentation:
- Pruritic, erythematous, edematous papules, and plaques
- Vesicles and bullae common (Fig. 6)
- Linear lesions or pattern of contact
- Toxicodendron species (poison ivy, oak, sumac) common culprits

Histology:
- Acute spongiotic pattern (Fig. 7)
- Marked spongiosis with intraepidermal spongiotic vesicles
- Orthokeratosis
- Eosinophils and lymphocytes—within the dermis and sometimes in the epidermis
- Collections of Langerhan cells in epidermis

Histologic Differential Diagnosis:
See Table 4.

Subacute spongiotic pattern is commonly seen in these clinical entities:
- Nummular dermatitis
- Pityriasis rosea
- Seborrheic dermatitis
- Fungal/dermatophyte infection
- Figurate erythema/erythema annulare centrifugum
- Pruritic dermatoses of pregnancy
- Gianotti-Crosti syndrome/papular acrodermatitis of childhood
- Polymorphous light eruption; "spongiotic" variant

NUMMULAR DERMATITIS

Clinical Presentation:
- Pruritic round to oval "coin" shaped pink plaques (Fig. 8)
- May be vesicular, but more often with scale and crust
- Lower extremities commonly involved in men

Histology (Fig. 9):
- Mild to moderate epidermal acanthosis
- Mild to moderate spongiosis
- Usually no spongiotic vesicles
- Focal parakeratotic stratum corneum
- Superficial perivascular lymphocytes, sometimes eosinophils
- Surface scale crust

Table 4 Histologic Differential Diagnosis: Allergic Contact Dermatitis

	Allergic Contact Dermatitis	Dyshidrotic Eczema	Early Nummular Dermatitis	Id Reaction	Bullous Dermatophyte
Acute spongiosis	Yes	Yes	Yes	Yes	Yes
Periodic acid Schiff/ Grocott methenamine silver stain for hyphae	Negative	Negative	Negative	Negative	Positive

PITYRIASIS ROSEA

Clinical Presentation:
- Often starts with a herald patch (Fig. 10A), one to four centimeter, round to oval, salmon-pink-patch
- Central collarette of scale (Fig. 10B)
- Followed after a few days by a generalized eruption
- "Fir tree" truncal distribution
- Usually lasts six to eight weeks

Histology:
- Mild spongiosis
- Focal mounds of parakeratosis
- Mild acanthosis; more prominent in herald patch
- Erythrocyte extravasation in papillary dermis
- Mild dermal lymphocytic inflammation

Pathophysiology:
- Unknown

Histologic Differential Diagnosis:
See Table 5.

Chronic spongiotic pattern is commonly seen in these clinical entities:
- Lichen simplex chronicus
- Prurigo nodules
- Chronically traumatized areas
- Old verrucae

LICHEN SIMPLEX CHRONICUS

Clinical Presentation:
- Thick, lichenified papules, nodules, or plaques (Fig. 11)
- Often pruritic

Histology (Fig. 12):
- Hyperkeratotic ortho or parakeratotic stratum corneum
- Hypergranulosis
- Moderate to marked irregular epidermal acanthosis
- Minimal to absent spongiosis
- Lymphocytic inflammation
- Thickened suprapapillary plates
- Dermal fibrosis with vertical "streaking" of thickened collagen bundles in the papillary dermis

Pathophysiology:
- Lesions secondary to chronic trauma from picking, scratching, rubbing, exogenous devices (e.g., prostheses), occupational/recreational (e.g., surfers)

FUNGAL/DERMATOPHYTE

Clinical Presentation:
- Faint pink to red scaly thin plaques (Fig. 13)

Pustules:
- Peripheral "satellite"—common with *Candida* infections
- Edge of plaque—dermatophyte erroneously treated with topical steroids

Histology (Fig. 14A):
- Mild epidermal acanthosis

Mild Spongiosis:
- Marked spongiosis in bullous dermatophyte
- Focal parakeratosis
- Intraepidermal pustules possible
- PAS or GMS stain positive for organisms within the stratum corneum
- Hyphae—dermatophyte (Fig. 14B)
- Spores/Pseudohyphae—Yeast (*Candida* or *Pityrosporum*)

Reference:
1. Ackerman AB, Boer A, Bennin B, Gottlieb GJ. Histologic Diagnosis of Inflammatory Skin Disease. An Algorithmic Method Based on Pattern Analysis. 3rd ed. New York: Ardor Scribendi Ltd, 2005.

Table 5 Histologic Differential Diagnosis: Pityriasis Rosea

	Nummular Dermatitis	Pityriasis Rosea	Seborrheic Dermatitis	Fungal Dermatophyte
Parakeratosis	Focal to diffuse	Small focal mounds	Perifollicular	Mild
Acanthosis	Mild	Mild	Mild	Mild
Spongiosis	Mild	Mild focal	Mild	Mild
Extravasated red blood cells	No	Yes	No	No
Eosinophils	Yes	No	No	Sometimes
Periodic acid Schiff	Negative	Negative	Often positive (pityrosporum)	Positive (hyphae)

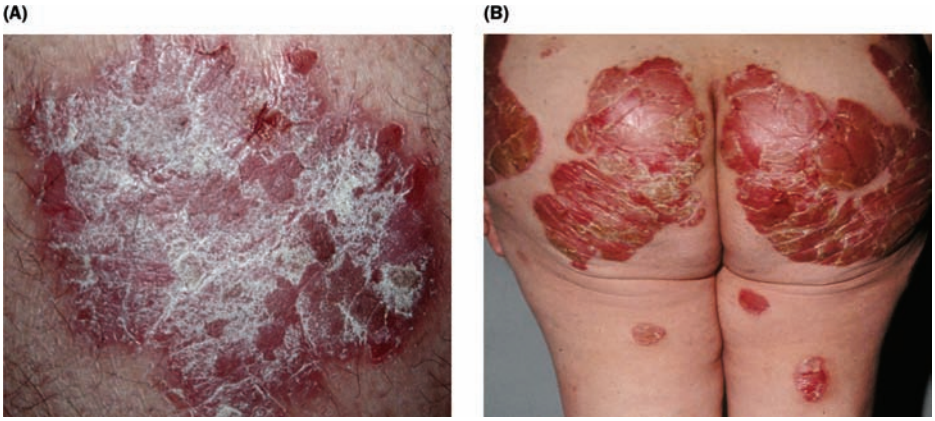

Figure 1 Psoriasis.

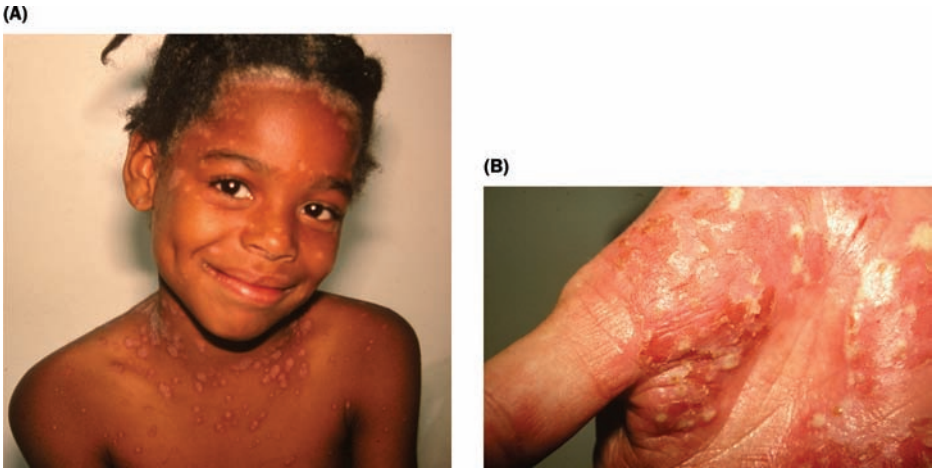

Figure 2 (**A**) Guttate psoriasis. (**B**) Palmar pustular psoriasis.

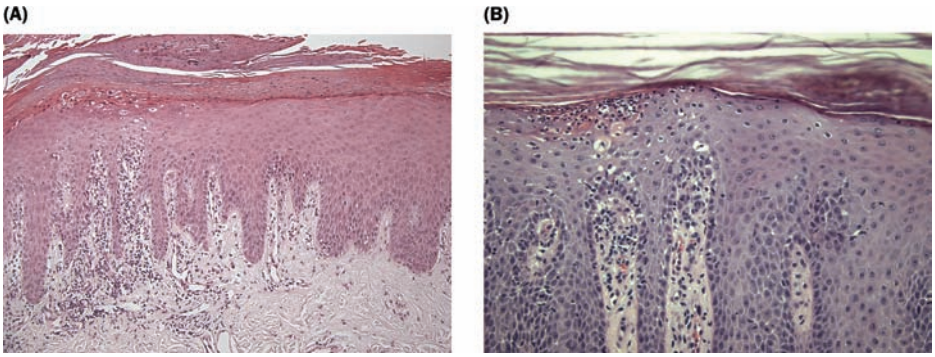

Figure 3 (**A**) Psoriasis histology. (**B**) Spongiform pustule.

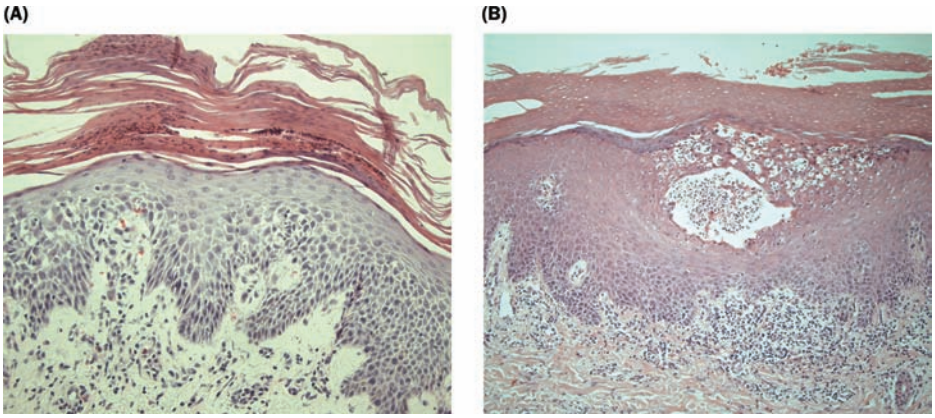

Figure 4 (**A**) Guttate psoriasis histology. (**B**) Pustular psoriasis histology.

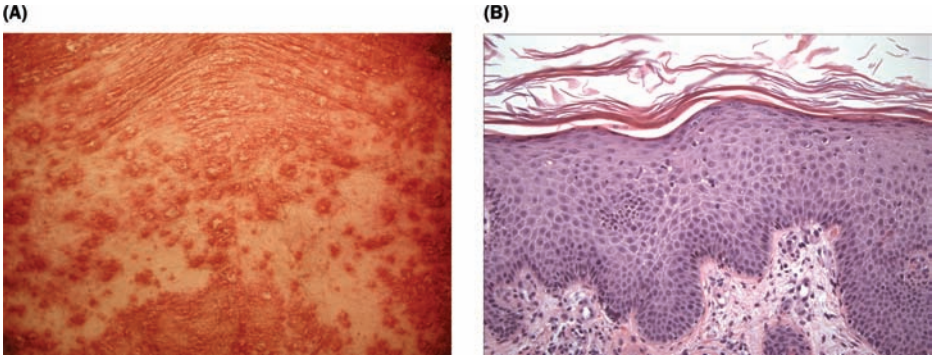

Figure 5 (**A**) Pityriasis rubra pilaris. (**B**) Pityriasis rubra pilaris histology.

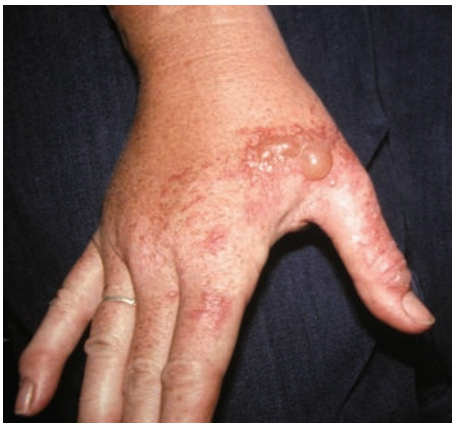

Figure 6 Acute contact dermatitis.

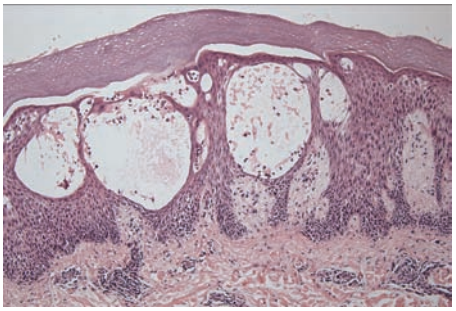

Figure 7 Acute spongiotic histology.

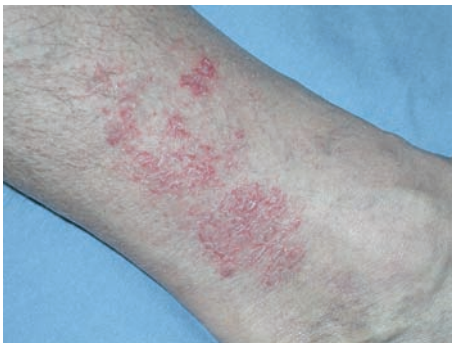

Figure 8 Nummular dermatitis.

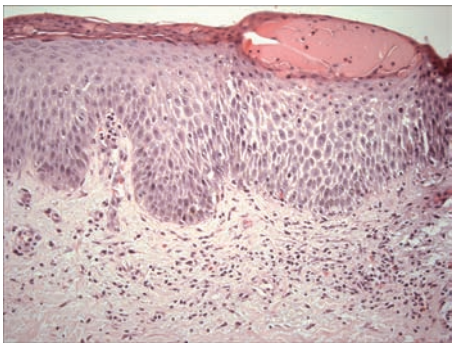

Figure 9 Subacute spongiotic histology.

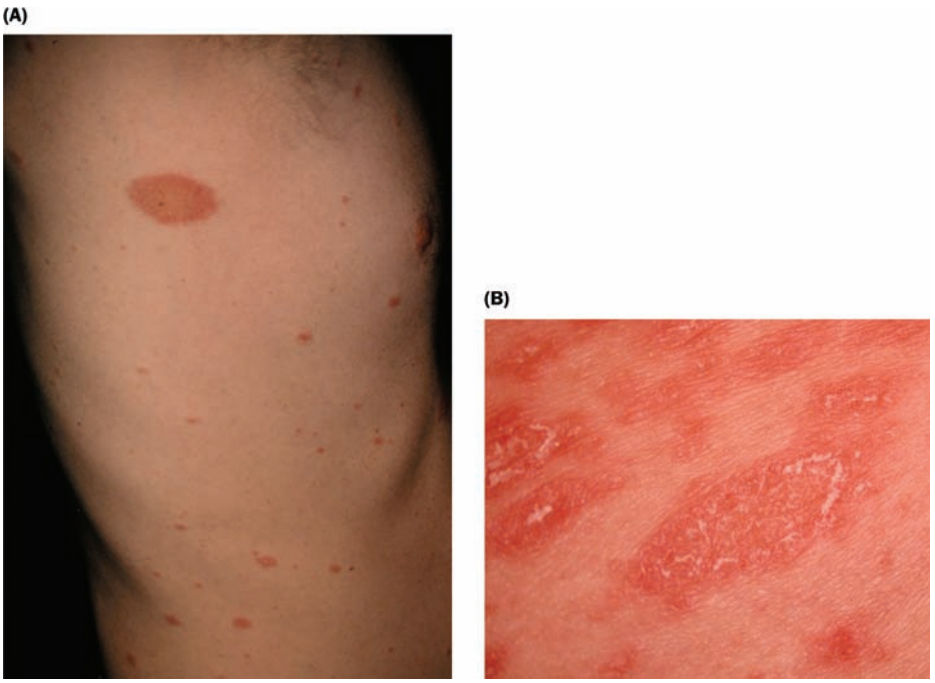

Figure 10 (**A**) Pityriasis rosea, Herald patch (**B**) Pityriasis rosea.

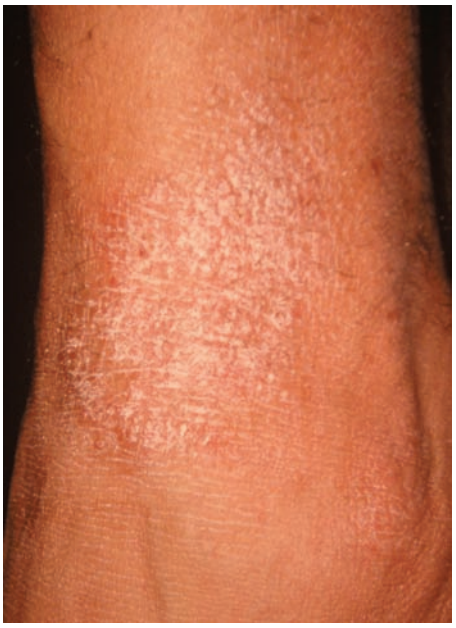

Figure 11 Chronic dermatitis.

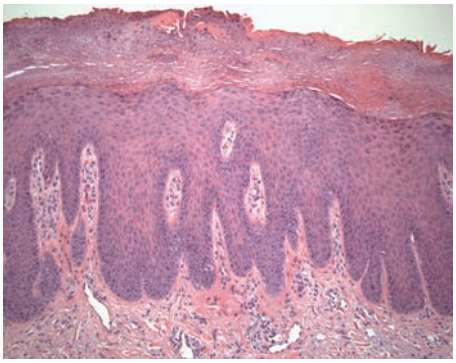

Figure 12 Chronic dermatitis histology.

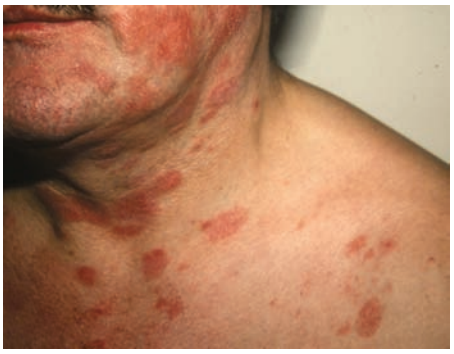

Figure 13 Tinea corporis.

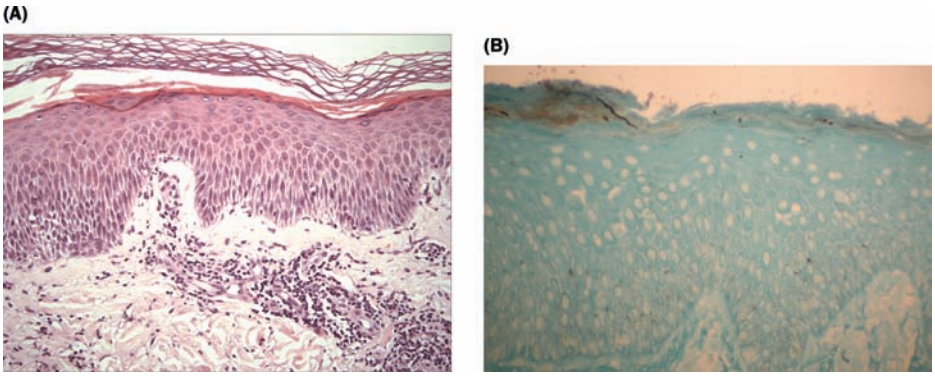

Figure 14 (**A**) Tinea corposis with mild subacute spongiotic changes. (**B**) Grocott methanamine silver stain showing fungal hyphae within stratum corneum.

5

Intraepidermal Vesicular and Pustular Dermatitis

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CONTENTS

This chapter discusses inflammatory disorders of the epidermis histologically characterized by vesicle and pustule formation. Systematically assessing only six histologic findings will facilitate classification, and therefore diagnosis of a biopsy specimen with an intraepidermal vesicle or pustule:

1. Determining where the primary split in the epidermis is occurring
   a. Stratum corneum
   b. Granular cell layer
   c. Stratum spinosum
   d. Basal layer
2. Determining the mechanism of vesicle formation
   a. Spongiosis
   b. Acantholysis
   c. Necrosis
   d. Cleft
   e. Pustule formation
3. Looking for specific keratinocyte alterations
   a. Acantholysis
   b. Apoptosis/cytolysis
   c. Necrosis
   d. Ballooned nucleus

Table 1 Disease Classification by Location of Vesicle/Pustule and Type of Accompanying Inflammation

	Intracorneal or Subcorneal	Intraepidermal	Suprabasilar	Intrabasilar
Noninflammatory	Staphylococcal scalded skin syndrome			Epidermolysis bullosa simplex
	Toxic shock syndrome			
Acantholytic	Pemphigus foliaceus	Herpesvirus infection	Pemphigus vulgaris	
	Pemphigus erythematosus	Benign familial pemphigus	Pemphigus vegetans	
			Keratosis follicularis	
			Transient acantholytic dermatosis	
Neutrophil	Impetigo; dermatophytosis; candidiasis			
	Subcorneal pustular dermatosis			
Spongiotic, lymphocytic		Eczematous dermatitis (contact, atopic, nummular, drug)		
Eosinophil	Pemphigus foliaceus	Incontinentia pigmenti	Pemphigus vulgaris	
			Pemphigus vegetans	

4. Determining the type of inflammatory cells, if present
5. Looking for microorganisms
6. Assessing for the presence of immunoreactants

The primary organization of this chapter will be based on the location of the vesicle or blister formation within the epidermis (Table 1).

INTRACORNEAL OR SUBCORNEAL VESICLE AND PUSTULE

STAPHYLOCOCCAL SCALDED SKIN SYNDROME AND TOXIC SHOCK SYNDROME

Synonyms: Staphylococcal scalded skin syndrome (SSSS); Ritter's disease.

Clinical Presentation:

SSSS (Fig. 1A):

- Primarily affects neonates in young children but may occur in adults, particularly if immunocompromised
- Sudden onset of malaise, fever, irritability, cutaneous tenderness, and erythema
- Erythema often accentuated in flexural and periorificial areas
- Flaccid blisters and erosions developed within one to two days
- Cultures of blisters are negative

Toxic Shock Syndrome:

- Sudden onset of macular erythroderma with desquamation of tips of fingers and toes
- Oropharyngeal hyperemia, conjunctival injection, edema of the hands and feet
- In children, infected burn wounds in hospita lized individuals, and bacterial tracheitis are high risk settings

Histology (Same for Both Disorders) (Fig. 1B):

- Separation of the stratum corneum from the epidermis
- Scant inflammatory dermal infiltrate

Clinicopathologic Correlation:

Clinical Feature	Pathologic Feature
Desquamating skin	Separation of stratum corneum from underlying epidermis

Differential Diagnosis Made on Frozen Sections of Desquamated Epidermis:

Staphylococcal Scalded Skin Syndrome and Toxic Shock Syndrome	Toxic Epidermal Necrolysis
Cleft occurs in the granular layer	Split occurs in the basement membrane zone
Stratum corneum is lifted off	Entire epidermis, including melanocytes in the basal layer, present
	Dyskeratotic keratinocytes in the epidermis

Pathophysiology:

- *Staphylococcal Scalded Skin Syndrome*: Caused by toxigenic strains of *Staphylococcus aureus* belonging to phage group II. Infections leading to SSSS typically originate in the nasopharynx, umbilicus, and urinary tract. Serologically distinct toxins, exfoliative toxin A and exfoliative toxin B have been identified.
- *Toxic Shock Syndrome*: Early cases were associated with tampon use; most cases now occur in the postoperative setting. Pyrogenic toxin super antigens made by *Staphylococcus aureus* and group A streptococci

References:

1. Hanakawa Y, Stanley JR. Mechanisms of blister formation by staphylococcal toxins. J Biochem (Tokyo) 2004; 136:747–750 (Review).
2. Hanakawa Y, Schechter NM, Lin C, et al. Molecular mechanisms of blister formation in bullous impetigo and staphylococcal scalded skin syndrome. J Clin Invest 2002; 110:53–60.

PEMPHIGUS FOLIACEUS AND PEMPHIGUS ERYTHEMATOSUS

Synonyms: Pemphigus foliaceus: superficial pemphigus, fogo selvagem (endemic form in South America); pemphigus erythematosus: Senear-Usher syndrome.

Clinical Presentation:

Pemphigus Foliaceus (Fig. 2A):

- Recurrent shallow erosions, erythema, scaling, and crusting
- Small flaccid blisters that rupture easily
- Mucous membrane involvement uncommon
- Occurs in all ages
- Occasionally drug induced

Pemphigus Erythematosus:

- Circumscribed patches of erythema and crusting, that are localized to nose, cheeks, and ears, and that resemble lesions of lupus erythematosus
- Crusting and bullae on the scalp, chest, and extremities, resembling pemphigus foliaceus

Histology (Similar for Both Diseases) (Fig. 2B):

- Subcorneal, intragranular, or upper epidermal clefting
- Acantholysis and dyskeratosis of keratinocytes in the granular layer
- Superficial perivascular infiltrate of lymphocytes and occasional eosinophils

Immunofluorescence Studies:

- Biopsy for direct immunofluorescence should be taken from epidermis immediately adjacent to a blister
- In pemphigus foliaceus IgG deposited in intercellular spaces
- In Pemphigus erythematosus IgG is not only deposited in intercellular spaces but also along basement membrane zone

Clinicopathologic Correlation:

Clinical Feature	Pathologic Feature
Superficial scale and crust	Acantholysis separating stratum corneum and upper epidermis from rest of the epidermis

Differential Diagnosis:

Pemphigus Foliaceus	Pemphigus Vulgaris	Transient Acantholytic Dermatosis
Separation is high in the epidermis	Separation is suprabasilar	Cleft may be in upper or mid epidermis or suprabasilar
DIF: intercellular IgG	DIF: intercellular IgG	DIF: negative

Abbreviation: DIF, direct immunofluorescence.

Pathophysiology:
- Pemphigus foliaceus: circulating antibodies directed against the cell surface of keratinocytes, specifically desmoglein 1

References:

1. Payne AS, Hanawaka Y, Amagai M, Stanley JR. Desmosomes and disease: pemphigus and bullous impetigo. Curr Opin Cell Biol 2004; 16:536–543.
2. Hoque S, Hextall J, Hay R. Clinicopathological case 3: pemphigus foliaceus; bullous impetigo; subcorneal pustular dermatoses. Clin Exp Dermatol 2003; 28:465–466.

IMPETIGO, CANDIDIASIS, AND DERMATOPHYTOSIS

Synonym: None.

Clinical Presentation:
Impetigo (Fig. 3A):
- Pustules that quickly break to form honey-colored crusts.
- Lesions may be found anywhere but most often are located on the face.

Candidiasis:
- "Beefy red" macular erythema with surrounding satellite papules and pustules
- Macules, papules, and pustules tend to occur in moist areas particularly the perineal, perianal, and intertriginous areas

Dermatophytosis:
- Pruritic scaly rash, occasionally annular ("ringworm") eruption on the trunk or extremities
- Confluent macular erythema with serpiginous, elevated, scaly margin in intertriginous areas
- Rarely may be pustular or bullous (Fig. 3B)

Histology (Similar for All Three Entities) (Fig. 3C):
- Subcorneal pustule containing neutrophils and a few acantholytic keratinocytes
- Adjacent epidermis has spongiosis and exocytosis of neutrophils
- Dermal infiltrate of lymphocytes and neutrophils

Adjuvant Tests:
- Bacteria may be difficult to find, but cocci will stain with tissue Gram stain
- Periodic acid Schiff (PAS) or methenamine silver stains highlight candida or dermatophyte organisms

Clinicopathologic Correlation:

Clinical Feature	Pathologic Feature
Fragile small pustule	Subcorneal pustule filled with neutrophils, admixed with an occasional acantholytic cell

Differential Diagnosis:
See Table 2.

Pathophysiology:
- Trauma to or alteration of the stratum corneum allows invasion by bacteria or fungi, which in turn release cytokines and mobilize inflammatory cells.

References:

1. Brown J, Shriner DL, Schwartz RA, Janniger CK. Impetigo: an update. Int J Dermatol 2003; 42:251–255.
2. Hirschmann JV. Impetigo: etiology and therapy. Curr Clin Top Infect Dis 2004; 22:42–51.

SUBCORNEAL PUSTULAR DERMATOSIS

Synonym: Sneddon-Wilkinson disease

Clinical Presentation:
- Rare, chronic, dermatosis of unknown etiology
- Crops of small flaccid pustules occur on trunk, intertriginous areas, and flexure skin (Fig. 4A)
- Relapsing and remitting course

Table 2 Differential Diagnosis: Impetigo, Candidiasis, and Dermatophytosis

Impetigo	Candidiasis	Dermatophytosis	Subcorneal Pustular Dermatosis	Pustular Psoriasis	Acute Generalized Exanthematous Pustulosis
			Spongiform pustules may also be present	Spongiform pustules may be present adjacent to subcorneal pustule	
Gram stain often shows gram-positive cocci in pustule	Periodic acid Schiff stain shows budding yeast forms in pustule	Periodic acid Schiff stain shows septate hyphae in adjacent stratum corneum	Special stains for organisms are negative	Special stains for organisms are negative	Special stains for organisms are negative
Mixed dermal infiltrate	Mixed dermal infiltrate	Mixed dermal infiltrate; often with eosinophils		Mixed dermal infiltrate; often with eosinophils	

Table 3 Differential Diagnosis: Subcorneal Pustular Dermatosis

Subcorneal pustular dermatosis	**Pustular psoriasis**	**IgA pemphigus**	**Acute generalized exanthematous pustulosis**
Subcorneal pustule with neutrophils and an occasional eosinophil	**Spongiform pustules adjacent to the subcorneal pustule**	**Mild acantholysis**	**Scattered dyskeratotic cells may be present**
DIF: negative	**DIF: negative**	**DIF: Intercellular deposition of IgA**	**DIF: negative**

***Abbreviations*: DIF, direct immunofluorescence; PAS, periodic acid schiff.**

Histology (Fig. 4B):
- Subcorneal pustule
- Adjacent epidermis may be spongiotic
- Superficial perivascular mononuclear cell infiltrate

Special Stains:
- Stains for organisms are negative

Clinicopathologic Correlation:

Clinical Feature	Histologic Feature
Minute flaccid pustules	**Discrete subcorneal collections of neutrophils**

Differential Diagnosis:
See Table 3.

Pathophysiology:
- Etiology and pathogenesis remain unknown.

References:

1. Wilkerson A, Smoller B. The pustular disorders. Semin Cutan Med Surg 2004; 23:29–38.
2. Bonifati C, Trento E, Cordiali Fei P, Muscardin L, Amantea A, Carducci M. Early but not lasting improvement of recalcitrant subcorneal pustular dermatosis (Sneddon-Wilkinson disease) after infliximab therapy: relationships with variations in cytokine levels in suction blister fluids. Clin Exp Dermatol 2005; 30:662–665.

INTRAEPIDERMAL VESICLES

VIRAL DISEASES

Clinical Presentation:
Herpesvirus Infection:
Herpes Simplex (Fig. 5A):
- Primary infection usually occurs in childhood and may be subclinical with acute gingivostomatitis
- Recurrent lesions occur at a similar site each time, usually on the lips, face, or genitalia

Herpes Varicella-Zoster:
- Initial infection results in a generalized vesicular eruption (chickenpox)
- Recurrent infection results in an acute, self-limiting, vesicular eruption occurring in a dermatomal distribution
- Vesicles become pustular, then form crusts that may lead to scarring
- Pain, tenderness, or paresthesias precede or accompany the acute eruption

Hand-Foot-Mouth Disease (Fig. 5B):
- Small vesicles appear in the posterior portion of the mouth and are accompanied by similar lesions on the palms and soles
- Lesions last 7 to 10 days
- Infection is caused by coxsackievirus A-26

Histology:
Herpesvirus Infection (Fig. 5A):
- Unilocular or multilocular intraepidermal vesicle
- Ballooning and reticular degeneration of epidermis
- Acantholytic keratinocytes
- Multinucleate giant cells with steel-gray nuclei; margination of nuclear chromatin, and nuclear molding
- Intranuclear and eosinophilic inclusion body surrounded by a faint, clear halo
- Destruction of the basal layer may give the false impression of a subepidermal vesicle
- Perivascular infiltrate of mononuclear cells and neutrophils may extend into the deep reticular dermis
- Leukocytoclastic vasculitis may be present

Hand-Foot-Mouth Disease (Fig. 5B):
- Unilocular microvesicle
- Necrotic blister roof with dyskeratosis and acantholysis
- Reticular degeneration (intracellular and intercellular edema of keratinocytes) abruptly demarcated from the normal epidermis
- Ballooning degeneration of keratinocytes
- Destruction of the basal layer may give the false impression of a subepidermal vesicle
- Edematous upper dermis containing a polymorphous infiltrate

Immunohistochemical Stains:
- Immunohistochemical stains for herpes simplex virus are available and can be used to detect antigen in biopsy specimens.

Clinicopathologic Correlation:

Clinical Feature	Histologic Feature
Herpesvirus: small, tense clustered vesicles	**Intraepidermal acantholytic vesicle with multinucleate giant cells**
Hand-foot-mouth disease: oval pustules on extremities and in mouth	**Intraepidermal ballooning and reticular degeneration of keratinocytes**

Differential Diagnosis:

Herpesvirus	Hand-Foot-Mouth	Smallpox
Distinctive giant multinucleate cells present in epidermis and follicular epithelium	No giant multinucleate cells	No giant multinucleate cells
Intranuclear inclusion bodies	No inclusion bodies	Intracytoplasmic inclusion bodies
	Prominent reticular degeneration of epidermis	

Pathophysiology:
- *Herpes Simplex Virus*: Infection of the skin with HSV results in vesicular eruption. Viruses traverse cutaneous nerves and lie dormant in paraspinous ganglia until reactivated to produce recurrent disease.
- *Herpes Varicella Zoster*: Respiratory infection with HV virus subsequently spreads to involve the skin. Reactivation of dormant viruses produces localized HZ infection.
- *HFM*: Infection of the oropharynx or gastrointestinal tract with coxsackievirus A-16 or enterovirus 71 results in a viremia that spreads to many organs, including the skin and oral mucosa.

References:

1. Toney JF. Skin manifestation of herpesvirus infections. Curr Infect Dis Rep 2005; 7:359–364.
2. Gnann JW Jr. Varicella-Zoster virus: atypical presentations and unusual complications. J Infect Dis 2002; 186 (suppl 1): S91–S98.
3. Scott LA, Some MS. Viral exanthems. Dermatol Online J 2003; 9:4.

SUPRABASILAR VESICLES

BENIGN FAMILIAL PEMPHIGUS

Synonym: Hailey-Hailey disease

Clinical Presentation:
- Recurrent vesicles and erosions involving flexural areas, particularly the axillae, groin, inframammary folds, and neck (Fig. 6A)
- Signs may appear for the first time from late teens to the third or fourth decades
- Disease is generally of relatively limited extent; however, widespread involvement can occur

Histology (Fig. 6B):
- Hyperkeratosis
- Acanthosis
- Partial acantholysis of spinous layer of epidermis
- "dilapidated brick wall"
- Suprabasilar clefts
- Perivascular infiltrate of lymphocytes and eosinophils

Immunofluorescence Studies:
- Negative

Clinicopathologic Correlation:

Clinical Feature	Histologic Feature
Crusted plaques	Hyperkeratosis and acanthosis
Erosions	Acantholysis throughout the epidermis

Differential Diagnosis:
See Table 4.

Pathophysiology:
- Genodermatosis caused by primary defect in the calcium-pump mechanism.

References:

1. Foggia L, Hovnanian A. Calcium pump disorders of the skin. Am J Med Genet C Semin Med Genet 2004; 131C:20–31.
2. Dhitavat J, Fairclough RJ, Hovnanian A, Burge SM. Calcium pumps and keratinocytes: lesson from Darier's disease and Hailey-Hailey disease. Br J Dermatol 2004; 150:821–828.
3. Porgpermdee S, Yu X, Takagi A, Mayuzumi N, Ogawa H, Ikeda S. Expression of SPCA1 (Hailey-Hailey disease gene product) in acantholytic dermatoses. J Dermatol Sci 2005; 40:137–140.

INTRAEPIDERMAL VESICLES

SPONGIOTIC DERMATITIS

Spongiotic dermatitis is a histologic rather than a clinical diagnosis that is characterized by intraepidermal, intercellular edema (spongiosis) with or without microvesicle formation.

Table 4 Differential Diagnosis: Benign Familial Pemphigus

Benign Familial Pemphigus	Keratosis Follicularis	Pemphigus	Transient Acantholytic Disease
Thick hyperkeratosis	Acantholytic dyskeratosis; corps ronds and corps grains	Stratum corneum relatively normal	Focal hyperkeratosis
Acantholysis occurs throughout the epidermis	Acantholysis in granular layer and suprabasilar locations	Suprabasilar acantholysis	Acantholysis may occur anywhere in the epidermis but is very focal
	Dermal papillae (villi)	Prominent dermal papillae (villi)	
Superficial perivascular infiltrate	Sparse mononuclear cell infiltrate in the upper dermis	Mixed dermal infiltrate with eosinophils	
Immunofluorescence: negative	Immunofluorescence: negative	Immunofluorescence: positive	Immunofluorescence: negative

Clinical Presentation:

Eczematous Dermatitis:

Eczematous dermatitis is a general term for a pruritic rash composed of minute papules and intraepidermal vesicles. Common types of eczematous dermatitis include

- Contact dermatitis (allergic and irritant) (Fig. 7A)
  - Vesicles and juicy papules
  - Sharp margins
  - Geometric or linear configuration
  - Conforms to area of contact
- Atopic dermatitis
  - Chronic pruritic disease that begins in childhood and follows the remitting/recurrent course that may continue through life
  - Occurs in patients with the personal or family history of atopy (hay fever, asthma, dry skin, and eczema)
  - Juicy papules and vesicles; lichenified plaques
  - Head, neck, antecubital, and popliteal fossae
- Dyshidrotic dermatitis
  - Pruritic deep-seated vesicles involving lateral aspects of digits, palms, and soles
- Nummular dermatitis
  - Oval patches or plaques with crusted papules and vesicles
  - Trunk and extremities
- Eczematous drug eruption
  - Nonspecific dermatitis that is usually widespread and pruritic
- Id reaction
  - Poorly defined papular eruption that follows an acute dermatitis of the hands or feet

Vesicular Dermatophytosis:

- erythematosus, scaly patches, and plaques on the feet and in intertriginous areas

Pityriasis Rosea:

- erythematosus round to oval patches with overlying scale that is located near the border
- widespread eruption commonly preceded by solitary large lesion on trunk termed "herald patch"
- lesions on neck and trunk follows the skin lines in a pattern that has been compared to that of a Christmas tree

Seborrheic Dermatitis:

- scaling erythematosus papules and patches
- scalp, eyebrows, nose, and sternum

Stasis Dermatitis:

- pruritic erythematous and hyperpigmented papules and lichenified plaques
- lower legs

Histology:

Acute Spongiotic Dermatitis (Fig. 7B):

- Normal basket-woven stratum corneum
- Intercellular edema often with intraepidermal microvesicles
- Superficial perivascular infiltrate of lymphocytes +/− eosinophils

Subacute Spongiotic Dermatitis:

- Parakeratosis
- Mild acanthosis
- Intercellular edema
- Superficial perivascular infiltrate of lymphocytes +/− eosinophils

Special Stains:

- Vesicular dermatophytosis: PAS stain highlights septate hyphae in the stratum corneum

Clinicopathologic Correlation and Differential Diagnosis of Spongiotic Microvesicles:

	Distinguishing Clinical Features	Distinguishing Histologic Features
Allergic contact dermatitis	Pruritic vesicular eruption often in linear array	Spongiosis and spongiotic microvesicles with lymphocytes
Atopic dermatitis	Flexural surfaces	
Dyshidrotic eczema	"Tapioca pudding" vesicles on lateral fingers and toes; palms and soles may be involved	Intraepidermal vesicles and pustules on acral surfaces; special stains for organism are negative
Nummular dermatitis	Round patches and plaques; typically on the extremities	Psoriasiform hyperplasia with retention of the granular layer; variably sized microvesicles throughout the epidermis
Eczematous drug eruption	Widespread pruritic dermatitis that may resemble atopic dermatitis	Dermal infiltrate is superficial and deep; eosinophils usually (but not always) present in the infiltrate
Id reaction	Pruritic papule and vesicular eruption that may be localized or widespread; occurs in association with a localized inflammatory reaction	Spongiosis; dermal infiltrate is lymphocytes admixed with eosinophils
Vesicular dermatophyte infection	Nonpruritic vesicles on plantar surfaces of feet accompanied by toe-web maceration and diffuse scale in a moccasin distribution	Neutrophils in the stratum corneum; eosinophils in the upper dermis; fungal elements demonstrated with special stains
Inflammatory pityriasis rosea	Nonpruritic oval patches on the trunk following the skin lines	"Caps" of parakeratotic scale over epidermis with focal spongiosis; scattered dyskeratotic cells focal extravasastion of erythrocytes in papillary dermis
Stasis dermatitis	Oozing, often pruritic diffuse scaling rash on lower legs bilaterally	Hyperkeratosis, acanthosis, spongiosis, lobular hyperplasia of superficial dermal blood, extravasated erythrocytes and hemosiderin deposition, dermal fibrosis

Pathophysiology:

- *Contact Dermatitis*: Cell-mediated, delayed type IV immunologic reaction
- *Atopic Dermatitis*: Results from a complex interaction between immunologic, genetic, environmental, and pharmacologic factors.

References:

1. Beltrani VS, Beltrani VP. Contact dermatitis. Ann Allergy Asthma Immunol 1997; 78:160–173.
2. Machado-Pinto J, McCalmont TH, Golitz LE. Eosinophilic and neutrophilic spongiosis: clues to the diagnosis of immunobul-

lous diseases and other inflammatory disorders. Semin Cutan Med Surg 1996; 15:308–316.
3. Cooper KD. Atopic dermatitis: recent trends in pathogenesis and therapy. J Invest Dermatol 1994; 102:128–137.
4. Hurwitz RM, DeTrana C. The cutaneous pathology of atopic dermatitis. Am J Dermatopathol 1990; 12:544–551.

INCONTINENTIA PIGMENTI—FIRST STAGE

Synonym: Bloch-Sulzberger's disease.

Clinical Presentation (Fig. 8):
- Appears in female neonates during the first weeks
- Distinctive vesicular eruption that follows the lines of Blaschko
- Vesicular phase replaced by verrucous lesions after several weeks to months

Histology (Fig. 8):
- Spongiosis with numerous intraepidermal eosinophils
- Intraepidermal microvesicles containing eosinophils
- Dyskeratotic keratinocytes (may be extensive)
- Superficial perivascular infiltrate of eosinophils

Clinicopathologic Correlation:

Clinical Feature	Histologic Feature
Small vesicles in a linear array on the trunk and extremities	Intraepidermal spongiotic microvesicles

Differential Diagnosis of Eosinophilic Spongiosis:

	Distinguishing Clinical Findings	Distinguishing Histologic Findings
Pemphigus family	Scaling, crusted lesions with erosions	Acantholysis Positive immunofluorescence
Allergic contact dermatitis	Vesicular eruption	Spongiotic microvesicles with lymphocytes and eosinophils
Urticarial plaques, pemphigoid family	Pruritic erythematous plaques	Intraepidermal eosinophilic spongiosis
Epidermolysis bullosa acquisita	Vesicles, pustules, and scars on exposed surfaces	Mixed dermal infiltrate
Erythema neonatorum toxicum	Acute pustular eruption in neonates	Eosinophilic microvesicles
Scabies infestation	Intensely pruritic generalized papular eruption	Organisms occasionally found in the stratum corneum
Arthropod assault	Papules and vesicles on exposed surfaces	Central punctum may be present; superficial and deep dermal mixed infiltrate
Incontinentia pigmenti, first stage	Small vesicles in a linear array on the trunk and extremities	Eosinophilic microvesicles; dyskeratosis

Pathophysiology:
- Genodermatoses caused by a mutation on the X chromosome, that is, localized to Xq28; lethal in males.

References:
1. Phan TA, Wargon O, Turner AM. Incontinentia pigmenti case series: clinical spectrum of incontinentia pigmenti in 53 female patients and their relatives. Clin Exp Dermatol 2005; 30:474–480. Erratum in: Clin Exp Dermatol 2005; 30:618.
2. Hadi-Rabia S, Froievaux S, Bodak N, et al. Clinical study of 40 cases of incontinentia pigmenti. Arch Dermatol 2003; 139:1163–1170.

SUPRABASILAR VESICLES

PEMPHIGUS VULGARIS AND PEMPHIGUS VEGETANS

Clinical Presentation:
Pemphigus Vulgaris (Fig. 9A):
- Occurs in older individuals
- May be localized or generalized
- Predilection for mucous membranes, scalp, face, chest, axillae, and groin
- Flaccid bullae occur in a normal skin
- Blisters rupture easily resulting in erosions

Pemphigus Vegetans (Fig. 9B):
- Uncommon variant of pemphigus vulgaris
- Oral lesions common
- Flaccid bullae that become erosions and form on vegetating or papillomatosis proliferations
- Predilection for body folds

Histology:
Pemphigus Vulgaris (Fig. 9C):
- Early lesions may show only intraepidermal eosinophils
- Mature lesions have suprabasilar clefts and vesicles containing neutrophils and eosinophils
- Acantholysis
- Prominent dermal papillae (villi) with acantholytic basal cells (tomestones on a hill)
- Scant perivascular infiltrate of lymphocytes and eosinophils with occasional neutrophils or plasma cells

Pemphigus Vegetans:
- Changes noted earlier
- Intraepidermal eosinophilic microabscesses
- Epidermal hyperplasia (Fig. 9D)
- Perivascular papillary and upper reticular dermal infiltrate of eosinophils often admixed with mononuclear cells

Immunofluorescence Studies:
- Biopsy for direct immunofluorescence should be taken from epidermis immediately adjacent to a blister
- Immunoglobulin (IgG) and complement (C3) deposited in intercellular spaces (Fig. 9E)
- Circulating antibodies to intercellular space detected with indirect immunofluorescence (serum) studies

Clinicopathologic Correlation:

Clinical Feature	Histologic Feature
Bullae and erosions	Acantholysis
Vegetating plaques (pemphigus vegetans)	Epidermal hyperplasia

Differential Diagnosis of Disorders with Acantholysis:

	Distinguishing Clinical Features	Distinguishing Histologic Features
Pemphigus, foliaceus, and erythematosus	Superficial crusted erosions on head and trunk	Intragranular acantholysis
Pemphigus vulgaris and pemphigus vegetans	Cutaneous and mucosal bullae and erosions	Suprabasilar acantholysis
Benign familial pemphigus	Verrucous plaques in intertriginous areas	Hyperkeratosis, acanthosis, and diffuse acantholysis throughout the spinous layer of the epidermis
Keratosis follicularis	Warty hyperkeratotic papules and plaques on face, trunk, and flexural areas of the extremities	Acantholytic dyskeratosis in the upper epidermis forming corps grains and corps ronds Suprabasilar acantholysis
Transient acantholytic dermatosis	Small, pruritic crusted papules on the trunk	Focal acantholytic changes at any level of the epidermal
Herpesvirus infections	Tense vesicles, clustered (HSV) or in a dermatomal distribution (HV-Z)	Ballooned and multinucleate acantholytic keratinocytes
Impetigo	Honey-crusted lesions typically on the face and extremities	Intraepidermal pustule with scattered acantholytic keratinocytes
Subcorneal pustular dermatosis	Minute flaccid pustules	Intraepidermal pustule with a few acantholytic keratinocytes
Tumors of the epidermis (actinic keratoses, warty dyskeratoma, squamous cell carcinoma) may at times have acantholysis associated with the keratinocytic proliferation		

Abbreviation: HSV, herpes simplex virus.

Differential Diagnosis of Intraepidermal Eosinophilic Microabscesses:

	Distinguishing Clinical Features	Distinguishing Histologic Features in Addition to Eosinophilic Microabscesses
Pemphigus vegetans	Cutaneous and mucosal bullae and erosions on a verrucous or vegetating surface	Epidermal hyperplasia Suprabasilar acantholysis
Incontinentia pigmenti, first stage	Vesicular eruption that follows the lines of Blaschko	Dyskeratotic keratinocytes (may be extensive)
Halogenodermas (bromoderma and iododerma)	Papules and vesicles progress to vegetating plaques	Pseudoepitheliomatous hyperplasia

(Continued)

Differential Diagnosis of Intraepidermal Eosinophilic Microabscesses: *Continued*

	Distinguishing Clinical Features	Distinguishing Histologic Features in Addition to Eosinophilic Microabscesses
Erythema toxicum neonatorum	Macules, papules, and pustules on the trunk of a neonate	Subcorneal and intraepidermal eosinophilic pustules adjacent to hair follicles
Scabies infestation	Widespread pruritic papules and a few linear burrows	Superficial and deep perivascular infiltrate of eosinophils admixed with lymphocytes

Pathophysiology:

- *Pemphigus Vulgaris*: circulating autoantibodies attack normal proteins within the desmosome structure (desmoglein 3) that causes cell-to-cell separation

References:

1. Liu Z, Diaz LA. Immunopathological mechanisms of acantholysis in pemphigus vulgaris: an explanation by ultrastructural observations. J Invest Dermatol 2004; 122:XIII–XIV.
2. Robinson ND, Hashimoto T, Amagai M, Chan LS. The new pemphigus variants. J Am Acad Dermatol 1999; 40:649–671.

KERATOSIS FOLLICULARIS

Synonyms: Darier's disease; Darier-White disease.

Clinical Presentation (Fig. 10A):

- Rare genodermatosis with onset during adolescence or adulthood
- Warty, papular, greasy, crusted lesions that coalesce into patches and plaques
- Involve symmetrical areas of face, trunk, and flexures of the extremities
- Distinctive nail changes
- Worse in the summer

Histology (Fig. 10B):

- Hyperkeratosis and parakeratosis
- Epidermal hyperplasia
- Acantholytic dyskeratosis resulting in
  - Corps grains (within cleft and parakeratotic stratum corneum)
  - Corps ronds (granular layer and upper epidermis)
- Suprabasilar acantholysis with formation of clefts
- Irregular upward proliferation of dermal papillae to form villi
- Sparse lymphocytic superficial infiltrate

Immunofluorescence Studies:

- Negative

Clinicopathologic Correlation:

Clinical Feature	Histologic Feature
Warty, greasy surface	Hyperkeratosis
Crusted papules	Epidermal hyperplasia with suprabasilar acantholysis

Differential Diagnosis:

Keratosis Follicularis	Warty Dyskeratoma	Transient Acantholytic Dermatosis
Marked hyperkeratosis, parakeratosis	Hyperkeratosis and parakeratosis within epidermal invagination	Hyperkeratosis and parakeratosis are not prominent
Epidermal hyperplasia; suprabasilar acantholysis	Cup-shaped invagination lined by epidermis with hyperplasia and suprabasilar acantholysis	Mild, focal epidermal hyperplasia; acantholysis may occur at any level of the epidermis
Acantholytic dyskeratosis resulting in corps grains and corps ronds	Acantholytic dyskeratosis at the base of invagination	Variable acantholytic dyskeratosis

Pathophysiology:
- Genodermatosis of autosomal dominant inheritance produced by abnormalities in desmosomal adhesion between keratinocytes. ATP2A2 has been identified as the causative gene for keratosis follicularis.

References:

1. Kosann MK. Keratosis follicularis. Dermatol Online J 2003; 9:35.
2. Dhitavat J, Fairclough RJ, Hovnanian A, Burge SM. Calcium pumps and keratinocytes: lessons from Darir's disease and Hailey-Hailey disease. Br J Dermatol 2004; 150:821–828.
3. Sehgal VN, Srivasrava G. Darier's (Darier-White) disease/keratosis follicularis. Int J Dermatol 2005; 44:184–192.

TRANSIENT ACANTHOLYTIC DERMATOSIS (FIG. 11)

Synonym: Grover's disease.

Clinical Presentation:
- Pruritic, papular, and vesicular eruption typically occurring on the trunk
- More common in middle-aged and elderly individuals, particularly males
- Predominantly self-limited but may pursue a chronic course

Histology:
- Focal changes
- Mild epidermal hyperplasia
- Four patterns within the epidermis that may occur independently or intermixed:
  - Pemphigus pattern with suprabasilar acantholysis
  - Familial pemphigus pattern with partial acantholysis
  - Keratosis follicularis pattern with corps ronds and corps grains
  - Spongiotic pattern

Immunofluorescence Studies:
- Negative

Clinicopathologic Correlation:

Clinical Feature	Histologic Feature
Papules	Epidermal acanthosis
Vesicles	Acantholysis

Differential Diagnosis:
See "Differential Diagnosis" table under section "Keratosis Follicularis."

Pathophysiology:
The etiology is unknown, but excessive ultraviolet light exposure, heat, sweating, and ionizing radiation have been linked to the disease.

Reference:

1. Davis MD, Dinneen AM, Landa N, Gibson LE. Grover's disease: clinicopathologic review of 72 cases. Mayo Clin Proc 1999; 74:229–234.

INTRABASILAR VESICLES

EPIDERMOLYSIS BULLOSA SIMPLEX

Synonyms: Koebner [generalized form of epidermolysis bullosa simplex (EBS)]; Weber-Cockayne (localized form of EBS).

Clinical Presentation (Fig. 12A):
Koebner (Generalized Form of EBS):
- Occurs at birth or shortly thereafter; may improve with time
- Vesicles, bullae, and milia over the joints of the hands, elbows, knees, feet, and other sites subject to repeated trauma
- Lesions are sparse and do not lead to atrophy or severe scarring
- Worse during summer; improves during winter

Weber-Cockayne (Localized Form of EBS):
- Recurrent bullous eruption of the head and some feet
- Appears in infancy or later in life
- Worse in hot weather

Histology (Fig. 12B):
- Disruption of the basal keratinocytes leading to the appearance of a subepidermal blister
- Sparse to absent dermal infiltrate

IH, IF , Special Stains:
- Not helpful

Clinicopathologic Correlation:

Clinical Feature	Histopathologic Feature
Vesicles	Disruption of basal cells

Differential Diagnosis:

- Other forms of EB; distinction is made based on clinical presentation, immunofluorescence mapping on salt-spit skin, and electron microscopic findings.

Pathophysiology:

Autosomal dominant inheritance; EBS (Koebner) is a disease in which keratin gene mutations cause the production of defective intermediate filaments, which lead to epidermal basal cell fragility and subsequent blistering.

Reference:

1. Petronius D, Bergman R, Ben Izhak O, Leiba R, Sprecher E. A comparative study of immunohistochemistry and electron microscopy used in the diagnosis of epidermolysis bullosa. Am J Dermatopathol 2003; 25:198–203.

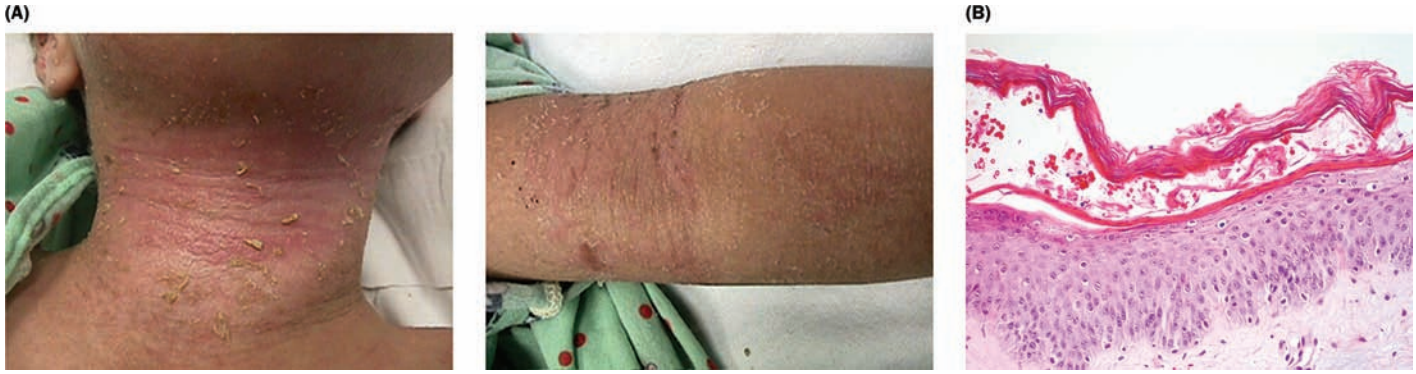


Figure 1 (**A**) Staphylococcal scalded skin syndrome (clinical). (**B**) Staphylococcal scalded skin syndrome (histological).

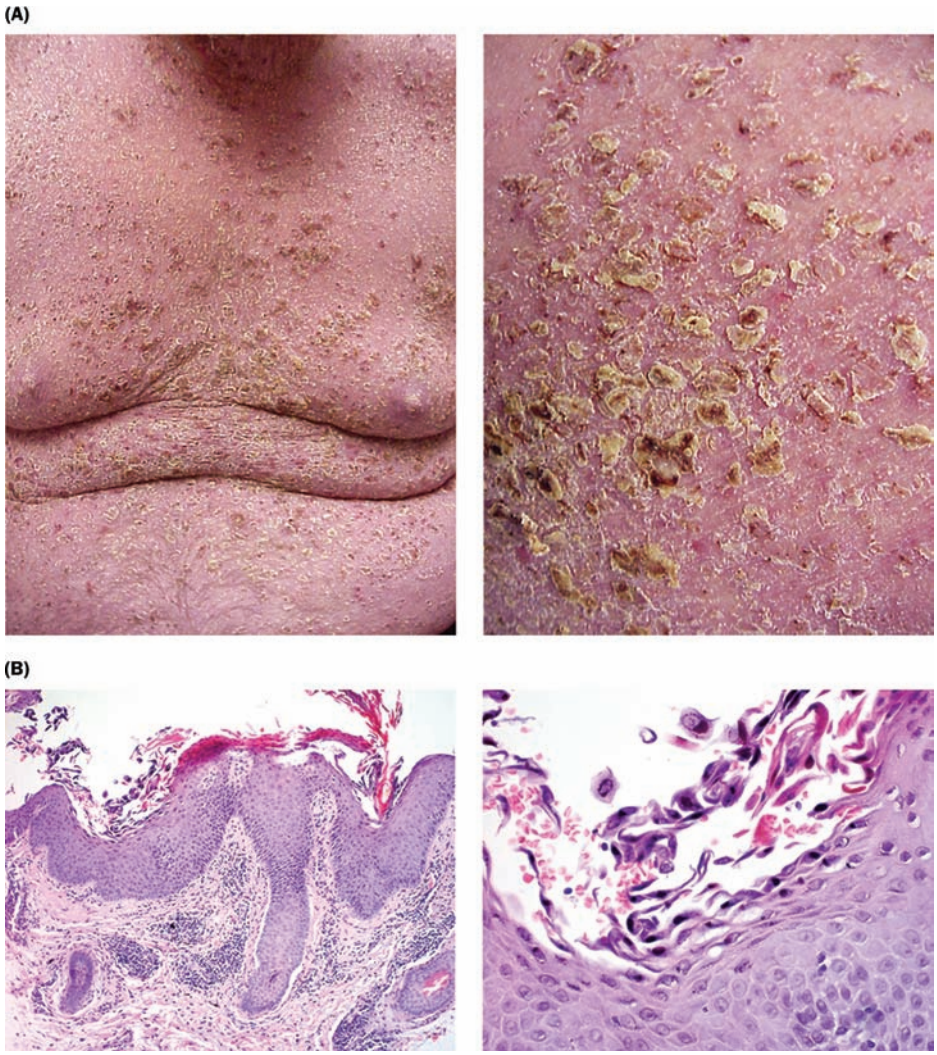


Figure 2 (**A**) Pemphigus foliaceus (clinical). (**B**) Pemphigus foliaceus; (histological) Pemphigus erythematosus.

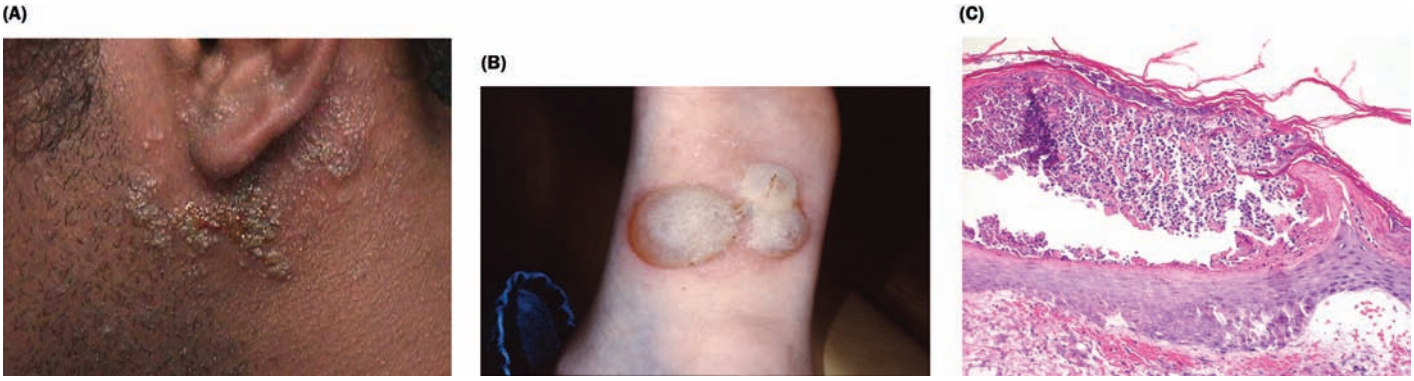


Figure 3 (**A**) Impetigo (clinical). (**B**) Dermatophytosis (clinical). (**C**) Impetigo; candidiasis; dermatophytosis (histological).

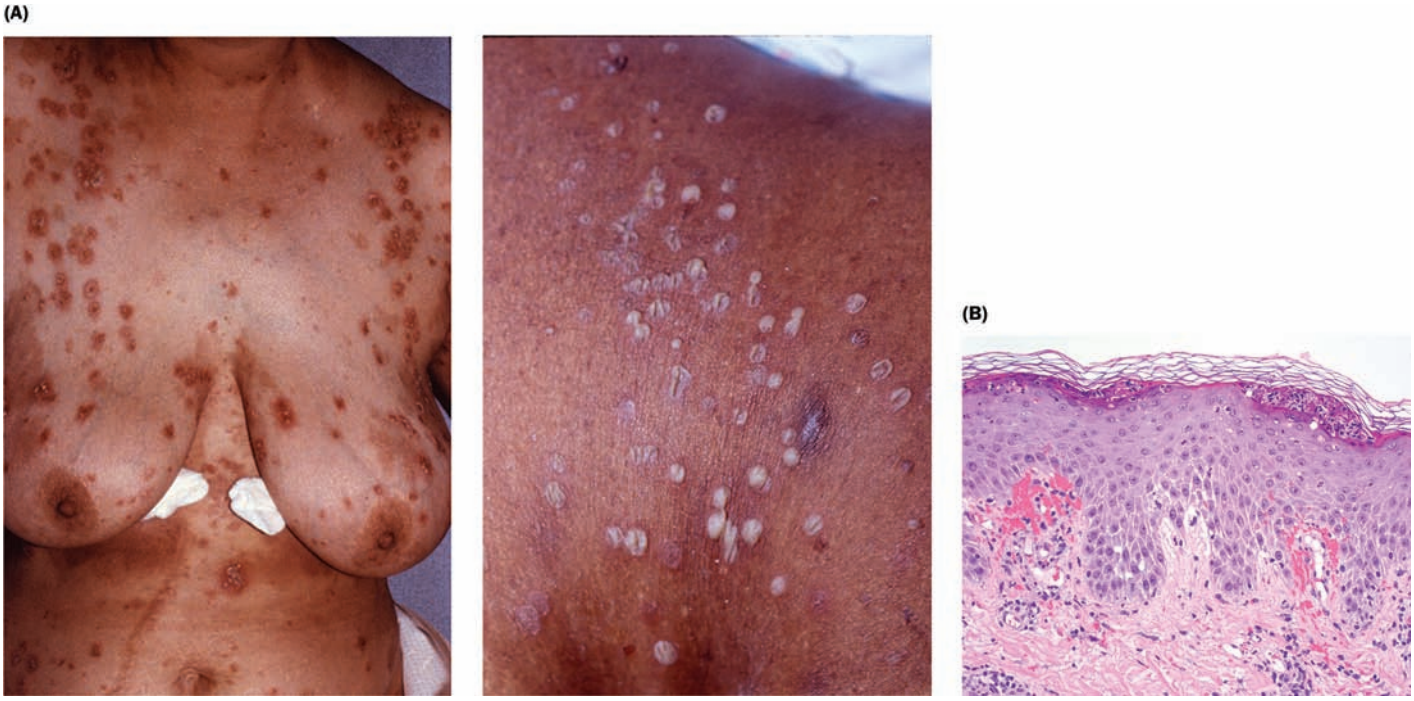


Figure 4 (**A**) Subcorneal pustular dermatosis (clinical). (**B**) Subcorneal pustular dermatosis (histological).

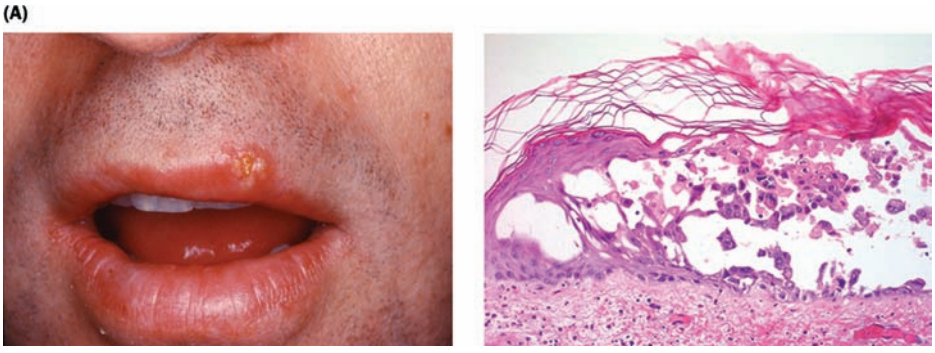


Figure 5 (**A**) Herpes simplex (clinical and histological). (**B**) Hand-foot-mouth disease (clinical and histological). (*Continued*)

(B)

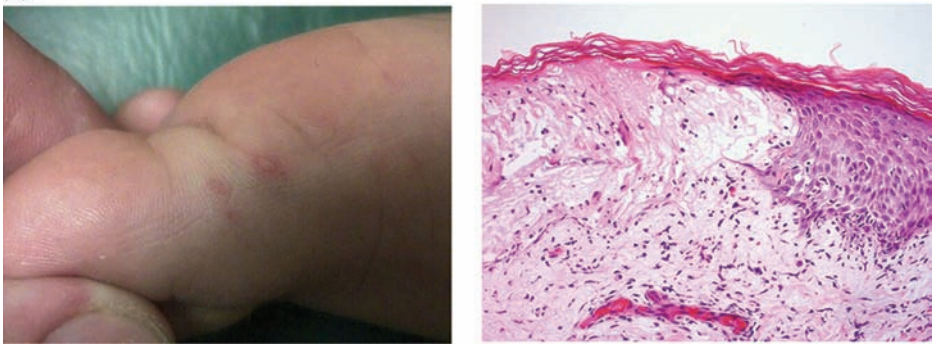


Figure 5 *Continued.*

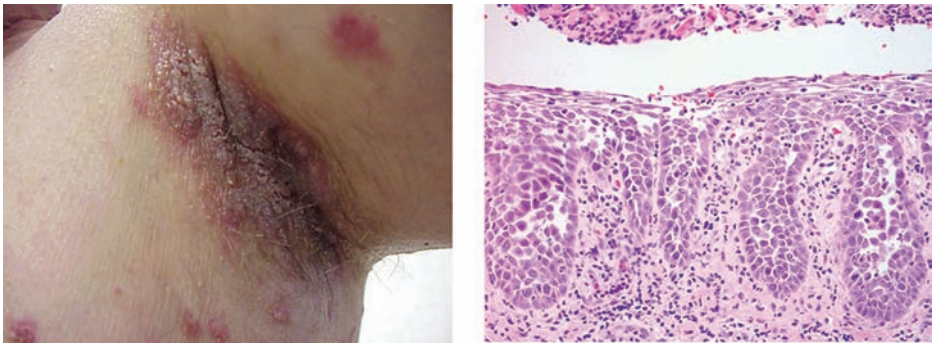
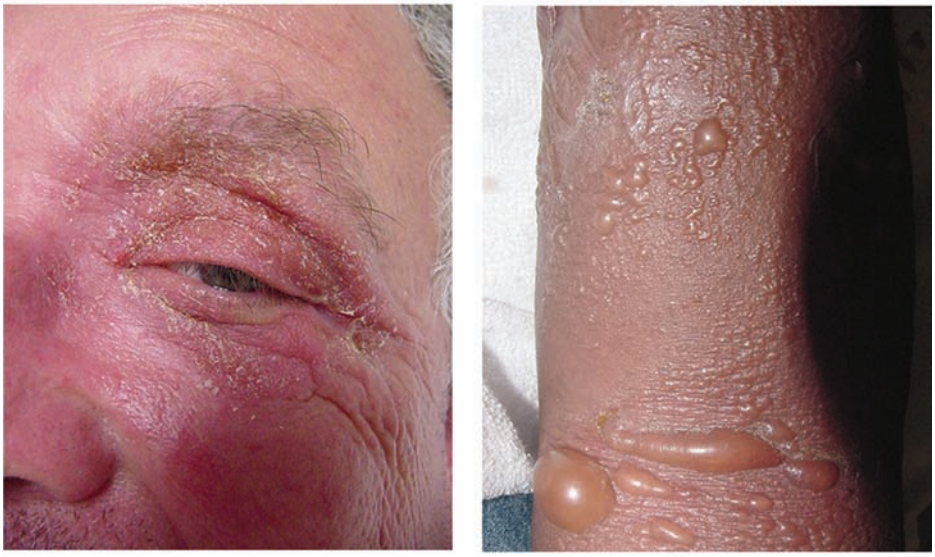


Figure 6 Benign familial pemphigus (clinical and histological).

(A)



(B)

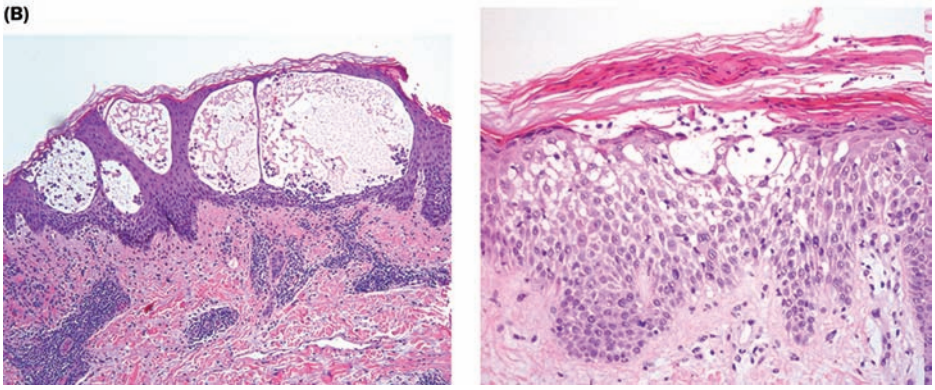


Figure 7 (**A**) Contact dermatitis (clinical). (**B**) Acute spongiotic dermatitis (histological).

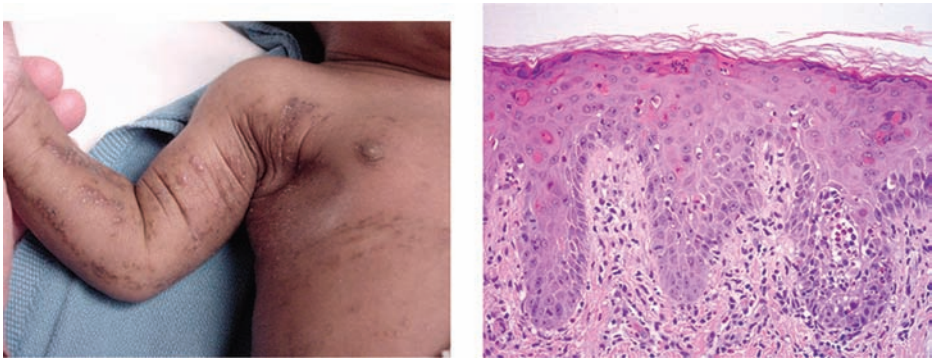


Figure 8 Incontinentia pigmenti, first stage (clinical and histological).

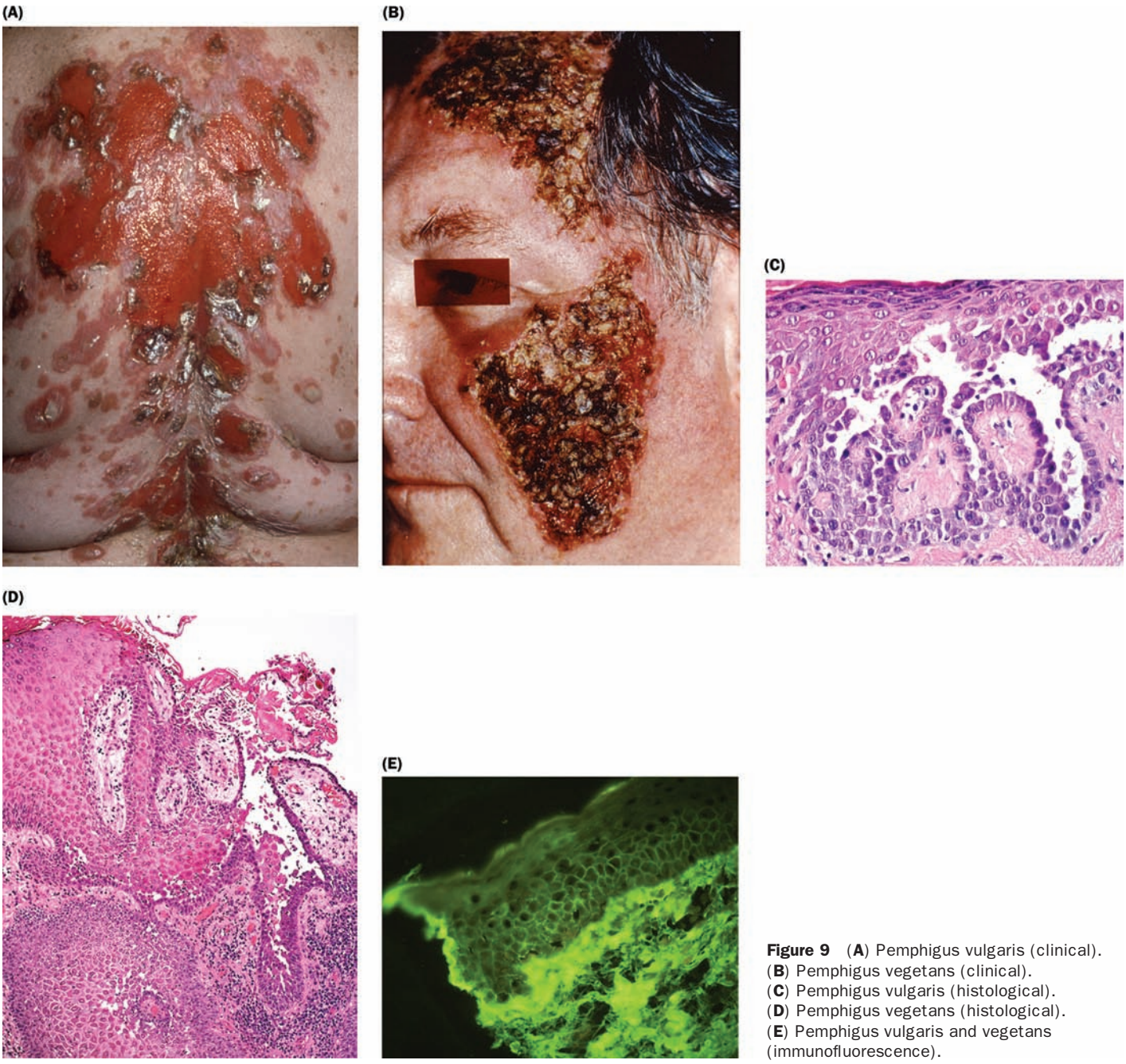


Figure 9 (**A**) Pemphigus vulgaris (clinical). (**B**) Pemphigus vegetans (clinical). (**C**) Pemphigus vulgaris (histological). (**D**) Pemphigus vegetans (histological). (**E**) Pemphigus vulgaris and vegetans (immunofluorescence).

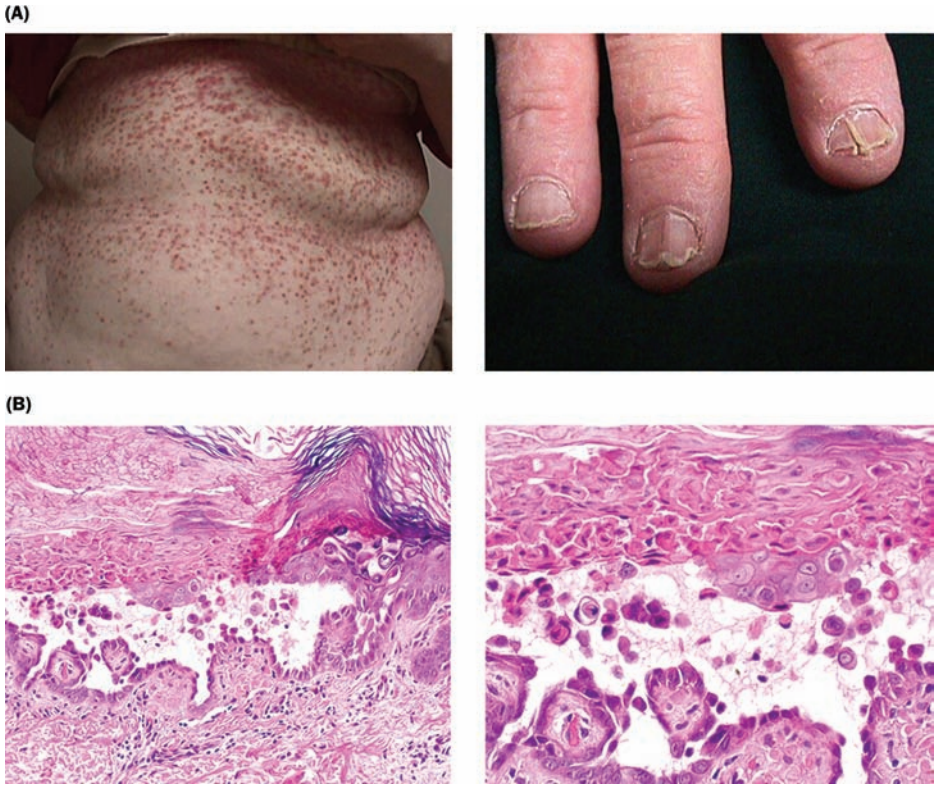


Figure 10 (**A**) Keratosis follicularis (clinical). (**B**) Keratosis follicularis (histological).

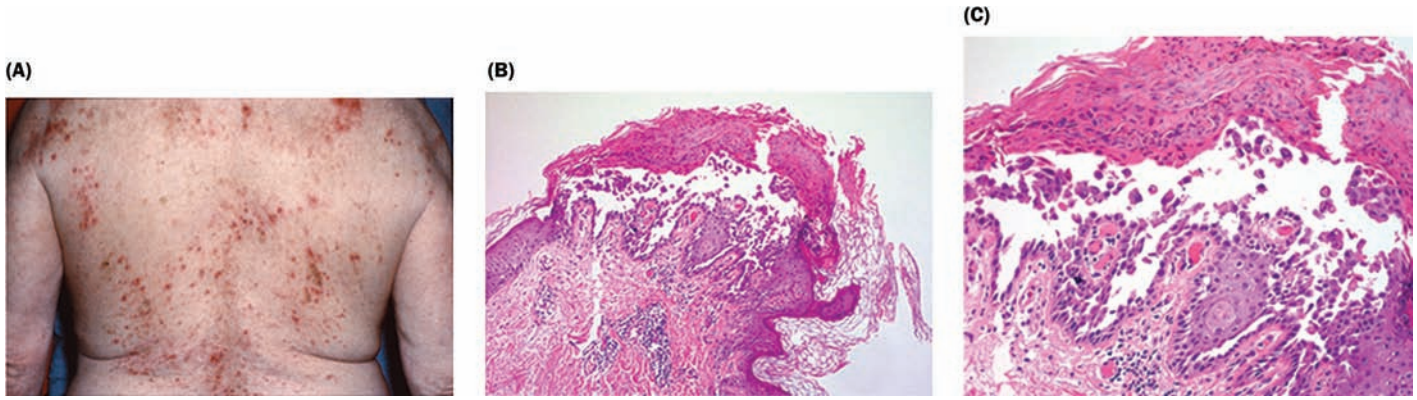


Figure 11 Transient acantholytic dermatosis (clinical and histological).

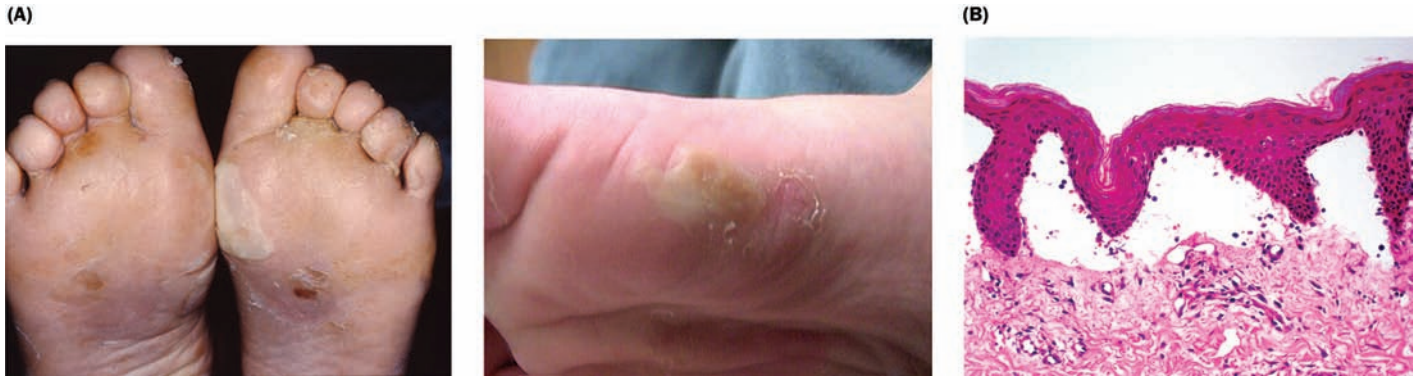


Figure 12 (**A**) Epidermolysis bullosa simplex (clinical). (**B**) Epidermolysis bullosa simplex (histological).

6

Subepidermal Vesiculobullous Dermatitis

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CONTENTS

The subepidermal vesiculobullous disorders are characterized by vesicles or bullae that are by definition located in the basement membrane zone area between the dermis and epidermis of skin or between the epithelium and submucosa of mucous membranes. There are several different ways to group the subepidermal vesiculobullous disorders. They are based on:

1. Immunologic criteria and location of bulla formation
2. Autoimmune versus nonimmunologic etiology
3. Composition of the inflammatory infiltrates and other histologic features
4. Immunofluorescence patterns and molecular studies

In all of these subepidermal vesiculobullous disorders, a final diagnosis often depends on cumulative information about clinical presentation, histological features, and immunofluorescence studies. It can be difficult to tell them apart by histological features alone.

IMMUNOLOGIC CRITERIA AND LOCATION OF BULLA FORMATION

There is a group of autoimmune disorders in which antibodies are formed to different epidermal or mucosal basement membrane components. The location of the antigens in the basement membrane determines the level of the split between epidermis and dermis and the character of the vesicle or bulla, clinically. These disorders are:

- Bullous pemphigoid (BP)
- Pemphigoid gestationis (PG)
- Mucous membrane pemphigoid (MMP)/cicatricial pemphigoid (CP)
- Dermatitis herpetiformis (DH)
- Linear IgA bullous disease (LABD)
- Chronic bullous disease of childhood (CBDC)
- Bullous lupus erythematosus (BLE)
- Epidermolysis bullosa acquisita (EBA)

Characterization of the antigenic molecules of the basement membrane zone in these disorders using patient sera has allowed investigators to generate an elegant diagram of the epidermal and mucosal basement membrane molecular structure (Fig. 1).

AUTOIMMUNE VS. NONIMMUNOLOGIC ETIOLOGY

AUTOIMMUNE

The autoimmune blistering diseases are listed above.

NONIMMUNOLOGIC

The subepidermal vesiculobullous disorders that have no immunologic basis include the hereditary mechanobullous disorders in which a mutation in a keratin or an epidermal basement membrane structural component allows easy blister formation. These are:

- Hereditary epidermolysis bullosa (EB) (simplex, junctional, and dystrophic)—EB simplex has intraepidermal blisters rather than subepidermal blisters, but it is included here for completeness.

There are also systemic metabolic disorders in which acquired alterations in the basement membrane molecules of epidermis and nearby vessels allow easy injury and blister formation. They are:

- Porphyria and pseudoporphyria
- Bullous drug eruption

Blisters can also form due to severe external injury to otherwise normal epidermis. These are:

- Friction bulla
- Thermal injury

The blisters due to the metabolic disorders and severe injury can be intraepidermal as well as subepidermal, a histologic clue to their diagnosis.

COMPOSITION OF THE INFLAMMATORY INFILTRATES AND OTHER HISTOLOGIC FEATURES

Histologic features are also used to classify the subepidermal vesiculobullous disorders. They can be identified by the presence of:

- Eosinophils (BP, PG)
- Eosinophils and neutrophils (EBA, MMP)
- Neutrophils (BLE, LABD, DH)
- Nonspecific infiltrates (bullous drug, porphyrias)
- Vessel injury (EBA)
- Very little inflammation (porphyrias, hereditary bullous disorders, and external injury)

IMMUNOFLUORESCENCE PATTERNS AND MOLECULAR STUDIES

Immunofluorescence (IF) pattern studies are very helpful in grouping the immunologic disorders. They can also be used to map the location of the dermal–epidermal split in the hereditary bullous disorders. A diagram and description of each method commonly used for skin disorders is shown in Figure 2.

- Direct immunofluorescence (DIF) (Fig. 2A)
- Indirect immunofluorescence (IIF) (Fig. 2B)
- IIF utilizing salt-split skin (SSS) (Fig. 2C)
- Immunoblotting (IB) to determine molecular weight of antigens

SUBEPIDERMAL VESICULOBULLOUS DISORDERS

BULLOUS PEMPHIGOID

Clinical:

Bullous pemphigoid is an acquired blistering disease of the elderly, usually over the age of 60. Multiple medications have been reported to induce bullous pemphigoid, however, only furosemide has been convincingly implicated. Tense bullae form on flexor arms and legs, abdomen, and groin that heal without scarring. In urticarial BP, there are erythematous edematous plaques without overt blisters that resemble urticaria and sometimes eczema (Fig. 3A).

Histology:

- Subepidermal bulla forms a "clean split" of epidermis from dermis (Figs. 3B–D)
- Blister roof smooth, not ragged (Fig. 3D)
- Usually no injury to epidermis (no apoptotic keratinocytes)
- Eosinophils usually the predominant cells within the blister cavity and in dermis
- Eosinophils along the basement membrane zone—the key to the diagnosis (Figs. 3C and E)
- Eosinophilic spongiosis (eosinophils in the epidermis), occasionally
- In urticarial bullous pemphigoid, no blister seen, but eosinophils tag the basal layer of keratinocytes of spongiotic epidermis (Fig. 3E) and the papillary dermis is edematous

Differential Diagnosis:

Mucous membrane pemphigoid; pemphigoid gestationis; epidermolysis bullosa acquisita

Immunofluorescence:

- *DIF*: linear IgG and third component of complement (C_3) at the basement membrane zone of perilesional skin (Fig. 3F). IgG4 predominates.
- *IIF*: circulating antibodies to the basement membrane zone of human skin or monkey esophagus in about 70% of patients with bullous pemphigoid
- *IIF-SSS*: immunoreactants localized to the epidermal side (roof) of the blister in 90% of patients (Fig. 3G)

Antigens:

- Hemidesmosomal proteins BPAg1 (230 kDa) and BPAg2 (180 kDa, which is also known as collagen XVII)

Pathophysiology:

IgG antibodies bind to BP antigens and activate C_3 and inflammatory mediators. Eotaxin, a chemokine, may recruit eosinophils to the basement membrane zone. Inflammatory cells release proteases at the basement membrane zone, and hemidesmosomal proteins are degraded, leading to blister formation.

Clinicopathologic Correlation:

Clinical Feature	Pathologic Feature
No scale	No epidermal changes; stratum corneum usually normal
Tense blister	Split between epidermis and dermis in the lamina lucida
Urticarial plaque	Dermal edema

Classification Variants, Mutations, and Other:

- Chronic localized scarring pemphigoid (Brunsting-Perry) is limited to skin (no mucous membranes) and is sometimes classified with mucous membrane pemphigoid
- Other variants include vesicular, vegetative, erythrodermic, urticarial, and nodular
- Individuals with BP can have oral lesions (up to 1/3 of patients) and the distinction between BP with oral involvement and mucous membrane pemphigoid is often a clinical one
- A new ELISA for BPAg2 is very sensitive and can be helpful in diagnosis of difficult cases

PEMPHIGOID GESTATIONIS

Synonym: Herpes gestationis.

Clinical:

- PG is a blistering disorder of young women during late pregnancy (last trimester) or in the early postpartum period. It can be exacerbated by oral contraceptives and by repeat pregnancy with same partner
- PG is characterized clinically by urticarial plaques or wheals that evolve to vesicles and bullae (Fig. 4A). The eruption begins in the periumbilical area. About 5% of neonates born to mothers with pemphigoid gestationis may develop transient blisters.

Histology (Figs. 4C and D):

- Subepidermal blister with eosinophils; can resemble bullous pemphigoid

- Necrotic basal keratinocytes occasionally (not seen in bullous pemphigoid)
- Usually more subtle than bullous pemphigoid

Differential Diagnosis:
Bullous pemphigoid; mucous membrane pemphigoid; EBA

Immunofluorescence:
- *DIF*: C_3 at the basement membrane zone (Fig. 4B)
- *IIF*: Routine IIF usually negative. However, a special complement fixing IIF study is usually positive

Antigens:
Hemidesmosomal protein 180 kDa BPAg2. Placenta may be the source of antigens.

Pathophysiology:
Similar to bullous pemphigoid

Clinicopathological Correlation:
Similar to bullous pemphigoid (refer to the Clinicopathologic Correlation table, under the section "Bullous Pemphigoid").

Classification Variants, Mutations, and Other:
- There is a high association with HLA-B8 and DR3, DR4 haplotypes.
- There is a higher incidence of other autoimmune diseases (Hashimoto's, Graves, pernicious anemia) in individuals with pemphigoid gestationis.

MUCOUS MEMBRANE PEMPHIGOID/CICATRICIAL PEMPHIGOID

Clinical:
- Mucous membrane pemphigoid is a chronic blistering and scarring disorder involving mucosa, typically of elderly patients. Oral involvement is seen in 80%, ocular in 70%, and skin involvement in 20%. The oropharynx and nasopharynx are most commonly involved.
- Eroded mucosal lesions are seen early, scarring is seen later (Fig. 5A). Eye involvement leads to symblepheron, where the scarred conjunctivae fuse together (Fig. 5B).

Histology (Figs. 5C–F):
- Mucosal–submucosal separation with submucosal fibrosis (Figs. 5C and D)
- Blisters are uncommon, more typically, denuded submucosa and a strip of epithelium are present because the blister roof is sloughed (Fig. 5D)
- Like BP, smooth not ragged blister roof
- Submucosal infiltrates of lymphocytes, histiocytes, plasma cells, eosinophils, and neutrophils (Figs. 5E and F)
- Neutrophils predominate over eosinophils compared with bullous pemphigoid

Differential Diagnosis:
- Bullous pemphigoid with mucosal involvement

Immunofluorescence:
- *DIF*: linear IgG and/or IgA and C_3 at the epidermal basement membrane zone (Fig. 5G)
- *IIF*: low titer IgG and IgA antibodies that bind to the basement membrane zone
- *IIF-SSS*: most patients have immunoreactants on the epidermal side of the salt-split skin (Fig. 5H); patients with antibodies to laminin have immunoreactants on the dermal side (base) of the salt-split skin.

Antigens:
Mucous membrane pemphigoid is a complex disease phenotype. Immunoreactants include:
- Pure ocular with antibodies to β4 integrin
- Mucous membrane and skin with antibodies to BP180
- Antibodies to laminin 5 (epiligrin) and laminin 6

Pathophysiology:
- Similar to bullous pemphigoid

Clinicopathologic Correlation:

Clinical Feature	Pathologic Feature
Scarring	Immune cells making TGF-beta
Multiple variants (ocular, mucosal, cutaneous)	Different antigens
Mucosal or ocular localization	Different antigens

***Abbreviation*: TGF, transforming growth factor.**

Classification Variants, Mutations, and Other:
- Patients with antibodies to laminin may have increased risk of an underlying solid neoplasm

DERMATITIS HERPETIFORMIS

Synonym: Duhring's disease.

Clinical:
- Dermatitis herpetiformis is characterized by a symmetric extremely pruritic papulovesicular eruption on the extensor extremities (Fig. 6A).
- A diffuse "herpetiform" distribution of lesions that are preceded by stinging sensation can also be seen (Fig. 6B). The mean age of patients is 40.
- Dermatitis herpetiformis is associated with gluten-sensitive enteropathy in up to 90% of patients, but most patients are asymptomatic.

Histology (Figs. 6D and E):
- Infiltration of the papillary tips with neutrophils (microabscesses), diagnostic of dermatitis herpetiformis

Differential Diagnosis:
Bullous lupus erythematosus; linear IgA bullous disease. A rare variant of vasculitis, pustular vasculitis, has not only papillary dermal pustules, but also vasculitis involving the papillary dermal vessels.

Immunofluorescence:
- *DIF*: granular IgA in papillary tips on perilesional skin of dermatitis herpetiformis (Fig. 6C)
- *IIF*: circulating IgA antibodies to papillary tip immunoreactants not seen

Antigens:
- Circulating antibodies to endomysium of smooth muscle, gliadin, and thyroid microsomal proteins are present, but are probably not directly pathogenic.

Pathophysiology:
- IgA deposits in skin promote neutrophil recruitment to basement membrane zone, where proteases are released and degrade the basement membrane zone proteins, leading to blister formation.

Clinicopathologic Correlation:

Clinical Feature	Pathologic Feature
Location on extensor elbows, knees	Exposed areas likely to be traumatized
Excoriations	Areas of epidermal necrosis
Small vesicles	Inflammation localized to papillary tips

Classification Variants, Mutations, and Other:
- HLA A1/B8/DR3, DQ2 common (95–100%) in dermatitis herpetiformis
- Increased incidence of GI lymphoma and non Hodgkin lymphoma
- Hypochlorohydria and atrophic gastritis (antiparietal cell antibodies); pernicious anemia associations
- Other associations: thyroid disease (thyroid microsomal antibodies) and other autoimmune diseases (dermatomyositis, myasthenia gravis, rheumatoid arthritis, and lupus erythematosus)

LINEAR IGA BULLOUS DISEASE AND CHRONIC BULLOUS DISEASE OF CHILDHOOD

This is the same disease in different age groups.

Clinical:
Linear IgA bullous disease is an acquired autoimmune blistering disease that may be idiopathic or drug induced. In children the disease is referred to as chronic bullous disease of childhood. Cutaneous lesions of linear IgA bullous disease (LABD) are usually nonscarring blisters, often extensive on trunk and extremities. They are characterized by the "cluster of jewels" sign, with vesicles and bullae at edges of polycylic lesions (Fig. 7A). Linear IgA bullous disease resembles dermatitis herpetiformis or bullous pemphigoid, but is usually not symmetric. Patients with LABD may occasionally have ocular involvement that can be indistinguishable from mucous membrane pemphigoid. Chronic bullous disease of childhood has a predilection for vesicles and blisters in the diaper area.

Histology:
Linear IgA bullous disease and chronic bullous disease of childhood are similar (Figs. 7C–F).
- Subepidermal bullae with eosinophil or neutrophil predominance (Fig. 7C)
- Neutrophils lined up along the basement membrane zone—the best clue (Figs. 7D and E)
- Neutrophilic microabscesses like dermatitis herpetiformis can be present (Figs. 7C and F)
- Effacement of the epidermal architecture

Differential Diagnosis:
- Bullous lupus erythematosus; bullous pemphigoid; dermatitis herpetiformis

Immunofluorescence:
- *DIF*: linear IgA at the basement membrane zone (Fig. 7B)
- *IIF*: circulating IgA antibodies that bind to monkey esophagus in 30% to 50% of patients
- *IIF-SSS*: most circulating antibodies bind to the epidermal side of the split, but some bind to the dermal side, suggesting complex antigens

Antigen:
Ladinin (LAD-1, now known to be an epitope of BPAg2). Some patients have antibodies to collagen VII.

Pathophysiology:
Antibody deposits lead to complement activation and neutrophil accumulation at the basement membrane zone. Release of proteases by neutrophils and degradation of basement membrane proteins produces blister.

Clinicopathologic Correlation:

Clinical Feature	Pathologic Feature
Vesicles and bullae on polycyclic lesions	Neutrophils at the DEJ
Nonscarring	Split in lamina lucida area

***Abbreviation*: DEJ, dermal-epidermal junction.**

Classification Variants, Mutations, and Other:
- Vancomycin the best-documented causative drug
- Preceding infection and hematopoietic malignancy also associated with linear IgA bullous dermatosis

BULLOUS LUPUS ERYTHEMATOSUS

Clinical:
Bullous lupus erythematosus is characterized by widespread or localized nonscarring vesiculobullous eruption on the upper trunk, face, scalp, and/or extremities (Fig. 8A). The blistering is usually self-limiting and typically occurs in a patient with a flare of known systemic lupus erythematosus.

Histology (Figs. 8B and D):
- Linear neutrophilic interface dermatitis
- Sometimes papillary microabscesses of neutrophils as in dermatitis herpetiformis
- Neutrophilic dust and extension of infiltrates into papillary dermis (not seen in dermatitis herpetiformis or in linear IgA bullous disease)

Differential Diagnosis:
- Dermatitis herpetiformis; linear IgA bullous disease

Immunofluorescence:
- *DIF*: always IgG, usually IgA, and sometimes IgM and C along the basement membrane zone in granular (60%), linear (40%), and sometimes mixed patterns
- *IIF*: circulating antibodies not usually seen when utilizing monkey esophagus epithelium
- *IIF-SSS*: immunoreactants that bind to the dermal side of the split

***Antigen*:**
- Collagen VII; same as EBA

Pathophysiology:
Autoantibodies to the noncollagenous domain of collagen type VII attract neutrophils, which release proteases and cause disruption of the basement membrane zone. Blister formation is below the lamina lucida because of the location of collagen VII.

Clinicopathologic Correlation:

Clinical Feature	Pathologic Feature
Localization on extremities	Sun-exposed areas
Small fragile blisters	Sparse infiltrates of neutrophils along the BMZ

***Abbreviation*: BMZ, basement membrane zone.**

Classification Variants, Mutations, and Other:
- Patients with systemic lupus erythematosus that develop bullous lupus have a high incidence of HLA-DR2.

EPIDERMOLYSIS BULLOSA ACQUISITA

Clinical:
There are three types of EBA characterized by:
- Acral blisters that heal with milia and scarring (chronic noninflammatory mechanobullous disease) (Fig. 9A)
- Widespread vesiculobullous disease like BP (inflammatory)
- Scarring oral lesions in 30% to 50%. Many of these reclassified with mucous membrane pemphigoid

Histology:
- Subepidermal blister (Fig. 9B)
- Mixed infiltrates of lymphocytes, many neutrophils and eosinophils at the basement membrane zone (Figs. 9C and D)
- Fibrin and mixed inflammatory cells (neutrophils, eosinophils) in the lumen of bulla (Fig. 9D)

Differential Diagnosis:
- Bullous lupus erythematosus; bullous pemphigoid; antiepiligrin mucous membrane pemphigoid

Immunofluorescence:
- *DIF*: linear IgG (100%) and C′(50%) at the basement membrane zone (Fig. 9E)
- *IIF*: circulating antibodies that bind to the basement membrane zone in 50% of individuals
- *IIF-SSS*: immunoreactants that bind to dermal side of dermal–epidermal split (Fig. 9F)

Antigens:
- The noncollagenous domains (NC1 and NC2) of collagen VII—a component of anchoring fibrils

Pathophysiology:
Antibodies to collagen may destabilize collagen fibers, and combined with trauma could contribute to blistering.

Clinicopathologic Correlation:

Clinical Feature	Pathologic Feature
Scarring vs. nonscarring variants	Different antigens
Exposed areas likely to be traumatized	Location of scarring on extremities

Classification Variants, Mutations, and Other:
- A subset of patients with milder disease has antibodies to the collagenous domain of Type VII collagen.
- There is a strong association with inflammatory bowel disease (Crohn disease), other autoimmune diseases, and HLA-DR2 in blacks.

JUNCTIONAL EPIDERMOLYSIS BULLOSA

Clinical:
Junctional EB (JEB) is a rare nonscarring mechanobullous disease due to heterogeneous autosomal recessive mutations in basement membrane zone proteins. There are six clinical variants with variable clinical expression depending on the mutation.

Histology:
Depends on the variant form and severity of the mutation
- Pauci-inflammatory subepidermal bulla (Fig. 10B)
- Split between epidermis and dermis is above the lamina densa in the lamina lucida

Immunofluorescence:
There is no immunologic basis for hereditary JEB. However, the location of the split can be mapped with antibodies to known basement membrane zone antigens, helping to distinguish junctional EB from EB simplex or dystrophic EB (see later).

Pathophysiology:
Mutations in structural molecules in the lamina lucida cause the basement membrane zone to be easily damaged by friction, leading to a blister after trauma.

Clinicopathologic Correlation:

Clinical Feature	Pathologic Feature
Hereditary mechanobullous	Pauci-inflammatory
Nonscarring	Split in lamina lucida
Variable severity	Different molecular defects due to different mutations

Classification Variants, Mutations, and Other:

- Mutations in laminin 5, BPAG 180, α6 integrin, β4 integrin laminin have been identified.
- The clinical subvariants reflect the different phenotypes generated by these different mutations.
- Lethal JEB (Herlitz type) is due to a severe defect or absence of laminin 5.
- Nonlethal JEB (mitis) is due to less severe mutations in several genes.
- Generalized atrophic benign epidermolysis bullosa is often due to missense mutations in laminin 5.
- More than half of JEB cases have one or two recurrent nonsense mutations in the *LAMB3* gene, useful for mutation analysis and prenatal testing.

DYSTROPHIC EPIDERMOLYSIS BULLOSA (AUTOSOMAL DOMINANT AND RECESSIVE)

Clinical:

Dystrophic epidermolysis bullosa (DEB) is an inherited mechanobullous disorder. The clinical subvariants reflect the different phenotypes generated by several different mutations. Dominant inherited DEB is milder (Figs. 11A and B). Recessive inherited DEB (Hallopeau-Siemens) is usually severe, causing loss of digits in a chronic scarring and disfiguring disease (Fig. 11C). Aggressive squamous cell carcinomas develop in areas of chronic erosions in patients with recessive dystrophic EB who survive childhood.

Histology:

Both types of dystrophic EB are similar, but vary in degree of scarring

- Pauci-inflammatory subepidermal bulla (Fig. 11D)
- Split between epidermis and dermis is below the lamina densa
- Little scarring in autosomal dominant form
- Prominent scarring in autosomal recessive form (Figs. 11D and E)
- Invasive squamous cell carcinomas can develop in the autosomal recessive form (Fig. 11F)

Immunofluorescence:

There is no immunologic basis for dystrophic EB, but the location of the split can be mapped by immunologic methods.

Pathophysiology:

Mutations in structural proteins of the anchoring fibril result in a blister that forms below the lamina densa after trauma.

Clinicopathologic Correlation:

Clinical Feature	Pathologic Feature
Hereditary mechanobullous	Pauci-inflammatory
Scarring vs. nonscarring	Location of the dermal-epidermal split within or below lamina lucida and severity of the mutations

Classification Variants, Mutations, and Other:

- Anchoring fibrils are diminished (autosomal dominant) or absent (autosomal recessive) due to mutations in collagen VIIA

PORPHYRIA AND PSEUDOPORPHYRIA

Clinical:

- Porphyria is a photo-induced bullous disease due to circulating porphyrins that are endogenous phototoxic agents. Porphyria cutanea tarda is the most common form seen by dermatologists. Dyspigmentation and skin fragility with bullae, scarring, and milia in sun-exposed areas are seen (Fig. 12A). Hands and face are commonly involved. Increased facial hair growth can be present (Fig. 12B). Porphyrin studies are abnormal.
- Pseudoporphyria is similar to porphyria, but the mechanism of blistering is unknown.
- Pseudoporphyria can be triggered by drugs (naprosyn, ibuprofen) and by chronic renal failure in an individual on dialysis. Porphyrin studies are usually normal.

Histology:

Porphyria:

- Pauci-inflammatory subepidermal bulla with variable neutrophils, depending on the degree of necrosis (Fig. 12C)
- "Festooning" with preservation of dermal papillae on the floor of the blister, another diagnostic feature (Figs. 12C and D)
- Dramatic homogeneous eosinophilic PAS+ deposits around thickened elongated papillary dermal vessels—a diagnostic feature (Figs. 12D and E)
- "Caterpillar bodies" (rows of dead keratinocytes in the epidermis) less often seen

Pseudoporphyria:

- Like porphyria, but characteristic features "downgraded"
- Less festooning
- Less prominent PAS+ deposits around vessels

Immunofluorescence:

- *DIF*: mantle of Ig deposits (all classes) around vessels and at basement membrane zone in both porphyria and pseudoporphyria, due to nonspecific "sticking", not autoimmune basis (Fig. 12F). Granular C5b-9 in vessel walls
- *IIF*: no circulating antibodies

Pathophysiology:

Porphyrias are photoactive molecules that absorb in the visible violet light spectrum, and mediate oxidative damage to molecules in the skin. Basement membranes of epidermis and superficial vessels are targets producing lesions in sun-exposed skin.

Clinicopathologic Correlation:

Clinical Feature	Pathologic Feature
Photoproduct damage to basement membrane zones and keratinocytes explains localization on sun-exposed acral skin	Thickened basement membranes of epidermis and vessels leads to "festooning"
	Damage to keratinocytes leads to caterpillar bodies (necrotic keratinocytes)
Chronic injury to epidermis and dermis	Scarring and milia

Classification Variants, Mutations, and Other:

- Porphyria cutanea tarda (PCT) can be familial or sporadic. In both, exposure to environmental factors can trigger disease.
- Patients with PCT may have predisposing mutation in hemachromatosis (HCT) gene.
- Polyhalogenated aromatic hydrocarbons can cause "epidemic" toxic porphyria.
- Hepatitis C virus is a common precipitating factor for PCT.

BULLOUS DRUG ERUPTION

Clinical:

Uncommon severe reaction to drug/medication

Histology:

- Cytotoxic dermatitis with damage to basal keratinocytes leading to bulla (Fig. 13A and B)
- "Ragged split" at DEJ (Fig. 13B)
- Apoptotic keratinocytes in epidermis (Fig. 13A)
- Eosinophils in perivascular dermal infiltrates—good clue to drug eruption

Immunofluorescence:

- *IF*: negative, not usually done

Pathophysiology:

Cytokines and chemokines released in hypersensitivity reaction lead to inflammatory cell influx. Injury to epidermal keratinocytes occurs directly via cytotoxic T cells and indirectly via secreted cytokines such as TNF-α.

Clinicopathologic Correlation:

Clinical Feature	Pathologic Feature
Intraepidermal and subepidermal vesicles and bullae	Injury to keratinocytes causes blister and apoptotic keratinocytes in mid-spinous layer of epidermis
Drug-induced Type IV hypersensitivity	Perivascular lymphocytic infiltrates with eosinophils

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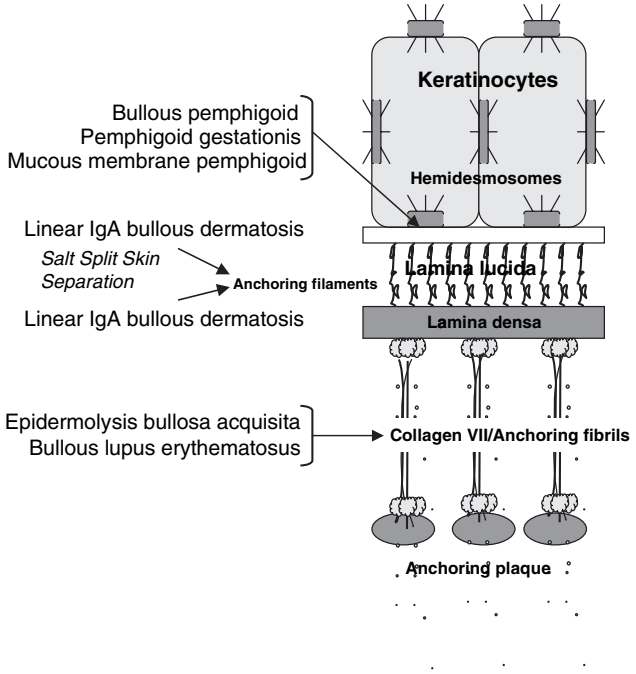

Figure 1 Schematic of the basement membrane zone antigens recognized by autoantibodies in the immune-mediated subepidermal vesiculobullous disorders. Salt split skin separation occurs in the lamina lucida, where anchoring filaments are found. Hemidesmosomes are the target antigens in bullous pemphigoid, pemphigoid gestationis, and mucous membrane pemphigoid. Mucous membrane pemphigoid is heterogeneous with most individuals having immunoreactants on the epidermal side of the blister while occasional patients have immunoreactants on the dermal side of the blister. Linear IgA bullous disease antibodies are complex and bind a variety of antigens above and below the lamina lucida. Collagen VII/anchoring fibrils are the target antigens of epidermolysis bullosa acquisita and bullous lupus erythematosus.

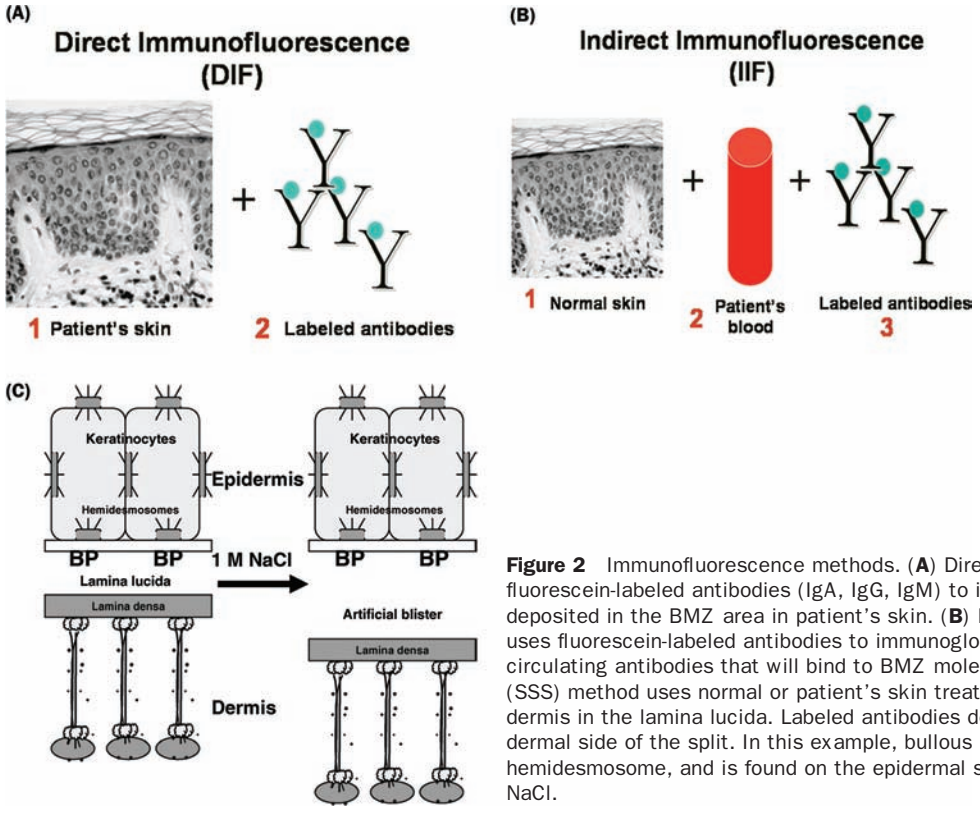

Figure 2 Immunofluorescence methods. (**A**) Direct immunofluorescence (DIF) method uses fluorescein-labeled antibodies (IgA, IgG, IgM) to immunoglobulins or complement that is deposited in the BMZ area in patient's skin. (**B**) Indirect immunofluorescence (IIF) method uses fluorescein-labeled antibodies to immunoglobulins to test if patient's blood contains circulating antibodies that will bind to BMZ molecules in normal skin. (**C**) Salt split skin (SSS) method uses normal or patient's skin treated with 1 M NaCl to separate epidermis and dermis in the lamina lucida. Labeled antibodies determine if antigens are on the epidermal or dermal side of the split. In this example, bullous pemphigoid antigen (BP) is part of the hemidesmosome, and is found on the epidermal side of the artificial blister induced by 1 M NaCl.

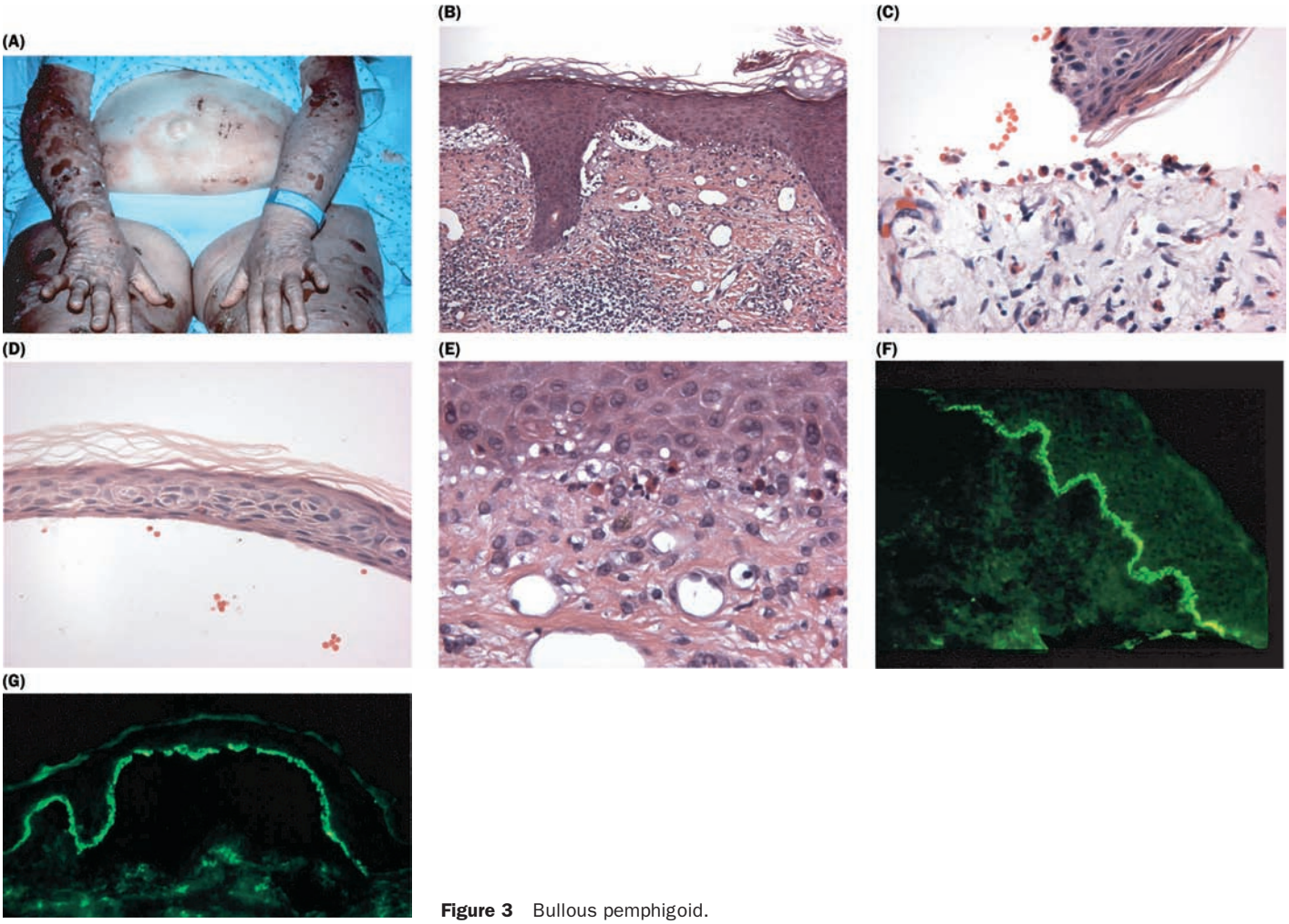

Figure 3 Bullous pemphigoid.

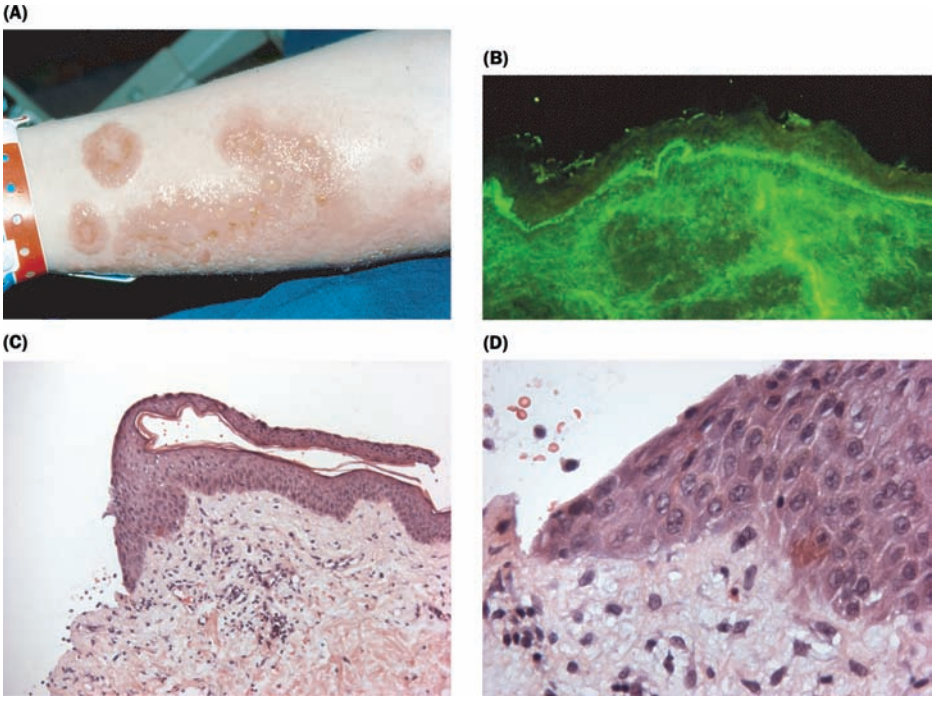

Figure 4 Pemphigoid gestationis.

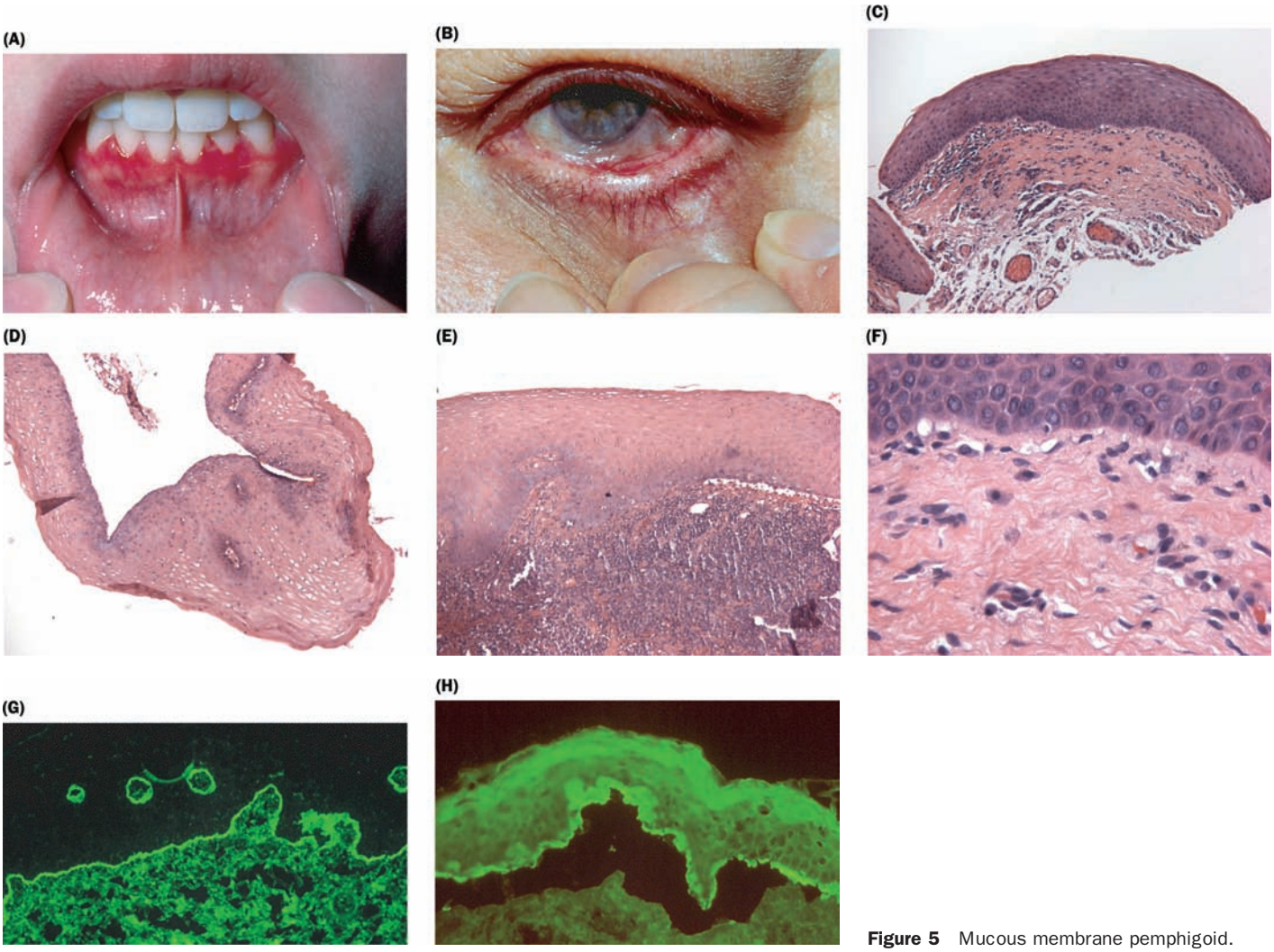

Figure 5 Mucous membrane pemphigoid.

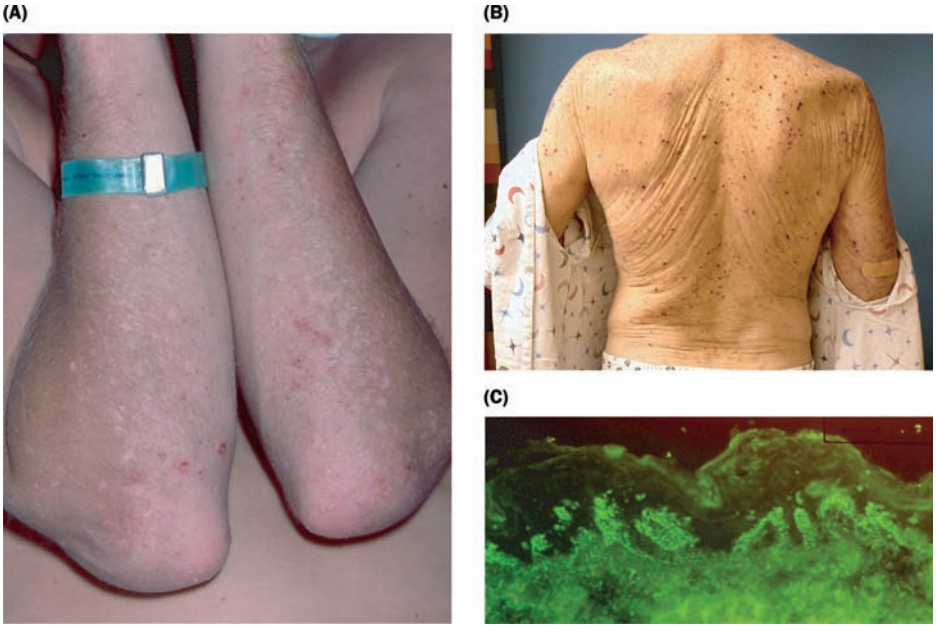

Figure 6 Dermatitis herpetiformis. (*Continued*)

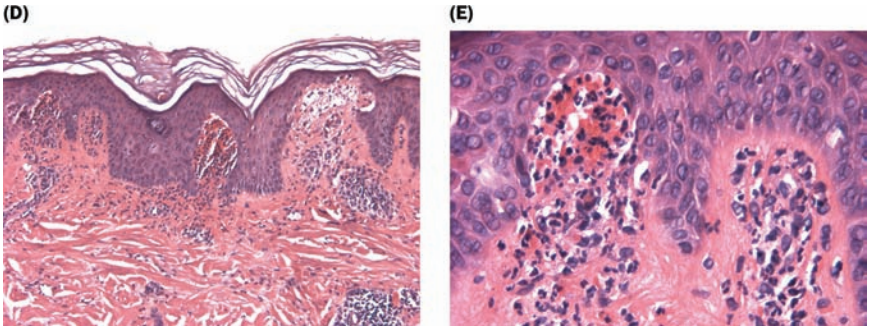

Figure 6 *Continued.*

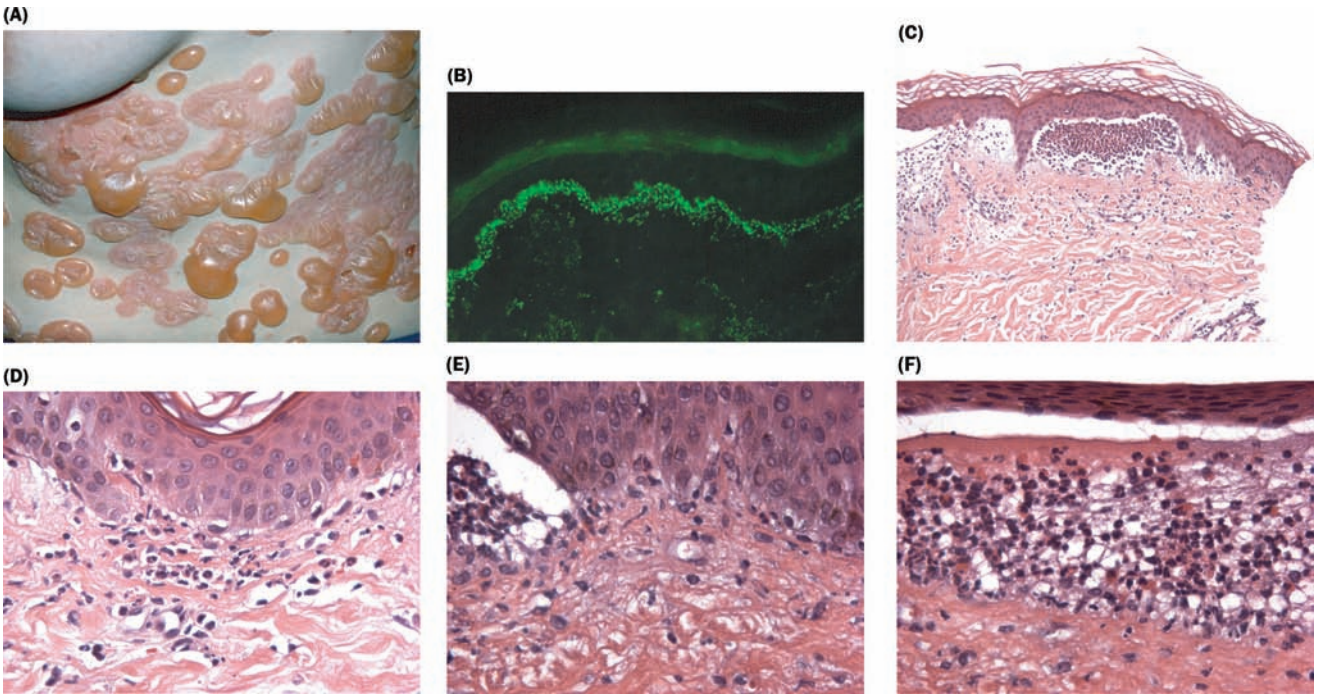

Figure 7 Linear IgA bullous dermatosis.

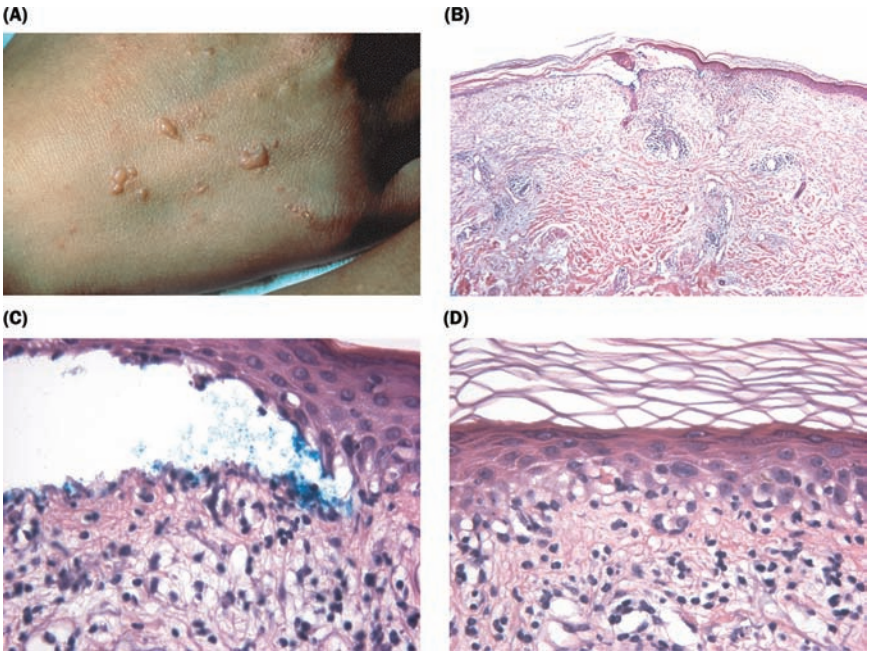

Figure 8 Bullous lupus erythematosus.

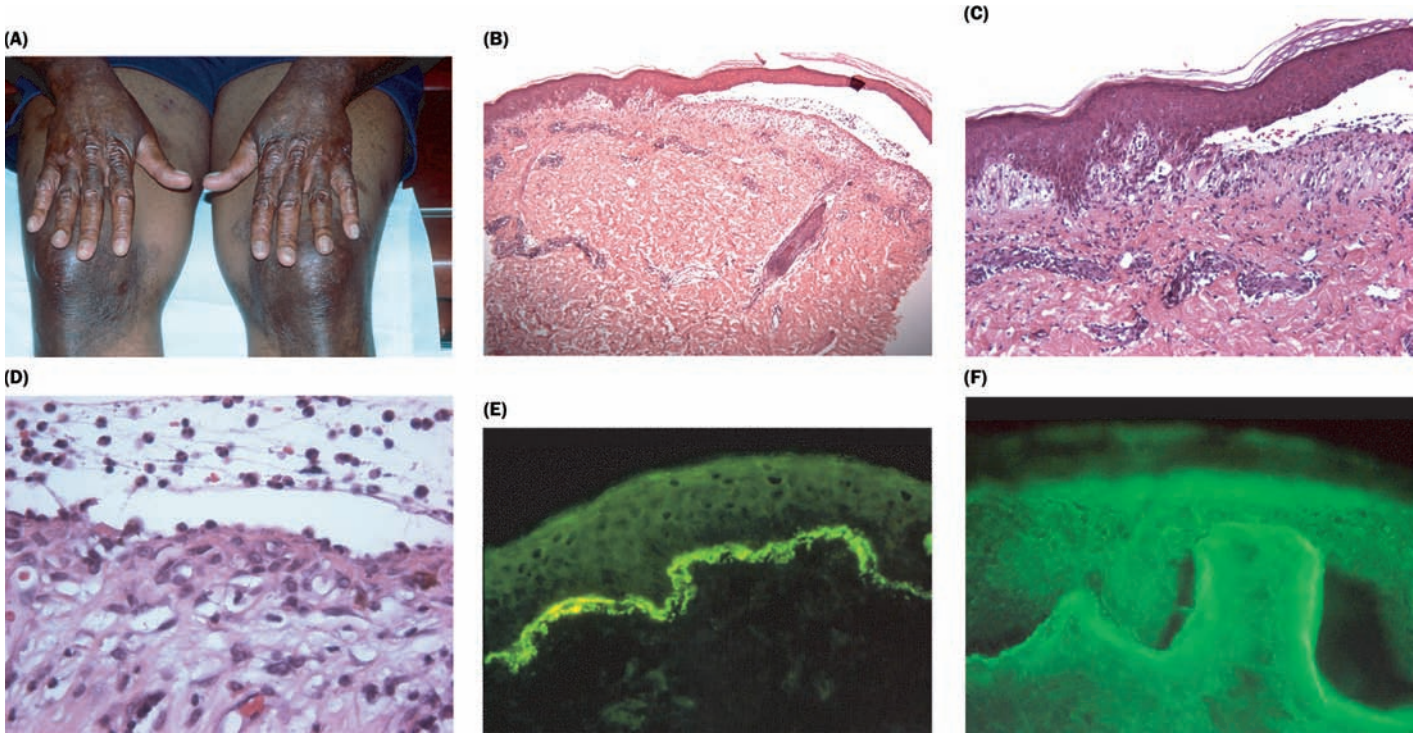

Figure 9 Epidermolysis bullosa acquisita.

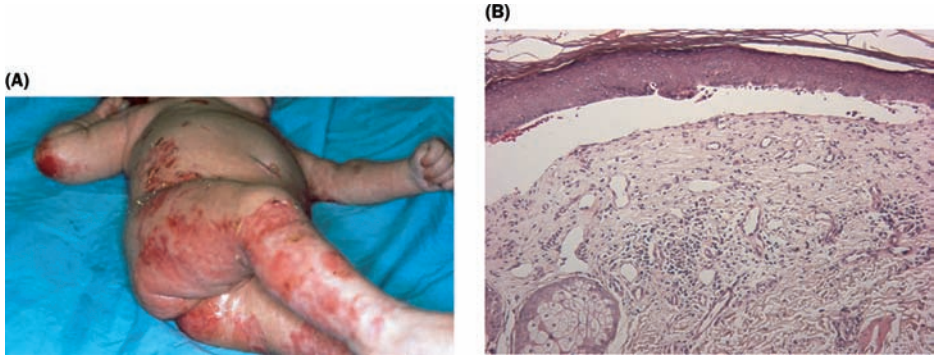

Figure 10 Junctional epidermolysis bullosa.

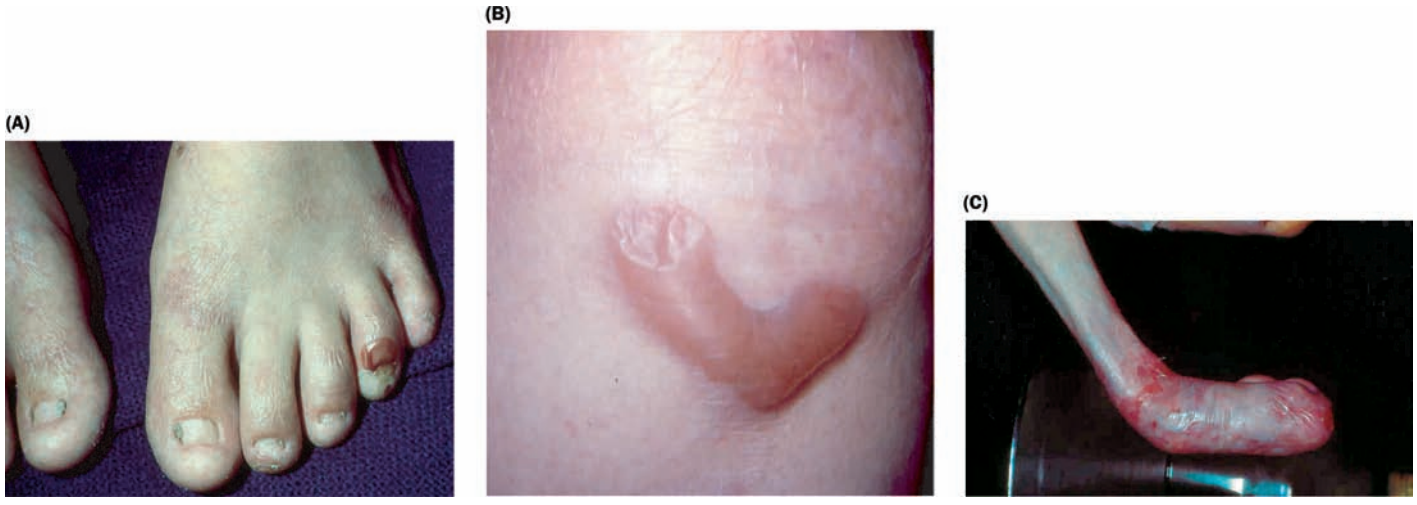

Figure 11 Dystrophic epidermolysis bullosa. (*Continued*)

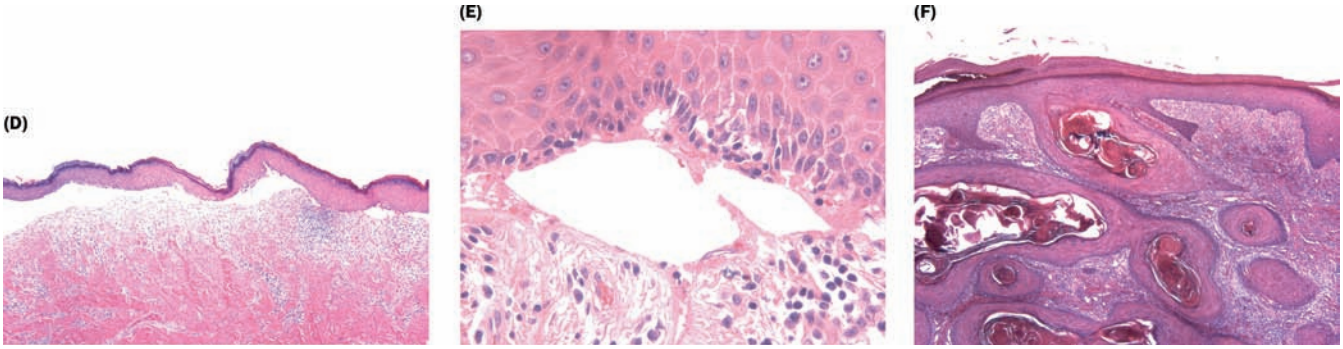

Figure 11 *Continued.*

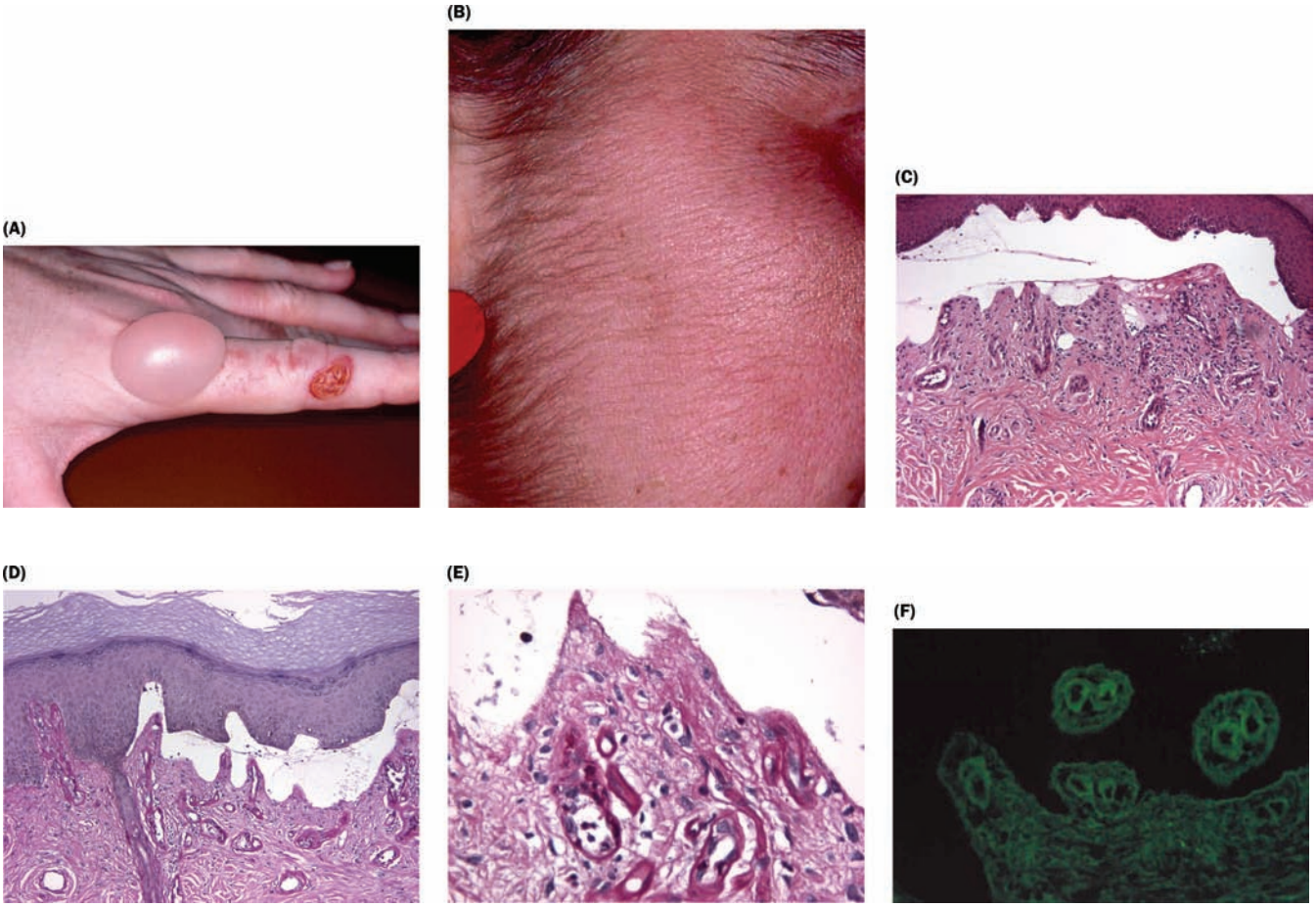

Figure 12 Porphyria.

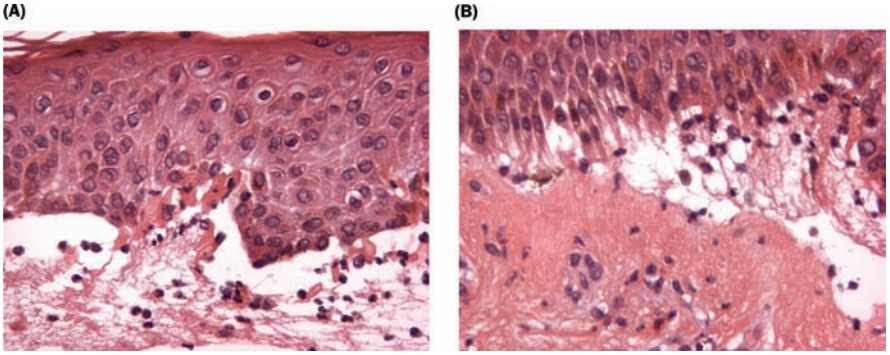

Figure 13 Bullous drug eruption.

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Cutaneous Vasculitis

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CONTENTS

VASCULITIS: AN OVERVIEW

Vasculitis is an inflammation directed at blood vessels, which can lead to vessel wall destruction with hemorrhage and aneurysm formation or stenosis, due to intimal hyperplasia. Vasculitis can be a primary process (no known cause or association, e.g., Wegener's granulomatosis), a disorder secondary to drug ingestion, infection, or the presence of a systemic disease (e.g., rheumatoid arthritis), or an incidental phenomenon, the happenstance of a local factor such as trauma or degradative enzymes and reactive oxygen species from a neutrophilic dermatosis. Systemic and localized vasculitis syndromes often affect the skin and subcutis, probably due to the skin's large vascular bed, local hemodynamic factors (e.g., stasis in lower extremities), and environmental influences (e.g., cold exposure, chronic inflammation). To definitively diagnose vasculitis, evidence of inflammatory vessel wall destruction must be found. When a vasculitis syndrome affects the skin, cutaneous biopsy is the most effective method to determine the presence of vasculitis and exclude pseudovasculitis disorders such as purpura fulminans or cholesterol embolus syndrome. Nonetheless, a biopsy diagnosis of vasculitis cannot stand by itself, as it must be correlated with clinical history, physical and laboratory findings, and/or angiographic features to make a more specific diagnosis. For instance, the diagnosis of cutaneous leukocytoclastic angiitis (a.k.a., allergic or hypersensitivity vasculitis) requires that the systemic manifestations of vasculitis be sought and found absent by review of systems, physical exam, and laboratory studies. In contrast, the confident diagnosis of Wegener's granulomatosis requires the fulfillment of several criteria: (*i*) biopsy or surrogate marker (infiltrates or cavities) for granulomatous inflammation of the respiratory tract, (*ii*) biopsy verified neutrophilic vasculitis in small-to-medium sized vessels or biopsy/surrogate marker for glomerulonephritis/proteinuria and hematuria, or positive circulating antineutrophil cytoplasmic antibodies (cANCA), and (*iii*) lack of eosinophilia in blood and biopsy samples.

Classification:

Classification of vasculitis is based on the dominant blood vessel size involved, the distinction between primary and secondary vasculitis, and the incorporation of pathophysiologic markers such as direct immunofluorescent (DIF) examination for vascular and/or basement membrane zone immune-complexes, and antineutrophil cytoplasmic antibodies (ANCA). In skin hematoxylin and eosin stained sections, separating vasculitic disorders first by vessel size and extent of involvement, that is, superficial perivascular versus pandermal and/or subcutaneous, then by the predominant inflammatory cellular component allows for quick classification and determination of a relevant differential diagnosis. Consideration of DIF data (presence of vascular immune complexes) and ANCA status will further narrow the differential diagnosis. (Fig. 1 and Table 1). In general, Henoch Schönlein purpura (HSP) and cutaneous leukocytoclastic angiitis (CLA) affect the superficial vessels of the skin whereas polyarteritis nodosa (PAN), nodular vasculitis (Nod Vas) and giant cell arteritis (GCA) affect deep muscular vessels found at the dermal-subcutis junction or in subcutis. Cryoglobulinemic vasculitis (CV), connective tissue disease (CTD) vasculitis, and antineutrophilic antibody associated vasculitides (ANCA + vasculitis) can affect both small and muscular vessels (although not necessarily in the same biopsy). The diagnostic yield of a skin biopsy is greatly influenced by the depth biopsy. In general, punch biopsy or excision biopsy extending into the subcutis is the preferred means to sample a vasculitic lesion in order to sample vessels of all sizes.

Clinical Presentation of Vasculitis:

- All ages affected, range 1 to 90; adults $\gg$ children, females $\geq$ males
  - Adults, mean age 47 years
  - Children, mean age seven years
- Seven to ten days interval after exposure to a trigger such as a drug or infection

Table 1 Classification of Cutaneous Vasculitis by Histologic Findings and Laboratory Studies

SMALL VESSEL VASCULITIS
- Neutrophilic
  - Immune-complex mediated (DIF+)
    - Cutaneous leukocytoclastic angiitis (a.k.a. hypersensitivity vasculitis and LCV)
    - Henoch-Schonlein purpura
    - Acute infantile hemorrhagic edema
    - Urticarial vasculitis
    - Chronic localized fibrosing vasculitis: Erythema elevatum diutinum, granuloma faciale, inflammatory pseudotumors
  - Incidental vasculitis (DIF+)
    - Sweet's syndrome and Pustular vasculitis of the dorsa of the hands
- Eosinophilic
  - Eosinophilic vasculitis, primary or secondary to connective tissue disease or parasites, and in some cases of Churg Strauss Syndrome
- Granulomatous
  - Postherpetic eruptions
  - Necrobiosis lipoidica (some lesions)
- Lymphocytic
  - Rickettsial and viral infections
  - Lichenoid dermatitides, some cases, e.g., pityriasis lichenoides, graft vs. host disease, perniosis
  - T cell lymphomas: angiocentric T cell lymphoma, lymphomatoid papulosis, mycosis fungoides
  - Rare drug reactions and arthropod assaults

MIXED, PREDOMINATELY SMALL, AND MEDIUM VESSEL VASCULITIS
- Neutrophilic
  - Immune-complex mediated (DIF+)
    - Cryoglobulinemic vasculitis
    - Hypocomplementemic urticarial vasculitis syndrome
    - Connective tissue disease vasculitis (e.g., lupus, rheumatoid arthritis, Sjögren's syndrome)
  - ANCA associated/pauci-immune (DIF−)
    - Wegener's granulomatosis
    - Microscopic polyangiitis (microscopic polyarteritis nodosa)
    - Churg-Strauss syndrome
    - Drug-induced ANCA vasculitis
  - Miscellaneous/other
    - Behçet's disease
    - Septic vasculitis
- Lymphocytic
  - Degos' disease
  - Rickettsial and viral infections
  - Collagen tissue disease vasculitis (e.g., Sjögren's syndrome, lupus vasculitis)
  - Behçet's disease

MEDIUM (TO LARGE) MUSCULAR VESSEL VASCULITIS
- Neutrophilic
  - Polyarteritis Nodosa, classic, and cutaneous
  - Nodular vasculitis (erythema induratum)
- Eosinophilic
  - Juvenile temporal arteritis
- Granulomatous
  - Giant cell (temporal) arteritis
  - Takayasu's arteritis
  - Postherpetic eruptions
- Lymphocytic
  - Sneddon's syndrome
  - Degas' disease
  - Beurger's disease (thromboangiitis obliterans)
  - Superficial thrombophlebitis (Mondor's disease, sclerosing lymphangiitis)
  - Kawasaki disease

Abbreviations: ANCA, antineutrophil cytoplasmic antibody; CLA, cutaneous leukocytoclastic angiitis; DIF+, direct immunfluorescence examination of skin lesions shows vessel wall immune-complexes and/or complement deposition; LCV, leukocytoclastic vasculitis.

- Mean interval time of six months, range days to years, for cutaneous vasculitis developing secondary to coexisting systemic disease
- Course of cutaneous vasculitis follows three patterns:
  - Single acute, self-limited episode of vasculitis (single crop of lesions, which resolve in several weeks, no longer than six months) typically associated with a drug or infectious trigger (~60% of all cases)
  - Relapsing disease (recurring crops) with symptom free periods (~20%) usually found in patients with HSP and connective-tissue disease associated vasculitis
  - Chronic, unremitting disease often associated with cryoglobulinemia and malignancy (~20%)
    - Fatal disease with cutaneous vasculitis occurs in a small minority of patients (<4%)
- Overall duration of cutaneous vasculitis has a mean of 28 months, median of 3.7 months, and ranges from 1 week to 318 months. Duration is dependent on etiology (see subsequently).

Sites Affected:
- Lower extremities, dependent areas, and regions covered by tight fitting clothes (e.g., sock collar) most frequently affected
- Upper extremities > trunk > head and neck

Clinical Morphologies:
- Most common
  - Erythematous and purpuric macules
  - Palpable purpura
  - Hemorrhagic vesicles and bullae
  - Nodules, dermal and subcutaneous
- Less common
  - Pustules
  - Urticaria and annular lesions
  - Ulcers
  - Livedo reticularis
- Infrequent/rare
  - Splinter hemorrhages and nail fold infarcts (Bywater lesions)
  - Infarcts
  - Digital gangrene
  - Pyoderma gangrenosum-like lesions
  - Palmar or digital erythema

Clinicopathologic Correlation:
The size of vessel affected by vasculitis correlates with clinical morphology (Fig. 2). Sparse superficial perivascular neutrophilic infiltrates associated with nuclear debris and extravasated red blood cells result in urticarial papules and plaques, which resolve with residual pigmentation. Cutaneous leukocytoclastic vasculitis most commonly presents with purpura, palpable, and nonpalpable, of the lower extremities, which correlates with superficial dermal small vessel vasculitis (Fig. 2A). Extensive vesicle and bullae formation with epidermal necrosis superimposed on purpura will most often show pandermal small vessel neutrophilic vasculitis (Fig. 2B). Biopsy of infarcts, digital gangrene and ulcers as pictured herein will demonstrate muscular vessel arteritis at the base of the lesion, if sampled well (Fig. 2C).

Table 2 Clinical Manifestations of Vasculitis Based on Vessel Size Affected

Large	Medium	Small
Limb claudication	Cutaneous nodules	Purpura
Asymmetric blood pressure	Ulcers	Urticaria
Absence of pulses	Livedo reticularis	Vesiculobullous lesions
Aortic dilation	Pitted palmar/ digital scars	Splinter Hemorrhages
Bruits	Digital Gangrene	Scleritis, episcleritis, uveitis
	Mononeuritis	Palisaded neutrophilic granulomatous dermatitis[a]
	Aneurysms	Glomerulonephritis
	Infarct	Gastric colic
	Hypertension (renal artery)	Pulmonary hemorrhage

Note: Constitutional symptoms: fever, weight loss, malaise, arthralgias, and arthritis are common to vasculitic syndromes of all vessel sizes
[a]a.k.a extravascular necrotizing granuloma. Small vessel neutrophilic vasculitis is frequently seen in the vicinity of granulomas and necrosis.
Source: Saleh and Stone, 2005.

Table 2 details the clinicopathologic correlation of vessel caliber affected by vasculitis with clinical findings.

Definition and Histologic Criteria:

The term vasculitis should reflect conditions in which inflammatory cells significantly damage vessels and not merely transverse them to enter the surrounding tissue and impart the histologic picture of perivasculitis. Fibrinoid necrosis (fibrin deposition within and around the vessel wall) is a common histologic feature of nearly all, early vasculitic lesions and is due to the accumulation of plasma proteins, including coagulation factors that are converted to fibrin, at sites of vessel wall destruction. The diagnosis of vasculitis can be unequivocally made if there are inflammatory infiltrates within and around the walls of vessels accompanied by fibrin deposition (fibrinoid necrosis). Table 3 lists the histologic criteria required for the diagnosis of vasculitis, and Figure 3 illustrates diagnostic histology for small and medium vessel vasculitis. Albeit sparse, the presence of neutrophils and nuclear debris and fibrin in the wall of this capillary-post capillary venule is sufficient histologic findings for the diagnosis of vasculitis (Fig. 3A). Extensive intramural fibrin deposits associated with perivascular neutrophils and nuclear debris is the most common histologic finding in cutaneous leukocytoclastic angiitis (Fig. 3B). Muscular vessel arteritis can be diagnosed when inflammatory cells infiltrate and disrupt the vessel intima and/or media (Fig. 3C). Elastic tissue stain reveals segmental loss of the elastic lamina (red arrow), scarring of the media, and residual giant cell inflammation in this biopsy from patient with polyarteritis nodosa (Fig. 3D).

In addition, some patients with systemic disease will exhibit histologic findings concomitant to the vasculitis that will point to etiology and/or diagnosis, such as granulomatous dermatitis, dermal eosinophilia, or dermal neutrophilia (Table 4 and Fig. 4). Angiocentric fibrosis associated with foci of leukocytoclasis (Fig. 4A) can be seen in some cases of cutaneous inflammatory pseudotumor. Eosinophilic or "red" extravascular granulomas (palisaded neutrophilic

Table 3 Histologic Diagnostic Criteria for Cutaneous Vasculitis

Histologic signs of acute (active) vasculitis
Demal small vessels (venules and arterioles) (2 of 3[a] criteria needed)
Angiocentric[a,b] and/or angioinvasive inflammatory infiltrates
Disruption and/or destruction of vessel wall by inflammatory infiltrate[a]
Intramural and/or intraluminal fibrin deposition ("fibrinoid necrosis")[a]
Dermal-Subcutaneous muscular vessels (small arteries and veins)
Infiltration of muscular vessel wall by inflammatory cells[a]
Intramural and/or intraluminal fibrin deposition ("fibrinoid necrosis")[a,c]
Secondary changes of active vasculitis (suggestive of, but not diagnostic of vasculitis)[b]
RBC extravasation (petechiae, purpura, hematoma)
Nuclear dust, perivascular (leukocytoclasia)
Endothelial swelling, sloughing or necrosis
Eccrine gland necrosis (or regeneration with basal cell hyperplasia)
Ulceration
Necrosis/infarction
Histologic Sequelae of Vasculitis (chronic signs and healed lesions of vasculitis)
Lamination (onion-skinning) of vessel wall constituents[b]
(concentric proliferation of pericytes and smooth muscle cells)
Lumenal obliteration (endarteritis obliterans)[b]
Intimal or medial proliferation of cellular elements leading to lumenal occlusion with preservation of the internal elastic lamina
Segmental or complete loss of elastic lamina in medium and large vessels associated with acellular scar tissue[a]
Reactive angioendotheliomatosis
Neo-vascularization of vessel adventitia

[a]Required for diagnosis of vasculitis.
[b]Other types of vessel injury can cause same pattern.
[c]Intraluminal fibrin deposition can be found in nonvasculitic arterial lesions such as malignant hypertension and antiphospholipid antibody syndrome.
Source: From Ref. 1.

Table 4 Histologic Patterns Associated with Systemic Vasculitis and/or Indicative of Etiology

Lamellar or Storiform Fibrosis
Erythema elevatum diutinum, granuloma faciale or inflammatory pseudotumor
Diffuse (sparse) Dermal Granulocytic Infiltrates
Tissue neutrophilia
Urticarial vasculitis associated with systemic lupus erythematosus
Tissue eosinophilia
Churg Strauss syndrome, hypereosinophilic syndrome with vasculitis
Palisaded and Neutrophilic Granulomatous Dermatitis[a]
"Red" extravascular granuloma (eosinophils, flame figures)
Churg Strauss syndrome, Wegener's granulomatosus (rarely)
"Blue" extravascular granuloma (neutrophils, nuclear dust)
Wegener's granulomatosus, rheumatoid vasculitis
Churg Strauss syndrome (rarely)
Vacuolar Interface Dermatitis (Sometimes Dermal Mucin Deposition)
Connective tissue diseases: lupus erythematosus, dermatomyositis
"Pustular" Dermatosis with Intraepidermal or Subepidermal Neutrophilic Abscesses
Infectious trigger, septic vasculitis

[a]Also known as Winklemann's granuloma, Churg-Strauss granuloma, extravascular necrotizing granuloma, and rheurmatoid papules.
Source: From Ref. 1.

Table 5 Frequency of Specific Vasculitic Syndromes Associated with Biopsy Proven Vasculitis

Cutaneous Vasculitic Syndrome	Frequency[a]
Cutaneous (idiopathic) leukocytoclastic angiitis	39.0%, 3–72%
Henoch-Schönlein purpura	10.1%, 0–88%
Primary systemic vasculitis	4.4%, 0–13%
Wegener's Granulomatosis	1.1%, 0–6%
Polyarteritis nodosa	2.5%, 0–10%
Churg-Strauss syndrome	0.6%, 0–8%
Giant cell arteritis	0.1%, 0–2%
Microscopic polyangiitis	≤1%[b]
Connective tissue disease	11.7%, 0–44%
Systemic lupus erythematosus	3.5%, 0–19%
Rheumatoid arthritis	5.2%, 0–20%
Sjögren syndrome	1.3%, 0–25%
Other systemic disorders	4.2%, 0–15%
Behçets disease	0.6%, 0–3%
Sarcoidosis	0.2%, 0–2%
Inflammatory bowel disease	0.7%, 0–8%
Cryoglobulinemic vasculitis	2.9%, 0–28%
Infections (mostly upper respiratory tract)	22.5%, 0–62%
Viral hepatitis	3.1%, 0–22%
Streptococcus sp	2.1%, 0–28%
Septicemia/severe bacterial infections	1.2%, 0–11%
Drugs	20.1%, 0–69%
Malignancy	4.3%, 0–16%

[a]Mean %, range.
[b]Many cases reported in the older literature labeled as polyarteritis nodosa would be classified today as microscopic polyangiitis per Chapel Hill Consensus conference criteria. Greater than 100% sum for associations is due to coexistence of suspected drug and infection and/or systemic inflammatory disease in some instances.
Source: From Ref. 1.

granulomatous dermatitis with eosinophils) are found in the papular and nodular extremity lesions of Churg-Strauss syndrome (Fig. 4B). Early "blue" extravascular granulomas (palisaded neutrophilic granulomatous dermatitis) are found in some papular and nodular lesions in rheumatoid vasculitis and Wegener's granulomatosis (Fig. 4C). Subepidermal pustules are seen in this case of cutaneous vasculitis triggered by bacterial pharyngitis (Fig. 4D).

Etiology and Epidemiology

Cutaneous vasculitis can represent a primary or idiopathic process, a secondary process associated with another systemic, often chronic inflammatory disease, or an eruption triggered by infection or recent drug ingestion. Table 5 lists the frequency of finding coexisting systemic disease, specific vasculitis triggers (drug or infection), or primary systemic vasculitis syndrome in patients presenting with cutaneous vasculitis. The annual incidence of biopsy-proven cutaneous vasculitis ranges from 39.6 per million to 59.8 per million. In contrast, the rate for primary systemic vasculitis is 115.04 per million.

Pathophysiology:

Fibrinoid necrosis is the morphologic endpoint for most forms of inflammatory mediated vascular injury. Many different pathogenic mechanisms such as immune complex-Arthus reaction, endotoxin-Schwartzman reaction, and venom from *Loxoscelism* all lead to activation of neutrophils and abnormal neutrophil diapedesis—two factors that may be common denominators in pathogenesis of neutrophil associated small vessel vasculitis. Other morphologic patterns of inflammatory-mediated vessel injury (vasculitis) exist, which include lymphocytic endarteritis and endarteritis obliterans of transplant vascular rejection (so-called transplant endarteritis and sclerosing transplant vasculopathy). This form of inflammatory vascular injury is not typically associated with abundant fibrin deposits and destruction of the vessel wall with loss of the elastic lamina. This latter histology can overlap with vaso-occlusive disorders such as the antiphospolipid antibody syndrome. Although nonimmunologic factors such as direct infection of endothelial cells can cause vasculitis, most vasculitic lesions are mediated by immunopathogenic mechanisms that can be classified into four basic types of hypersensitivity reactions per Coombs and Gell (Table 6). Other immunopathologic mechanisms such as antibody neutralization (e.g., activation/deactivation of endothelial cell function by antibody binding), granulomatous inflammation resulting from nonimmune mechanisms, and T-cell mediated cytotoxic reactions may also cause some forms of vasculitis. The majority of cutaneous lesions of vasculitis are due to immune complex deposition/type III hypersensitivity reactions as approximately 80% (range 54–100%) of DIF exams are positive for vessel wall immunoglobulin and/or complement deposition (Fig. 5). Complement, specifically, C3, is the most common and the longest lasting immunoreactant detected in cutaneous vasculitis; Figure 4, top left shows extensive C3 vascular deposition. Activation of the membrane attack complex (C5b-9) is thought to mediate endothelial damage due to immune complex mediated vasculitis (Fig. 5A, inset). Isolated or dominant IgA vascular deposits characterize lesions of HSP (Fig. 5B). Indirect immunofluorescence is used to detect and monitor the presence of ANCA. Cytoplasmic or cANCA is both relatively sensitive and specific for Wegener's granulomatosis (Fig. 5C). Perinuclear or pANCA are less specific than cANCA for systemic vasculitis and are frequently detected in Churg Strauss syndrome and microscopic polyangiitis (Fig. 5D).

Table 6 Pathogenic Mechanisms of Vasculitis and Their Clinical Diagnostic and Histologic Correlates

Pathogenic Mechanism	Vasculitic Syndrome	Vasculitis Pattern
Direct infection	Rickettsial infections	Lymphocytic small vessel vasculitis
Type I Anaphylactic	Eosinophilic vasculitis	Eosinophilic small vessel vasculitis
	Churg Strauss Syndrome	Eosinophilic small and medium vessel vasculitis[a]
Type II Cytotoxic-cytolytic antibody	Wegener's granulomatosis	Neutrophilic mostly small and medium vessel vasculitis
	Microscopic polyangiitis	Neutrophilic mostly small and medium vessel vasculitis
Type III Immune complex	Henoch-Schönlein Purpura	Neutrophilic small vessel vasculitis
	Cutaneous leukocytoclastic angiitis	Neutrophilic small vessel vasculitis
	Cryoglobulinemic vasculitis	Neutrophilic mostly small and medium vessel vasculitis
	Polyarteritis nodosa	Neutrophilic medium vessel vasculitis
Type IV Delayed hypersensitivity	Giant cell arteritis	Granulomatous medium vessel vasculitis
	Chronic graft vs. host disease	Lymphocytic small vessel vasculitis
	Sneddon's Syndrome	Lymphocytic medium vessel vasculitis followed by endarteritis obliterans
	Dego's disease	

[a]Eosinophils are as numerous or more numerous than neutrophils.
Source: From Ref. 1.

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1. Carlson JA, Ng BT, Chen KR. Cutaneous vasculitis update: diagnostic criteria, classification, epidemiology, etiology, pathogenesis, evaluation and prognosis. Am J Dermatopathol 2005; 27(6):504–528.
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CUTANEOUS LEUKOCYTOCLASTIC ANGIITIS

Synonyms: Hypersensitivity vasculitis; allergic vasculitis; necrotizing vasculitis; leukocytoclastic vasculitis; primary cutaneous small vessel vasculitis.

Clinical Presentation (Fig. 6):

- All ages, both sexes affected, mostly middle-aged adults
- Most cases idiopathic; prolonged exercise, infectious or drug trigger in remainder
- Single or recurrent crops of palpable purpura affecting lower extremities
  - Dependent areas of buttocks, lower legs, ankles and feet
    - Areas of friction or constant pressure such as skin underlying belt, or sock collar are also frequently affected
  - Symptoms of pruritus, stinging, tenderness, and/or burning are common
  - Resolution of individual lesion over three to four weeks
    - Residual ecchymosis or hyperpigmentation
    - Minority of patients (<10%) have relapsing or persistent disease
      - Cryoglobulins, arthralgias, normal temperature, and ulcers are associated with relapsing or persistent vasculitis
    - Rarely, a minority of patients will show severe disease in the form of:
      - Necrosis, ulceration, bullae, or nodules
      - Trunk and upper extremity involvement
- Minor arthralgias and constitutional symptoms of fever and/or malaise
- No evidence of systemic disease by review of systems, physical exam (e.g., no neuropathy), or laboratory exam (normal complete blood count, urine analysis)

Histology (Fig. 6):

- In lesions less than 48 hours old:
  - Small vessel neutrophilic vasculitis affecting superficial dermal vessels
    - Varying degrees of extravasation of red blood cells
    - ± subepidermal vesicle formation and/or epidermal necrosis
    - Perivascular eosinophils often prominent in drug related cases
  - DIF: vascular C3, IgM, and fibrinogen, less frequent IgG and IgA
- In lesions greater than 48 hours of age
  - Mixed infiltrates with lymphocytes predominating with increasing age
  - Rare nuclear debris, fibrin deposits and variable presence of extravasated red blood cells
  - DIF, mostly negative; vascular C3 deposits can be detected in minority

Differential Diagnosis:

- Systemic vasculitis syndromes with cutaneous involvement (Table 7).

Table 7 Findings Indicating the Probability of Coexisting Systemic Vasculitis or Systemic Disease

Findings	Suspected Systemic Vasculitis Syndrome
Clinical signs or symptoms	
High fever	Infection, systemic inflammatory disorders
Paresthesias, foot drop	CSS, PAN
Abdominal pain	HSP, CSS
Frank arthritis	RV, infection, PAN, systemic inflammatory disorder
Hypertension	PAN
Purpura above waist, upper extremities	HSP, MPA, WG, CSS
>1 type of vasculitic lesion[a]	HSP, MPA, WG, CSS
Punctate palmar lesions	LV
Laboratory evaluation	
ESR >40 mm/hr	Infection, hematologic malignancies, systemic inflammatory disorders
Elevated RF, cryoglobulins and low complement	CV
Chest x-ray: infiltrates or cavities	WG, CSS, MPA, malignancy
Hematuria and/or proteinuria and/or abnormal creatinine	Dermal-renal vasculitis syndrome: WG, MPA, HSP, SLE
Hypocomplementemia	UV associated with SLE
Abnormal blood count	Infection, hematologic malignancy, systemic inflammatory disorders
cANCA (PR3)	WG
pANCA (MPO)	MPA, CSS
Histologic Examination	
Deep dermal and/or subcutaneous small and/or muscular vessel vasculitis	Systemic vasculitis syndrome (WG, CSS, MPA, CV, RV, LV, septic vasculitis)
Palisaded neutrophilic and granulomatous dermatitis	WG, CSS, LV, RV
Tissue neutrophilia or tissue eosinophilia	SLE or CSS, respectively
Direct immunofluorescence	
Isolated or predominate IgA vascular deposits	HSP
Lupus band (IgG, IgM, and/or C3 at the BMZ)	LV, UV associated with SLE

[a]Purpura plus ulcers, nodules, bullae, livedo reticularis, etc.
Abbreviations: CSS, Churg Strauss syndrome; CV, cryoglobulinemic vasculitis; HSP, Henoch Schonlein purpura; LV, lupus vasculitis; MPA, microscopic polyangiitis; MPO, myeloperoxidase; PAN, polyarteritis nodosa; PR3, proteinase 3; RF, rheumatoid factor; RV, rheumatoid vasculitis; SLE, systemic lupus erythematosus; UV, Urticarial vasculitis.

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1. Carlson JA, Ng BT, Chen KR. Cutaneous vasculitis update: diagnostic criteria, classification, epidemiology, etiology, pathogenesis, evaluation and prognosis. Am J Dermatopathol 2005; 27(6):504–528.
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HENOCH SCHÖNLEIN PURPURA

Synonyms: HSP; Acute infantile hemorrhagic edema (putative variant).

Clinical Presentation (Fig. 7):

- Most common vasculitis in children (~90% all cases); affects adults as well
  - Preceding upper respiratory tract infection occurs in up to 50%
  - Recent drug or food ingestion triggers in minority
- Clinical tetrad: skin involvement universal, other findings less frequent
  - Purpura (100%)
  - Retiform or patterned purpura and retiform margins considered specific to HSP
  - Arthritis (82%)
  - Abdominal pain (63%)
    - Gastrointestinal hemorrhage (33%)
  - Nephritis (40%)
- Features with high sensitivity and specificity for diagnosis:
  - Isolated or predominate IgA vascular deposits, and
  - Two or more of these clinical features:
    - age $\leq$ 20 years
    - gastrointestinal involvement (colicky pain or hematochezia)
    - upper respiratory tract infection prodrome
    - hematuria or renal biopsy showing mesangioproliferative glomerulonephritis with or without IgA deposits
- Long term follow up is important; renal impairment can be seen many years after the initial diagnosis
  - $\leq$20% of children develop chronic renal failure 20 years after diagnosis
    - Nephrotic syndrome, hypertension, and renal failure at onset are associated with poor outcome
  - In adult patients, those who present with fever, purpura above the waist, and elevated erythrocyte sedimentation rate are significantly more likely to have IgA glomerulonephritis

Histology (Fig. 7):

- Small vessel neutrophilic vasculitis restricted to the superficial dermis in over half
  - Rare muscular vessel vasculitis in patients with underlying monoclonal gammopathy

- DIF shows isolated or predominate IgA deposits in both involved and uninvolved vessels from lesions less than 48 hours old

References:

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3. Tancrede-Bohin E, Ochonisky S, Vignon-Pennamen MD, Flageul B, Morel P, Rybojad M. Schonlein-Henoch purpura in adult patients. Predictive factors for IgA glomerulonephritis in a retrospective study of 57 cases. Arch Dermatol 1997; 133(4):438–442.
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URTICARIAL VASCULITIS

Synonyms: Urticarial venulitis; hypocomplementemic or normocomplementemic urticarial vasculitis; hypocomplementemic urticarial vasculitis syndrome.

Clinical Presentation (Fig. 8):

- Women more than men (3:2–4:1), fourth decade peak incidence
- ≤20% of patients presenting with chronic urticaria have urticarial vasculitis (UV)
- Cutaneous differences between UV and urticaria
  - Painful, tender, burning or pruritic papules, and plaques
    - Urticaria is mostly pruritic
  - Lesions persist less than 24 hours and greater than 72 hours
  - Urticaria lasts between 8 to 24 hours
- Residual purpura or hyperpigmentation
  - No residua in urticaria
- No site predilection
  - Urticaria more common on lower extremities
- Systemic signs include: low-grade fever, angioedema, arthralgias and arthritis, and abdominal pain
- Hypocomplementemia can be observed in 18% to 32%
  - Hypocomplementemic UV have more severe disease compared to normocomplementemic UV:
    - Mostly female
    - Tissue neutrophilia and +lupus band test on skin biopsy
    - Coexisting connective tissue disease, frequently systemic lupus erythematosus
  - hypocomplementemic urticarial vasculitis syndrome:
    - Arthralgias or arthritis
    - Glomerulonephritis
    - Uveitis or episcleritis
    - Recurrent abdominal pain
    - Obstructive lung disease
  - Up to 70% of UV patients with + lupus band test have renal disease (e.g., membranoproliferative glomerulonephritis, focal necrotizing vasculitis)

Histology (Fig. 8):

- Sparse perivascular and interstitial neutrophilic infiltrate with either:
  - Focal small vessel neutrophilic vasculitis, or
  - Focal perivascular neutrophilic nuclear debris without fibrin deposits, and with or without extravasated red blood cells.
    - Minimal histologic criteria for the diagnosis of UV:
      - Nuclear debris or fibrin deposits, with or without extravasated red blood cells
- Diffuse neutrophilic infiltrates more common in hypocomplementemic UV
- Dermal eosinophils more common in normocomplementemic UV
- DIF evaluation reveals vascular C3 and/or immunoglobulins, mostly IgM, in 47%
  - Vascular immunoreactants found frequently in patients with hypocomplementemic UV, 87% to 100%
  - Normocomplementemic UV have significantly less frequent vascular immunoreactants, 29%
  - Positive lupus band test (basement membrane zone deposits of C3 and/or immunoglobulin ranges) ranges from 18% to 34% in all UV patients
    - Hypcomplementemic UV, 70% to 96% + lupus band test
    - Normocomplementemic UV, 1% to 18% + lupus band test

References:

1. Davis MD, Daoud MS, Kirby B, Gibson LE, Rogers RS III. Clinicopathologic correlation of hypocomplementemic and normocomplementemic urticarial vasculitis. J Am Acad Dermatol 1998; 38(6 Pt 1):899–905.
2. Davis MD, Brewer JD. Urticarial vasculitis and hypocomplementemic urticarial vasculitis syndrome. Immunol Allergy Clin North Am 2004; 24(2):183–213.
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4. Wisnieski JJ, Baer AN, Christensen J, et al. Hypocomplementemic urticarial vasculitis syndrome. Clinical and serologic findings in 18 patients. Medicine (Baltimore) 1995; 74(1):24–41.

SEPTIC VASCULITIS

Clinical Presentation (Fig. 9):

- Acute vasculitis caused by septic states due to infective endocarditis or infection with gonococci, meningococci, pseudomonads, staphylococci, streptococci, certain rickettsial infections, and other microorganism
- Clinical lesions are characterized by:
  - Purpura (petechiae and ecchymoses)
  - Vesiculopustules, often with grey roofs signifying necrosis
  - Hemorrhagic bullae
  - Ulceration, rarely
- Chronic gonococcemia and chronic meningococcemia patients have triad of
  - Intermittent fewer
  - Arthralgias
  - Fewer clinical lesions, distributed over extremities, particularly acral surfaces, which are mostly:
    - Petechiae surrounded by a rim of erythema
    - Vesiculopustules with grey necrotic roof
    - Hemorrhagic bullae, rarely

Histology (Fig. 9):
- Mixed neutrophilic small and muscular vessel vasculitis with deep dermal and subcutaneous vessel involvement
  - Scant perivascular fibrin
  - Fibrin thrombi common (Fig. 9D, arrow)
  - Muscular arteritis common (Fig. 9D, block arrow)
  - No or little nuclear debris (differentiates septic vasculitis)
  - Epidermal spongiosis, intraepidermal vesicles, and pustules common
  - Neutrophils within or underlying the epidermis
  - Eosinophils absent or sparse
  - Organisms are rare in skin lesions except in acute meningococcemia
  - Vascular immune complexes can be detected by direct immunofluorescence
  - Necrosis of adnexal sturctures (Fig. 9C)

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3. Plaut ME. Staphylococcal septicemia and pustular purpura. Report of cases. Arch Dermatol 1969; 99(1):82–85.
4. Rodriguez-Pla A, Stone JH. Vasculitis and systemic infections. Curr Opin Rheumatol 2006; 18(1):39–47.
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CHRONIC LOCALIZED FIBROSING LEUKOCYTOCLASTIC VASCULITIS

Specific Disorders:
Granuloma faciale, erythema elevatum diutinum, and some cutaneous inflammatory pseudotumors.

Clinical Presentation:
Granuloma Faciale (Fig. 10):
- Asymptomatic, slowly enlarging reddish-brown papules or plaques on the face of middle-aged adults (Fig. 10A)
  - One third will have multiple facial site involvement
  - Less than 10% will have extra facial lesions
  - Clinically mistaken for sarcoidosis, lymphoma, discoid lupus erythematosus, and basal cell carcinoma

Erythema Elevatum Diutinum:
- Systemically ill patients with connective tissue disease, infection, acquired immune deficiency, and hematologic abnormalities
  - IgA gammopathy is often present
- Symmetric, violaceous to red-soft papules that evolve into firm, fibrous brown-yellow papules, plaques, or nodules located over extensor surfaces of extremities

Cutaneous Inflammatory Pseudotumor:
- Solitary cutaneous nodule or nodules with histologic features that mimic either erythema elevatum diutinum or granuloma faciale histologically, but not clinically
- Pathogenesis is believed to be due to either systemic or local immune complexes producing recurrent vessel damage to the small, easily injured vessels of fibrosing granulation tissue

Histology (Fig. 10):
- All three disorders are characterized by small vessel neutrophilic vasculitis, patterned fibrosis, and dense nodular mixed, neutrophilic rich inflammatory infiltrates (plasma cells, macrophages, lymphocytes, and granulocytes)
  - Vasculitis is subtle in most cases with focal regions of nuclear dust and/or fibrin surrounding and within vessels (Fig. 10C)
  - Fibrosis is progressive
    - Mature lesions show granulation tissue with vertically oriented capillaries and horizontally arrayed collagen bundles and fibroblasts (lamellar fibrosis)
      - Late lesions show lamellar, storiform, or angiocentric fibrosis (Fig. 10D) admixed with scattered macrophages with foamy and/or hemosiderin laden cytoplasm
  - Granuloma faciale has numerous eosinophils in its polymorphous infiltrate separated from the epidermis and adnexae by a grenz (clear) zone
  - Erythema elevatum diutinum lacks a grenz zone
- DIF examination can show both vascular and/or basement membrane zone complement and immunoglobulin deposits

References:

1. Carlson JA, LeBoit PE. Localized chronic fibrosing vasculitis of the skin: an inflammatory reaction that occurs in settings other than erythema elevatum diutinum and granuloma faciale. Am J Surg Pathol 1997; 21(6):698–705.
2. El Shabrawi-Caelen L, Kerl K, Cerroni L, Soyer HP, Kerl H. Cutaneous inflammatory pseudotumor—a spectrum of various diseases? J Cutan Pathol 2004; 31(9):605–611.
3. LeBoit PE, Yen TS, Wintroub B. The evolution of lesions in erythema elevatum diutinum. Am J Dermatopathol 1986; 8(5):392–402.
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CRYOGLOBULINEMIC VASCULITIS

Synonym: Essential cryoglobulinemic vasculitis.

Clinical Presentation (Fig. 11):
- Cryoglobulins are cold-precipitating immunoglobulins that persist in the serum and resolubilize when rewarmed; there are three types of cryoglobulins:
  - Type I, monoclonal cryoglobulins compose 10% to 15% of all cases
    - Produce noninflammatory small vessel hyaline thrombi
  - Type II, mixed monoclonal IgM rheumatoid factor, polyclonal IgG cryoglobulins, 50% to 60% of all cases
  - Type III, mixed polyclonal IgM (with rheumatoid factor activity), and IgG cryoglobulins; 30% to 40% of all cases

- Mixed cryoglobulins (types II and III) are associated with connective tissue, hematologic malignancies, or infectious diseases, particularly hepatitis C infection
  - >50% of hepatitis C patients have mixed cryoglobulins, with a lesser frequency of vasculitis
- Cryoglobulinemic vasculitis (mixed cryoglobulinemia with vasculitis) is characterized by the clinical triad of:
  - Purpura (Fig. 11A)
  - Triggered by cold exposure or prolonged standing
    - Arthralgias
    - Weakness (asthenia)
- Other cutaneous manifestations can include polyarteritis nodosa-like lesions, ulcers, splinter hemorrhages (Fig. 11B), and palmar erythema (Fig. 11C)
- Other systemic disease includes glomerulonephritis (55%), neuropathy (40%), and/or pulmonary symptoms of hemoptysis and dyspnea (5%)
  - High titers of rheumatoid factor (RF) and low C4 levels are often observed

Histology (Fig. 11):

- Small vessel neutrophilic vasculitis equally affecting superficial dermal and subcutis vessels
  - Neutrophilic muscular vessel vasculitis (PAN-like) in a minority
    - Reactive angioendotheliomatosis (lobular proliferation of capillaries harboring fibrin microthrombi) can be a sign of muscular vessel vasculitis (Fig. 11, elastic tissue stain).
  - Rare lymphocytic small vessel vasculitis can be seen
  - Intravascular hyaline deposits can be seen in association with ulcerative vasculitic lesions (Fig. 11D)
- Direct immunofluorescence exam demonstrates vascular immunoglobulins, mostly IgM, and/or complement deposits, in the majority of patients
  - Basement membrane zone immunoreactants identified less frequently

References:

1. Cohen SJ, Pittelkow MR, Su WP. Cutaneous manifestations of cryoglobulinemia: clinical and histopathologic study of seventy-two patients. J Am Acad Dermatol 1991; 25(1 Pt 1):21–27.
2. Gorevic PD, Kassab HJ, Levo Y, et al. Mixed cryoglobulinemia: clinical aspects and long-term follow-up of 40 patients. Am J Med 1980; 69(2):287–308.
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CONNECTIVE TISSUE DISEASE VASCULITIS

Synonyms: Lupus vasculitis; rheumatoid vasculitis.

Clinical Presentation:

- Cutaneous vasculitis occurs frequently in systemic lupus erythematosus, rheumatoid arthritis (RA), and Sjögren's syndrome, and less commonly in dermatomyositis, scleroderma, and polychondritis
- More widespread organ involvement is found and the caliber of vessel affected shows more variation in connective tissue disease vasculitis than cutaneous leukocytoclastic angiitis
- Coexistence of prothombotic antiphospholipid antibodies, which can lead to the rapid evolution of vascular insufficiency with progressive tissue ischemia and infarction
- Arterioles and post-capillary venules are most commonly affected by vasculitis, manifested as purpura, vesiculobullous lesions, urticaria, and splinter hemorrhages
  - Suspect arterial involvement if cutaneous ulcers, nodules, digital gangrene, (necrotizing) livedo reticularis, punctate acral scars (Fig. 12), or pyoderma gangrenosum (PG)-like lesions occur.
- Connective tissue disease patients can also show pANCA (mostly), or cANCA by indirect immunofluorescence.

Histology:

- Mixed, mostly small and muscular vessel neutrophilic vasculitis is most often seen in connective tissue disease vasculitis
  - Lesions can resemble polyarteritis nodosa and or typical cutaneous leukocytoclastic angiitis
- Chronic lymphocytic vasculitis with small and/or muscular vessel is found in a minority of cases, mostly systemic lupus erythematosus and Sjögren's syndrome (Fig. 12C, arrow)
  - This pattern of vasculitis is likely responsible for the slow, progressive occlusion of blood vessels (endarteritis obliterans) with end organ ischemia found in some connective disease patients (Figs. 12E–F)
- Extravascular histologies can provide a clue to diagnosis of connective tissue disease vasculitis
  - Interface dermatitis with dermal mucin deposition in lupus erythematosus and dermatomyostitis (Figs. 12B, C, and F)
  - Dermal and/or subcutaneous sclerosis in scleroderma
  - Palisaded neutrophilic and granulomatosis dermatitis in rheumatoid arthritis or systemic lupus erythematosus
  - Tissue neutrophilia (not a neutrophilic dermatosis) in systemic lupus erythematosus and Sjögren's syndrome

References:

1. Chen KR, Toyohara A, Suzuki A, Miyakawa S. Clinical and histopathological spectrum of cutaneous vasculitis in rheumatoid arthritis. Br J Dermatol 2002; 147(5):905–913.
2. Drenkard C, Villa AR, Reyes E, Abello M, Alarcon-Segovia D. Vasculitis in systemic lupus erythematosus. Lupus 1997; 6(3):235–242.
3. Kao AH, Sabatine JM, Manzi S. Update on vascular disease in systemic lupus erythematosus. Curr Opin Rheumatol 2003; 15(5):519–527.
4. Luqmani RA, Pathare S, Kwok-Fai TL. How to diagnose and treat secondary forms of vasculitis. Best Pract Res Clin Rheumatol 2005; 19(2):321–336.

WEGENER'S GRANULOMATOSIS

Synonym: Pathergic granulomatosis.

Clinical Presentation (Fig. 13):

- Predilection to affect the upper and lower respiratory tracts with necrotizing granulomatous inflammation and kidneys as glomerulonephritis

- Granulomatous lesions can affect any organ in the body
- Generalized vasculitis occurs in a wide variety of sites, particularly the lungs
- ≤ 15% will present with cutaneous disease
- ≤ 50% will develop cutaneous disease during the course of disease

- Three categories of cutaneous disease exist in WG
  - Palpable or nonpalpable purpura due to small vessel neutrophilic vasculitis
  - Subcutaneous nodules, ulcers, and digital infarcts (gangrene) secondary to medium vessel vasculitis
  - Polymorphic lesions consisting of
    - Rheumatoid papules: papules and nodules (necrotic over extensor surfaces, often the elbows)
    - PG-like ulcers (a.k.a. malignant pyoderma) (Fig. 13A)
    - Gingival hyperplasia (strawberry gingivitis)
- Proposed criteria for the diagnosis of WG
  - Biopsy or surrogate marker (infiltrates or cavities) for granulomatous inflammation of the respiratory tract
  - Biopsy verified necrotizing vasculitis in small-to-medium sized vessels or biopsy/surrogate marker for glomerulonephritis/proteinuria and hematuria, or positive cANCA
    - ~80% Wegener's granulomatosis patients are positive for cANCA
  - Lack of eosinophilia in blood and biopsy samples
- Untreated, WG has a one-year mortality rate of more than 80%
  - 75% will undergo remission with a regimen of cyclophosphamide and glucocorticoids
  - Relapse, the most important clinical problem, occurring in up to 50% of patients by five years of follow up

Histology (Fig. 13):

- Three histologic patterns of inflammation can be found in cutaneous lesions of Wegener's granulomatosis, either alone (mostly) or together:
  - Geographic ("pathergic") necrosis (Fig. 13C)
  - Granulomatous extravascular inflammation
  - Neutrophilic, predominately small vessel vasculitis (Fig. 13B) and less commonly muscular vessel vasculitis (Fig. 13D)
    - ≤50% cutaneous lesions show small vessel neutrophilic vasculitis
    - Authentic granulomatous vasculitis is exceptional and if present affects muscular vessels

References:

1. Barksdale SK, Hallahan CW, Kerr GS, Fauci AS, Stern JB, Travis WD. Cutaneous pathology in Wegener's granulomatosis. A clinicopathologic study of 75 biopsies in 46 patients. Am J Surg Pathol 1995; 19(2):161–172.
2. Daoud MS, Gibson Le, DeRemee RA, et al. Cutaneous Wegener's granulomatosis: clinical, histopathologic, and immunopathologic features of thirty patients. J Am Acad Dermatol 1994; 31(4): 605–612.
3. Frances C, Du LT, Piette JC, et al. Wegener's granulomatosis. Dermatological manifestations in 75 cases with clinicopathologic correlation. Arch Dermatol 1994; 130(7):861–867.

CHURG STRAUSS SYNDROME

Synonym: Allergic granulomatosis (with asthma).

Clinical Presentation (Fig. 14):

- Characterized by
  - Asthma, usually of adult onset and other allergic symptoms (allergic rhinitis)
  - Peripheral and tissue eosinophilia
  - Systemic vasculitis
- Three phases have been described in Churg Strauss syndrome
  - *First phase*: persistent asthma and other atopic diatheses
  - *Second phase*: onset and relapses of eosinophilia affecting one or more organs (e.g., eosinophilic pneumonia) and blood
  - *Third phase*: systemic vasculitis
- Disease has been triggered by massive inhalation of particles, rapid steroid tapering, desensitization, or exposure to drugs such as leukotriene receptor antagonists.
- Compared to Wegener's granulomatosis patients, Churg Strauss syndrome patients have less frequent renal disease (<40%) more frequent cutaneous (<80%), peripheral nerve (≤80%), and cardiac disease (≤50%)
- Skin manifestations of CSS include:
  - Palpable purpura, petechiae, ecchymoses and/or hemorrhagic bullae (≤50%) (Fig. 14A)
  - Dermal and subcutaneous papules and nodules often located on the scalp or symmetrically distributed over the extremities (elbows) (~30%)
  - Urticaria and/or erythematous macules (≤25%), and livedo reticularis

Histology (Fig. 14):

- Three broad categories of changes are identified, which can frequently be identified together:
  - Vasculitis
    - Mostly small vessel eosinophil rich neutrophilic vasculitis affecting superficial and mid-dermal vessels (Fig. 14B)
    - Eosinophilic rich neutrophilic muscular vessel vasculitis (Fig. 14B)
  - Dermal eosinophilia
  - Palisading neutrophilic and granulomatous dermatitis with abundant eosinophils and eosinophilic granules and debris coating degenerated collagen bundles ("red" granulomas)

References:

1. Davis MD, Daoud MS, et al. Cutaneous manifestations of Churg-Strauss syndrome: a clinicopathologic correlation. J Am Acad Dermatol 1997; 37(2 Pt 1):199–203.
2. Della Rossa A, Baldini C, Tavoni A, et al. Churg-Strauss syndrome: clinical and serological features of 19 patients from a single Italian centre. Rheumatology (Oxford) 2002; 41(11): 1286–1294.
3. Guillevin L, Cohen P, Gayraud M, Lhote F, Jarrousse B, Casassus P. Churg-Strauss syndrome. Clinical study and long-term follow-up of 96 patients. Medicine (Baltimore) 1999; 78(1):26–37.

4. Kawakami T, Soma Y, Kawasaki K, Kawase A, Mizoguchi M. Initial cutaneous manifestations consistent with mononeuropathy multiplex in Churg-Strauss syndrome. Arch Dermatol 2005; 141(7):873–878.

MICROSCOPIC POLYANGIITIS

Synonyms: Microscopic polyarteritis; renal-dermal vasculitis syndrome.

Clinical Presentation (Fig. 15):

- Systemic neutrophilic small vessel vasculitis without extravascular granulomas or asthma
- Commonly associated with rapidly progressive renal disease (focal segmental necrotizing glomerulonephritis), skin involvement, and antibodies to pANCA (mostly MPO) (≤80%)
- Skin lesions found in MPA
  - Palpable purpura and petechiae (≥75%) (Fig. 15A)
  - ≤20% splinter hemorrhages (Fig. 15B), nodules, palmar erythema, and livedo
- Criteria for diagnosis:
  - Lack of biopsy or surrogate markers of granulomatous inflammation (e.g., lung cavities or infiltrates more than one month duration)
  - Biopsy confirmation of neutrophilic small vessel vasculitis and/or glomerulonephritis with few or no immune deposits
  - Involvement of more than one organ system documented by biopsy or surrogate marker such as proteinuria and hematuria for glomerulonephritis

Histology (Fig. 15):

- Small vessel neutrophilic vasculitis (Fig. 15C)

References:

1. Jennette JC, Thomas DB, Falk RJ. Microscopic polyangiitis (microscopic polyarteritis). Semin Diagn Pathol 2001; 18(1):3–13.
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CUTANEOUS POLYARTERITIS NODOSA

Synonyms: Cutaneous periarteritis nodosa; localized polyarteritis nodosa.

Clinical Presentation (Fig. 16):

Skin Manifestations:

- Painful 0.5 cm to 2 cm lower to upper extremity nodules associated with livedo reticularis (Fig. 16C)
- Ulcers
- Gangrene and digital necrosis, rare
- Atrophie blanche can be a manifestation in patients who have:
  - No evidence of venous insufficiency and thrombophilia
  - Signs of mononeuritis multiplex
- Benign course in most patients including children
  - Patients with ulcers have more prolonged course and associated neuropathy
  - Rare cases have progressed to systemic polyarteritis nodosa after more than 15 years follow up
- Infectious causes can be found in some cases such as streptococcal infection or infectious hepatitis due to hepatitis B virus
- Absence of immunologic abnormalities such as positive ANA (antinuclear antibody), rheumatoid factor, cryoglobulins, or low complement level

Severity Classification:

- *Class I, mild disease*: Nodular skin lesions, livedo reticularis and/or mild polyneuropathy
- *Class II, severe disease*: Prominent livedo, ulcers, pain, polyneuropathy, and constitutional symptoms of fever, malaise, arthralgias
- *Class III*: Progressive systemic disease—necrotizing livedo, acral gangrene, foot drop, progressive musculoskeletal involvement, positive autoimmune tests, and eventual visceral involvement

Histology (Fig. 16):

- Neutrophilic muscular vessel vasculitis occurring typically at the dermal-subcutis junction where arteries bifurcate or within the subcutis (Fig. 16B)
  - Biopsy site selection is aided by having the patient in the standing position for a few moments to make the nodose lesions more readily palpable
  - Repeated and deep biopsies, accompanied by serial sections may be necessary to demonstrate the vasculitis as vessel involvement is segmental and focal
  - Giant cells and macrophages can rarely be found in the lumen and wall of PAN lesions
- Older, advanced lesions exhibit vessel wall fibrosis, loss of the internal elastic lamina (Fig. 16D), and neovascularization of the adventitia (Fig.16C)

References:

1. Chen KR. Cutaneous polyarteritis nodosa: a clinical and histopathological study of 20 cases. J Dermatol 1989; 16(6): 429–442.
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3. Diaz-Perez JL, Winkelmann RK. Cutaneous periarteritis nodosa. Arch Dermatol 1974; 110(3):407–414.
4. Mimouni D, Ng PP, Rencic A, Nikolskaia OV, Bernstein BD, Nousari HC. Cutaneous polyarteritis nodosa in patients presenting with atrophie blanche. Br J Dermatol 2003; 148(4):789–794.

NODULAR VASCULITIS

Synonym: Erythema induratum.

Clinical Presentation (Fig. 17):

- Nodular vasculitis (lobular panniculitis with vasculitis) was originally defined as erythema induratum (red, indurated plaques on the lower legs) associated with tuberculosis, treatment of which leads to clearing of skin lesions (Fig. 17A)
  - Other etiologic agents include drugs and nonmycobacterial infections associated with circulating immune complexes

- Occurs in young to middle-aged females
  - Presents as painful, tender, violaceous, and indurated nodules affecting the calves, with less frequent involvement of shins, ankles, thighs, and upper extremities
  - Ulceration common
  - Healing is often accompanied by scarring with hyperpigmentation

Histology (Fig. 17):

- Lobular panniculitis (Fig. 17D) surrounding central muscular vessel showing a vasculitis that can be lymphocytic (Fig. 17B), neutrophilic or granulomatous
  - Varying degrees of coagulative and caseous necrosis and granulomatous inflammation are found surrounding the vasculitis focus (Fig. 17C)
    - In contrast, lesions of cutaneous polyarteritis nodosa exhibit inflammation that does not extend past the adventitia of the artery

References:

1. Kwok CY, Goh CL, Ong BH. Retrospective study of the epidemiology of nodular vasculitis followed up in the National Skin Centre, Singapore. Clin Exp Dermatol 1997; 22(1):17–19.
2. Parish WE, Rhodes EL. Bacterial antigens and aggregated gamma globulin in the lesions of nodular vasculitis. Br J Dermatol 1967; 79(3):131–147.
3. Requena L, Sanchez Yus E. Panniculitis. Part II. Mostly lobular panniculitis. J Am Acad Dermatol 2001; 45(3):325–361.

GIANT CELL ARTERITIS

Synonyms: Temporal arteritis.

Clinical Presentation (Fig. 18):

- Marked fair-skinned Caucasian female predominance and restriction to old age, and association with polymyalgia rheumatica
- Clinical manifestations due to ischemia secondary to endarteritis obliterans, or exuberant systemic systems of malaise, weight loss, and fever due to release of inflammatory cytokines
- Signs and symptoms include headache, jaw claudication, and visual and neurological disturbances
  - Cutaneous signs consist of scalp tenderness, scalp blanching, decreased or loss of temporal artery pulses, and/or temporal artery thickening (cord-like)
- Complications consist of scalp necrosis (Fig. 18A), visual loss, gangrene of the tongue, and nasal septum necrosis
- Accurate and timely diagnosis is important because serious morbidity, even death may occur if proper treatment is delayed

Histology (Fig. 18):

- Granulomatous muscular vessel wall vasculitis with giant-cell containing inflammatory infiltrates (Figs. 18B–D); diagnostic features are:
  - Segmental inflammation and disruption of temporal artery media and intima
  - Fragmentation of the internal elastic lamina
- Late lesions exhibit segmental loss of the elastic lamina and stenotic lumen secondary to replacement of the arterial wall and lumen by myointima hyperplasia, myxomatous stroma, and scattered inflammatory cells

References:

1. Currey J. Scalp necrosis in giant cell arteritis and review of the literature. Br J Rheumatol 1997; 36(7):814–816.
2. Langford CA. Vasculitis in the geriatric population. Clin Geriatr Med 2005; 21(3):631–647, viii.
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INCIDENTAL NEUTROPHILIC VASCULITIS

Neutrophilic small vessel vasculitis can sometimes be noted underlying an ulcer formed by another process (trauma or surgery), or within a diffuse neutrophilic infiltrate, or adjacent to an abscess. This is incidental vascular injury and can usually be differentiated from primary vasculitis by correlation with history and the focal nature of the vessel damage that is restricted to the area of trauma or ulceration; the vessels in the surrounding skin will be unaffected. (The term secondary vasculitis is not used as it refers to vasculitis developing secondarily in systemic disease, for example, rheumatoid or lupus vasculitis). Neutrophilic dermatoses, for example Sweet's syndrome, can also exhibit neutrophil-mediated vessel damage that can resemble small vessel neutrophilic vasculitis in approximately 29% of the cases, typically affecting vessels within the diffuse dermal neutrophilic infiltrate compared to the angiocentric neutrophilic infiltrate of leukocytoclastic vasculitis (LCV). In the setting of a neutrophilic dermatosis, vasculitis is suspected to be an epiphenomenon due to neutrophil byproducts such as reactive oxygen species and degradative enzymes, and not a primary immune-mediated event. Figure 19 shows a case of neutrophilic dermatosis of the dorsum of the hands (a.k.a., pustular vasculitis) with incidental, neutrophilic small vessel vasculitis (Fig. 19B, circle).

References:

1. Carlson JA, Ng BT, Chen KR. Cutaneous vasculitis update: diagnostic criteria, classification, epidemiology, etiology, pathogenesis, evaluation and prognosis. Am J Dermatopathol 2005; 27(6):504–528.
2. DiCaudo DJ, Connolly SM. Neutrophilic dermatosis (pustular vasculitis) of the dorsal hands: a report of 7 cases and review of the literature. Arch Dermatol 2002; 138(3):361–365.

PSEUDOVASCULITIS

As the clinical manifestations of vasculitis are protean, and diagnosis is based on a constellation of clinical, histologic, imaging and laboratory features, it is not surprising that nonvasculitis disorders can mimic vasculitis. Many of these pseudovasculitic disorders will involve dermal hemorrhage and/or occlusion of vessels with infarction by emboli, thrombi, vasospasm, fibro-intimal-medial hyperplasia secondary to vessel trauma, or noninflammatory vessel wall pathology such as calcification or amyloid deposition. Pseudovasculitis can be subdivided into those disorders that primarily cause hemorrhage (purpura) and those that primarily occlude vessels. Table 8 lists common, uncommon, and rare pseudovasculitic disorders. Like vasculitic lesions, pseudovasculitis is rare and results in a varied clinical

Table 8 Mimickers of Vasculitis (Pseudovasculitis)

Relative Frequency	Pseudovasculitic Disorder	Mechanism
Common	Antiphospholipid antibody syndrome	Thrombosis
	Cholesterol embolization	Embolus
	Infective endocarditis	Infection & Embolus
	Pigmented purpuric dermatitis	Hemorrhage
	Solar purpura	Hemorrhage
	Purpura fulminans	Thrombosis
	Warfarin necrosis	Thrombosis
	Livedo vasculopathy	Thrombosis
Less frequent than vasculitis	Hypothenar hammer syndrome (Fibromuscular dysplasia)	Vascular trauma
	Scurvy	Hemorrhage
	Thrombotic thrombocytopenic purpura	Thrombosis
Rare	Amyloidosis	Vessel wall pathology
	Calciphylaxis	Vessel wall pathology
	Cardiac myxoma	Embolus
	Ergotamine and cocaine abuse	Vasospasm
	Angiotropic B cell lymphoma	Intravascular proliferation/embolus
Signs indicating the possibility of pseudovasculitis		
Atherosclerosis, significant disease		
Nonconfirmatory biopsies for vasculitis		
Cardiac murmur		
Livedo reticularis		
Absence of inflammatory markers (e.g., normal ESR)		
Abnormal eating habits (e.g., chronic alcoholism)		
Isolated vascular lesions on imaging studies		

Abbreviation: ESR, erythrocyte sedimentation rate.
Source: From Ref. 1.

picture that includes manifestations such as livedo reticularis, purpura, "purple toe syndrome," ulcer, infarct, and erythromelalgia. Biopsy of the skin allows separation of these vaso-occlusive disorders from vasculitis (Figs. 20–22).

Figure 20 shows a case of antiphospholipid antibody syndrome can present as cutaneous infarcts (Fig. 20A) that can mimic vasculitis. This syndrome is characterized by venous and arterial thromboses, fetal losses and thrombocytopenia, which are associated with the presence of antiphospholipid antibodies. Histologically, noninflammatory vascular thrombi are identified (Figs. 20B and C) that affect arterioles, arteries, and veins. At most sparse, lymphocytic infiltrates will be found around the involved vessels associated with rare pyknotic endothelial nuclei. Incompetent or "leaky" blood vessels due to chronic inflammation, vessel wall pathology (e.g., amyloidosis), or dietary deficiencies (Scurvy—vitamin C deficiency) can lead to hemorrhage into the dermis that can be mistaken clinically for vasculitis. Solar or senile purpura, characterized by large ecchymoses over the extensor surfaces of forearms and hands of elderly individuals or in this case the forehead (Figs. 21A), is believed to be the result of minor injury to poorly supported vessels in the dermis as these patients typically have abundant solar elastotic material and atrophic dermal collagen bundles (Fig. 21B). Pigmented purpuric dermatoses are a group of chronic inflammatory, nonvasculitic dermatoses that all have in common a purpuric clinical appearance (Fig. 21C) and variable numbers of extravasated erythrocytes and hemosiderin deposits associated with perivascular lymphocytic inflammatory infiltrates without fibrinoid necrosis of vessels, histologically (Fig. 21D). Lastly, livedo vasculopathy (a.k.a., atrophie blanche, livedo vasculitis, and segmental hyalinizing vasculitis) is one relatively common disorder that can mimic, both clinically and histologically, vasculitis. It is a chronic thrombo-occlusive disorder of the feet and lower legs. Early lesions show petechiae, but characteristic features are recurrent, bizarrely shaped ulcers that heal leaving hyperpigmentation and white atrophic stellate scars (atrophie blanche) (Figs. 22A and B). Most morphological studies have shown fibrin deposition within both the wall and lumen of affected vessels associated with ulcer, dermal fibrosis, and a perivascular lymphocytic infiltrates (Figs. 22B and C). If neutrophils are present, they are few and do not disrupt vessels or show leukocytoclasis, and are often sign of adjacent ulceration.

References:

1. Grau R. Pseudovasculitis: mechanisms of vascular injury and clinical spectrum. Curr Rheumatol Rep 2002; 4(1):83–89.
2. Sacks KE. Mimickers of vasculitis. In: Koopman WJ, Moreland LW, eds. Arthritis and Allied Conditions. 15th ed. Philadelphia: Lippincott Williams and Wilkins; 2005:1845–1867.

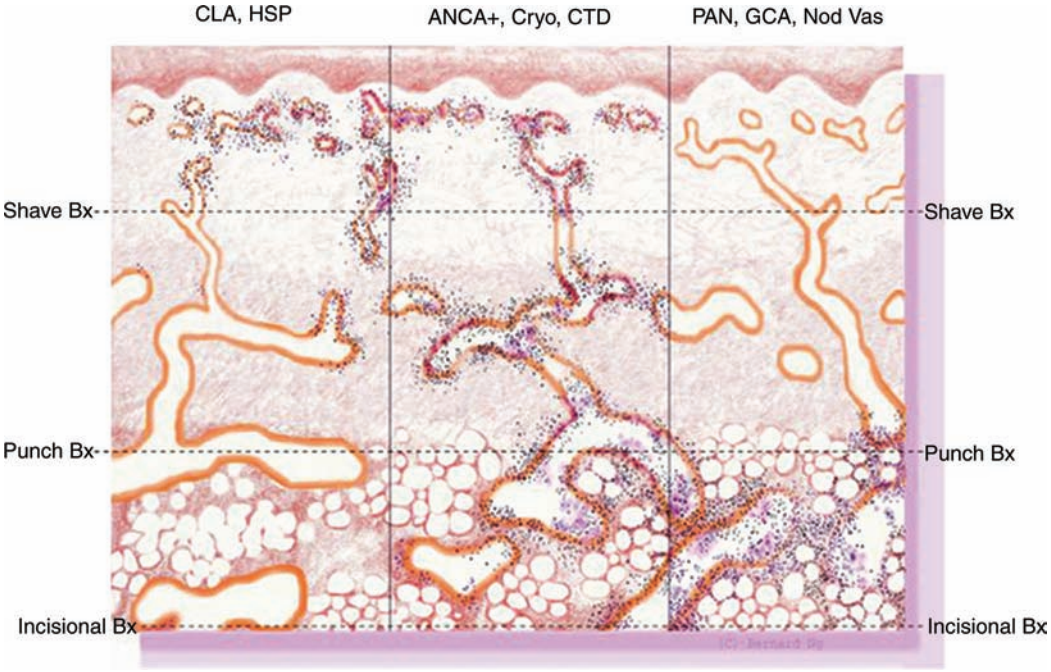

Figure 1 Cutaneous vasculitis classification is based on the size of vessels involved. *Source*: From Ref. 1.

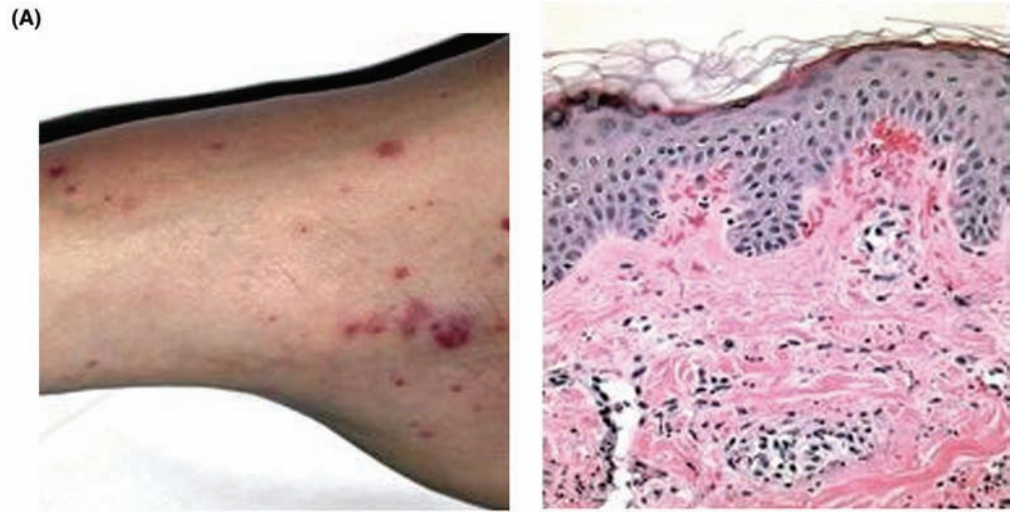

Figure 2 Clinicopathologic correlation: cutaneous manifestations correlate with size of vessel affected by vasculitis. (*Continued*)

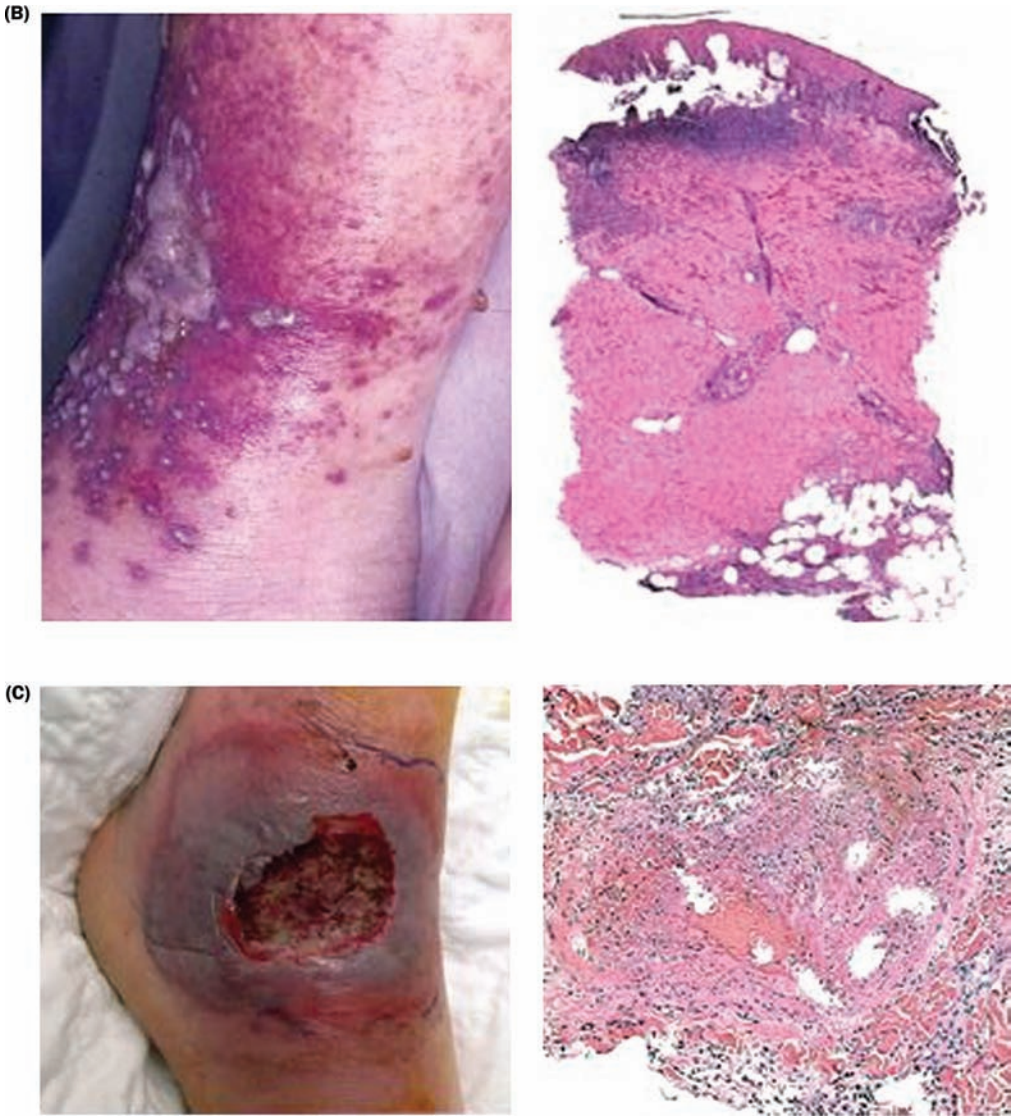

Figure 2 *Continued.*

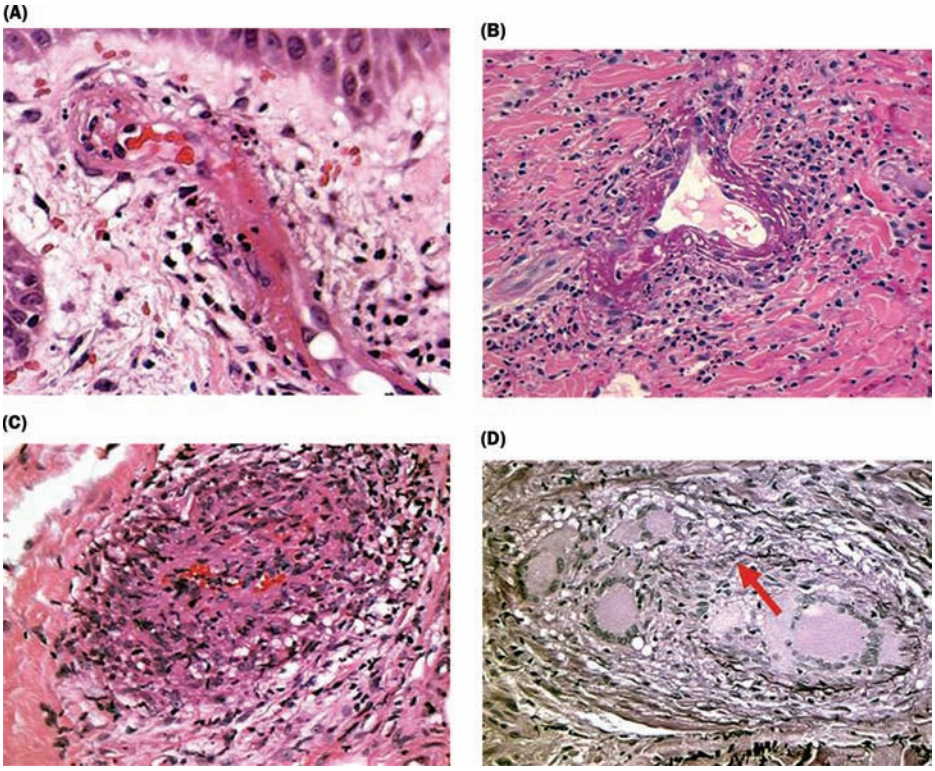

Figure 3 Diagnostic histologic criteria for vasculitis.

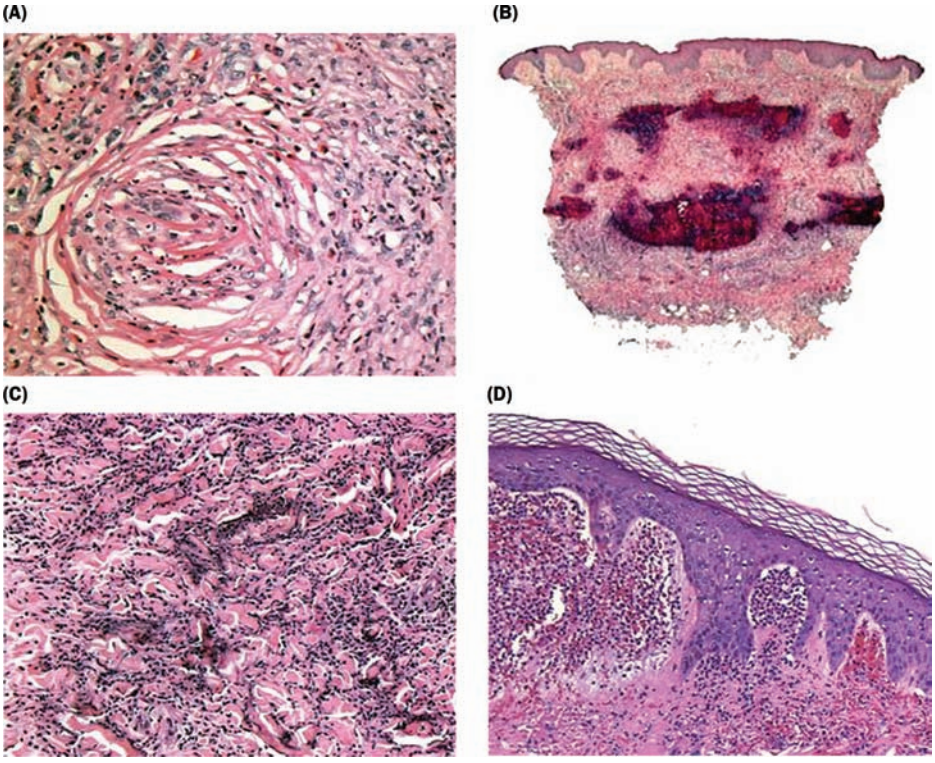

Figure 4 Histologic patterns indicative of etiology.

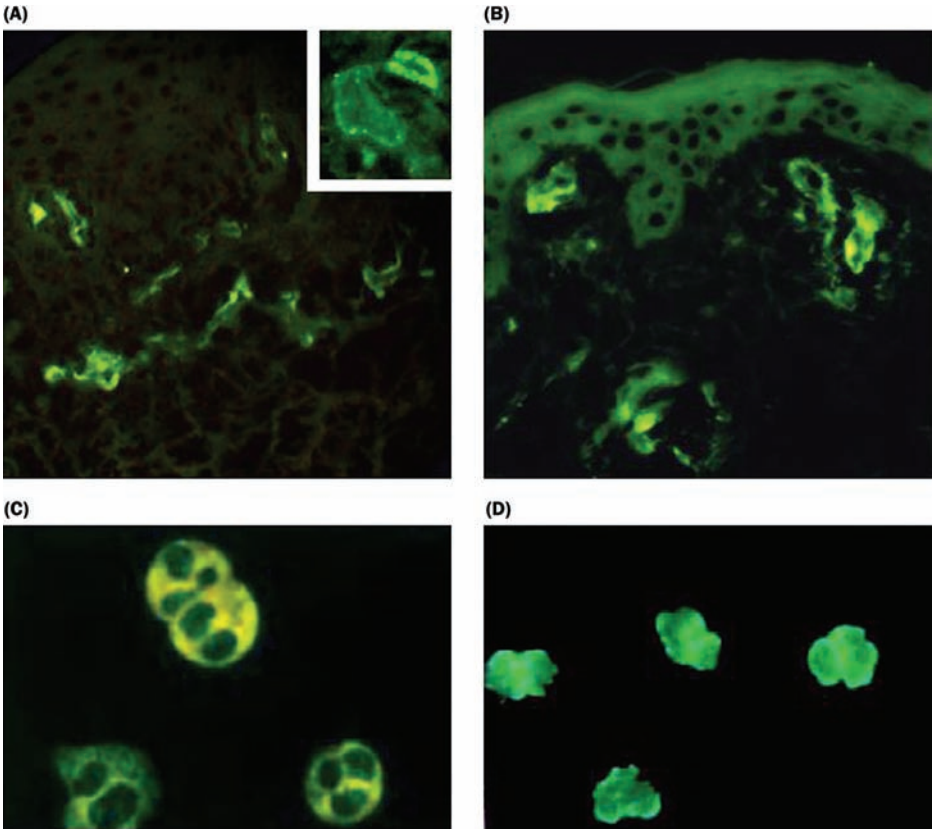

Figure 5 Direct immunofluorescence findings and pathophysiology of vasculitis. *Source*: **C** and **D** reproduced with permission from Savige JA et al. J Clin Pathol 1998; 51(8):568–575.

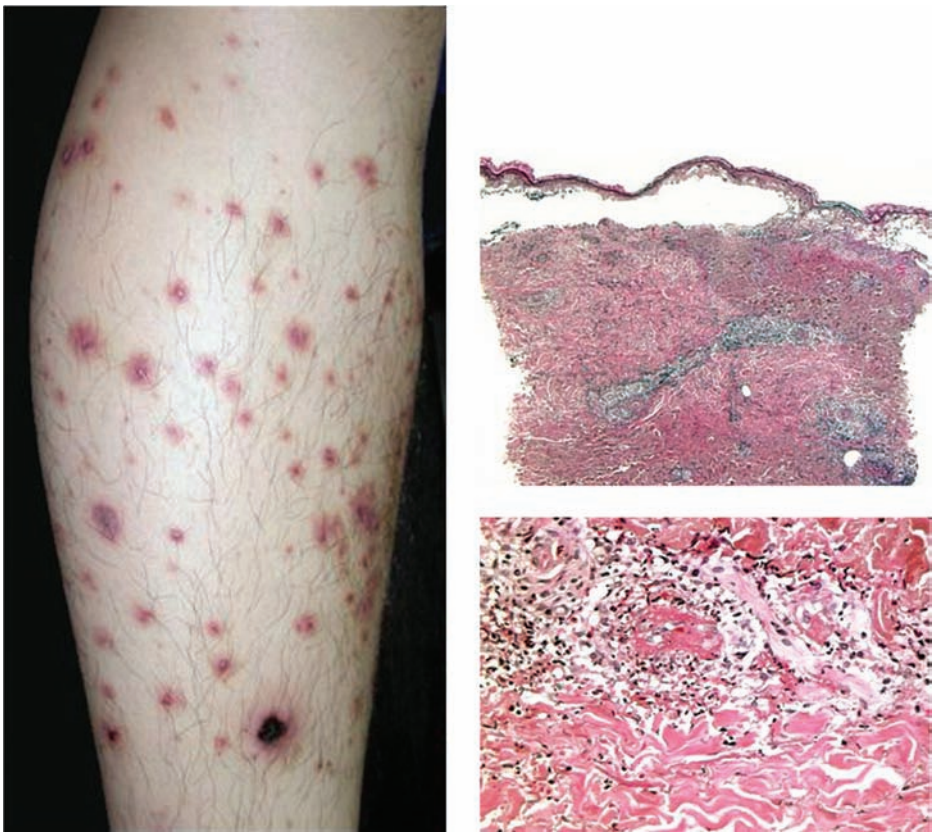

Figure 6 Cutaneous leukocytoclastic angiitis (leukocytoclastic vasculitis).

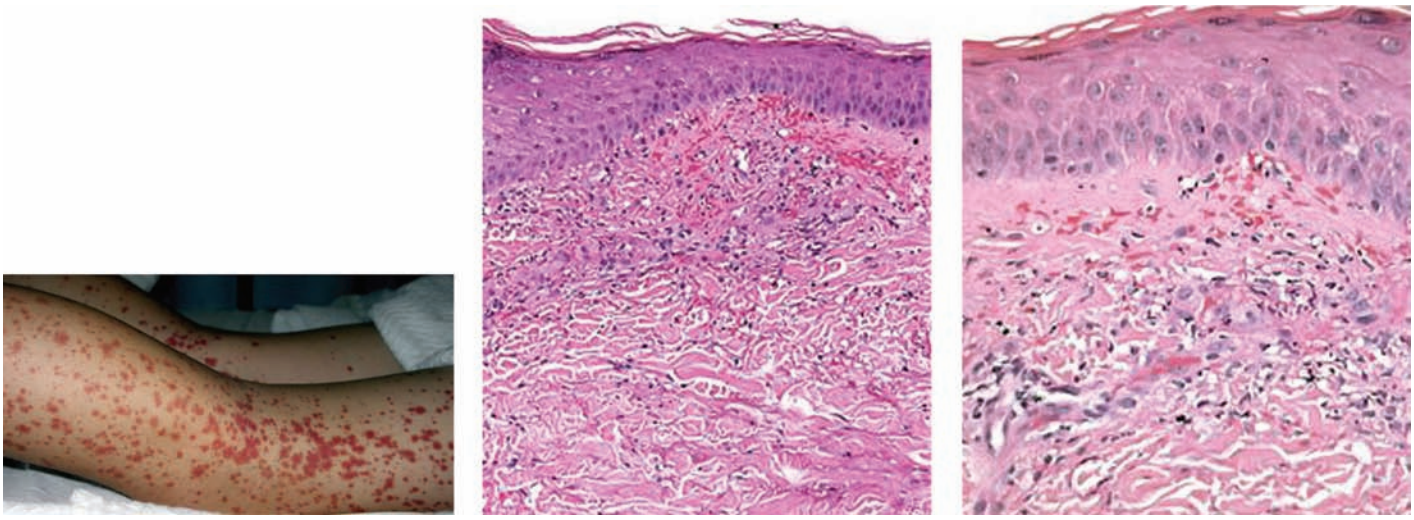

Figure 7 Henoch Schonlein purpura.

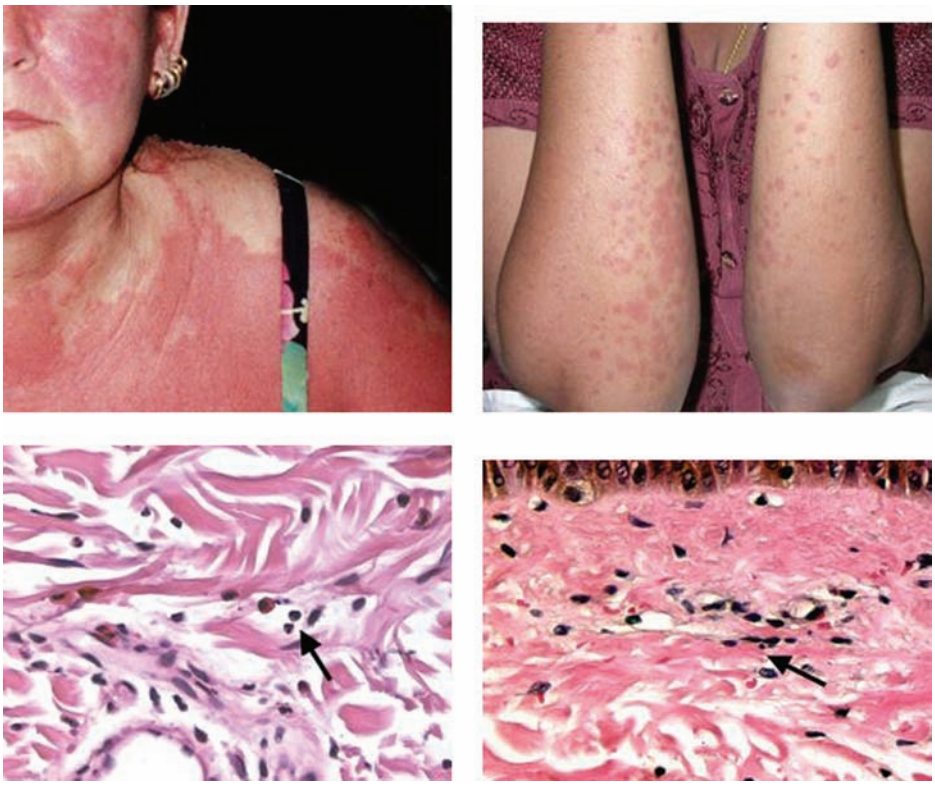

Figure 8 Urticarial vasculitis: two patients with urticarial vasculitis, both of whom showed perivascular nuclear debris (*arrows*) on biopsy are rare extravasated red blood cells.

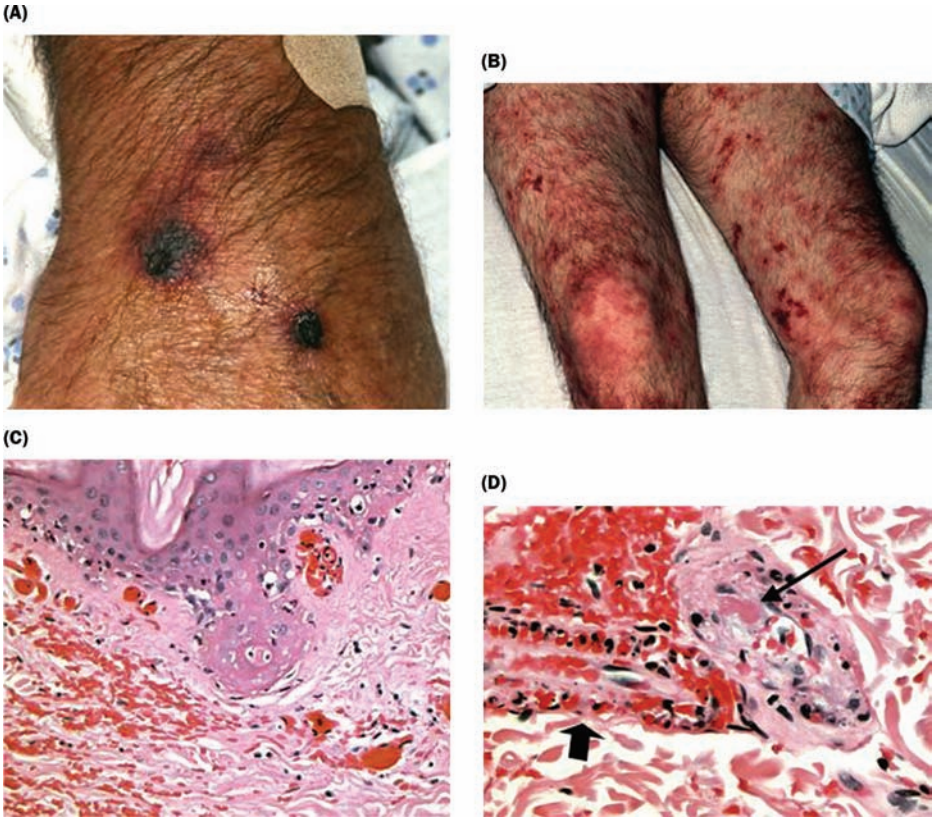

Figure 9 Septic vasculitis due to *Capnocytophaga canimorsus*. Necrosis at the site of dog bite is a clinical clue to infection with *Capnocytophaga canimorsus* (**B**).

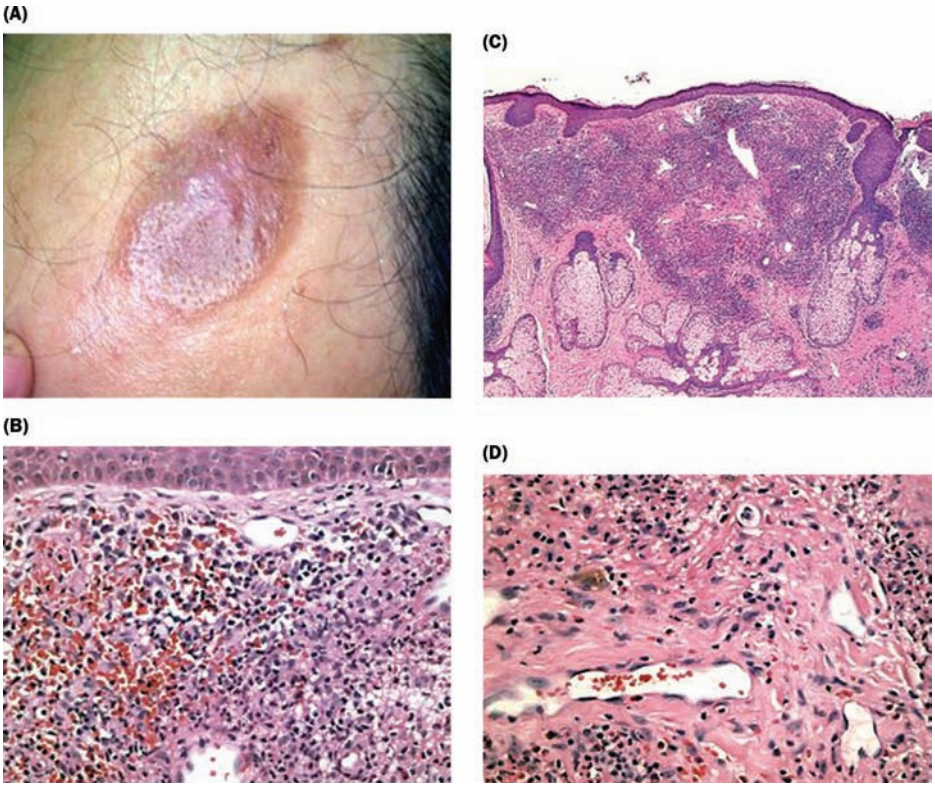

Figure 10 Granuloma faciale.

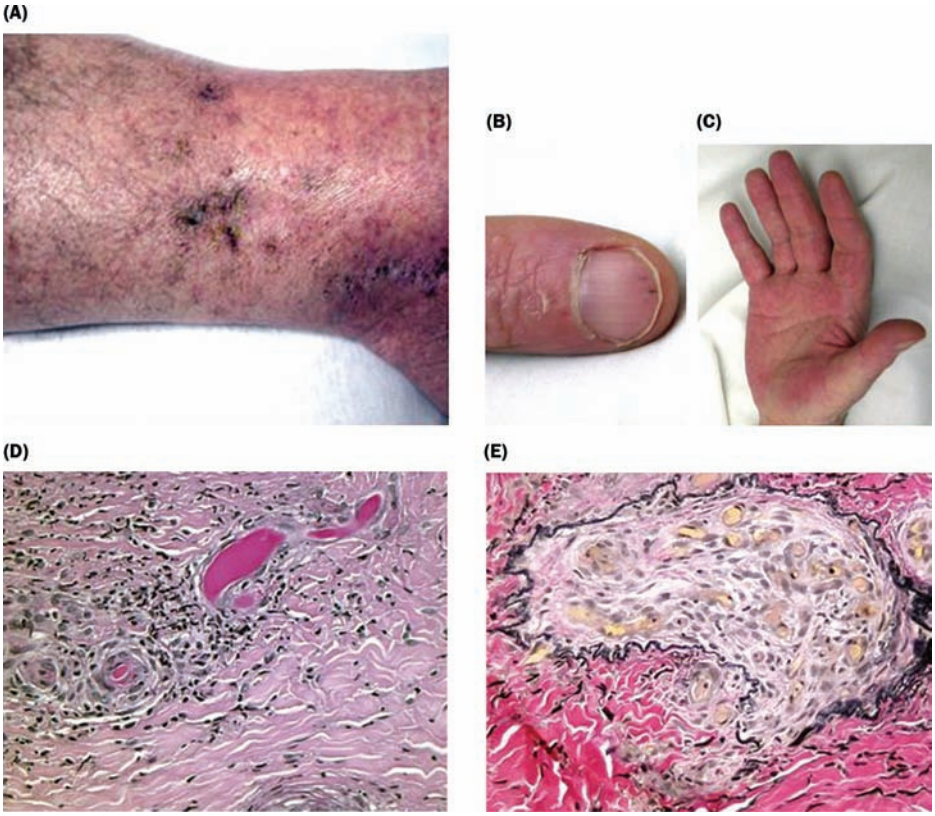

Figure 11 Cryoglobulinemic vasculitis related to hepatitis C infection in a 52-year-old man with a history of multiple blood transfusions after car accident 30 years prior.

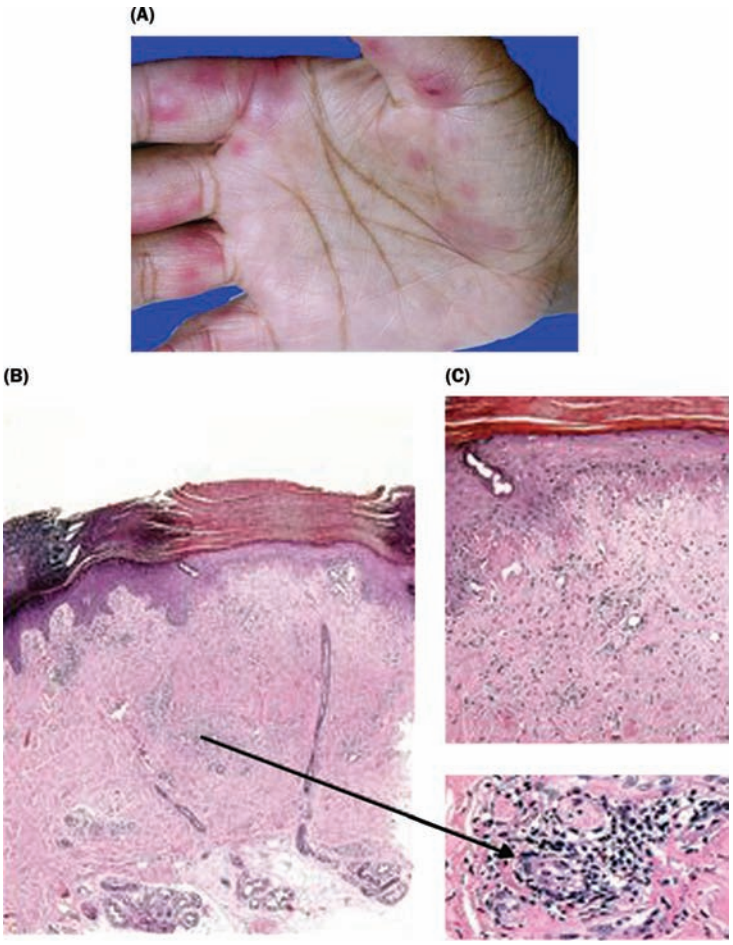

Figure 12 Lupus vasculitis: two patients with painful palmar erythematous macules (**A**) and punctate palmar scars (**D**). (*Continued*)

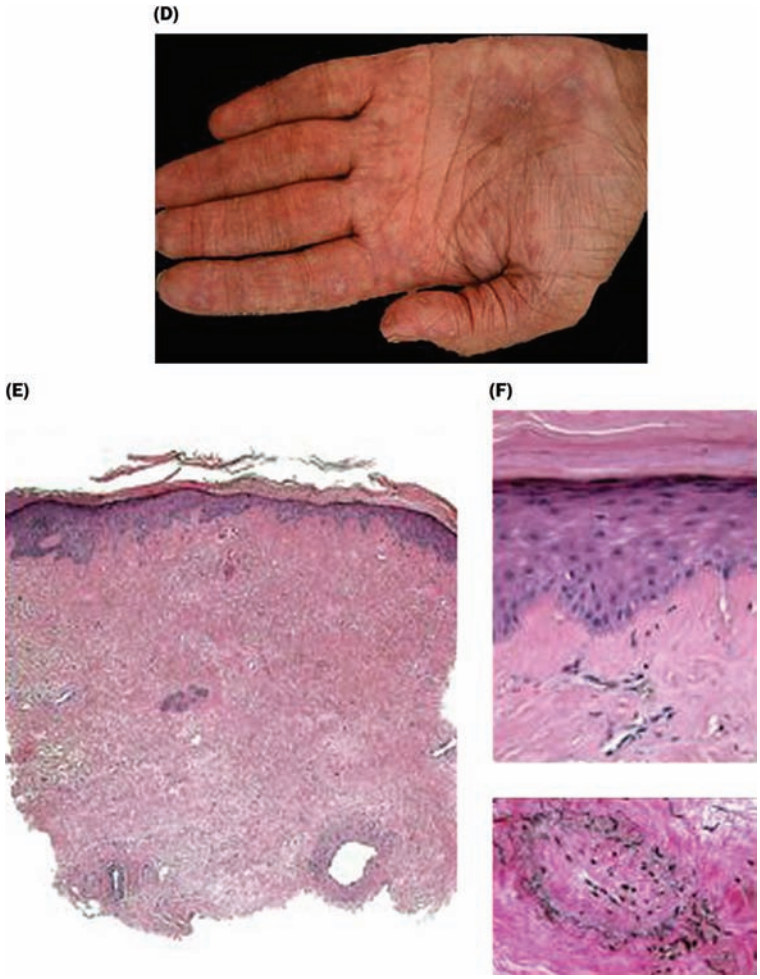

Figure 12 *Continued.*

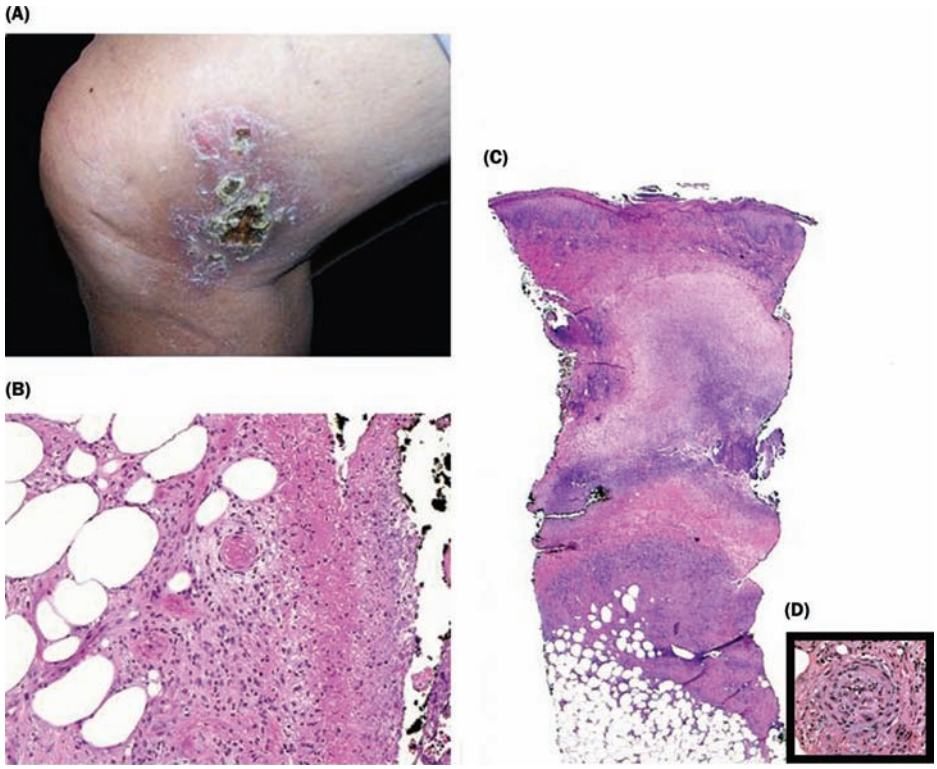

Figure 13 (Limited) Wegener's granulomatosis showing a cribiform (pyoderma gangrenosum-like) ulcer over medial thigh (**A**).

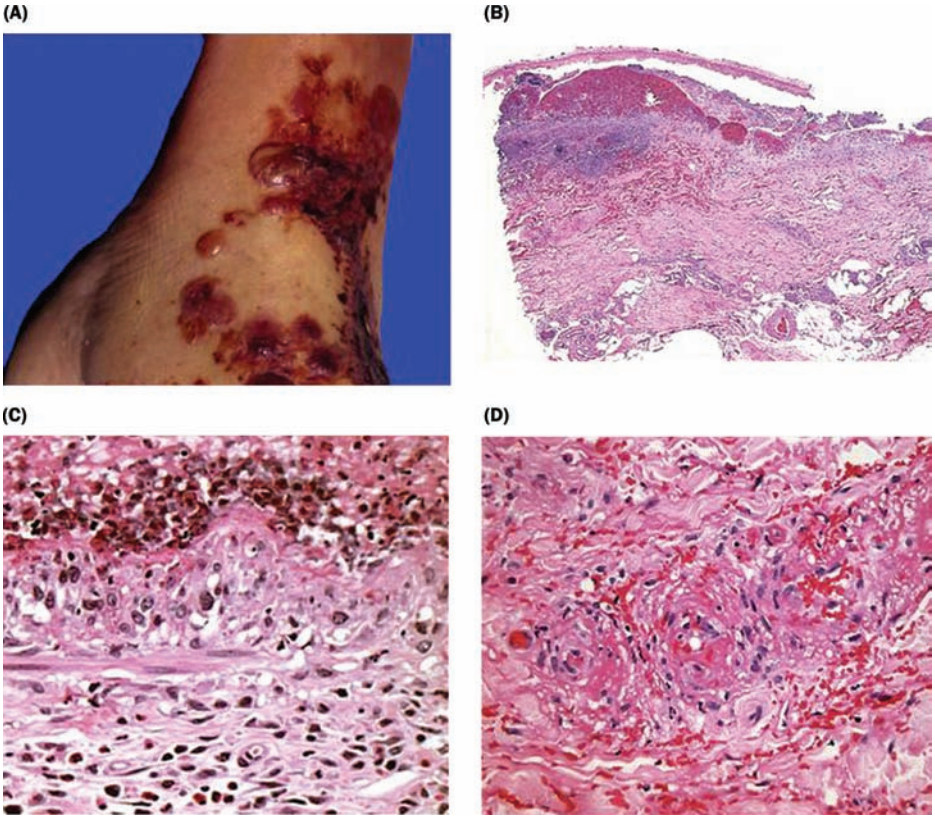

Figure 14 Churg-Strauss syndrome presenting as hemorrhagic bullae over lower extremities (**A**).

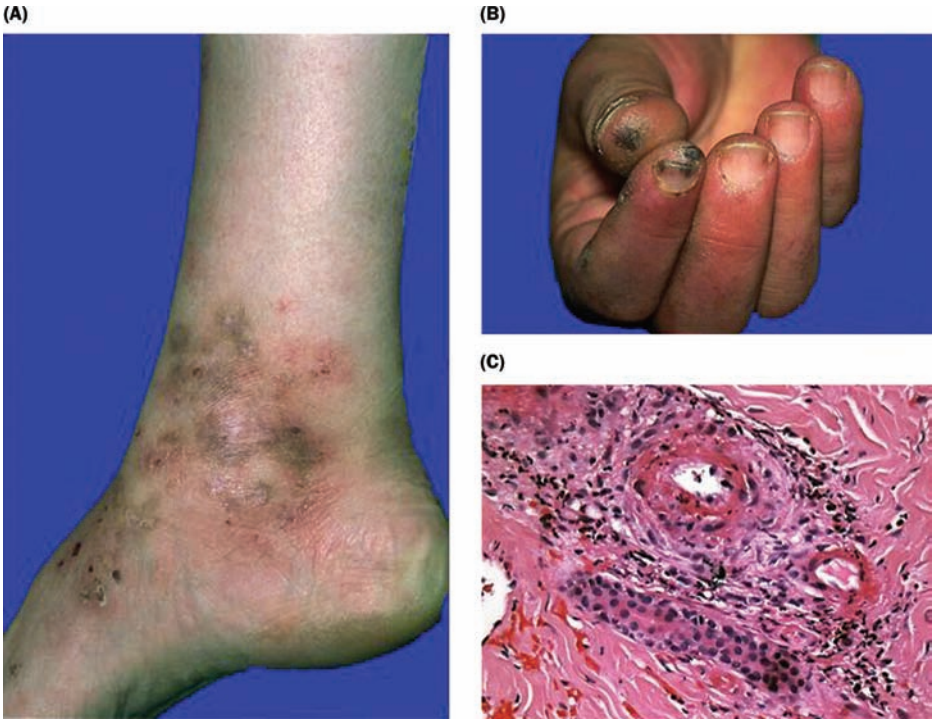

Figure 15 Microscopic polyangiitis. *Source*: Courtesy of Jörg Schaller, Bochum, Germany.

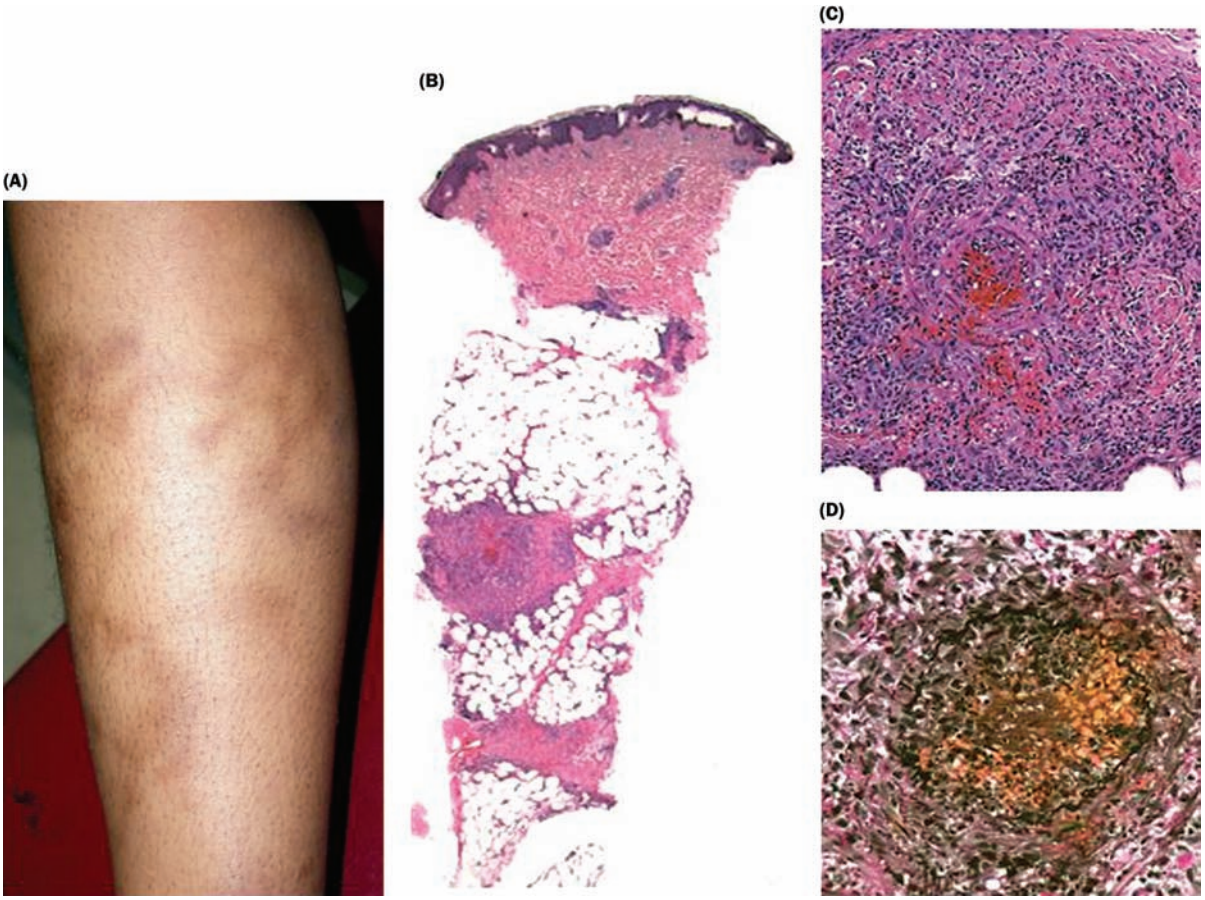

Figure 16 Cutaneous polyarteritis nodosa presenting as livedo reticularis (**A**).

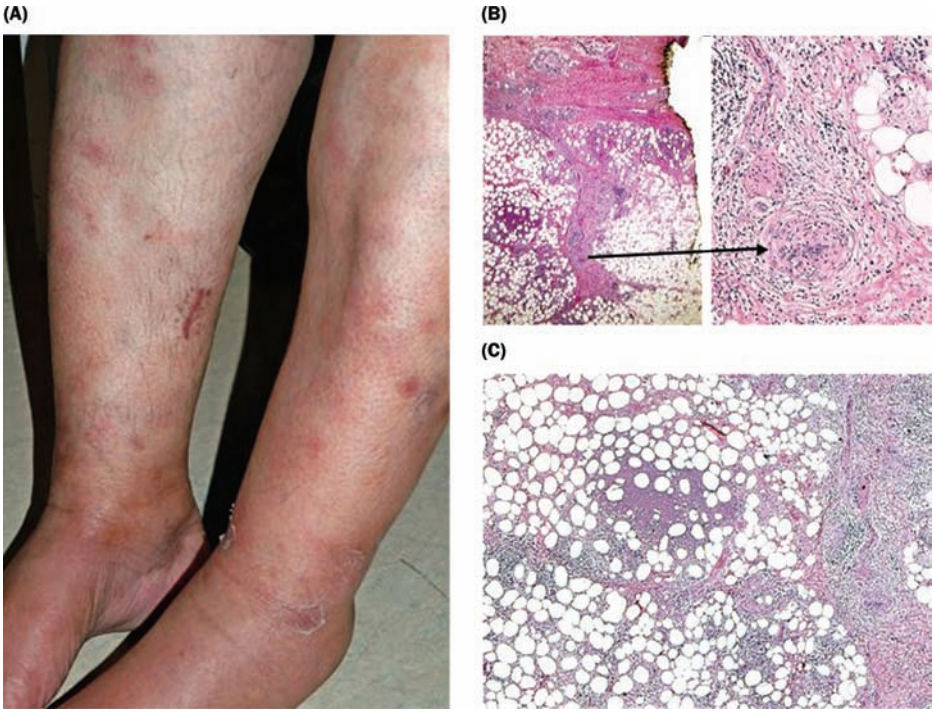

Figure 17 Nodular vasculitis due to tuberculosis (erythema induratum). *Source*: Clinical photo and histologic material courtesy of Harvey Lui MD and Nigel Ball MD, Vancouver, Canada.

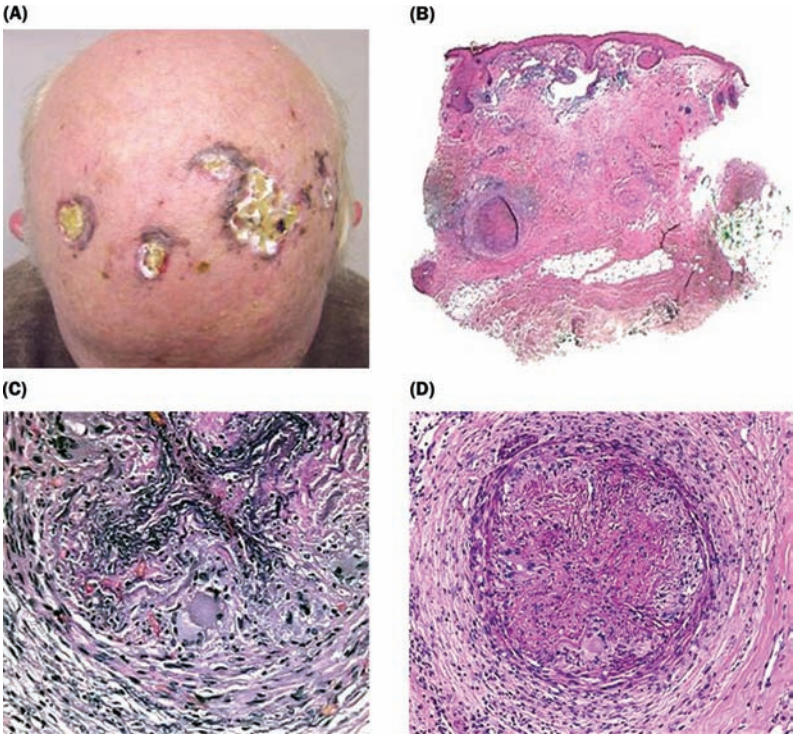

Figure 18 Giant cell arteritis presenting as scalp necrosis.

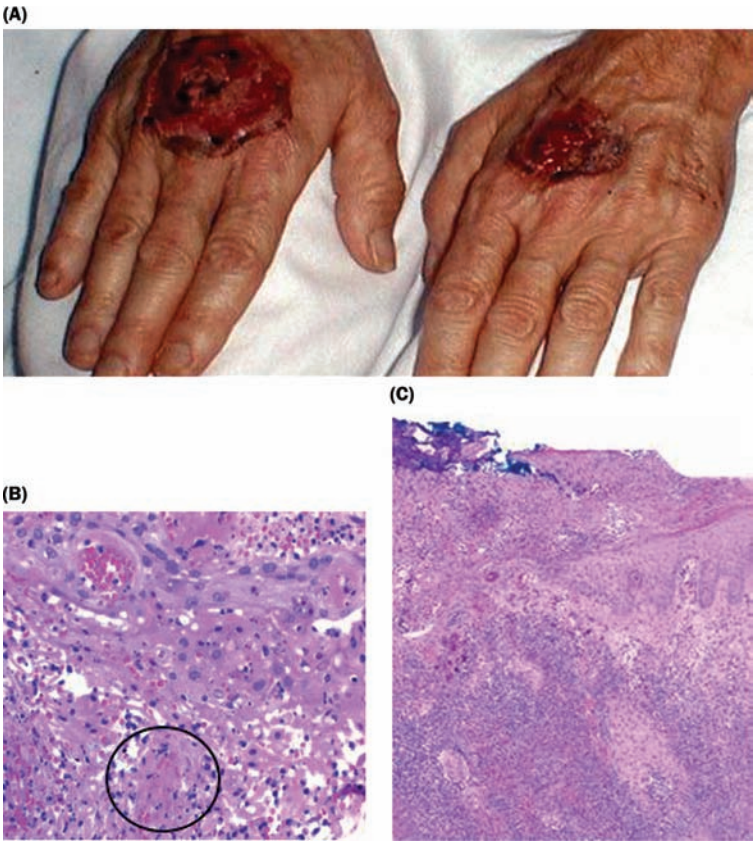

Figure 19 Pustular dermatosis of the dorsum of the hands.

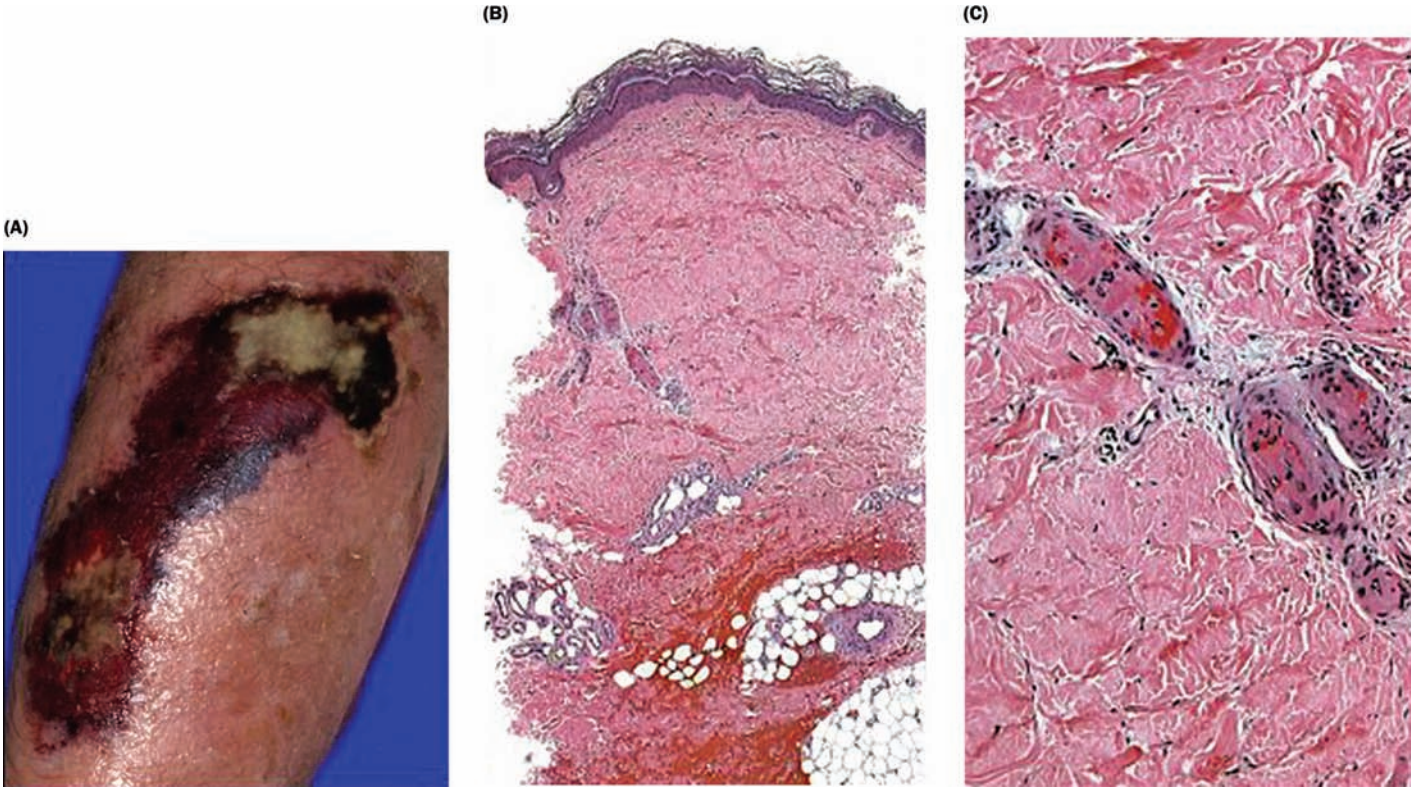

Figure 20 Thrombosis due to antiphospholipid antibody syndrome.

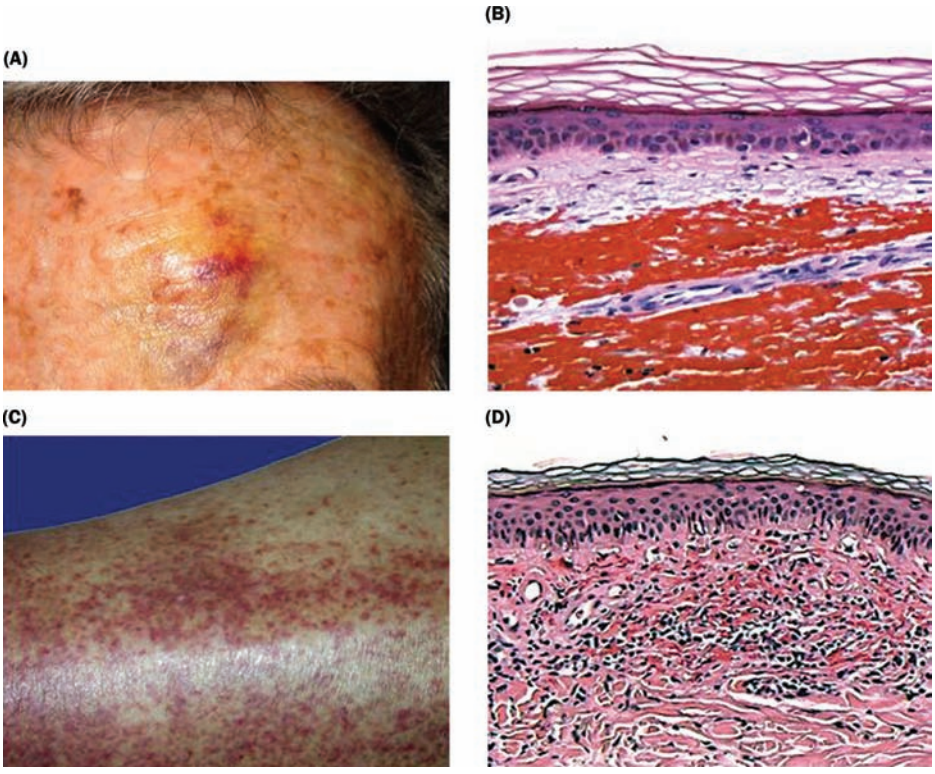

Figure 21 Hemorrhage due to solar purpura (**A**,**B**) and pigmented purpuric dermatitis (**C**,**D**).

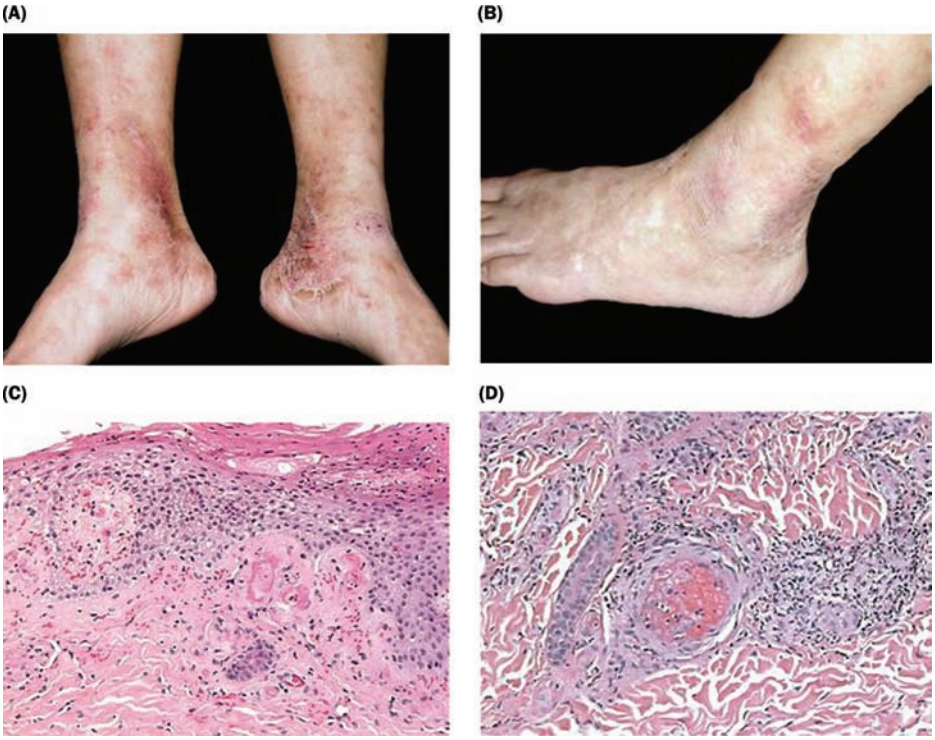

Figure 22 Livedo vasculopathy (atrophie blanche).

8

Nodular and Diffuse Dermatitis

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CONTENTS

NODULAR AND DIFFUSE DERMATITIS

Nodular and diffuse dermatitis represents a group of diverse inflammatory conditions, each of which presents with inflammatory cells present in nodules filling portions of the dermis or diffusely filling the entire dermis. As with all inflammatory patterns, there is significant overlap between nodular dermatitis and diffuse dermatitis—many of the same diseases may present with either pattern. Similarly, cutaneous inflammatory conditions which are most often superficial or superficial and deep perivascular infiltrates may at times present with a nodular or diffuse pattern.

In this chapter, we will emphasize utilizing an algorithmic approach in diagnosing nodular and diffuse dermatitis. The concept of recognizing inflammatory conditions by their scanning power or architectural appearance is utilized to some degree in virtually every current dermatopathology text. The pattern approach to histologic diagnosis was firmly established by A. Bernard Ackerman in "Histologic Diagnosis of Inflammatory Skin Diseases, an Algorithmic Method Based on Pattern Analysis," first published in 1978. Much of this discussion is derived from Ackerman's method.

Diagnosis by pattern analysis has now been in use for almost 30 years. It has stood the test of time and its current popularity is due to the fundamental appeal and accessibility of an algorithmic approach and most importantly its utility and accuracy in arriving at a correct diagnosis. While the concept is simple, the application requires understanding of subtleties and much practice. The method involves recognition of various inflammatory patterns at scanning power, in this case nodules and diffuse infiltrates of inflammatory cells. Most patterns and their subdivisions are characterized by prototypes—that is, diseases which are the most common or best known examples of that pattern. Knowing the prototypes is exceedingly helpful in utilizing this approach to pathologic diagnosis. At each "fork" in the algorithm, decisions based on microscopic findings are made by the microscopist until reaching a limited differential diagnosis or specific diagnosis.

In inflammatory infiltrates determined to consist of nodules or diffuse involvement of the dermis, the next key question is "what are the preponderant inflammatory cells that make up the inflammatory infiltrates?" On this basis, nodular dermatitis can be subdivided into inflammatory conditions in which the following cells predominate: lymphocytes; neutrophils, neutrophils eosinophils, and plasma cells; eosinophils and plasma cells with lymphocytes; and histiocytes (granulomatous). Diffuse cutaneous inflammatory infiltrates, similarly, may be composed predominantly of the following inflammatory cells: lymphocytes; neutrophils; neutrophils and eosinophils; plasma cells; mast cells; abnormal leukocytes; and histiocytes (granulomatous). Nodular and diffuse infiltrates of histiocytes (granulomatous dermatitis) are the subject of Chapter 9. It is of some importance to note that diagnosis of neoplasms also is facilitated by a similar pattern approach. As a consequence, various neoplasms are considered in the differential discussion of inflammatory conditions that follow.

In summary, when first viewing a microscopic slide of a skin biopsy containing nodules or diffuse infiltrates of inflammatory cells, the key question is "which inflammatory cell or cells are predominant?" The following table lists examples of cutaneous conditions that may be characterized by nodular or diffuse cellular infiltrates.

NODULAR DERMATITIS
- **Lymphocytes predominate**
  - **Pseudolymphoma and lymphoma**
- **Neutrophils predominate**
  - **Acute febrile neutrophilic dermatosis**
  - **Leukocytoclastic vasculitis**
  - **Granuloma faciale**
  - **Follicular cyst, ruptured**
- **Neutrophils, eosinophils, and plasma cells prominent**
  - **Granuloma faciale/erythema elevatum diutinum**
  - **Granuloma gluteale infantum**
- **Eosinophils and plasma cells prominent with lymphocytes**
  - **Pseudolymphoma**
  - **Lymphoma**
- **Histiocytes predominate (granulomatous)**
  - **See Chapter 9**

(*Continued*)

NODULAR DERMATITIS (*Continued*)

- **Lymphocytes predominate**
  - **Pseudolymphoma**
  - **Lymphoma**
- **Neutrophils predominate**
  - **Sweet's syndrome**
  - **Pyoderma gangrenosum**
  - **Follicular cyst, ruptured**
  - **Granuloma faciale/erythema elevatum diutinum**
- **Neutrophils and eosinophils prominent**
  - **Granuloma faciale/erythema elevatum diutinum**
- **Plasma cells prominent**
  - **Rhinoscleroma, leishmaniasis, syphilis**
  - **Chancroid**
- **Mast cells prominent**
  - **Urticaria pigmentosa, nodular**
- **Abnormal leukocytes**
  - **Extramedullary hematopoiesis**
  - **Pseudolymphoma and lymphoma**
- **Histiocytes predominate (granulomatous)**
  - **See Chapter 9**

EXAMPLES OF NODULAR DERMATITIS

PSEUDOLYMPHOMA

Nodular dermatitis consisting predominantly of lymphocytes.

Synonyms: Cutaneous lymphoid hyperplasia; B- or T-cell lymphoid hyperplasia; lymphadenosis benigna cutis; lymphocytoma cutis.

Clinical Presentation:
- Commonly involves head, neck, and upper trunk
- Usually asymptomatic red-brown papules or nodules (Fig. 1A)
- Usually single, may be multiple, rarely widespread

Histopathology:
- Nodular to diffuse infiltrates of lymphocytes throughout the dermis and subcutaneous tissue (Fig. 1B)
- Polymorphous infiltrate usually (lymphocytes, plasma cells, histiocytes, eosinophils) (Fig 1C)
- Accentuation of the infiltrate in the upper dermis ("top heavy") rather than the lower dermis and subcutaneous fat ("bottom heavy")
- Lymphoid follicles with mantles uncommon
- Monoclonal antibodies usually demonstrate mixture of T-cells and B-Cells
- B-cells are usually polyclonal

Pathophysiology:
- Typically unknown
- There are various reports of the following uncommon causes of lymphoid hyperplasia: arthropod bites, gold exposure (jewelry/injections), cobalt, tattoos, red pigment, medications (phenytoin), hyposensitization injection, *Borrelia* infection (Europe)

Differential Diagnosis:
- Cutaneous follicle center lymphoma and extranodal marginal zone B-cell lymphoma—MALT type.

References:
1. Rodel RT, Santa Cruz DJ. Cutaneous pseudolymphomas. Dermatol Clint 1985; 3:719–735.
2. Cerroni L, Signoretti S, et al. Primary cutaneous marginal zone B-cell lymphoma. Am J Surg Pathol 1997; 21:1307–1315.

SWEET'S SYNDROME

Nodular dermatitis consisting predominantly of neutrophils.

Synonym: Acute febrile neutrophilic dermatosis.

Clinical Presentation:
- Tender erythematous plaques and nodules
- Face, extremities, and trunk
- Associated with fever, malaise, and neutrophilia
- Associated with leukemia; hematopoietic dyscrasias, chronic inflammatory conditions, infections, and medications

Histopathology:
- Nodular to diffuse infiltrates of neutrophils in the upper half of the dermis (Fig. 2A)
- Many of the neutrophils have fragmented nuclei (leukocytoclasis) (Fig. 2B)
- Characteristic marked papillary dermal edema (Fig. 2C)
- Extravasated red cells
- Lymphocytes and eosinophils in varying numbers
- Rarely, fibrin deposition within and around dermal vessel walls (i.e., vasculitis)

Pathophysiology:
- Sweet's syndrome may represent a hypersensitivity reaction associated with a variety of stimuli. In addition to malignancies, infections, hematologic dyscrasias, medications, and infections are other associations.

References:
1. Draft KS, Wiser EB, Elenitsas R. Dermatopathology update of "newer" dermatologic manifestations of systemic disease. Adv Dermatol 2005; 21:102–132.
2. Walling HW et al. The relationship between neutrophilic dermatosis of the dorsal hands and Sweet's syndrome. Arch Dermatol 2006; 142(1):57–163.

GRANULOMA FACIALE

Nodular dermatitis with neutrophils, eosinophils, and plasma cells prominent.

Clinical Presentation:
- Uncommon to rare condition
- Solitary or several reddish brown nodules to plaques (Fig. 3A)
- Typically on the face although rarely extrafacial
- Persistent and asymptomatic

Histopathology:
- Nodular mixed infiltrate with characteristic sparing of the papillary and periadnexal dermis (together known as the adventitial dermis) (Fig. 3B).
- Polymorphous infiltrate consisting of numerous neutrophils, many of them with fragmented nuclei (leukocytoclasis), eosinophils, plasma cells, as well as lymphocytes (Fig. 3C).
- Despite its name (which is based on the clinical appearance), histiocytes are not a histologic feature.

Differential Diagnosis:
- Erythema elevatum diutinum—shares a similar pattern (nodular to diffuse predominantly neutrophilic infiltrate with leukocytoclasis) although fewer eosinophils and plasma cells.

Pathophysiology:
- No known cause although in view of the presence of vasculitis in early lesions, a localized Arthus-like process has been suggested.

References:
1. Lever WF, Leeper RW. Eosinophilic granuloma of the skin. Arch Dermatol 1950; 62:85–96.
2. Selvaag E, Roald B. Immunohistochemical findings in granuloma faciale. The role of eosinophilic granulocytes. J Eur Acad Dermatol Venereol 2000; 14:517–518.

CUTANEOUS HODGKIN'S DISEASE

Nodular mixed infiltrate with eosinophils, plasma cells, and lymphocytes.

Clinical Presentation:
- Cutaneous involvement by Hodgkin's disease is rare and controversial
- Late manifestation of the lymphoma (rarely the initial manifestation)
- Cutaneous involvement often adjacent to the vicinity of involved lymph nodes
- Papules, nodules, and plaques (Fig. 4A)

Histopathology:
- Nodular to diffuse infiltrate involving the dermis and subcutaneous tissue (Fig. 4B)
- Mixed infiltrate with characteristic large atypical lymphocytes, some of them binucleate (Reed-Sternberg cells) (Fig. 4C)
- Small lymphocytes, eosinophils, plasma cells, and neutrophils
- Occasional epithelioid granulomas

Differential Diagnosis:
- Lymphomatoid papulosis/anaplastic large cell lymphoma. Both are characterized by CD 30 positive, CD15 positive lymphocytes.

Pathophysiology:
- Epstein Barr virus is a suspected causative agent in Hodgkin's disease.

References:
1. Cerroni L, Behim-Schmid C, Kerl H. Cutaneous Hodgkin's disease: an Immunohistochemical Analysis. J Cutan Pathol 1995; 22:229–235.
2. Guitart J, Fretzin D. Skin as the primary site of Hodgkin's disease. Am J Dermapathol 1998; 20:218–222.

EXAMPLES OF DIFFUSE DERMATITIS

LYMPHOMA

Diffuse lymphocytic infiltrate.

Clinical Presentation:
- Reddish papules to nodules of varying size, may be ulcerated (Fig. 5A)

Histopathology:
- Diffuse infiltrates of lymphocytes fill much of the dermis (Fig 5B)
- Two patterns: B-cell and T-cell
- B-cell pattern characterized by nodules of dermal lymphocytes, which spare the epidermis and adnexae
- T-cell pattern characterized by lymphocytes involving the epidermis and adnexae (e.g., mycosis fungoides) (Fig 5C)

Differential Diagnosis:
- Pseudolymphoma/cutaneous lymphoid hyperplasia
- Cell marker antibodies, flow cytometry, and gene rearrangement studies often necessary to accurately distinguish between lymphoma and pseudolymphoma.

References:
1. Chu Pg, Chang KL, et al. Immunophenotyping of hematopoietic neoplasms. Semin Diagn Pathol 2000; 17:236–256.
2. Kerl H, Cherroni L. Primary cutaneous B-cell lymphomas: then and now. J Cutan Pathol 2006; 33(suppl 1):1–5.

ERYTHEMA ELEVATUM DIUTINUM

Diffuse dermatitis with neutrophils and eosinophils prominent.

Clinical Presentation:
- Rare dermatitis
- Extensor and acral surfaces
- Plaques, nodules, pedunculated lesions, and occasional vesicles (Fig. 6A)
- Associated with myeloid dyscrasias, myeloma, monoclonal gammopathy, lymphoma, and inflammatory bowel disease

Histopathology:
- Diffuse leukocytoclastic vasculitis including fibrin deposition within and around vessel walls (Fig. 6B)
- Neutrophils with leukocytoclasis (Fig. 6C)
- Chronic lesions characterized by fibrosis with fasicular appearance

Pathophysiology:
- Etiology unknown
- Variant of leukocytoclastic vasculitis

Differential Diagnosis:
- Neutrophilic dermatoses (Sweet's syndrome, pyoderma gangrenosum, Behcet's disease)
- Granuloma faciale has a similar polymorphous infiltrate with a predominance of eosinophils while erythema elevatum diutinum has a predominance of neutrophils.

References:
1. Yannias JA et al. Erythem elevatum diutinum. J Am Acad Dermatol 1992; 26:38–44.
2. LeBoit PE et al. The evolution of lesions in erythema elevatum diutinum. Am J Dermatopathol 1986; 8:392–402.

LEISHMANIASIS

Diffuse dermatitis with plasma cells prominent.

Clinical Presentation:
Three Types of Leishmaniasis:
- Cutaneous (Oriental) Leishmaniasis caused by *Leishmania tropica* (Asia and Africa) and *Leishmania mexicana* (Central and South America).
- Mucocutaneous (American) Leishmaniasis caused by *Leishmania brasiliensis*.
- Visceral Leishmaniasis (kala-azar) caused by *Leishmania donovani*.

Nodules and papules frequently ulcerated (Fig. 7A). Chronic lesions (1–2 years) including single or multiple plaques

Histopathology:
- Diffuse dermal infiltrate of lymphocytes, plasma cells, and histiocytes. Numerous protozoal organisms within macrophages (Figs. 7B and C)
- Two to four microns with kinetoplast
- Kinetoplast is metachromatically red with Giemsa stain

Differential Diagnosis:
Other Intracytoplasmic Organisms:
- Histoplasmosis—*Histoplasma capsulatum* (fungus)
- Rhinoscleroma—*Klebsiella rhinoscleromatis* (gram-negative bacillus)
- Granuloma inguinale-*Calymmatobacterium granulomatis*—gram-negative bacillus (Donovan body).

References:
1. Hepburn MC. Cutaneous leishmaniasis. Clin Exp Dermatol 2000; 25:363–370.
2. Grevlink SA, Lerner EA. Leishmaniasis. J M Acad Dermatol 1996; 34:257–272.

URTICARIA PIGMENTOSA, NODULAR

Diffuse dermatitis with prominent mast cells.

Synonym: Mastocytosis

Clinical Presentation:
- Generalized eruption
- Orange–brown macules papules and nodules on trunk less often extremities (Fig. 8A)
- Often pruritic
- Lesions develop wheal and flare following trauma (positive Darier's sign)
- Pediatric disease (75% of cases)

Histopathology:
- Diffuse mast cell infiltrates throughout much of the dermis (Fig. 8B)
- Monomorphous mononuclear cells with round to oval centrally placed nuclei and granular amphophilic cytoplasm ("fried egg") (Fig. 8C)
- Granules are metachromatic (red) with Giemsa stain (Fig. 8D)
- Tryptase and CD 117 positive

Pathophysiology:
- Aberrations in C-kit pathway have been implicated

References:
1. Yang F et al. Paraffin section immunophenotype of cutaneous and extracutaneous mast cell disease. comparison to other hematopoietic neoplasms. Am J Surg Pathol 2000; 24:703–709.
2. Buttner C et al. Identification of activating C-kit mutations in adult but not in childhood onset indolent mastocytosis. J Invest Dermatol 1998; 111:1227–1231.

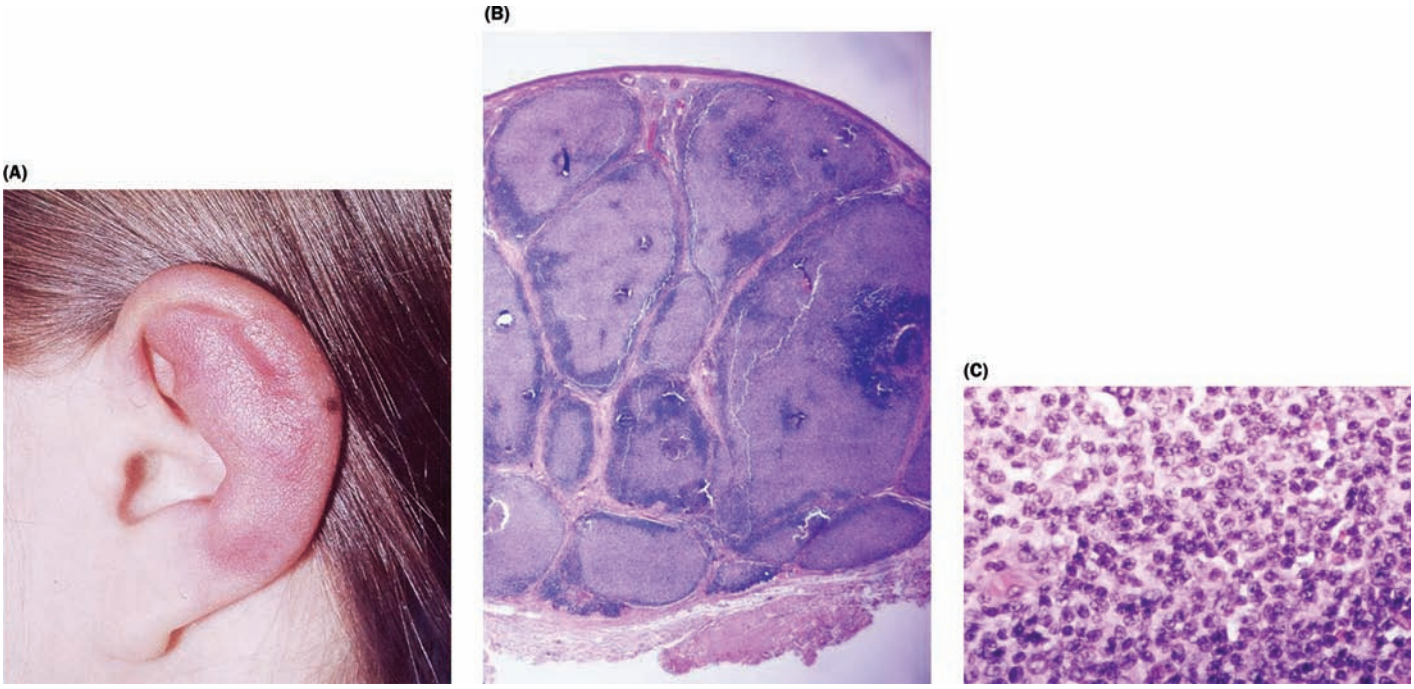

Figure 1 Psuedolymphoma. (**A**) Red brown nodule. (**B**) Nodular infiltrate of lymphocytes. (**C**) Polymorphic infiltrate.

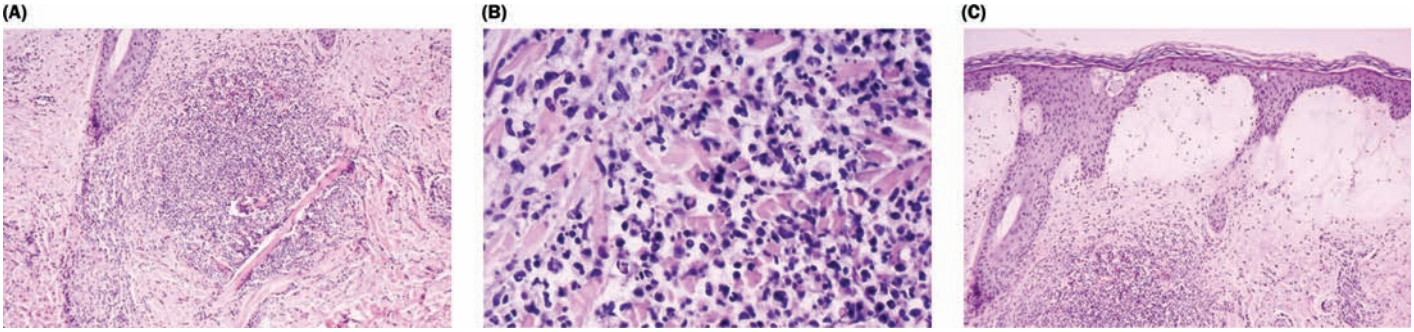

Figure 2 Sweet's syndrome. (**A**) Nodular infiltrate of neutrophils. (**B**) Neutrophilic fragmentation (leukocytoclasis). (**C**) Marked papillary dermal edema.

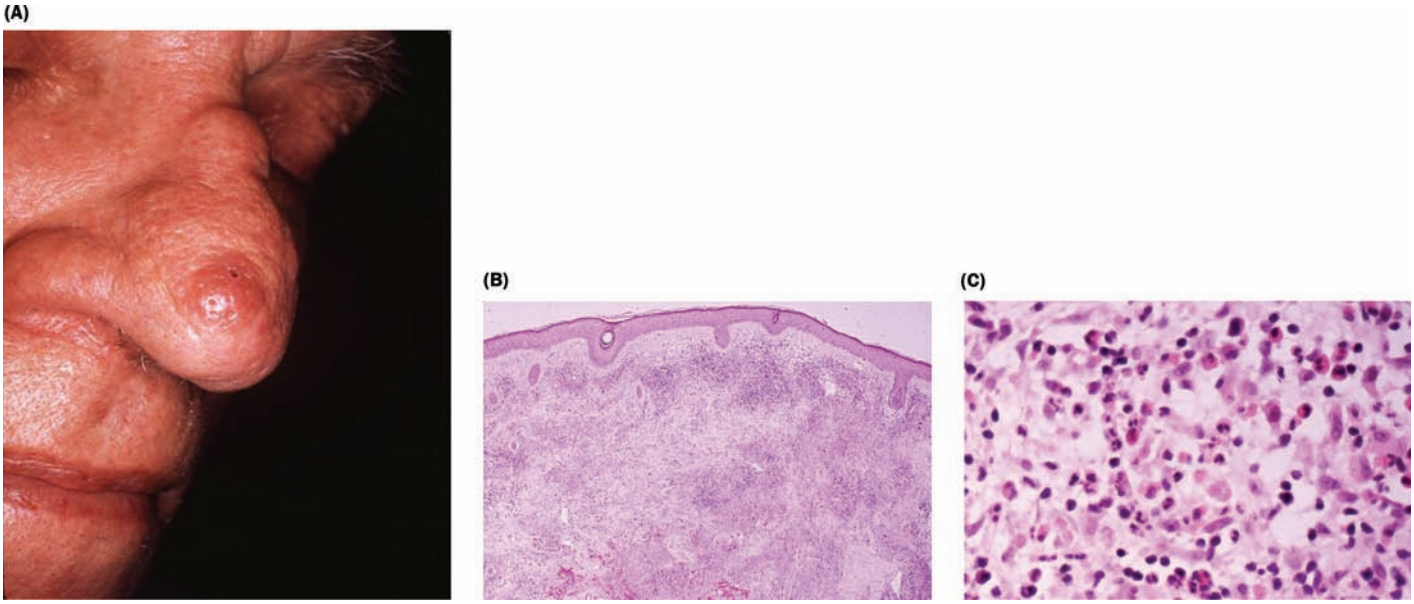

Figure 3 Granuloma faciale. (**A**) Reddish brown nodules. (**B**) Nodular mixed infiltrate sparing the papillary and perifollicular dermis. (**C**) Neutrophils, nuclear dust, eosinophilis, and plasma cells.

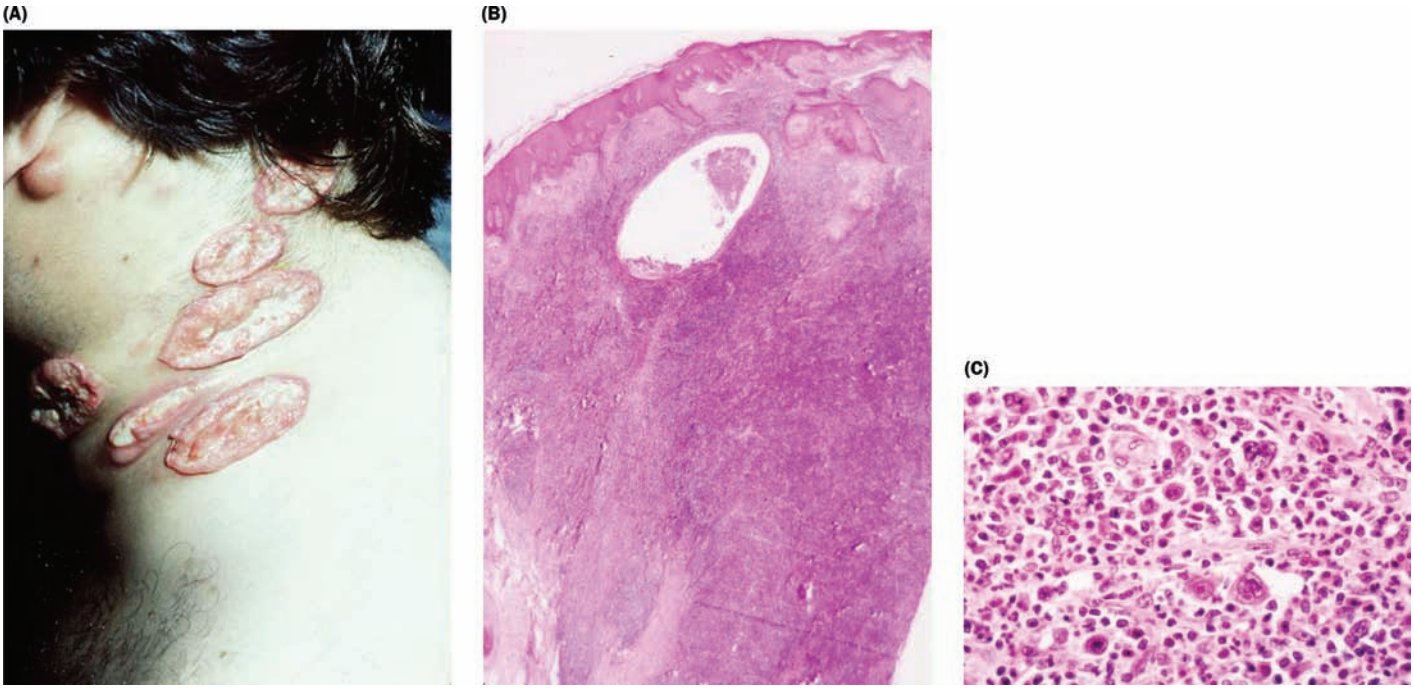

Figure 4 Cutaneous Hodgkin's disease. (**A**) Ulcerated plaques. (**B**) Nodular infiltrate of lymphocytes, eosinophils and plasma cells. (**C**) Reed-Sternberg cells.

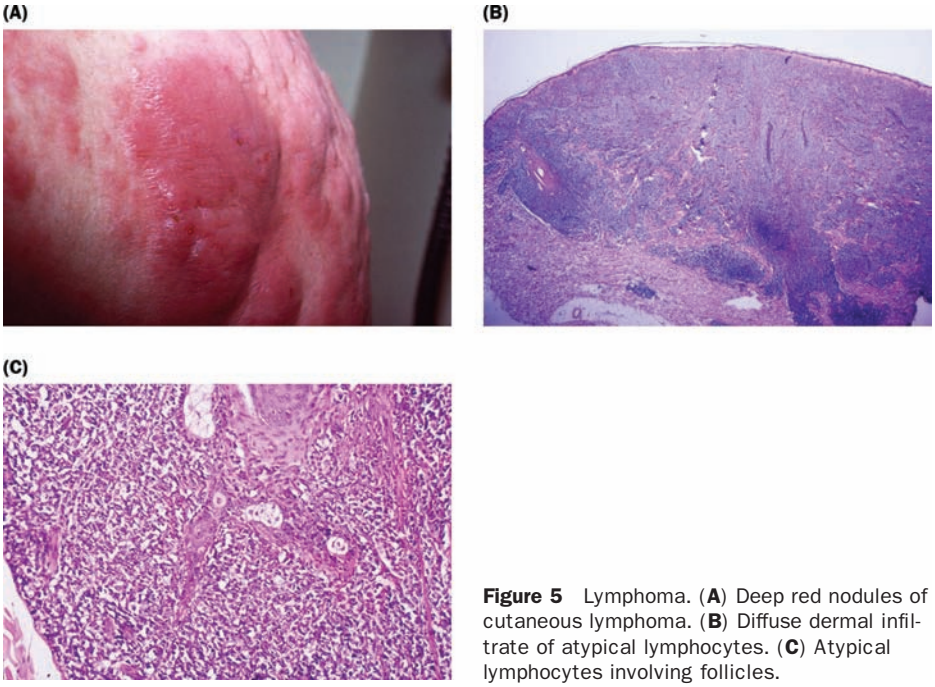

Figure 5 Lymphoma. (**A**) Deep red nodules of cutaneous lymphoma. (**B**) Diffuse dermal infiltrate of atypical lymphocytes. (**C**) Atypical lymphocytes involving follicles.

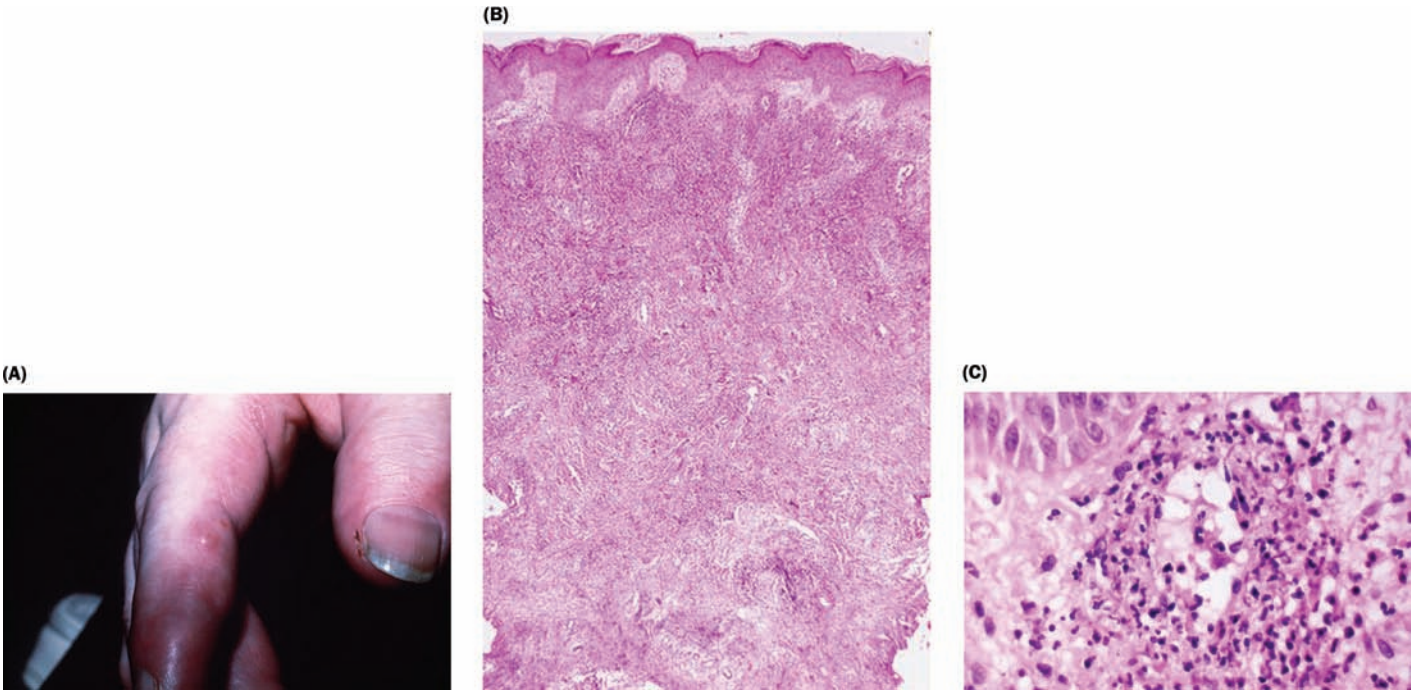

Figure 6 Erythema elevatum diutinum. (**A**) Reddish nodules on the fingers. (**B**) Diffuse neutrophilic infiltrate. (**C**) Neutrophils with leukocytoclasis (nuclear dust).

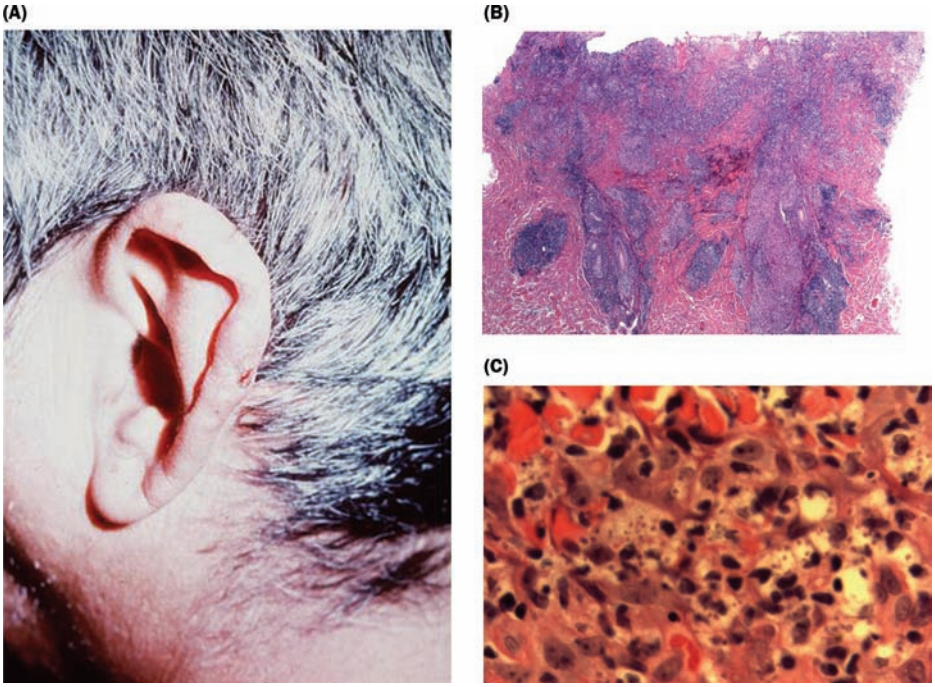

Figure 7 Leishmaniasis. (**A**) Ulcer on helix (Chiclero's ulcer). (**B**) Diffuse dermal infiltrate of plasma cells and histiocytes. (**C**) Parasitized histiocytes with numerous leishmania organisms.

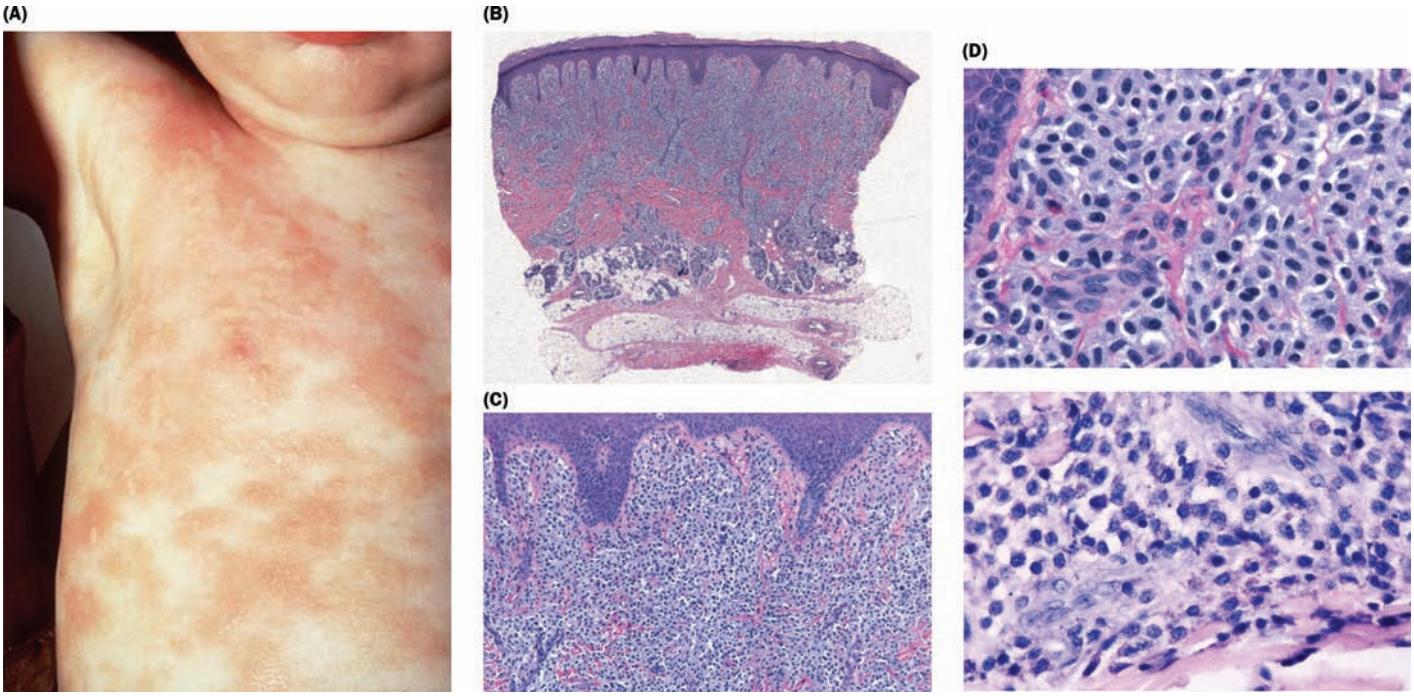

Figure 8 Urticaria pigmentosa, nodular. (**A**) Orange-brown nodules. (**B**) Diffuse infiltrate of mast cells. (**C**) Mast cells with oval nuclei and granular cytoplasm. (**D**) Giemsa stain-reddish cytoplasmic granules.

9

Granulomatous Dermatitis

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CONTENTS

GRANULOMATOUS DERMATITIS

Granulomatous dermatitis is a nodular or diffuse inflammatory pathologic process that is composed predominantly of histiocytes. The reaction pattern forms in response to an antigen that is usually insoluble, nondegradable, or slowly released.

Deciding whether a pattern is perivascular, interstitial, nodular, or diffuse is rather subjective. A pattern is considered nodular when discrete perivascular inflammation extends beyond a single perivascular region and is relatively large and dense. One or more nodules may be present. Diffuse dermatitis is the term applied when the cellular infiltrate is dense enough that discrete cellular aggregates cannot be recognized and the dermis contains a more massive poorly circumscribed inflammatory infiltrate. The dermal infiltrate can be uniformly dense or denser in the upper (or lower) dermis. Once the pattern has been recognized on scanning magnification, the patterns are subdivided by inflammatory cell composition and the presence or absence of necrosis, foreign bodies, infectious organisms, epidermal hyperplasia, and so on.

The categories for granulomatous dermatoses are not absolute and are only useful as a skeletal framework from which to start one's interpretation of a histologic section. For example: (*i*) rarely cutaneous sarcoidosis may demonstrate tuberculoid granulomas or foreign body granulomas; (*ii*) cutaneous infections as tuberculosis or leprosy most commonly present as tuberculoid granulomas but can be sarcoidal or palisading in type; (*iii*) some infectious granuloma can be palisaded (as some fungal, mycobacterial infections and so on); (*iv*) foreign body granulomata can be nodular (sarcoidal, palisaded, or foreign body) or diffuse and mixed. Therefore, although pattern analysis is a helpful way to begin the evaluation of a slide, often evaluation of a granulomatous dermatitis must exceed routine light microscopy with hematoxylin-eosin staining.

Infectious agents may need to be excluded by special stains:

Organisms	Stains
Fungi/yeast*	PAS with and without diastase GMS (methenamine silver)
Mycobacteria*	Ziehl-Neelsen (detects tubercle bacillus)
	Fite (detects leprosy bacillus and tubercle bacillus)
Bacteria*	Gram
Actinomycosis and Nocardiosis	Gram GMS (methenamine silver)
Leishmaniasis	Giemsa
Spirochete	Warthin-Starry
Amoeba	Phosphotungstic acid hematoxylin

*Stains most commonly utilized: periodic acid-Schiff (PAS); Gomori methenamine silver (GMS).

Polariscopic examination can be accomplished to investigate the presence of a polarizable foreign body. Using two disks composed of polarizing plastic that are easily inserted into the microscope (with one disk below the condenser to act as a polarizer and the other disk placed in the eyepiece to act as the analyzer) the light from all rays except those vibrating in one plane can be excluded. Doubly refractile substances on the slide will break the polarization when the analyzer disk is rotated and appear as bright white bodies on a dark field. Examples of doubly refractile foreign bodies include silica, talc, wooden splinters, suture, and urate crystals.

Immunohistochemical techniques using a panel of antibodies directed against infectious agents and the

technique of polymerase chain reaction are now available to detect possible microorganisms within fixed tissue.

Finally, electron-probe microanalysis (scanning electron microscopy with the aid of backscattered electron imaging and X-ray energy spectrometry) or chemical analysis can be used to identify inorganic material in a lesion.

In summary, when reviewing a slide that demonstrates a granulomatous dermatitis, the following questions should be addressed in attempting to establish a diagnosis:

1. Is the infiltrate nodular or diffuse?
2. If the infiltrate is nodular, is the pattern tuberculoid, sarcoidal, palisaded, or foreign body in type?
3. Is there any evidence of necrosis or necrobiosis?
4. Are there other inflammatory cells present in addition to the histiocytic infiltrate (as lymphocytes, neutrophils, etc.)? Are there distinctive features to the histiocytes composing the infiltrate?
5. Is the infiltrate perifollicular?
6. Is there associated epidermal hyperplasia?
7. Is there an associated vasculitis?
8. Special stains and polarizing lenses should be used routinely to exclude an infectious etiology and polarizable foreign body. Immunohistochemical techniques and electron probe microanalysis are only employed rarely.

The histologic patterns of granulomatous dermatoses are given in Table 1.

Table 1 Histologic Patterns of Granulomatous Dermatoses

Nodular granulomatous dermatitis	Tuberculoid	Tuberculosis
		Tuberculoid leprosy
		Leishmaniasis, chronic cutaneous
		Syphilis, late secondary or tertiary
		Rosacea and perioral dermatitis
	Sarcoidal	Sarcoidosis
		Allergic foreign-body reactions: Silica, beryllium, and zirconium granulomas Tattoo dyes (most commonly with red dye containing mercuric sulfide)
		Crohn's disease
		Melkersson-Rosenthal syndrome (cheilitis granulomatosa)
	Palisaded	Granuloma annulare
		Necrobiosis lipoidica
		Rheumatoid nodule
		Gout
		Necrobiotic xanthogranuloma
		Some foreign body reactions (ex. bovine collagen)
	Foreign body (nonallergic foreign-body reaction)	Ruptured follicular cysts
		Tattoo
		Suture
		Splinter
		Silica
		Talc
		Starch
		Calcium
Lichenoid and granulomatous		Drug reactions
		Lichen striatus
		Lichen nitidus
		Underlying systemic diseases: Crohn's disease, Rheumatoid arthritis, etc.
		Infections: Hepatitis C, Herpes, atypical mycobacteria, etc.
Interstitial granulomatous dermatitis		Interstitial type of granuloma annulare
		Interstitial granulomatous drug reaction (reported due to calcium channel blockers, angiotensin converting enzyme inhibitors, beta-blockers, lipid-lowering agents, antihistamines, anticonvulsants, and antidepressants)
		Interstitial granulomatous dermatitis with plaques or cords (with arthritis and a systemic autoimmune disorder)
Nodular or diffuse mixed granulomatous dermatitis with neutrophils (suppurative granulomatous)	Infectious	Bacterial, fungal, yeast, mycobacterial, actinomycotic, parasitic, etc.
	Noninfectious	Halogenodermas
		Follicular-occlusion tetrad
		Ruptured follicular cyst and other foreign body reactions

(Continued)

Table 1 Histologic Patterns of Granulomatous Dermatoses *(Continued)*

Diffuse granulomatous dermatitis	**Foamy histiocytes**	**Xanthoma**
		Xanthogranuloma
	Granular histiocytes	**Reticulohistiocytic granuloma**
	Infectious	**Lepromatous leprosy**
		Leishmaniasis—acute lesions
Granulomatous vasculitis	**Small vessel**	**Necrobiosis lipoidica**
	Large vessel	**Allergic granulomatous (Churg–Stauss)**
		Wegener's granulomatous, etc.

Definition of Terms:

Granulomatous dermatitis: A nodular or diffuse inflammatory skin disease composed predominantly of histiocytes that form in response to insoluble, nondegradable, or slowly released antigens

Nodular dermatitis: An inflammatory process in which the perivascular infiltrates have enlarged and coalesced to form one or multiple nodules.

Diffuse dermatitis: An inflammatory process that is so dense that nodules or a perivascular pattern can no longer be discerned.

Histiocyte: This is a tissue macrophage, which can be identical histologically to a fibroblast or endothelial cell. Very often you can differentiate these cells by their neighbors or "the company they keep." For example, a cell that looks like a histiocyte, fibroblast, or endothelial cell but is arranged with other similar appearing cells in an annular configuration, and with red blood cells in the center is obviously an endothelial cell and not a histiocyte. Usually a histiocyte has a large, ovoid, pale nucleus that can be eccentric and indented. The nucleolus usually is distinct, small, and can be single or multiple. The cytoplasm may be abundant but is indistinct.

Epithelioid histiocyte: This is an activated histiocyte with abundant eosinophilic granular cytoplasm and poorly defined cell borders; it has been so named because it can resemble epithelial cells that are contiguous and touch one another.

Multinucleated histiocyte: As histiocytes age, they have a tendency to fuse rather than to divide. Thus a histiocyte with more than one nucleus is referred to as multinucleated. There is evidence that lymphocyte-derived lymphokines released in type IV immune reactions play a role in their development. There are three types of multinucleated cells: Langerhan's, Touton, and foreign body.

- Langerhan's cell (Fig. 1A) has nuclei in a peripheral circular or semicircular (horseshoe) pattern.
- Touton cell (Fig. 1B) has a central homogeneous amphophilic core of cytoplasm, surrounded by a circumferential wreath of nuclei, which in turn is surrounded by abundant foamy cytoplasm.
- Foreign body cell (Fig. 1C) has nuclei in the center or in a haphazard pattern.

Giant cells may contain Schaumann or asteroid bodies. Schaumann bodies are round or oval basophilic laminated concentric whorls (calcified, especially at their periphery) within histiocytic giant cells that are thought to be derived from residual lysosomes. Asteroid bodies (Fig. 1D) are stellate (star-shaped) eosinophilic concretions within histiocytic giant cells thought to represent trapped collagen. When stained with phosphotungstic acid-hematoxylin, the center of the asteroid body is brown–red and the spikes are blue. Neither Schaumman nor asteroid bodies are specific to any one granulomatous disease process.

Foam cell: This is a lipid-laden histiocyte with foamy or vacuolated cytoplasm.

Granuloma: When histiocytes aggregate to enhance phagocytosis, they form a nodular aggregate called a granuloma. A granuloma is usually composed of epithelioid histiocytes and often multinucleated histiocytes. Granulomas can be seen in association with other inflammatory cells, with or without necrosis. There are three major types of granulomas:

- Tuberculoid granuloma (Fig. 2A): A well circumscribed collection of epithelioid histiocytes in association with a surrounding relatively dense infiltrate of lymphocytes. Necrosis within the center is variable (none to much).
- Sarcoidal granuloma (Fig. 2B): A well-circumscribed collection of epithelioid histiocytes with relatively few or no lymphocytes.
- Palisaded granuloma (Fig. 2C): Histiocytes arranged in a palisade or "like staves around a central focus."

Necrobiosis: Focal alteration or degeneration of collagen.

Caseation necrosis: This term is identical to ischemic necrosis and coagulation necrosis. The necrotic tissue has lost its structure and appears amorphous, pale pink, and somewhat granular (Fig. 2D).

EXAMPLES OF GRANULOMATOUS DISEASES

LUPUS VULGARIS

Nodular tuberculoid type of granulomatous disease.

Synonym: Tuberculosis luposa.

Clinical Presentation:

- The most common variant of cutaneous tuberculosis presents as reddish brown papules, nodules, or plaques (Fig. 3A) that have an apple jelly color especially noted on diascopy.
- As the lesions expand, they often are associated with central scarring that can cause significant tissue destruction.

Histopathology:

- Aggregates of epithelioid histiocytes generally in the upper half of the dermis surrounded by a mantle of lymphocytes (Figs. 3B and D) and associated with overlying epidermal thinning (rather than hyperplasia as seen in primary tuberculosis inoculation).

- Usually none or minimal caseation necrosis (Figs. 2D and 3D) (as seen more commonly in primary tuberculosis inoculation, scrofuloderma, and miliary tuberculosis) and no identifiable acid-fast bacilli (as can be seen in early primary tuberculosis inoculation, scrofuloderma, and miliary tuberculosis).

Clinicopathologic Correlation:

Clinical Feature	Pathologic Feature
Lesions are indurated	Predominantly dermal granulomas
Apple jelly colored lesions on diascopy	Granulomas in lupus vulgaris tend to be located in the upper half of the reticular dermis; the overlying epidermis is thinned. Granulomas seen through a thinned epidermis look apple jelly in color.

In those variants of tuberculosis of the skin seen in association with caseation necrosis (most commonly primary, miliary, or scrofuloderma) one can also clinically discern ulceration with drainage from the granulomatous site.

Differential Diagnosis:
See Table 2.

Pathophysiology:
Cutaneous tuberculosis can occur by three routes: direct inoculation (primary), hematogenous spread (lupus vulgaris, miliary tuberculosis), or by direct extension of an underlying tuberculous lymph node or bone (scrofuloderma). Lupus vulgaris usually occurs in previously sensitized individuals. Primary cutaneous tuberculosis, miliary tuberculosis, and scrofuloderma demonstrate central caseation necrosis (cheesy material) which appears pink and granular surrounded by epithelioid histiocytes and multinucleated epithelioid histiocytes (Langhans'). A mantle of lymphocytes is noted at the periphery of the granuloma. Acid-fast bacilli of tuberculosis (4 microns in length and less than 1 micron in diameter) can be identified within the center of some granuloma with special stains. Lupus vulgaris lesions have superficial granulomata and are usually devoid of necrosis and demonstrable organisms.

References:

1. Macgregor RR. Cutaneous tuberculosis. Clinics in Dermatology 1995; 13:245–255.
2. Arora SK, Kumar B, Sehgal S. Development of a polymerase chain reaction dot-blotting system for detecting cutaneous tuberculosis. Br J Dermatol 2000; 142:72–76.
3. Bartralot R, Pujol RM, Garcia–Patos V, Sitjas D, Martin–Casabona N, et al. Cutaneous infections due to nontuberculous mycobacteria: histopathological review of 28 cases. Comparative study between lesions observed in immunosuppressed patients and normal hosts. J Cutan Pathol 2000; 27:124–129.
4. Hsiao P-F, Tzen C-Y, Chen H-C, Su H-Y. Polymerase chain reaction based detection of Mycobacterium tuberculosis in tissues showing granulomatous inflammation without demonstrable acid-fast bacilli. Int J Dermatol 2003; 42:281–286.

TUBERCULOID LEPROSY

Nodular tuberculoid type of granulomatous disease.

Synonym: Hansen's disease.

Clinical Presentation:
- One to just a few asymmetrically scattered hypopigmented well demarcated anesthetic plaques (Fig. 4A)
- Occasionally, plaques may demonstrate erythema, central clearing, and more peripheral induration

Histopathology:
- Elliptical aggregates of epithelioid histiocytes surrounded by lymphocytes, multinucleated histiocytes, and occasional plasma cells especially in the lower dermis (Figs. 4B and E).
- Granulomas can be identified around small nerves, hair erector muscles, follicles, and sweat glands (Figs. 4C–G)
- Although the lepra bacilli are usually not identifiable in tuberculoid leprosy, very rarely lepra bacilli are found at the periphery of active lesions

Table 2 Differential Diagnosis: Lupus Vulgaris

Lupus Vulgaris	Tuberculoid Leprosy	Secondary or Tertiary Syphihlis	Sarcoid	Rosacea or Perioral Dermatitis
	Elliptical granulomas		Round granulomas	Perifollicular granulomas
Superficial granulomas below thinned epidermis	Granulomas predominantly in lower dermis. Epidermis often atrophic and effaced		Superficial and deep granulomas	Granulomas around or near follicular units
Lymphocytes around granulomas	Lymphocytes plus plasma cells around granulomas	Lymphoctyes plus plasma cells around granulomas	Scant or no mantle of lymphocytes (naked tubercles)	Lymphocytes around granulomas
				Early on can identify some neutrophils
Caseation necrosis minimal; no identifiable acid fast bacilli	Very rarely lepra bacilli are found at the periphery of active lesions		Fibrin often present in center of granuloma	Necrosis can be identified in some cases within granuloma
	Granulomas around nerves and adnexa (hair and sweat glands)	Blood vessels thick walled with enlarged endothelial cells		Starts as suppurative folliculitis → progresses to granulomatous folliculitis

Clinicopathologic Correlation:

Clinical Feature	Pathologic Feature
Infiltrated plaques	Elliptical granulomas usually deep in the dermis and fewer in number
Absence of apple jelly color as seen in lupus vulgaris	Granulomas deeper in the dermis
Hypopigmented lesions	Epidermis is often thinned and effaced
Lesions usually anesthetic	Granulomas in and around nerves
Lesions often hairless (alopecia)	Granulomas around hair follicles

Differential Diagnosis (Table 2):
In addition, although the hypopigmentation of tuberculoid leprosy lesions can cause confusion with some other common diseases, the absence of fungal elements in the stratum corneum (tinea versicolor), spongiosis (pityriasis alba), and epidermotropism of mononuclear cells (hypopigmented mycosis fungoides) makes establishing the correct diagnosis not too difficult.

Pathophysiology:
Leprosy is caused by the bacillus, *Mycobacterium leprae*, which is an intracytoplasmic parasite of macrophages and Schwann cells. Tuberculoid leprosy is the variant seen in individuals with a high level of specific cell-mediated immunity.

References:

1. Cuevas-Santos J, Contreras F, McNutt NS. Multibacillary leprosy: lesions with macrophages positive for S100 protein and dendritic cells positive for Factor 13a. J Cutan Pathol 1998; 25:530–537.
2. Abulafia J, Vignale RA. Leprosy: pathogenesis updated. Int J Dermatol 1999; 38:321–334.
3. Abulafia J, Vignale RA. Leprosy: accessory immune system as effector of infectious, metabolic, and immunologic reactions. Int J Dermatol 2001; 40:673–687.
4. Moschella SL. An update on the diagnosis and treatment of leprosy. J Am Acad Dermatol 2004; 51:417–426.

SYPHILIS, LATE SECONDARY STAGE

Nodular tuberculoid type of granulomatous disease.

Clinical Presentation:
- Late secondary syphilis lesions are often widespread papules and nodules (Fig. 5A)

Histopathology:
- Aggregates of epithelioid histiocytes surrounded by plasma cells and lymphocytes (Figs. 5B–D)
- Blood vessels are thick walled with plump endothelial cells (Fig. 5E)
- Perivascular inflammation with many plasma cells (Fig. 5E)
- Spirochetes are very rarely detectable

Clinicopathologic Correlation:

Clinical Feature	Pathologic Feature
Reddish lesions	Prominent vessels with perivascular inflammation
Papules and nodules	Nodular granulomatous inflammation

Differential Diagnosis:
See Table 2.

Pathophysiology:
Syphilis is an infectious disease caused by the spirochete *Treponema pallidum*. Primary lesions occur two to six weeks after inoculation. The secondary stage is due to dissemination and multiplication of the organism in different tissues. Late secondary and tertiary stage lesions are due to a high cellular immune response against the organism; at this stage only a small number of organisms remain.

References:

1. Wu SJ, Nguyen EQ, Nielsen TA, Pellegrini AE. Nodular tertiary syphilis mimicking granuloma annulare. J Am Acad Dermatol 2000; 42:378–380.
2. Phelps RG, Knispel J, Tu ES, Cernainu G, Saruk M. Immunoperoxidase technique for detecting spirochetes in tissue sections: comparison with other methods. Int J Dermatol 2000; 39: 609–613.
3. Hoang MP, High WA, Molberg KH. Secondary syphilis: a histologic and immunohistochemical evaluation. J Cutan Pathol 2004; 31:595–599.
4. Zeltser R, Kurban AK. Syphilis. Clinics in Dermatology 2004; 22:461–468.

ROSACEA AND PERIORAL DERMATITIS

Nodular tuberculoid type of granulomatous disease.

Clinical Presentation:
- Red to red–brown follicular papules and pustules on the face (Fig. 6A)

Histopathology:
- Aggregates of epithelioid histiocytes surrounded by lymphocytes usually around or adjacent to hair follicles (Figs. 6B and C)
- Necrosis can be identified within the granulmata
- Starts as a suppurative follilculitis; progresses to a granulomatous folliculitis

Clinicopathologic Correlation:

Clinical Feature	Pathologic Feature
Reddish follicular pustules	Suppurative folliculitis
Reddish follicular papules	Perifollicular granulomas

Differential Diagnosis:
See Table 2.

Pathophysiology:
Pathophysiology is multifactorial. Vascular hyper-reactivity is known to be related and is manifest clinically as easy blushing. It has been postulated that the repeated vasodilation ultimately induces inflammation. The association with *Helicobacter pylori* and the etiologic role of the cutaneous mite *Demodex folliculorum* remain controversial.

References:

1. Crawford GH, Pelle MT, James WD. Rosacea: I. Etiology, pathogenesis, and subtype classification. J Am Acad Dermatol 2004; 51:327–341.
2. Powell FC. Rosacea. N Engl J Med 2005; 352:793–803.

SARCOID

Nodular sarcoidal type of granulomatous disease.

Synonyms: Darier-Roussy disease; lupus pernio.

Clinical Presentation:
- Firm pink, erythematous, red–brown, yellow–brown, or violaceous papules and plaques (Fig. 7A)
- Apple jelly color noted on diascopy (with pressure inducing blanching)
- Lesions most commonly located on the face, neck, upper trunk, and extremities in a symmetrical distribution
- Variants: nodules, annular plaques, scaling and psoriasiform, subcutaneous nodules, alopecia, ulcerated, hypopigmented, ichthyosis, and infiltration of pre-existing scars

Histopathology:
- Well circumscribed round noncaseating collections of epithelioid histiocytes with few or no surrounding lymphocytes ("naked tubercles") (Figs. 7B-D)
- Fibrin can be found in the center of some tubercles (Fig. 7E)

Clinicopathologic Correlation:

Clinical Feature	Pathologic Feature
Indurated papules and plaques	Granulomas predominantly in the dermis
Apply jelly color on diascopy	Granulomas can be superficial in the dermis and the overlying epidermis is not thickened

Differential Diagnosis (Table 2):
Foreign body reactions should be excluded with polarizing lenses and rarely spectrographic techniques if clinically indicated. In addition, sarcoidal granulomas should be evaluated with special stains to rule out infectious agents. (as PAS with and without diastase or GMS, Fite, Gram, Giemsa, Warthin-Starry silver stain, etc.)

Pathophysiology:
Sarcoid is a multisystem systemic granulomatous disease. Approximately 25% to 33% of the patients demonstrate cutaneous manifestations. The exact etiology of sarcoidosis remains unknown but there is a known association with increased cell-mediated immunity activity and an increase in CD4+ T-helper cells of the Th1 subtype after antigen presentation. Th1 cytokines are increased (including interleukin 2 and interferon), which ultimately leads to B-cell stimulation. Granuloma forming T lymphocytes and monocytes are in peripheral tissues leading to decreased delayed cellular immunity and lymphopenia with resultant anergy. The antigen responsible for initiating these events is unknown. Sarcoid is considered a diagnosis of exclusion both histologically and clinically. Infections and other systemic diseases must be excluded as the cause of noncaseating granulomas in the skin or other organ systems. However, the identification of a foreign body or infectious agent within the granuloma does not exclude sarcoidosis; these diagnoses are not mutually exclusive. Foreign body reactions in patients with sarcoidosis have been reported. These foreign bodies may have represented the hypothetical antigen or nidus in the above outlined immune altered scenario.

References:

1. Kim YC, Triffet MK, Gibson LE. Foreign bodies in sarcoidosis. Am J Dermatopathol 2000; 22:408–412.
2. English III JC, Patel PJ, Greer KE. Sarcoidosis. J Am Acad Dermatol 2001; 44:725–743.
3. Marcoval J, Mana J, Moreno A, Gallegro I, Fortuno Y, Peyri J. Foreign bodies in granulomatous cutaneous lesions of patients with systemic sarcoidosis. Arch Dermatol 2001; 137:427–430.
4. Thomas KW, Hunningshake GW. Sarcoidosis. JAMA 2003; 289:3300–3303.
5. Ball NJ, Kho GT, Martinka M. The histologic spectrum of cutaneous sarcoidosis: a study of twenty-eight cases. J Cutan Pathol 2004; 31:160–168.
6. Ahmed I, Harshad SR. Subcutaneous sarcoidosis: is it a specific subset of cutaneous sarcoidosis frequently associated with systemic disease? J Am Acad Dermatol 2006; 54:55–60.

FOREIGN BODY GRANULOMAS (ALLERGIC SARCOIDAL GRANULOMATOUS REACTION)

Nodular sarcoidal type of granulomatous disease.

Some foreign bodies can induce an allergic granulomatous reaction that simulates a sarcoidal granulomatous reaction. Granulomata secondary to silica (usually from glass or sand) can occur; the foreign body can be detected as doubly refractile crystals with polarizing lenses. Beryllium (from cuts due to broken fluorescent light bulbs manufactured prior to 1950) results in granulomata often associated with central necrosis. Beryllium granuloma and zirconium granuloma (secondary to deodorants) are nonpolarizable and require spectrographic techniques to identify the foreign body. Finally, some tattoo dyes (most commonly red dye containing mercuric sulfide) can induce a sarcoidal granulomatous reaction (Figs. 8A and B).

CHEITILITS GRANULOMATOSA

Nodular sarcoidal type of granulomatous disease.

Synonym: Orofacial granulomatosis.

Clinical Presentation:
- Recurrent labial edema that eventuates into permanent enlargement of lips with nodularity (Fig. 9A)
- This can be part of a syndrome: chronic, fluctuating swelling of the lips associated with recurrent facial pareses and lingua plicata (Melkersson–Rosenthal syndrome)

Histopathology:
- Small noncaseating granulomas with scant or no surrounding lymphocytes and plasma cells on mucosal skin (Fig. 9B)
- Initially only marked edema noted

Clinicopathologic Correlation:

Clinical Feature	Pathologic Feature
Recurrent labial swelling	Stromal edema
Permanent enlargement of lips	Noncaseating granulomas

Differential Diagnosis:
Noninfectious, noncaseating granulomas of the lips can be seen in Crohn's disease, sarcoidosis, or in cheilitis granulomatosa.

Pathophysiology:
The etiology remains unknown. Some have suggested a role for an allergic reaction to an allergen that has come in contact with the lips and that can induce a cell-mediated hypersensitivity response.

References:

1. van der Waal RIF, Schulten EAJM, van der Meij EH, van de Scheur MR, Starink TM, van der Waal I. Cheilitis granulomatosa: overview of 13 patients with long-term follow-up—results of management. Int J Dermatol 2002; 41:225–229.
2. Rees TD. Orofacial granulomatosis and related conditions. Periodontol 2000; 1999; 21:145–157.

GRANULOMA ANNULARE

Nodular palisaded type of granulomatous disease (could also be classified as interstitial granulomatous dermatitis)

Synonym: Pseudorheumotoid nodule (for subcutaneous granuloma annulare).

Clinical Presentation:
- Skin colored or pink to red papules classically arranged in an annular or arciform pattern (Fig. 10A)
- Most commonly located on the hands, arms, feet, and legs
- Hyperpigmentation or normal skin noted in the center of the annular or circular lesions
- A generalized form is composed of widely distributed papules symmetrically on the trunk and extremities
- Subcutaneous, perforating, and patch-plaque variants have been described

Histopathology:
- Predominantly, in the upper half of the dermis there are palisades of histiocytes around displaced/degenerated collagen and foci of mucin (Figs. 10B–D)
- Histiocytes interposed between collagen bundles (interstitial pattern) associated with increased mucin between collagen fibers
- Rare aggregates of epithelioid histiocytes resembling sarcoidal granulomas
- Areas of normal or spared dermis between palisaded granulomas
- Superficial and deep perivascular predominantly lymphohistiocytic infiltrate with some mast cells

Clinicopathologic Correlation:

Clinical Feature	Pathologic Feature
Papular eruption	Pathology predominantly in the dermis
	Focal, not diffuse, granulomatous process
Pink papules	Perivascular inflammation

Differential Diagnosis of Palisaded Granulomas:

Disease	Central Focus	Other Distinguishing Features
Granuloma annulare	Mucin	Areas of normal dermis
		Focal dermal involvement
		Associated superficial and deep perivascular infiltrate with mast cells
		Interstitial histiocytes
		Mucin between collagen fibers
		Sarcoidal granulomas
Rheumatoid nodule	Fibrin	Pathology within subcutaneous fat (and/or deep dermis)
Necrobiosis lipoidica	Degenerated collagen	Diffuse dermal involvement Often subcutaneous involvement
		Plasma cells present
		Granulomatous vasculitis may be present
Gout	Urates	Best if fixed in alcohol rather than formalin. Crystals refractile with polarized light
Necrobiotic xanthogranuloma	Degenerated collagen	Extensive granulomatous dermatitis arranged in intersecting bands
		Palisaded granulomas around areas of confluent necrobiosis
		Foam cells
		Touton and foreign body type giant cells
		Cholesterol clefts

Pathophysiology:
There is no known etiology to explain granuloma annulare. It is known that certain traumas (such as insect bites, skin testing, sun exposure, viral infections) can precipitate the lesions at local sites. It has been postulated that a delayed

type hypersensitivity reaction to an unknown antigen may play a role in the pathophysiology of granuloma annulare. Cytokine and interferon producing lymphocytes in response to an unknown antigen could induce degradation of the dermal matrix thus inducing a granulomatous reaction. The identification of elastic fiber degeneration in the midst of the palisaded granulomas of granuloma annulare in some studies has suggested that the disease may be related to elastic tissue injury. Finally, although vasculitis has been identified within the center of some palisaded granulomas of granuloma annulare, its role in the etiology of granuloma annulare is not understood.

References:

1. Smith MD, Downie JB, DiCostanzo D. Granuloma annulare. Int J Dermatol 1997; 36:326–333.
2. Mutasim DF, Bridges AG. Patch granuloma annulare: clinicopathologic study of 6 patients. J Am Acad Dermatol 2000; 42:417–421.
3. Bandel C, DePrisco G, Cockerell CJ, Ehrig T. Abundance of interstitial heparan sulfate in granuloma annulare but not in other mucinous skin disesases. J Cutan Pathol 2002; 29:524–528.
4. Groisman GM, Schafer I, Amar M, Sabo E. Expression of the histiocytic marker PG-M1 in granuloma annulare and rheumatoid nodules of the skin. J Cutan Pathol 2002; 29:590–595.
5. Barzilai A, Huszar M, Shapiro D, Nass D, Trau H. Psuedorheumatoid nodules in adults. A juxta-articular form of nodular granuloma annulare. Am J Dermatopatho 2005; 27:1–5.

NECROBIOSIS LIPOIDICA

Nodular palisaded type of granulomatous disease.

Synonym: Necrobiosis lipoidica diabeticorum (NLD).

Clinical Presentation:

- Papules that evolve into violaceous plaques most commonly located on the shins
- Borders of plaques are infiltrated and red–brown in color, while the center of plaques become atrophic and yellow–brown in color with telangiectasias (Fig. 11A)
- Ulceration, particularly after trauma, occurs in over one-third of the cases
- Lesions are usually asymptomatic with decreased sensation to pin prick testing

Histopathology:

- Palisaded granulomas noted throughout the entire dermis, horizontally oriented in a tiered or layered pattern. The deep dermis is especially involved (Fig. 11B)
- Palisades of histiocytes around foci of collagen degeneration (Fig. 11C)
- The granulomatous inflammation can extend into the subcutaneous fat resulting in a septal panniculitis
- Superficial and deep perivascular infiltrate composed of lymphocytes, histiocytes, and plasma cells (Fig. 11D)
- Endothelial cell swelling and granulomatous vasculitis can be identified
- Dermal and subcutaneous septal sclerosis noted in the center of older lesions
- Epidermis is normal or atrophic (especially in the center of the lesion)
- Telangiectasia can be noted especially beneath an atrophic epidermis (Fig. 11D)

Clinicopathologic Correlation:

Clinical Feature	Pathologic Feature
Indurated plaques	Diffuse dermal (usually with no intervening normal dermis noted within the biopsy) and even subcutaneous septal inflammation
Yellowish color within plaques	Fat stains on frozen tissue reveal lipid droplets within the dermal infiltrate
Redness within the lesions	Superficial and deep perivascular inflammatory infiltrate beneath an atrophic epidermis; dilated blood vessels
Telangiectasias in older plaques	Dilated superficial dermal blood vessels beneath an atrophic epidermis
Atrophy and sclerosis in older plaques	Atrophic epidermis
	Sclerosis of dermis as lesions resolve
Ulceration	Epidermal atrophy plus granulomatous vasculitis can result in ulceration

Differential Diagnosis:

See Differential Diagnosis table under the section "Granuloma Annulare."

Pathophysiology:

The etiology of NLD remains unknown. There is a known association with diabetes.

Although only 0.03% of diabetics develop NLD, 65% of patients who develop NLD are diabetic and another 12% to 15% will demonstrate an abnormal glucose tolerance test even though they are not overtly diabetic. Of those patients with NLD who do not have diabetes or an abnormal glucose tolerance test, over half of them have a family history of diabetes. It is unclear how hyperglycemia and NLD are pathophysiologically linked.

It has been postulated that the vascular changes associated with diabetes might play a role in the collagen degeneration that precipitates the inflammatory process that is the hallmark of NLD.

References:

1. Boulton AJM, Cutfield RG, Abouganem D, Angus E, Flynn HW, Skyler JS, Penneys NS. Necrobiosis lipoidica diabeticorum: a clinicopathologic study. J Am Acad Dermatol 1988; 18:530–537.
2. Gibson LE, Reizner GT, Winkelmann RK. Necrobiosis lipoidica diabeticorum with cholesterol clefts in the differential diagnosis of necrobiotic xanthogranuloma. J Cutan Pathol 1988; 15:18–21.
3. Lowitt MH, Dover JS. Necrobiosis lipoidica. J Am Acad Dermatol 1991; 25:735–748.
4. Magro CM, Crowson AN, Regauer S. Granuloma annulare and necrobiosis lipoidica tissue reactions as a manifestation of systemic disease. Hum Pathol 1996; 27:50–56.

RHEUMATOID NODULE

Nodular palisaded type of granulomatous disease.

Clinical Presentation:

- Subcutaneous firm dome-shaped skin colored nodules that are usually painless and semi-mobile (Fig. 12A)
- Lesions most commonly located in periarticular sites over extensor surfaces at sites subjected to trauma or pressure

Histopathology:
- Palisaded granulomatous dermatitis in the subcutaneous fat (Fig. 12B)
- Palisades of histiocytes around fibrin that stains homogeneously red (Fig. 12C)

Differential Diagnosis:
See "Differential Diagnosis" table under the section "Granuloma annulare."

If a patient has what appears to be a rheumatoid nodule but is rheumatoid factor negative, the patient is most likely to be suffering from subcutaneous granuloma annulare or another palisaded granulomatous dermatitis.

Pathophysiology:
Rheumatoid nodules are present in 20% of patients with rheumatoid arthritis and are associated with a relatively high titer of rheumatoid factor.

Reference:
1. Patterson JW. Rheumatoid nodule and subcutaneous granuloma annulare. A comparative histologic study. Am J Dermatopathol 1988; 10:1–8.

GOUT

Nodular palisaded type of granulomatous disease (but could also be classified as a foreign body granulomatous dermatitis or as a deposition disease with granulomatous inflammation).

Synonyms: Urate deposition disease; urate arthropathy.

Clinical Presentation:
- Firm dermal or subcutaneous papules or nodules located especially on the helix of the ears, near small joints of the hands and toes, and bursa of elbow (Fig. 13A)
- The lesions can be skin colored or white–yellow or erythematous
- Large lesions can ulcerate and discharge a clear fluid with white flecks or a chalky material

Histopathology:
- Palisades of histiocytes arranged around urate deposits within the dermis or subcutanous fat (Fig. 13B)
- If the specimen is fixed in formalin → the urate crystals dissolve and leave only an amorphous feathery basophilic matrix (Figs. 13B and C)
- If the specimen is properly fixed in alcohol (ethanol based preservative as Carnoy's fluid) instead of formalin → urate crystals are preserved and appear needle-shaped, multicolor or brownish in color, and can be bundled
- Intact preserved crystals appear yellow to blue when examined with polarizing lenses. When the polarizing lenses are turned, the crystals demonstrate negative birefringence
- The overlying epidermis may be normal or ulcerated

Clinicopathologic Correlation:

Clinical Feature	Pathologic Feature
Discharge of material from ulcerated lesions	Discharge of urate crystals that have deposited in the skin

Differential Diagnosis:
See Differential Diagnosis table under the section "Granuloma Annulare."

Pathophysiology:
Gout is a metabolic disease associated with underlying hyperuricemia. The skin and joint manifestations are secondary to deposits of monosodium urate crystals. When urate crystals deposit within and around various joints the result is the chronic arthritis of gout. The same crystals can deposit in the dermis or subcutaneous tissue resulting in the skin manifestations of gout, known as tophi.

References:
1. Touart DM, Sau P. Cutaneous deposition diseases. Part II. J Am Acad Dermatol 1998; 39:527–544.
2. Rott KT, Agudelo CA. Gout. JAMA 2003; 289:2857–2860.

NECROBIOTIC XANTHOGRANULOMA

Nodular palisaded type of granulomatous disease.

Synonym: Necrobiotic xanthogranuloma with paraproteinemia.

Clinical Presentation:
- Firm asymptomatic yellowish nodules and plaques with atrophy, telangiectasia, and occasional ulceration
- Lesions located most commonly in the periorbital region (Fig. 14A)
- This is a multisystem disease. Common associated findings include various ocular manifestations, hepatomegaly, and splenomegaly
- At least 80% of the patients have an associated IgG monoclonal gammopathy
- There is an associated increased risk of lymphoproliferative disorders and plasma cell dyscrasias

Histopathology:
- Palisades of histiocytes and focal and/or intersecting bands of granulomatous dermatitis around extensive necrobiosis in the mid and deep dermis with extension into and through the subcutaneous lobules (Figs. 14B and C)
- Numerous foam cells and giant cells (Touton and foreign body giant cells) (Fig. 14D)
- Extracellular deposits of lipids and cholesterol clefts
- Perivascular (superficial and deep dermal and subcutaneous) lymphoplasmacytic infiltrate with lymphoid follicles

Clinicopathologic Correlation:

Clinical Features	Pathologic Features
Firm plaques and nodules	Site of pathology in deep dermis and subcutis
Yellowish color of lesions	Presence of foam cells, Touton giant cells, extracellular deposits of lipids and cholesterol clefts

Differential Diagnosis:

Necrobiosis Lipoidica	Necrobiotic Xanthogranuloma
Focal necrobiosis in tiers	More extensive necrobiosis in broad bands
No foamy histiocyctes	Foamy histiocytes
No Touton giant cells	Touton giant cells
Granulomatous vasculitis	Vascular involvement rare
Pannicular involvement reported	Pannicular involvement common

Pathophysiology:
The pathophysiology remains unknown. The associated paraproteinemia has been postulated to be the inciting event in eliciting the subsequent granulomatous reaction.

References:

1. Kossard S, Winkelmann RK. Necrobiotic xanthogranulomas with paraproteinemia. J Am Acad Dermatol 1980; 3:257–270.
2. Finan MC, Winkelmann RK. Histopathology of necrobiotic xanthogranuloma with paraproteinemia. J Cutan Pathol 1987; 14:92–99.
3. Mehregan DA, Winkelmann RK. Necrobiotic Xanthogranuloma. Arch Dermatol 1992; 128:94–100.
4. Kossard S, Chow E, Wilkinson B, Killingsworth M. Lipid and giant cell poor necrobiotic xanthogranuloma. J Cutan Pathol 2000; 27:374–378.

FOREIGN BODY GRANULOMAS

Nodular foreign body type of granulomas.

Clinical Presentation:
- Red to red-brown papules, nodules, or plaques that can ulcerate
- Occasionally, these lesions can drain or develop a fistula

Histopathology:
- Aggregates of epithelioid histiocytes
- Many multinucleated (especially foreign-body type) histiocytes
- Identifiable foreign body may be present
- Some foreign bodies polarize with polarizable lenses

Pathophysiology:
Foreign body granulomas are an inflammatory response to inorganic or high-molecular-weight organic materials that have been introduced into the skin. The skin responds to this foreign material with granulomatous inflammation. Routes of entry include accidental, self inflicted, surgery, topical medications, or a normally sequestered part of our own body that becomes treated as a foreign body if it comes into direct contact with the dermis (keratin, nails, hair, etc.) Examples of foreign body granulomatous reactions include ruptured follicular cysts (Figs. 15A–C) in which a portion of the epithelial lined cyst or cornified cells (squames) are surrounded or engulfed by histiocytes. Initially the inflammatory response to a ruptured cyst is suppurative; ultimately, there is granuloma formation and eventually fibrosis. Splinters (slivers of wood demonstrating a "stepladder" pattern of cellulose), sutures (Figs. 16A–D) (homogeneous pale yellowish material that is polarizable), and starch (often secondary to surgical gloves) are refractile with polarizing lenses. Some dyes in tattoos histologically can elicit a granulomatous inflammatory response (which can be foreign body, sarcoidal, or tuberculoid). Most tattoo material appears black in color in routine histologic sections. Calcium (calcinosis cutis) (Figs. 17A and B) can be seen in association with tissue injury, inflammatory processes, or as a manifestation of abnormal calcium and/or phosphorus metabolism.

LICHEN NITIDUS

Lichenoid and granulomatous disease.

Clinical Presentation:
- Tiny, shiny, flat topped, skin colored to pink papules (Fig. 18A)
- Papules can be clustered
- Papules can be linear in array secondary to Koebner phenomenon

Histopathology:
- Aggregates of histiocytes and Langerhan's giant cells in widened dermal papillae (Figs. 18B and C)
- Adjacent epidermal rete ridges form "ball-and-claw" appearance (Fig. 18B)
- The overlying epidermis is atrophic with focal parakeratosis
- Vacuolar alteration
- Underlying superficial perivascular and lichenoid lymphohistiocytic infiltrate

Clinicopathologic Correlation:

Clinical Feature	Pathologic Feature
Tiny papules	Granulomatous infiltrate fills 1–3 widened dermal papillae
Flat topped papules	Lichenoid infiltrate
Shiny papules	Atrophic epidermis
Pink papules	Superficial and lichenoid inflammation

Differential Diagnosis:

Lichen Nitidus	Lichen Planus	Papular Sarcoid
Vaculoar alterations	Vacuolar alteration	No vacuolar alteration
Epidermal atrophy with a "cap" of parakeratosis	Irregular "sawtooth" epidermal hyperplasia, focal hypergranulosis, hyperkeratosis without parakeratosis	No specific epidermal changes
Lichenoid and granulomatous	Lichenoid only	Granulomatous only

Pathophysiology:
The pathophysiology of lichen nitidus is not known. Immunologic mechanisms are postulated to be causative.

References:

1. Smoller BR, Flynn TC. Immunohistochemical examination of lichen nitidus suggests that it is not a localized papular variant of lichen planus. J Am Acad Dermatol 1992; 27:232–236.
2. Murillo EDE, Yus ES, Lens RN. Lichen nitidus of the palms: a case with peculiar histopathologic features. Am J Dermatopathol 1999; 21:161–164.

INFECTIOUS GRANULOMAS

Nodular or diffuse suppurative and/or granulomatous disease.

Clinical Presentation:
- Crusted, verrucous nodules or plaques
- Lesions can be ulcerated (Fig. 19A)

Histopathology:
- Nodular granulomatous (histiocytic) and/or nodular suppurative (neutrophilic infiltrate that can form abscesses) inflammation can be present (Fig. 19B)
  - Nodular abscesses as well as nodular granulomatous dermatitis (Fig. 19C)
- Diffuse infiltrate of neutrophils and/or histiocytes may be present
- Overlying epidermis often hyperplastitc
- Special stains to highlight or identify organisms often required (Fig. 19D)

Pathophysiology:
Nodular or diffuse granulomatous dermatitis with neutrophils (suppurative granulomatous dermatitis) can be seen secondary to infectious processes (deep fungal such as coccidioidomycosis, cryptococcosis, sporotrichosis, histoplasmosis, chromoblastomycosis, North American blastomycosis, South American blastomycosis or paracoccidioidomycosis; candida granuloma; kerion; atypical mycobacterial infections and tuberculosis verrucosa cutis; actinomycosis, nocardiosis, eumycetoma; bacterial mycetoma or botryomycosis; parasitic as prototheocosis, etc.). Special stains and cultures are often required to identify the infectious agent.

NONINFECTIOUS GRANULOMAS

Nodular or diffuse suppurative and/or granulomatous disease.

Clinical Presentation:
- Crusted and/or verrucous nodules (Fig. 20A) and plaques
- Pustules may be identified on the surface of the plaques

Histopathology:
- Follicular involvement (dilated follicular infundibula often containing abscesses and evidences of infundibula rupture) can be prominent in halogenodermas (Fig. 20B) (which may be induced by halogen containing medications as iodides, bromides, and fluorides) and in the follicular-occlusion tetrad group of diseases (including acne conglobata, dissecting cellulitis of the scalp, hidradenitis suppurativa, and pilonidal sinus)
- Both granulomatous (histiocytic) and suppurative (neutrophilic infiltrate that can form abscesses) inflammation present (Figs. 20C and D)
  - Nodular abscesses as well as nodular granulomatous dermatitis may be present
- Diffuse infiltrate of neutrophils and/or histiocytes may be present
- No infectious agents identified
- Epidermis may be normal (as in ruptured follilcular cysts or foreign body reactions) or hyperplastic
- Ruptured follicular cysts and even foreign body reactions can also histologically demonstrate a suppurative granulomatous dermatitis, usually without overlying epidermal hyperplasia

References:
1. Alpay K, Kurkcuoglu N. Ioderma: an unusual side effect of iodide ingestion. Ped Dermatol 1996; 13:51–53.
2. Anzai S, Fujiwara S, Inuzuka M. Bromoderma. Int J Dermatol 2003; 42:370–371.

XANTHOMA

Diffuse granulomatous disease.

Xanthomas could be categorized as an inflammatory (granulomatous), benign hyperplasia, benign neoplastic, or deposition disease process.

Clinical Presentation:
- Papules with a yellowish to orange hue (Fig. 21A)

Histopathology:
- Foamy histiocytes (foam cells) or lipid-laden macrophages are initially noted, perivascularly. As the lesions mature the infiltrate of foam cells becomes nodular and then ultimately diffuse (Figs. 21B and 21C)
- Sparse infiltrate of lymphocytes
- Overlying epidermis is atrophic

Clinicopathologic Correlation:

Clinical Feature	Pathologic Feature
Yellow papules	Infiltrate in the dermis composed of lipid laden macrophages

Differential Diagnosis:
Diffuse granulomatous dermatoses have been described and differentiated by the characteristics of the predominant histiocyte composing the infiltrate, that is, foamy, granular, or infectious-laden histiocytes.

Diffuse Granulomatous Disease	Characteristic Histiocyte Composing Infiltrate
Xanthoma	Foamy or lipid-laden histiocytes
Xanthogranuloma	Foamy or lipid-laden histiocytes; Touton giant cells; admixture of eosinophils, lymphocytes, and plasma cells
Reticulohistiocytic	Large granular (ground-glass cytoplasm) histiocytes; granulomas often with multinucleated histiocytes
Lepromatous leprosy	Foamy histiocytes with gray granular cytoplasm containing numerous acid-fast lepra bacilli (globi)
Leishmaniasis, acute cutaneous	Histiocytes laden with round to oval-shaped Leishman-Donavan bodies (visualized with H&E, Giemsa, and Wright's stains)

Pathophysiology:
Xanthoma formation in those patients with hyperlidemia is postulated to be secondary to increased circulating plasma lipoproteins permeating through dermal capillary blood vessels and ultimately being phagocytized by macrophages thus forming foam cells within the dermis.

Reference:

1. Maher-Wiese VL, Marmer EL, Grant-Kels JM. Xanthomas and the inherited hyperlipoproteinemias in children and adolescents. Pediatr Dermatol 1990; 7:166–173.
2. Breier F, Zelger B, Reiter H, et al. Papular xanthoma: a clinicopathological study of 10 cases. J Cutan Pathol 2002; 29:200–206.

XANTHOGRANULOMA

Diffuse granulomatous disease.

Synonym: Juvenile xanthogranuloma.

Clinical Presentation:
- Tan to pink to red–brown, to yellow to yellow–orange papules, plaques or nodules. More yellow coloration noted in fully-developed lesions (Fig. 22A)
- Can present as many small nodules or one or a few large nodules
- Rare in adults, where it is usually a solitary persistent lesion
- In children often multiple and usually spontaneously resolve
- In infants and children can be associated with extracutaneous lesions, particularly ocular lesions
- Juvenile xanthogranuloma can be associated with café-au-lait lesions and neurofibromatosis 1
- Juvenile xanthogranuloma can be associated with juvenile chronic myelogenous leukemia
- Patients with juvenile xanthogranuloma and neurofibromatosis 1 may have up to a 20 times increased risk of developing juvenile chronic myelogenous leukemia; this has been referred to as the "triple association"

Histopathology:
- Dense diffuse infiltrate composed of histiocytes, foamy histiocytes, and Touton giant cells (Figs. 22B and C)
- Infiltrate admixed with scattered eosinophils, lymphocytes, and plasma cells
- Overlying epidermis usually thin but can be hyperplastic at the periphery
- Older lesions demonstrate fibrosis
- The histiocytes stain positively for CD68, HAM56, and factor XIIIa and negatively for CD1a

Clinicopathologic Correlation:

Clinical Feature	Pathologic Feature
Plaques and nodules	Dense dermal infiltrate that can fill the dermis and extend into the subcutis
Tan to pink–brown to yellow in color	Initially lesions are composed of hisitocytes and appear tan to pink–brown in color. As the lesions mature the infiltrate becomes predominantly composed of lipid-laden histiocytes and the lesion appears more yellow in color clinically

Differential Diagnosis:
See Differential Diagnosis table from the section "Xanthoma."

Pathophysiology:
The pathophysiology of xanthogranuloma is not known. Although there is some evidence that the lesions are composed of reactive histiocytes, the stimuli that the cells are reacting to remains a mystery. Why the cells become lipid laden in the absence of hyperlipidemia is also not understood.

References:

1. Hernandez-Martin A, Baselga E, Drolet BA, Esterly NB. Juvenile Xanthogranuloma. J Am Acad Dermatol 1997; 36: 355–367.
2. Chang MW. Update on Juvenile Xanthogranuloma: unusual cutaneous and systemic variants. Seminars in Cutaneous Medicine and Surgery 1999; 18:195–205.
3. Kraus MD, Haley JC, Ruiz R, Essary L, Moran CA, Fletcher CDM. "Juvenile" Xathogranuloma. An immunophenotypic study with a reappraisal of histogenesis. Am J Dermatopathol 2001; 23:104–111.

RETICULOHISTIOCYTOMA

Diffuse granulomatous disease.

Synonyms: Solitary reticulohistiocytosis, giant cell reticulohistiocytosis.

Clinical Presentation:
- Single or multilple reddish brown papules and nodules (Fig. 23A)
- Lesions found predominantly on head, hands, and elbows. Fifty percent of patients develop oral mucosal and nasopharyngeal lesions
- Two Clinical Variants
  - A single (or rarely multiple) papule or small nodule usually on the head without any evidence of systemic disease. The skin lesion tends to resolve spontaneously
  - Multiple lesions on the skin and mucous membranes that are part of a multisystem systemic disease (multicentric reticulohistiocytosis) associated with destructive arthritis; other less common associations include an elevated sedimentation rate, anemia, systemic vasculitis, hypercholesterolemia, IgG hypergammaglobulinemia, cryoglobulinemia, and in about a quarter of the patients an internal malignancy

Histopathology:
- Single or multiple lesions essentially demonstrate the same pathology
- Histiocytes with granular eosinophilic "ground-glass" cytoplasm
  - The center of the histiocyte is granular and dark eosinophilic–purple in color while the periphery of the cell is lighter eosinophilic in color and granular (Figs. 23B–D)
- Multinucleated histiocytes with the same ground glass cytoplasm (Figs. 23D and E)

- Infiltrate admixed with neutrophils, lymphocytes, rare eosinophils, and plasma cells
- The overlying epidermis is thinned
- Older lesions demonstrate fibrosis

Differential Diagnosis:
See Differential Diagnosis table from the section "Xanthoma."

The histiocytes composing reticulohistiocytomas and xanthogranulomas are both non-Langerhans cell histiocytes. They are S100 and CD1a negative but stain for macrophage markers (CD68). No Birbeck granules are noted on electron microscopy.

Pathophysiology:
The pathophysiology for reticulohistiocytosis is unknown but it has been postulated that it is a reactive, abnormal, response of histiocytes to some unknown stimulus or stimuli.

References:

1. Perrin C, Lacour JP, Michiels JF, Flory P, Ziegler G, Ortonne JP. Multicentric reticulohistiocytosis. Immunohistological and ultrastructural study: A pathology of dendritic cell lineage. Am J Dermatopathol 1992; 14:418–425.
2. Rapini RP. Multicentric reticulohistiocytosis. Clinics in Dermatology 1993; 11:107–111.
3. Zelger B, Cerio R, Soyer HP, Misch K, Orchard G, Wilson-Jones E. Reticulohistiocytoma and multicentric reticulohistiocytosis. Histopathologic and immunophenotypic distinct entities. Am J Dermatopathol 1994; 16:577–584.

LEPROMATOUS LEPROSY

Diffuse granulomatous disease.

Synonym: Hansen's disease.

Clinical Presentation:
- Erythematous papules, nodules, and ultimately confluent plaques
- Infiltrative lesions on the face can result in a leonine facies (Fig. 24A)
- Lesions are widespread and symmetrical in distribution
- The most common sites of involvement include the face, buttock, and lower extremities

Histopathology:
- Diffuse dermal infiltrate composed of predominantly foam cells admixed with lymphocytes and plasma cells (Figs. 24B and C)
- Virchow cells are foam cells or histiocytes which are grayish in color and are filled with lipid-containing acid-fast organisms
- A grenz zone or a thin band of normal appearing dermis separates the epidermis from the underlying infiltrate (Fig. 24B)
- Within the dermis small nerves are surrounded by the inflammatory cells and foam cells. (Fig. 24D and E)
- Organisms stain red with the Fite stain. Globi are masses of densely packed acid-fast bacilli within histiocytes (Fig. 24F)

Clinicopathologic Correlation:

Clinical Feature	Pathologic Feature
Anesthesia in a stocking or glove distribution	Enlarged peripheral nerves involved because the parasite lives within Schwann cells as well as macrophages
Lesions noted symmetrically and especially involving the nose, testicles, ear lobes, regions where peripheral nerves are close to the skin	*M. Leprae* requires a temperature of around 35°C to grow and therefore prefers cooler areas of the body. As a result, macrophages laden with the acid fast bacilli infiltrate these areas

Differential Diagnosis:
See Differential Diagnosis table from the section ''Xanthoma.''

Pathophysiology:
Lepromatous leprosy due to *Mycobacterium leprae* is the form of leprosy associated with the least cellular immunity and greatest number of bacilli. Lesions are therefore widespread, numerous and infiltrated. The organism is an obligate intracellular microorganism and lives within macrophages and Schwann cells. Macrophages attempt to eliminate the bacilli unsuccessfully and release cytokines that attract more macrophages resulting in the infiltrated lesions that subsequently destroy normal structures like the nose (saddle nose), and so on. Destruction of peripheral nerves results in neurotropic changes.

References:

1. Cuevas-Santos J, Contreras F, McNutt NS. Multibacillary leprosy: lesions with macrophages positive for S100 protein and dendritic cells positive for Factor 13A. J Cutan Pathol 1998; 25:530–537.
2. Abulafia J, Vignale RA. Leprosy: pathogenesis updated. Int J Dermatol 1999; 38:321–334.
3. Abulafia J, Vignale RA. Leprosy: accessory immune system as effector of infectious, metabolic, and immunologic reactions. Int J Dermatol 2001; 40:673–687.
4. Moschella SL. An update on the diagnosis and treatment of leprosy. J Am Acad Dermatol 2004; 51:417–426.

ACUTE CUTANEOUS LEISHMANIASIS

Diffuse granulomatous disease.

Synonyms: Oriental sore; Baghdad sore.

Clinical Presentation:
- After a bite by a sandfly, the patient develops a papule that grows into a nodule or plaque
- The nodule/plaque ultimately will ulcerate (Fig. 25A) or become verrucous. Most resolve spontaneously with a scar
- Exposed areas are most commonly involved
- Most often solitary but can be multiple lesions

Histopathology:
- There is a diffuse dermal infiltrate composed of histiocytes containing obvious parasites manifested as dark-staining round or ovoid cytoplasmic dots (Leishman-Donovan bodies) (Figs. 25B and C)

- Organisms stain with hematoxylin-eosin, Giemsa, and Wright's stains
- The infiltrate is admixed with lymphocytes, plasma cells, and occasionally neutrophils
- The epidermis may demonstrate pseudoepitheliomatous hyperplasia but eventually ulcerates

Clinicopathologic Correlation:

Clinical Feature	Pathologic Feature
Verrucous surface	Pseudoepitheliomatous epidermal hyperplasia
Nodule or plaque	Diffuse dermal infiltrate composed of histiocytes

Differential Diagnosis:
See Differential Diagnosis table under section "Xanthoma."

Pathophysiology:
Leishmaniasis is due to an obligate intracellular protozoan parasite. It multiplies in the gut of the sandfly, migrates to the proboscis, and is transmitted to humans, rodents, and dogs via the sandfly bite. The organism then multiplies within cells of the reticuloendothelial system or macrophages.

References:
1. Willard RJ, Jeffcoat AM, Benson PM, Walsh DS. Cutaneous leishmaniasis in soldiers from Fort Campbell, Kentucky returning from Operation Iraqi Freedom highlights diagnostic and therapeutic options. J Am Acad Dermatol 2005; 52: 977–987.
2. Pehoushek JF, Quinn DM, Crum WP. Cutaneous leishmaniasis in soldiers returning from deployment in Iraq. J Am Acad Dermatol 2004; 51:S125–S128.
3. Faber WR, Oskam L, van Gool T, Kroon NCM, Knegt-Junk KJ, et al. Value of diagnostic techniques for cutaneous leishmaniasis. J Am Acad Dermatol 2003; 49:70–74.

GRANULOMATOUS VASCULITIS

Granulomatous vasculitis (Chapter 7) is marked by histiocytes within and around blood vessel walls in association with fibrin and/or degenerative and necrotic changes (vascular damage). Small vessel (capillary-venule) granulomatous vasculitis can be identified in some sections of necrobiosis lipoidica (refer to palisaded granulomatous dermatitis section). Large vessel (arterial) granulomatous dermatitis has been described in various diseases, but is prominent and even fairly characteristic of allergic granulomatosis (Churg-Strauss syndrome) and Wegener's granulomatosis.

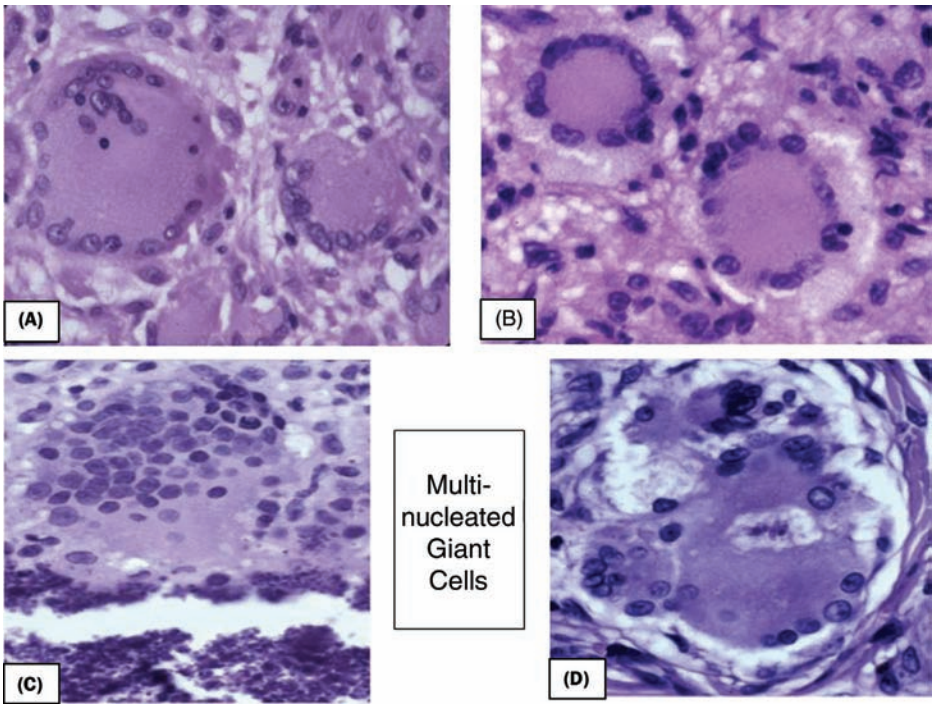

Figure 1 Multinucleated giant cells. (**A**) Langhan's multinucleated giant cell. (**B**) Touton multinucleated giant cell. (**C**) Foreign body multinucleated giant cell. (**D**) Asteroid body in a multinucleated giant cell.

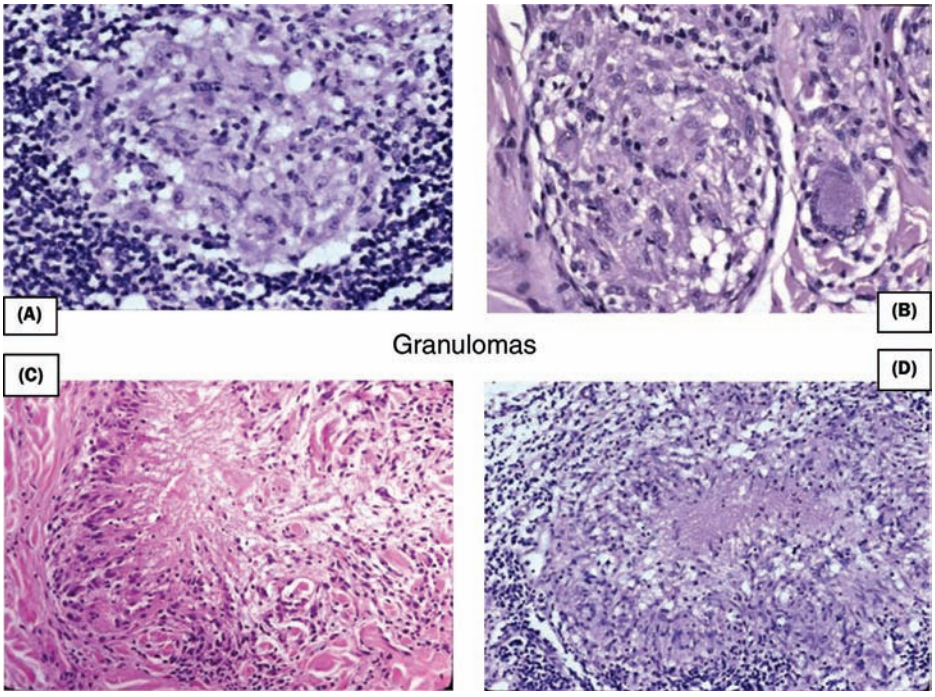

Figure 2 Granulomas. (**A**) Tuberculoid granuloma. (**B**) Sarcoidal granuloma. (**C**) Palisaded granuloma. (**D**) Caseation necrosis within a granuloma.

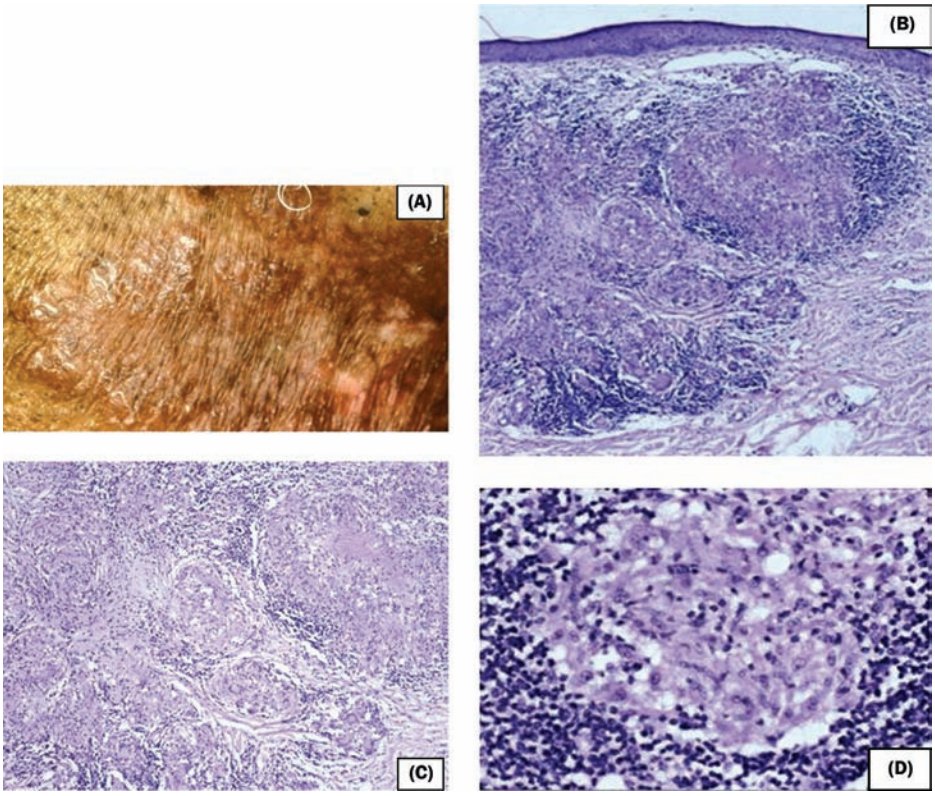

Figure 3 Lupus vulgaris. (**A**) Reddish brown plaque. (**B**) and (**C**) Nodular tuberculoid granulomas. (**D**) Caseation necrosis.

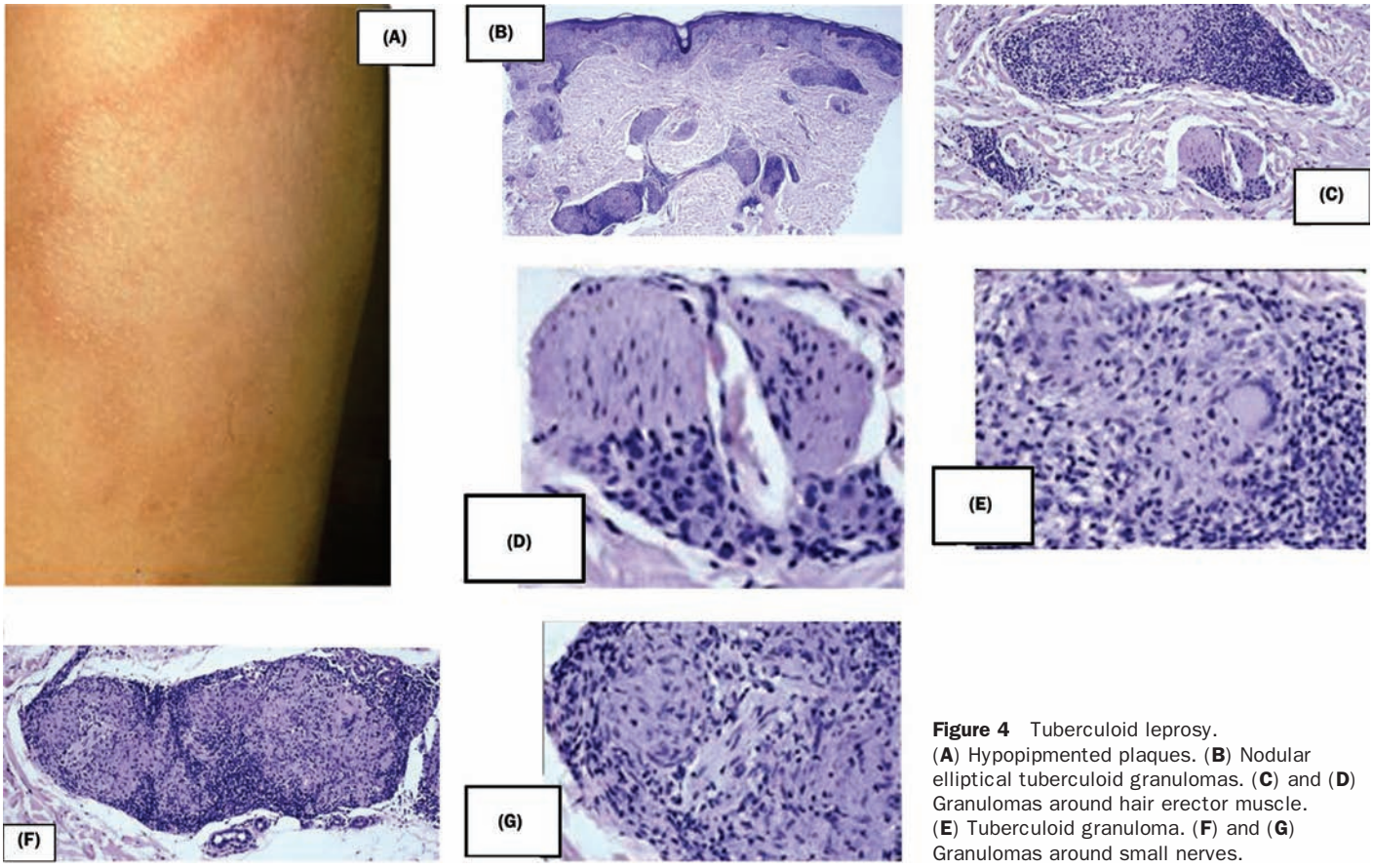

Figure 4 Tuberculoid leprosy. (**A**) Hypopipmented plaques. (**B**) Nodular elliptical tuberculoid granulomas. (**C**) and (**D**) Granulomas around hair erector muscle. (**E**) Tuberculoid granuloma. (**F**) and (**G**) Granulomas around small nerves.

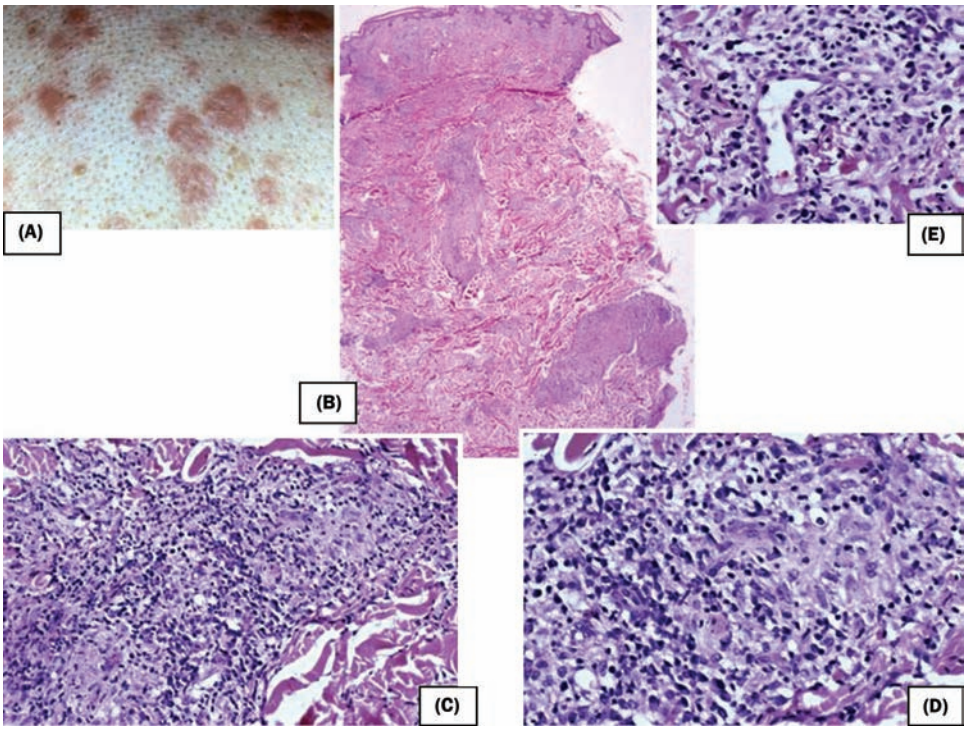

Figure 5 Syphilis, late secondary stage. (**A**) Papules. (**B–D**) Nodular tuberculoid granulomas. (**E**) Plump endothelial cells surrounded by many plasma cells.

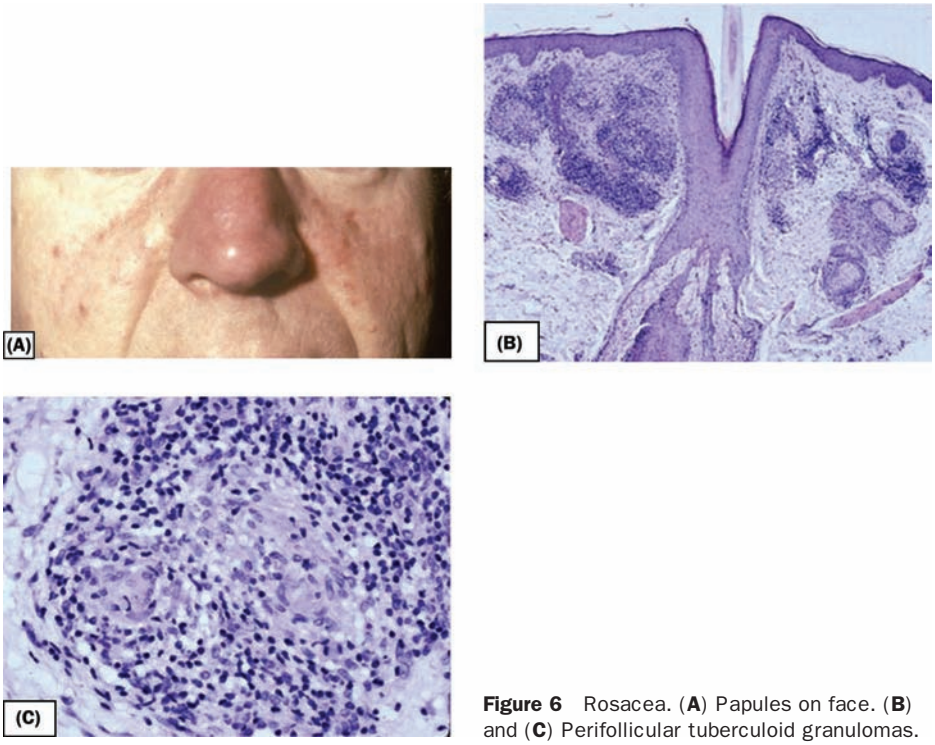

Figure 6 Rosacea. (**A**) Papules on face. (**B**) and (**C**) Perifollicular tuberculoid granulomas.

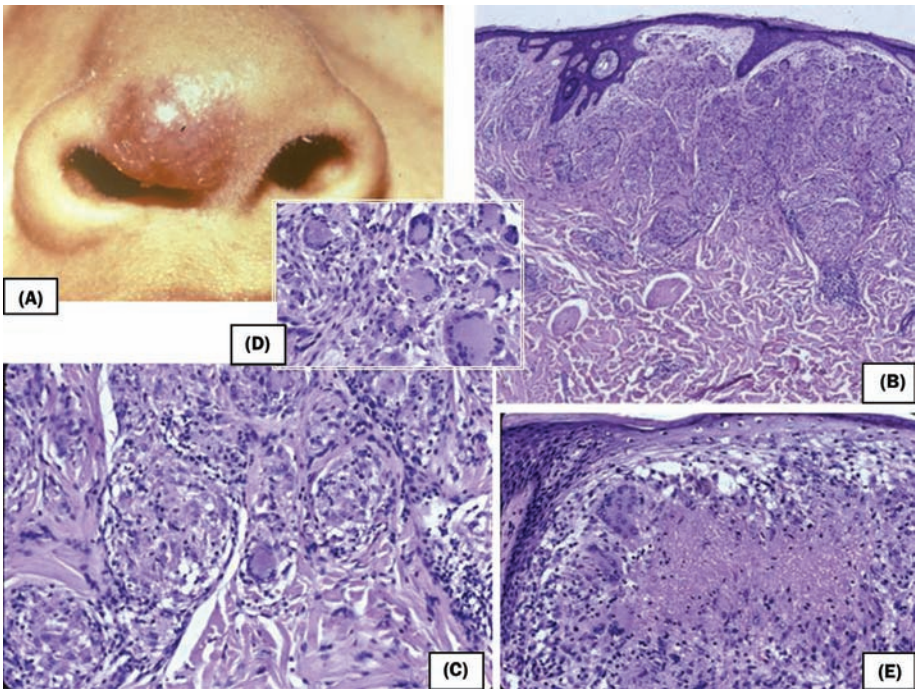

Figure 7 Sarcoid. (**A**) Lupus pernio, red nodule on nose. (**B–D**) Round sarcoidal granulomas. (**E**) Fibrin within a tubercle.

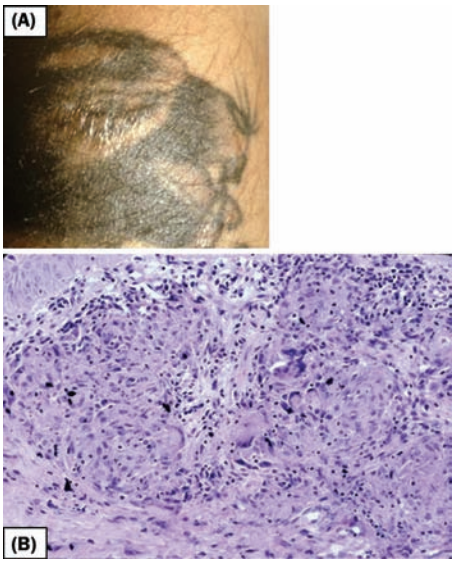

Figure 8 Tattoo dye allergic reaction. (**A**) Focal swelling within a tattoo. (**B**) Allergic sarcoidal granulomas containing tattoo granules that appear histologically black.

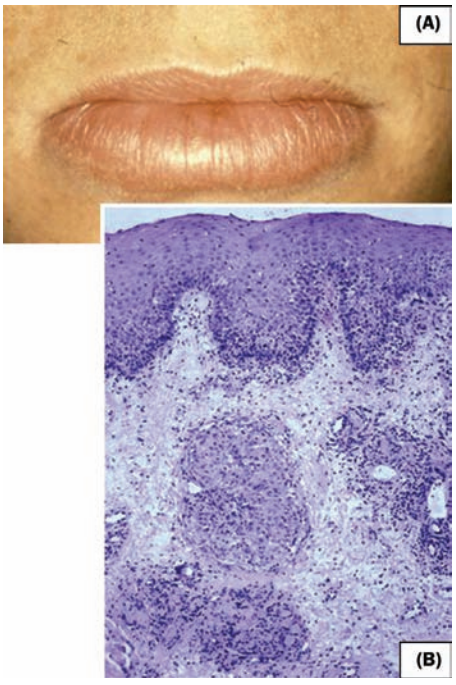

Figure 9 Cheilitis granulomatosa. (**A**) Enlargement of lower lip. (**B**) Sarcoidal granulomas within mucosal skin.

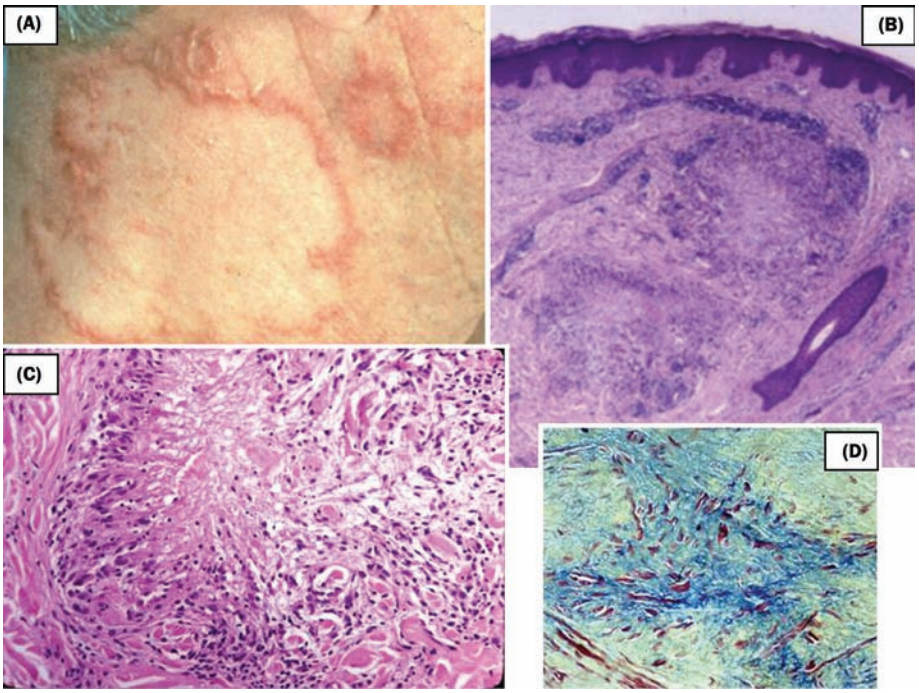

Figure 10 Granuloma annulare. (**A**) Pink papules annularly arranged. (**B**) and (**C**) Palisaded granulomas with mucin in the center. (**D**) colloidal iron stain highlighting increased mucin.

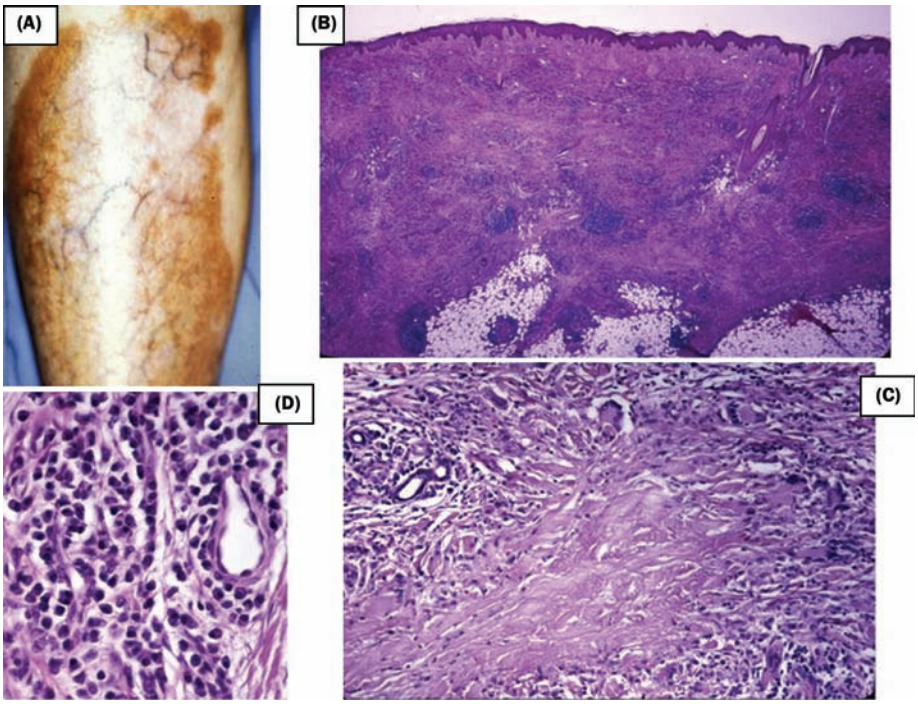

Figure 11 Necrobiosis lipoidica. (**A**) Yellowish atrophic plaque with telangiectasia on the skin. (**B**) Entire specimen with tiers of nodular palisaded granulomas. (**C**) Palisaded granuloma around degenerated collagen. (**D**) Telangiectasias with surrounding plasma cells.

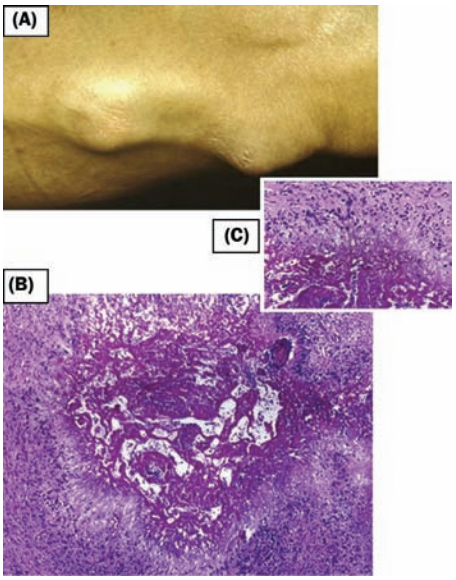

Figure 12 Rheumatoid nodule. (**A**) Skin colored nodule. (**B**) Subcutaneous palisaded granuloma with central fibrin.

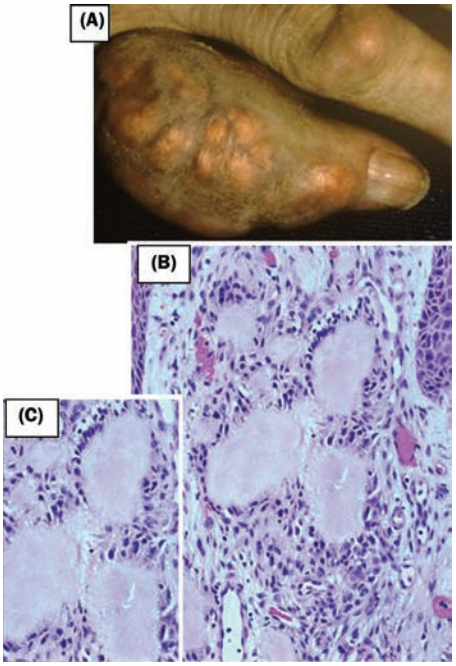

Figure 13 Gout. (**A**) White chalky papule on toes. (**B**) and (**C**) Palisaded granulomas around amorphous feathery basophilic matrix.

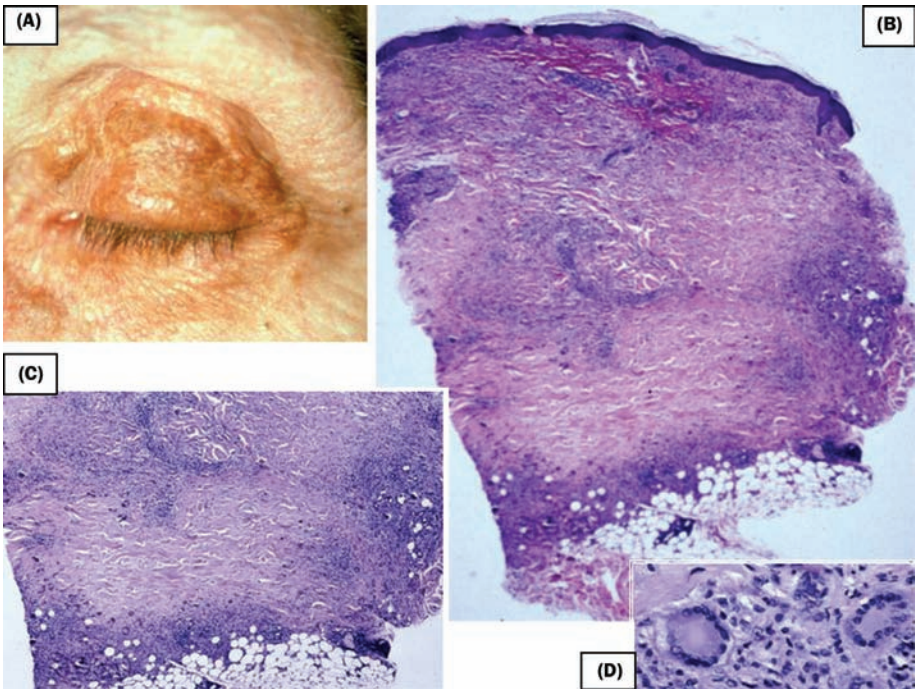

Figure 14 Necrobiotic xanthogranuloma. (**A**) Yellowish plaques periorbitally. (**B**) and (**C**) Extensive palisading granulomas in intersecting bands with extensive necrobioisis. (**D**) Touton giant cells.

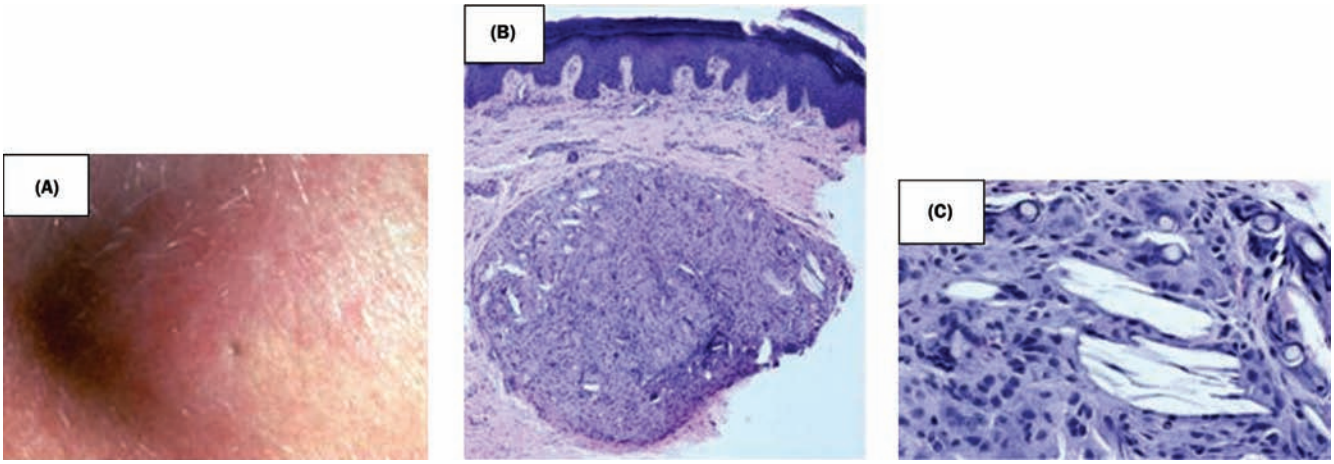

Figure 15 Ruptured follicular cyst. (**A**) Nodule with central punctum. (**B**) and (**C**) Granulomatous nodule with fragment of keratin and hair.

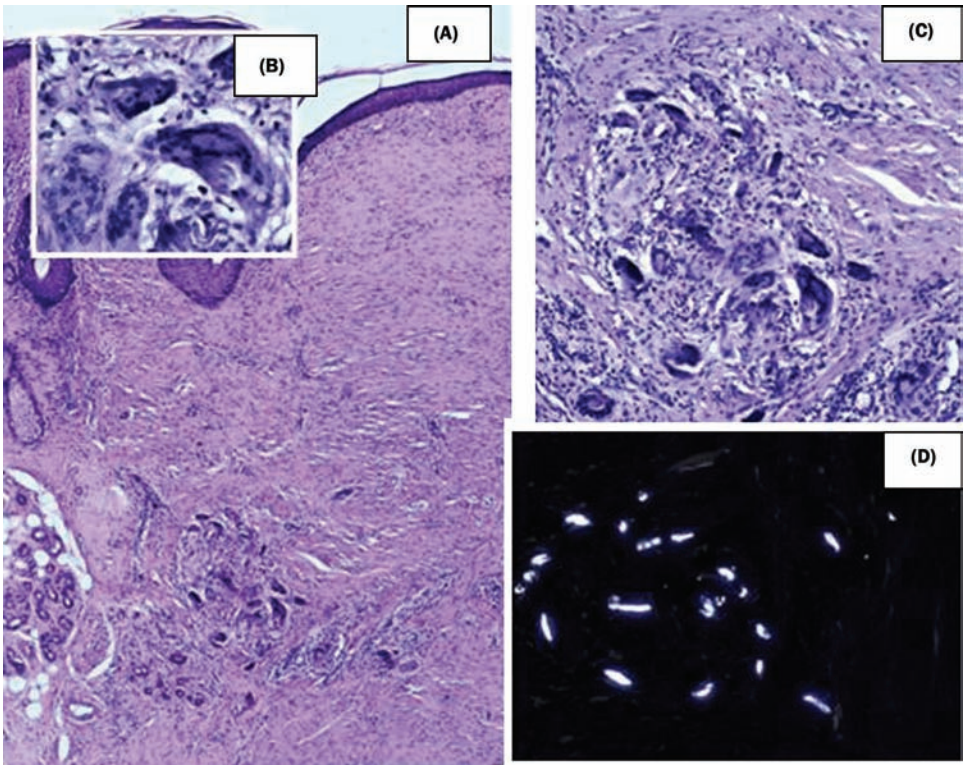

Figure 16 Suture foreign body reaction. (**A**) Scar with focal granulomatous inflammation. (**B**) and (**C**) Granulomatous reaction with suture material. (**E**) Polarized suture material.

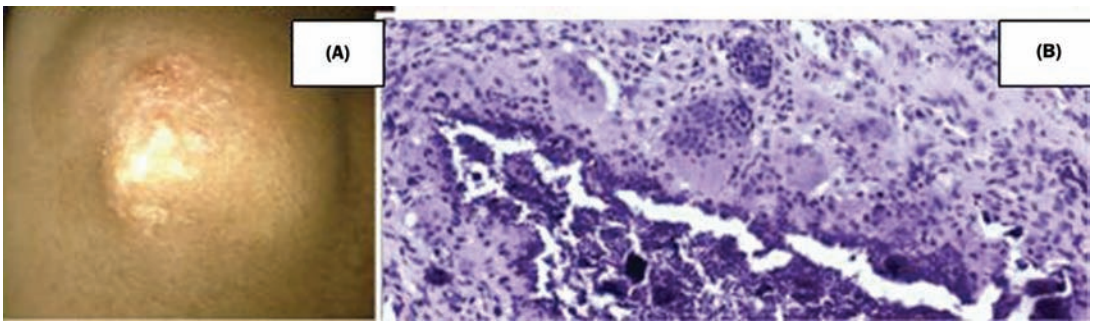

Figure 17 Calcinosis cutis. (**A**) Whitish papules. (**B**) Foreign body granulomatous reaction around blue staining calcium within the dermis.

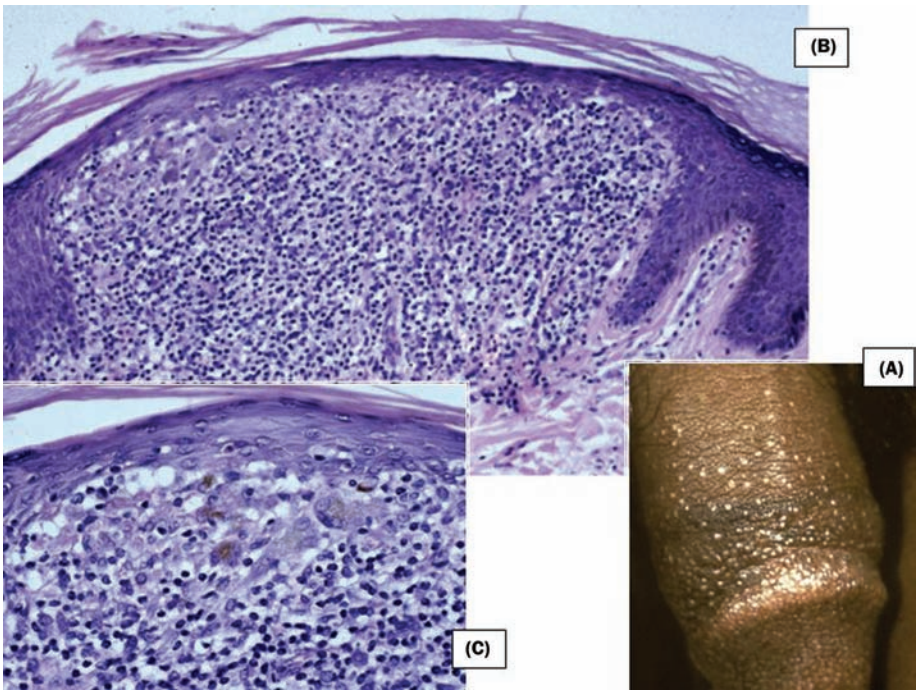

Figure 18 Lichen nitidus. (**A**) Tiny papules. (**B**) and (**C**) Histiocytes in the widened dermal papillae beneath which is a band of lymphocytes and around which the rete ridges form a "ball-and-claw" appearance.

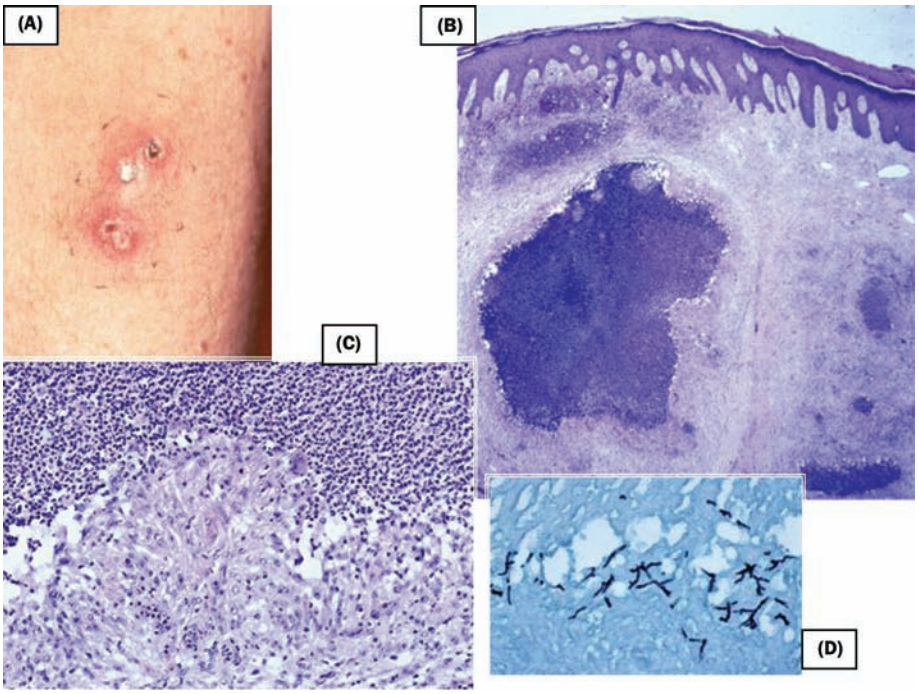

Figure 19 Aspergillosis. (**A**) Nodules at site of an intravenous line in an immunosuppressed patient. (**B**) and (**C**) Suppurative granulomatous nodular infiltrate. (**D**) GMS stain demonstrating branching hyphae.

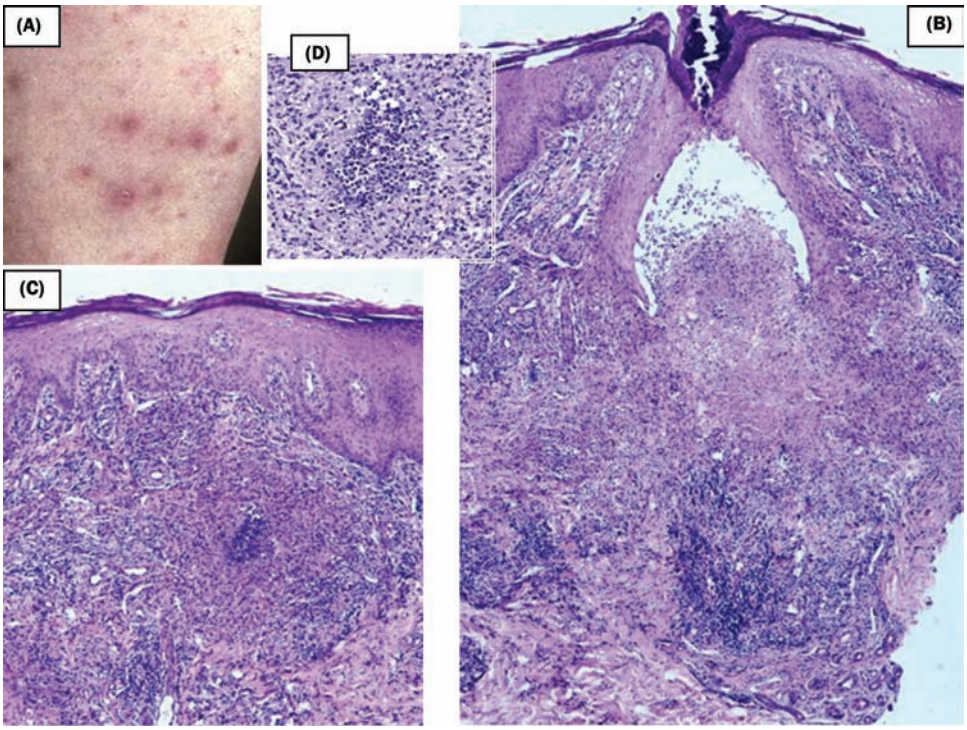

Figure 20 Bromoderma. (**A**) Papulonodules on the leg. (**B**) Ruptured follicle with a nodular suppurative and granulomatous infiltrate. (**C**) and (**D**) Suppurataive and granulomatous nodule.

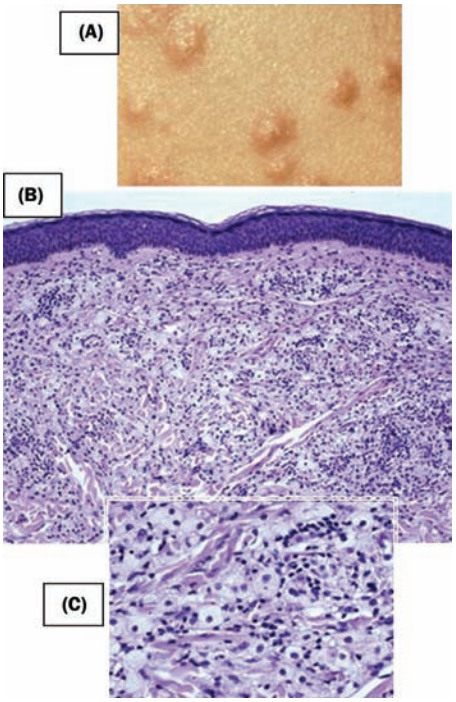

Figure 21 Xanthoma. (**A**) Yellowish papules. (**B**) and (**C**) Diffuse infiltrate of foam cells.

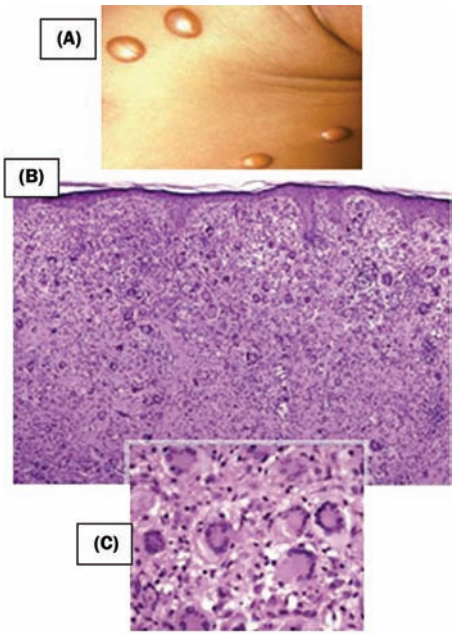

Figure 22 Xanthogranuloma. (**A**) Yellow tan nodules. (**B**) and (**C**) Diffuse infiltrate of foam cells and Touton giant cells.

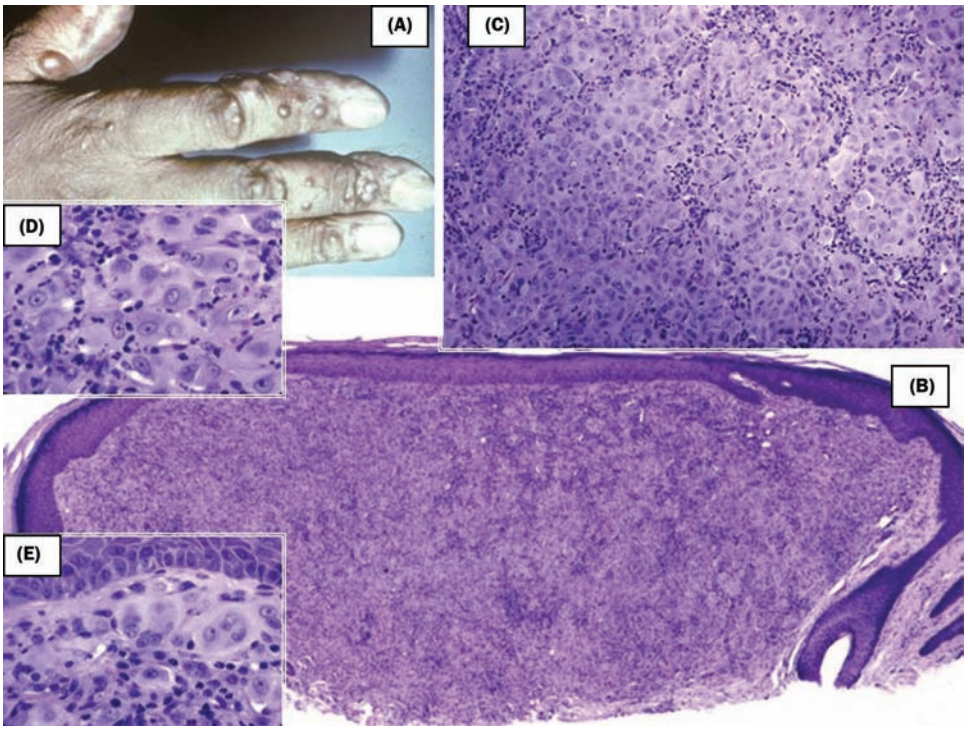

Figure 23 Reticulohistiocytoma. (**A**) papules on the hands. (**B**), (**C**), and (**D**) diffuse infiltrate of histiocytes with ground glass cytoplasm.

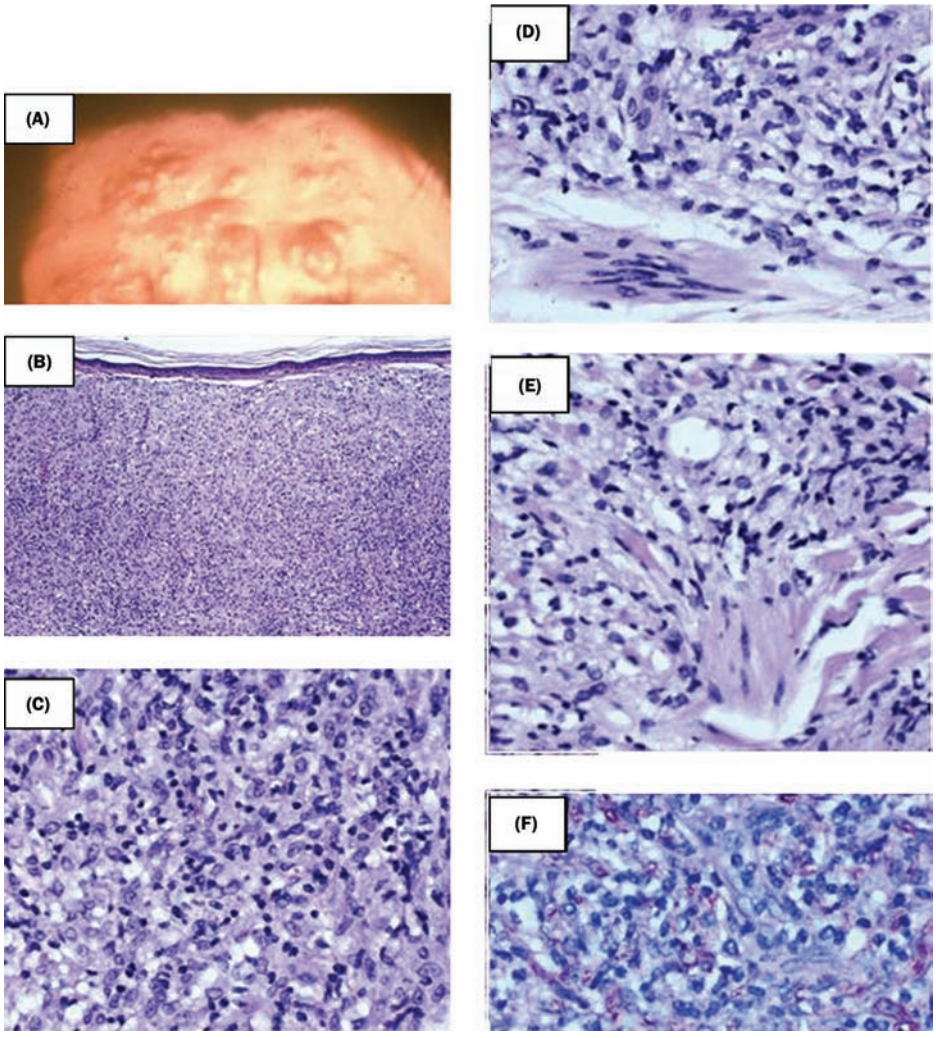

Figure 24 Lepromatous leprosy. (**A**) Nodules on the face. (**B**) and (**C**) Diffuse infiltrate of histiocytes with gray cytoplasm. (**D**) and (**E**) Small nerves surrounded by infiltrate. (**F**) Fite stain demonstrating acid-fast organisms.

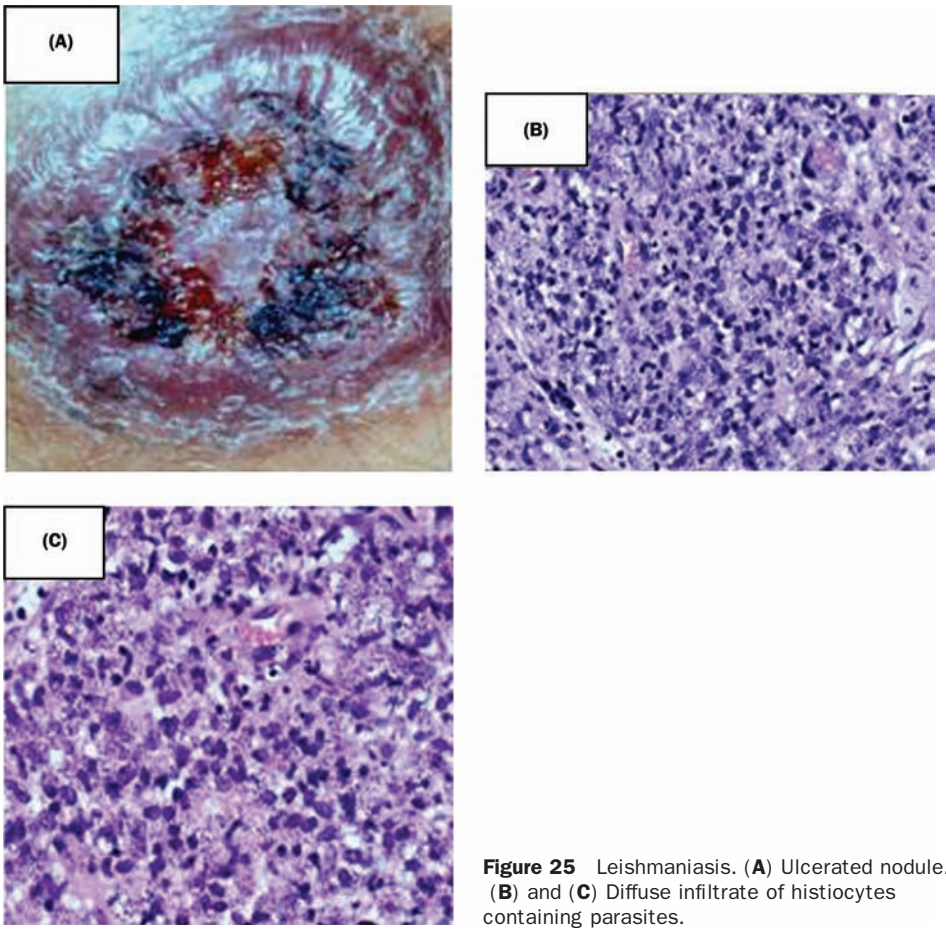

Figure 25 Leishmaniasis. (**A**) Ulcerated nodule. (**B**) and (**C**) Diffuse infiltrate of histiocytes containing parasites.

10

Follicular Diseases Causing Nonscarring and Scarring Alopecia

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CONTENTS

Many diseases of hair follicles result in alopecia, which is simply defined as any type of hair loss. The alopecias are conventionally grouped into nonscarring and scarring categories. Nonscarring alopecias may be localized or diffuse. Since the follicles are not destroyed in the nonscarring alopecias, there is potential for regrowth or return to normal hair density in these conditions. Follicular diseases that result in follicular destruction and permanent hair loss are termed scarring alopecias. There is some confusion in this categorization scheme because some of the nonscarring alopecias can eventuate over many years into areas of permanent alopecia through follicular "drop-out."

Definition of Terms:

- *Follicular density*: Number of hair follicles per surface area obtained by counting the total number of follicles in a horizontally sectioned scalp biopsy and dividing by the area of the biopsy. (The area of a 4 mm punch biopsy is 12.57 mm^2.) Normal follicular density in Caucasians is approximately 2 to 2.5 follicles/mm^2 and for African-Americans is 1.6 follicles/mm^2.
- *Terminal to vellus (T/V) ratio*: Obtained by counting the number of terminal hairs and dividing by the number of vellus hairs. This counting is performed at the level of the infundibula. A normal T/V ranges from 5/1 to 7/1.
- *Terminal hair*: Hair shaft measuring $\geq$0.03 mm in diameter, with a diameter greater than that of its inner root sheath.
- *Vellus hair*: Hair shaft measuring $<$0.03 mm in diameter. The thickness of a vellus hair shaft is less than or equal to the thickness of its inner root sheath. Vellus bulbs are usually found high in the dermis.

FOLLICULAR DISEASES CAUSING NONSCARRING ALOPECIA

The nonscarring alopecias are the most common type of hair loss and result from changes or abnormalities in the hair cycle, follicular miniaturization, and/or inflammation of the hair follicles that does not lead to follicular destruction. However, some of the nonscarring alopecias can eventuate over many years into permanent alopecia, by an unknown mechanism referred to as follicular "drop-out."

ALOPECIA AREATA

Clinical Presentation:

- Sudden, usually circumscribed, areas of hair loss
- Most common pattern is round or oval patches of alopecia on the scalp (Fig. 1A)

Other Clinical Patterns:

- Ophiasis hair loss (bands of hair loss at the scalp margins) (Fig. 1B)
- inverse ophiasis pattern (loss of hair on the crown with retention of hair along the scalp margins)
- alopecia totalis (loss of all scalp hair)
- alopecia universalis (loss of all scalp and body hair)
- diffuse alopecia areata (diffuse thinning without discrete areas of hair loss, although tiny discrete areas can sometimes be found on careful examination) (Fig. 1C)
- Exclamation point hairs (short broken-off hairs that taper proximally) are often found at the periphery of active areas of alopecia areata and are felt to be pathognomonic for the condition (Fig. 1D)
- Natural history of alopecia areata is completely unpredictable from patient to patient. The condition can come and go over an entire lifetime, with spontaneous regrowth and relapses common

Histology (Figs. 2A–D):

- Normal to slightly decreased follicular density
- Marked follicular miniaturization with a T/V $\leq$ 2/1

- Prominent increase in the number of telogen/catagen follicles (often >40%). Peribulbar lymphocytic infiltrates (CD 4-positive) affect terminal follicles in early disease and miniaturized follicles in subsequent episodes
- Empty infundibula are common in chronic disease
- Pigment casts may be present

Clinicopathologic Correlation:

Clinical Feature	Pathologic Feature
Area of hair loss looks bald	Marked follicular miniaturization and empty infundibula
Markedly positive hair pull	Marked increase in telogen/catagen follicles
Exclamation point hairs in active disease	Sudden follicular miniaturization causes sudden decrease in hair shaft diameter and causes hair to break off at scalp

Pathophysiology:
The cause of alopecia areata is unknown. There is a genetic component to the condition. The immune system may play a role in the disease (either nonspecific inflammation or autoimmune reaction). Cytokines, neuropeptides, and abnormal follicular keratinocytes and/or melanocytes have also been proposed as potential factors in the pathophysiology of the disease.

References:
1. Madani S, Shapiro J. Alopecia areata update. J Am Acad Dermatol 2000; 42:549–566.
2. Whiting DA. Histopathologic features of alopecia areata. A new look. Arch Dermatol 2003; 139:1555–1559.

ANDROGENETIC ALOPECIA

Synonyms: Male pattern hair loss/balding; female pattern hair loss (FPHL).

Clinical Presentation:
- Usually gradual thinning of hair over the vertex and anterior crown
- There are several patterns of thinning for both men and women
- Onset after puberty
- Can affect up to 50% of men and women
- Earliest change in men and women often an increased part width on crown compared with occiput (Figs. 3A and B)
- Increase shedding of hair sometimes present, especially in early disease
- Can lead to baldness in men with retention of hair on occipital and supra-auricular scalp
- Results in thinning hair in women without overt baldness (Figs. 3C and D) except in rare extremely severe cases
- Women usually retain scalp hair in frontal marginal zone

Histology (Figs. 4A–D):
- Normal to slightly decreased follicular density
- Follicular miniaturization with T/V <4/1 in females and <1.5/1 in males
- Increased numbers of telogen/catagen follicles (often 12–20%)
- Significant superficial fibrosis and inflammation in about one-third of cases may be associated with a worse prognosis

Clinicopathologic Correlation:

Clinical Feature	Pathologic Feature
Men may become bald	Marked follicular miniaturization with T/V <1.5/1
Women usually just have thin hair	Moderate follicular miniaturization with T/V <4/1
Men and women may complain of increased hair shedding	Increased numbers of telogen follicles (12–20%)
Scalp may appear slightly red	Marked superficial perivascular inflammation in one-third of patients; moderate inflammation in one-third of patients

Pathophysiology:
Male androgenetic alopecia (AGA) results from the effect of androgens on susceptible hair follicles in men who are genetically susceptible to the condition. The role of androgens in male AGA was first appreciated by Hamilton in 1942. He observed that males castrated before puberty never developed patterned baldness. If these men were given exogenous androgens, baldness could develop. Testosterone is transformed to dihydrotestosterone (DHT) by the enzyme 5α-reductase. This enzymatic reaction occurs in the hair follicle in addition to other sites in the body. DHT binds to follicular receptors and results in follicular miniaturization in susceptible scalp follicles. The mechanism of the follicular miniaturization is unknown. The follicles in men with AGA can be markedly reduced in size and resemble primary vellus follicles. The inheritance pattern of male AGA is not known, but it may be autosomal dominant with incomplete penetrance or polygenic.

The cause of FPHL is unknown, but it is felt to be multifactorial. Genetics probably plays a large role in the condition. As in men, the inheritance pattern may be autosomal dominant or polygenic. Many patients with FPHL have a family history of baldness in first-degree male relatives. The role of hormones in the pathogenesis of FPHL has not been completely worked out. It is known that women with hyperandrogenism may develop FPHL in addition to acne, hirsuitism, and virilization. However, the vast majority of women with FPHL (98%) do not have elevated androgen levels. It is known that FPHL results from progressive miniaturization of follicles. Large follicles producing terminal hairs are transformed into smaller vellus-like follicles producing vellus hairs. Scalp biopsies of patients with FPHL demonstrate this phenomenon by showing a range of hair shaft diameters with progressively smaller than normal shafts.

References:
1. Chartier MB, Hoss DM, Grant-Kels JM. Approach to the adult female patient with diffuse nonscarring alopecia. J Am Acad Dermatol 2002; 47:809–818.
2. Hamilton JB. Male hormone stimulation is prerequisite and an incitant in common baldness. Am J Anat 1942; 71:451–480.
3. Olsen EA. Female pattern hair loss. J Am Acad Dermatol 2001; 45:S70–S80.

4. Whiting DA. Diagnostic and predictive value of horizontal sections of scalp biopsies in female pattern androgenetic alopecia. Br J Dermatol 1991; 125:94.
5. Whiting DA. Diagnostic and predictive value of horizontal sections of scalp biopsies in male pattern androgenetic alopecia. J Am Acad Dermatol 1993; 28:755–763.

ACUTE TELOGEN EFFLUVIUM

Clinical Presentation:

- Abrupt onset of increased hair shedding (>120 hairs/day)
- The active shedding usually lasts one to four months (self-limited)
- Most cases occur in women
- May cause thinning of the hair over the entire scalp, although bitemporal areas are most obviously affected (Figs. 5A and B)
- Occurs two to five months after a specific trigger which can be identified in 75% of cases
- Possible triggering events include severe medical illness, high fever, surgery, accidents, medications, crash diets, significant weight loss, delivering a baby, discontinuation of oral contraceptive pills, or psychological trauma. Thyroid and iron deficiency can also lead to telogen effluvium (TE)
- Complete resolution with return to normal hair thickness occurs in >90% of patients by one year after the onset of shedding (Figs. 5C and D)

Histology (Figs. 6A–D):

- Normal follicular density
- No follicular miniaturization (T/V normal >5/1)
- Increased numbers of telogen follicles during acute episode (12–30% of follicles in telogen)
- Noninflammatory

Clinicopathologic Correlation:

Clinical Feature	Pathologic Feature
Marked increased hair shedding	Increased numbers of telogen follicles
Scalp appears normal	Absence of inflammation
Vast majority of patients experience complete resolution with return to normal hair thickness	Normal follicular density and lack of follicular miniaturization

Pathophysiology:

TE is a condition characterized by increased daily hair shedding. Normally, up to 100 telogen (club) hairs are shed daily. This is due to the fact that up to 10% of a person's 100,000 scalp follicles are in telogen (the resting phase) at any given time (10% of 100,000 hair follicles is 10,000 hair follicles; with telogen lasting an average of 100 days this leads to an average shedding of 100 hairs/day). Most people actually shed 60 to 80 hairs a day because 6% to 8% of their follicles are in telogen. TE is a perturbation of the hair cycle that results in shedding of at least 120 hairs a day. TE is caused by a sudden shift of growing anagen hairs into the catagen and subsequent telogen phases, culminating in shedding of these hairs.

Reference:

1. Headington JT. Telogen effluvium: new concepts and review. Arch Dermatol 1993; 129:356–363.

CHRONIC TELOGEN EFFLUVIUM (FORMERLY CALLED "DIFFUSE" ALOPECIA)

Clinical Presentation:

- Increased shedding lasting at least six months, but usually greater than one year
- Lasts for many years with fluctuating severity
- Onset may be abrupt (an acute TE that does not completely resolve) or gradual
- A definite trigger is usually not identified in patients with chronic TE
- Chronic TE usually affects middle-aged women, many of whom give a history of extremely thick hair prior to the onset of the condition
- Women with chronic TE may have normal-appearing hair (albeit with less volume than normal for the patient) or may show shorter frontal hairs or bitemporal thinning (Figs. 7A–D).
- Women with chronic TE often state that they have "lost" one-third to one-half of their hair
- A woman with chronic TE may complain that she is unable to grow her hair to the same length that she could in the past
- Unlike in FPHL, the occipital and crown part widths are approximately the same in patients with chronic TE (although the mid-frontal hairline at the "bangs" may show some thinning) (Figs. 7A and B).

Histology (Figs. 8A–D):

- Normal follicular density
- No follicular miniaturization (T/V often 7/1)
- Telogen counts often normal or just slightly elevated (10–20%)
- Scalp biopsy may appear completely normal

Clinicopathologic Correlation:

Clinical Feature	Histologic Feature
Part widths same throughout scalp	No follicular miniaturization
Patient complains of increased hair shedding that waxes and wanes	Slightly increased or normal numbers of telogen follicles, depending on "phase" of the disease
Scalp appears normal	Absence of inflammation

Pathophysiology:

The cause of chronic TE is not known. The increased shedding is probably due to the shortening of the growth phase of the hair cycle (anagen). It is not known why this occurs. The follicles in chronic TE continue to grow and cycle, however, the follicles are simply cycling too fast. Every shed hair is replaced and patients do not become "bald." The reason that the hair volume feels (and is) less overall in chronic TE is due to an increased daily shedding. Even though each shed hair is replaced, it takes months for a new hair to grow long enough to contribute to the overall hair thickness. For example, if double the normal number of hairs is shed daily, the overall hair volume will be cut in half. Since the condition is chronic and lasts for years, the decrease in overall hair volume persists.

Reference:

1. Whiting DA. Chronic telogen effluvium: increased scalp hair shedding in middle-aged women. J Am Acad Dermatol 1996; 35:899–906.

LOOSE ANAGEN HAIR SYNDROME

Clinical Presentation:
- Occurs predominantly in young children with blonde or light brown hair
- Slightly more common in girls
- Characterized by the painless extraction of increased numbers of anagen hairs on a pull test
- The affected child's hair is often described as "not growing" and may demonstrate hairs of varying lengths (Fig. 9A)
- Usually improves with age but may persist into adulthood
- Most cases of loose anagen hair syndrome (LAHS) occur sporadically, however, it has also shown an autosomal dominant inheritance pattern has been seen in some families.

Histology:
- Scalp biopsies usually normal
- No increase in telogen follicles (decreased telogen follicles in some reports)
- No follicular miniaturization
- Some reports describe abnormalities of the outer or inner root sheath and clefting between the inner root sheath and the hair cuticle and between the hair cuticle and the hair cortex
- Anagen hairs obtained by pull tests often demonstrate dysmorphic bulbs, longitudinal grooves, and ruffled cuticles (Figs. 9B and C)

Clinicopathologic Correlation:

Clinical Feature	Pathologic Feature
Hair described as "not growing"	Anagen hairs are dystrophic and easily pulled out, therefore, hair "does not grow"
Hair of varying lengths	Not a synchronized shedding, hair shaft abnormalities cause easy mechanical loss of anagen hairs of varying lengths
No increase in telogen hairs on hair pull	Telogen follicles normal to decreased in number

Pathophysiology:
The affected hairs in LAHS are anagen (growing) hairs that may lack an inner and outer root sheath on a pull test. The anagen bulbs are often dysmorphic and the hairs may demonstrate longitudinal grooves and ruffled cuticles. Poor cohesion of outer root sheath cells has been described in LAHS. The underlying cellular defect(s) allow the easy and painless extraction of the growing anagen hair from its follicular epithelium.

References:

1. Baden HP, Kvedar JC, Magro CM. Loose anagen hair as a cause of hereditary hair loss in children. Arch Dermatol 1992; 128:1349–1353.
2. Hamm H, Traupe H. Loose anagen hair of childhood: the phenomenon of easily pluckable hair. J Am Acad Dermatol 1989; 20:242–248.
3. O'Donnell BP, Sperling LC, James WD. Loose anagen hair syndrome. Int J Dermatol 1992; 31:107–109.
4. Price VH, Gummer CL. Loose anagen syndrome. J Am Acad Dermatol 1989; 20:249–256.
5. Tosti A, Peluso AM, Misciali C, Venturo N, Patrizi A, Fanti PA. Loose anagen hair. Arch Dermatol 1997; 133:1089–1093.

TRICHOTILLOMANIA

Clinical Presentation:
- Characterized by hair pulling.
- It may be a syndrome by itself, or may be a symptom of several other psychiatric disorders including obsessive-compulsive disorder, impulse control disorder, body dysmorphic disorder, and depression and personality disorders.
- Hair pulling in early childhood may be a separate condition because it is often self-limited and a response to a stressful situation.
- When the condition occurs in adolescence and adulthood it is usually chronic, difficult to treat and associated with underlying psychopathology.
- Women are more commonly affected than men by a ratio of 3.5:1.
- The scalp is most commonly affected; however, patients may also pull out eyebrows, eyelashes, pubic hairs, and body hairs.
- The pulling results in areas of hair loss that contain broken-off hairs of varying lengths (Fig. 10).
- Patients with trichotillomania often deny any type of hair manipulation. Parents of adolescents with the condition often participate in the denial.

Histology (Figs. 11A–C):
- Follicles normal in size to slightly miniaturized (T/V 4/1 to 7/1)
- Marked increase in catagen and telogen follicles (average 35%)
- Follicular plugging, perifollicular hemorrhage, separation of follicular epithelium from the surrounding connective tissue, and trichomalacia may be present
- Pigment casts common
- Empty infundibula common
- Normal follicular density initially, long-standing disease may lead to scarring and loss of follicles

Clinicopathologic Correlation:

Clinical Feature	Histopathologic Feature
"Broken-off hairs" of varying lengths	Empty infundibula followed by regrowth
Patient pulls hairs	Perifollicular hemorrhage, separation of follicular epithelium from connective tissue
Pulling traumatizes the follicles	Prominent increase in catagen and telogen follicles, pigment casts

Pathophysiology:
Trichotillomania, characterized by hair pulling, may be a syndrome by itself, or may be a symptom of several other psychiatric disorders including obsessive-compulsive disorder, impulse control disorder, body dysmorphic disorder, and depression and personality disorders.

TRACTION ALOPECIA

Clinical Presentation:
- Hair loss caused by prolonged traction on hair follicles.
- The traction is produced by various hair styling practices including tight ponytails, tight braids, straightening or

curling procedures, such as hot combs, relaxers/permanents, or the use of tight curlers, and the use of hair weaves that may be attached too tightly or may be pulled off before reapplication to the proximal part of the growing hair shafts.
- These hair styling practices are often shared by members of specific ethnic groups and thus certain patterns of traction alopecia are more common in certain groups.
- The most common groups to present with traction alopecia are young Latina women who style their hair in tight ponytails at the vertex of the scalp, African-American children due to tight braiding practices, and African-American women due to various straightening practices and the use of hair weaves.
- Initially the alopecia caused by chronic traction is reversible.
- If the traction continues over months to years, the alopecia becomes permanent due to permanent loss of hair follicles.
- The margins of the scalp are most commonly affected by traction alopecia. There is usually preservation of the "marginal fringe" of hair because these marginal fringe hairs are too short to be involved in the traction process (Figs. 12A and B).
- In active disease, there may be a folliculitis as evidenced by small follicular pustules.
- Over time the involved area seems devoid of any large follicles and only small vellus "peach fuzz" type follicles remain. Unlike usual scarring alopecias, the affected area in permanent traction alopecia does not appear shiny or atrophic, and the skin seems normal.

Histopathology:
- Increased telogen/catagen follicles early in disease (often 15–25% telogen follicles)
- Superficial perifollicular and follicular lymphocytic inflammation
- Long-standing disease demonstrates marked decrease in follicular density, resulting from loss of terminal hair follicles. The vellus follicles remain unaffected
- Sebaceous epithelium often preserved and follicular units often consist of sebaceous glands and one or two vellus follicles, without terminal follicles (Fig. 12C)
- Scarring and replacement of follicular units by fibrosis may occur

Clinicopathologic Correlation:

Clinical Feature	Histopathologic Feature
Traction traumatizes follicles	Increased numbers of telogen/catagen follicles
Long-standing disease is permanent	Markedly decreased follicular density with loss of terminal follicles
"Peach fuzz" hairs in areas of permanent loss	Vellus hairs do not get pulled (they are too short) and they remain unaffected
Although hair loss is permanent, the area does not look "scarred"	Sebaceous epithelium preserved, therefore, skin not atrophic, true fibrosis often focal or absent

Pathophysiology:
Chronic traction on hairs initially causes follicles to enter into catagen, then telogen and eventually shed. If the traction is short lived, the hairs will regrow. If the traction continues, the terminal hairs are eventually lost, by an unknown mechanism. The sebaceous glands are often unaffected, an unexpected finding in a process eventuating in permanent follicular loss. Vellus hairs remain because they are too short to be involved in the process causing the traction.

Reference:
1. Sperling LC, Lupton GP. Histopathology of non-scaring alopecia. J Cutan Pathol 1995; 22:97–114.

FOLLICULAR DISEASES CAUSING SCARRING ALOPECIA

Follicular destruction results in scarring alopecia that can be classified as primary or secondary. In primary scarring alopecias, the follicle is the target of inflammation. In secondary scarring alopecias, the follicle is an "innocent bystander" that, nevertheless, is destroyed. Examples of secondary scarring alopecias include morphea and tumors (alopecia neoplastica). In this chapter, we will consider only the primary scarring alopecias. In this group of diseases, the inflammation can be primarily lymphocytic or neutrophilic. Although all parts of the follicle can be involved, the disease is felt to destroy the "bulge area" of the follicle, where the arrector pili muscles insert. This area contains the follicular stem cells necessary for regeneration of the lower follicle during normal follicular cycling. When this part of the follicle is destroyed, the follicle is doomed. The sebaceous glands are also destroyed in primary scarring alopecias. The destruction of these structures and the dermal fibrosis results in skin that is firm and shiny and lacks follicular orifices.

LICHEN PLANOPILARIS

Clinical Presentation :
- Several clinical presentations of lichen planopilaris (LPP).
- Some patients present with small areas of scarring alopecia that often involve the vertex. There are minute red follicular papules with fine scaling at the base of the terminal hairs at the periphery of the areas of scarring (Fig. 13A). These papules indicate active inflammation that will eventually lead to scarring and loss of the affected follicles.
- Extremely early LPP presents as plaques of these minute red scaling follicular papules without associated hair loss.
- Other patients with LPP have a large area of central scarring alopecia on the crown, the so-called central centrifugal cicatricial alopecia (CCCA) or central centrifugal scarring alopecia (CCSA). The area of hair loss slowly expands centrifugally. The active edges of the lesion again demonstrate minute red follicular scaling papules.
- Patients with LPP often complain of pain, stinging, or burning in the areas of active disease.
- A rare presentation of LPP is fulminant disease that can result in complete alopecia in months to a year's time (Fig. 13B). These patients have very inflamed red scaling plaques, which on biopsy show changes of LPP.
- Some patients with LPP have concomitant cutaneous, oral, and/or genital lichen planus.
- Most patients with LPP do not have lichen planus elsewhere on the body.
- Frontal fibrosing alopecia (FFA) is felt to be a distinctive clinical variant of LPP. Patients with FFA are usually

postmenopausal women with scarring alopecia of the frontal scalp margin and associated eyebrow loss (Fig. 13C). The advancing edge of the area of alopecia may demonstrate minute perifollicular papules at the bases of terminal hairs.
- LPP is a progressive disease that can eventually "burn out" after many years. This form of LPP may be indistinguishable from the so-called "pseudopelade of Brocq" (Fig. 13D).

Histology (Figs. 14A–D):
- Band-like lymphocytic infiltrate obscuring the interface between the follicular epithelium and the dermis, with associated necrotic keratinocytes and occasionally formation of colloid bodies.
- Inflammation is most dense at the level of the infundibula and isthmus, but can extend around the inferior portions of follicles.
- Early disease demonstrates just the lymphocytic inflammation, without loss of follicles or sebaceous glands.
- Well-developed lesions demonstrate concentric perifollicular fibrosis; the lymphocytes are seen beyond this area of fibrosis, no longer in the follicular epithelium.
- Late disease demonstrates follicular destruction, with formation of hair granulomas, replacement of follicular units by fibrosis, and loss of sebaceous glands.
- Typical changes of lichen planus are occasionally present in the interfollicular epidermis.

Clinicopathologic Correlation:

Clinical Feature	Histopathologic Feature
Minute perifollicular red papules with scale at the base of terminal hairs in areas of active disease	Lymphocytic inflammation around infundibula and isthmus portions of follicles and slight hyperkeratosis overlying the infundibula
Late disease characterized by slightly atrophic areas of complete scarring alopecia with no possibility of regrowth	Replacement of follicular units by fibrosis with loss of follicles and sebaceous glands

Pathophysiology:
LPP is a primary lymphocyte-mediated scarring alopecia of unknown etiology. In this condition, lymphocytes attack the epithelium of the infundibula and isthmus areas of hair follicles and sometimes the interfollicular epidermis. The histologic changes are identical to those seen in lichen planus, that is, interface changes consisting of band-like lymphocytic inflammation with necrotic keratinocytes. With time, there is perifollicular fibrosis and decreasing inflammation. Sebaceous glands are destroyed. The follicular antigen(s) targeted by these lymphocytes are not known.

References:

1. Kossarrd S, Lee M-S, Wilkinson B. Postmenopausal frontal fibrosing alopecia: a frontal variant of lichen planopilaris. J Am Acad Dermatol 1997; 36:59–66.
2. Matta M, Kibbi A-G, Khattar J, Salman SM, Zaynoun ST. Lichen planopilaris: a clinicopathologic study. J Am Acad Dermatol 1990; 22:594–598.
3. Mehregan DA, Van Hale HM, Muller SA. Lichen planopilaris: clinical and pathologic study of forty-five patients. J Am Acad Dermatol 1992; 27:935–942.
4. Sperling LC, Solomon AR, Whiting DA. A new look at scarring alopecia. Arch Dermatol 2000; 136:235–242.

DISCOID LUPUS ERYTHEMATOSUS

Clinical Presentation:
- A form of chronic cutaneous lupus erythematosus characterized by hyperkeratotic inflammatory plaques that eventuate into areas of scarring (Fig. 15)
- Only 5% of discoid lupus erythematosus (DLE) patients go on to develop systemic lupus erythematosus (SLE)
- However, 25% of SLE patients have discoid lesions
- DLE lesions occur most commonly on the head and neck. Patients with generalized DLE lesions involving the skin above and below the neck are more likely to develop SLE
- Scalp lesions occur in 60% of DLE patients and usually result in scarring alopecia
- DLE lesions are red to purple plaques with hyperkeratotic scale
- Follicular hyperkeratotic plugs cause a carpet tack appearance as they project from the undersurface of the scale when it is removed from advanced lesions
- The dyspigmentation of older lesions often presents as central hypopigmentation and peripheral hyperpigmentation (Fig. 15)
- Patients may have scalp lesions only or concomitant lesions on the face, neck, and especially the external ears

Histology (Figs. 16A–C):
- Interface changes at the dermal-epidermal junction and the basement zone region of follicular epithelium
- Necrotic keratinocytes and lymphocytic inflammation are present in these interface areas
- There is superficial and deep perivascular, perifollicular, and follicular inflammation consisting of lymphocytes and plasma cells
- Prominent hyperkeratosis overlying follicular infundibula
- The follicles are eventually replaced by fibrosis (hair granulomas may be present) and there may be interfollicular dermal scarring
- Increased dermal mucin is often present
- Direct immunofluorescence may show linear granular deposits of C3 and IgG at the dermal–epidermal junction and in the basement membrane zone area of follicular infundibula

Clinicopathologic Correlation:

Clinical Feature	Histopathologic Feature
Dyspigmentation in old lesions	Interface changes at the dermal-epidermal junction causes postinflammatory hyper and hypopigmentation
"Carpet tack" keratotic plugs when removing scale overlying clinical lesion	Prominent follicular hyperkeratosis
Scarring of skin and permanent alopecia	Follicles are destroyed and replaced by fibrosis, interfollicular dermal scarring also present

Pathophysiology:
The cause of DLE is unknown. It is felt to be an immune-mediated disease, with drugs, ultraviolet light, genetic predisposition, and/or hormones playing a role in the pathogenesis and expression of the condition in individual patients.

Reference:
1. Weedon D, Strutton G. Skin Pathology, 2nd ed. London: Churchhill Livingstone, 2002:47–52.

FOLLICULAR DEGENERATION SYNDROME (SOMETIMES CALLED CENTRAL CENTRIFUGAL SCARRING ALOPECIA OR CENTRAL CENTRIFUGAL CICATRICIAL ALOPECIA)

Clinical Presentation (Figs. 17A–C):
- Occurs in African-Americans with a female to male ratio of 3:1
- Patients present with an area of slowly expanding scarring alopecia (CCSA) on the vertex or crown
- The condition may be asymptomatic or accompanied by pruritus or tenderness
- Often, the lesion does not appear inflamed, but there may be erythema and/or pustules at the periphery of the area of scarring
- Chemical or mechanical processing of the hair may play a role

Histology (Figs. 18A–D):
- Degeneration of the internal root sheaths occurs below the level of the isthmus
- Involved follicles may also demonstrate eccentric placement of the hair shafts with thinning of follicular epithelium, concentric lamellar perifollicular fibrosis, superficial perifollicular and perivascular lymphocytic inflammation
- Late lesions show follicular destruction with resultant hair granulomas

Clinicopathologic Correlation:

Clinical Feature	Histopathologic Feature
Late disease characterized by areas of scarring alopecia, without chance of regrowth	Advanced lesions show total follicular destruction with formation of hair granulomas

Pathophysiology:
The etiology of follicular degeneration syndrome (FDS) is unknown; however, hair care practices such as chemical straightening and use of hot combs may play a role in some patients.

References:
1. Sperling L, Sau P. The follicular degeneration syndrome in black patients: "hot comb alopecia" revisited and revised. Arch Dermatol 1992; 128:68–74.
2. Sperling L, Skelton H, Smith K, Sau P, Friedman K. The follicular degeneration syndrome in men. Arch Dermatol 1994; 130: 763–769.

FOLLICULITIS DECALVANS

Clinical Presentation (Fig. 19A):
- A form of CCSA characterized by the presence of numerous pustules at the periphery of the scarred area(s)
- The lesions may be quite painful and patients often complain of drainage and/or bleeding on the pillow at night when the disease is active
- More common in men, reported in Caucasians and African-Americans
- "Tufted folliculitis," characterized by several (up to 30) terminal hairs emerging from the same follicular orifice in the center of an area of scarring, is often seen in patients with folliculitis decalvans (Fig. 19A). However, tufted folliculitis is a nonspecific endpoint seen in several types of scarring alopecia

Histology (Figs. 19B and C):
- Prominent superficial and deep follicular and perifollicular inflammation consisting of lymphocytes, plasma cells, neutrophils, and macrophages
- It is common to see a follicle in which the epithelium is completely destroyed and replaced by macrophages and other inflammatory cells
- Gram positive bacteria can often be seen in the superficial areas of suppurative inflammation
- The pathologist needs to rule out a fungal folliculitis that can show identical histological findings

Clinicopathologic Correlation:

Clinical Feature	Histopathologic Feature
Pustules at the periphery of areas of scarring alopecia (active disease)	Prominent superficial suppurative inflammation
No chance for regrowth in scarred areas	Complete follicular destruction
Tufted folliculitis	Large follicular infundibulum containing numerous hair shafts and surrounded by dermal scarring

Pathophysiology:
The etiology of folliculitis decalvans is unknown; however, *Staph aureus* is often cultured from the pustules. Some authors postulate that the condition results from an altered immune response of some patients to superantigens produced by the bacteria found in hair follicles.

Reference:
1. Powell JJ, Dawber RPR, Gatter K. Folliculitis decalvans including tufted folliculitis: clinical, histological and therapeutic findings. Br J Dermatol 1999; 140:328–333.

DISSECTING CELLULITIS OF THE SCALP (PERIFOLLICULITIS CAPITIS ABSCEDENS ET SUFFODIENS)

Clinical Presentation:
- Uncommon condition that mainly affects African-American adult males
- It is one of the "occlusion triad" along with hidradenitis suppurativa and acne conglobata. Most patients with dissecting cellulitis do not have the other two conditions in the triad
- Presents as boggy, painful inflammatory nodules that coalesce with subsequent sinus tract formation usually on the crown and vertex scalp
- Old inactive disease is characterized by areas of scarring alopecia with fibrotic ridges, sinus tracts, and comedo formation (Fig. 20A)

- Patients complain of pain, drainage of active nodules, and the eventual scarring hair loss that occurs

Histology (Figs. 20B and C):

- Deep inflammation (primarily in the subcutis) consisting of lymphocytes, neutrophils, and plasma cells
- Increased telogen follicles in early disease
- With time the inflammation involves the dermis, including the follicles that are eventually destroyed
- Old lesions reveal dermal fibrosis and epithelial-lined sinus tracts

Clinicopathologic Correlation:

Clinical Feature	Histopathologic Feature
Boggy, painful inflammatory nodules	Massive deep inflammation
Purulent discharge	Neutrophilic inflammation
No chance for regrowth in old lesions	Follicular destruction

Pathophysiology:

The cause of dissecting cellulitis of the scalp is unknown. The initial hair loss is a TE caused by the massive inflammation. With time, the inflammation involves the dermis, including the follicles, which are eventually destroyed. Old lesions reveal dermal fibrosis and epithelial-lined sinus tracts.

ACNE KELOIDALIS NUCHAE (ALSO KNOWN AS FOLLICULITIS KELOIDALIS)

Clinical Presentation (Fig. 21A):

- Folliculitis that occurs on the occipital scalp and results in scarring alopecia
- Mainly affects African-American men, however, African-American women and occasionally other ethnic groups may develop the disease
- The earliest clinical lesions are follicular papules and occasional pustules
- With time, these papules become fibrotic with associated hair loss
- A small number of patients develop large scars resembling keloids on the nape

Histology (Figs. 21B and C):

- Lymphoplasmacytic inflammation of the upper portions of the follicles early in the course of the disease
- Perifollicular fibrosis with loss of sebaceous glands then occurs
- Eventually, hair follicles are destroyed with resultant hair granulomas
- The dermis may develop hypertrophic scarring; however, true histologic keloid formation is not observed

Clinicopathologic Correlation:

Clinical Feature	Histopathologic Feature
Follicular red papules	Lymphoplasmacytic inflammation of the upper portions of follicles
Areas of scarring alopecia that do not regrow	Follicular destruction with hair granulomas
Large areas of scarring (resembling keloids) can occur on the nape	Hypertrophic scars

Pathophysiology:

The cause of acne keloidalis nuchae (AKN) is not known. In the past, close clipping of the curly African American hair was implicated, similar to the pathogenesis of pseudofolliculitis barbae. However, the disease occurs in the absence of this type of hair styling and in other ethnic groups and, therefore, other factors must contribute to the development of the folliculitis. Bacterial overgrowth has not been documented in AKN.

Reference:

1. Sperling L, Homoky C, Pratt L, Sau P. Acne keloidalis is a form of primary, scarring alopecia. Arch Dermatol 2000; 136:479–484.

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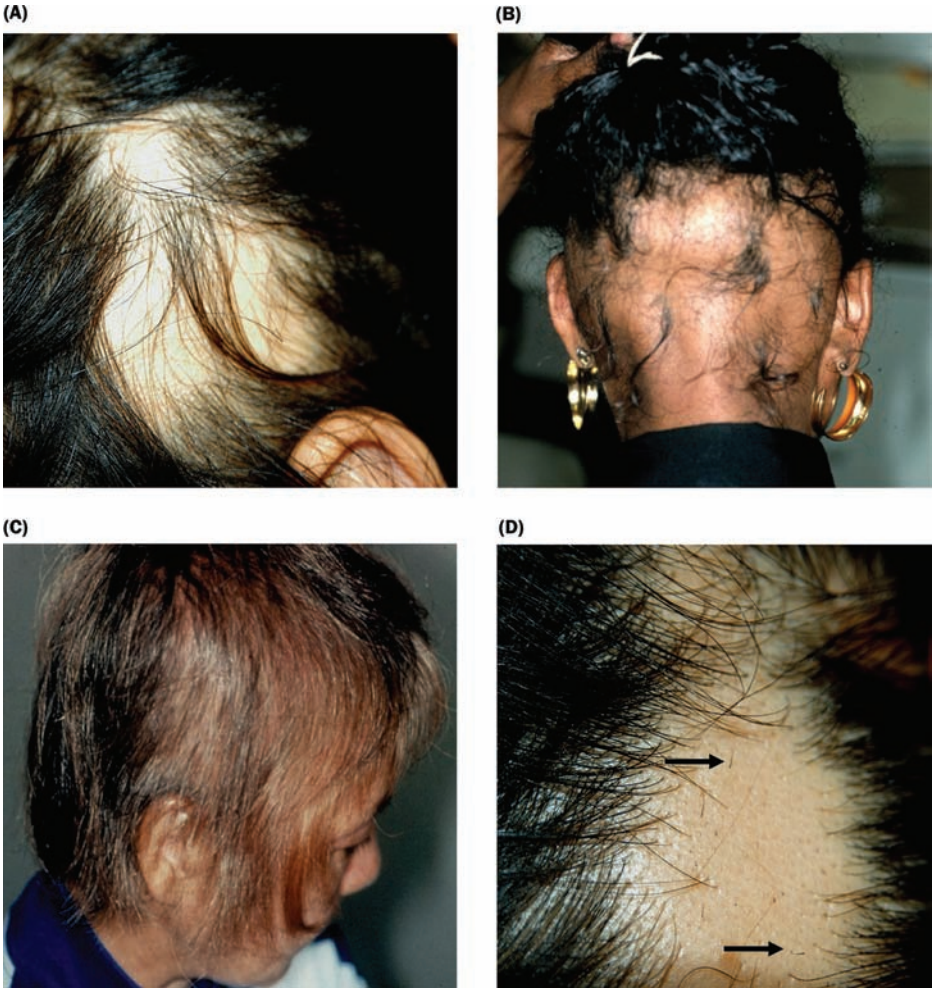

Figure 1 (**A**) Well-circumscribed areas of nonscarring hair loss in typical alopecia areata. (**B**) Marginal hair loss in ophiasis pattern alopecia areata. (**C**) Diffuse hair loss in diffuse alopecia areata. (**D**) Exclamation point hairs (*arrows*) in an active patch of alopecia areata.

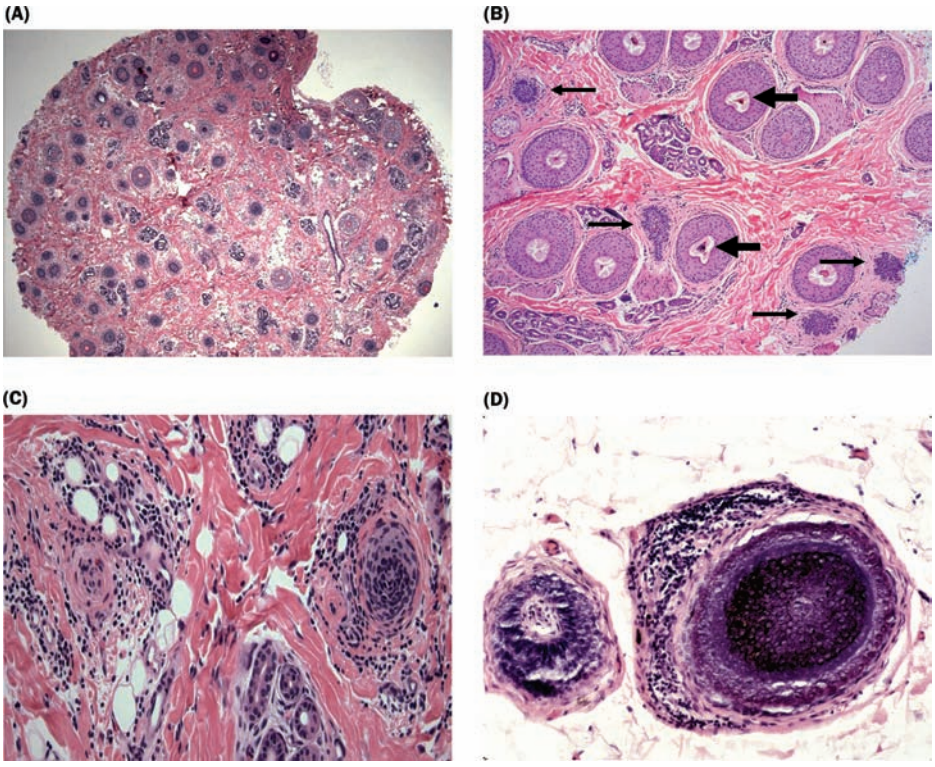

Figure 2 (**A**) Low power view demonstrating normal follicular density, numerous telogen follicles (>90%), and follicular miniaturization in alopecia areata (T/V = 1/3). (**B**) Four telogen germinal units (*thin arrows*) and several pigment casts (*thick arrows*) in a biopsy of alopecia areata. (**C**) Peribulbar lymphocytic infiltrates around vellus hair follicles in alopecia areata. (**D**) Peribulbar lymphocytic infiltrate around a terminal hair follicle in alopecia areata.

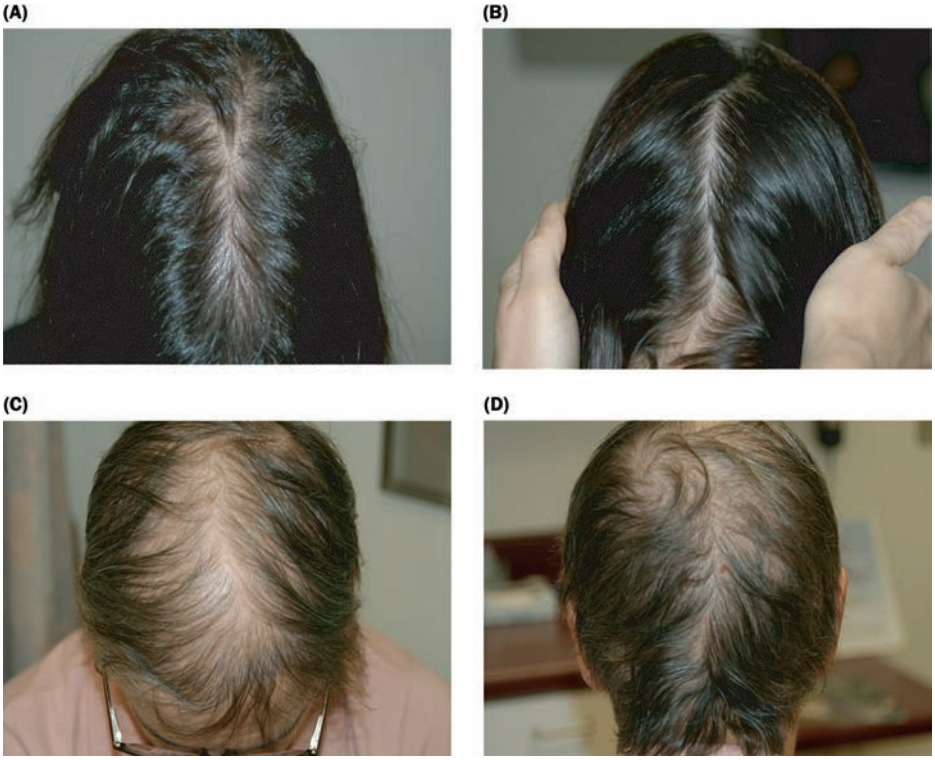

Figure 3 Mild female pattern hair loss (FPHL) with early widening of the part on the crown (**A**), compared with the occipital scalp (**B**). Severe female pattern hair loss with thinning hair over the entire crown, vertex, and posterior vertex (**C**) with relative sparing of only the lower occipital scalp (**D**).

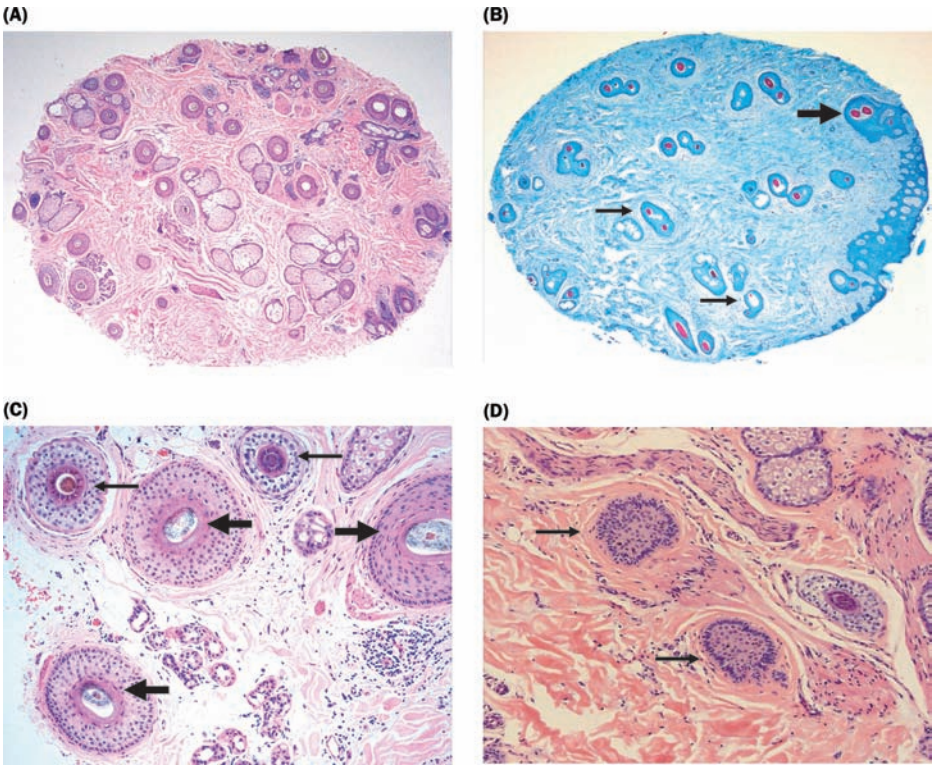

Figure 4 Low power view at the level of the isthmus (**A**) and infundibula (**B**) demonstrating normal to slightly decreased follicular density, variability in hair shaft diameter and miniaturized follicles (T/V = 2/1) in a scalp biopsy from the patient in Figure 3A and 3B. Medium-sized terminal hair shafts (*thick arrow*) and vellus hair shafts (*thin arrows*) are better visualized with AFB (acid-fast bacillus, Ziehl-Neelsen) stain (**B**). (**C**) Higher power view of teminal hairs (*thick arrows*) and vellus hairs (thin arrows) in the same patient with FPHL. (**D**) Two telogen germinal units (*arrows*) in the scalp biopsy from the same patient with FPHL.

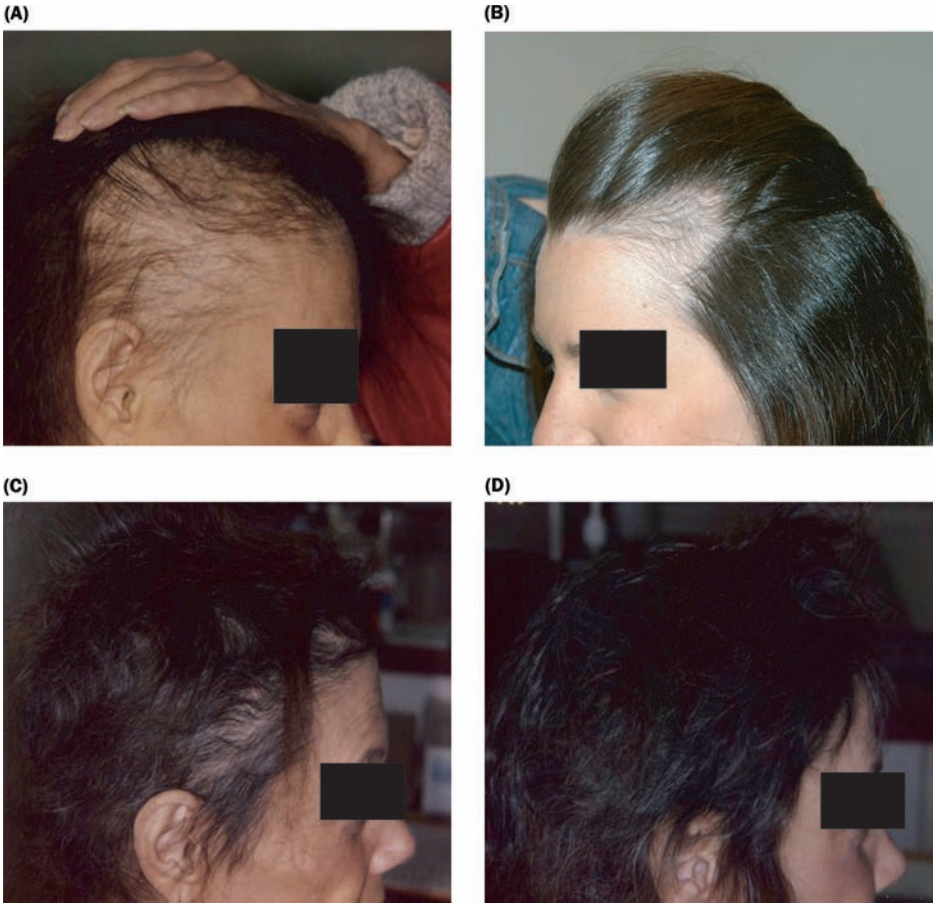

Figure 5 (**A**) Severe thinning of the parietal scalp hair in a woman with severe acute telogen effluvium (TE) that occurred four months after hospitalization for pneumonia and cirrhosis. (**B**) Acute TE causing temporal thinning in a woman three months postpartum. (**C**) Same patient as in A demonstrating partial regrowth of hair after four months. (**D**) Photograph taken nine months after A demonstrating complete resolution of the patient's acute TE and full hair regrowth.

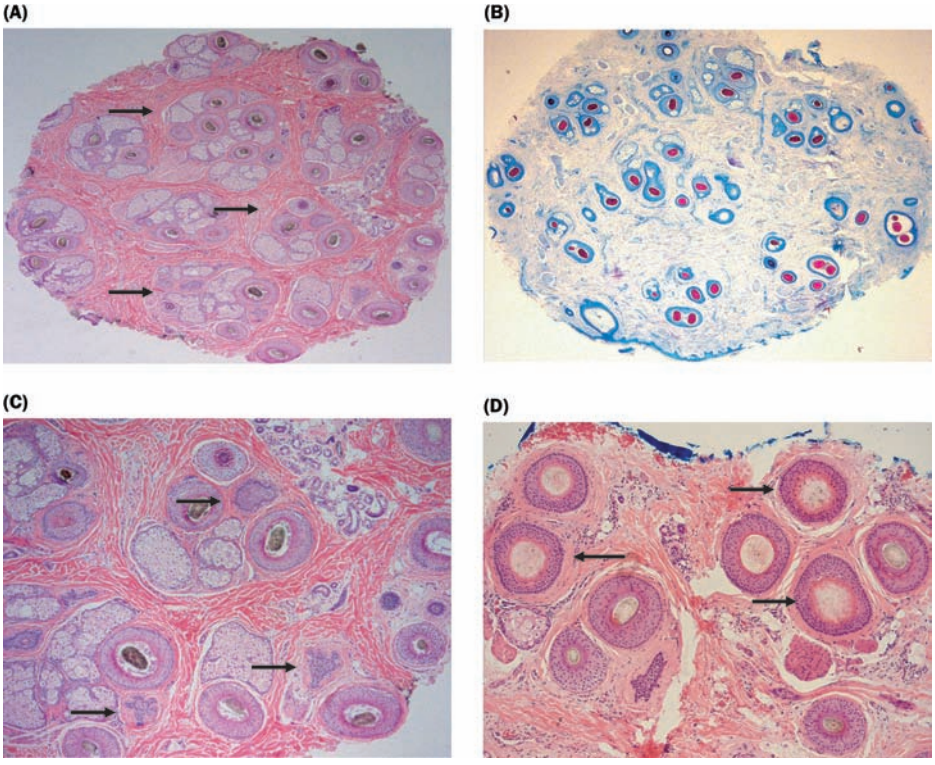

Figure 6 (**A**) Low power view of telogen effluvium (TE) demonstrating normal numbers of follicular units (*arrows*). (**B**) Low power view demonstrating lack of follicular miniaturization (T/V = 5/1) in TE (AFB stain). (**C**) Higher power view demonstrating numerous telogen germinal units (*arrows*) in a patient with acute TE. (**D**) High power view of telogen follicles (*arrows*) in a patient with acute TE.

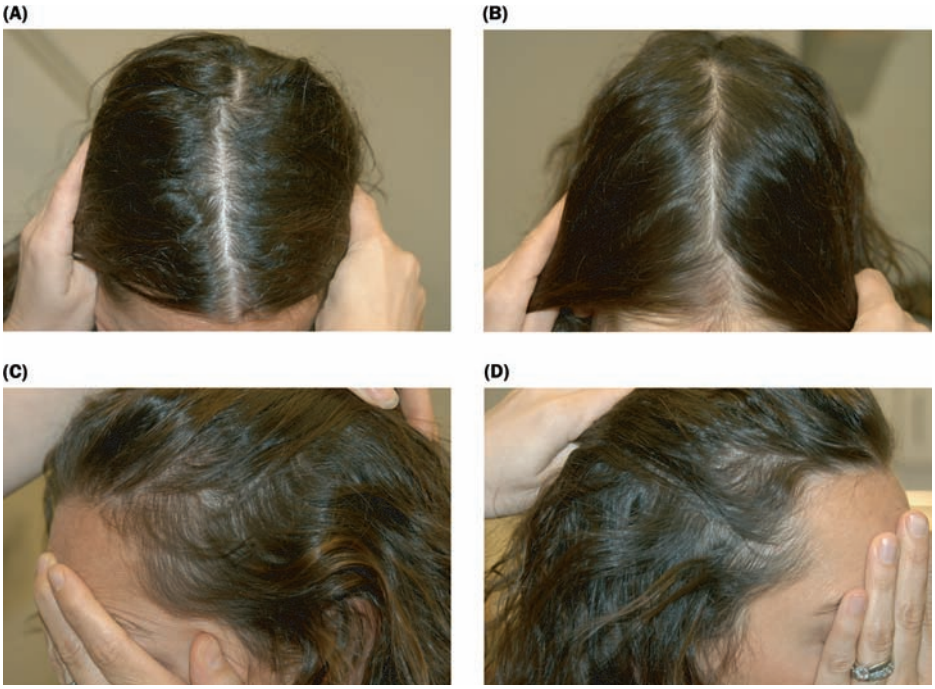

Figure 7 Woman with chronic telogen effluvium demonstrating essentially the same part widths on crown (**A**) and occiput (**B**); and mild bitemporal thinning (**C**,**D**).

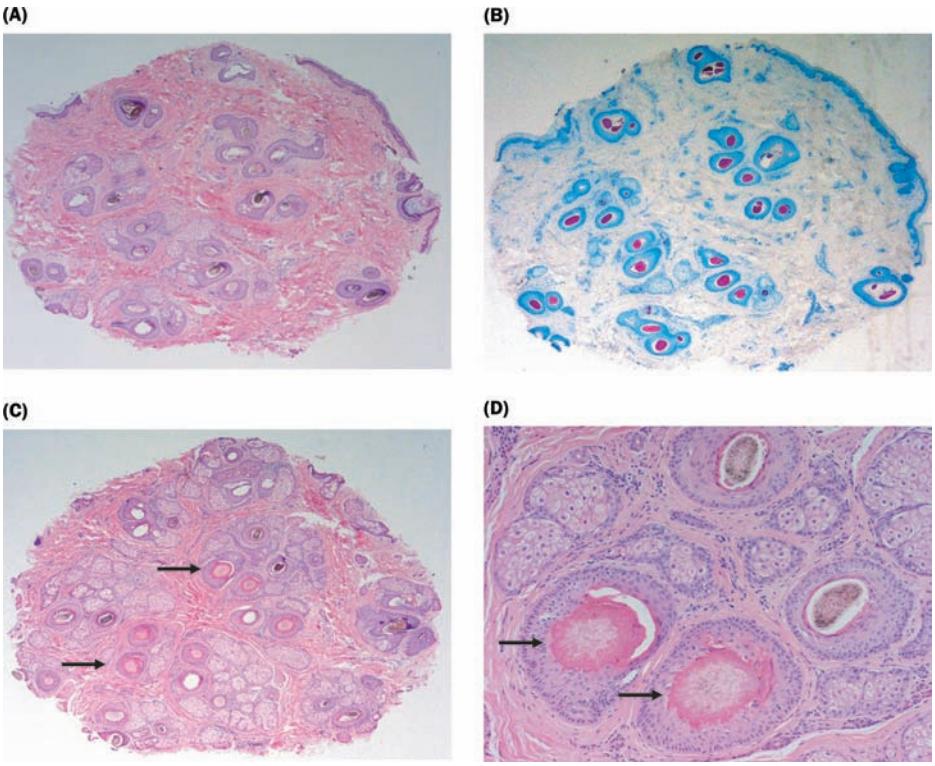

Figure 8 (**A**) Biopsy of chronic telogen effluvium (TE), horizontally sectioned at the level of the infundibula, demonstrating minimal follicular miniaturization (T/V = 5/1). (**B**) Hairs are best visualized on the AFB stain. (**C**) Normal follicular units, normal follicular density, and increased numbers of telogen follicles (*arrows*) in active phase of chronic TE. (**D**) Higher power view of one follicular unit with two telogen follicles (*arrows*) and two terminal anagen follicles.

Figure 9 (**A**) Young girl with loose anagen syndrome and thinning of hair on the parietal scalp. Hairs obtained from the patient in (**A**) by loosely pulling demonstrate a dystrophic anagen bulb (**B**) and ruffling of the cortex (**B**,**C**).

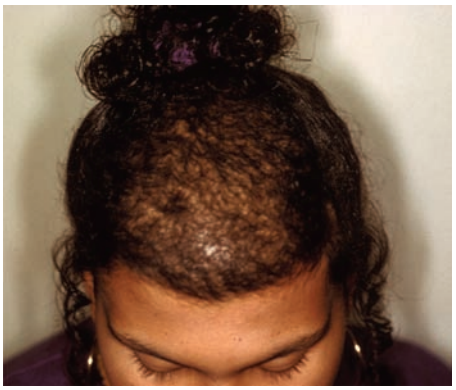

Figure 10 Adolescent female with trichotillomania, demonstrating broken-off hairs on the frontal crown. Her scalp exam was completely unchanged on several visits over a nine-month period.

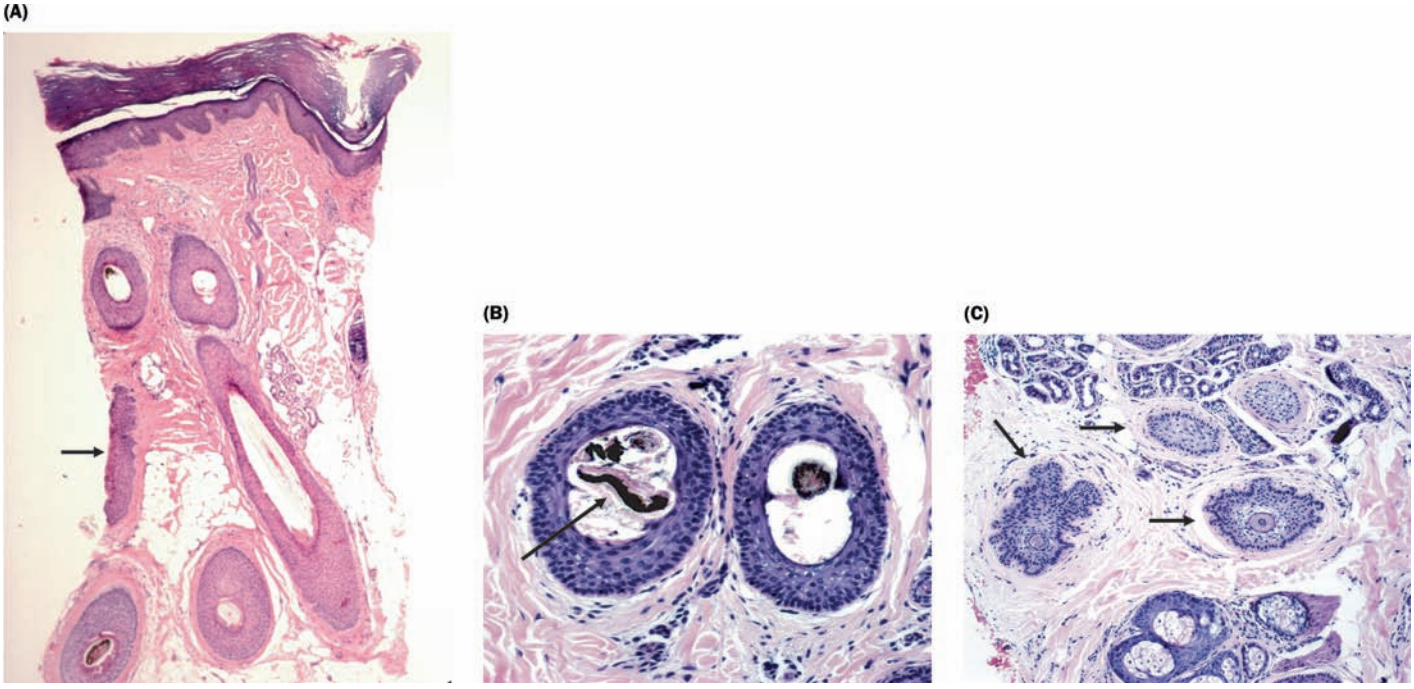

Figure 11 (**A**) Vertical section of trichotillomania demonstrating hyperkeratosis, slight superficial perifollicular fibrosis, and a catagen hair follicle (*arrow*). (**B**) Pigment casts (*arrow*) in an infundibulum of a patient with trichotillomania. (**C**) Increased numbers of telogen germinal units (*arrows*) in a patient with trichotillomania.

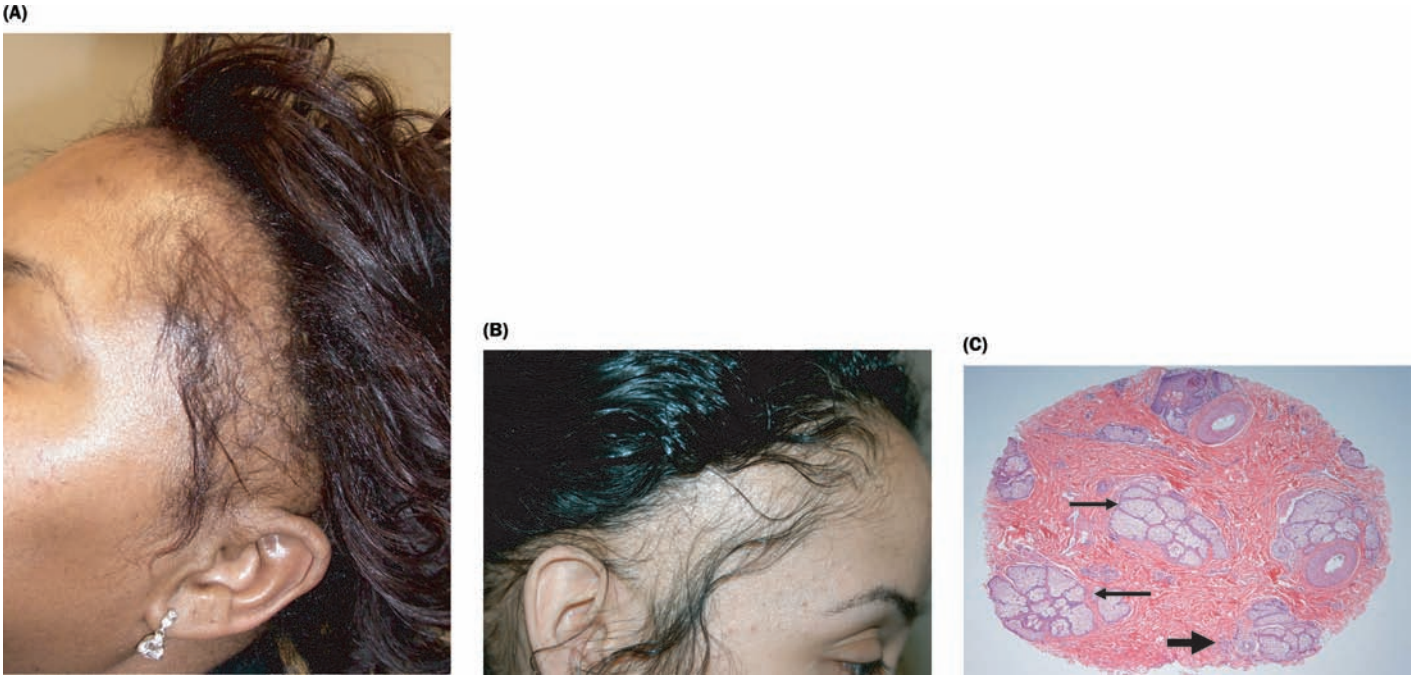

Figure 12 Marginal hair loss with preservation of the "marginal fringe" in an African-American woman (**A**) and Latina woman (**B**) with permanent traction alopecia. (**C**) Scalp biopsy from the patient in (**B**) demonstrates preservation of sebaceous glands. However, several follicular units contain no follicles (*thin arrows*) or one to two follicles, often vellus follicles (*thick arrow*).

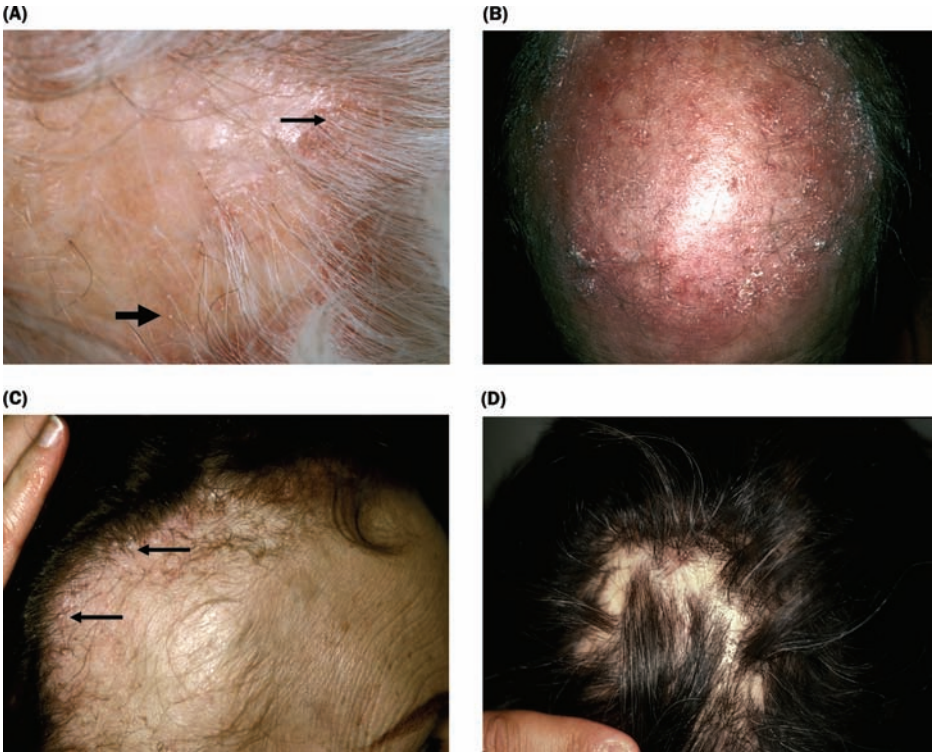

Figure 13 (**A**) Erythema (*thin arrow*) and minute scales (*thick arrow*) at bases of hair shafts at the periphery of an area of scarring alopecia in a patient with typical lichen planopilaris (LPP). (**B**) Woman with fulminant LPP that eventuated into complete scalp alopecia. Erythema and scaling typical of LPP is seen at the periphery of the involved areas. (**C**) Postmenopausal frontal fibrosing alopecia (variant of LPP) characterized by a band of scarring alopecia on the frontal scalp with erythema and scaling typical of LPP (*arrows*) at the advancing border. (**D**) End-stage scarring alopecia (pseudopelade of Brocq pattern) can be seen in old LPP lesions.

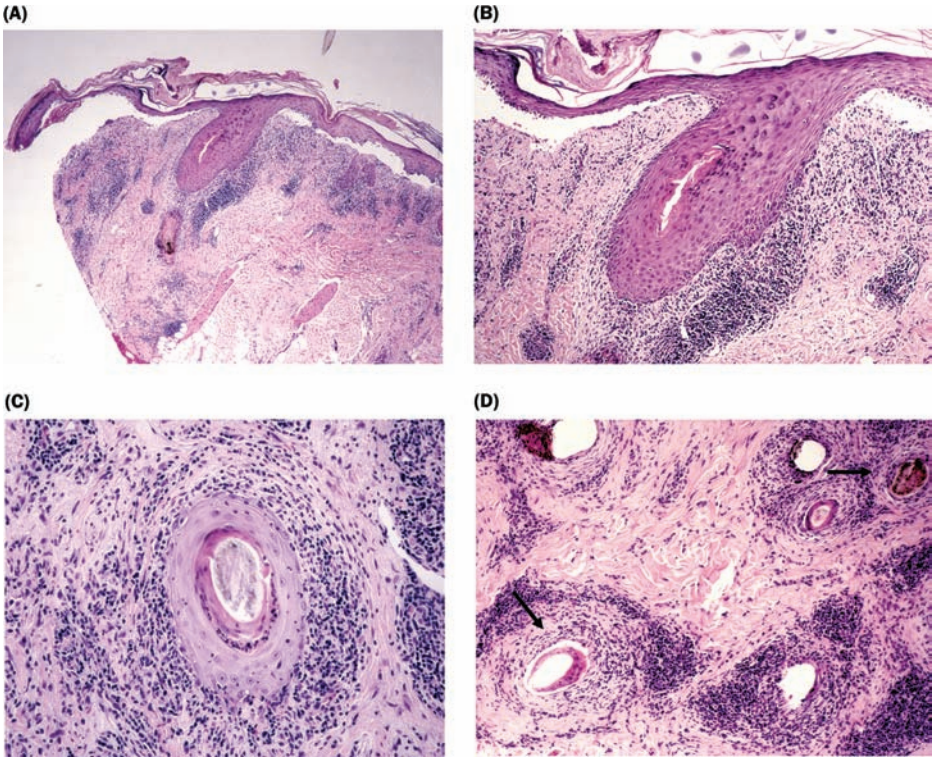

Figure 14 (**A**) A band-like lymphocytic infiltrate in the papillary dermis obscures the dermal–epidermal junction and is dense around a follicular infundibulum in a scalp biopsy of fulminant lichen planopilaris (LPP) (patient in Fig. 13B). Although the inflammation extends into the deep dermis, it is much denser in the superficial dermis, favoring LPP over discoid lupus erythematosus. (**B**) Typical changes of lichen planus, such as saw-toothing of the rete ridges, hypergranulosis, and Max Joseph spaces, are sometimes identified in the interfollicular epidermis in LPP, as demonstrated in this case. (**C**,**D**) There is dense perifollicular and follicular lichenoid lymphocytic inflammation that has resulted in follicular destruction (*arrows*) in this patient with LPP. The inflammation is starting to "back away" from some of the follicles that are surrounded by fibrosis (**D**).

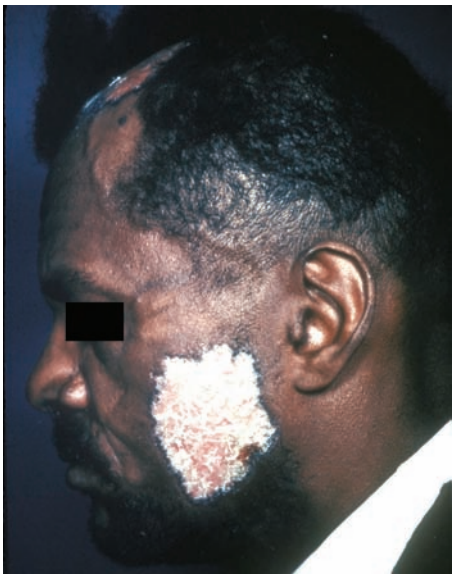

Figure 15 Discoid lupus erythematosus lesions on the left cheek and scalp demonstrating hyperkeratosis and hyperpigmentation at the periphery of lesions.

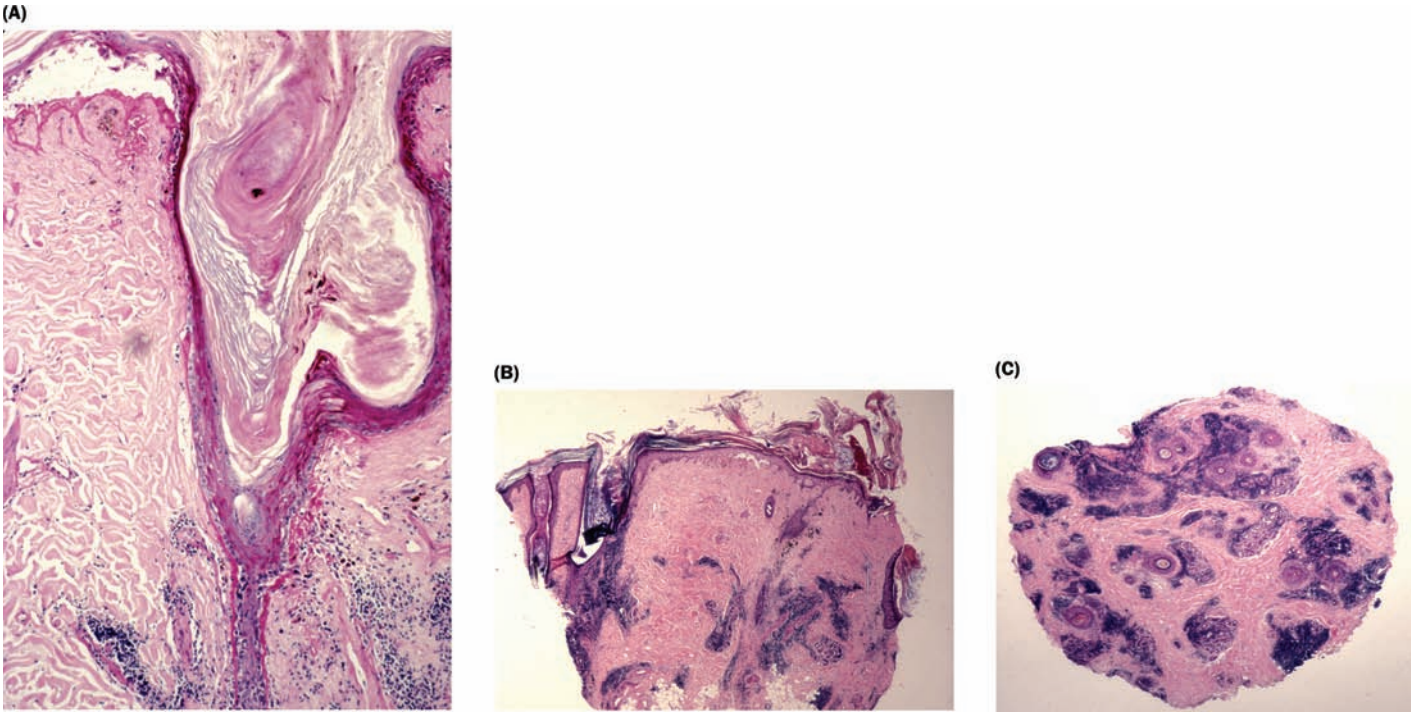

Figure 16 (**A**) Periodic-acid Schiff (PAS) stain demonstrates marked basement membrane zone thickening in discoid lupus erythematosus (DLE). (**B**) Dilated plugged infundibula, interface changes, and prominent deep perivascular and perifollicular inflammation characterized this vertically sectioned scalp biopsy from a DLE lesion. (**C**) A horizontal section through the deep dermis of a DLE scalp lesion demonstrates a dense perivascular and follicular mononuclear cell infiltrate.

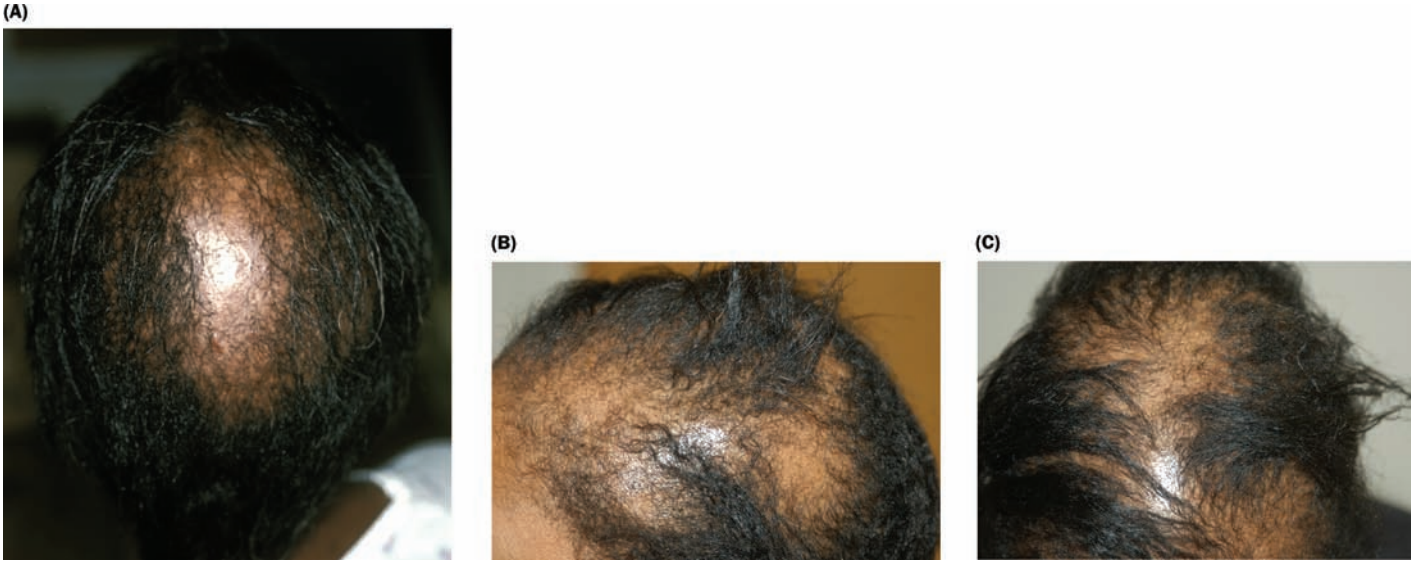

Figure 17 (**A–C**) Areas of scarring alopecia on the scalp appear noninflammatory in these African-American women with the follicular degeneration syndrome.

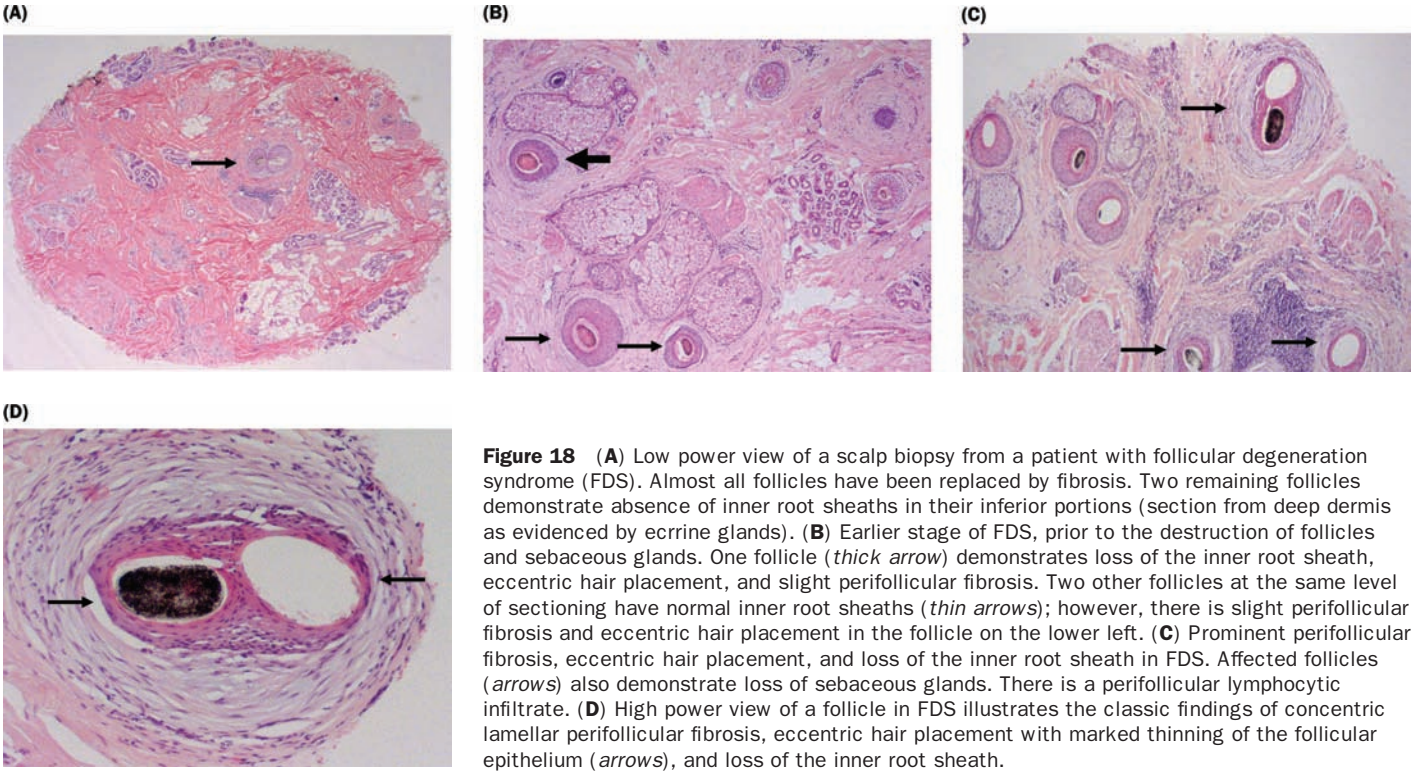

Figure 18 (**A**) Low power view of a scalp biopsy from a patient with follicular degeneration syndrome (FDS). Almost all follicles have been replaced by fibrosis. Two remaining follicles demonstrate absence of inner root sheaths in their inferior portions (section from deep dermis as evidenced by ecrrine glands). (**B**) Earlier stage of FDS, prior to the destruction of follicles and sebaceous glands. One follicle (*thick arrow*) demonstrates loss of the inner root sheath, eccentric hair placement, and slight perifollicular fibrosis. Two other follicles at the same level of sectioning have normal inner root sheaths (*thin arrows*); however, there is slight perifollicular fibrosis and eccentric hair placement in the follicle on the lower left. (**C**) Prominent perifollicular fibrosis, eccentric hair placement, and loss of the inner root sheath in FDS. Affected follicles (*arrows*) also demonstrate loss of sebaceous glands. There is a perifollicular lymphocytic infiltrate. (**D**) High power view of a follicle in FDS illustrates the classic findings of concentric lamellar perifollicular fibrosis, eccentric hair placement with marked thinning of the follicular epithelium (*arrows*), and loss of the inner root sheath.

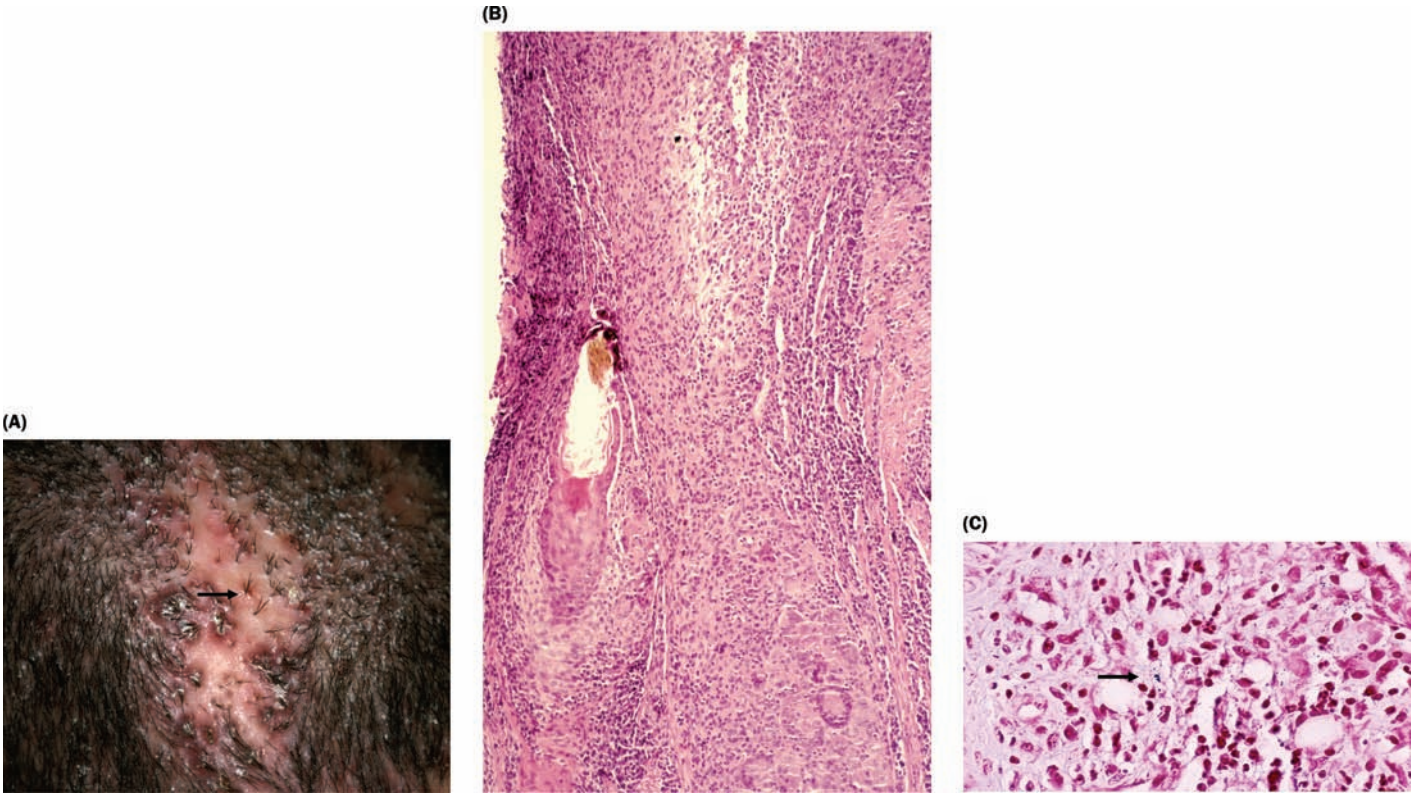

Figure 19 (**A**) Folliculitis decalvans is characterized by areas of scarring hair loss with pustules at the active periphery and the so-called "tufted folliculitis" (*arrow*). (**B**) There is complete follicular destruction in folliculitis decalvans, with marked inflammation consisting of lymphocytes, neutrophils, plasma cells, and macrophages. (**C**) Gram-positive cocci (*arrow*) are often found in the dermis in areas of inflammation in lesions of folliculitis decalvans.

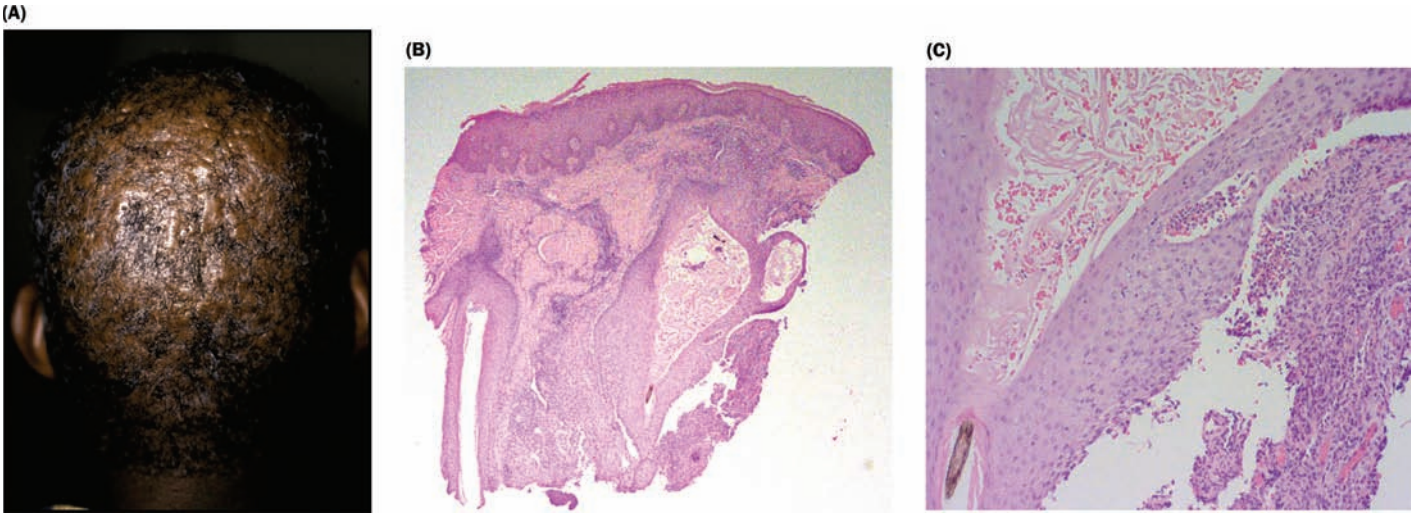

Figure 20 (**A**) African-American male with long history of dissecting cellulitis of the scalp, resulting in large areas of scarring alopecia, fibrotic ridges, and sinus tract formation. (**B**) Low power view of dissecting cellulitis demonstrating cystically dilated follicles that result in sinus tract formation and surrounding inflammation. (**C**) High power view of the same biopsy shows mixed follicular and perifollicular inflammation consisting of neutrophils and lymphocytes.

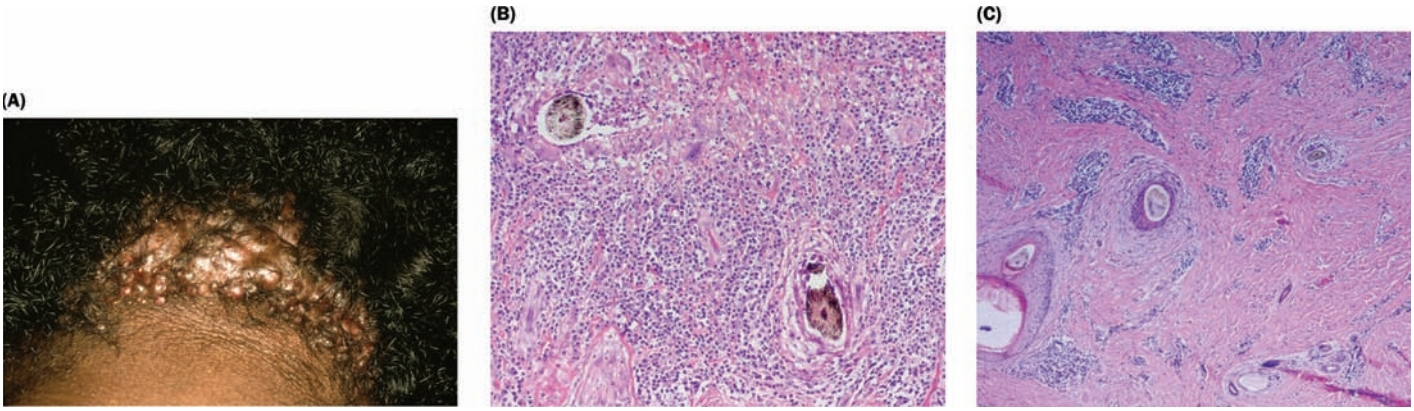

Figure 21 (**A**) Area of scarring hair loss with "keloidal" papules at the nape in this African-American man with acne keloidalis nuchae (AKN). (**B**) Dense inflammation and follicular destruction with resultant hair granulomas in AKN. (**C**) AKN scars look clinically like keloids, but histologically they are typical or hypertrophic scars, as shown in this biopsy.

11

Panniculitis

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CONTENTS

Panniculitis refers to inflammation of the subcutaneous tissue. This chapter will focus on common and unusual types of noninfectious primary panniculitis and review several examples of secondary panniculitis that may be due to multiple etiologies. In most cases of panniculitis, special stains should be performed to exclude an infectious etiology; polarized light examination should also be performed to identify foreign material. Clinical evaluation and directed laboratory studies may be necessary to confirm the diagnosis.

Definition of Terms and Anatomy:

The subcutaneous fat (panniculus adiposus) is located below the reticular dermis and extends to the superficial fascia. The tissue is divided into lobules composed of aggregates of adipocytes (fat cells, lipocytes) separated by a meshwork of fibrous septae (trabeculae). The fibrous septae extend down from the reticular dermis and house small- to medium-sized arteries, arterioles, venules, lymphatics, and nerves. An arteriole supplies the center of each lobule with drainage to peripheral venules in the fibrous septae. Lymphatics are not present within the lobules. Each adipocyte is supplied by capillaries. Therefore, venous processes are associated with septal alterations (septal panniculitis) and arterial involvement tends to result in lobular changes (lobular panniculitis). Other mechanisms are also involved in disorders that produce lobular panniculitis. Some diseases may show mixed septal and lobular panniculitis. Additionally, the histologic features observed will vary, depending on the size and timing of the biopsy. A deep incisional or excisional wedge biopsy of an active, developed lesion is preferred over punch biopsies.

Classification of Panniculitis:

Primary Panniculitis:

Septal	Lobular	Combined Septal/ Lobular
Erythema nodosum	Sclerema neonatorum	Nodular vasculitis/ erythema induratum
Erythema nodosum migrans/ subacute nodular migratory panniculitis	Subcutaneous fat necrosis of the newborn	Lupus erythematosus profundus/connective tissue panniculitis
	Poststeroid panniculitis	
	Cold panniculitis	
	Foreign body/factitial panniculitis	
	Cytophagic histiocytic panniculitis (±septal)	
	Pancreatic fat necrosis (± septal)	
	Neutrophilic panniculitis/ subcutaneous Sweet's syndrome	
	Weber-Christian disease	

Secondary Panniculitis:

See Table 1.

Table 1 Secondary Panniculitis

Vascular Disease	Fibrosing Disease	Infections	Malignancy	Miscellaneous
Leukocytoclastic vasculitis begins as septal process and becomes lobular (septal → lobular)	Morphea/scleroderma (septal → lobular)	Fungal (lobular ± septal)	Lymphoma (lobular → septal)	Subcutaneous granuloma annulare (septal)
Polyarteritis nodosa (septal)	Eosinophilic fasciitis (septal)	Bacterial (lobular ± septal)	Subcutaneous panniculitis like T cell lymphoma (lobular → septal)	Rheumatoid nodule (septal)
Thrombophlebitis (septal)	Nephrogenic fibrosing dermopathy (septal)	Viral (lobular ± septal)	Atypical lymphocytic panniculitis (lobular)	Necrobiotic xanthogranuloma (septal)
Lipodermatosclerosis/ sclerosing panniculitis, lipomembranous panniculitis (septal + lobular)		Infestations (lobular ± septal)	Leukemia (lobular → septal)	Necrobiosis lipoidica (septal)
			Malignant histiocytosis (lobular → septal)	Sarcoidosis (septal + lobular)
				Metastatic Crohn's disease (septal + lobular)
				Oxalosis (septal + lobular)
				Calcifying panniculitis of renal disease, calciphylaxis (septal → lobular)

ERYTHEMA NODOSUM

Clinical Presentation:
- Most common form of panniculitis
- Female predominance; second to fourth decades of life
- Tender, bright red, or bruised subcutaneous nodules on the anterior or lateral shins (Fig. 1A)
- ±Prodrome of fever, malaise, and/or arthralgias
- Individual lesions last three to six weeks
- Recurrences common
- No ulceration, scarring, or atrophy

Histology:
Early Lesion:
- Septal edema with inflammation composed of a mixed infiltrate of neutrophils, lymphocytes, occasional eosinophils; hemorrhage may be present (Figs. 1B and C)
- Miescher's radial granulomas: small nodular aggregates of histiocytes around central stellate or banana-shaped cleft (Fig. 1D)
- "Lacelike" inflammation extending from septae into lobules
- Rare true focal leukocytoclastic vasculitis
- Dermal vascular dilatation
- Superficial and deep lymphocytic dermal infiltrate

Fully Developed Lesion:
- Septal inflammation composed of lymphocytes, macrophages, and multinucleated giant cells (Fig. 1E)
- Miescher's granulomas
- Early septal widening
- Occasional foam cells in lobules

Late Lesion:
- Septal fibrosis and thickening
- Less prominent septal inflammation
- Increased foam cells in fat lobules

Clinicopathologic Correlation:

Clinical Feature	Pathologic Feature
Bright red subcutaneous nodules with bruising	Septal edema and hemorrhage with mixed inflammation

Differential Diagnosis:
See Table 2.

Pathophysiology:
- Reaction pattern to a variety of antigens

Most Common Etiologic Agents:
- *Infections*: Group A beta-hemolytic Streptococcus, Yersinia, tuberculosis, deep fungal, viral, etc.
- *Drugs*: oral contraceptive pills, sulfonamides, iodine, bromine, penicillin, phenacetin, pyritinol, all-trans-retinoic acid, Echinacea herbal therapy, and etc.
- Inflammatory bowel disease
- Sarcoidosis (Lofgren's syndrome)
- Pregnancy
- Malignancy

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2. Requena L, Yus ES. Panniculitis. Part I. Mostly septal panniculitis. J Am Acad Dermatol 2001; 45(2):163–183.

SCLEREMA NEONATORUM

Clinical Presentation:
- Rare panniculitis seen in debilitated and premature newborn infants
- Onset during first few days of life
- Symmetric, diffuse, rigid, waxy board-like, induration

Table 2 Differential Diagnosis: Erythema Nadosum

Erythema Nodosum	Erythema Nodosum Migrans	Superficial Migratory Thrombophlebitis	Subcutaneous Polyarteritis Nodosa	Morphea/Scleroderma	Subcutaneous Sarcoidosis
Tender nodules on shins Mixed septal inflammation Miescher's radial granulomas Septal widening and fibrosis	Unilateral annular plaque with central clearing Marked septal fibrosis Numerous epithelioid granulomas Granulation tissue–like capillary proliferation	Multiple tender nodules on lower extremities, upper extremities, or trunk with cord-like induration Small- to medium-sized veins show thrombosis with infiltration of the vessel wall With neutrophils early on, followed later by mononuclear cells Little surrounding panniculitis	Livedo reticularis with ulcerations, nodules, or palpable purpura Vasculitis of medium-sized arteries	Localized or generalized sclerosis, ± lilac-colored border Septal lymphoplasmacytic inflammation admixed with eosinophils and neutrophils Early edema followed by later sclerosis May see reticular dermal, fascial, and perimysial extension	Erythematous or flesh-colored nodules most common on upper extremities Larger sarcoidal "naked" granulomas in septae and lobules

Metastatic Crohn's Disease	Infectious Panniculitis	Traumatic Panniculitis	Factitial Panniculitis	Panniculitis Associated with Palisading Granulomas	Ruptured Follicular Cyst
Solitary or multiple nodules, plaques, or ulcers on the extremities, intertriginous areas, abdomen, or genitalia May involve dermis Noncaseating granulomas in septae or lobules May be associated with lymphocytic vasculitis of medium-sized vessels at dermal subcutaneous junction	Nodules, ulcers, and abscesses, most common on legs and feet For example, subcutaneous tuberculosis Positive AFB stains May spare upper subcutis	Variable clinical features Organizing hematoma, granulation tissue, fat necrosis with microcyst formation ±lipomembranous (membranocystic) change Suppuration with numerous neutrophils	Nodules and ulcers with bizarre patterns Variably-sized vacuoles with "Swiss cheese" pattern in dermis and subcutis ±lipomembranous (membranocystic) change, fibrosis ±suppuration, fat necrosis, microcyst formation Variable mixed and granulomatous inflammation ±Calcification ±Polarizable birefringent material	Subcutaneous nodules most common on extremities Subcutaneous granuloma annulare, rheumatoid nodules, rheumatic nodules, NLD Palisading granulomas localized to subcutaneous septae NLD also shows dermal involvement	Tender cystic nodule with surrounding erythema Granulomatous and suppurative inflammation often with dermal extension Keratin fragments

Abbreviations: AFB, acid fast bacillus; NLD, necrobiosis lipoidica.

- Begins on buttocks and thighs and spreads upward
- 75% mortality rate within several days

Histology:
- Lobular expansion, little inflammation (Fig. 2A)
- Enlargement of adipocytes (Fig. 2B)
- Septal thickening and fibrosis
- Needle-shaped clefts arranged radially in lipocytes
- Rarely mixed inflammation

Clinicopathologic Correlation:

Clinical Feature	Pathologic Feature
Premature neonate with waxy board-like induration	Septal thickening and fibrosis Expanded lobules and enlarged adipocytes

Differential Diagnosis:

Sclerema Neonatorum	Subcutaneous Fat Necrosis of the Newborn	Poststeroid Panniculitis
Scant lobular inflammation	Mixed lobular inflammation	Presents in young children after discontinuing high-dose steroids without taper
Crystals seen only in lipocytes	Crystals seen in giant cells and lipocytes	Identical histologic features as subcutaneous fat necrosis

Pathophysiology:
- May be secondary to insufficient enzymes in neonates, which are needed to desaturate fatty acid chains
- Results in higher saturated to unsaturated fatty acid ratio
- Crystallization of subcutaneous tissue occurs in setting of hypothermia
- Increased blood lipid peroxidation and dimished superoxidase dismutase activity
- Raise the possibility that free radicals may also be involved in pathogenesis

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SUBCUTANEOUS FAT NECROSIS OF THE NEWBORN

Clinical Presentation:
- Full-term infants up to six weeks of age
- Asymptomatic, indurated, red to violaceous plaques and nodules (Fig. 3A)
- Predilection for buttocks, shoulders, cheeks, and thighs
- Resolves spontaneously in one to three months (usually without scarring)
- Rarely ulcerate and discharge milky material

Histology:
Early Lesion:
- Lobular panniculitis composed of macrophages, giant cells, granulomas, lymphocytes, rare eosinophils, and neutrophils (Fig. 3B)
- Needle-shaped clefts radially arranged in giant cells and lipocytes (Figs. 3C and D)
- Occasional calcification

Clinicopathologic Correlation:

Clinical Feature	Pathologic Feature
Healthy infant with indurated plaque or nodule after birth trauma	Granulomatous lobular panniculitis with crystal formation in giant cells and lipocytes

Differential Diagnosis:
See "Differential Diagnosis" table under the section "Sclerema Neonatorum."

Pathophysiology:
- Newborn has large body-surface-area-to-weight ratio
- Greater saturated to unsaturated fatty acid ratio
- Favors release of hydrolases that induce breakdown of saturated fatty acids
- Results in subcutaneous fat necrosis

Associations:
- Hypercalcemia
- Obstetric trauma
- Induced hypothermia for cardiac surgery
- After prostaglandin E administration; newborns with brown fat deficiency; infants with lipoprotein abnormalities

References:

1. Hicks MJ, Levy ML, Alexander J, Flaitz CM. Subcutaneous fat necrosis of the newborn and hypercalcemia: case report and review of the literature. Pediatric Dermatol 1993; 10(3): 271–276.
2. Tran JT, Sneth AP. Complications of subcutaneous fat necrosis of the newborn: case report and review of the literature. Pediatr Dermatol 2003; 20(3):257–261.

FACTITIAL PANNICULITIS

Synonyms: Foreign body panniculitis; sclerosing lipogranuloma; chemical panniculitis.

Clinical Presentation:
- Tender nodules and plaques in unusual sites (Fig. 4A)
- Unusual geometric shapes (Fig. 4A)
- Ulceration, scarring, bruising, infection, etc.
- Secondary to injection of milk, oils, feces, etc.
- Patients often have healthcare backgrounds and psychiatric disorders

Histology:
- Epidermal ulceration
- Mixed inflammation in dermis ± paraffinoma-like vacuoles; "Swiss cheese" pattern

Table 3 Differential Diagnosis: Factitial Panniculitis

Factitial Panniculitis	Infectious Panniculitis	Pancreatic Panniculitis	Alpha-1-Antitrypsin Deficiency Panniculitis	Cold Panniculitis	Traumatic Panniculitis
Vacuoles with "Swiss cheese" pattern in dermis and subcutis	Lobular or mixed septal and lobular inflammation, hemorrhage, necrosis	Center of lobule shows fat necrosis with "ghost cells"	Septal suppurative inflammation with liquefactive necrosis and collagenolysis	Indurated plaque on face of infants or children 1–3 days after cold exposure; prolonged direct ice application or after sucking ice cubes or popsicles. Similar lesions on outer thighs of equestrians	Hemorrhage, organizing hematoma, granulation tissue
Mixed inflammation necrosis;	Often dermal extension	Basophilic calcium deposition	Lobular panniculitis with fat necrosis and massive neutrophilic inflammation	Dermal edema and inflammation	± suppuration with fat necrosis and microcyst formation
±microcyst formation	Organisms identified with special stains or culture	Periphery shows suppuration	Often dermal involvement	Mixed suppurative lobular inflammation	
±polarizable birefringent material			± transepidermal elimination	Pseudocyst formation	

- Lobular panniculitis composed of neutrophils, lymphocytes, granulomas, fat necrosis, hemorrhage (Figs. 4B and C)
- ± Polarizable material
- ± Microcyst formation or lipomembranous change

Clinicopathologic Correlation:

Clinical Feature	Pathologic Feature
Tender ulcerated nodules with geometric shapes in psychiatric patient	Ulceration, paraffinoma-like vacuoles, suppurative and granulomatous inflammation, fat necrosis, microcyst formation

Differential Diagnosis:
See Table 3.

Pathophysiology:
- Results from self injection or implantation of foreign or organic materials or medications

References:

1. Oh CC, McKenna DB, McLaren KM, Tidman MJ. Factitious panniculitis masquerading as pyoderma gangrenosum. Clin Exp Dermatol 2005; 20(3):253–255.
2. Winkelmann RK, Barker SM. Factitial traumatic panniculitis. J Am Acad Dermatol 1985; 13:988–994.

CYTOPHAGIC HISTIOCYTIC PANNICULITIS

Clinical Presentation:
- Crops of asymptomatic nodules ± bruising or ulceration
- Localized to the extremities (Fig. 5A)
- Associated with fever, hepatosplenomegaly, pancytopenia, and lymphadenopathy
- ±Hemophagocytic syndrome
- Phagocytic histiocytes replace bone marrow and lymph nodes
- Development of severe anemia, thrombocytopenia, coagulation defects, hypocalcemia, and liver failure
- Reported in viral, bacterial, fungal, and protozoan infections, systemic lupus erythematosus (SLE)
- T-cell lymphoma, B-cell lymphoma, NK-cell lymphoma, atypical-lymphocytic panniculitis

Histology:
- Lobular panniculitis composed of numerous histiocytes, lymphocytes, rare neutrophils (Fig. 5B)
- Sheets of "beanbag cells": phagocytosis of erythrocytes, leukocytes, and nuclear debris (cytophagocytosis) (Figs. 5C–E)
- Prominent karyorrhexis (Fig. 5C)
- Lymphocytes ring around necrotic adipocytes (Fig. 5C)
- Fat necrosis; focal hemorrhage
- ±Cytologic atypia: consider malignancy

Clinicopathologic Correlation:

Clinical Feature	Pathologic Feature
Asymptomatic nodules with bruising associated with hemophagocytic syndrome	Lobular panniculitis with necrosis, hemorrhage and characteristic "bean bag" cells

Pathophysiology:
- Elaboration of interferons and macrophage inflammatory protein 1 alpha by neoplastic and nonneoplastic lymphocytes, endothelial cells, and macrophages; this activates macrophages to phagocytize

Differential Diagnosis:

Cytophagic Histiocytic Panniculitis	Lupus Panniculitis	Rosai-Dorfman Disease (Sinus Histiocytosis With Massive Lymphadenopathy)
Lobular panniculitis with hemophagocytic histiocytes	Vacuolar interface dermatitis	Diffuse dermal mixed infiltrate
"Bean bag" cells	Dermal superficial and deep perivascular and periadnexal inflammation	Prominent emperipolesis (S100+, CD68+ histiocytes engulf whole blood cells without digestion)
Fat necrosis with lymphocyte ringing	Inflammation and dermal mucin	± subcutaneous involvement
Prominent karyorrhexis	Mixed septal and lobular panniculitis	Thick-walled venules cuffed by plasma cells
	Eosinophilic hyalin fat necrosis	Lymphoid aggregates

References:

1. Harada H, Iwatsuki K, Kaneko F. Detection of Epstein-Barr virus genes in malignant lymphoma with clinical and histologic features of cytophagic histiocytic panniculitis. J Am Acad Dermatol 1994; 31:379–383.
2. Go RS, Wester SM. Immunophenotypic and molecular features, clinical outcomes, treatments, prognostic factors associated with subcutaneous panniculitis-like T-cell lymphoma: a systematic analysis of 156 patients reported in the literature. Cancer 2004; 101(6):1404–1413.
3. McNutt NS, Fund MA. More about panniculitis and lymphoma. J Cutan Pathol 2004; 31(4):297–299.

PANCREATIC FAT NECROSIS

Clinical Presentation:

- One or more tender, fluctuant nodules (Fig. 6A)
- Oily drainage
- Most commonly located on distal lower extremities (pretibial area), ankles, knees, and buttocks
- Two to three percent of all patients with pancreatic disease
- May predate pancreatic disease and be sole presentation
- Reported with acute and chronic pancreatitis and sulindac therapy
- Associated with abdominal pain and arthralgic ankle pain (or true arthritis)
- Schmid's triad: nodular subcutaneous necrosis, polyarthritis, and eosinophilia; associated with poor prognosis
- ± Increased amylase and lipase
- ± Pleural effusion and ascites

Histology:

Early Lesion:

- Lobular panniculitis with fat necrosis and formation of "ghost cells" clustered in the center of lobule (Fig. 6B)
- Neutrophilic inflammation in the periphery (Fig. 6B)

Fully Developed Lesion:

- Mixed lobular and septal panniculitis
  - ± Basophilic granular calcium deposition (Fig. 6C)
  - Mixed inflammation composed of foamy histiocytes, lymphocytes, neutrophils, hemorrhage
  - Pseudocysts

Late Lesion:

- Fibrosis
- Lipoatrophy

Clinicopathologic Correlation:

Clinical Feature	Pathologic Feature
Fluctuant nodule on the ankle with oily drainage and arthritis	Epidermal ulceration with mixed septal and lobular inflammation with suppuration
	Ghost cells with basophilic calcium deposition

Differential Diagnosis:

See Table 4.

Table 4 Differential Diagnosis: Pancreatic Fat Necrosis

Pancreatic Panniculitis	Alpha-1-Antitrypsin Deficiency Panniculitis	Infectious Panniculitis	Factitial Panniculitis	Traumatic Panniculitis	Subcutaneous Leukocytoclastic Vasculitis	Neutrophilic Panniculitis/ Subcutaneous Sweet's Syndrome
Center of lobule shows fat necrosis with ghost cells and basophilic calcium deposition	Septal suppurative inflammation with liquefactive necrosis and collagenolysis	Lobular or mixed septal and lobular inflammation, hemorrhage, necrosis	Vacuoles with "Swiss cheese" pattern in dermis and subcutis	Hemorrhage; organizing hematoma, granulation tissue	Septal leukocytoclastic vasculitis	Lobular neutrophilic panniculitis
Periphery shows suppuration	Lobular panniculitis with fat necrosis and massive neutrophilic inflammation	Often dermal extension	Mixed inflammation; necrosis	± suppuration with fat necrosis and microcyst formation	Absence of liquefactive necrosis or collagenolysis	Absence of liquefactive necrosis and collagenolysis
	Often dermal involvement	Organisms identified with special stains or culture	± Microcyst formation			Variable atypical myeloid cells when associated with leukemia
	± Transepidermal elimination		± Polarizable birefringent material			

Pathophysiology:
- Lipase and, less importantly, amylase and trypsin released from the inflamed pancreas into the bloodstream are responsible for the subcutaneous fat necrosis
- Dystrophic calcification in ghost cells results from hydrolytic action of pancreatic enzymes on fat followed by calcium deposition (saponification)

References:

1. Shehan JM, Kalaaji AN. Pancreatic panniculitis due to pancreatic carcinoma. Mayo Clin Proc 2005; 80(8):822.
2. Dahl PR, Su WPD, Culbiemere KC, Dicken CH. Pancreatic panniculitis. J Am Acad Dermatol 1995; 33:413–417.

ALPHA-1-ANTITRYPSIN DEFICIENCY PANNICULITIS

Autosomal dominant; genetic deficiency of alpha-1-antitrypsin (serine protease inhibitor).

Features of Alpha-1-Antitrypsin Deficiency:
- Panacinar emphysema
- Hepatitis and cirrhosis
- Hemorrhagic diathesis
- Ehlers-Danlos-like syndrome
- Pancreatic disease
- Marshall's syndrome (Sweet's syndrome leading to acquired cutis laxa)
- Cold urticaria and angioedema
- Panniculitis (uncommon)

Clinical Presentation:
- Panniculitis affects children and more commonly adults
- Recurrent, tender, pink-purpuric nodules
- Most common on proximal extremities, buttocks, trunk (Fig. 7A)
- Associated with fever; may mimic cellulitis
- Ulceration and drainage of oily, clear, or serosanguinous fluid
- May be precipitated by trauma or excessive physical activity; can be exacerbated by surgical debridement
- Resolves with atrophic scars

Histology:
- Septal panniculitis with liquefactive necrosis and collagenolysis with masses of neutrophils and histiocytes (Fig. 7B)
- Neutrophils extend into reticular dermis between collagen (splaying of neutrophils) (Fig. 7C)
- ± Dermal collagenolysis with transepidermal elimination (Fig. 7D)
- Numerous neutrophils may destroy fat lobules (Fig. 7E)
- Normal fat lobules adjacent to necrotic fat lobules

Clinicopathologic Correlation:

Clinical Feature	Pathologic Feature
Tender nodule on thigh after trauma in a patient with panacinar emphysema	Lobular and septal suppurative inflammation with liquefactive necrosis and collagenolysis

Differential Diagnosis:
See Table 4.

Pathophysiology:
- Greater than 90 allelic variants of alpha-1-antitrypsin allele
- Two alleles combine to determine the genotype of alpha-1-antitrypsin
- The most common protease inhibitor (Pi) allele associated with normal levels of alpha-1-antitrypsin is M (PiMM)
- Homozygous genotype PiZZ have severe alpha-1-antitrypsin deficiency:
  - Most commonly associated with panniculitis
  - Heterozygous deficiency with genotype MZ or MS also implicated.
- Deficiency of alpha-1-antitrypsin accelerates activation of lymphocytes and phagocytes producing inflammation and tissue necrosis secondary to protease action.

References:

1. Walling H, Geraminejad P. Determine alpha-1 antitrypsin level and phenotype in patients with neutrophilic panniculitis. J Am Acad Dermatol 2005; 52(2):373–374
2. Geraminejad P, DeBloom JR II, Walling HW, Sontheimer RD, Van Beek M. Alpha-1-antitrypsin associated panniculitis. The MS variant. J Am Acad Dermtol 2004; 51(4):645–655.

NODULAR VASCULITIS/ERYTHEMA INDURATUM OF BAZIN

Synonym: Bazin's disease.

Clinical Presentation:
- Predilection for middle-aged females
- Painful nodules or plaques
- Ulceration and atrophic scarring are common (Fig. 8A)
- Protracted and recurrent episodes over years
- Most frequently located on calf (Fig. 8A)
- Erythrocyanosis, column-like calves, erythema surrounding follicular pores, cutis marmorata
- Hypersensitivity reaction precipitated by tuberculosis: "erythema induratum"

Histology:
- Combined lobular and septal panniculitis with vasculitis (Fig. 8B)

Early Lesion:
- Inflammation of medium-sized vessels with thrombosis, fibrin deposition, and necrosis of vessel walls (Fig. 8C)
- Surrounding lymphocytic inflammation

Fully Developed Lesion:
- Fat necrosis with mixed inflammation composed of lymphocytes, neutrophils, histiocytes, multinucleated giant cells
- Granulomas ± caseation necrosis (Fig. 8D)
- ± Epidermal ulceration
- Acid fast bacilli (AFB) stains: typically negative
- PCR: *Mycobacterium tuberculosis* DNA in 25% to 77% of patients

Late Lesion:
- Fibrosis

Differential Diagnosis:
See Table 5.

Table 5 Differential Diagnosis: Nodular Vasculitis/Erythema Induration of Bazin

Nodular Vasculitis	Infectious Panniculitis	Subcutaneous Sarcoidosis	Superficial Thrombophlebitis	Polyarteritis Nodosa	Erythema Nodosum
Septal and lobular panniculitis with lymphocytic vasculitis of medium-sized vessels	Variable septal and lobular panniculitis	Larger naked granulomas in septae and lobules	Small- to medium-sized veins show thrombosis with infiltration of vessel wall with neutrophils early on, followed later by mononuclear cells	Vasculitis of medium-sized arteries	Septal panniculitis with mixed inflammation
Granulomatous inflammation ± caseation necrosis	May spare upper subcutis		Little surrounding panniculitis		Typically lacks vasculitis of medium-sized vessels
	For example, subcutaneous tuberculosis				Lacks prominent fat necrosis

Clinicopathologic Correlation:

Clinical Feature	Pathologic Feature
Painful ulcerated nodules on calf of middle-aged women	Epidermal ulceration; vasculitis of medium-sized vessels
	Fat necrosis; mixed inflammation; and granulomas

Pathophysiology:

- Many authors reserve the term erythema induratum when lesions develop in association with tuberculosis
- Although the pathogenesis is unknown, a hypersensitivity or immune-complex–mediated reaction has been implicated

Reference:

1. Bayer-Garner IB, Cox MD, Scott MA, Smoller BR. Mycobacteria other than Mycobacterium tuberculosis are not present in erythema induratum/nodular vasculitis: a case series and literature review of the clinical and histologic findings. J Cutan Pathol 2005; 32(3):220–226.

LUPUS ERYTHEMATOSUS PROFUNDUS

Synonyms: Lupus panniculitis; lupus profundus.

Clinical Presentation:

- Female predominance
- Red, asymptomatic, or tender nodules ± ulceration
- May develop in crops
- Most commonly located on face, buttocks, thighs, and arms
- Resolve with scarring or lipoatrophy (Fig. 9A)
- May be associated with SLE or discoid lupus erythematosus (DLE) (25–50%)
- Trauma may be a precipitating factor

Histology:

Septal Features:

- Perivascular lymphocytic inflammation ± thrombosis (Fig. 9B)
- Rarely septal granulomas/palisaded granulomas
- ± Lymphocytic vasculitis
- Septal fibrosis and hyalinization of vessels
- ± Membranocystic changes

Lobular Features:

- Lymphocytic inflammation ± plasma cells (Figs. 9B and C)
- Lymphocytes may show karyorrhexis (nuclear dust)
- Eosinophilic hyaline fat necrosis (Figs. 9B and D)
- ± Focal calcification
- Lymphoid follicles with germinal centers in up to 50% cases

Epidermal Features (25% to 50% of Cases):

- Vacuolar interface dermatitis
- Follicular plugging
- Basement membrane zone thickening

Dermal Features:

- Superficial and deep, perivascular, and periadnexal infiltrate composed of lymphocytes and plasma cells
- Increased dermal mucin

Clinicopathologic Correlation:

Clinical Feature	Pathologic Feature
Indurated plaque on extremity with overlying hyperkeratotic scale and follicular plugging	Hyperkeratosis; vacuolar interface dermatitis; basement membrane thickening; superficial and deep perivascular and periadnexal inflammation with dermal mucin
	Lobular and septal panniculitis with lymphocytes, plasma cells, and hyaline fat necrosis

Differential Diagnosis:

See Table 6.

Pathophysiology:

Refer to Chapter 3, under the section "Lupus."

References:

1. Magro CM, Crowson AN, Kovatich AJ, et al. Lupus profundus, indeterminate lymphocytic lobular panniculitis and subcutaneous T-cell lymphoma: a spectrum of subcuticular T-cell lymphoid dyscrasia. J Cutal Pathol 2001; 28:235–247.
2. Massone C, Kodama K, Salmhofer W, et al. Lupus erythematosus panniculitis (lupus profundus): clinical, histopathological and molecular analysis of nine cases. J Cutan Pathol 2005; 32(6):396–404.

Table 6 Differential Diagnosis: Lupus Erythematosus Profundus

Lupus Erythematosus Profundus	Cytophagic Histiocytic Panniculitis	Morphea Profundus	Erythema Induratum	Dermatomyositis	Eosinophilic Fascitis	Necrobiosis Lipoidica
± Vacuolar interface dermatitis	More prominent karyorrhexis	Pronounced thickening and hyalinization of septae	Lacks mucin	Mostly lobular panniculitis composed of lymphocytes and plasma cells	Deep sclerosis including fascia	Palisaded granuloma involving dermis
± Superficial and deep; perivascular and periadnexal inflammation and mucin	Lymphocyte rimming	No necrosis	More prominent granulomatous inflammation	Septal hyaline sclerosis	Variable eosinophils	May extend into septae
Lobular and septal panniculitis with hyaline necrosis	"Beanbag cells"	Lymphoplasmacytic inflammation		Less common hyaline necrosis		Lacks hyaline necrosis or lobular involvement
Calcification		Deep calcification		Variable immunofluorescent studies		
		Occasional eosinophils				
		Aggregates of lymphocytes				

LIPODERMATOSCLEROSIS/SCLEROSING PANNICULITIS

Clinical Presentation:

- Female predominance
- Circumscribed, wood-like, indurated, painful plaques on lower extremities
- ± Mottled hyperpigmentation
- Inverted champagne bottle deformity of lower leg (Fig. 10A)
- Early on may mimic cellulitis
- Associated with venous insufficiency, arterial ischemia, previous thrombophlebitis, or chronic lymphedema

Histology:

Early Lesion:

- Septal and lobular panniculitis composed primarily of lymphocytes
- Variable fat necrosis
- Prominent blood vessels ± capillary congestion; thrombosis

Fully Developed Lesion:

- Septal and lobular fibrosis with dramatic atrophy of subcutaneous fat with mixed inflammation (Fig. 10B)
- Lipomembranous (membranocystic) fat necrosis and fatty microcytes lined by crenulated PAS-positive eosinophilic material with fine feathery projections (Figs. 10C and D)
- May form pseudopapillae

Clinicopathologic Correlation:

Clinical Feature	Pathologic Feature
Inverted bottle deformity of lower leg	Septal and lobular fibrosis with subcutaneous atrophy and lipomembranous (membranocystic) fat necrosis

Differential Diagnosis:

Lipomembranous (membranocystic) fat necrosis has been reported in the following entities:

- Erythema nodosum
- Factitial panniculitis
- Traumatic panniculitis
- Infectious panniculitis
- Pancreatic panniculitis
- Lupus panniculitis
- Erythema induratum of Bazin (nodular vasculitis)

Pathophysiology:

- Pathogenesis of lipodermatosclerosis involves prolonged venous tension with leakage of fibrinogen into the dermis
- Polymerization of fibrinogen into fibrin with pericapillary fibrin cuffing results in decreased oxygen and nutrient delivery to the dermis and subcutis
- Characteristic "inverted bottle" appearance of the lower extremities results from subcutaneous atrophy and fibrosis

References:

1. Diaz-Cascajo C, Borghi S. Subcutaneous pseudomembranous fat necrosis: new observations. J Cutan Pathol 2002; 29(1):5–10.
2. Snow JL, Su WPD. Lipomembranous (membranocystic) fat necrosis. Clinicopathologic correlation of 38 cases. Am J Dermatopath 1996; 18:151.

CALCIPHYLAXIS

- Uremic small artery disease with medial calcification and intimal hyperplasia
- Life-threatening condition of progressive cutaneous necrosis secondary to small vessel calcification

Clinical Presentation:

- Seen most frequently in the setting of end-stage renal disease with secondary hyperparathyroidism
- Firm, intensely painful violaceous plaques
- Livedo reticularis-like pattern (Fig. 11A)

Table 7 Differential Diagnosis: Calciphylaxis

Coumadin Necrosis, Protein C or S Deficiency, Cryoglobulinemia	Primary Hyperoxaluria with Cutaneous Oxalosis	Septic Vasculitis	Mönckeberg Medial Calcific Sclerosis	Atherosclerotic Gangrene	Cholesterol Emboli	Panniculitis with Calcification
Intraluminal fibrin or cryoglobulin thrombi	Histologic features similar to calciphylaxis	Fibrinoid change in vessel walls	Calcification of larger deeper vessels	Intimal calcification and fibrosis of larger vessels	Vascular thrombosis of small vessels with cholesterol clefts (needle-shaped clefts)	Ghost cells
Dermal hemorrhage without vascular calcification	Calcium oxalate crystals may form rosettes, ellipses, prisms, or radial patterns	Occlusive thrombi with increased neutrophils				More inflammation without vascular calcification
		Subepidermal edema ± organisms				
		Absence of vascular calcification				

- Bilaterally symmetric
- Flaccid bulla may precede ulceration (Fig. 11A)
- Superficial or deep ulcerations (Fig. 11A)
- Necrotizing gangrene

Histology:

- Medial calcification with intimal fibroplasia of small vessels (30–600 microns; average 100 microns) in the dermis and subcutaneous tissue (Fig. 11B)
- ± Intraluminal debris or fibrin thrombi in the dermis and subcutis (Figs. 11C and D)
- ± Epidermal ischemic necrosis (may be characteristic depending on the area of biopsy) (Fig. 11B)
- ± Lobular panniculitis with subcutaneous calcification and fat necrosis

Clinicopathologic Correlation:

Clinical Feature	Pathologic Feature
Firm, symmetric, painful, violaceous plaques with overlying eschars in livedo reticularis pattern on lower abdomen and proximal thighs	Epidermal ischemic necrosis, intraluminal fibrin thrombi
	Medial calcification with intimal fibroplasia of arterioles in dermis and subcutis

Differential Diagnosis:

See Table 7.

Pathophysiology:

- Selye coined the term calciphylaxis as a condition of induced hypersensitivity in which sensitized tissues respond to appropriate challenging agents with calcium deposition.

Two-Stage Process:

1. *Sensitization*: creates a conducive environment for calcium deposition
2. *Challenge*: insult resulting in calcium precipitation

Implicated Sensitizing Agents	Suspected Challenging Agents
Elevated PTH levels	Albumin
Elevated calcium–phosphate product (70 or higher)	Corticosteroids
Vitamin D	Immunosuppressives
	Metallic salts
	Local trauma
	HIV
	Calcitriol
	Lymphoma

***Abbreviations*: HIV, human immunodeficiency virus; PTH, parathyroid hormone.**

Other Associated Risk Factors:

- Obesity
- Lower serum albumin
- Substantial weight loss
- Warfarin therapy
- Hypercoaguable states
- Diabetes mellitus
- Female gender

References:

1. Oh D, Eulau D, Tokugawa DA, McGuire JS, Kohler S. Five cases of calciphylaxis and a review of the literature. J Am Acad Dermatol 1999; 40:979–987.
2. Dahl PR, Winkelmann RK, Connolly SM. The vascular calcification-cutaneous necrosis syndrome. J Am Acad Dermatol 1995; 33:53–58.
3. Edsall LC, English JC III, Patterson JW. Calciphylaxis and metastatic calcification associated with nephrogenic fibrosing dermopathy. J Cutan Pathol 2004; 31:247–253.

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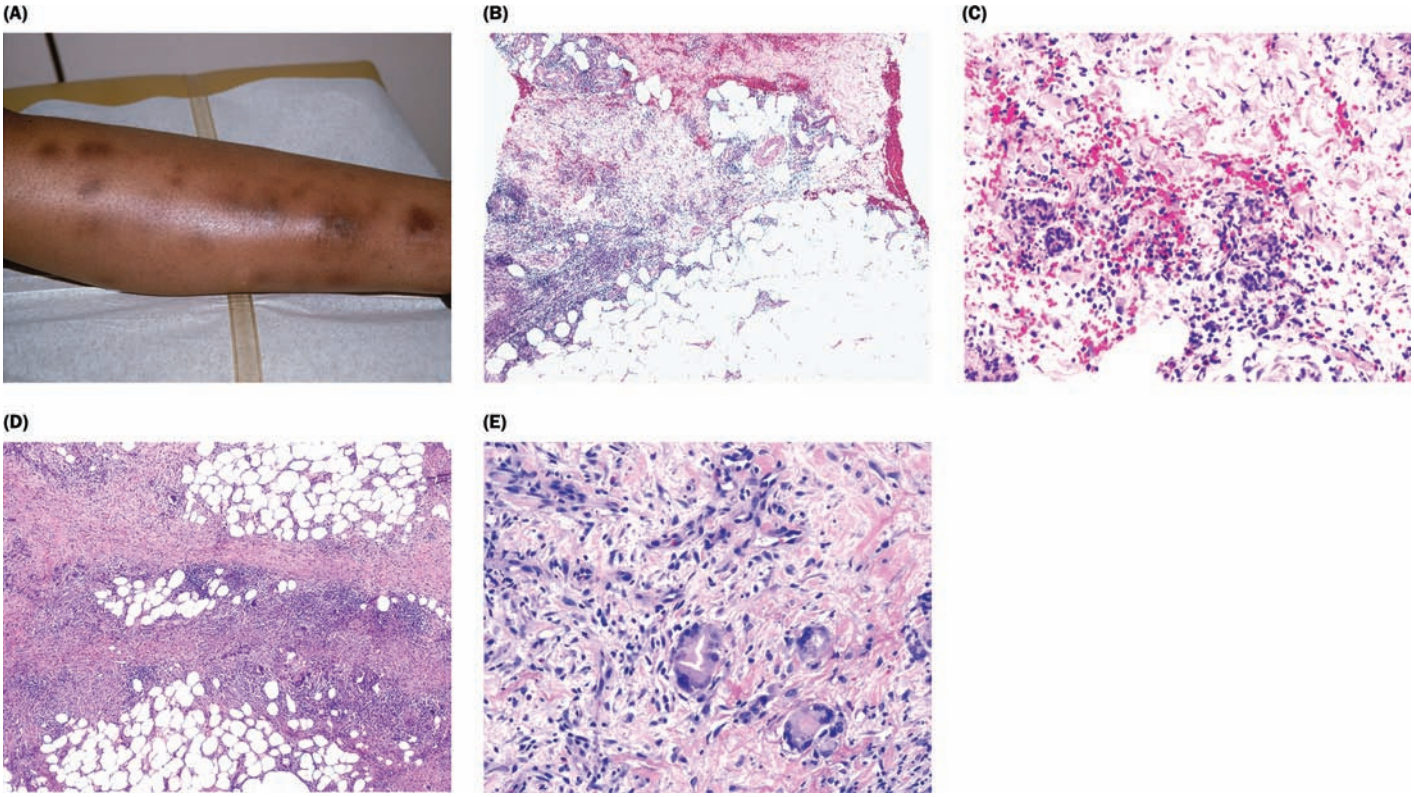

Figure 1 (**A**) Hyperpigmented subcutaneous nodules on the anterior shins. (**B**) Septal edema with mixed inflammation and hemorrhage [hematoxylin and eosin (H & E) stain, original magnification 40x]. (**C**) Higher magnification showing septal edema, septal inflammation composed of neutrophils, lymphocytes, eosinophils, and hemorrhage (H & E stain, original magnification 200x). (**D**) Septal inflammation composed of lymphocytes, macrophages, and giant cells in a fully developed lesion (H & E stain, original magnification 40x). (**E**) Miescher's radial granuloma (H & E stain, original magnification 200x).

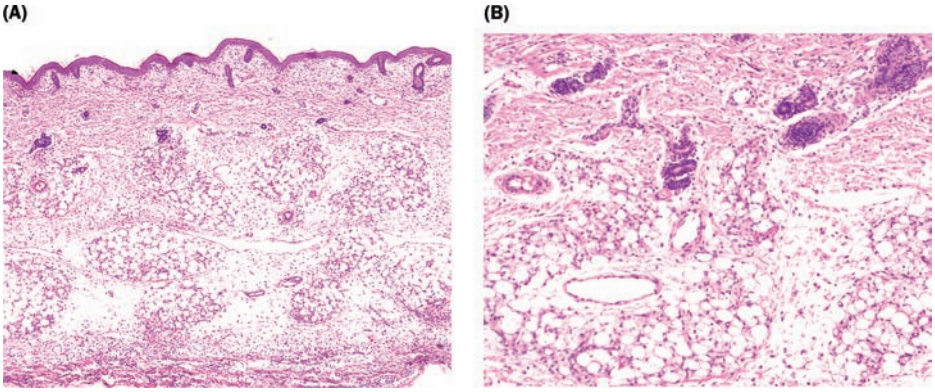

Figure 2 (**A**) Lobular expansion, scant inflammation [hematoxylin and eosin (H & E) stain, original magnification 40x]. (**B**) Variability in adipocyte size and enlargement of some adipocytes (H & E stain, original magnification 100x).

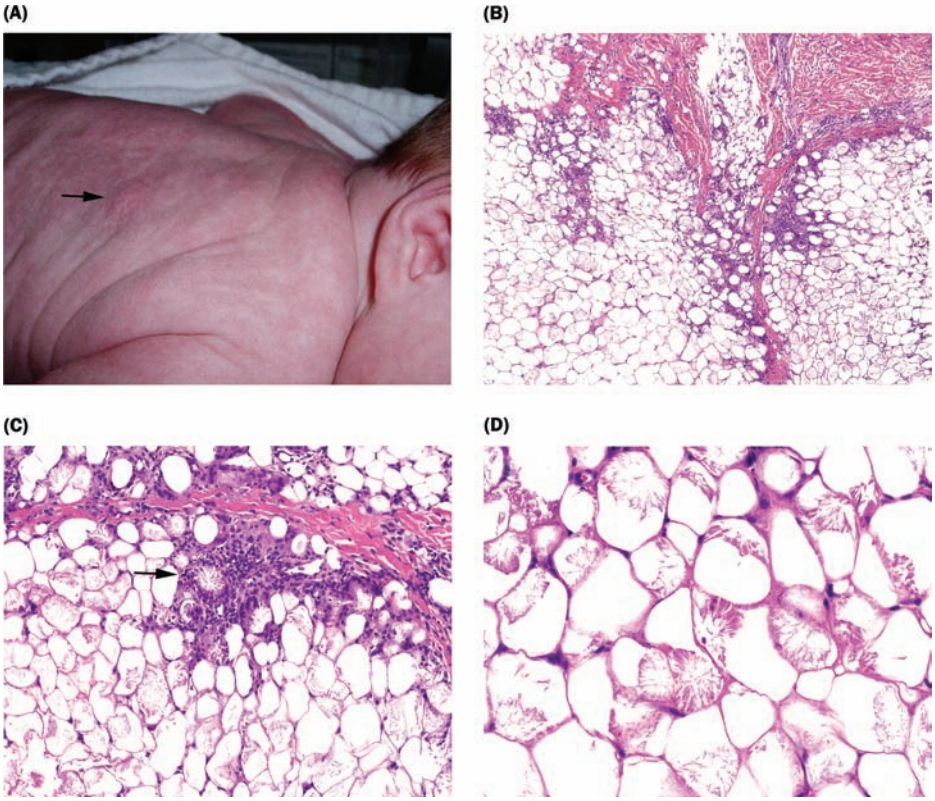

Figure 3 (**A**) Multiple erythematous papules on the back of an infant. (**B**) Lobular mixed inflammation [hematoxylin and eosin (H & E) stain, original magnification 40x]. (**C**) Needle-shaped clefts, radially arranged in giant cells and lipocytes (H & E stain, original magnification 100x). (**D**) High magnification of prominent needle-shaped clefts radially arranged in lipocytes (H & E stain, original magnification 200x).

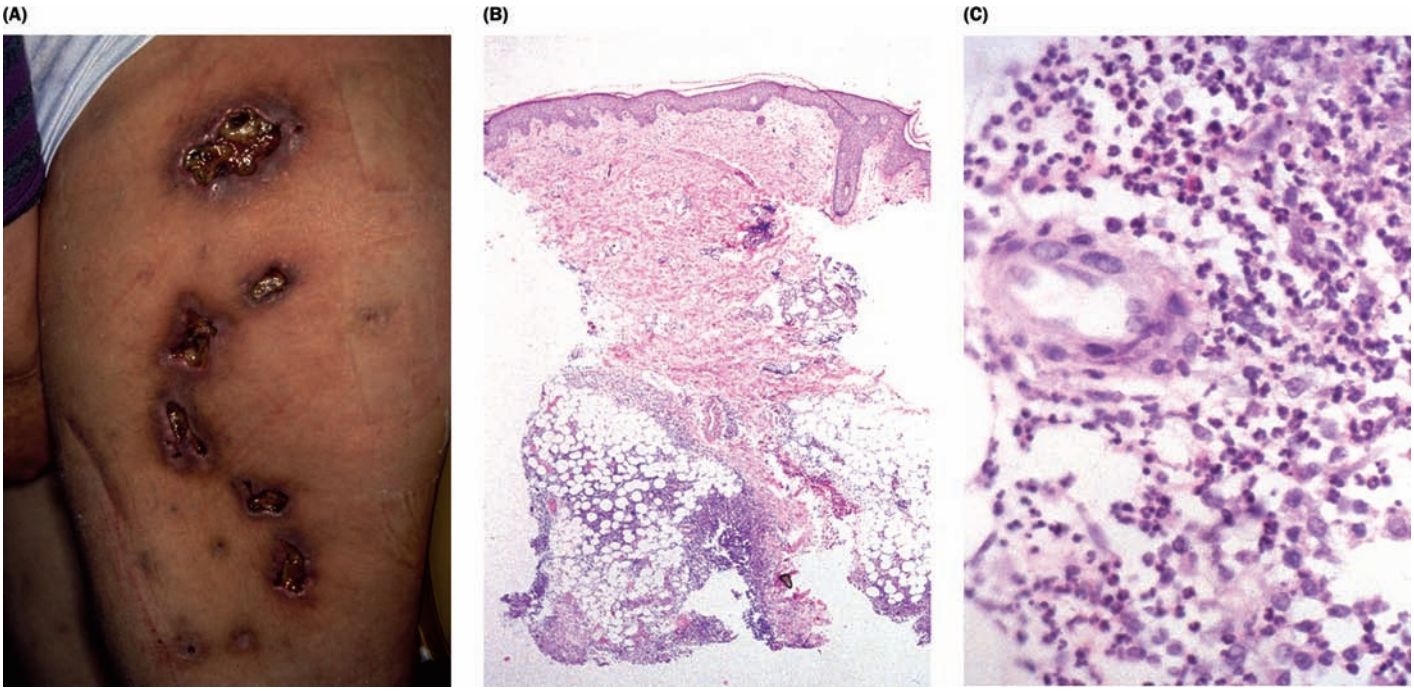

Figure 4 (**A**) Ulcerated plaques with unusual geographic shapes on the anterior thigh. (**B**) Suppurative lobular panniculitis [hematoxylin and eosin (H & E) stain, original magnification 40x]. (**C**) High magnification of intralobular neutrophils (H & E stain, original magnification 200x). *Source*: Lisa Cohen MD, Cohen Dermatopathology, Newton, Massachusetts, U.S.A.

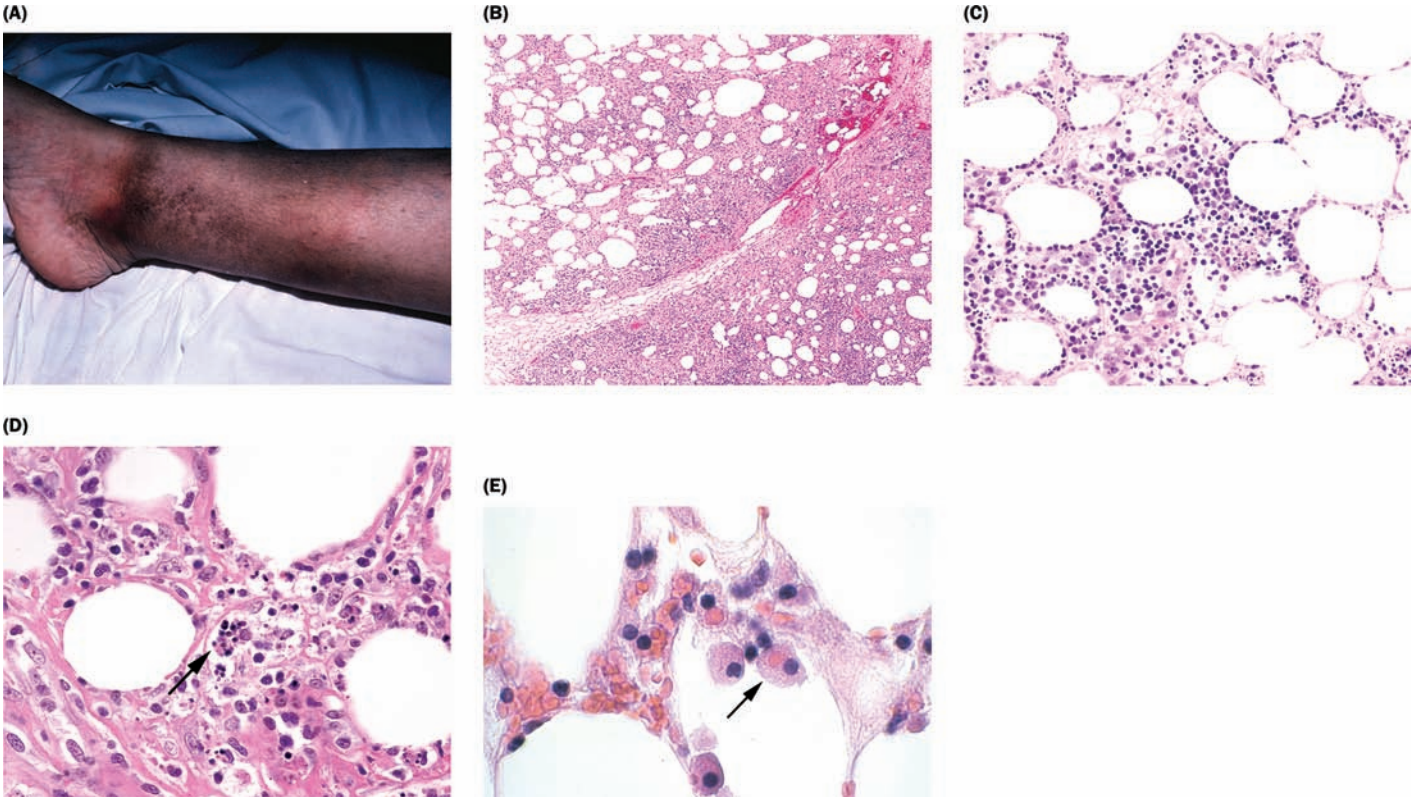

Figure 5 (**A**) Erythematous nodule on medial shin. (**B**) Lobular panniculitis composed of lymphoplasmacytic inflammation [hematoxylin and eosin (H & E) stain, original magnification 40x]. (**C**) Lymphocytes ring around necrotic adipocytes (H & E stain, original magnification 200x). (**D**) "Beanbag cell" with surrounding karyorrhexis (H & E stain, original magnification 400x). (**E**) Erythrophagocytosis (H & E stain, original magnification 400x). *Source*: Lisa Cohen, MD, Cohen Dermatopathology, Newton, Massachusetts, U.S.A.

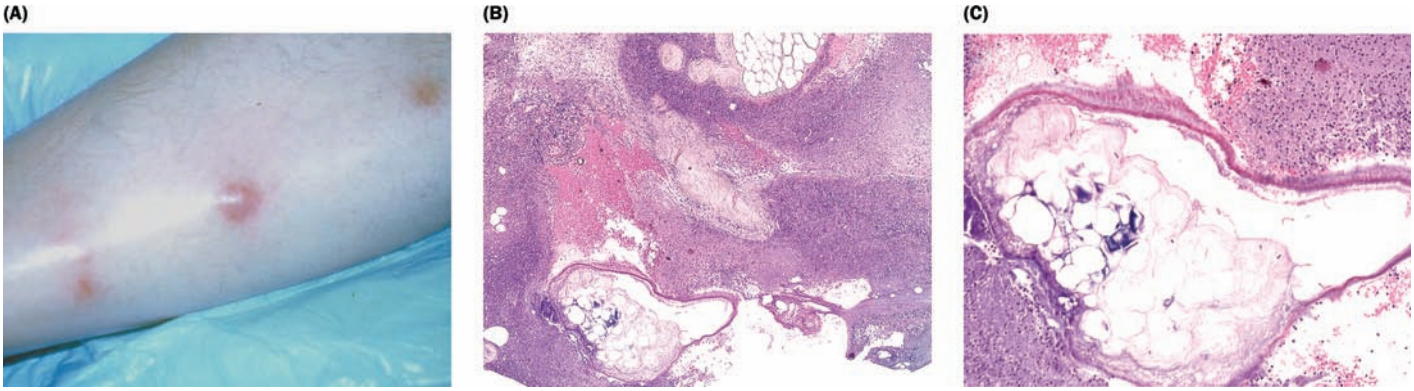

Figure 6 (**A**) Fluctuant erythematous nodules on anterior shins. *Source*: Lynn Goldberg, M.D., Boston University, Boston, Massachusetts, U.S.A. (**B**) Lobular panniculitis with fat necrosis and ghost cells in center of lobule and suppuration at the periphery [hematoxylin and eosin (H & E) stain, original magnification 40x]. (**C**) High magnification of "ghost cells" lined by basophilic granular calcium deposition (H & E stain, original magnification 100x).

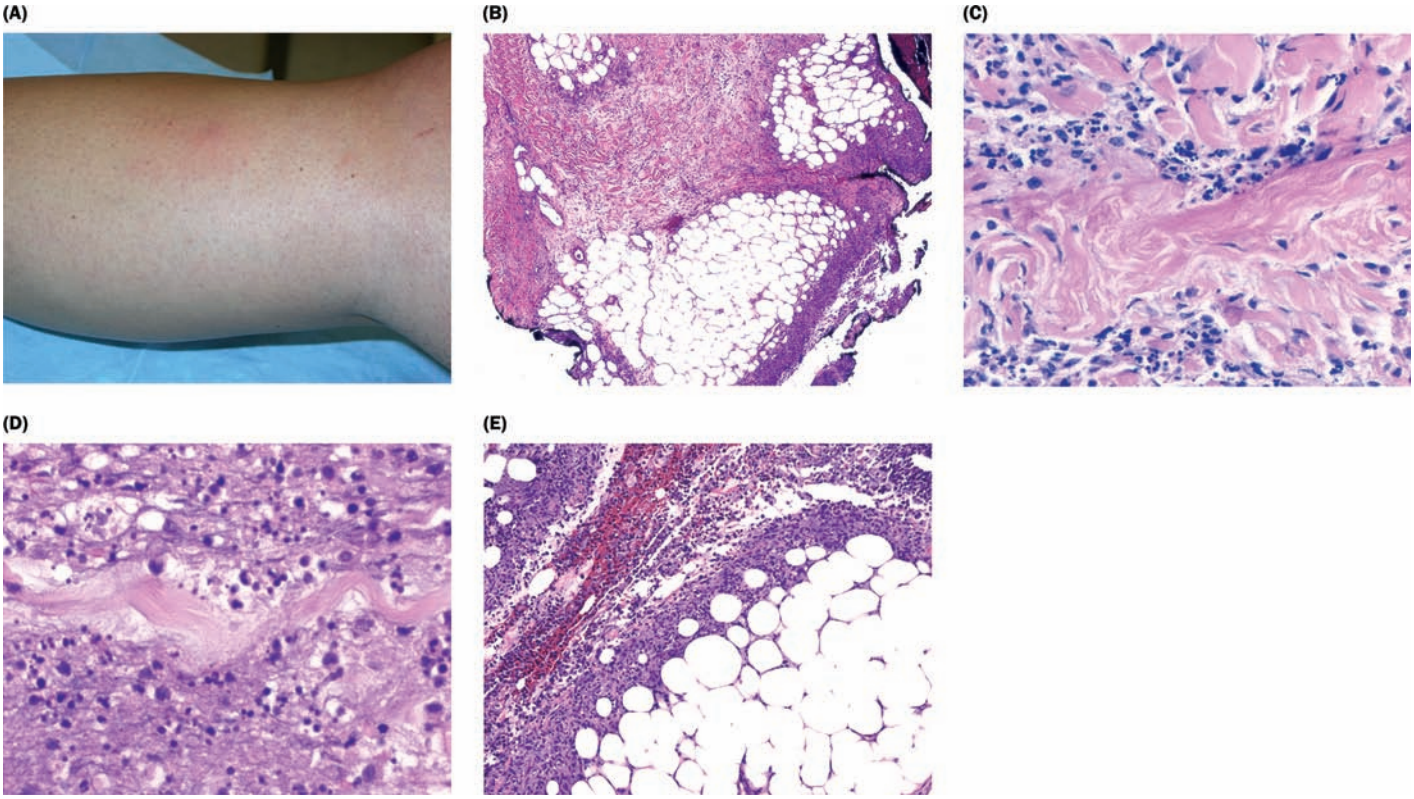

Figure 7 (**A**) Erythematous nodules on medial lower leg. (**B**) Septal neutrophilic inflammation with liquefactive necrosis and collagenolysis [hematoxylin and eosin (H & E) stain, original magnification 40x]. (**C**) "Splaying of neutrophils" between collagen bundles in the reticular dermis (H & E stain, original magnification 200x). (**D**) Dermal collagenolysis (H & E stain, original magnification 200x). (**E**) Numerous neutrophils destroying lobules (H & E stain, original magnification 200x).

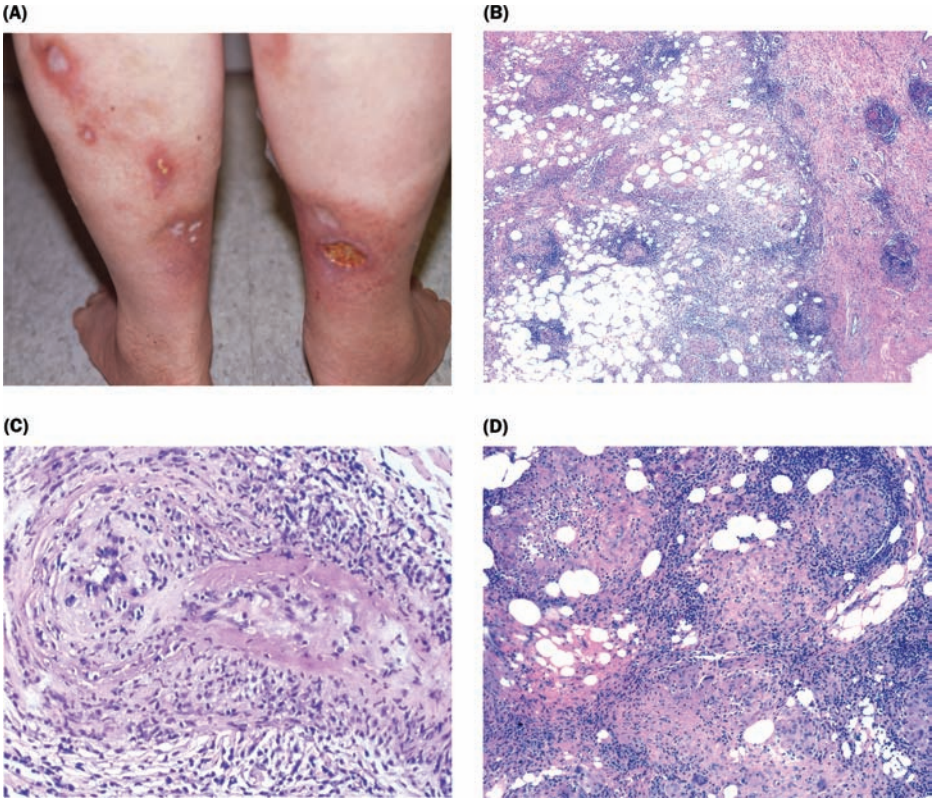

Figure 8 (**A**) Ulcerated nodules on calves. (**B**) Combined lobular and septal panniculitis with vasculitis [hematoxylin and eosin (H & E) stain, original magnification 40x]. (**C**) Vasculitis of medium-sized vessel (H & E stain, original magnification 100x). (**D**) Tuberculoid granulomas (H & E stain, original magnification 100x).

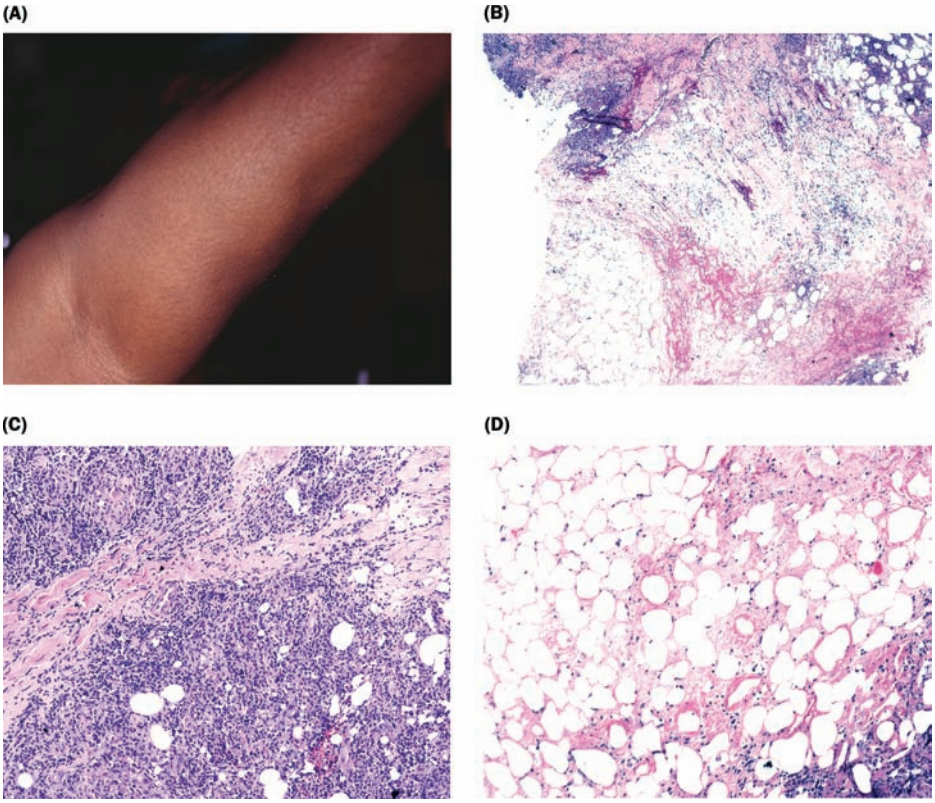

Figure 9 (**A**) Lipoatrophy involving forearm. (**B**) Septal and lobular lymphoplasmacytic inflammation and eosinophilic hyaline fat necrosis [hematoxylin and eosin (H & E) stain, original magnification 40x]. (**C**) High magnification of lobular lymphoplasmacytic inflammation (H & E stain, original magnification 200x). (**D**) Eosinophilic hyaline fat necrosis (H & E stain, original magnification 200x).

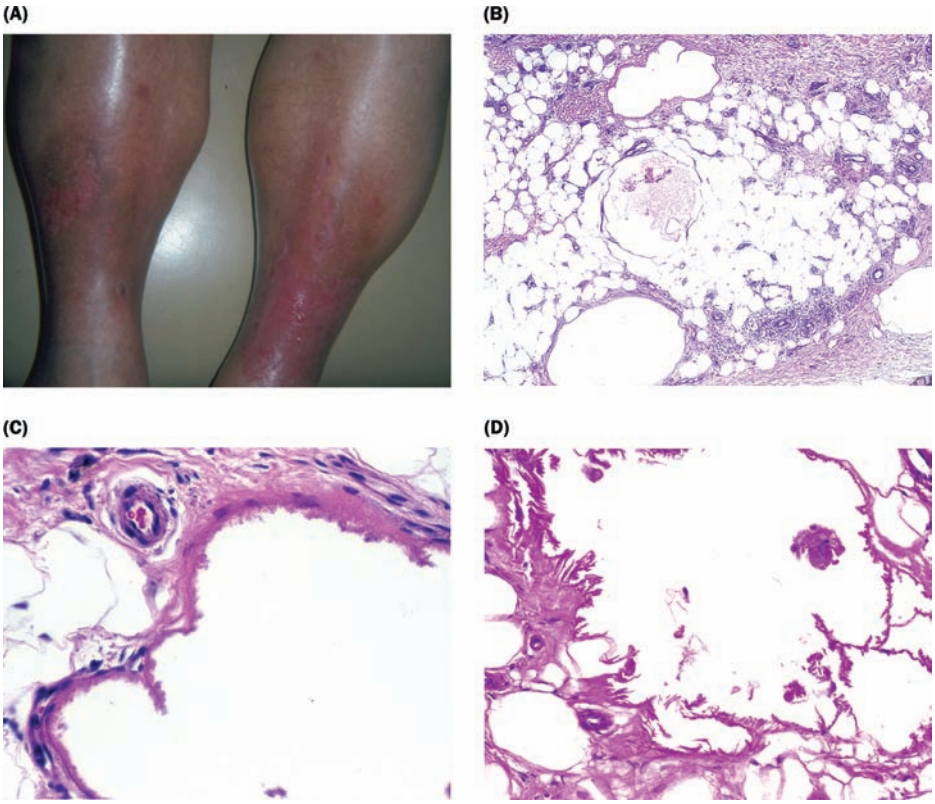

Figure 10 (**A**) Inverted champagne bottle deformity of lower legs. *Source*: Courtesy of Louis Fragola MD, Providence, Rhode Island, U.S.A. (**B**) Septal and lobular fibrosis and atrophy with mixed inflammation [hematoxylin and eosin (H & E) stain, original magnification 40x]. (**C**) Lipomembranous (membranocystic) fat necrosis and fatty microcysts lined by eosinophilic proteinaceous material with fine feathery projections (H & E stain, original magnification 200x). (**D**) Fuscia colored feathery projections highlighted with positive eosinophilic material (PAS) stain (PAS stain, original magnification 200x).

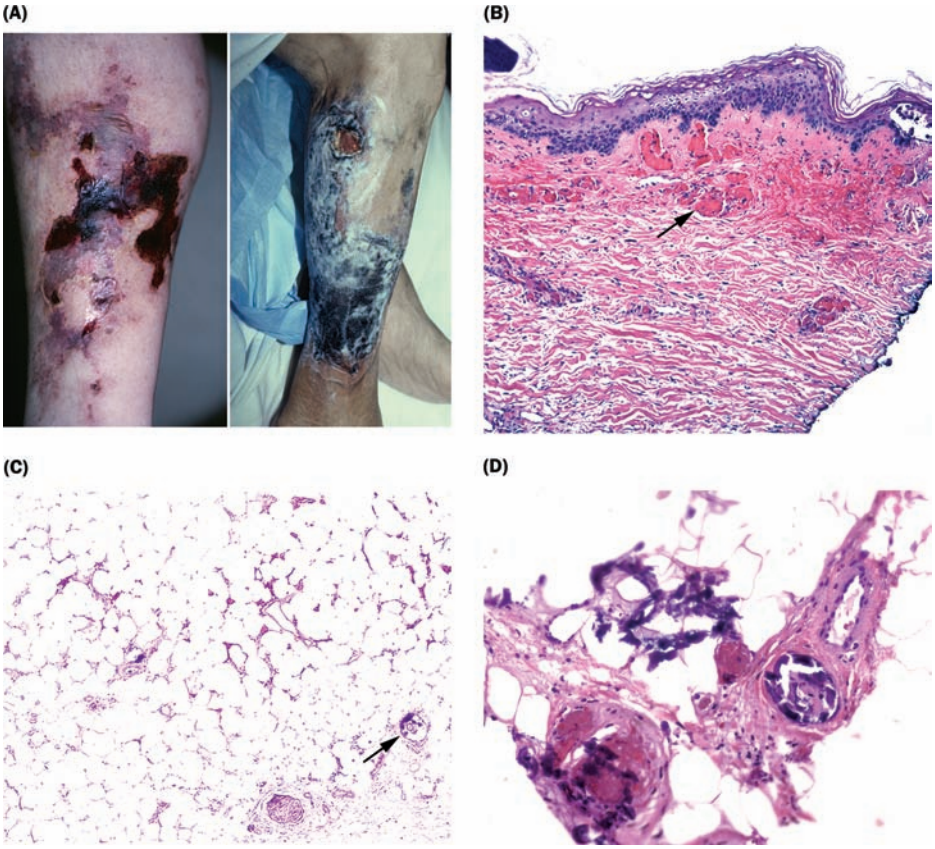

Figure 11 (**A**) Violaceous plaques with livedo reticularis-like pattern, flaccid bullae, and ulcerations. (**B**) Epidermal ischemic necrosis with prominent intradermal intraluminal fibrin thrombi mimicking a thrombogenic vacsulopathy [hematoxylin and eosin (H & E) stain, original magnification 100x]. (**C**) Medial calcification with intimal fibroplasia of small arterioles in the subcutis (H & E stain, original magnification 40x). (**D**) Higher magnification showing intravascular calcification and subcutaneous intraluminal fibrin thrombi (H & E stain, original magnification 200x).

12

Fibrosing Dermatoses

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CONTENTS

This chapter is devoted to those diseases characterized by fibrosis. This process principally affects the dermis, though the epidermis is often affected to a lesser degree. Diseases that are characterized by dermal fibrosis histopathologically exhibit a firm, "fibrous" change to the skin clinically. Some lesions that exhibit dermal fibrosis are elevated above the surrounding skin, such as a hypertrophic scar. Others are depressed below the surrounding skin, such as morphea. Dermal atrophy is also observed as a depression in the contour of the skin, though the texture would not be fibrotic on palpation. Epidermal atrophy is observed histopathologically as epidermal thinning and loss of the rete ridges; clinically, it is observed as a subjective "thin" feeling of the superficial skin on palpation and is often associated with a smooth, wrinkled surface. Induration is a clinical term used to describe the firm, "thickened" texture of skin due to subacute to chronic inflammation.

Conditions characterized by fibrotic changes that are covered in other chapters include scleroderma/morphea and lichen sclerosus et atrophicus.

Definition of Terms:

- *Sclerosis*: Hardening or thickening of a body part, organ, or its constituents, especially by the formation of excessive interstitial fibrous tissue with or without chronic inflammation
- "*Hyalinized" collagen*: Collagen that is altered (usually by inflammatory mediators) such that it appears glassy or translucent as observed under light microscopy using standard hematoxylin and eosin staining
- *Fibrosis*: Formation of excess collagenous fibrous tissue
- *Induration*: Firm, thickened texture of tissue due to inflammation

DISEASES CHARACTERIZED BY DERMAL FIBROSIS

SCAR

Synonym: Cicatrix.

Clinical Presentation:

- Occurs days to months after injury
- Initially erythematous and slightly raised; typically becomes hypopigmented with time
- Within one to two years, becomes flat or slightly depressed compared to surrounding skin (Fig. 1)
- Remains within boundary of original injury

Histopathology:

Early:

- Epidermis often acanthotic; +/− cleavage at dermal-epidermal junction (since the epidermis has yet to fully attach to the dermis).
- Granulation tissue-like changes: polymorphous dermal infiltrate of lymphocytes, histiocytes, neutrophils, and eosinophils in association with plump fibroblasts, deposition of ground substance, increased vascularization and mild edema.

Later:

- Epidermis is often atrophic (thinned, with loss of rete ridges) (Fig. 2)
- Thickened collagen bundles that are mostly oriented parallel to the epidermis (Fig. 2)
- Dilated blood vessels orientated perpendicular to the epidermis
- Inflammation resolves gradually

Histopathologic Differential Diagnosis:

Early Scar	Late Scar
Epidermal thickening	Epidermal thinning
Dermis resembles granulation tissue	Dermis shows thickened collagen bundles parallel to the epidermis and dilated vessels perpendicular to the epidermis

HYPERTROPHIC SCAR

Clinical Presentation:

- Occurs days to months after injury
- Initially erythematous and slightly raised; with time becomes moderately to significantly raised and nodular and paler pink in color (Fig. 3)
- Often flattens and becomes hypopigmented spontaneously within one to two years
- Remains within boundary of the original injury
- More prevalent in areas of chronic skin stretching

Histopathology:

Early:

- Same as with ordinary scar

Later:

- Same as with ordinary scar except that the mid- and deep-dermis is now filled with thickened collagen bundles in rounded whorls and nodules (Fig. 4)

Clinicopathologic Correlation:

Clinical Feature	Pathologic Feature
Thin, smooth epidermal texture	Epidermal atrophy
Early erythema → paler pink → late hypopigmentation	Inflammation and dilated vessels initially → slowly resolves → postinflammatory hypopigmentation
Firm, fibrotic, and indurated dermis	Increased and thickened collagen bundles; inflammation

KELOID

Clinical Presentation:

- Most occur within a year after injury
- Painful or pruritic nodular scar that grows beyond the area of the original injury (Fig. 5)
- Most common sites include earlobe, upper arm, shoulder, upper back, and anterior chest
- Does not regress with time
- Recurrence rate ~50% to 80% at site after attempt to remove by surgical excision
- More common in African-Americans and Asians
- Familial predilection
- Rubinstein-Taybi syndrome associated with spontaneous keloids in early adulthood: mental retardation, beaked nose, microcephaly, broad terminal phalanges of toes and thumbs

Histopathology:

- Relatively normal overlying epidermis and superficial dermis with subjacent whorls and nodules of thickened and "keloidal" collagen bundles in the mid- and deep-dermis (Fig. 6)
- The keloidal collagen is characteristic and shows the following features
  - Markedly eosinophilic
  - Thickened
  - Haphazardly arranged and hyalinized
  - Present in an acellular or mucinous ground substance (Fig. 6)
- Infiltrative advancing edge as keloid extends laterally
- Fascia-like fibrous bands of collagen in deepest portion
- Absence of vertically orientated blood vessels

Histopathologic Differential Diagnosis:

Hypertrophic Scar	Keloid
Epidermal atrophy	Relatively normal epidermis
Fibrosis of the papillary dermis	Minimal fibrosis of the papillary dermis
No or very little keloidal collagen	Prominent keloidal collagen
Disarray of fibrocollagenous fascicles/nodules	Significant disarray of fibrocollagenous fascicles/nodules
Vertically orientated blood vessels	Absence of vertically orientated blood vessels
Absence of infiltrative advancing edge	Presence of infiltrative advancing edge

Clinicopathologic Correlation:

Clinical Feature	Pathologic Feature
Nodule that grows beyond the boundary of the original injury and does not regress with time	Whorls and nodules of thick, hyalinized collagen bundles and keloidal collagen with an infiltrative advancing lateral edge

Reference:

1. Lee JY, et al. Histopathological differential diagnosis of keloid and hypertrophic scar. Am J Dermatopathol 2004; 26:379.

EOSINOPHILIC FASCIITIS

Synonyms: Eosinophilic fasciitis of Shulman; Shulman syndrome.

Clinical Presentation:

- Rapid onset of painful inflammation and progressive induration and fibrosis of the skin and subcutaneous tissues of the extremities (Fig. 7)
- Usually spares the fingers; rarely affects the trunk or viscera
- Often produces deep grooving around superficial veins
- Accompanied by peripheral eosinophilia and hypergammaglobulinemia
- Onset may follow physical exertion
- Most experience complete or near-complete remission after two to four years usually with treatment but rarely spontaneously

Histopathology:

Early:

- Edema and an infiltrate composed of lymphocytes, eosinophils, histiocytes, and plasma cells affect the fibrous septa separating the subcutaneous fat lobules and extends into the fascia (Fig. 8A)

Later:
- The inflammatory infiltrate is now accompanied by marked thickening of the interlobular septa and fascia with fibrosis and hyalinization of the collagen (Fig. 8B)
- Often also affects the deep dermis resulting adnexal atrophy
- +/− Involvement of the underlying muscle

Differential Diagnosis:
- Scleroderma may show many of the same deep dermal and subcutaneous fibrous/collagenous changes, though almost never with the same degree of inflammation or number of eosinophils seen in eosinophilic fasciitis

Pathophysiology:
- Regarded by many as a variant of scleroderma; progression to scleroderma has been reported; morphea-like lesions are sometimes present on the trunk
- Reported associations include *Borrelia burgdorferi* infection, trichloroethylene exposure, radiation exposure, phytonadione injections, and L-tryptophan supplementation

References:

1. Hayashi N, et al. Eosinophilic fasciitis following exposure to trichloroethylene: successful treatment with cyclosporine. Br J Dermatol 2000; 142:830.
2. Desruelles F, et al. Radiation myo-fasciitis. Acta Derm Venereol 2000; 80:310.
3. Janin-Mercier A, et al. Cutaneous sclerosis with fasciitis and eosinophilia after phytonadione injections. Arch Dermatol 1985; 121:1421.

SCLERODERMOID GRAFT-VS.-HOST DISEASE

Clinical Presentation:
- GVHD is a syndrome occurring in patients receiving allogeneic immunocompetent lymphocytes, usually bone marrow transplantation
- GVHD is typically divided into acute and chronic types, and the chronic type is further divided into an early lichen planus-like stage and a later sclerodermoid stage; poikilodermatous changes may also occur in the chronic form of GVHD
- Most cases of chronic GVHD are preceded by clinically apparent acute GVHD
- Sclerodermoid changes may be localized or generalized and are characterized by discrete and confluent, poorly demarcated, indurated, depressed plaques; resembles scleroderma/morphea and/or lichen sclerosis (Fig. 9)
- Predilection for trunk and proximal extremities
- May involve entire dermis, subcutis, and fascia resulting in joint contractures
- UV irradiation, physical trauma, and herpes zoster may precipitate

Histopathology:
Common Findings:
- Atrophic epidermis
- Vacuolar alteration of the epidermis with necrotic keratinocytes
- Follicular plugging and/or milia
- Basilar epidermal hyperpigmentation and melanophages in the superficial dermis
- Greatly thickened dermis extending into the subcutaneous tissue
- Thickened and hyalinized collagen bundles (Fig. 10)
- Loss of adnexal structures (Fig. 10)
- Coexistence of lichen planus-like and sclerodermoid patterns

Less Common Findings:
- Septal panniculitis
- Fasciitis
- Mucin deposits

Differential Diagnosis:
- The diagnosis of sclerodermoid GVHD is usually differentiated from scleroderma based on clinical information. Scleroderma usually shows less epidermal change and a greater degree of deep dermal collagen proliferation and alteration

Clinicopathologic Correlation:

Clinical Feature	Pathologic Feature
Indurated and fibrotic texture of the dermis	Thickened collagen bundles and inflammation

References:

1. Penas PF, et al. Sclerodermatous graft-versus-host disease: clinical and pathological study of 17 patients. Arch Dermatol 2002; 138:924.
2. Aractingi S, Chosidow O. Cutaneous graft-versus-host disease. Arch Dermatol 1998; 134:602.
3. Fimiani M, De Aloe G, Cuccia A. Chronic graft versus host disease and skin. J Eur Acad Dermatol & Venereol 2003; 17:512.

RADIATION DERMATITIS

Clinical Presentation:
- Due to cutaneous injury that develops months to years after exposure to ionizing radiation during a diagnostic or interventional radiologic procedure
- Indurated and fibrotic dermal plaque with overlying poikiloderma (Fig. 11)
- Increases the frequency of nonmelanoma skin cancer and precursor lesions

Histopathology:
- Variable epidermal atrophy
- Atypical spindle-shaped and stellate dermal fibroblasts (radiation fibroblasts) (Fig. 12, left)
- Hyalinization and fibrosis of the dermal collagen (Fig. 12, right)
- Loss of adnexal structures
- Vascular dilatation and intimal proliferation
- Pigmentary alteration, both in the form of increased or decreased pigment in the basal layer of the epidermis, and increased melanophages in the upper dermis

Clinicopathologic Correlation:

Clinical Feature	Pathologic Feature
Skin texture: smooth, thinned, and wrinkled epidermis with dermal fibrosis	Epidermal atrophy overlying hyalinized and fibrotic dermal collagen
Skin color: pigmentary alteration	Increased or decreased pigment in the basilar epidermis and increased melanophages in the upper dermis

Pathophysiology:

Radiotherapy disrupts normal maturation and reproduction of the epidermis, cutaneous adnexae, dermal fibroblasts, and cutaneous vasculature.

References:

1. Moretto JC, Soslow RA, Smoller BR. Atypical cells in radiation dermatitis express factor XIIIa. Am J Dermatopathol 1998; 20(4):370.
2. Hymes SR, Strom EA, Fife C. Radiation dermatitis: clinical presentation, pathophysiology, and treatment 2006. J Am Acad Dermatol 2006; 54(1):28.

NEPHROGENIC FIBROSING DERMOPATHY

Clinical Presentation:

- Acute onset with thickening and hardening of the skin in patients with renal failure
- Well-defined erythematous fibrotic or indurated papules and/or plaques with irregular edges and hyperpigmented border (cobblestone appearance) (Fig. 13)
- Predilection for extremities, back and buttocks
- Often painful and pruritic

Histopathology:

- Proliferation of elongated spindle cells associated with interstitial mucin and collagen bundles of varying thickness (Fig. 14A)
- The spindle cell proliferation involves the papillary and reticular dermis and may extend into and widen the septa of subcutaneous fat lobules
- Clefts surround the thickened collagen bundles
- The spindle cells are positive for CD-34 (Fig. 14B)
- There are also factor XIIIa and CD-68 positive mono- and multi-nucleated cells
- Elastic fibers are increased, thickened, and parallel to the collagen bundles
- +/− Dystrophic dermal calcification

Differential Diagnosis:

- Dermatofibroma, dermatofibrosarcoma protuberans, scar, sarcoma, eosinophilic fasciitis, eosinophilia-myalgia syndrome, and especially, scleromyxedema and scleroderma (Table 1)

Clinicopathologic Correlation:

Clinical Feature	Pathologic Feature
Firm, well-defined papules and plaques	Thickened collagen bundles and mucin in the papillary and reticular dermis with extension into the subcutis

References:

1. Cowper SE, et al. Nephrogenic fibrosing dermopathy. Am J Dermapathol 2001; 23(5):383.
2. Cowper SE, Bucala R. Nephrogenic fibrosing dermopathy: suspect identified, motive unclear. Am J Dermatopathol 2003; 25(4):358.

Table 1 Histopathologic Differential Diagnosis: Nephrogenic Fibrosing Dermopathy

Nephrogenic Fibrosing Dermopathy	Scleroderma	Scleromyxedema
Collagen bundles of various thickness	Thickened collagen bundles	Thickened collagen bundles that are haphazardly arranged
CD-34 positive dermal dendrocytes increased	CD-34 positive dermal dendrocytes normal or decreased	CD-34 positive dermal dendrocytes increased
Sparse or absent inflammation	Superficial and deep, perivascular and interstitial lymphohistiocytic infiltrate, sometimes containing plasma cells and eosinophils	Lymphocytes and sometimes plasma cells
Interstitial dermal mucin in small amounts	Interstitial dermal mucin is increased (early)	Interstitial dermal mucin is significantly increased
Multinucleated cells present	Multinucleated cells not present	Multinucleated cells not present
No loss of adnexal structures	Loss of adnexal structures	No loss of adnexal structures
Elastic fibers are increased	Elastic fibers may be reduced	Elastic fibers are fragmented
Widening of the septa of the subcutaneous fat	Widening of the septa of the subcutaneous fat	No widening of the septa
Clefts surround the thickened collagen bundles (early)	No clefts surround the collagen bundles	No clefts surround the collagen bundles

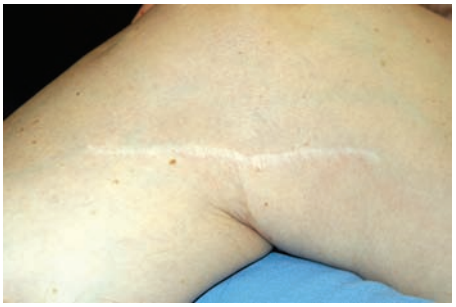

Figure 1 Scar. Mature scar is flat and hypopigmented.

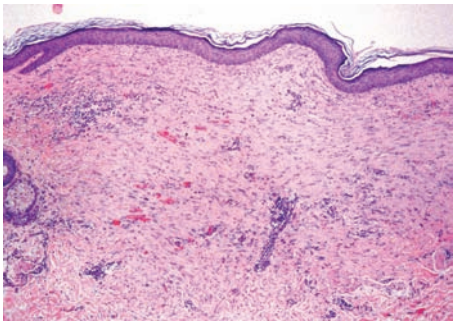

Figure 2 Scar. Thinned epidermis with flattened rete ridges, thickened collagen bundles parallel to the epidermis and vessels perpendicular to the epidermis, and lymphohistiocytic inflammation.

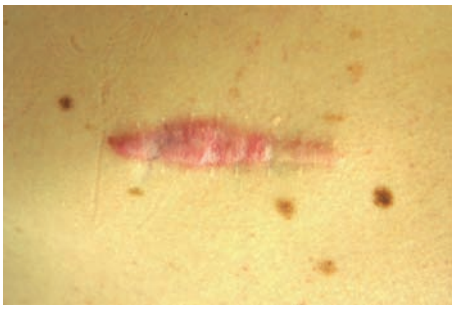

Figure 3 Hypertrophic scar. Raised with a smooth, shiny surface. The scar remains within boundaries of suture marks.

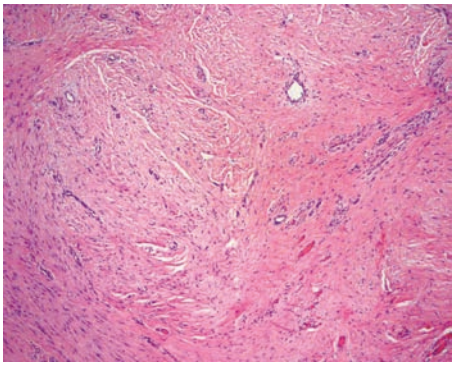

Figure 4 Hypertrophic scar. Thickened collagen bundles in rounded whorls and nodules. Note the increased vascularity and mild inflammatory cell infiltrate.

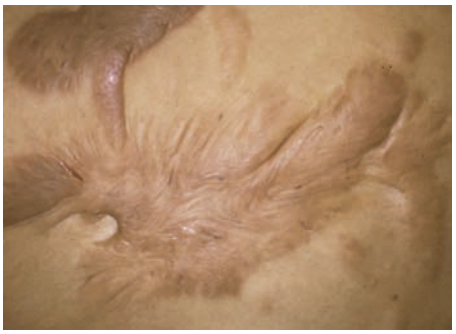

Figure 5 Keloid. Nodular scar that extends beyond the area of injury. *Source*: Courtesy of Yale University, Department of Dermatology, residency slide collection.

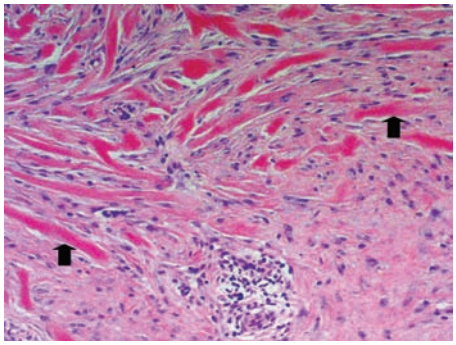

Figure 6 Keloid. Characteristic "keloidal" collagen bundles (*arrows*) that are thickened, brightly eosinophilic, and hypocellular.

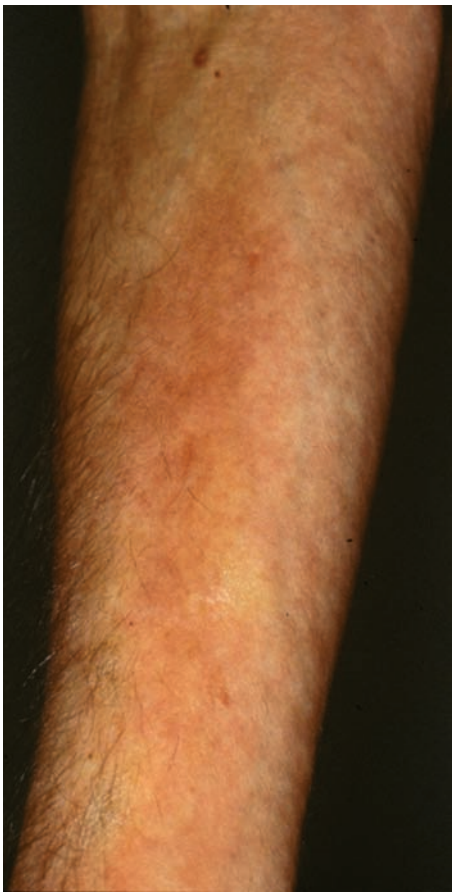

Figure 7 Eosinophilic fasciitis. There is linear induration and fibrosis of the deep dermis and subcutaneous tissue. *Source*: Courtesy of Yale University, Department of Dermatology, residency slide collection.

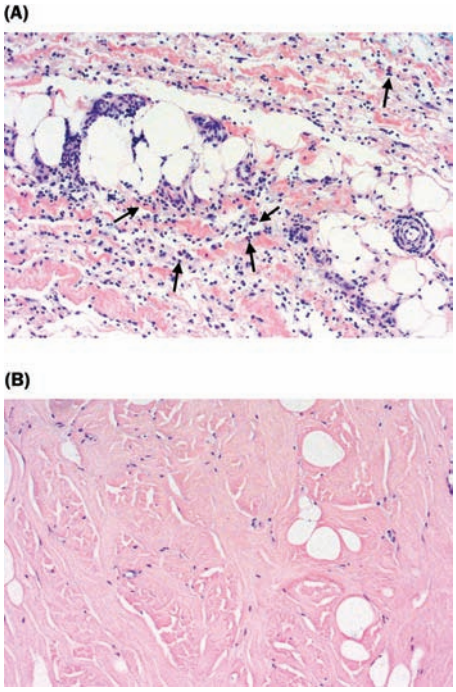

Figure 8 Eosinophilic fasciitis. (**A**) A mixed inflammatory cell infiltrate containing numerous eosinophils (*arrows*) affecting the deep dermis and subcutaneous fat. (**B**) End-stage fibrosis and hyalinized collagen bundles.

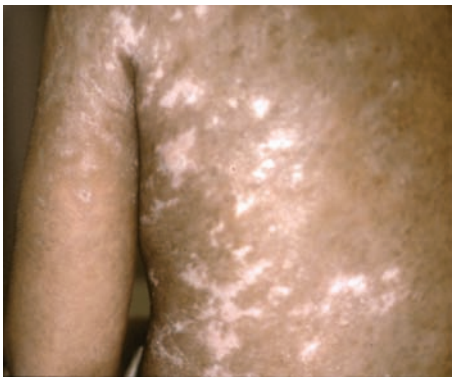

Figure 9 Chronic graft-versus-host disease. There are discrete and coalescent, hypopigmented and pink, scaling papules and plaques. *Source*: Courtesy of Yale University, Department of Dermatology, residency slide collection.

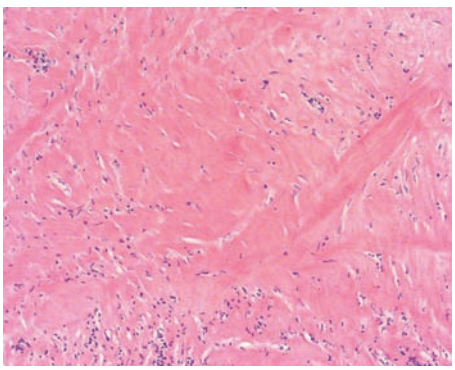

Figure 10 Sclerodermoid graft-versus-host disease. Thickened and hyalinized collagen bundles, loss of adnexal structures and inflammatory cell infiltrate.

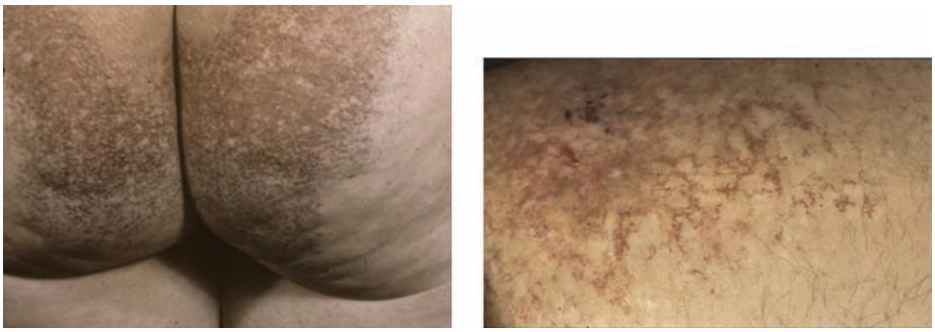

Figure 11 Radiation dermatitis. High and low power views of previously radiated areas demonstrating poikilodermatous changes, including hyperpigmentation and hypopigmentation, atrophy, and telangiectasia. *Source*: Courtesy of Yale University, Department of Dermatology, residency slide collection.

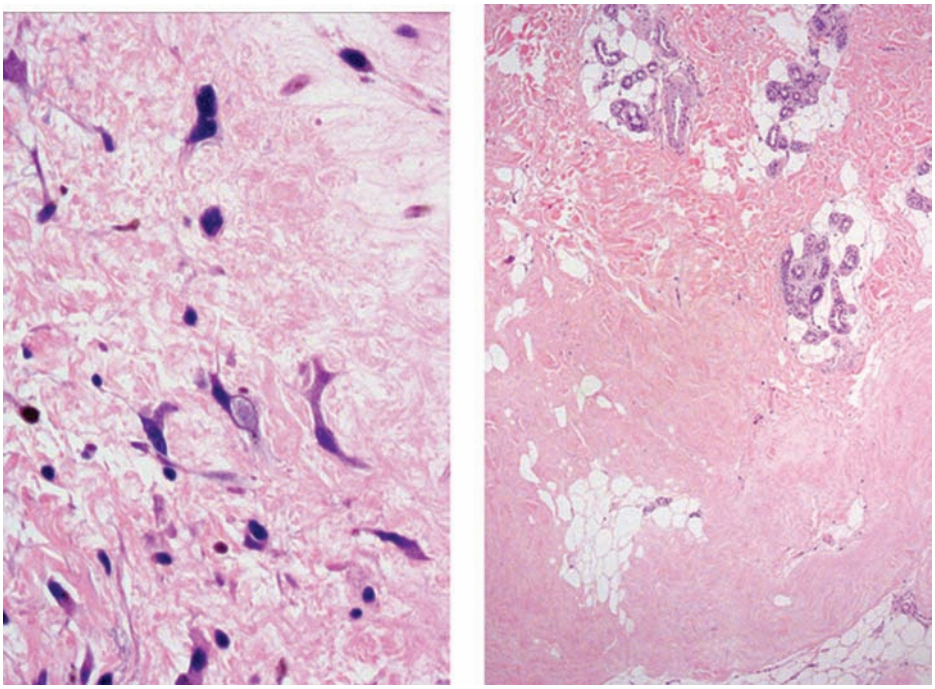

Figure 12 Radiation dermatitis. High-powered view (*left*) shows several atypical spindle-shaped and stellate dermal dendrocytes (radiation fibroblasts). Low-powered view (*right*) demonstrates hyalinized collagen and fibrosis of the deep dermis, extending into and replacing subcutaneous fat.

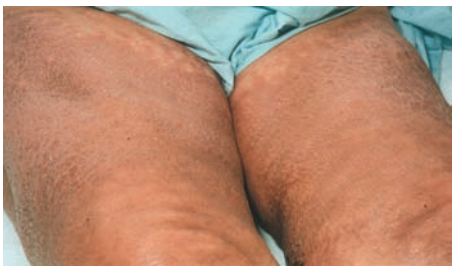

Figure 13 Nephrogenic fibrosing dermopathy. Indurated, brawny scaling plaques irregular border and cobblestoning. *Source*: Courtesy of Philip LeBoit, MD.

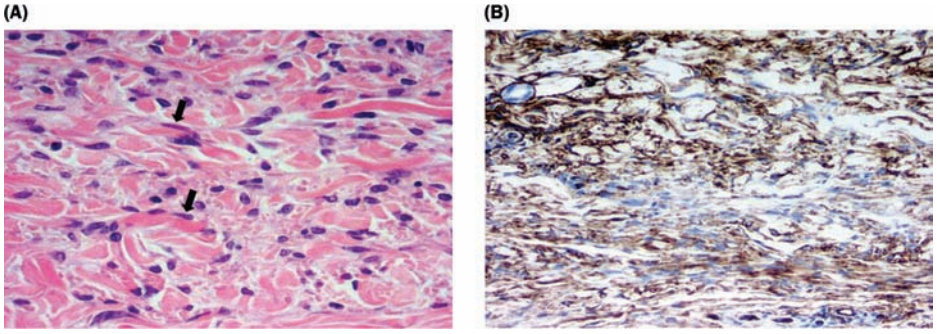

Figure 14 Nephrogenic fibrosing dermopathy. (**A**) Reticular dermal collagen bundles are thickened and separated from one another by prominent clefts and interposed thin collagen bundles. Spindled cells with hyperchromatic nuclei (*arrows*) are closely apposed to collagen bundles. (**B**) The CD-34 positive population consisted of elongated spindle cells that formed a dense interconnecting dermal network, entwining elastic fibers and collagen bands.

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Benign Epithelial Neoplasms and Cysts

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BENIGN EPITHELIAL NEOPLASMS

There are numerous benign neoplasms of the epidermis and these have many basic histologic features in common. They are usually well circumscribed and symmetric. Most often they demonstrate a proliferation of fairly uniform keratinocytes with varying degrees of squamous differentiation. Inflammation often leads to dyskeratotic changes along with mild to moderate nuclear atypia. Architecturally, they are usually more exophytic (protrude above the plane of the epidermis) than endophytic (extend into the dermis). They demonstrate both epidermal hyperplasia, as manifested by papillomatosis or elongation of the rete ridges, and acanthosis or thickening of the stratum spinosum. Normal mitotic figures may be seen in rapidly proliferating lesions.

SEBORRHEIC KERATOSIS, CLASSIC TYPE

Clinical Presentation:

- Extremely common, begin appearing mid-life
- Most often multiple (Fig. 1A)
- Trunk, scalp, face, may occur at any site
- Usually 0.5 to 3.0 cm in diameter
- Superficial or "stuck on" appearance
- Hyperkeratotic or verrucous (velvety) surface
- Light brown, dark brown, or black
- May be red (inflamed), crusted, or impetiginized

Histology:

- Exophytic, well circumscribed, symmetric (Fig. 1B)
- Variations of papillated epidermal hyperplasia (papillomatosis) and thickening of the spinous layer (acanthosis)
- Interconnecting and bridging of the elongated rete ridges
- Numerous pseudohorn cysts created by cross-sectioning the keratin filled crypts between proliferations (Fig. 1C)
- Composed predominantly of small, uniform basaloid keratinocytes with a 1:1 to 1:0.5 nuclear to cytoplasmic ratio (Fig. 1D)
- Basalar keratinocytes are often hyperpigmented
- Melanocytes are normal or slightly increased in number

Clinicopathologic Correlation:

Clinical Feature	Pathologic Feature
"Stuck on" papule	Exophytic
Symmetric with easily defined border	Papillomatosis and acanthosis are symmetric with a sharp margin
Rough or velvety surface	Papillations with overlying thickened stratum corneum
Tan to brown to black	Hyperpigmentation of basalar keratinocytes, seen throughout epidermis in darker lesions
Keratin filled plugs	Pseudohorn cysts

Differential Diagnosis:

Seborrheic Keratosis	Verruca Vulgaris
Broad—more horizontal	High—more vertical
Papillomatosis (gentle)	Digitated (spiking)
Normal granular layer	Prominent granular layer
No koilocytes	Vacuolated koilocytes in superficial layers of epidermis
Basket-weave hyperkeratosis with scattered parakeratosis	Columns of parakeratosis above tips of digitations
No serum in horn	Serum often seen above digitations
Slightly dilated blood vessels in dermal papillae	Markedly dilated and tortuous blood vessels in dermal papillae

Pathophysiology:

- Suspect autosomal dominant transmission
- Preliminary evidence to support a monoclonal or neoplastic origin versus polyclonal or hyperplastic
- May be derived from keratinocytes of the infundibulum of the hair follicle

References:

1. Nakamura H, Hirota S, Adachi S, et al. Clonal nature of seborrheic keratosis demonstrated by using the polymorphism of the human androgen receptor locus as a marker. J Invest Dermatol 2001; 116:506.
2. Kossard S, Berman A, Winkelmann R. Seborrheic keratosis and trichostasis spinosa. J Cutan Pathol 1979; 6:492.

SEBORRHEIC KERATOSIS, COMMON HISTOLOGIC VARIANTS

Variants:

- Early, developing from a solar lentigo, pigmented, inflamed or irritated, hyperkeratotic, pedunculated, acanthotic, reticulated, clonal, melanoacanthoma.

Clinical Presentation:

- Many histologic variants cannot be clinically distinguished
- Early; small, macular to slightly papular, tan
- Derived from solar lentigo; light tan macule with raised border, progresses to a reticulated seborrheic keratosis (Fig. 2A)
- Pigmented; dark brown to black (Fig. 2C)
- Inflammed or irritated; pruritic or painful, erythematous base or border, surface maybe crusted (Fig. 3A)
- Hyperkeratotic; thick horn on surface
- Clonal; may occur as large, slightly raised plaque on legs, termed "intraepidermal epitheliomas"
- Melanoacanthoma; rare, small, darkly pigmented, may occur on mucous membranes

Histology:

- Early; less papillated and acanthotic, keratinocytes often less basaloid, no or few pseudohorn cysts
- Derived from solar lentigo; thin epidermis laterally with bulbous rete ridges, often hyperpigmented, gradual acanthosis, proliferation of small basaloid cells in strands, development of pseudohorn cysts (Fig. 2B)
- Pigmented; abundant melanin in keratinocytes throughout the epidermis. No significant increase in melanocytes (Fig. 2D)
- Inflamed or irritated
  - Perivascular or lichenoid, predominantly lymphocytic inflammatory infiltrate in the dermis (Fig. 3B)
  - Gradual change from basaloid to more squamous differentiation (Fig. 3C)
  - Squamous eddies (whorls) often appear
  - Individual keratinocytes may have mild to moderate nuclear atypia (Fig. 3D)
- Reticulated; thin, anastomosing strands of small, uniform basaloid cells extend into the dermis (Fig. 4A).
- Clonal; intraepidermal nests or localized collections of very uniform basaloid or large squamous cells separated by ordinary basaloid cells (Fig. 4B).
- Melanoacanthoma
  - Acanthotic proliferation of basaloid keratinocytes (Fig. 4C)
  - Dendritic melanocytes sprinkled at all levels of the epidermis (Fig. 4D)
  - Melanin prominent in cytoplasms of melanocytes, not in keratinocytes

Clinicopathologic Correlation:

Clinical Feature	Pathologic Feature
Solar lentigo: macular tan border	Hyperpigmented bulbous rete ridges
Pigmented: dark brown or black	Abundant melanin in keratinocytes throughout the epidermis
Hypertrophic: thick horn	Massive compact orthokeratosis
Pedunculated: polypoid protrusion	Exophytic polypoid architecture
Melanoacanthoma: black	Heavily pigmented melanocytes with dendrites at all levels of the epidermis

Differential Diagnosis:

Inflammed Seborrheic Keratosis	Papillated Squamous Cell Carcinoma In Situ (Figs. 5A and B)
Well circumscribed and symmetric	Usually well circumscribed
Variable papillomatosis and acanthosis	Variable papillomatosis and acanthosis
Focal parakeratosis	Confluent parakeratosis
Squamous differentiation and dyskeratosis, more prominent superficially	Dyskeratosis throughout the epidermis
Mild to moderate keratinocytic atypia, more prominent in association with inflammatory cells	Moderate to severe atypia of keratinocytes throughout the epidermis

(Continued)

Differential Diagnosis: ***Continued***

Pigmented Seborrheic Keratosis	Verrucous Malignant Melanoma (Figs. 5C and D)
Well circumscribed and symmetric	Poorly circumscribed and asymmetric
Mild papillomatosis and acanthosis	Verrucous epidermal hyperplasia
Basaloid keratinocytes, may have mild nuclear atypia	Atypical melanocytes, both singly and nested in the epidermis
Intraepidermal	Usually extends into the dermis at time of biopsy
Heavily pigmented keratinocytes, no increase in melanocytes	Dusty pigment in cytoplasms of melanocytes
Rare mitotic figures	Mitotic figures common, some atypical

Pathophysiology:
- Melanoacanthoma; the transfer of melanin from the dendritic melanocytes is partially or completely blocked in this lesion.

Reference:
1. Schlappner O, Rowden G, Phillips T, et al. Melanoacanthoma: ultrastructural and immunological studies. J Cutan Pathol 1978; 5:127.

DERMATOSIS PAPULOSA NIGRA

Clinical Presentation:
- Most common on face, neck, and upper trunk on darker skin
- Small, smooth surfaced, "stuck on," pedunculated (Fig. 6A)
- Dark brown to black

Histology:
- Similar to small seborrheic keratoses
- Acanthotic or reticulated pattern (Fig. 6B)
- Rare pseudohorn cysts

STUCCO KERATOSIS

Clinical Presentation:
- Elderly patients
- Symmetric distribution on lower legs
- Small, 1 to 4 mm, hyperkeratotic papules with adherent horn (Fig. 6C)
- Light tan, uniform in color

Histology:
- Variant of seborrheic keratosis
- Church spire digitations, mild acanthosis (Fig. 6D)
- Compact orthokeratosis
- Rare pseudohorn cysts

INVERTED FOLLICULAR KERATOSIS

Clinical Presentation:
- Usually on face or scalp of elderly patients (Fig. 7A)
- 2 to 10 mm papules with central scale
- Difficult to distinguish from a seborrheic keratosis or verruca vulgaris

Histology:
- Well circumscribed and symmetric
- Exo-endophytic (Fig. 7B)
- Parakeratosis common
- Proliferation of bland keratinocytes seen as bulbous projections into the dermis
- Squamous eddies usually seen near base (Figs. 7C and D)
- Foci with acantholysis, mucinous change, or duct-like structures
- Atypia of keratinocytes maybe prominent in areas of inflammation

Differential Diagnosis:
In the author's opinion, an inverted follicular keratosis is not a distinct lesion. It is either a verruca vulgaris or seborrheic keratosis, although clinical and histological features may not allow precise recognition of the precursor lesion.

Inverted Follicular Keratosis	Inflamed Seborrheic Keratosis	Verruca Vulgaris
Symmetric and circumscribed	Symmetric and circumscribed	Symmetric and circumscribed
Exo-endophytic less papillomatosis	More exophytic broader papillomatosis	More exophytic vertical digitations
Rare koilocytes	No koilocytes	Koilocytes common
Abundant eosinophilic staining cytoplasms	More basaloid keratinocytes	Large keratinocytes common
Squamous eddies common, especially near base	Rare squamous eddies	Rare squamous eddies
Atypia of keratinocytes may mimic squamous cell carcinoma	Mild keratinocytic atypia	Rare keratinocytic atypia

VERRUCA VULGARIS

Verrucae often simulate seborrheic keratoses, both clinically and histologically.

Clinical Presentation:
- Common on face, hands, may occur at any site
- 3 to 6 mm
- Hyperkeratotic with velvety surface, smooth if rubbed (Fig. 8A)
- Skin color to pink, no pigment

Histology:
- Digitated or spiking epidermal hyperplasia (Fig. 8B)
- Prominent granular layer
- Koilocytes in the superficial layer of the epidermis
- Columns of parakeratosis and/or serum above the tips of digitations
- Dilated blood vessels in the dermal papillae

Clinicopathologic Correlation:
See Clinicopathologic Correlation (p. 173).

Differential Diagnosis:
See Differential Diagnosis for Seborrheic Keratosis (p. 174).

VERRUCOUS KERATOSIS

This is not a specific clinical or histologic entity with criteria for diagnosis. Most dermatopathologists employ a diagnostic term to describe lesions, which do not have sufficient characteristic histologic features to render a diagnosis of a specific type of benign keratosis or acanthoma. The great majority of these lesions represent inflamed seborrheic keratoses or verrucae with histologic features of both entities (Figs. 8C and D).

EPIDERMAL NEVI

Epidermal nevi and seborrheic keratoses share many clinical and histological features. They may be genetically related with epidermal nevi representing congenital and seborrheic keratoses acquired lesions.

Clinical Presentation:
- Multiple variants including common, inflammatory linear verrucous (ILVEN), nevus unius lateris, nevus comedonicus, and many others
- Epidermal nevus syndrome associates epidermal nevi with abnormalities of the underlying bone, cartilage, and muscle, along with systemic findings
- Congenital or appear early in life
- Groupings of individual small papules simulating small seborrheic keratoses, often with normal skin between papules (Figs. 9A and C)
- Multiple architectural patterns; linear or zosteriform, plaque-like, some bilateral, may follow lines of Blaschko

Histology:
- Too much epidermis with varying degrees of hyperkeratosis, hyperplasia, papillomatosis, and acanthosis (Fig. 9B)
- Changes may be barely perceptible or quite pronounced
- Pseudohorn cysts rarely seen
- ILVEN with epidermal hyperplasia, a dense inflammatory infiltrate, and often with alternating hypergranulosis with overlying orthokeratosis and hypogranulosis with overlying parakeratosis (Fig. 9D)
- Widely dilated infundibulae in nevus comedonicus

Clinicopathologic Correlation:
See p. 173.

Differential Diagnosis:
See Differential Diagnosis for Seborrheic Keratosi (p. 174).

CLEAR CELL ACANTHOMA

Synonym: Degos acanthoma

Clinical Presentation:
- Solitary, rarely multiple, usually on lower legs of adults
- Well circumscribed papule or small plaque (Fig. 10A)
- Pink to red
- May have shiny or moist appearing surface
- Often with a peripheral collarette of scale

Histology:
- Circumscribed zone of acanthosis
- Proliferation of keratinocytes with normal nuclei and clear or pale staining cytoplasms filled with glycogen (Fig. 10B)
- Sharp circumscription and sparing of adnexal epithelium (Fig. 10C)
- Neutrophils or neutrophil particles scattered throughout epidermis (Fig. 10D)
- Pale cytoplasms are PAS positive before diastase digestion

Clinicopathologic Correlation:

Clinical Feature	Pathologic Feature
Circumscribed papule	Well-demarcated zone of acanthosis
Pink to light red	Clear or pale staining keratinocytes Dilated blood vessels
Moist appearance	May have partial erosion

Differential Diagnosis:

Clear Cell Acanthoma	Pyogenic Granuloma	Amelanotic Malignant Melanoma
Proliferation of keratinocytes with pale cytoplasms	Proliferation of small blood vessels	Proliferation of atypical melanocytes without pigment
Limited to epidermis	Dermal, often ulcerated	Epidermal and dermal involvement

Pathophysiology:
- Glycogen deposited in keratinocytes due to absence of a phosphorylase enzyme

Reference:
1. Desmons F, Brevillard F, Thomas P, et al. Multiple clear cell acanthoma (Degos). J Invest Dermatol 1977; 16:203.

EPIDERMOLYTIC ACANTHOMA

Synonyms: Solitary or multiple epidermolytic acanthomas. Component of dominantly inherited bullous congenital ichthyosiform erythroderma. Some linear epidermal nevi. Palmar plantar keratodermas. Incidental finding in normal skin.

Clinical Presentation (Solitary or Multiple Type):
- Keratotic papule resembling a seborrheic keratosis or verruca vulgaris
- Brownish, 2 to 8 mm in diameter

Histology:
- Hyperkeratosis with focal parakeratosis
- Well-circumscribed zone of acanthosis (Fig. 11A)
- Granular degeneration throughout the epidermis, spares the basal layer

- Epidermolytic or granular changes include (Fig. 11B)
  - Intracellular and intercellular edema
  - Pale staining cytoplasms
  - Large coarse keratohyalin-like granules
  - Eosinophilic trichohyalin-like granules in thickened granular layer
  - Remnants of keratinized cells seen as eosinophilic globules in stratum corneum

Differential Diagnosis:

Epidermolytic Acanthoma	Verruca Vulgaris
Acanthosis prominent	Papillated or digitated epidermal hyperplasia
Prominent granular layer	Prominent granular layer
Epidermolytic or granular degeneration, throughout the epidermis	True koilocytes near or in granular layer
Mild vascular dilatation in dermal papillae	Prominent vascular dilatation in dermal papillae

Pathophysiology:
- Mutations in the K1 and K10 genes (keratin) have been proposed in both the inherited and solitary types.

Reference:
1. Cohen P, Ulmer R, Theriault A, et al. Epidermolytic acanthomas: clinical characteristics and immunohistochemical features. Am J Dermatopathol 1997; 19(3):232.

ACANTHOLYTIC AND/OR DYSKERATOTIC ACANTHOMA

Clinical Presentation:
- No distinguishing clinical features, similar to seborrheic keratosis and other acanthomas
- Single (common) or multiple (rare)
- Small scaling, brownish papule on trunk or extremities, may occur on genitalia

Histologic Features:
- Typical architecture of a seborrheic keratosis
- Rare pseudohorn cysts
- Only distinguishing features are acantholytic (Fig. 11C) and/or dyskeratotic (Fig. 11D) keratinocytes which may occur at all levels of the epidermis

FIBROEPITHELIAL POLYP

Synonyms: Skin tag; papilloma; acrochordon.

Clinical Presentation:
- Hanging or protruding polyps (Fig. 12A)
- Common in areas of friction; axillae, groin, inframammary, neck
- Small (usually) to several centimeters
- Flesh to light tan
- Maybe inflamed (red) or infarcted
- Sometimes a thin stalk with bulbous tip

Histology:
- Two common variants
- Polypoid projection, smooth surface, flattened rete ridges, fibrillated collagen in central core (Fig. 12B)
- Polypoid projection, verrucous surface, papillated epidermal hyperplasia and acanthosis, indistinguishable from a papillated seborrheic keratosis
- May demonstrate inflammation and/or necrosis

BENIGN LICHENOID KERATOSIS

Synonym: Lichen planus-like keratosis.

Clinical Presentation:
- Usually solitary
- Chest, back, neck, upper extremities of adults over 40
- 3 to 20 mm diameter
- Mildly scaly
- Light brown to red, may notice brown at periphery
- Often associated with or arising in a solar lentigo (Fig. 12C)

Histology:
- Variety of histologic subtypes including atypical and bullous
- Atrophic to hyperplastic epidermis
- Compact ortho- and parakeratosis
- Lichenoid, predominantly mononuclear cell infiltrate, obscures dermal–epidermal junction (Fig. 12D)
- Variable vacuolar change
- Scattered necrotic keratinocytes
- May have mild keratinocytic atypia
- Often residual portions of a solar lentigo are seen laterally

Clinicopathologic Correlation:

Clinical Feature	Pathologic Feature
Scale	Compact ortho- and parakeratosis
Firm papule and erythema	Dense lichenoid infiltrate in dermis
Tan border	Hyperpigmentation of basalar keratinocytes, laterally

Differential Diagnosis:

Benign Lichenoid Keratosis	Squamous Cell Carcinoma In Situ	Basal Cell Carcinoma
Compact ortho- with scattered parakeratosis	Confluent, tightly packed parakeratosis	Minimal parakeratosis
Lichenoid infiltrate always	May have dense lichenoid infiltrate	No lichenoid infiltrate
Mild keratinocytic atypia	Moderate to severe keratinocytic atypia	Proliferation of basal cells

Reference:
1. Morgan M, Stevens G, Switlyk S. Benign lichenoid keratosis, a clinical pathologic reappraisal of 1040 cases. Am J Dermatopathol 2005; 27(5):387.

KERATOACANTHOMA

Clinically and histologically may mimic a hyperkeratotic seborrheic keratosis or other benign acanthoma. Most authors regard it as a low-grade squamous cell carcinoma, which may have rapid growth and may involute spontaneously.

Clinical Presentation:
- Nodule with central keratin filled plug (Fig. 13A)
- Pink to light red or tan
- Usually on sun-exposed skin of more elderly adults

Histology:
- Exo-endophytic architecture (Fig. 13B)
- Compact ortho- and parakeratosis
- Keratin filled central crater with overhanging epidermal "lips"
- Proliferation of large keratinocytes with glassy, eosinophilic staining cytoplasms
- Mild to moderate keratinocytic nuclear atypia, especially at base
- Mild to moderate inflammatory infiltrate at base, often with eosinophils

Differential Diagnosis:

Keratoacanthoma	Inverted Follicular Keratosis
Exo-endophytic	Exo-endophytic
Usually well circumscribed	Usually well circumscribed
Central keratin filled plug	No central plug
Overhanging epithelial lips	No overhanging epithelial lips
Large keratinocytes with eosinophilic cytoplasms	Mild dyskeratosis of keratinocytes
May have true horn pearls	Squamous eddies common
May have infiltrating strands of keratinocytes at base	Usually with smooth base

WARTY DYSKERATOMA

Not a true acanthoma, but may simulate both clinically and histologically.

Clinical Presentation:
- Solitary papule on face, scalp, or neck
- Crusted, keratotic
- Slightly umbilicated or depressed, keratin filled center

Histology:
- Central invagination, cup-shaped (Fig. 13C)
- May demonstrate association with the infundibulum of a hair follicle
- Acantholytic and dyskeratotic keratinocytes, often in papillary projections (Fig. 3D)
- May have villous pattern with normal basaloid cell layer, progressing to acantholysis and dyskeratosis

EPITHELIAL CYSTS OF THE SKIN

EPIDERMOID CYST

Synonyms: Keratin cyst; epidermal inclusion cyst; sebaceous cyst; follicular cyst (infundibular type).

Clinical Presentation:
- Extremely common, face, scalp, trunk, extremities
- Slow growing, round, firm, intradermal tumors (Fig. 14A)
- 1 to 5 or 6 cm diameter
- Normal skin surface, usually
- May have overlying pore or dell
- May be red, tender, or painful when inflamed
- Milia are very small cysts, usually on the face, often derived from vellus hairs

Histology:
- Intradermal (may extend into fat) cystic structure (Fig. 14B), round to oval, well circumscribed
- True epidermal lining with melanocytes and Langerhans cells
- Basal layer and one to several layers of squamous cells, fewer in older lesions
- Granular layer present (Fig. 14C)
- Rete ridges usually not present
- Cyst is filled with keratin in a laminated or whorled pattern
- Calcification infrequently
- May be inflamed with break in the lining and a surrounding dense granulomatous inflammatory infiltrate (Fig. 14D) with both foreign body and Langhans giant cells

Clinicopathologic Correlation:

Clinical Feature	Pathologic Feature
Smooth, slightly dome-shaped surface	Normal epidermis, may be slightly elevated
Round or marble-like to palpation	Well circumscribed, round dermal nodule
Firm	Compacted laminated layers of keratin
Red and tender	Rupture of cyst wall with dense inflammatory infiltrate

Differential Diagnosis:

Epidermoid Cyst	Pilar Cyst
Intradermal cystic structure	Intradermal cystic structure
Well circumscribed and round	Well circumscribed and round
Lining mimics true epidermis, similar to that of the infundibulum of a hair follicle	Lining mimics the isthmus of a hair follicle
Basal layer, one to several squamous layers	Palisaded basal layer, one or two layers, well differentiated squamous cells, swollen and pale keratinocytes next to contents
Granular layer	No granular layer
Laminated keratin core	Homogeneous, pale staining keratin core
Calcification rare	Calcification common

Pathophysiology:
- Most epidermoid cysts are acquired and appear to be derived from the infundibular portion of a hair follicle. Follicular plugging or inflammation may lead to dilatation of the infundibulum and formation of a cyst. Multiple cysts are common, but large numbers may be seen in Gardner's syndrome, a dominantly inherited genodermatosis associated with colonic polyposis, fibrous tumors, osteomatosis, and dental anomalies.

PILAR CYST

Synonyms: Wen; trichilemmal cyst; follicular cyst (isthmus-catagen type).

Clinical Presentation:
- Common, occur most frequently on scalp, other areas with terminal hairs (Fig. 15A)
- Firm, round nodule, movable on palpation
- No overlying pore or dell
- Except for site, indistinguishable from an epidermoid cyst
- May be red, tender, or painful when inflamed

Histology:
- Intradermal (may extend into the fat) cyst, round or well circumscribed (Fig. 15B)
- Epithelial lining differs from normal epidermis, simulates isthmus portion of hair follicle
- Palisaded basal layer, one or two layers of well differentiated squamous cells, pale and swollen keratinocytes next to keratin (Fig. 15C)
- No granular layer
- Homogeneous, pale to pink staining keratin core (Fig. 15D)
- Calcification in core is common
- Surrounding dense granulomatous inflammation when ruptured

Clinicopathologic Correlation:
See p. 174.

Differential Diagnosis:
See p. 174, under Seborrheic Keratosis, Common Histologic Variants.

Pathophysiology:
- More common in women; 80% on scalp. Autosomal dominant transmission has been postulated. Thought to derive from the outer root sheath of the isthmus portion of a hair follicle.

PROLIFERATING PILAR CYST

Synonym: Proliferating trichilemmal cyst.

Clinical Presentation:
- Arise on scalp of females (90%)
- Usually larger than an ordinary pilar cyst (Fig. 16A)
- May be more exophytic and ulcerated
- Tight feeling, but not painful

Histology:
- Dermal cystic structure (Fig. 16B)
- Maybe multilobular
- Compressed, often appearing layered, epithelial lining
- Epithelial lining similar to pilar cyst with acanthosis, multiple layers of well differentiated squamous cells, swollen-appearing keratinocytes (Figs. 16C and D)
- Rare lesions may have a lining similar to an epidermoid cyst
- May have both squamous eddies and horn pearls in the epithelial lining
- Mild nuclear atypia of keratinocytes
- Homogeneous keratin
- May have focal calcification or ghost cells in contents
- Surrounding granulomatous inflammation when ruptured
- Rare malignant transformation with severe keratinocytic nuclear atypia, infiltrating pattern at lateral and deep margins, and scattered mitotic figures. Lymph node and distant metastases and penetration to cerebral sinuses have been reported.

Reference:
1. Sau P, Graham J, Helwig E. Proliferating epithelial cysts. Clinicopathologic analysis of 96 cases. J Cutan Pathol 1995; 22:394.

STEATOCYSTOMA

Synonyms: Steatocystoma simplex (solitary); steatocystoma multiplex (multiple).

Clinical Presentation:
- Single or multiple nodulocystic lesions (Fig. 17A)
- Arms, chest, upper back, axillae, and face
- 1 to 3 or 4 mm in diameter, may be larger
- Smooth, dome-shaped, flesh colored surface
- Discharge an oily, creamy fluid when punctured or incised

Histology:
- Intradermal, round to oval cystic structure
- One to three layers of keratinocytes
- Eosinophilic staining, compact, crenulated, and folded lining of lumen

- Sebaceous lobules associated with cyst wall and emptying into the cavity (Fig. 17B)
- Homogeneous, light staining cyst contents, partially destroyed in processing
- Vellus hairs occasionally seen

ERUPTIVE VELLUS HAIR CYST

Clinical Presentation:
- Usually arise in children and young adults
- Asymptomatic, flesh to bluish, 1 to 2 mm papules or small superficial cysts
- Follicular pattern
- Usually on chest, rarely on upper back or upper extremities
- 50 to 100 cysts may be noted (Fig. 17C)
- Puncturing demonstrates creamy fluid with small hair fragments

Histology:
- Small round cyst in superficial dermis
- Epithelial lining of small squamous cells with fine granular layer
- Homogeneous, fine keratin in core
- Numerous portions of small vellus hairs in cavity (Fig. 17D)

Pathophysiology:
These cysts are thought to arise in a developmental or genetic defect of vellus hair follicles. There is occlusion at the level of the infundibulum with retention of hair shafts and cystic dilatation of the proximal portions of the follicle.

RARE AND UNUSUAL CYSTS

These lesions are cystic and clinically recognized only by their unusual locations. The diagnoses depend on multiple specific criteria with the type of epithelial lining being most important.

Clinical Presentation and Histology:
Pigmented Follicular Cyst:
- Brown cystic lesion, face and neck, may resemble other pigmented neoplasms, usually solitary
- Epithelial lining similar to normal epidermis of the infundibulum of a hair follicle
- Amorphous pigmented keratin in cavity, with or without portions of pigmented hair shafts (Fig. 18A)

Dermoid Cyst:
- Occurs on face, often around eyes
- Usually present at or near birth
- Thought to arise from rests of skin occurring along lines of embryonic closure
- Epithelial lining: stratified squamous epithelium similar to normal skin
- Mature epidermal appendages arising from or entering the cyst wall (Fig. 18B)
- Hair shafts may extend into the lumen
- Sebaceous, eccrine, and apocrine structures may be seen in surrounding dermis
- Creamy, homogeneous, keratinous contents

Cutaneous Ciliated Cyst:
- Usually solitary lesions on the lower extremities of women
- Unilocular with clear to amber fluid
- Epithelial lining; papillary projections lined by simple cuboidal or columnar epithelium, usually with cilia (Fig. 18C)

Median Raphe Cyst of the Penis:
- Ventral surface of penis on young men, near or on glans
- Solitary and small
- Epithelial lining; pseudostratified columnar epithelium, similar to transitional epithelium of the urethra (Fig. 18D)
- May arise from the urethra embryologically

Bronchogenic and Thyroglossal Duct Cysts:
- Clinically indistinguishable
- Bronchogenic above sternal notch, thyroglossal on anterior neck
- Epithelial lining: pseudostratified columnar epithelium, may be ciliated and contain goblet cells (Fig. 19A)
- Wall may contain smooth muscle or cartilage

Branchial Cleft Cyst:
- Found along anterior border of sternocleidomastoid muscle from ear to sternum, may drain to surface
- Epithelial lining: stratified squamous or ciliated columnar epithelium
- Heavy lymphoid infiltrate in wall or surrounding (Fig. 19B)
- Smooth muscle rare

Cutaneous Endometriosis:
- Not a true cyst
- Most common in surgical scars near the umbilicus
- Dermal or subcutaneous nodule with multiple cystic spaces (Fig. 19C)
- Epithelial lining; columnar to cuboidal (Fig. 19D)
- There may be adjacent stromal cells similar to the endometrium with fibrosis and old hemorrhage

Mucocoele:
- Not a true cyst, mimics clinically
- Cystic swelling on lip, floor, or buccal wall of mouth (Fig. 20A)
- Amorphous zones of mucinous material with lymphocytes and neutrophils (Fig. 20B)
- No cyst wall
- Minor salivary glands or ducts may be seen

DIGITAL MYXOID CYST

- Not a true cyst
- Most common on the dorsal surface of the index or middle finger, overlying the distal interphalangeal joint, just above the proximal nail fold (Fig. 20C)
- No cyst wall
- Ill-defined collection of mucin in superficial dermis, may have overlying collarette of epidermis (Fig. 20D)
- Mild inflammation at the periphery

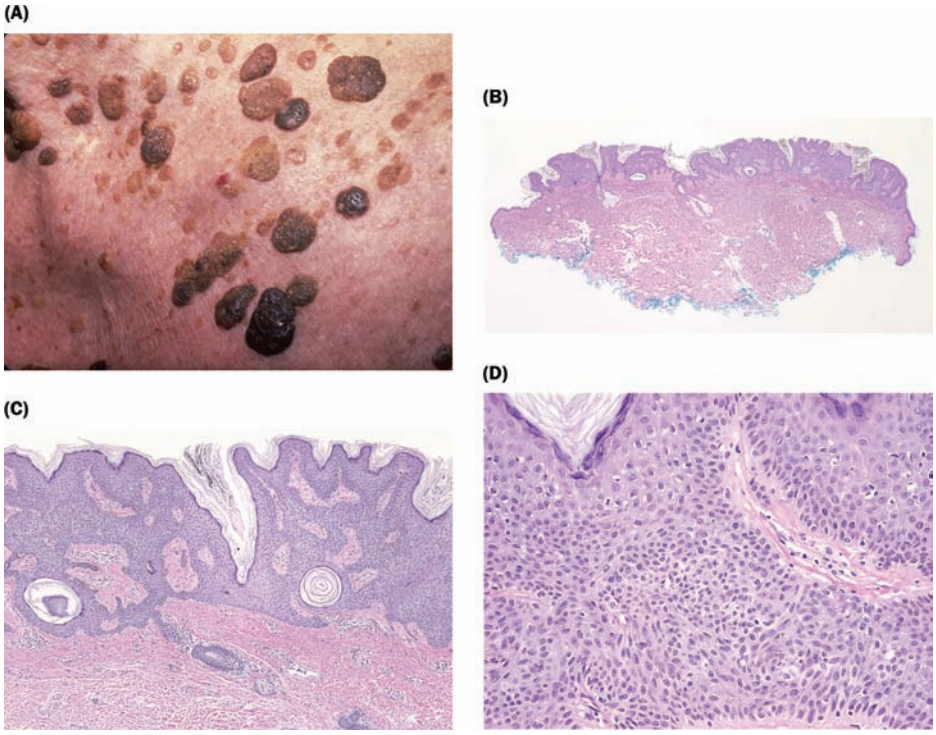

Figure 1 (**A**) Multiple well circumscribed, hyperpigmented, verrucous plaques with a "stuck-on" appearance. (**B**) Well circumscribed and symmetric lesion demonstrating papillomatosis and acanthosis of the epidermis. Predominantly exophytic. (**C**) Scattered pseudohorn cysts created by cross-sectioning the keratin-filled crypts. (**D**) Proliferation of small, relatively uniform basaloid keratinocytes with an approximately 1:1 nuclear to cytoplasmic ratio. No significant nuclear atypia.

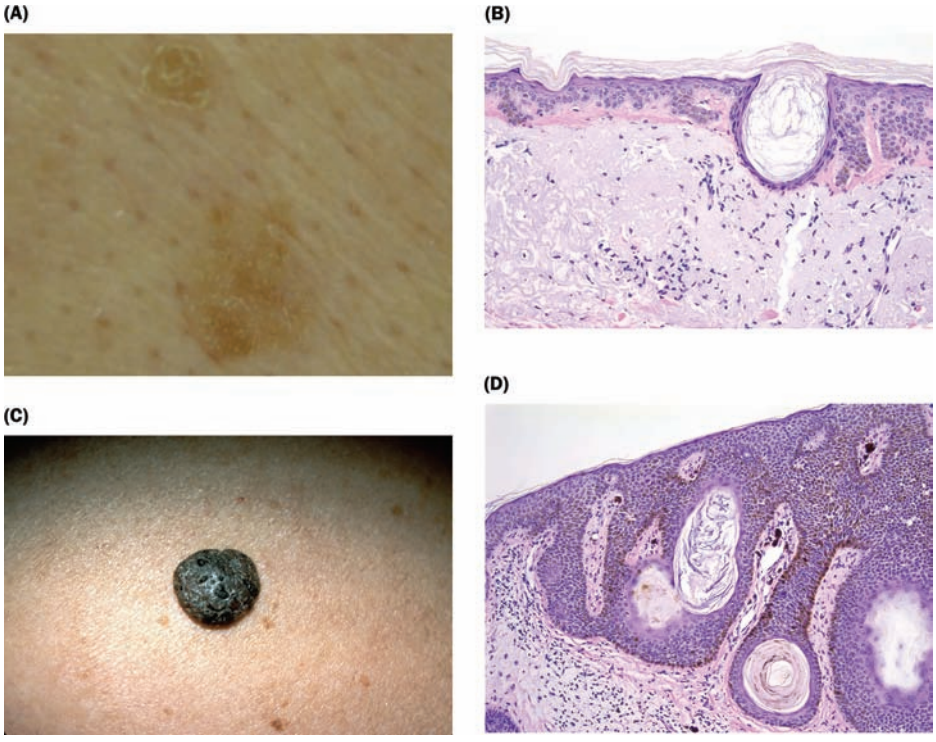

Figure 2 (**A**) Well circumscribed, light tan patch with slightly raised border, progressing to a plaque. (**B**) Hyperpigmented basalar keratinocytes of a solar lentigo with proliferation of small basaloid cells in strands and development of pseudohorn cysts. (**C**) Well circumscribed, dark brown to black plaque with pebbly surface. No extension of pigment into surrounding skin. (**D**) Proliferation of small basaloid keratinocytes with abundant melanin in their cytoplasms, no significant increase in melanocytes.

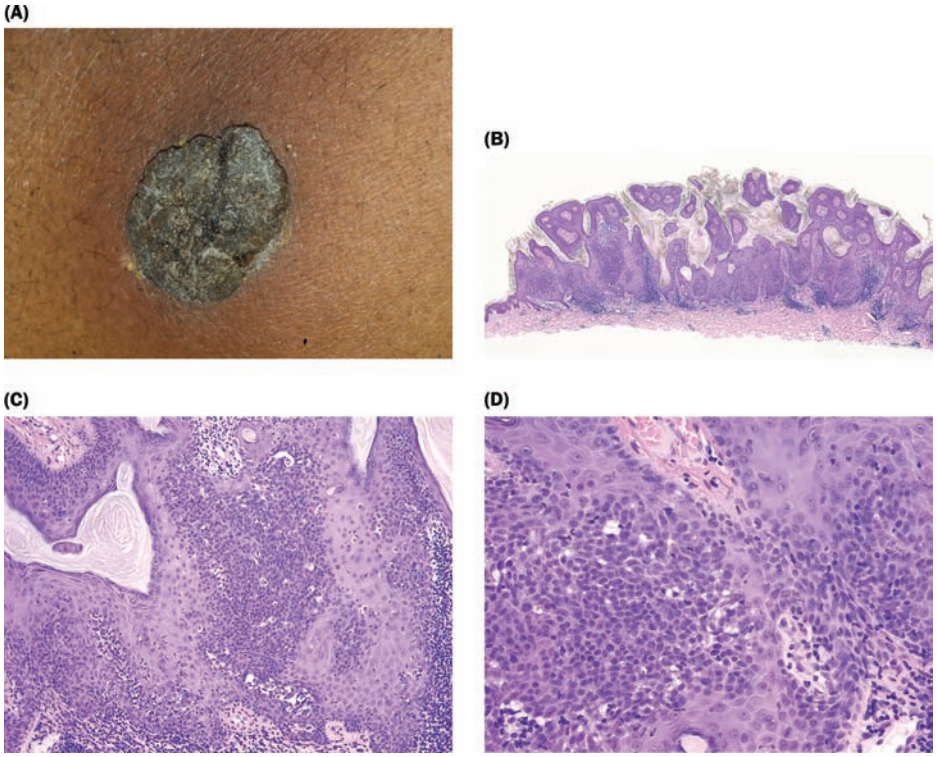

Figure 3 (**A**) Circumscribed reddish-brown papule with an erythematous base. (**B**) Seborrheic keratosis with a dense superficial perivascular and lichenoid, predominantly lymphocytic inflammatory infiltrate. (**C**) Gradual change from small basaloid keratinocytes to large keratinocytes with abundant keratin (squamous differentiation). (**D**) Individual keratinocytes may demonstrate mild to moderate nuclear atypia.

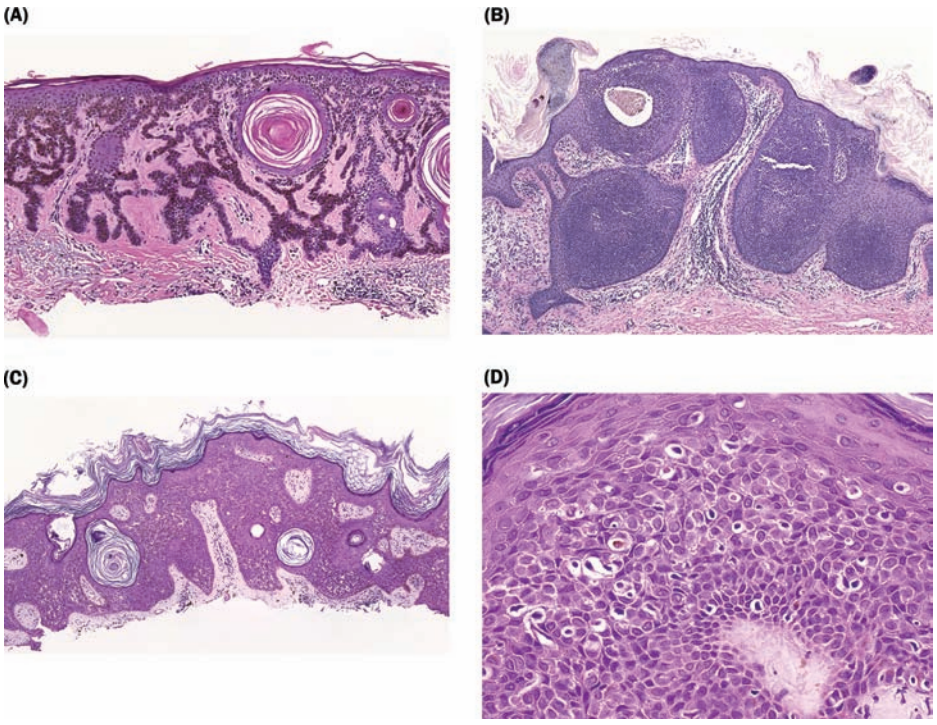

Figure 4 (**A**) Thin anastomosing strands of small, uniform basaloid cells extending into the dermis. (**B**) Round or nested aggregates of uniform basaloid cells separated by larger keratinocytes with squamous differentiation. (**C**) Acanthotic proliferation of small basaloid keratinocytes. (**D**) Dendritic melanocytes sprinkled at all levels of the epidermis.

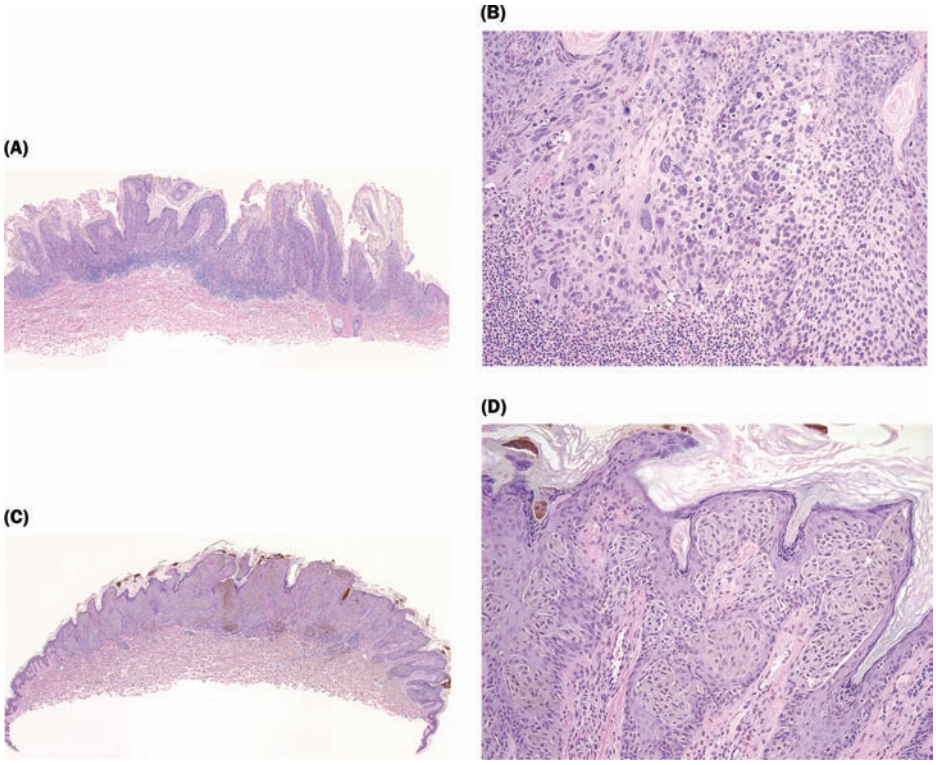

Figure 5 (**A**) Papillated epidermal hyperplasia simulating a seborrheic keratosis. (**B**) Atypical keratinocytes with large hyperchromatic and pleomorphic nuclei, along with scattered mitotic figures. (**C**) Well circumscribed and symmetric melanocytic proliferation simulating a seborrheic keratosis. (**D**) Single and nested atypical melanocytes at all levels of the epidermis.

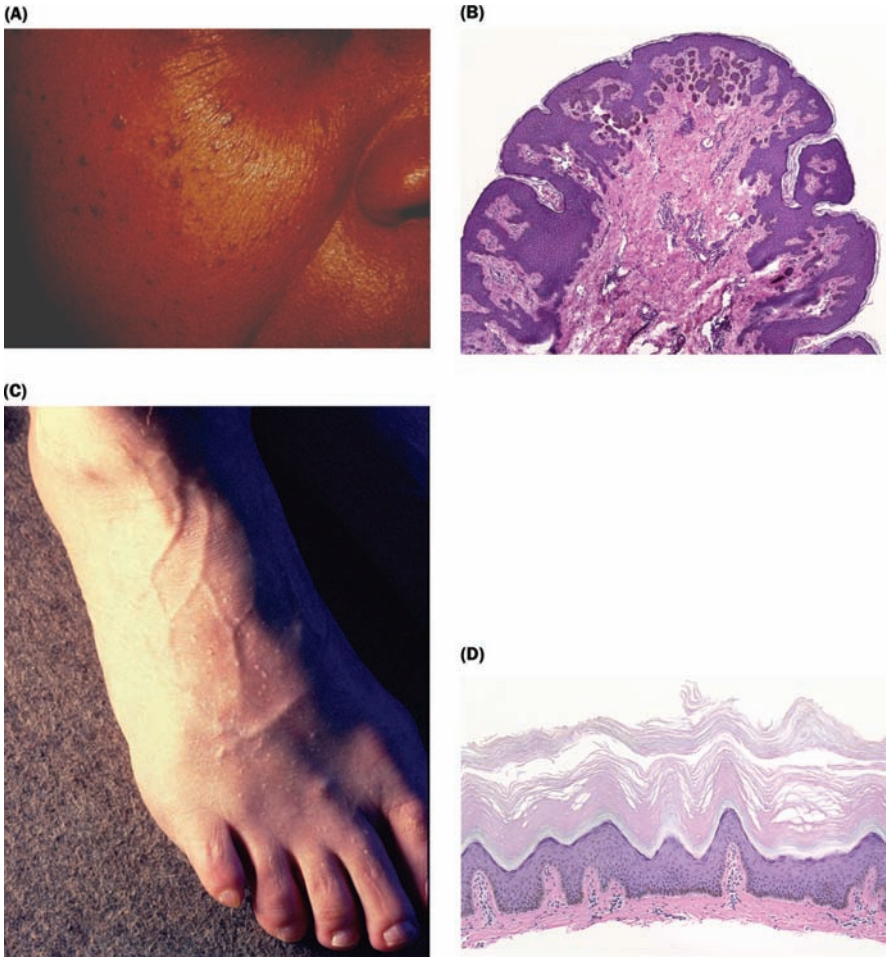

Figure 6 (**A**) Multiple small, hyperpigmented, smooth papules on face. (**B**) Dome-shaped papule with epidermal hyperplasia and a central collagenous core. (**C**) Multiple small hyperkeratotic papules on the lower leg and dorsal foot. (**D**) Digitated epidermal hyperplasia with overlying compact orthokeratosis.

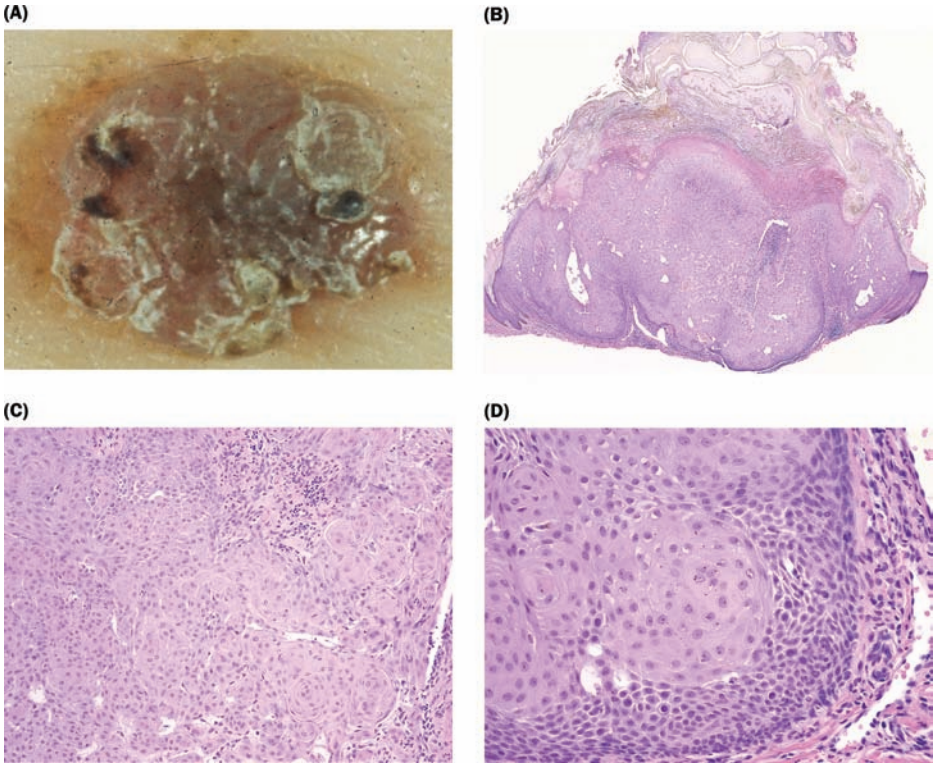

Figure 7 (**A**) Dome-shaped papule with rough, scaly surface. (**B**) Exo-endophytic proliferation of small basaloid and larger keratinocytes with a digitated and bulbous architectural pattern. (**C**) Numerous squamous eddies in the endophytic portion of this lesion. (**D**) Squamous eddy with mild nuclear atypia and no keratin pearl.

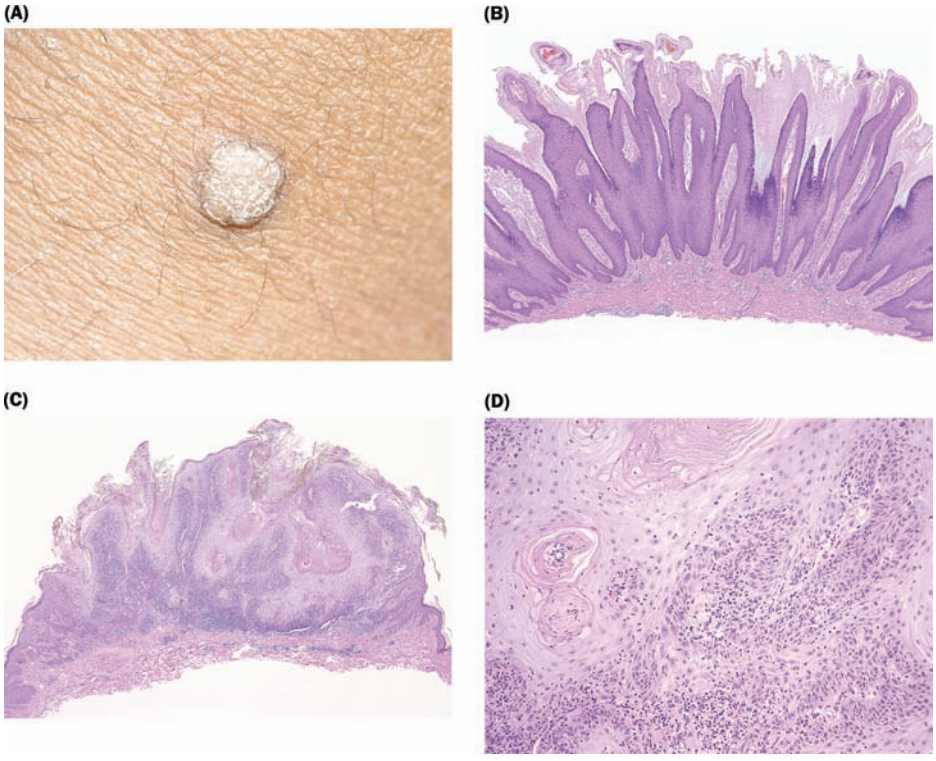

Figure 8 (**A**) Well circumscribed, hyperkeratotic tan papule on the arm. (**B**) Digitated epidermal hyperplasia with a prominent granular layer and koilocytes. (**C**) Verrucous epidermal hyperplasia and acanthosis with a proliferation of both basaloid and large keratinocytes. (**D**) Horn cyst with mild atypia of the surrounding keratinocytes and associated inflammation.

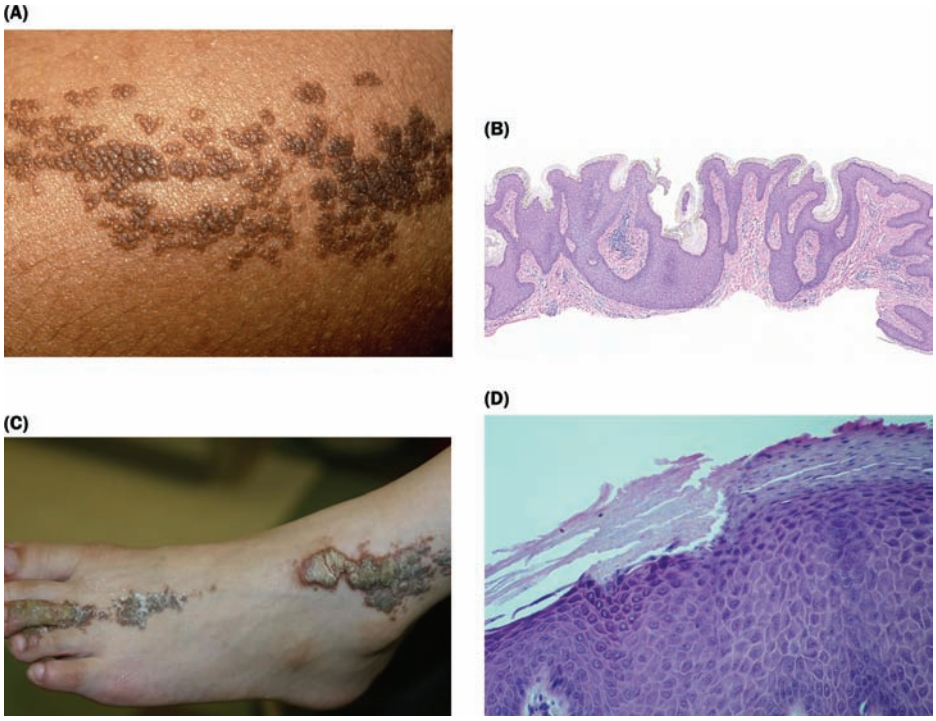

Figure 9 (**A**) Small tan papules with a linear distribution coalescing into a plaque. (**B**) Papillated epidermal hyperplasia without pseudohorn cysts. (**C**) Hyperpigmented verrucous papules in a linear distribution on the lower leg and dorsal foot. (**D**) Alternating zones of hypergranulosis with overlying orthokeratosis and hypogranulosis with overlying parakeratosis.

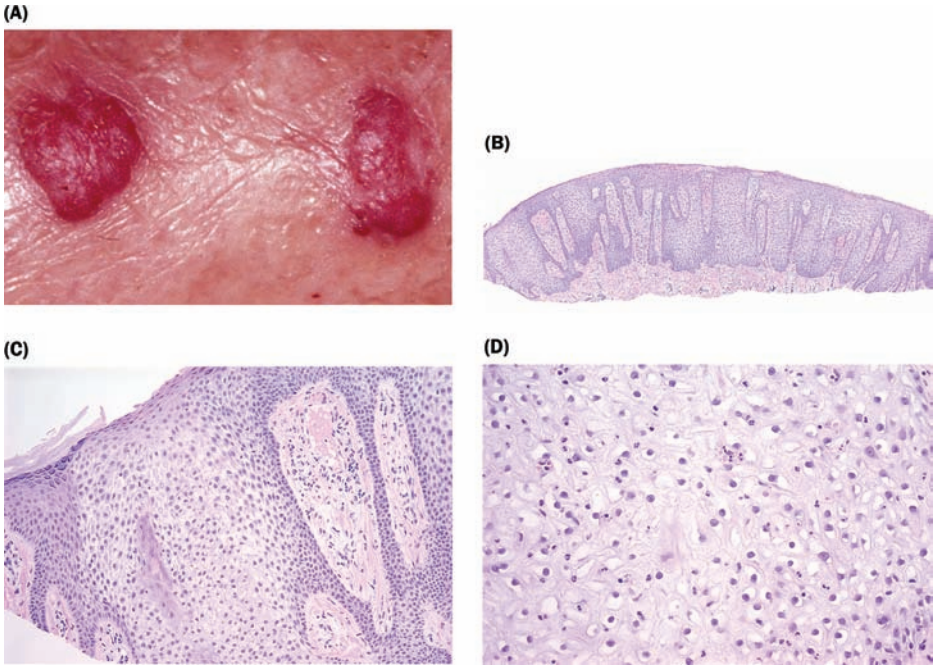

Figure 10 (**A**) Well circumscribed, dome-shaped, erythematous plaques with a glistening surface on the lower leg. (**B**) Proliferation of keratinocytes with normal nuclei and clear or pale-staining cytoplasms. (**C**) Zone of pale-staining keratinocytes with sharp separation from the surrounding basaloid keratinocytes. (**D**) Neutrophils and neutrophilic particles scattered throughout the zones of clear cells.

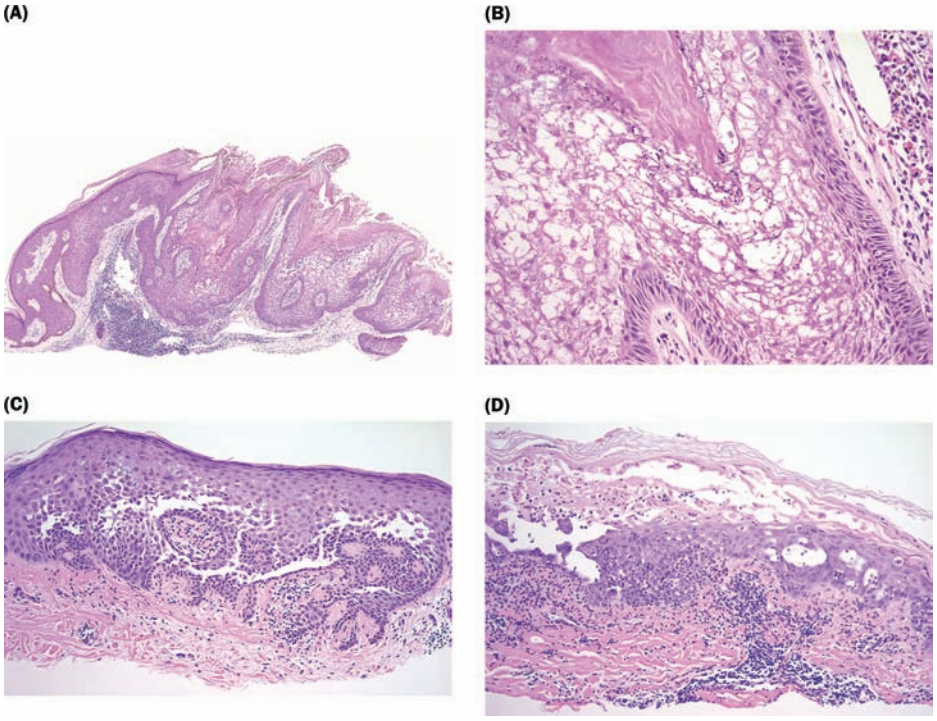

Figure 11 (**A**) Papillated epidermal hyperplasia and acanthosis with focal granular degeneration. (**B**) Granular or epidermolytic change with edema, pale-staining cytoplasms, coarse keratohyaline-like granules, and eosinophilic trichohyaline-like granules. (**C**) Architecture of a seborrheic keratosis with extensive acantholysis of keratinocytes. (**D**) Acantholysis and dyskeratosis of keratinocytes with the architecture of a seborrheic keratosis.

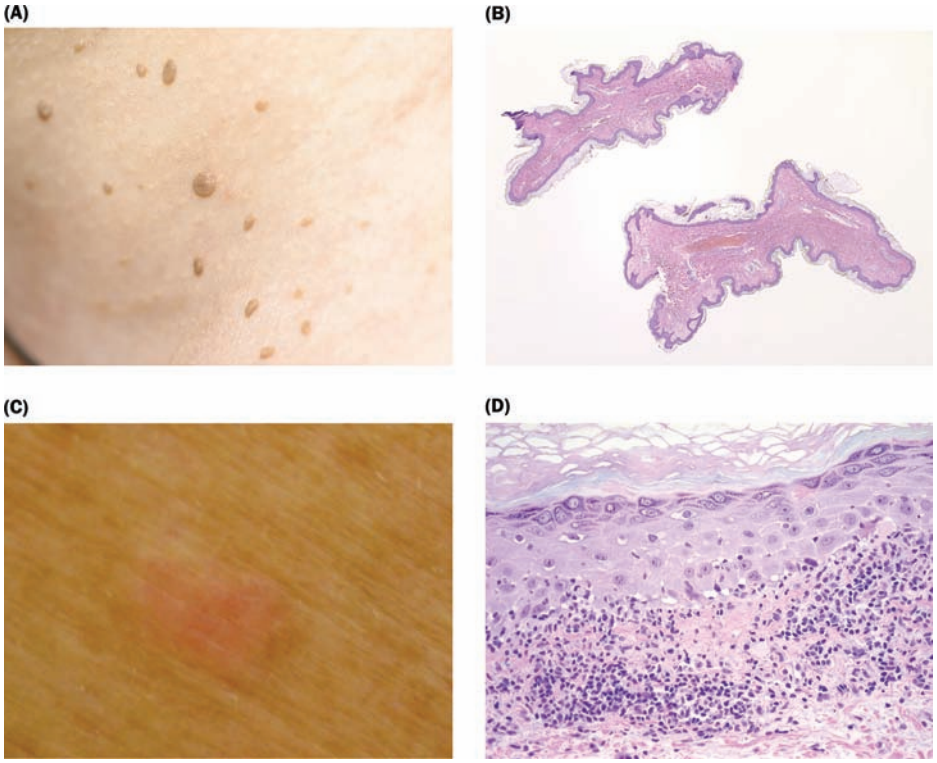

Figure 12 (**A**) Papillomas in the axilla. (**B**) Polypoid papules with smooth surface and flattened rete ridges. (**C**) Well circumscribed, slightly raised erythematous plaque with scale. (**D**) Dense lichenoid mononuclear cell infiltrate which obscures the dermal–epidermal junction and is seen in association with necrotic keratinocytes. There is minimal atypia of the keratinocytes.

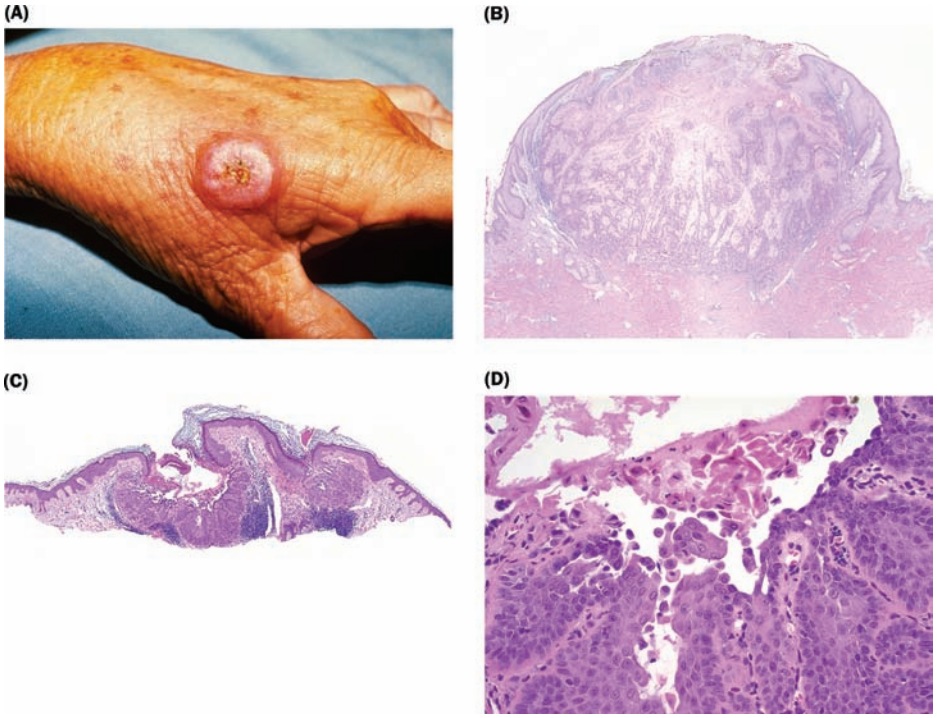

Figure 13 (**A**) Large nodule with raised borders and a central keratin-filled plug. (**B**) Exo-endophytic proliferation of large keratinocytes with a central keratin-filled plug and overhanging lips of epidermis. (**C**) Exo-endophytic proliferation of keratinocytes with a central cystic cavity. (**D**) Acantholytic and dyskeratotic keratinocytes filling the central invagination.

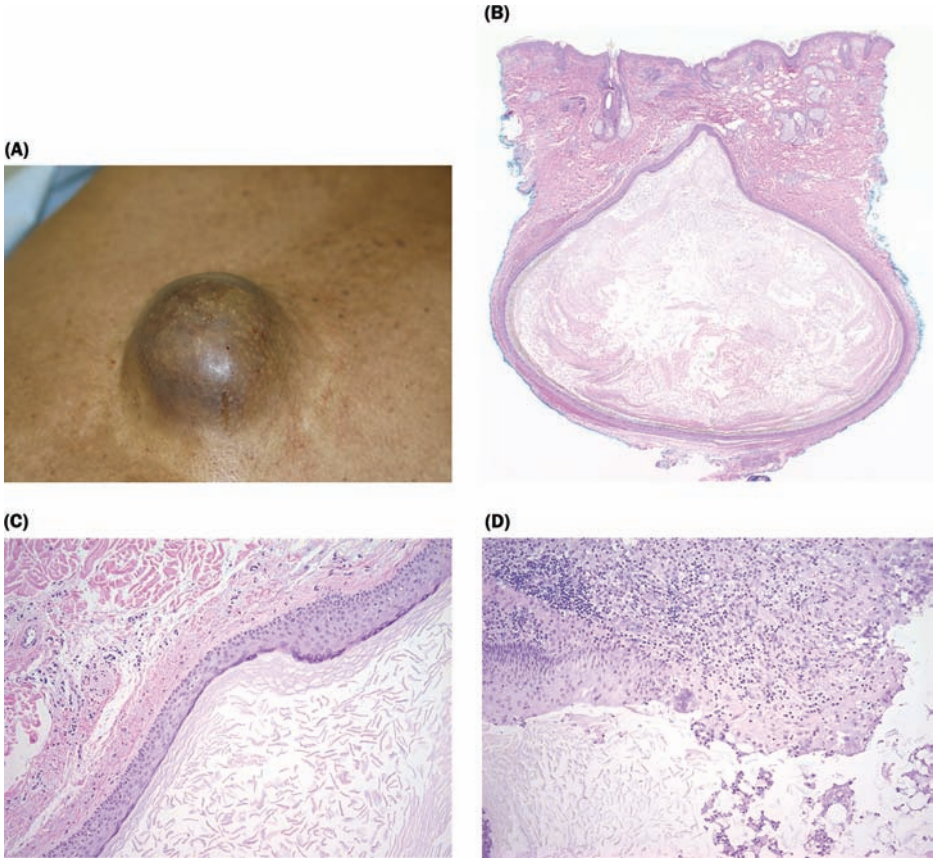

Figure 14 (**A**) Exo-endophytic round, firm, well circumscribed cystic nodule. (**B**) Well circumscribed dermal and subcutaneous nodule with epithelial lining and central keratin. (**C**) Epithelial wall simulating normal epidermis with a prominent granular layer. Laminated keratin centrally. (**D**) Dense granulomatous inflammation adjacent to a rupture of the cyst wall.

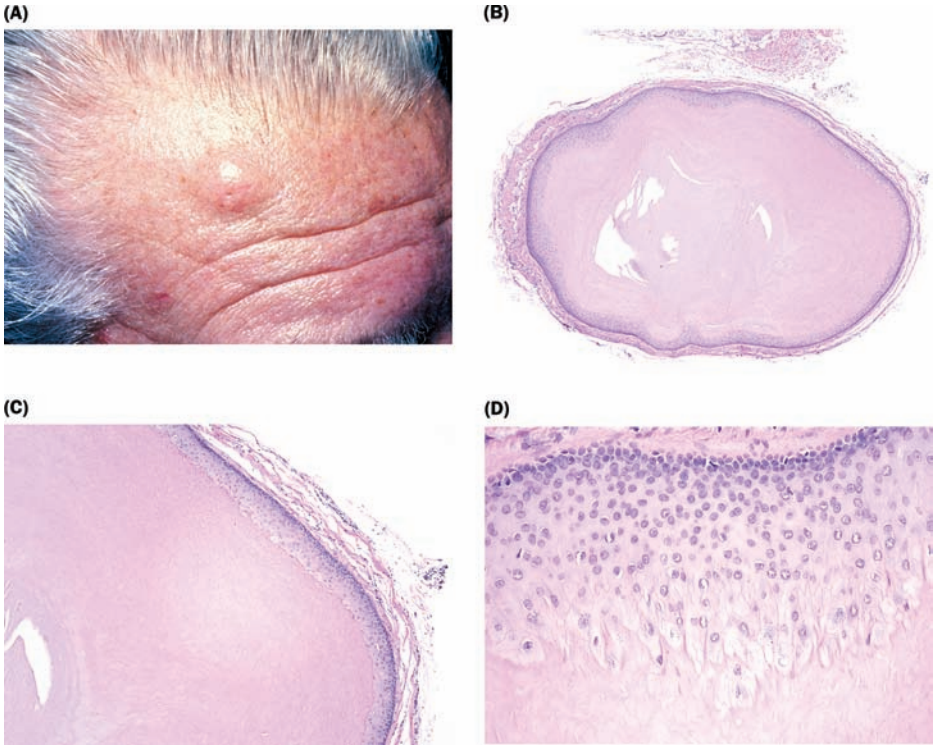

Figure 15 (**A**) Firm, round, well circumscribed nodule on the forehead. (**B**) Round dermal nodule with an epithelial lining and dense central keratin. (**C**) Epithelial lining with no granular layer and central homogeneous, pink staining keratin core. (**D**) Pale-staining, swollen keratinocytes next to homogeneous keratin.

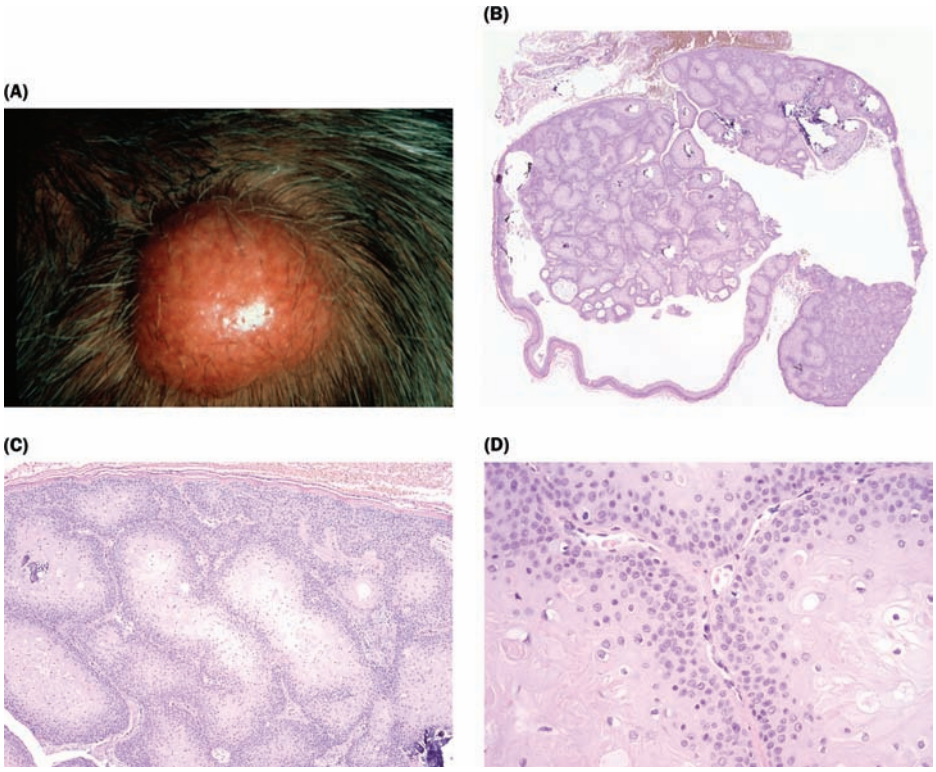

Figure 16 (**A**) Large, firm, cystic structure on scalp. (**B**) Relatively well circumscribed dermal cystic structure, appears multinodular. (**C**) Folded and layered cross-sections of epithelial wall similar to a pilar cyst. (**D**) Multiple layers of well differentiated squamous cells, swollen appearing keratinocytes adjacent to homogeneous keratin core.

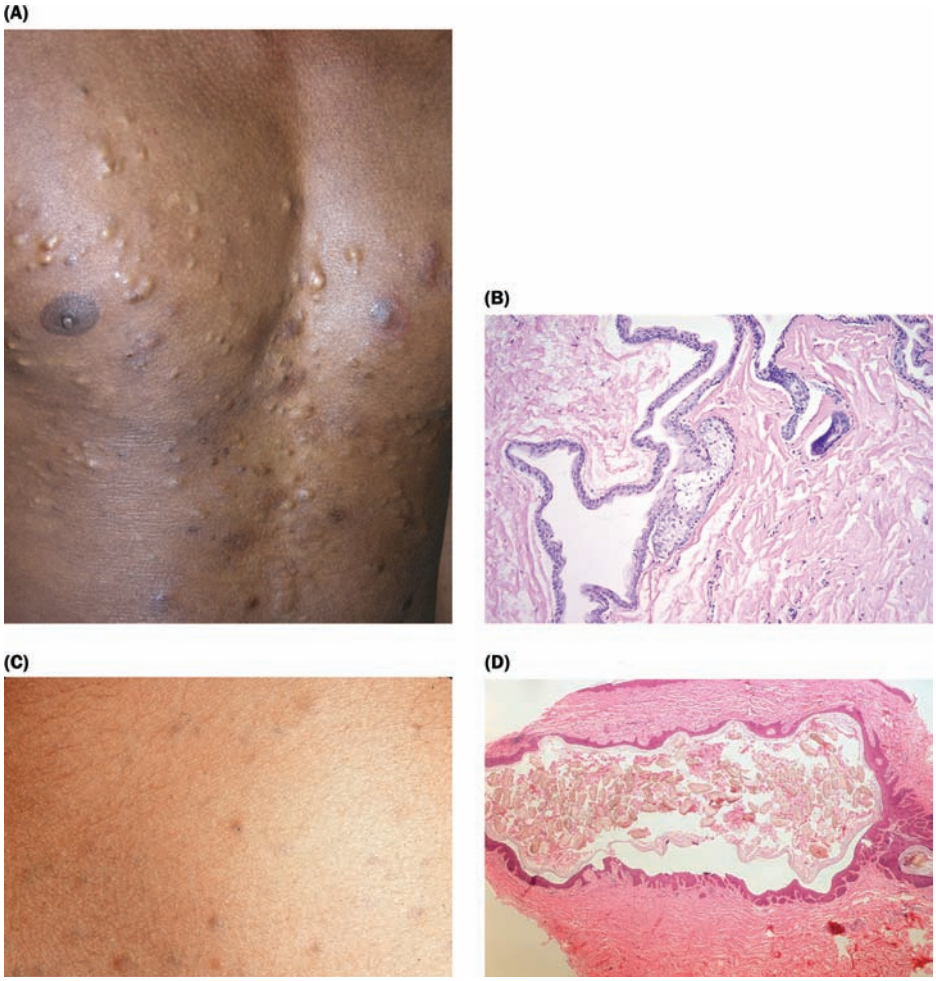

Figure 17 (**A**) Multiple nodular cystic, tan to yellow lesions on the chest. (**B**) Sebaceous lobules entering cyst in association with a crenulated epithelial lining of two to three layers of keratinocytes. (**C**) Tan to bluish cystic papules on the chest. (**D**) Dermal cyst with numerous vellus hairs in contents.

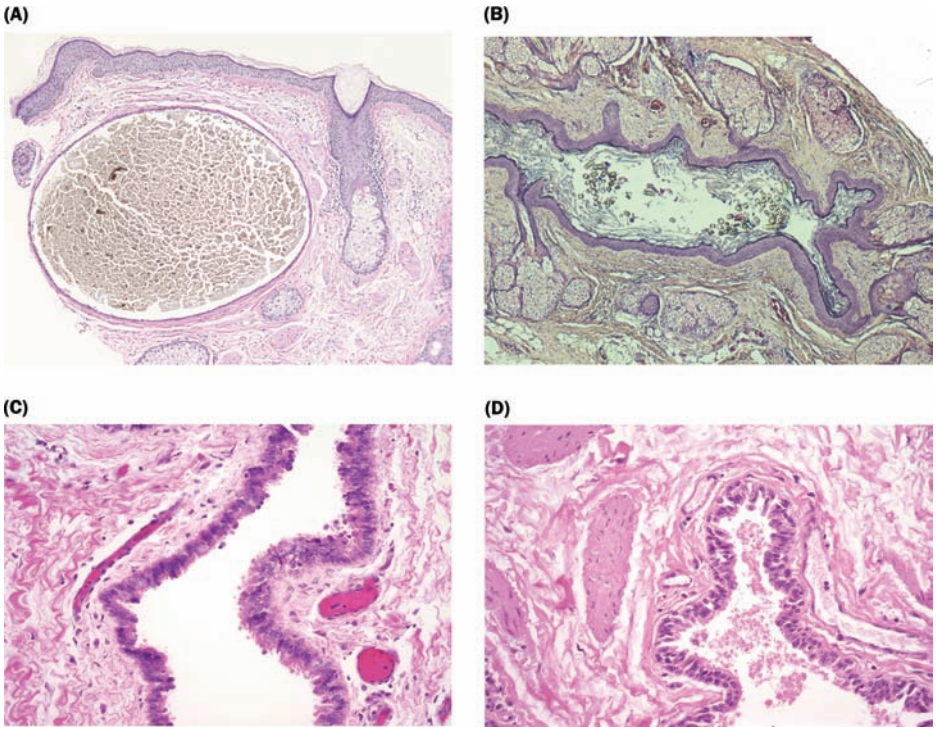

Figure 18 (**A**) Epidermoid cyst with amorphous pigmented keratin in center. (**B**) Multiple epidermal appendages arising from or entering the cyst wall. Hair shafts are seen in the lumen. (**C**) Epithelial lining with simple cuboidal and columnal epithelium with cilia. (**D**) Epithelial lining with pseudostratified columnal epithelium. Smooth muscle bundles seen in the surrounding stroma.

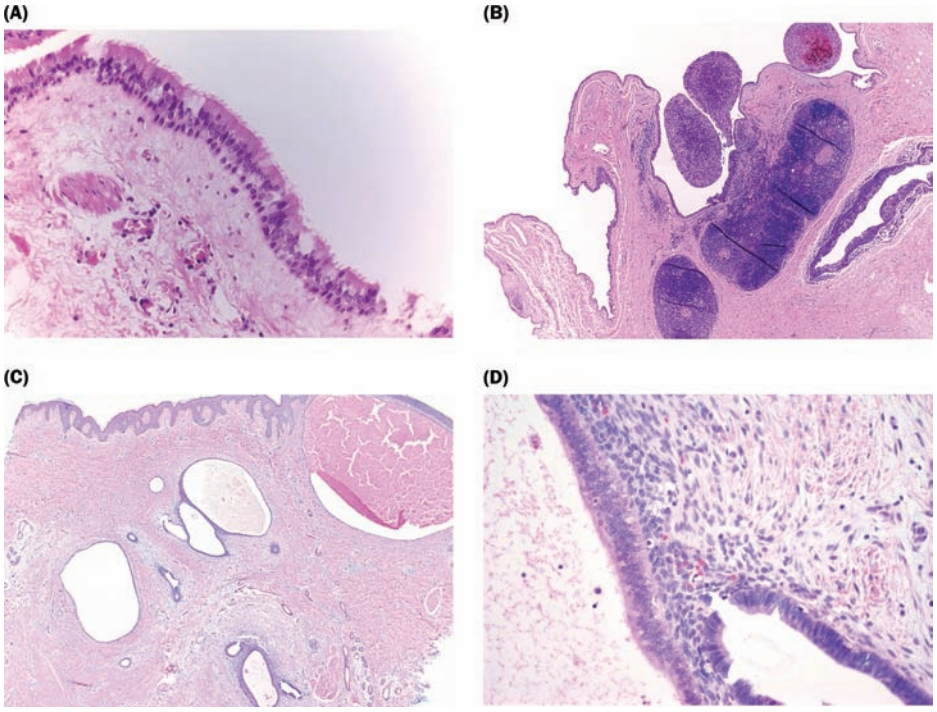

Figure 19 (**A**) Epithelial lining with pseudostratified columnal epithelium, cilia, and goblet cells. (**B**) Epithelial lining with stratified squamous and ciliated columnal epithelium. Dense lymphoid aggregates in surrounding stroma. (**C**) Multiple dermal cystic structures with epithelial linings. (**D**) Columnal epithelial lining with hemorrhage and fibrosis in the stroma.

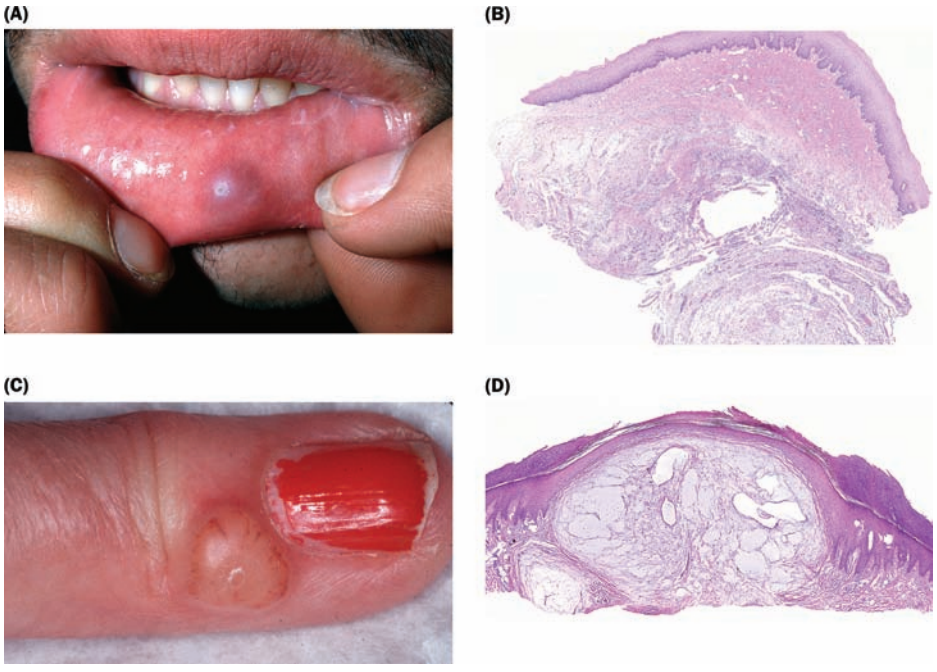

Figure 20 (**A**) Cystic swelling on the lower lip. (**B**) Amorphous zone of mucinous material with lymphocytes and neutrophils, but no epithelial lining. (**C**) Compressible cystic lesion on the dorsal finger. (**D**) Ill-defined collection of mucin in the superficial dermis with a surrounding epidermal collarette. No epithelial lining is present.

14

Premalignant and Malignant Epithelial Neoplasms

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CONTENTS

Premalignant and malignant epithelial neoplasms refer generally to tumors arising in or from surface epidermis, or mucosal surfaces such as lip, glans penis, and so on. Squamous cell carcinoma in situ is an example of premalignant epithelial neoplasm, while squamous cell carcinoma and basal cell carcinoma represent invasive cancers of the epidermis.

Squamous cell carcinoma in situ is histologically squamous cell carcinoma confined to the epidermis and is diagnosed when there is full thickness epidermal cytologic atypia analogous to the carcinoma in situ of the uterine cervix. Analogous to cervical intraepithelial neoplasia in the uterine cervix, there is a biologic continuum of squamous cell carcinoma in situ with early lesions showing cytologic atypia involving the lower layers of the epidermis as frequently seen in solar keratoses.

There are many controversial issues regarding these definitions. Indeed, some pathologists categorize these atypical intra-epithelial proliferations as frankly cancerous and others as precancerous because a subset appears to be associated with, or evolve into squamous cell carcinoma. On the other hand, others define them as not precancerous because the majority of the lesions do not evolve into invasive carcinoma. However, many of the lesions are treated or removed, and therefore, an accurate estimate of invasive potential cannot be rendered.

Squamous and basal cell carcinoma arise typically in sun exposed areas of the body. Squamous cell carcinoma arising in sun-exposed sites or arising in association with actinic keratosis does not commonly metastasize except those occurring in the lip or at sites exposed to radiation, former burn sites, chronic ulcers, or sinus tracts. Basal cell carcinoma is the most common skin cancer and only rarely metastasizes.

Various topics discussed here are adapted from the Dermatopathology Interactive Atlas. Bhawan J, Sau P, Byers HR, 2001. www.dermpathatlas.com

ACTINIC KERATOSIS

Synonyms: Solar keratosis; senile keratosis.

Clinical Presentation:

- Most commonly found on sun-exposed areas of fair-skinned individuals in middle- or later-age groups
- Remarkable variance in clinical and pathologic characteristics
- An isolated scaly plaque with an erythematous base (Fig. 1A)
- Few millimeters in diameter to rarely a plaque a few centimeters in diameter
- Often multiple (Fig. 1B) and widely or locally distributed
- May appear as papulonodules, atrophic plaques, or with cutaneous horns
- Variants include pigmented actinic keratosis, some of which have little scale, such as the spreading pigmented actinic keratosis that mimics lentigo maligna.
- Involvement of the vermilion border of the lip is called actinic cheilitis.

Microscopic Features:

- Microscopic features vary from minimal keratinocytic atypia that are confined to basal and suprabasal layers (Figs. 1C and 2A) with overlying normal stratum corneum to moderate keratinocytic atypia that does not reach the granular cell layer (Fig. 2A); with overlying hyperkeratosis and focal parakeratosis to focus fully evolved lesions of squamous cell carcinoma in situ; and with keratinocytic atypia reaching granular cell layer (full-thickness atypia) (Fig. 2B). When there are broad areas, where the squamous atypia involves the granular layer, the lesion is then considered to have evolved into squamous cell carcinoma in situ. In my opinion, even then the lesions should still be regarded and managed as an actinic keratosis if that diagnosis can be correlated with clinical features.
- The above variation may be seen within the same lesion (Fig. 3A).
- Marked solar elastosis is seen subjacent to actinic keratoses (Figs. 3A and B).
- Alternating parakeratosis and orthokeratosis of the actinic keratosis is secondary to the preservation of normal adnexal keratinocyte differentiation and is a useful diagnostic clue (Fig. 3B).
- Sharp demarcation of atypical cell cytoplasm (which is more eosinophilic or pink) from infundibular or acrosyringeal cytoplasm (which is more basophilic or blue) is seen (Fig. 3B).

- Early budding of actinic keratosis shows continuity to surface epidermis and may show only mild atypia.
- Extensive budding may be seen (Fig. 4A) and may even fill the papillary dermis.
- Hypertrophic actinic keratosis shows marked parakeratotic horn and hyperplastic epidermis with keratinocytic atypia (Fig. 4B).
- Atrophic actinic keratosis has scant parakeratosis, flattened and thinned epidermis, and basal layer cytologic atypia (Fig. 4C).
- Bowenoid actinic keratosis exhibits scant or absent parakeratosis with disordered anaplastic keratinocytes in a nested or "bowenoid" pattern.
- Acantholytic actinic keratosis is a variant that exhibits marked acantholysis due to disruption of cytoplasmic bridges (Fig. 3C).
- Lichenoid actinic keratosis shows lichenoid infiltrate, in addition to changes of actinic keratosis (Fig. 4C).
- Pigmented actinic keratosis typically exhibits increased basal layer pigmentation and keratinocytic atypia (Fig. 4A).
- Focal acantholysis of pigmented actinic keratosis may resemble dyshesive atypical lentiginous melanocytic hyperplasia and may be confused with lentigo maligna or melanoma in situ. Immunoperoxidase stains can be helpful. Melan A/Mart 1 and Mel-5 are not expressed in the neoplastic keratinocytes in actinic keratosis, but are observed in melanocytic lesions.

Differential Diagnosis:

- Histologic presentation of a fully evolved actinic keratosis in which the cytological atypia extends up to the granular zone is difficult to differentiate from squamous cell carcinoma in situ seen in Bowen's disease, bowenoid papulosis, arsenical keratosis, and erythroplasia of Queyrat.

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SQUAMOUS CELL CARCINOMA IN SITU

Squamous cell carcinoma in situ (SCCIS) is a histologic term with many diverse clinical presentations. The biologic importance is also variable from a benign course in bowenoid papulosis to possible invasive growth potential in Bowen's disease. It is extremely important to make a clinicopathologic correlation (CPC) when a histologic diagnosis of SCCIS is made. For example, bowenoid papulosis has the histologic features of SCCIS, which is considered to be a benign, virally induced condition. Lack of CPC can lead to unnecessary surgery. Similarly, SCCIS seen in the context of actinic keratosis should be managed as actinic keratosis and a wide excision is unnecessary just because it shows areas of SCCIS. The clinical and pathologic features of several variants of SCCIS are listed in Table 1.

Clinicopathologic Correlation:

See Table 1.

Microscopic Features:

- Keratinocytic atypia with increase in nuclear to cytoplasmic ratio and disorderly arrangement of the keratinocytes (Figs. 6 and 7)
- Keratinocytic nuclear atypia with large hyperchromatic nuclei and many dyskeratotic cells (Fig. 6B)
- Scattered mitoses (Fig. 6C) including atypical tripolar or tetrapolar forms
- Lesions with prominent clear-cell change may be observed (Fig. 6A).
  - Clear-cell pattern may be suprabasal and contiguous with preservation of basal layer eosinophilic cytoplasm, forming the "eyeliner" sign (Fig. 7A)
- Histologic atypia may not be transepidermal and the granular or upper layers may appear normal (Fig. 7B).
- Intraepithelial growth pattern forming distinct nests of atypical keratinocytes
- Figure 7C or scattered individual atypical keratinocytes suggestive of pagetoid growth pattern (Fig. 7D) can be seen
- Squamous cell carcinoma in situ may be pigmented (pigmented Bowen's disease) (Fig. 7E)

Table 1 Clinicopathologic Correlation: Squamous Cell Carcinoma In Situ

	Clinical	Pathology	Etiology
Actinic keratosis	Sun-exposed areas; keratotic lesions on erythematous base	Atypia limited to basal layer to full thickness atypia	Chronic sun exposure or X-radiation
Arsenical keratosis	Keratotic lesions or patches on hands	SCCIS; full thickness atypia may not be seen focally	Chronic arsenic ingestion
Bowen's disease	Usually nonexposed area well (Figs. 5A, B) circumscribed erythematous plaque	SCCIS; full thickness atypia may not be seen focally	Unknown
Bowenoid papulosis	Genital location; multiple skin colored or pigmented papules	SCCIS; full thickness atypia may not be seen focally	Human papilloma virus
Erythroplasia of Queyrat	Glans penis in elderly males; erythematous plaque	SCCIS; full thickness atypia may not be seen focally	Unknown

Abbreviation: SCCIS, squamous cell carcinoma in situ.

Differential Diagnosis:

- Small 1 to 3 mm red papules on the penis or vulva of sexually active, young- to middle-aged adults, which histologically appear as SCCIS should be diagnosed as bowenoid papulosis.
- Fully evolved lesions of actinic keratosis with atypia up to the granular zone can be difficult to distinguish from Bowen's disease where the atypia involves the granular zone; clinicopathologic correlation is helpful.
- Paget's disease or extramammary Paget's disease; clonal atypical intra-epidermal proliferation with cytoplasmic bridges and lack of mucin and gross cystic disease fluid protein (GCDFP)-15 immunostaining favors clonal SCCIS.

Bowen's Disease	Paget's/Extramammary Paget's Disease	Malignant Melanoma In Situ
Clonal atypical intra-epidermal proliferation with cytoplasmic bridges; lack of mucin and GCDFP-15	No intercellular bridges; positive for PAS and mucin; positive for GCDFP-15; positive for CK20	No intercellular bridges; negative for GCDFP-15, CK20; positive for Mel-5, Melan A/Mart-1

Abbreviation: PAS, periodic acid Schiff.

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SQUAMOUS CELL CARCINOMA

Clinical Features:

- Hyperkeratotic or ulcerated plaque, nodule or tumor on sun-exposed skin (Figs. 8A and B), or the lip of older adults.
- Minority occurs at radiotherapy sites, former burn sites, chronic ulcers, or chronic sinus tracts.
- Increase incidence following immunosuppression.
- The majority of the common sun-induced carcinomas rarely metastasize
- Tumors arising in irradiated sites, burn sites, chronic ulcers, sinus tracts, or on mucosal surfaces have higher incidences of metastasis.

Microscopic Features:

- Well-developed, well-differentiated squamous cell carcinoma exhibits hyperkeratosis, irregular epithelial hyperplasia, and irregular islands of squamous cells with central keratinization (squamous pearls) in the dermis. (Figs. 8C, 9A, and B).
- Neutrophilic intraepithelial microabscesses and dermal mixed inflammatory infiltrate may be seen (Fig. 9C).
- Moderately differentiated squamous cell carcinoma exhibits invasion of the dermis with irregular islands or sheets composed of squamous cells with distinct cytoplasmic bridges but incomplete keratinization (Fig. 10A and B).
- Poorly differentiated squamous cell carcinoma shows invasion of dermis with highly irregular islands, or strands, or individual cells with keratinization absent or formation of horn pearl (Figs. 10C and 11A).
- Immunoperoxidase staining for cytokeratin positivity (Fig. 11B) and absence of S-100, vimentin, CD-68, or actin staining are important to help confirm epidermal origin, and continuity of the tumor with the epidermis is a helpful clue to confirm the diagnosis of poorly differentiated squamous cell carcinoma.
- Some tumors may exhibit marked anaplasia with highly atypical mitoses yet show cytoplasmic bridges (Fig. 11C and D).
- Pagetoid pattern may be seen in normal epidermis due to extension from an adjacent squamous cell carcinoma (Fig. 12A).
- Acantholytic (adenoid) squamous cell carcinoma exhibits lobules of squamous cells with basal layer epithelial continuity and central marked acantholysis, suggesting gland formation or adnexal neoplasm.
- Acantholytic squamous cell carcinoma may show sheets of extensive acantholysis without glandular architecture (Fig. 12B).
- Spindle cell squamous cell carcinoma is a variant composed of spindle cells with or without focal keratinization (Fig. 12C).
- Other variants of squamous cell carcinoma include clear-cell type, signet-ring cell type, and pigmented type (Fig. 12D) with numerous melanocytes.
- Adjacent areas showing features of actinic keratosis are commonly seen in sun-exposed squamous cell carcinoma (SCC).

Differential Diagnosis:

- Hypertrophic actinic keratosis exhibits nuclear atypicality and downward extension of rete; separate irregular islands within the dermis indicate invasion, and favors squamous cell carcinoma.
- Keratotic basal cell carcinoma; despite squamous differentiation and horn pearl formation, focal basaloid hyperplasia is identified with focal mucinous stroma and retraction artifact.
- Pseudoepitheliomatous (pseudocarcinomatous) hyperplasia exhibits irregular continuous strands that may deeply extend into the reticular dermis; however, keratinocytic atypia appears less atypical and more reactive with large nuclei and abundant euchromatin ("open nuclei"). Often adnexal hyperplasia is noted in association with pseudocarinomatous hyperplasia. Associated granulomatous inflammation or dermal and/or intraepidermal abscesses can often be a clue to an underlying infectious cause for the reactive epidermal hyperplasia.
- Keratoacanthoma exhibits a symmetric, exo-endophytic architecture with a central horn filled crater and abundant hyalinized keratinocytic cell cytoplasm; definitive histologic distinction from a well-differentiated SCC is unreliable if the lesion is incompletely excised.
- Irritated seborrheic keratosis may be very difficult to differentiate from well-differentiated SCC. Low power architecture demonstrating a flat lower border, presence of uniform basaloid cells and numerous squamous eddies are helpful features.

References:
1. Evans HL, Smith JL. Spindle cell squamous carcinomas and sarcoma-like tumors of the skin: a comparative study of 38 cases. Cancer 1980; 45:2687–2697.
2. Johnson TM, Rowe DE, Nelson BR, et al. Squamous cell carcinoma of the skin (excluding lip and oral mucosa). J Am Acad Dermatol 1992; 26:467–484.
3. Johnson WC, Helwig EB. Adenoid squamous cell carcinoma (adenoacanthoma). A clinicopathologic study of 155 patients. Cancer 1966; 19:1639–1650.
4. Kuo T. Clear cell carcinoma of the skin. A variant of the squamous cell carcinoma that simulates sebaceous carcinoma. Am J Surg Pathol 1980; 4:573–583.
5. Phillips TJ, Salman SM, Bhawan J, Rogers GS. Burn scar carcinoma. Diagnosis and management. Dermatol Surg 1998; 24:561–565.

VERRUCOUS CARCINOMA

Clinical Features:

- Verrucous carcinoma, a variant (Figs. 13A and B), may be initially mistaken clinically or pathologically as a benign viral papilloma on the oral mucosa, genitalia, or other sites such as the plantar surfaces.
- Verrucous carcinoma is more slow growing and locally invasive; however, metastases are reported.

Microscopic Features:

- Verrucous carcinoma is a well-differentiated variant of SCC showing an exophytic verrucous architecture but with endophytic broad deep extension into the submucosa or dermis (Figs. 13C and 14).
- Superficial portion of verrucous carcinoma exhibits benign appearing papillomatous epidermal hyperplasia (Fig. 14A); however, markedly endophytic architecture is seen deeply.
- Minimal cytologic atypia at the invading border is usually seen (Fig. 14B); it is the infiltration of the submucosa or reticular dermis with an extensive endophytic growth pattern that favors the diagnosis of verrucous carcinoma.

Reference:
1. Kanik AB, Lee J, Wax F, et al. Penile verrucous carcinoma in a 37-year-old circumcised man. J Am Acad Dermatol 1997; 37:329–331.

KERATOACANTHOMA

Clinical Features:

- Solitary (Fig. 15A) or multiple (Fig. 15B), rapidly growing, firm, hyperkeratotic, dome-shaped nodule(s) with a central hyperkeratotic crater
- Grow rapidly for several weeks and then stabilize in size to eventually involute over a few months.
- Multiple lesions are associated with immunosuppression, Fergusson-Smith syndrome, or the Grzbowski syndrome.
- One to several can be seen in the Muir-Torre syndrome with or without associated sebaceous tumors.
- Some lesions arise at critical sites and may be indistinguishable from squamous cell carcinoma. Due to the difficulty in distinguishing these lesions from well-differentiated SCC and inability to prospectively predict involution, lesions without classical clinical and histologic features (see later) are best classified as squamous cell carcinoma, keratoacanthoma type.
- It is considered to be a variant of SCC as some cases have been shown to metastasize, and unequivocal histologic differentiation is not possible.

Microscopic Features:

- Exo-endophytic crateriform lesion (Fig. 15C) with symmetric epidermal "lips" on either side, central hyperkeratosis and marked squamous cell proliferation of cells with abundant hyalinized cytoplasm.
- Symmetric downward infiltration of irregular islands and broad strands into the reticular dermis; horn pearls may be seen in the outermost layer of the irregular infiltrating epithelial islands.
- Minimal nuclear atypia is present along the basal layer and within the glycogenated "hyalinized" cells (Fig. 16A).
- Early downward proliferation of the squamous sheet entraps reticular fibers or solar elastic fibers and typically does not elicit a stromal fibrous response (Fig. 16B).
- Lymphocytic infiltrate is often present adjacent to hyperplastic epithelium, and intraepithelial neutrophilic abscess (Fig. 16B) may be seen.
- Involuting or regressing stage of keratoacanthoma shows a crateriform lesion with collapse of the abundant eosinophilic hyalinized cell layers, formation of a keratotic plug with an underlying benign appearing epidermal cell layer, numerous colloid bodies, lymphocytic infiltrate, and fibrosis.

Differential Diagnosis:

Keratoacanthoma (KA)	Squamous Cell Carcinoma (SCC)
Rapid onset	Slow onset
Crateriform lesion	May be crateriform sometimes
Intraepithelial microabscess and intraepithelial elastic fibers	Can be seen in well-differentiated SCC but not as prominently as SCC
Can resolve spontaneously	Do not spontaneously resolve
Metastasis rare	Can metastasize

References:
1. Hodak E, Jones RE, Ackerman AB. Solitary keratoacanthoma is a squamous-cell carcinoma: three examples with metastases. Am J Dermatopathol 1993; 15:332–352.
2. LeBoit PE. Can we understand keratoacanthoma? Am Dermatopathol 2002; 24:166–168.
3. LeBoit PE. Is keratoacanthoma a variant of squamous cell carcinoma. New insights into an old controversy . . . soon? Am J Dermatopathol 1995; 17:319–320.
4. Schwartz RA. Keratoacanthoma. J Am Acad Dermatol 1994; 30:1–19.

PSEUDOCARCINOMATOUS (PSEUDOEPITHELIOMATOUS) HYPERPLASIA

Several disorders of the skin may induce marked downward proliferation of the epidermis and thus mimic well-differentiated SCC. Unfortunately, this may occur in sites where SCC is known to arise such as in chronic ulcers, draining sinuses of hidradenitis suppurativa, osteomyelitis, or after a burn. It may also be seen in bromoderma and blastomycosis. Clinical history is essential for proper diagnosis.

Microscopic Features:
- Marked epidermal hyperplasia with pale, glycogenized squamous cells and marked downward extension of irregular, broad, epidermal islands or strands into the reticular dermis (Fig. 17).
- Nuclei may be enlarged, but nuclear hyperchromasia is lacking (Fig. 17).
- Horn pearl formation or individual cell keratinization is absent (Fig. 17).
- Can be associated with a variety of chronic inflammatory (deep fungal infections) and neoplastic (granular cell tumor) conditions. Granulomatous inflammation and dermal and/or epidermal abscesses can be a hint of an associated inflammatory process (as an infection). Adnexal hyperplasia is often identified in association with pseudocarcinomatous hyperplasia.

Differential Diagnosis:
- Well-differentiated squamous cell carcinoma, exhibits nuclear atypia and deep horn pearl formation or individual cell keratinization.

References:
1. Freeman RG. On the pathogenesis of pseudoepitheliomatous hyperplasia. J Cutan Pathol 1974; 1:231–237.
2. Wagner RF Jr., Grande DJ. Pseudoepitheliomatous hyperplasia vs. squamous cell carcinoma arising from chronic osteomyelitis of the humerus. J Dermatol Surg Oncol 1986; 12:632–635.
3. Winer LH. Pseudoepitheliomatous hyperplasia. Arch Dermatol 1940; 42:856–867.

BASAL CELL CARCINOMA

Synonym: Basal cell epithelioma.

Clinical Features:
- Occurs in sites chronically exposed to the sun and increased in frequency from the third decade onward, although they have been reported in children and young adults.
- Most frequently on the face and scalp, rarely arises on the digits, the back of the hand, dorsum of the foot, or on the ears.
- Typically are solitary opalescent nodules with telangiectasia (Fig. 18A) or ulceration (Fig. 18B).
- Common variant is the superficial type (Fig. 18C), which often appears as a thin plaque.
- Morphea-form may present as hypopigmented, depressed firm plaque (Fig. 18D).
- Other variants include cystic type, fibroepithelioma of Pinkus type, and pigmented basal cell carcinoma (Fig. 18E), which can mimic melanocytic nevi or melanomas.
- Typically, basal cell carcinoma is locally aggressive, and may reach several centimeters in size, and if neglected may erode into muscle, bone, or brain. Basal cell carcinoma rarely metastasizes.

Microscopic Features:
- Nodular type basal cell carcinoma is an expansile tumor within the papillary dermis or extending into the reticular dermis (Fig. 19A).
- Composed of single or interconnected lobules of basaloid cells with scant cytoplasm.
- Adjacent mucinous stroma that forms open clefts with the periphery of the nodules; the so-called "retraction artifact" (Fig. 19B).
- Cells along the periphery of the nodules usually exhibit palisading cells with nuclear crowding (Fig. 19B).
- Tumors may exhibit central lobular cellular necrosis and, if extensive, as seen in breast carcinomas (Fig. 20A), gives rise to "comedo" carcinoma architecture.
- Tumors are often ulcerated with formation of crust.
- Superficial type basal cell carcinoma exhibits intermittent minute to large lobules of palisading basal cells extending downward from the base of the rete ridges or epidermis (Fig. 20C).
- Mucinous stroma with retraction artifact subjacent to the atypical basaloid budding; however, retraction is not always seen, particularly in early lesions.
- Cystic basal cell carcinoma exhibits single or multiple large cystic cavities (Fig. 20B) within the central region of the tumor and contains degenerative cellular debris.
- Pigmented basal carcinoma exhibits pigment within tumor cells and an increase in melanocytes with numerous melanophages in the tumor stroma (Fig. 20D).
- Infiltrating type of basal cell carcinoma exhibits irregular thin strands of basaloid cells with deep extension among collagen bundles, nerve, vessels, muscle, adipocytes, or bone.
- Infiltrative type basal cell carcinoma may show more broad sheets superficially (Fig. 21A) and an infiltrative pattern deeply (Fig. 21B).
- Infiltrative type basal cell carcinoma may show mild or marked fibrotic stroma and thus exhibits a spectrum in continuity with morphea-type basal cell carcinoma.
- Morphea-type or sclerosing basal cell carcinoma exhibits irregular thin branching strands of basaloid cells embedded in a dense fibrotic stroma (Fig. 22A).
- Perineural invasion (Fig. 20E) may be seen in any type of basal cell carcinoma but particularly with infiltrating and morphea types.
- Tumors with marked intralobular mucin production may form anastomosing cords of basal cells embedded in the mucin, or form multiple small islands of mucin deposition.
- Basal cell carcinomas may become a pseudoglandular or adenoid type (Fig. 23A) as mucin production within cords of basal cell carcinoma form pseudolumina.
- Basal cell carcinomas may exhibit appendageal differentiation such as eccrine or sebaceous differentiation (Fig. 23B).
- Keratotic basal cell carcinoma exhibits squamous differentiation with horn pearl formation (Fig. 24A), whereas presence of squamous eddies or squamous differentiation (Fig. 24B) is often seen in squamatized basal cell carcinoma.
- Fibroepithelioma of Pinkus is a variant of basal cell carcinoma with thin strands of anastomosing basal cells separating a fibrous stroma (Fig. 25).
- Marked amyloid or colloid bodies may be seen in the surrounding stroma representing necrotic tumor cell aggregates or maybe seen within the tumor as well.
- Architectural and cellular overlap of superficial, nodular, infiltrating, and other types of basal cell carcinoma is more often the rule than the exception.
- Basal cell carcinoma is a common tumor; therefore, collision of lesions with other epidermal and dermal neoplasms produces unusual clinical appearance and includes basal cell carcinoma and seborrheic keratosis, intradermal melanocytic nevus, verruca vulgaris, syringoma, and melanoma.

Clinicopathologic Correlation:

Clinical	Pathological
Nodular: Dome-shaped, nodule with pearly border and telangiectasia	Nodule of atypical basaloid cells with peripheral palisading and clefting
Nodulo-ulcerative: Same with ulceration	Same as above with overlying ulceration
Superficial erythematous patch/plaque: Can be confused with psoriasis or dermatitis	Usually multifocal atypical basaloid proliferation attached to the epidermis in the papillary dermis
Morphea-type: Sclerotic patch	Strands of atypical epithelium in dense fibrotic stroma
Cystic: Mass presenting as cystic lesion	Cystic lesion with variable amount of atypical basaloid cells in the periphery
Fibroepithelioma of Pinkus: Polypoid mass	Polypoid with thin anastomosing strands of basaloid epithelium in mucinous fibrous stroma
Pigmented: May be confused with melanoma	Pigment in tumor cells as well as stroma

Differential Diagnosis:

Trichoepithelioma	Basal Cell Carcinoma
More organoid	Not organoid
Papillary mesenchymal bodies	No papillary mesenchymal bodies
No mucinous stroma	Mucinous stroma
No infiltration	Infiltrating
No retraction artifact	Retraction artifact
Horn cysts	No horn cysts

References:

1. Bhawan J. Ultrastructure of melanocyte–keratinocyte interactions in pigmented basal cell carcinoma. Pigment Cell Res 1979; 5:38–47.
2. Bhawan J, Mehregan A, Legg YJ, et al. Pigmented basal cell carcinoma and superficial spreading malignant melanoma: An unusual combination. J Cutan Pathol 1984; 11:471–475.
3. Shoji T, Lee J, Hong SH, et al. Multiple pigmented basal cell carcinomas. Am J Dermatopathol 1998; 20:199–202.
4. von Domarus HV, Stevens PJ. Metastatic basal cell carcinoma. Report of five cases and review of 170 cases in the literature. J Am Acad Dermatol 1984; 10:1043–1060.

Acknowledgments:

Figures 13A, B and 15A, B have been reprinted with permission from the Dermatopathology Interactive Atlas (Bhawan J, Sau P, Byers HR, 2001).

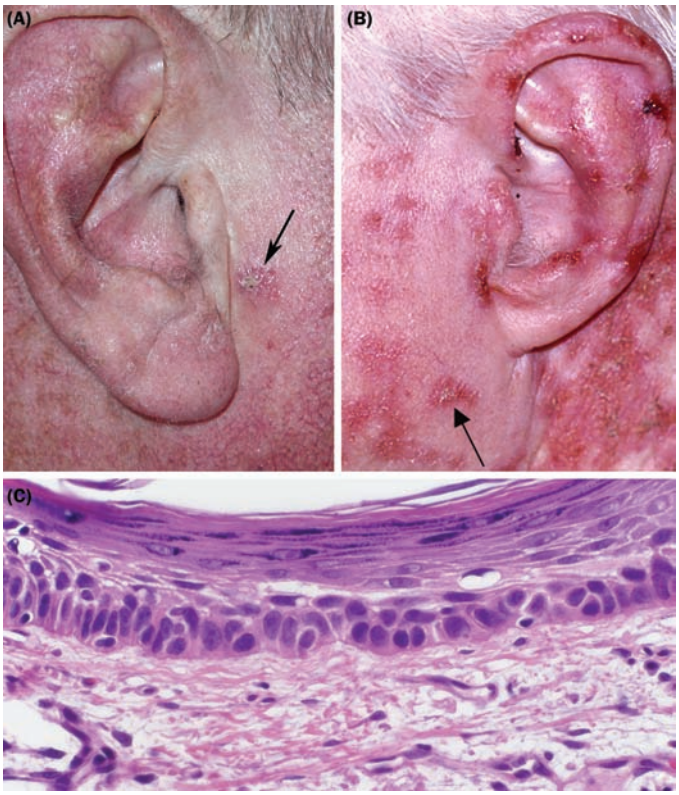

Figure 1 Clinical photograph showing scaly plaque with erythematous base (*arrow*) in preauricular area (**A**) and multiple (**B**) similar lesions on cheek and ear. Keratinocytic atypia involving the lower layers of the epidermis is seen (**C**).

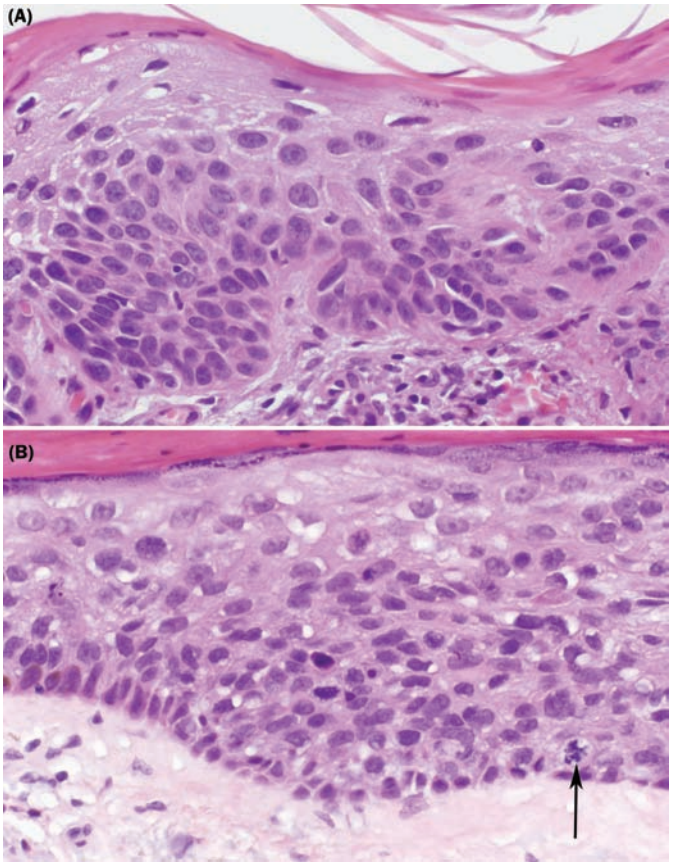

Figure 2 Keratinocytic atypia with disorderly arranged keratinocytes involve the lower two-thirds of the epidermis (**A**) while most of the epidermis appears atypical in (**B**). Note scattered dyskeratotic cells and suprabasal mitotic figure (*arrow*).

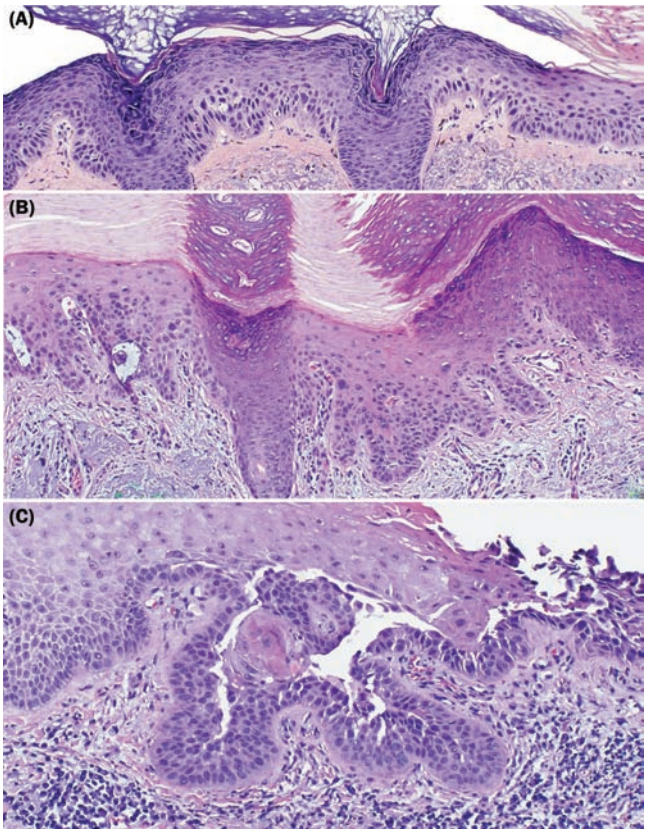

Figure 3 Actinic keratosis with atypia confined to the basal layer on the left, lower-third in the middle and lower half on the right, all in one lesion (**A**). Also note solar elastosis in the dermis. Alternate parakeratosis overlying atypical squamous epithelium and orthokeratosis overlying eccrine duct (**B**) is a useful diagnostic clue. Also note sharp demarcation of basophilic acrosyringeal cytoplasm from eosinophilic cytoplasm of atypical keratinocytes. Acantholysis of the atypical squamous epithelium (**C**). This should not be confused with acantholytic blistering disorders.

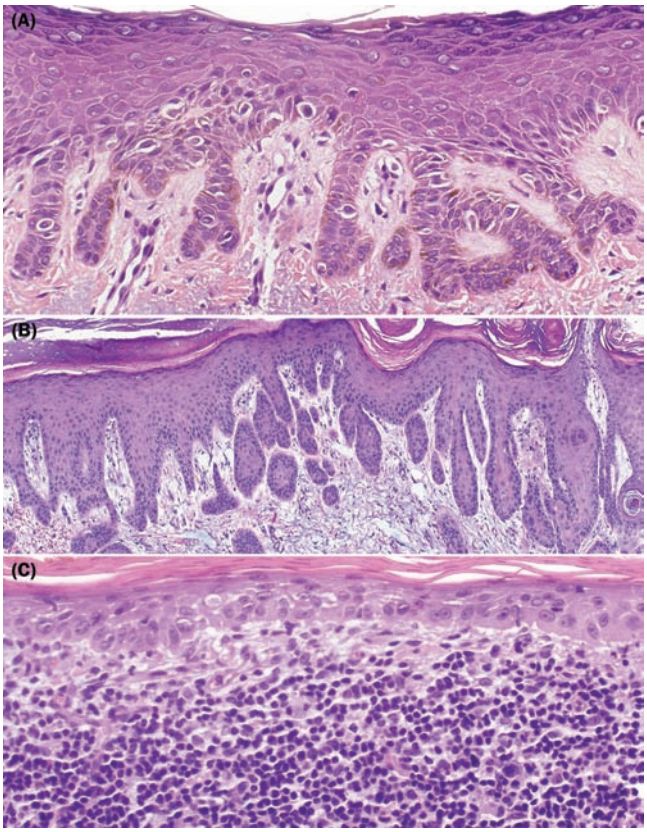

Figure 4 Atypia is confined to the downward budding of strands of squamous epithelium, while the bulk of the epidermis appears normal (**A**). Hyperplastic epidermis with atypia is seen in this hypertrophic variant of actinic keratosis (**B**). The atypical squamous epithelium is atrophic (**C**), microphotograph taken at 20x in comparison to hypertrophic type (**B**) taken at 4x. Also note the lichenoid lymphocytic infiltrate (**C**).

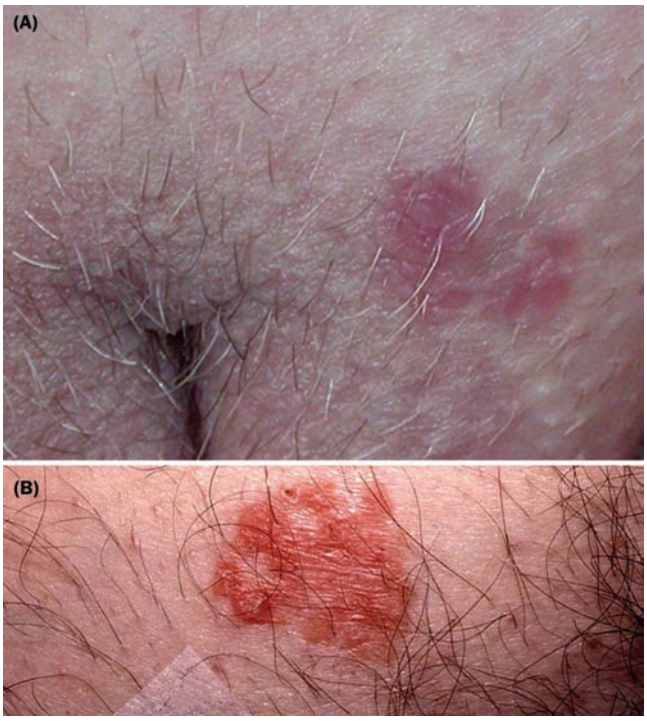

Figure 5 Clinical photograph of Bowen's disease in non sun-exposed pubic area (**A**) and lower abdomen (**B**). These are sharply defined erythematous plaques with minimal scaling.

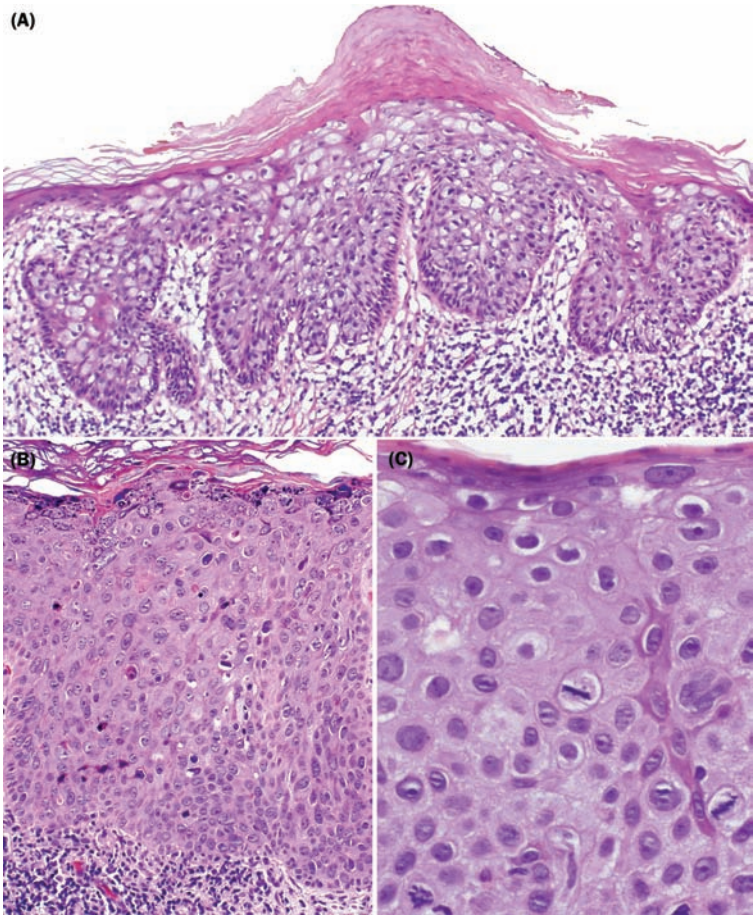

Figure 6 Transepidermal atypia of clear appearing keratinocytes in squamous cell carcinoma in situ (**A**). Note several dyskeratotic cells with large hyperchromatic nuclei and disorderly arrangement of keratinocytes (**B**) and scattered mitoses (**C**).

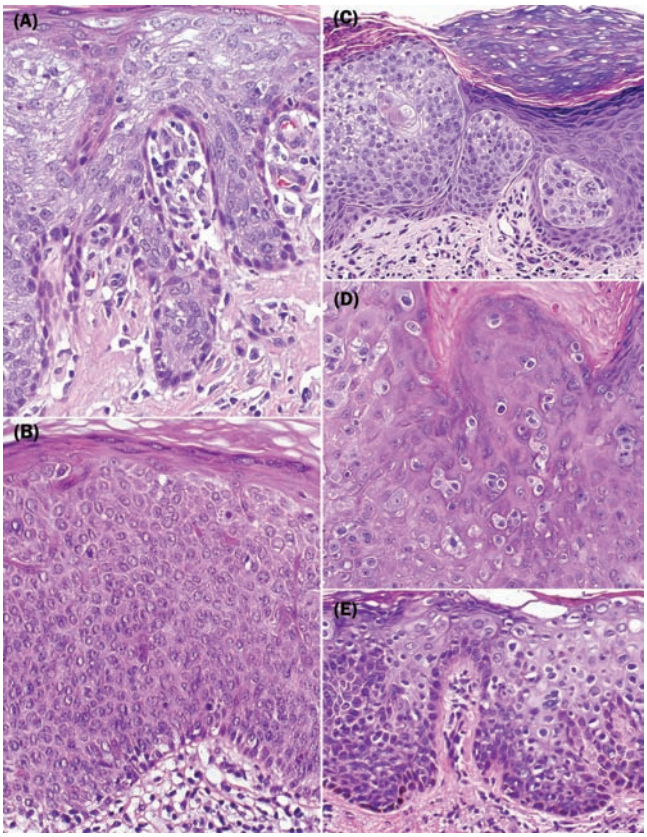

Figure 7 Basal cell layer with eosinophilic cytoplasm while the suprabasal atypical cells appear clear—the eyeliner sign (**A**). Note the granular and upper spinous layers appear normal in **B**. Clonal nests (**C**) of and scattered (**D**) atypical keratinocytes are seen in clonal and pagetoid pattern respectively. Abundant melanin is seen in lower layers of the atypical keratinocytes (**C**) in the pigmented variant of squamous cell carcinoma in situ.

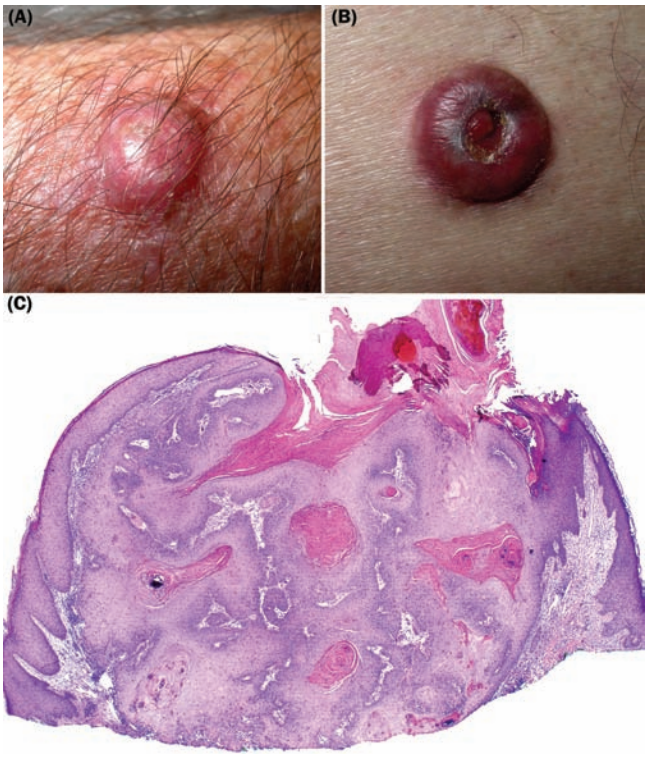

Figure 8 Dome-shaped hyperkeratotic nodule (**A**), with central ulceration (**B**). Scanning power centrally keratotic endophytic growth of atypical squamous epithelial islands (**C**).

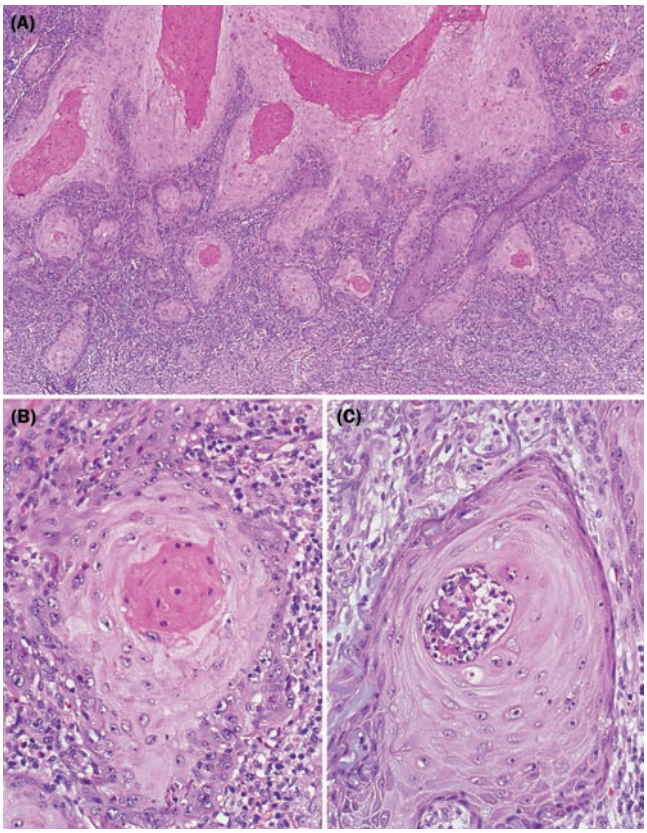

Figure 9 Well-differentiated squamous cell carcinoma. Irregular islands of squamous epithelioid cells invading in the dermis (**A**). Note the central keratinization, forming the so-called squamous pearls (**B**) and the intraepidermal microabscess (**C**).

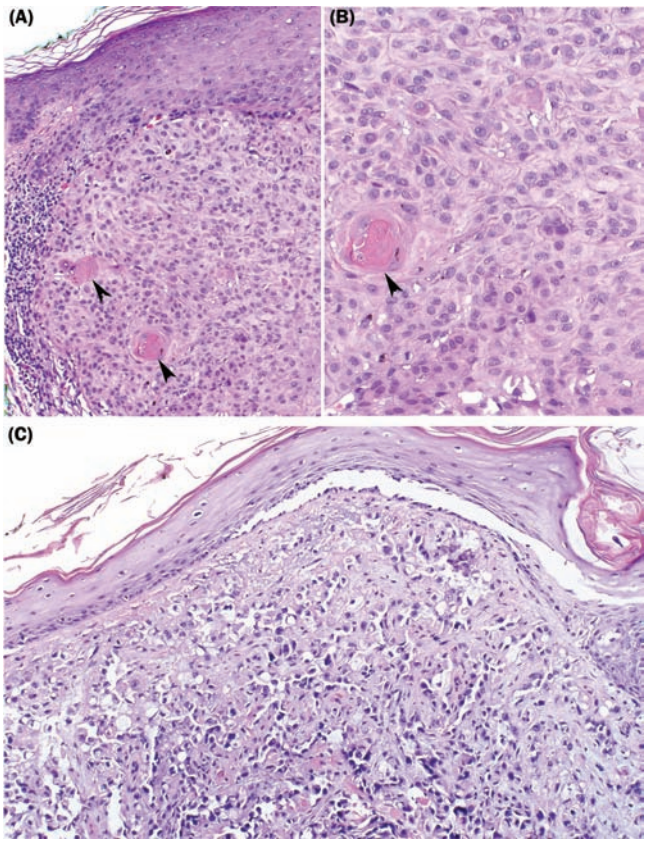

Figure 10 Moderately, well-differentiated squamous cell carcinoma (**A**, **B**) shows sheets of atypical squamous epithelium with intercellular bridges and occasional keratin pearl (*arrowheads*). Example of poorly differentiated squamous cell carcinoma (**C**). Note absence of keratinization or obvious evidence of squamous differentiation.

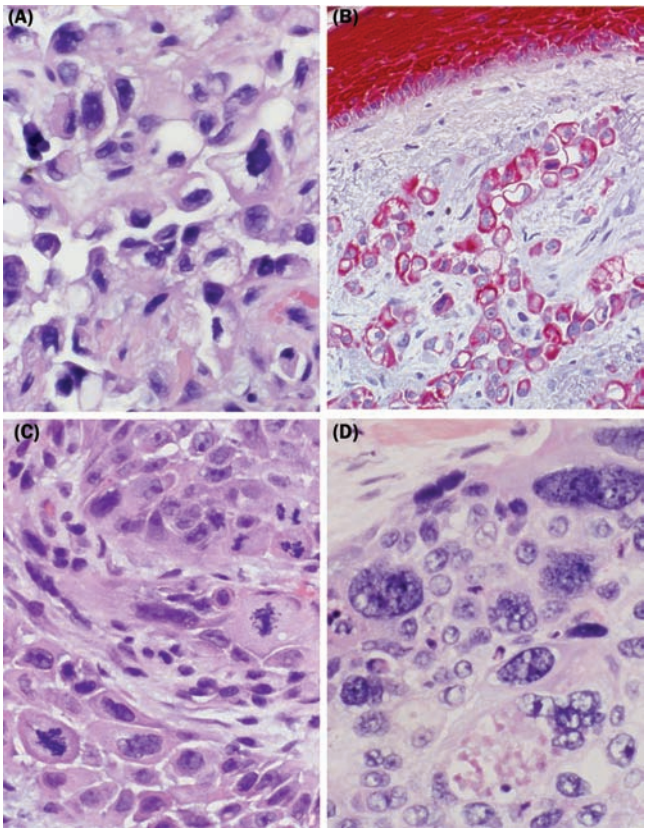

Figure 11 In the absence of keratinization and intercellular bridges (**A**), demonstration of cytokeratins by immunostaining (**B**) is diagnostic of poorly differentiated squamous cell carcinoma. Marked pleomorphism with numerous mitoses and hyperchromatic nuclei (**C**) and marked variation in the nuclear size with multiple or giant nuclei (**D**) can be seen in some squamous cell carcinomas.

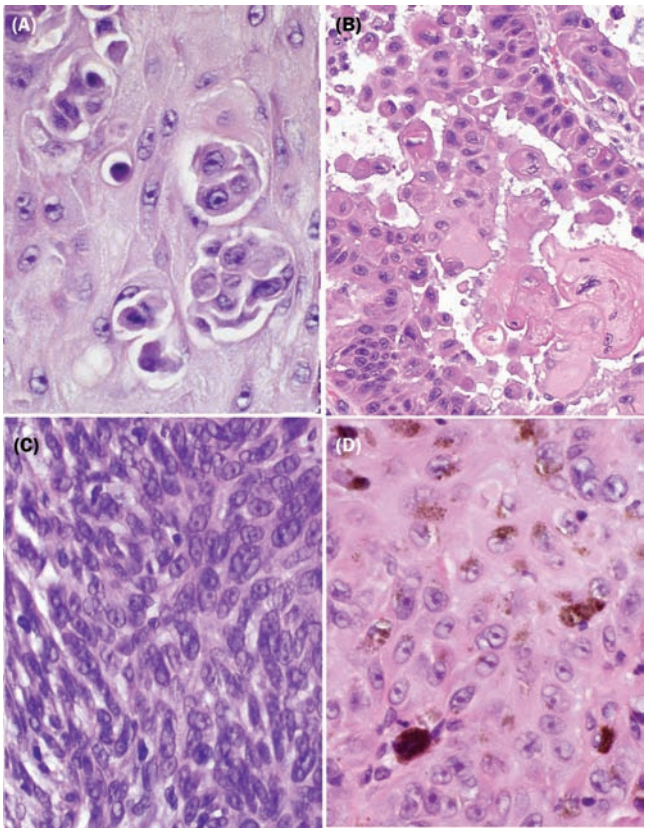

Figure 12 Scattered individual atypical keratinocytes (**A**) can be seen within the epidermis exhibiting pagetoid pattern similar to Paget's disease and melanoma in situ. Acantholysis may be extensive (**B**) within the islands of atypical squamous epithelial cells. Spindle cell morphology in the spindle cell variant (**C**). Melanin pigment can be seen in atypical epithelial cells (**D**) of pigmented type squamous cell carcinoma.

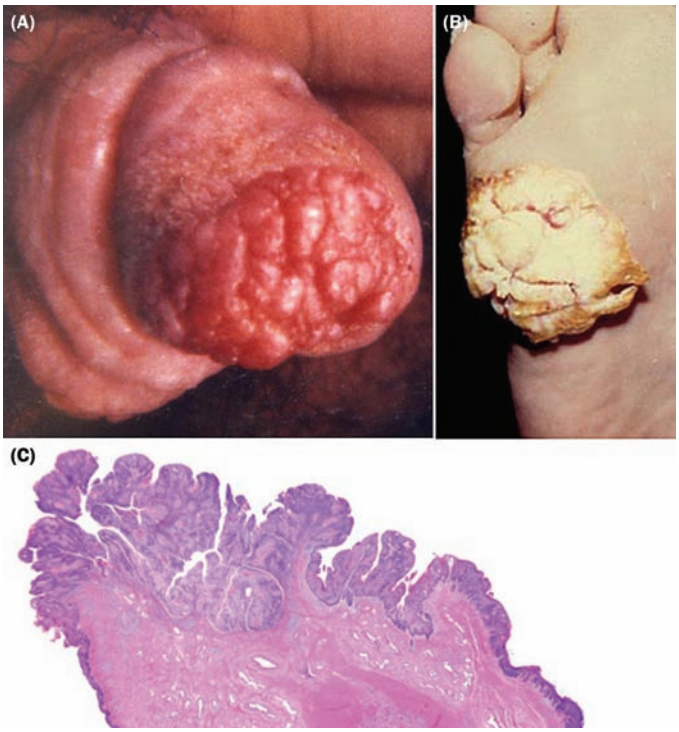

Figure 13 Verrucous carcinoma of the glans penis (**A**) and sole (**B**). Scanning photomicrograph showing mostly exophytic and minimally endophytic growth of squamous epithelium (**C**).

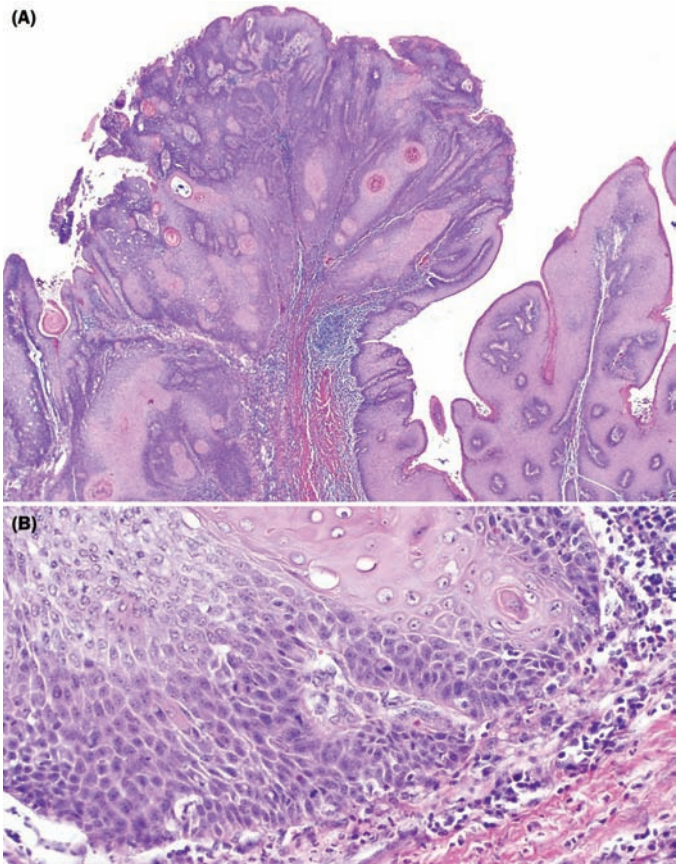

Figure 14 The nonpleomorphic hypertrophic squamous epithelium suggestive of verruca is seen (**A**) in the superficial aspect of the lesion. Minimal atypia of squamous epithelium is noted in the deeper areas (**B**).

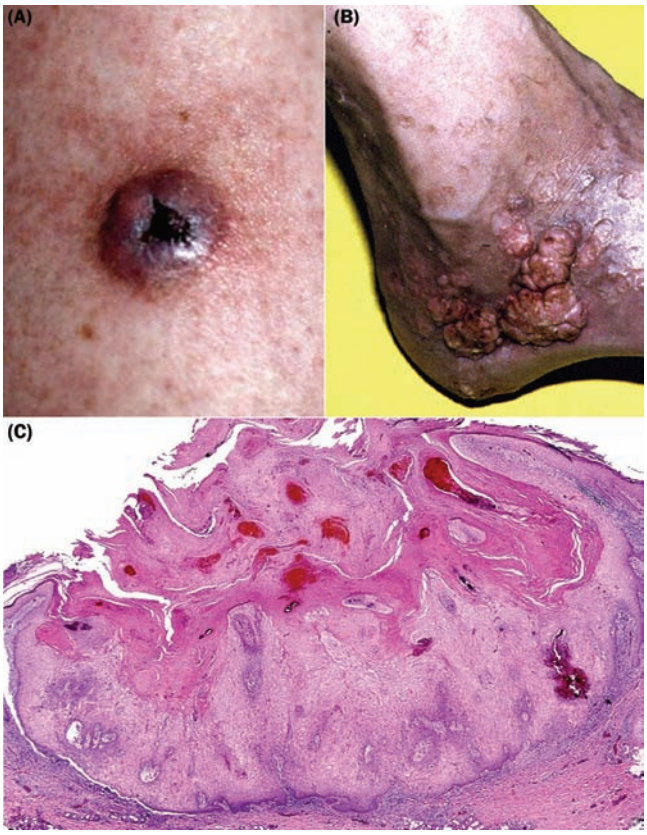

Figure 15 Clinical photograph showing (**A**) solitary dome-shaped nodule with central keratotic center and (**B**) multiple lesions of keratoacanthoma. Scanning photomicrograph (**C**) correspond to the clinical features with central keratotic lesion and lips of normal epidermis adjacent to the downward proliferation of squamous epithelium.

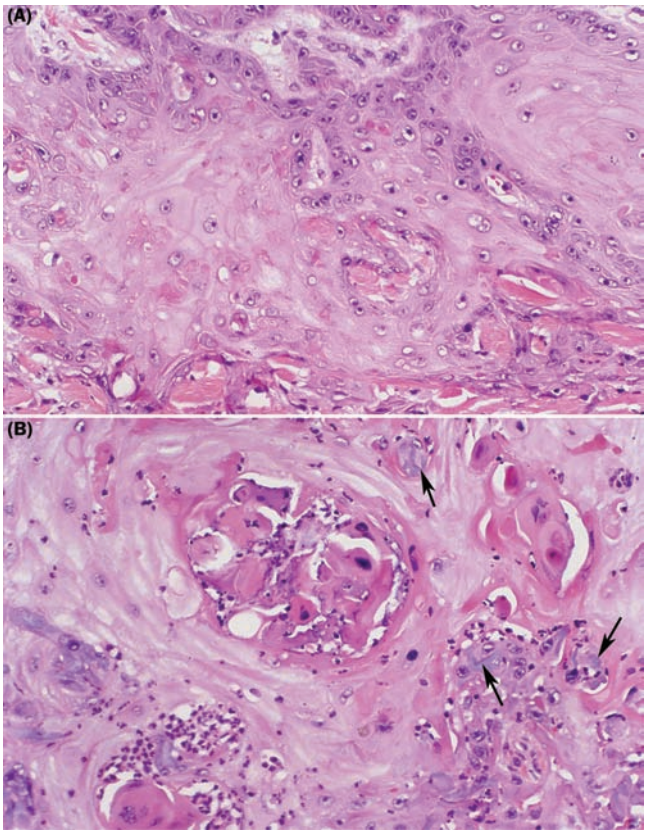

Figure 16 Lobules of squamous epithelial cells have pale, glassy cytoplasm with minimal atypia (**A**). Intraepithelial neutrophilic abscess and elastic fibers (*arrows*) are seen (**B**).

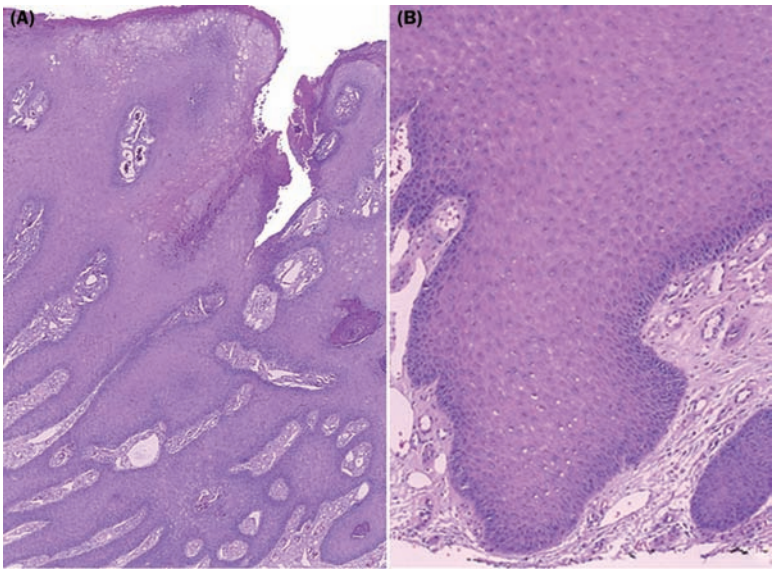

Figure 17 Irregular epidermal hyperplasia (**A**) without significant atypia (**B**) is seen in this example of pseudo epitheliomatous hyperplasia.

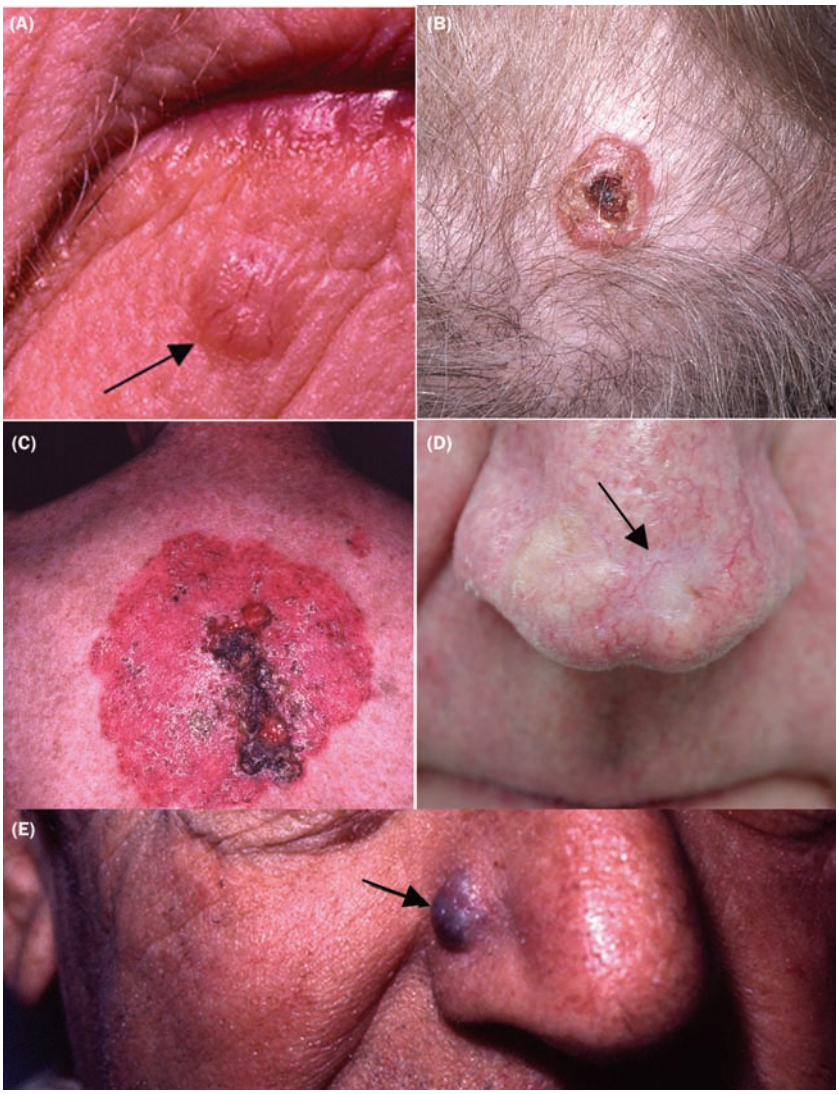

Figure 18 Clinical photographs of basal cell carcinoma: (**A**) nodular type with telangiectasia (*arrow*); (**B**) nodulo-ulcerative type; large (**C**), superificial erythematous plaque with ulceration in superficial type (**D**); sclerotic patch (*arrow*) on the nose in the morphea type; and (**E**) dark nodule (*arrow*) in the pigmented type.

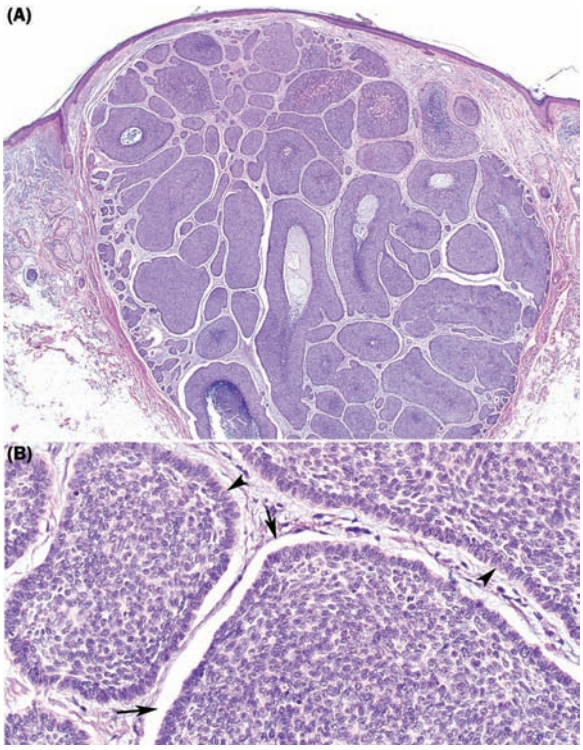

Figure 19 Scanning photomicrograph of well-circumscribed nodule made up of islands of basaloid cells (**A**). Peripheral palisading (*arrowheads*) and clefting (*arrows*) are seen in higher magnification (**B**).

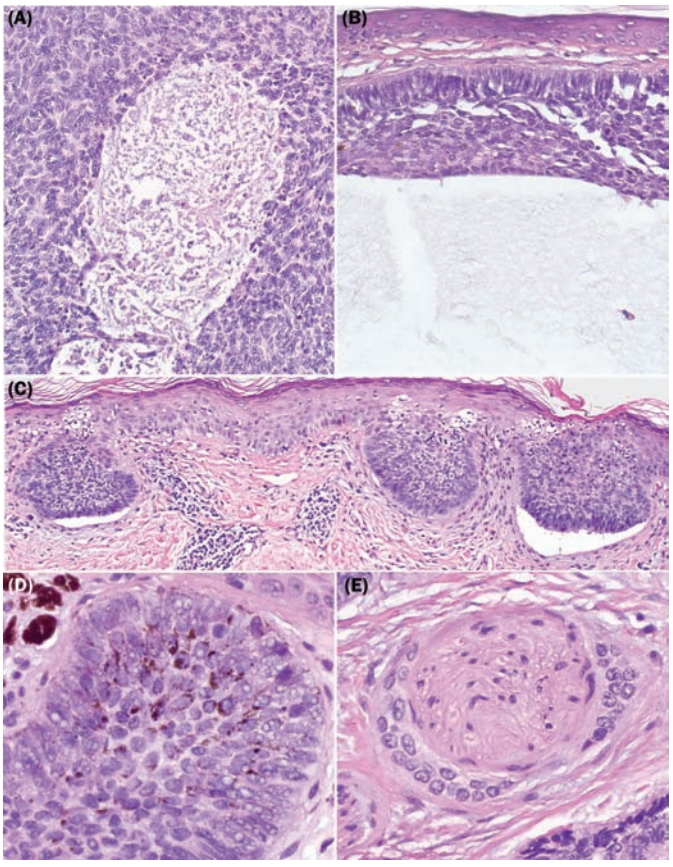

Figure 20 Photomicrographs of basal cell carcinoma showing central necrosis in the tumor islands resembling comedo pattern (**A**), large areas of tumor island with cystic degeneration (**B**), islands of atypical basaloid epithelium in superficial dermis attached to the epidermis (**C**), melanin in stroma as well as tumor cells (**D**), and perineural invasion (**E**).

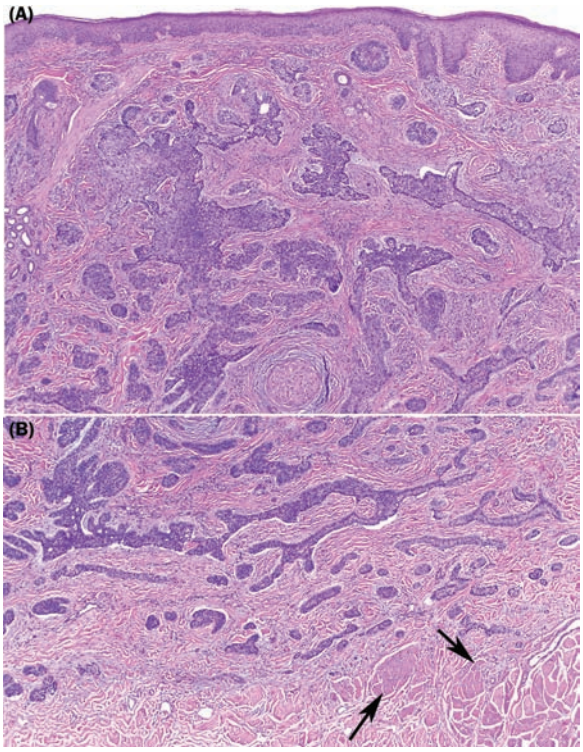

Figure 21 Irregular islands of atypical basaloid cells in minimally fibrotic stroma (**A**), extending deep into dermis (**B**), approaching the underlying skeletal muscle (*arrow*).

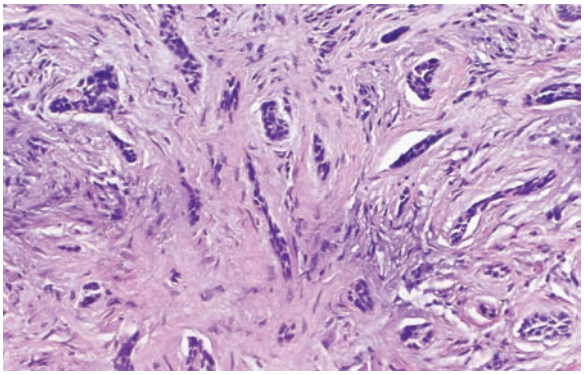

Figure 22 Irregular thin strands of basaloid cells in fibrotic stroma characterize the morphea type of basal cell carcinoma.

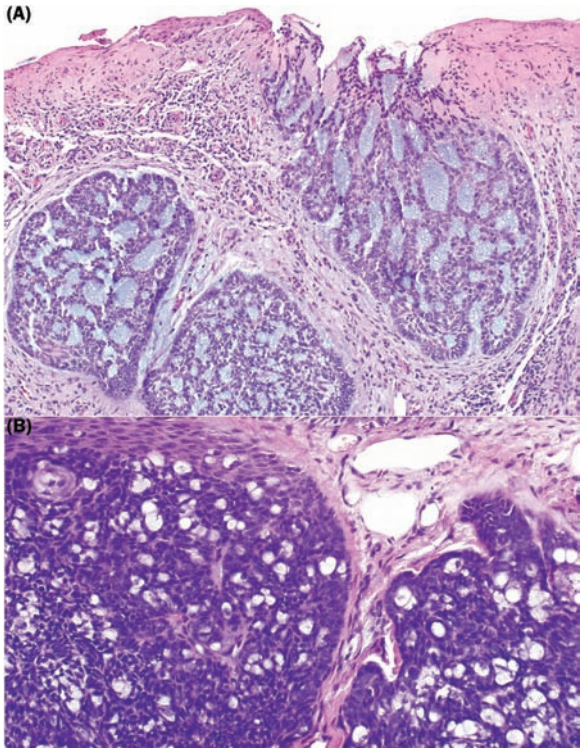

Figure 23 Abundant intraepidermal mucin (**A**) gives the pseudoglandular appearance of adenoid type. Vacuolated cells scattered within the atypical basaloid lobules (**B**) suggestive of sebaceous differentiation

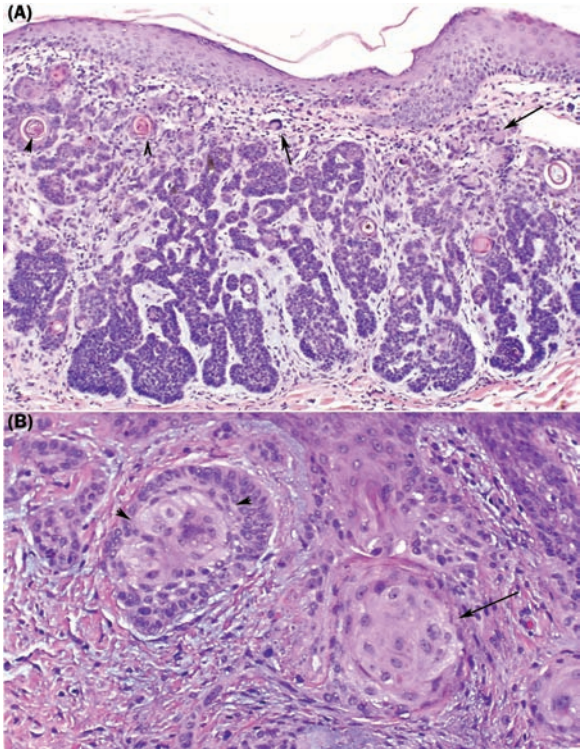

Figure 24 Keratin horn cysts (*arrowheads*) within the islands of basaloid cells (**A**) in the keratotic variant of basal cell carcinoma. Note scattered multinucleated foreign body type of giant cells (*arrows*) caused by ruptured keratotic cysts, central squamous differentiation (*arrowhead*) within the islands of atypical basaloid cells in squamatized basal cell carcinoma (**B**). Note the island on the right shows only squamous differentiation reminiscent of squamous cell carcinoma (*arrow*).

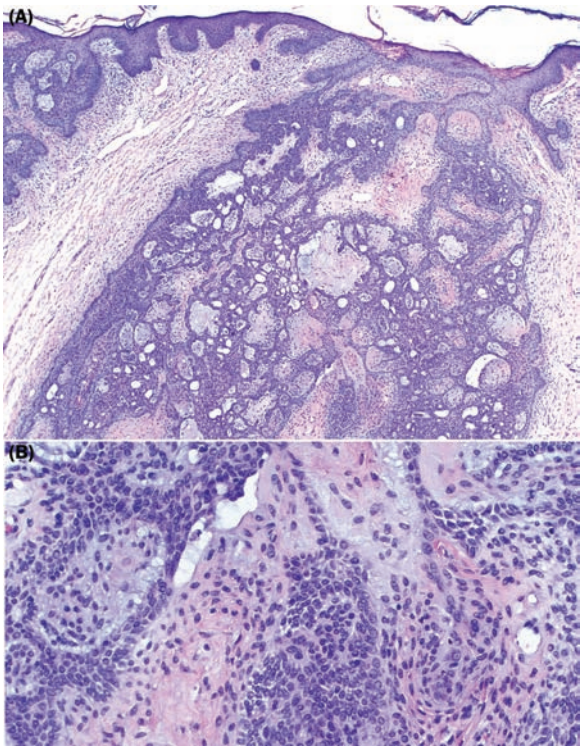

Figure 25 Thin strands of atypical basaloid cells in fibrotic and mucinous stroma in scanning (**A**) and low power (**B**) in the basal cell carcinoma of the fibroepithelioma of the Pinkus type.

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Follicular Neoplasms

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CONTENTS

Follicular tumors are one form of "adnexal tumors." The adnexa in dermatopathology are skin appendages: the hair follicles, sebaceous glands, and sweat glands. In gynecologic pathology, the adnexa are fallopian tubes and ovaries. Follicular, sebaceous and sweat gland tumors are not necessarily derived from such structures; we prefer to think that immature pluripotential cells demonstrate "differentiation toward" hair follicles, sebaceous glands, or sweat glands. It is quite common for some tumors to produce various combinations of hair follicle, sebaceous, and sweat ductal structures, all in the same tumor, making our artificial classification schemes oversimplified. Adnexal tumors are like snowflakes; many unusual unclassifiable variants are sometimes found. It is a fertile ground for "lumper-splitter" wars, where authorities often rename and reclassify tumors, and they argue about whether a neoplasm is a new entity or merely a variant of another tumor. Terminology varies according to the author.

Anatomy:

It is important to have knowledge of normal hair follicle anatomy to understand neoplasms with follicular differentiation.

Layers of the follicle are as follows (moving from the inside outwards):

- Hair medulla (center part of hair shaft, not readily identified with light microscopy)
- Hair cortex (most of hair shaft)
- Hair cuticle
- Inner root sheath cuticle
- Inner root sheath Huxley layer (2 cell layers, numerous trichohyaline granules)
- Inner root sheath Henle layer (1 cell layer, trichohyaline granules)
- Outer root sheath (PAS-positive pale cells due to glycogen when below isthmus)
- Vitreous layer (loose connective tissue)

Portions of the follicle from the top of the follicle downward:

- Infundibulum (from surface epidermis down to the sebaceous duct entrance into the follicle)
- Isthmus (from the sebaceous duct entrance down to the arrector pili muscle attachment)

At the lowest portion of the follicle, immature basaloid cells in the follicular bulb give rise to the other layers in the matrix zone (pilomatricoma is a tumor thought to simulate this zone, where there are shadow cells). A cluster of spindle cells known as the papillary mesenchymal body is clutched by the follicular bulb (see trichoepithelioma). As one moves from the bottom of the follicle upward, the inner root sheath disappears and does not contribute to the hair shaft, while the pale cells of the outer root sheath mature to become epithelial cells that blend with the surface epidermis in the infundibulum. Tumors that cornify gradually (such as trichilemmal cysts and pilar tumors) without a granular layer are said to exhibit trichilemmal keratinization resembling that of the outer root sheath. The pale cells of the trichilemmoma are also said to resemble those seen in the outer root sheath. Cysts (Chapter 13) derived from or resembling the uppermost part of the follicle are called follicular-infundibular cysts, whereas those from the central portion of the follicle (usually on the scalp) are called isthmus-catagen cysts.

Evidence that a tumor is follicular include the following: follicular bulbs, papillary mesenchymal bodies, typical fibrotic stromal features, pale cells resembling outer root sheaths with gradual cornification, trichohyaline granules, hair shafts, horn cysts, and shadow cells. A distinction between normal follicular structures, follicular neoplasms, and basal cell carcinoma is particularly important for dermatopathologists and Mohs surgeons. In particular, the "funny looking follicles" known as folliculocentric basaloid proliferation (FBP, mantleoma) can resemble basal cell carcinomas.

References:

1. Ackerman AB, Reddy VB, Soyer HP. Neoplasms with Follicular Differentiation. 2nd ed. New York: Ardor Scribendi, 2001.
2. Wick MR, Swanson PE. Cutaneous Adnexal Tumors. Chicago: Am Soc Clin Pathol Press, 1991.
3. Gross K, Steinman H, Rapini R. Mohs Surgery. St Louis: Mosby, 1999.

4. Rapini RP. Follicular differentiation in basal cell carcinoma and the trend to designate benign or questionable lesions as malignant. J Am Acad Dermatol 2002; 47:792–794.

TRICHOFOLLICULOMA (FIGS. 1 AND 2)

Clinical Presentation:
- Solitary papule or nodule on face, sometimes with central pore containing tufts of vellus hairs

Histopathology:
- Large open comedo, sometimes resembling a cyst, into which numerous small hair follicles with vellus hairs open
- Fibrotic stroma common
- Folliculosebaceous cystic hamartoma (sebaceous trichofolliculoma) may be a variant with additional finding of prominent sebaceous lobules

Differential Diagnosis:

Trichofolliculoma	Dilated Pore of Winer	Pilar Sheath Acanthoma
Usually on the face	Face or trunk	Usually on upper lip
Vellus hair shafts and follicles with trichohyaline granules open into "mother follicle"	Buds of epithelium extending from base of comedo without mature hair shafts, secondary budding follicles, or trichohyaline granules	More massive epithelial proliferation without mature secondary follicles

Pathophysiology:
Trichofolliculoma might not represent a neoplasm. Instead it may be a hamartoma (abnormal arrangement of normal elements) or just a cystic dilation of a follicular unit into which secondary follicles extend.

References:
1. Winer LH. The dilated pore, a trichoepithelioma. J Invest Dermatol 1954; 23:181.
2. Mehregan AH, Brownstein MH. Pilar sheath acanthoma. Arch Dermatol 1978; 114:1495–1497.
3. Kimura T, Miyazawa H, Aoyagi T, Ackerman AB. Folliculosebaceous cystic hamartoma. A distinctive malformation of the skin. Am J Dermatopathol 1991; 13:213–220.

HAIR NEVUS

Synonym: Vellus hamartoma may be the same thing as an accessory tragus in some cases.

Clinical Presentation:
- Exceedingly rare, onset at birth through young adulthood
- Often dome-shaped papule or plaque
- Localized proliferation of hairs

Histopathology:
- May resemble normal skin
- Increased numbers of mature hair follicles. Usually these are vellus hairs, except in the nevus pilosus variant in the scalp where terminal hairs are found
- May be associated with basal layer hyperpigmentation (lentigo-like changes in Becker's nevus) or with increased smooth muscle bundles (smooth muscle hamartoma)

Reference:
1. Labandeira J, Peteiro C, Toribio J. Hair follicle nevus: case report and review. Am J Dermatopathol 1996; 18:90–93.

NEVUS COMEDONICUS (FIGS. 2 AND 3)

Clinical Presentation:
- Onset at birth or early childhood
- A linear epidermal nevus with prominent comedones

Histopathology:
- Clusters of ordinary comedones (plugged follicular units with aborted hair shafts)

Reference:
1. Nabai H, Mehregan AH. Nevus comedonicus. Acta Derm Venereol 1973; 53:71.

TRICHOEPITHELIOMA (FIGS. 5 AND 6)

Clinical Presentation:
- Skin-colored papule or nodule
- Usually on central face, especially near nose
- Most often solitary, but an autosomal dominant multiple form does exist which may resemble adenoma sebaceum (angiofibroma) of tuberous sclerosis

Histopathology:
- Basaloid tumor aggregates, often in a cribriform (reticulated) pattern, sometimes resembling poorly developed hair follicles
- Horn cysts common, sometimes with granulomatous reaction to rupture
- Peripheral palisading of nuclei may occur, but no artifactual retraction between tumor and stroma
- Characteristic fibrous stroma
- Papillary mesenchymal bodies are localized collections of mesenchymal spindle cells next to the epithelium that resembles those found in the normal hair papillae

Clinicopathologic Correlation:

Clinical Feature	Pathologic Feature
Lesions are fleshy and less pearly than basal cell carcinoma, resembling a nevus	Lack of pearliness likely is due to less mucin than basal cell carcinoma

Differential Diagnosis:

Basal cell carcinoma may be impossible to distinguish in some cases. In the case of solitary lesions on sun-damaged skin, it may be wise to completely excise the neoplasm (when in doubt, cut it out). Also consider trichoblastoma and other basaloid neoplasms (sweat gland and sebaceous tumors). Basaloid follicular hamartomas may be a trichoepithelioma variant in which autosomal dominant multiple facial papules, with vertically-oriented basaloid cells are centered upon a comedo-like follicle.

Trichoepithelioma	Basal Cell Carcinoma
May start in childhood or early adulthood	Increasing incidence with age from solar damage
Fleshy appearance like intradermal nevus	Translucent pearly appearance, likely due to mucin
Autosomal dominant multiple lesion form	Usually solitary, but there is the autosomal dominant nevoid basal cell carcinoma syndrome
Stromal retraction between tumor and stroma	No stromal retraction, or retraction is present between collagen bundles
Horn cysts common	Horn cysts less common except in keratotic variant
Uncommon ulceration, necrosis, atypia	More likely to have ulceration, necrosis, atypia
Less mucin or solar elastosis	Mucin and solar elastosis common in stroma
Cribriform (netlike) pattern, follicular bulbs, and papillary mesenchymal bodies common	Less resemblance to follicular structures, except in "BCC with follicular differentiation"
Expression of bcl-2 mainly in basal layer	Expression of bcl-2 diffuse and more prominent

Clinicopathologic Correlation:

Clinical Feature	Pathologic Feature
Lesions are fleshy and less pearly than basal cell carcinoma, resembling a nevus	Lack of pearliness likely is due to less mucin than basal cell carcinoma

Pathophysiology:

The autosomal dominant form of multiple trichoepitheliomas (Brooke's disease) has been mapped to chromosome 9p21, and is not associated with significant other internal anomalies.

References:

1. Harada H, Hashimoto K, Ko MS. The gene for multiple familial trichoepithelioma maps to chromosome 9p21. J Invest Dermatol 1996; 107:41–43.
2. Bettencourt MS, Prieto VG, Shea CR. Trichoepithelioma: a 19-year clinicopathologic re-evaluation. J Cutan Pathol 1999; 26:398–404.
3. Brooke JD, Fitzpatrick JE, Golitz LE. Papillary mesenchymal bodies: a histologic finding useful in differentiating trichoepitheliomas from basal cell carcinomas. J Am Acad Dermatol 1989; 21:523–528.
4. Rapini RP. Follicular differentiation in basal cell carcinoma and the trend to designate benign or questionable lesions as malignant. J Am Acad Dermatol 2002; 47:792–794.
5. Wheeler CE Jr, Carroll MA, Groben PA, et al. Autosomal dominantly inherited generalized basaloid follicular hamartoma syndrome. J Am Acad Dermatol 2000; 43:189–206.

DESMOPLASTIC TRICHOEPITHELIOMA (FIG. 7)

Synonym: Sclerosing epithelial hamartoma.

Clinical Presentation:

- Annular solitary firm yellowish to translucent papule or plaque on face, with central depression
- Resembles sclerosing basal cell carcinoma or scar

Histopathology:

- As in ordinary trichoepithelioma, except that there are thin basaloid strands in a fibrotic (desmoplastic) stroma.
- Difficult to distinguish from basal cell carcinoma, as with other trichoepitheliomas.

Differential Diagnosis:

Sclerosing basal cell carcinoma may be distinguished by criteria similar to those listed under ordinary trichoepithelioma. Sclerosing BCC and microcystic adnexal carcinoma (a tumor with both sweat ductal and follicular differentiation) can be particularly problematic when superficial shave biopsies are received.

Desmoplastic Trichoepithelioma	Syringoma	Microcystic Adnexal Carcinoma
Usually on the face	Mainly eyelids, except multiple form	Common on nose or upper lip
Usually less than 10 mm	Usually 2 to 4 mm	Often subtle extension beyond 10 mm
Horn cysts, usually no sweat ducts	Small milial cysts, tadpole appearance of short epithelial strands, with sweat ducts	Horn cysts especially common in superficial portion, sweat ducts common deeper

References:

1. Brownstein MH, Shapiro L. Desmoplastic trichoepithelioma. Cancer 1977; 40:2979–2986.
2. Mac Donald DM, Wilson Jones E, Marks R. Sclerosing epithelial hamartoma. Clin Exp Dermatol 1977; 2:153–160.

TRICHOADENOMA (FIGS. 8 AND 9)

Synonym: Trichoadenoma of Nikolowski.

Clinical Presentation:

- Annular solitary firm yellowish to translucent papule or plaque on face, with central depression
- Resembles sclerosing basal cell carcinoma or scar

Histopathology:

- Similar to trichoepithelioma but with more mature squamatized (less basaloid) epithelium
- Prominent horn cysts

Reference:

1. Rahbari H, Mehregan A, Pinkus H. Trichoadenoma of Nikolowski. J Cutan Pathol 1977; 4:90–98.

PILOMATRIXOMA (FIGS. 10 TO 12)

Synonyms: Pilomatricoma; trichomatrioma; calcifying epithelioma of Malherbe.

Clinical Presentation:
- Solitary nodule that elevates the epidermis (tent sign)
- Often becomes red (inflamed, associated with granulomatous reaction histologically)
- Common on face, upper extremities of children or young adults (but also occurs in older adults at nearly any site). Often misdiagnosed clinically as a keratinous cyst

Histopathology:
- Circumscribed tumor in dermis or subcutaneous tissue with basaloid cells at periphery (may have ordinary squamous epithelium at periphery)
- Shadow (ghost) cells and transitional cells with pyknotic nuclei gradually becoming shadow cells
- Keratinous debris mostly in center of cystic space
- Calcification, ossification, and granulomatous reaction common

Clinicopathologic Correlation:

Clinical Feature	Pathologic Feature
Lesions are mistaken for cysts	Keratinous material is arranged into shards within circumscribed nodule in deep dermis or subcutaneous tissue
Lesions are erythematous	Granulomatous reaction to keratin is common

Differential Diagnosis:
- Some basal cell carcinomas may contain a few shadow cells (BCC with matrical differentiation)
- Other basaloid tumors such sweat gland tumors and sebaceous gland tumors are distinguished by differentiation characteristic of that class of neoplasms.
- Cutaneous cysts may resemble pilomatrixoma if basaloid and shadow cells are not appreciated
- Pilomatrix carcinoma is a malignant counterpart on the head or neck of adults, with larger size, less circumscription, more necrosis, and more atypia. Mitoses are actually quite common in benign pilomatrixomas and are less helpful.

Pathophysiology:
Mutations in CTNNB1 are present in these tumors, including both the benign and malignant counterparts. This gene encodes for beta-catenin, part of a signaling pathway that is involved in cellular differentiation and proliferation.

References:
1. Demircan M, Balik E. Pilomatricoma in children: a prospective study. Pediatr Dermatol 1997; 14:430–432.
2. Lazar AJ, Calonje E, Grayson W, et al. Pilomatrix carcinomas contain mutations in CTNNB1, the gene encoding beta-catenin. J Cutan Pathol 2005; 32:148–157.
3. Ambrojo P, Aguilar A, Simon P, et al. Basal cell carcinoma with matrical differentiation. Am J Dermatopathol 1992; 14:293–297.

PROLIFERATING PILAR CYST (FIGS. 13 TO 15)

Synonyms: Pilar tumor; proliferating trichilemmal cyst; proliferating follicular-cystic neoplasm.

Clinical Presentation:
- Nodule on scalp, more common in women
- Similar to pilar cyst; often larger, growing, ulcerated

Histopathology:
- Same as pilar cyst (isthmus-catagen cyst), but epithelial wall has proliferated to the extent of resembling well-differentiated squamous carcinoma
- Cytologic atypia may be present

Clinicopathologic Correlation:

Clinical Feature	Pathologic Feature
Lesions are mistaken for cysts	May be considered a cystic lesion in which the wall proliferated extensively

Differential Diagnosis:
This tumor has traditionally been considered a mimic of well-differentiated squamous cell carcinoma, and misdiagnosis may occur, especially if a small biopsy is submitted. Since some of these tumors have metastasized, larger tumors with more atypia and poor circumscription have sometimes been called malignant proliferating trichilemmal cysts. It has been advocated to consider all proliferating pilar cysts to be SCCs, but a middle-ground view would be to consider most of them benign, with some of them malignant.

Pathophysiology:
Proliferating trichilemmal cyst might possibly arise from benign pilar cysts, but proof of this is lacking. Some of them appear to arise, de novo, in patients without a preexisting cyst in that area.

References:
1. Brownstein MH, Arluk DJ. Proliferating trichilemmal cyst: a simulant of squamous cell carcinoma. Cancer 1981; 48:1207–1214.
2. Sleater J, Beers B, Stefan M, et al. Proliferating trichilemmal cyst. Report of four cases, two with nondiploid DNA content and increased proliferation index. Am J Dermatopathol 1993; 15:423–428.

TRICHILEMMOMA (FIG. 16)

Synonym: Tricholemmoma.

Clinical Presentation:
- Solitary verrucous papule on face, except in Cowden's disease
- Multiple papules on face in the rare autosomal dominant multiple hamartoma syndrome (Cowden's disease)
- Cowden's disease is associated with mucosal papillomas and fibromas, sclerotic fibromas of skin, carcinoma of the breast and other organs (less commonly thyroid or gastrointestinal carcinomas)

Histopathology:
- Hyperkeratosis, verrucous clear cell lobule of acanthosis containing glycogen (PAS+, diastase labile)
- Palisading of basal layer around lobule common
- Sometimes thickened basement membrane

Clinicopathologic Correlation:

Clinical Feature	Pathologic Feature
Lesions are mistaken for warts or sebaceous papules	Verrucous surface on small papule

Differential Diagnosis:
Besides the main differential culprits in the table, also consider other clear cell tumors, such as sebaceous neoplasms. It may resemble actinic keratosis, verruca vulgaris, and inverted follicular keratosis except for the presence of more clear cells. The malignant counterpart, trichilemmocarcinoma, is much larger, has more atypia, necrosis, or mitoses, and may be a variant of squamous cell carcinoma with clear cells. The desmoplastic variant of trichilemmoma can easily resemble a squamous cell carcinoma.

Trichilemmoma	Clear Cell Acanthoma	Clear Cell Bowen's Disease
Usually on the face	Usually on the leg	Most common on sun-damaged skin, but may occur anywhere
Warty papule	Red papule or small plaque	Crusted red plaque
Clear cell lobule grows downward, palisade of basal cells, thick basement membrane	Psoriasiform clear cells with sharp demarcation and neutrophils in stratum corneum	Cytologic atypia and mitoses, necrotic keratinocytes, clear cells only in some lesions

Pathophysiology:
Some authorities consider these to be old warts, but nearly all studies show no convincing evidence of papillomavirus infection by molecular techniques, and the paraneoplastic genetic form known as Cowden's disease would speak against a viral etiology.

References:

1. Requena L, Gutierrez J, Sanchez Yus E. Multiple sclerotic fibromas of the skin. A cutaneous marker of Cowden's disease. J Cutan Pathol 1992; 19:346–351.
2. Leonardi CL, Zhu WY, Kinsey WH, Penneys NS. Trichilemmomas are not associated with human papillomavirus DNA. J Cutan Pathol 1991; 18:193–197.
3. Hunt SJ, Kilzer B, Santa Cruz DJ. Desmoplastic trichilemmoma: histologic variant resembling invasive carcinoma. J Cutan Pathol 1990; 17:45–52.

INVERTED FOLLICULAR KERATOSIS (FIG. 17)

Synonym: IFK.

Clinical Presentation:
- Hyperkeratotic papule on face resembling a wart, seborrheic keratosis, actinic keratosis, keratoacanthoma, or squamous cell carcinoma.

Histopathology:
- Hyperplastic inward-growing acanthosis around a plugged follicle
- Sometimes with squamous eddies or clear cells

Pathophysiology:
IFK is probably a variant of inward-growing seborrheic keratosis. Ackerman has proposed that seborrheic keratosis in general is a hair follicle tumor, an interesting idea!

Reference:

1. Mehregan AH. Inverted follicular keratosis. Arch Dermatol 1964; 89:229.

TUMOR OF FOLLICULAR INFUNDIBULUM (FIG. 18)

Synonyms: TFI; infundibuloma; isthmicoma.

Clinical Presentation:
- Thin, flat-topped, hyperkeratotic, often hypopigmented papule on face
- Usually solitary, but multiple lesions may occur

Histopathology:
- Proliferation of horizontally oriented pale epidermal shelves that connect with the isthmus of adjacent follicles and surface epithelium
- Sweat ducts or sebaceous gland differentiation are found in some cases

Pathophysiology:
TFI may be a variant of reticulated seborrheic keratosis in the minds of lumpers.

References:

1. Horn TD, Vennos EM, Bernstein BD, Cooper PH. Multiple tumors of follicular infundibulum with sweat duct differentiation. J Cutan Pathol 1995; 22:281–287.
2. Cribier B, Grosshans E. Tumor of the follicular infundibulum: a clinicopathologic study. J Am Acad Dermatol 1995; 33:979–984.

FIBROFOLLICULOMA AND TRICHODISCOMA (FIGS. 19 TO 21)

Clinical Presentation:
- Multiple skin-colored papules on face, usually with autosomal dominant Birt-Hogg-Dube syndrome
- Acrochordons and papules sometimes on neck, scalp, and upper trunk
- Resembles multiple papules of tuberous sclerosis, less warty than papules of Cowden's disease
- Renal cell carcinoma and other neoplasms are associated

Histopathology:
- Hair follicle with extension of delicate strands of epithelium from the follicular isthmus into surrounding loose stroma.
- Trichodiscoma has just the loose fibrosis localized to a subepidermal area adjacent to a hair follicle.

Differential Diagnosis:
Fibroepithelioma has a similar name, but is completely different, and is a basal cell carcinoma variant presenting with anastomosing basaloid strands in a loose stroma within a plaque on the trunk. The angiofibromas of tuberous sclerosis can be similar clinically and pathologically.

Pathophysiology:
Trichodiscoma is not related to the haarscheibe (hair disc), despite old references to that structure (which may be mythical). Deeper sections of trichodiscoma may reveal the follicular strands of fibrofolliculoma, and the two neoplasms invariably appear in the same patient, so the two neoplasms probably are different manifestations of the same neoplasm. They may also be related to angiofibroma or perifollicular fibroma, which can be difficult to distinguish if the fine delicate epithelial strands are not found.

References:
1. Birt AR, Hogg GR, Dube WJ. Hereditary multiple fibrofolliculomas with trichodiscomas and acrochordons. Arch Dermatol 1977; 113:1674–1677.
2. Pinkus H, Coskey R, Burgess GH. Trichodiscoma: A benign tumor related to haarscheibe (hair disc). J Invest Dermatol 1974; 63:212–218.
3. Starink TM, Kisch LS, Meijer LM. Familial multiple trichodiscomas. Arch Dermatol 1985;121:888–891.

TRICHOBLASTOMA (FIG. 22)

Clinical Features:
- Skin-colored papule or nodule on the face or trunk, especially the nose

Histopathology:
- Well-circumscribed basaloid tumor aggregates in the dermis, without atypia
- No stromal retraction or solar elastosis
- Hair papillae and papillary mesenchymal bodies sometimes present

Differential Diagnosis:
The same general features used to distinguish trichoepithelioma from basal cell carcinoma often apply for trichoblastoma as well. The distinction between trichoblastoma and trichoepithelioma mainly depends upon the authority, but nowadays most consider trichoepithelioma to be a superficial type of trichoblastoma (closer to the epidermis), with the latter being an all-encompassing term. Trichoepithelioma is more likely to have a cribriform pattern (interconnecting cords or netlike).

Pathophysiology:
Many variants of trichoblastoma having immature basaloid epithelium with various attempts at follicular differentiation are in vogue at this time. Many of them were called trichoepitheliomas in the past. Variants in the past included trichoblastic fibroma, trichogenic trichoblastoma, trichogenic myxoma, and trichogerminoma (Headington). Ackerman et al. recognized five main types in their follicular neoplasm book (large nodular, small nodular, cribriform, racemiform, retiform). There does not seem to be any general agreement on how to classify these neoplasms. Trichoblastoma has been used as the new name for the BCCs or benign basaloid proliferations that occur in nevus sebaceus, so some consider it to be one of the most common neoplasms to develop in nevus sebaceus, considering them to be benign rather than malignant in most cases.

References:
1. Headington JT. Tumors of the hair follicle. Am J Pathol 1976; 85:480–505.
2. Headington JT. Differentiating neoplasms of hair germ. J Clin Pathol 1970; 23:464–471.
3. Ackerman AB, Reddy VB, Soyer HP. Neoplasms with Follicular Differentiation. 2nd ed. New York: Ardor Scribendi, 2001.
4. Jaqueti G, Requena L, Sanchez Yus E. Trichoblastoma is the most common neoplasm developed in nevus sebaceus of Jadassohn: a clinicopathologic study of a series of 155 cases. Am J Dermatopathol 2000; 22:108–118.

MALIGNANT FOLLICULAR TUMORS

The major two malignant follicular tumors, pilomatrix carcinoma (pilomatrical carcinoma) and trichilemmocarcinoma (trichilemmal carcinoma) (Fig. 23) have been discussed under their benign counterparts, pilomatrixoma and trichilemmoma respectively. Under the lumper philosophy, it has been proposed that both these are simply variants of squamous carcinoma, with shadow cells or clear cells being prominent features.

Reference:
1. Hardisson D, Linaves MD, Cuevas-Santos J, Contreas F. Pilomatrix carcinoma: a clinicopathologic study of six cases and review of the literature. Am J Dermatopathol 2001; 23: 394–401.

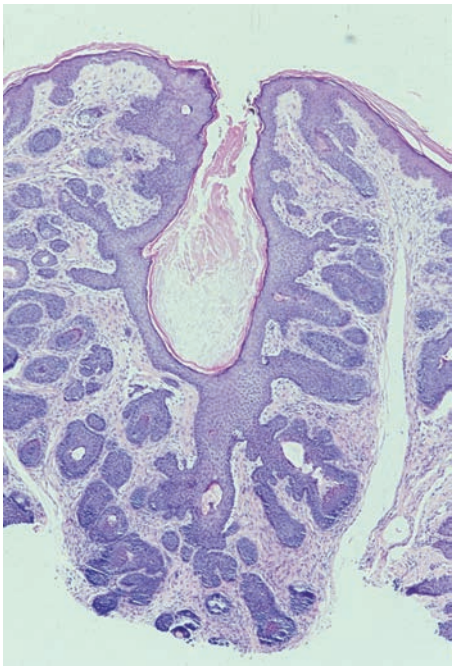

Figure 1 Trichofolliculoma. Mature follicles empty into "mother of all follicles."

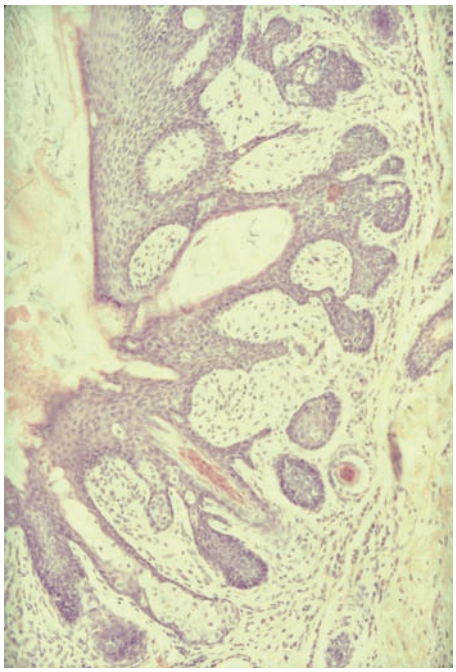

Figure 2 Trichofolliculoma, high magnification. The smaller secondary follicles have their own trichohyaline granules and hair shafts, unlike dilated pore of Winer.

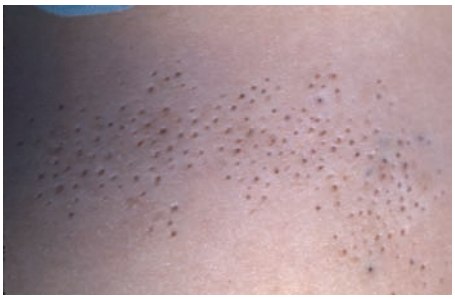

Figure 3 Nevus comedonicus. This is a birthmark with groups of comedones.

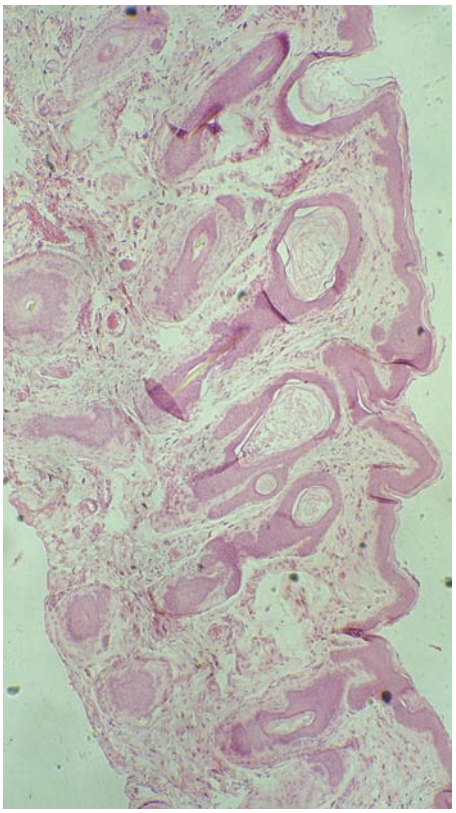

Figure 4 Nevus comedonicus. Grouped comedones.

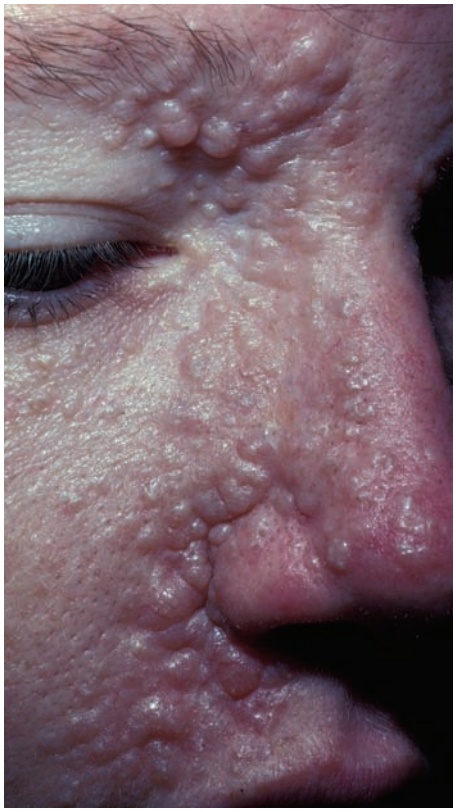

Figure 5 Trichoepitheliomas. Fleshy papules on central face.

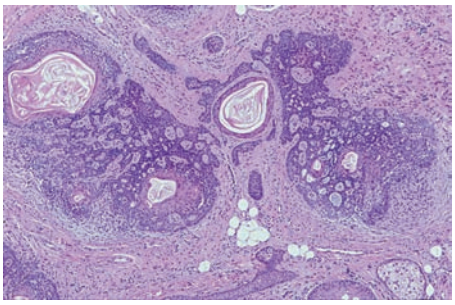

Figure 6 Trichoepithelioma. Basaloid aggregates with papillary mesenchymal bodies, fibrotic stroma without retraction from the tumor, and horn cysts.

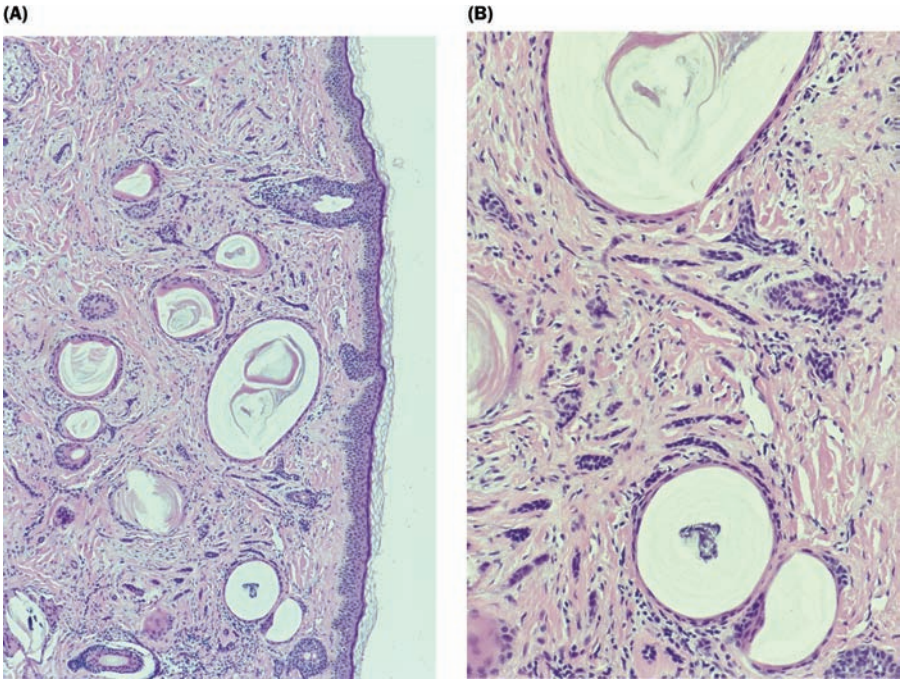

Figure 7 Desmoplastic trichoepithelioma. (**A**) Scanning magnification with strands of basaloid cells, and horn cysts. (**B**) Higher magnification. *Note*: Fibrotic stroma and no stromal retraction from the tumor.

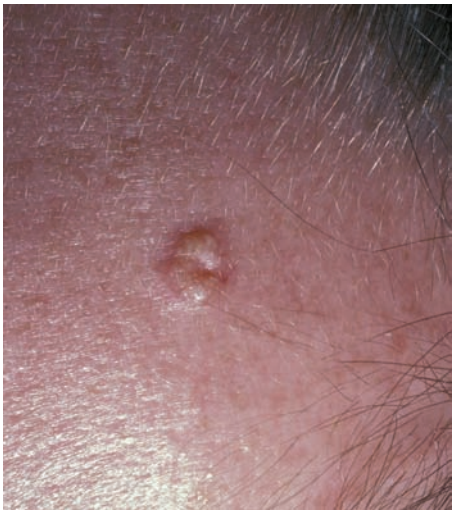

Figure 8 Trichoadenoma. Papule with central dell resembling sebaceous hyperplasia.

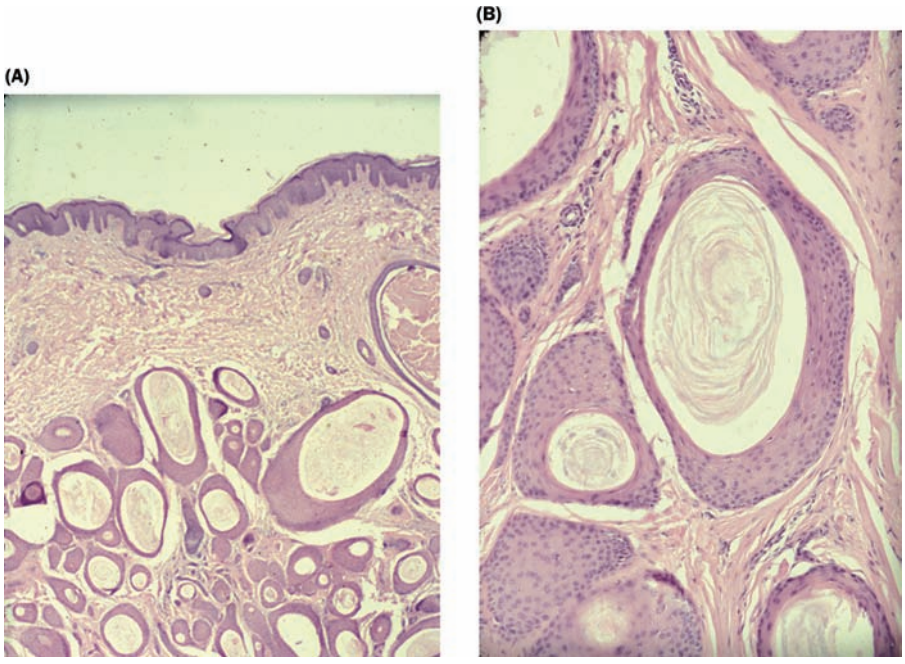

Figure 9 Trichoadenoma. (**A**) Scanning magnification of horn cysts with squamoid appearance. (**B**) Higher magnification of horn cysts.

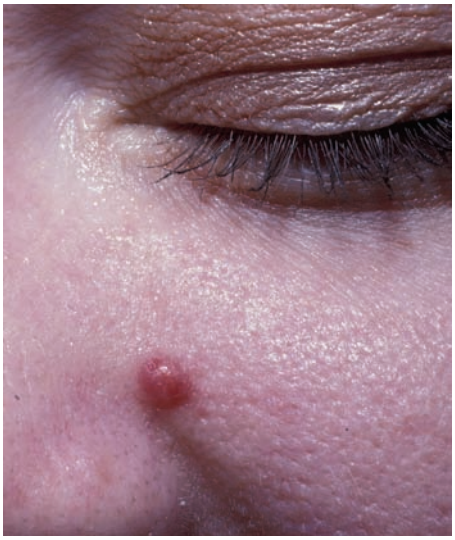

Figure 10 Pilomatrixoma. Erythematous papule elevates the skin ("tent sign").

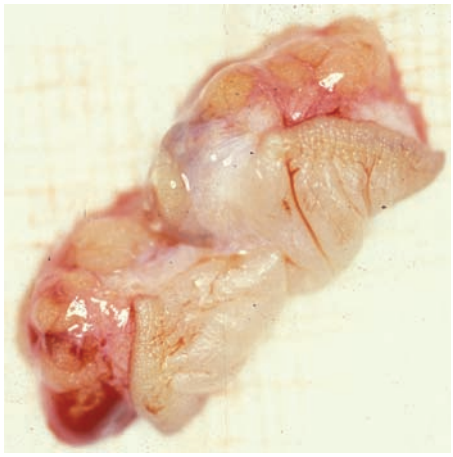

Figure 11 Pilomatrixoma. Gross specimen of nodule having appearance like a cyst.

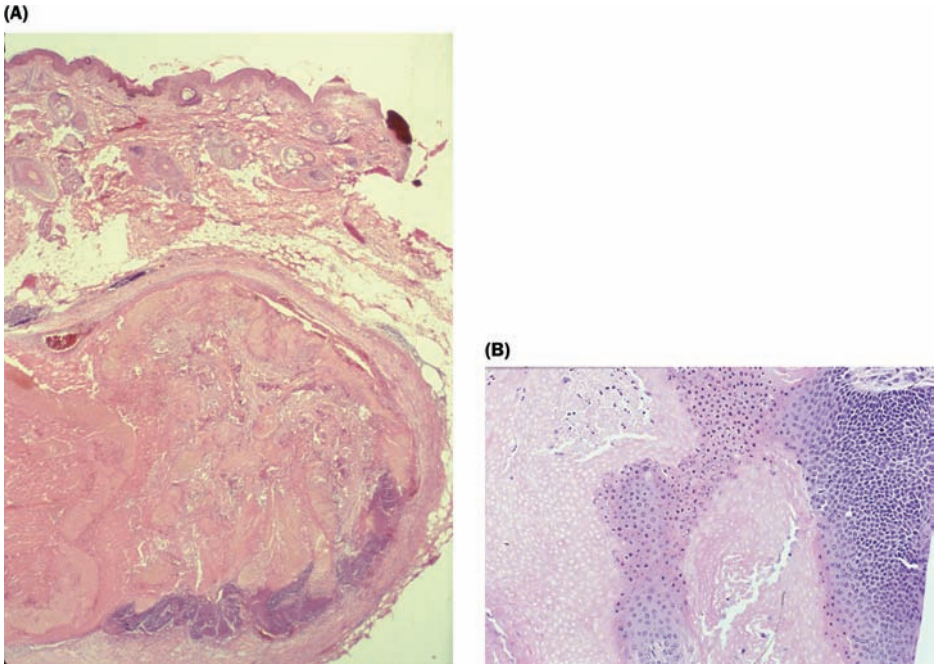

Figure 12 Pilomatrixoma. (**A**) Scanning magnification of cystic nodule with keratinous material and shadow cells in the center with basaloid cells around the edge. (**B**) Higher magnification of basaloid cells, shadow cells, and cells in transition that are losing their nuclei.

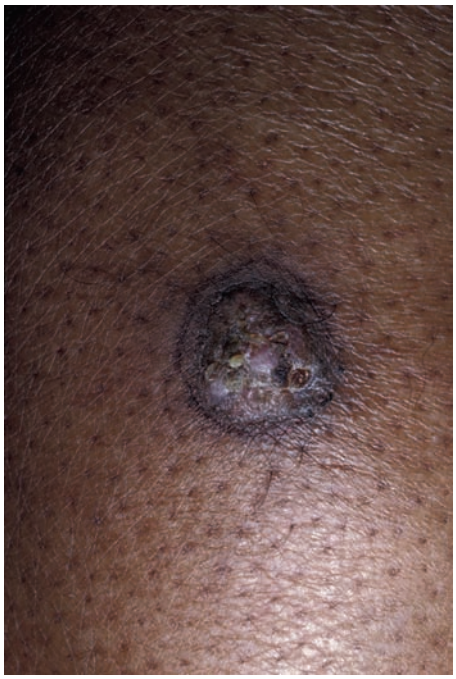

Figure 13 Proliferating pilar cyst. A relatively nonspecific nodule.

Figure 14 Proliferating pilar cyst. Gross cut specimen showing cystic nodule with proliferation of wall.

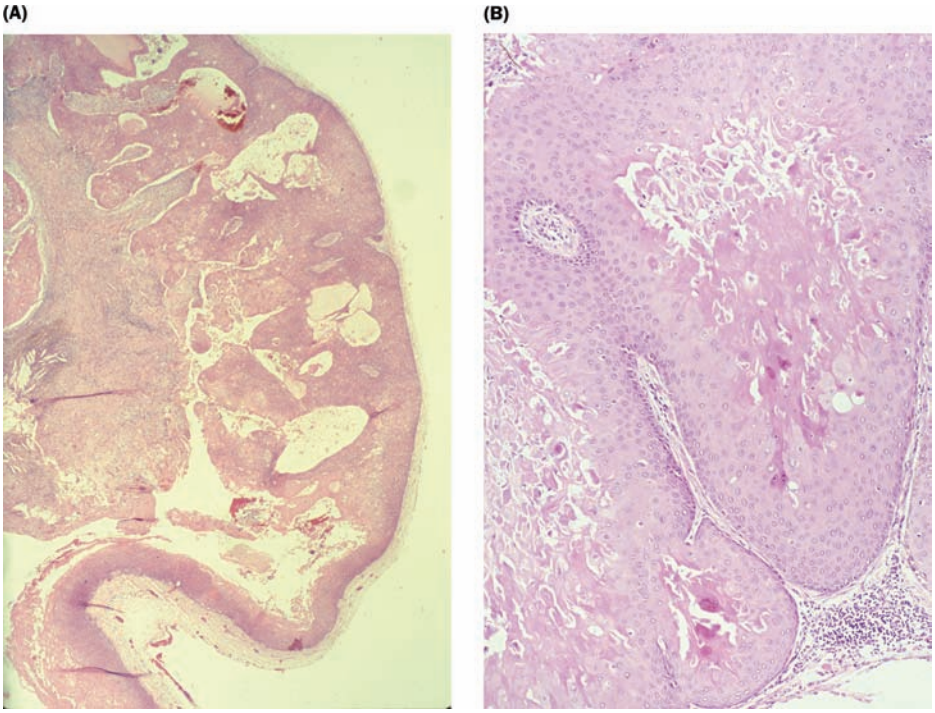

Figure 15 Proliferating pilar cyst. (**A**) Scanning view of cystic lining giving rise to area of proliferation of its wall. (**B**) Pale glassy squamous proliferation with abrupt keratinization.

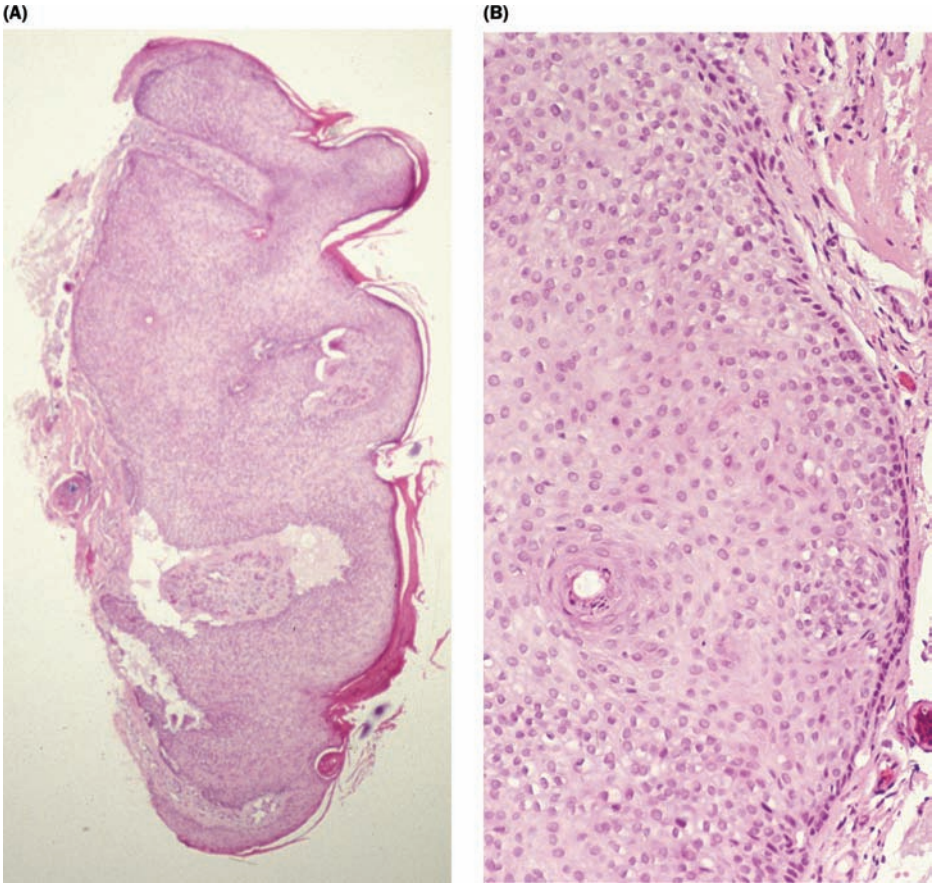

Figure 16 Trichilemmoma. (**A**) Scanning view of lobule of pale squamous proliferation growing downward. (**B**) Higher magnification of lobule of pale squamous lobule with palisade of basal cells.

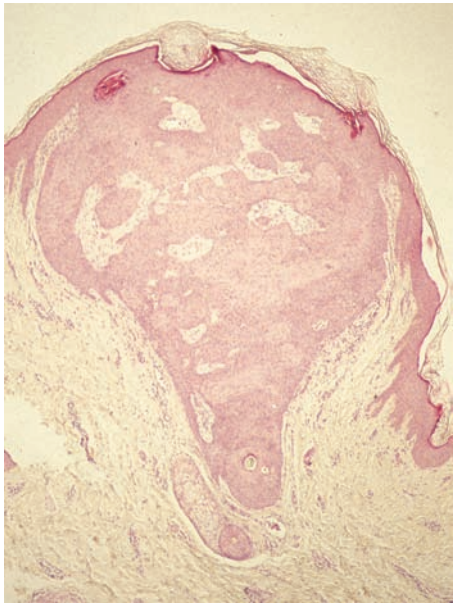

Figure 17 Inverted follicular keratosis. Downward growing lobule with more squamous eddies and less of a clear cell appearance than trichilemmoma.

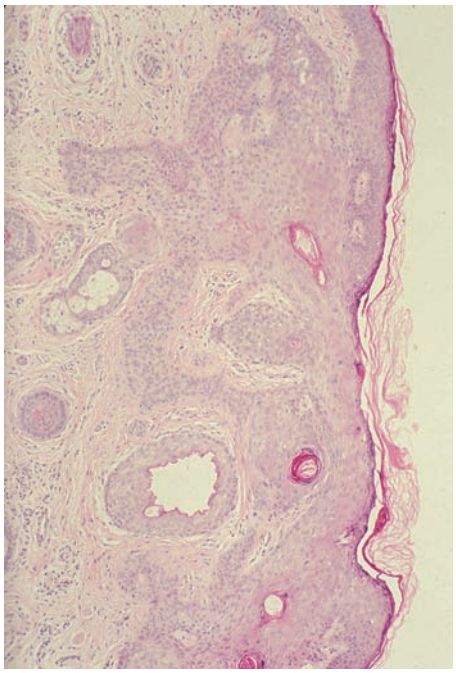

Figure 18 Tumor of follicular infundibulum. Shelves of pale epidermis bridge between follicles.

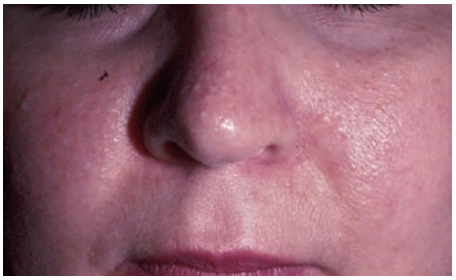

Figure 19 Birt-Hogg-Dube syndrome. Skin-colored papules are smooth and not conspicuous.

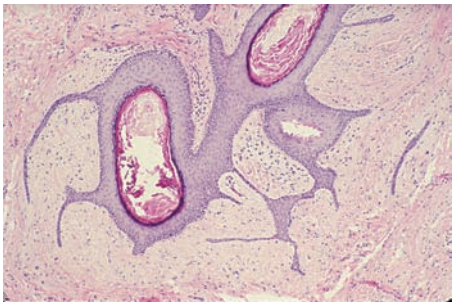

Figure 20 Fibrofolliculoma. Delicate epithelial strands extend from the follicle into the fibrous stroma.

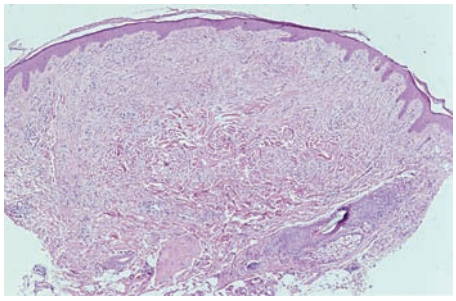

Figure 21 Trichodiscoma. The fibrous stroma of fibrofolliculoma is seen without the follicular strands.

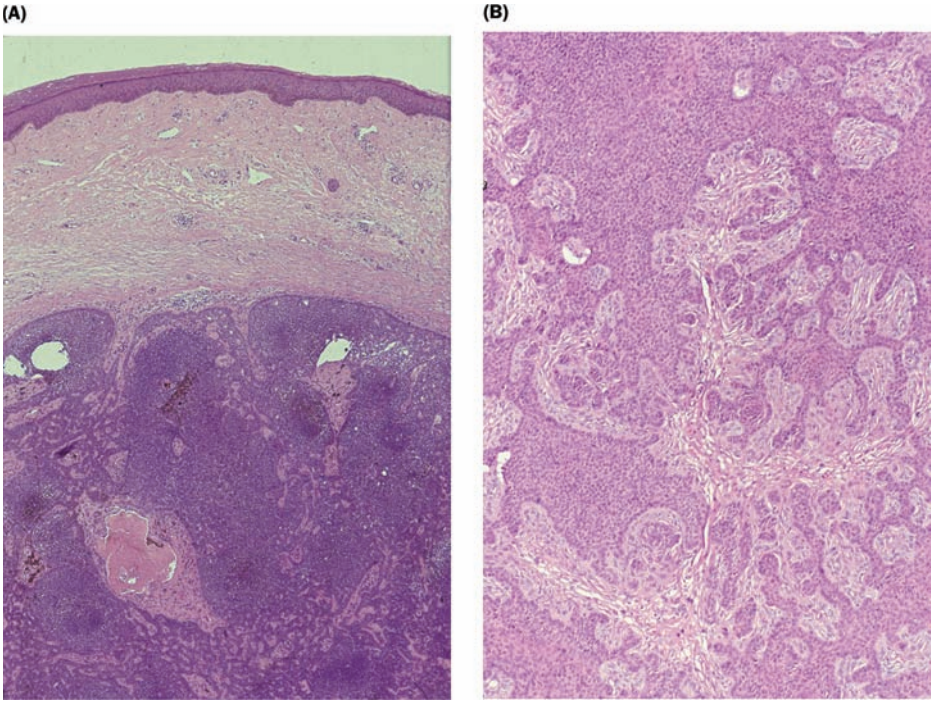

Figure 22 Trichoblastoma. (**A**) Scanning magnification of a basaloid lobule in the deep dermis. (**B**) Higher magnification of basaloid lobules without stromal retraction.

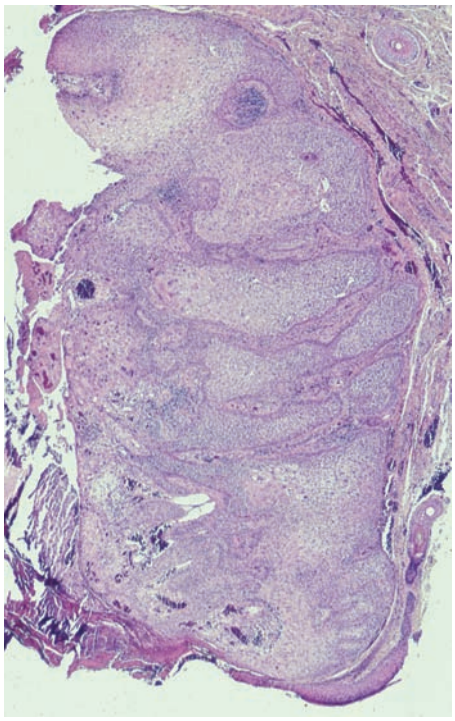

Figure 23 Trichilemmocarcinoma. Proliferation of invasive atypical pale cells resembles clear cell squamous cell carcinoma.

16

Sebaceous Neoplasms

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CONTENTS

Sebaceous neoplasms originate from the sebaceous unit, which is part of the folliculo-sebaceous unit. In this chapter, normal histology of the folliculo-sebaceous unit, various hamartomas and hyperplasias, as well as benign and malignant sebaceous neoplasms are discussed. Muir–Torre syndrome and its manifestations with different sebaceous neoplasms are also covered.

NORMAL HISTOLOGY

- Every folliculo-sebaceous unit is composed of a hair follicle and associated sebaceous unit (Fig. 1A)
- A sebaceous unit includes a sebaceous gland and a sebaceous duct (Fig. 1B)
- A mature sebaceous gland consists of several discrete sebaceous lobules (Fig. 1B)
- Each sebaceous lobule has a single row of immature sebocytes at the periphery and mature sebocytes in the center (Fig. 1C), which undergo complete disintegration and thus form the sebum, a process known as holocrine secretion
- Sebocytes have scalloped nuclei and vacuolated cytoplasm (Fig. 1C, inset)
- A sebaceous duct is a channel with thin, crenulated cornified lining that connects one or more sebaceous lobules to an infundibulum of a hair follicle (Fig. 1D)

ECTOPIC SEBACEOUS GLANDS

1. Fordyce's spots
2. Montgomery's tubercles

FORDYCE'S SPOTS AND MONTGOMERY'S TUBERCLES

Clinical Presentation:

Fordyce's Spots:

- Groups of tiny white or yellow discrete papules (Fig. 2A)
- Vermilion border of the lips, particularly upper lip, genital skin, or on the oral mucosa
- In 70% to 80% of elderly persons

Montgomery's Tubercles:

- Tiny slightly raised 1 to 2 mm papules on the areolae of breasts. Present in nearly every adult woman and sometimes in men

Histopathology:

- A single sebaceous gland or sebaceous lobules situated high in the submucosa or dermis (Figs. 2B and C)
- Direct opening onto the surface (Fig. 2C)
- Sometimes opening into a sebaceous duct leading to the surface epithelium (Fig. 2D)

Clinicopathologic Correlation:

Clinical Feature	Pathologic Feature
Grouped tiny white or yellow papules	Single sebaceous glands or lobules with direct opening onto the epidermal surface or through a small sebaceous duct

Pathophysiology:

- Ectopic sebaceous glands without attached follicles

HAMARTOMAS AND HYPERPLASIAS

1. Nevus sebaceus
2. Steatocystoma
3. Folliculo-sebaceous cystic hamartoma
4. Sebaceous hyperplasia

NEVUS SEBACEUS

Synonyms: Nevus sebaceus of Jadassohn; organoid nevus.

Clinical Presentation:

- Present at birth
- Usually on the scalp or face

- In infancy and childhood—well-circumscribed, only slightly raised, hairless plaque in an often linear configuration (Fig. 3A)
- At puberty and in adulthood—yellow verrucous, nodular plaque (Fig. 4A)

Histopathology:

- Acanthotic epidermis with papillomatosis and hyperkeratosis (Figs. 3C; 4B and C)
- Lack of normal mature hair follicles (Figs. 3B and C; 4B and C)
- Incompletely differentiated (immature) hair follicles (Figs. 3C and D)
- Ectopic apocrine glands in the dermis (Figs. 4C and D).
- Sebaceous glands follow the normal pattern during infancy, childhood, and adolescence
  1. In infancy—numerous sebaceous glands with prominent sebaceous lobules
  2. In childhood—sebaceous glands greatly reduced in size and number; flat epidermis (Figs. 3B and C)
  3. At puberty—markedly thickened epidermis with papillomatous hyperplasia, increased number of large sebaceous glands connecting directly to infundibula or to the skin surface (Figs. 4B and C)
- Neoplasms that can develop in nevus sebaceus: syringocystadenoma papilliferum, hidradenoma, syringoma, trichilemmoma, trichoblastoma, basal cell carcinoma (1,2)

Clinicopathologic Correlation:

Clinical Feature	Pathologic Feature
In childhood—only a slightly raised, often linear, hairless plaque present at birth, usually on the scalp or face	Flat epidermis, lack of normal terminal hair follicles but instead immature hair follicles, sebaceous glands greatly reduced in size and number, ectopic apocrine glands in the dermis
At puberty and in adulthood—yellow verrucous, nodular plaque	Thickened papillomatous epidermis, immature hair follicles as opposed to terminal hair follicles, increased number of large sebaceous glands connecting directly to infundibula or to the skin surface, ectopic apocrine glands in the dermis

Pathophysiology:

- Localized fault in the development of skin and subcutaneous fat characterized by abnormal arrangement of tissues that are present normally at this site—pilosebaceous units, epidermis, and often adnexal structures.

Differential Diagnosis:

Nevus Sebaceus	Epidermal Nevus
Epithelium but also pilosebaceous units and adnexal structures involved	Epidermal involvement only with hyperkeratosis and papillomatosis
Absence of terminal hairs but miniature incompletely differentiated follicles	Terminal follicles present; no immature hair follicles
Large sebaceous glands and apocrine glands in the underlying dermis	Usually no large sebaceous glands and no apocrine glands in the dermis

References:

1. Alessi E, Wong SN, Advani HH, et al. Nevus sebaceus is associated with unusual neoplasms. Am J Dermatopathol 1988; 10:116–127.
2. Misago N, Kodera H, Narisawa Y. Sebaceous carcinoma, trichoblastoma, and sebaceoma with features of trichoblastoma in nevus sebaceus. Am J Dermatopathol 2001; 23:456–462.

STEATOCYSTOMA

Clinical Presentation:

- Yellowish or skin-colored, moderately firm, papule or nodule
- Usually 1 to 3 cm in diameter
- Most commonly in the axillae, in the sternal region, and on the arms
- Steatocystoma simplex—a solitary lesion
- Steatocystoma multiplex—multiple lesions, sometimes hundreds; autosomal dominant inheritance in some patients (Fig. 5A) (1)

Histopathology:

- Cystically dilated space with folded wall (Fig. 5B). Lining comprised of three to four layers of epithelial cells covered by a homogeneous eosinophilic irregular horny layer (Fig. 5D). Flattened sebaceous gland lobules either within or close to the cyst wall (Fig. 5C).

Clinicopathologic Correlation:

Clinical Feature	Pathologic Feature
Yellow or flesh-colored firm papule	Cystically dilated space in the dermis lined by 3 to 4 layers of epithelial cells covered by pink irregular horny layer

Pathophysiology:

- Cystic hamartoma containing both epithelial and non-epithelial elements—sebaceous and follicular

Reference:

1. Cho S, Chang SE, Choi JH, Sung KJ, Moon KC, Koh JK. Clinical and histologic features of 64 cases of steatocystoma multiplex. J Dermatol 2002; 29:152–156.

FOLLICULO-SEBACEOUS CYSTIC HAMARTOMA

Clinical Presentation:

- Solitary papule or nodule 0.5 to 2 cm or more in diameter
- Usually on the face (1,2)

Histopathology:

- Cystically dilated infundibulum in the center with radiating sebaceous lobules (Figs. 6A and B) (1,3)
- Stroma that encircles the cystic structure and the follicular-sebaceous units contains fibrous and adipose tissue, numerous vessels, and sometimes mucin (Fig. 6C) (3)
- Clefts between the stroma and the adjacent normal dermis (Fig. 6D) (1,2)

Clinicopathologic Correlation:

Clinical Feature	Pathologic Feature
Dome-shaped papule or nodule up to 2 cm or more	Cystically dilated infundibulum with radiating sebaceous ducts and lobules, encircled by collagenous stroma

Pathophysiology:
Many structures present normally in skin, such as hair follicles, sebaceous units, fibrous and elastic tissue, adipocytes, and blood vessels, are arranged in abnormal fashion.

References:

1. Kimura T, Miyazawa H, Aoyagi T, Ackerman AB. Folliculosebaceous cystic hamartoma. A distinctive malformation of the skin. Am J Dermatopathol 1991; 13:213–220.
2. Templeton SF. Folliculosebaceous cystic hamartoma: a clinical pathologic study. J Am Acad Dermatol 1996; 34:77–81.
3. Yamamoto O, Suenaga Y, Bhawan J. Giant folliculosebaceous cystic hamartoma. J Cutan Pathol 1994; 21:170–172.

SEBACEOUS HYPERPLASIA

Clinical Presentation:
- Solitary or multiple yellowish papules, often umbilicated (Fig. 7A)
- Forehead and cheeks

Histopathology:
- Greatly enlarged sebaceous gland composed of numerous sebaceous lobules (Figs. 7B and C) (1)
- Large sebaceous lobules grouped around a centrally located dilated infundibulum (Figs. 7C and D) (1)

Clinicopathologic Correlation:

Clinical Feature	Pathologic Feature
Well-demarcated shiny yellowish papule with a central dell	Dilated follicular infundibulum surrounded by large sebaceous lobules

Reference:

1. Schirren CG, Jansen T, Lindner A, et al. Diffuse sebaceous gland hyperplasia. Am J Dermatopathol 1996; 18:296–301.

BENIGN NEOPLASMS

SEBACEOUS ADENOMA

Clinical Presentation:
- Flesh-colored or yellow solitary circumscribed nodule (Fig. 8A)
- Head and neck, especially face or scalp
- Usually <1 cm in diameter

Histopathology:
- Sharply demarcated, mainly endophytic neoplasm (Figs. 8B and 9A) (1)
- Large sebaceous lobules with irregular size and shape (Figs. 8B and D; 9B)
- Sebaceous lobules oriented vertically, which either connect directly to the skin surface or lead to channels that serve both as sebaceous duct and infundibulum (Figs. 8C; 9C and D) (1)
- Sebaceous lobules comprised of undifferentiated basaloid cells peripherally and mature sebaceous cells centrally, which outnumber the darker basaloid cells (Figs. 8D and 9C)

Clinicopathologic Correlation:

Clinical Feature	Pathologic Feature
Solitary yellow or flesh-colored circumscribed nodule	Endophytic and well-demarcated lesion comprised of irregular large sebaceous lobules oriented vertically with direct opening at the skin surface

Differential Diagnosis:

Sebaceous Adenoma	Sebaceous Hyperplasia
Large sebaceous lobules with vertical orientation and direct opening at the surface	Large sebaceous lobules centered around and opening within a dilated infundibulum
A mixture of mature and immature sebocytes, with 50% or more of the cells being mature sebocytes	More than 90% of the cells are mature sebocytes with only a single row of basaloid cells at the periphery of the lobules

Reference:

1. Singh AD, Mudhar HS, Bhola R, Rundle PA, Rennie IG. Sebaceous adenoma of the eyelid in Muir–Torre syndrome. Arch Ophthalmol 2005; 123:562–565.

SEBACEOMA

Synonym: Sebaceous epithelioma (old term).

Clinical Presentation:
- Solitary yellowish circumscribed nodule or an ill-defined plaque (Fig. 10A)
- Usually on the face or scalp
- May be multiple in Muir–Torre syndrome

Histopathology:
- Usually small size, symmetric, and well-circumscribed (Figs. 10B and 11A)
- Broad histologic spectrum
- Aggregations of neoplastic cells with great variation in size and shape (Figs. 10B and 11A) (1)
- Sebaceous lobules comprised of small, undifferentiated basaloid cells and mature sebocytes. The ratio of basaloid undifferentiated sebocytes to mature sebocytes varies from case to case as well as from field to field in the same case (Figs. 10C; 11B, C, and D)
- The basaloid cells in the sebaceous aggregates outnumber the mature sebaceous component (Figs. 10C; 11B and C) (1,2)
- Mitoses may be numerous but not atypical (Fig. 11D)
- Sebaceous duct-like structures seen throughout the aggregates (Fig. 10D) (1,2)

Clinicopathologic Correlation:

Clinical Feature	Pathologic Feature
Yellow or flesh-colored circumscribed nodule or an ill-defined plaque	Well-circumscribed and symmetric lesion comprised of sebaceous lobules and aggregates with great variation in size and shape, in which immature sebocytes predominate

Differential Diagnosis:

Sebaceous Adenoma	Sebaceoma
Large sebaceous lobules with vertical orientation and direct opening at the surface	Aggregations do not resemble normal sebaceous lobules and vary markedly in size and shape
A mixture of mature and immature sebocytes with 50% or more of the cells being mature sebocytes	An irregular mixture of mature and immature sebocytes with >50% basaloid immature cells
Mitoses are few or absent	Mitoses may be numerous but are not atypical

References:

1. Dinneen AM, Mehregan DR. Sebaceous epithelioma: a review of twenty-one cases. J Am Acad Dermatol 1996; 34:47–50.
2. Troy JL, Ackerman AB. Sebaceoma. A distinctive benign neoplasm of adnexal epithelium differentiating toward sebaceous cells. Am J Dermatopathol 1984; 6:7–13.

SEBACEOUS CARCINOMA

1. Ocular
2. Extraocular

OCULAR SEBACEOUS CARCINOMA

Clinical Presentation:

- More common
- One percent of all eyelid neoplasms
- Often masquerades as an inflammatory disease (3)
- Slight female preponderance
- Upper eyelid more commonly involved than lower eyelid (1,3)
- Up to one-third develop lymph node metastases
- Twenty percent five-year mortality

Histopathology:

- Usually superficial location
- Asymmetry, poor circumscription
- Aggregations of neoplastic sebocytes vary in sizes and shapes (1,3)
- Maturation of neoplastic sebocytes varies from immature (nonvacuolated) to mature (vacuolated)
- Nuclei of neoplastic cells range from being nearly normal to strikingly atypical (1,3)
- Numerous mitoses, many of which abnormal
- Necrosis of neoplastic sebocytes as solitary units and en masse
- Often intraepidermal involvement by neoplastic cells (3)

Clinicopathologic Correlation:

Clinical Feature	Pathologic Feature
Poorly defined erythematous or yellowish nodule or plaque	Asymmetrical neoplasm with infiltrative borders comprised of large irregular aggregates of neoplastic sebocytes that vary in size and shape

EXTRAOCULAR SEBACEOUS CARCINOMA

Clinical Presentation:

- Uncommon
- Men affected predominantly
- Usually on the head and neck of elderly patients (2)
- Yellowish firm nodules, often ulcerated, 1 to 4 cm or more in diameter (Fig. 12A)
- Rarely metastasizes

Histopathology:

- Located superficially or deep (Figs. 12B and 13A)
- Asymmetric lesion with infiltrative borders (Fig. 13A)
- Neoplastic aggregates with variation in sizes and shapes bear little resemblance to normal sebaceous lobules (Figs. 12B; 13A, B, and C) (1,2)
- Mixture of immature and mature neoplastic sebocytes (Figs. 12C and D; 13B, C, and D)
- Markedly pleomorphic neoplastic cells with hyperchromatic irregular nuclei (Figs. 12D and 13D) (2)
- Numerous and abnormal mitotic figures (Fig. 12C)
- Foci of necrosis (Fig. 12B)
- Intraepidermal involvement by neoplastic cells is rare

Clinicopathologic Correlation:

Clinical Feature	Pathologic Feature
Firm yellowish nodule, often ulcerated	Asymmetrical and with infiltrative borders; irregular aggregates of neoplastic sebocytes with a great variation in size and shape, atypical cells with pleomorphic nuclei and a different degree of sebaceous differentiation

Differential Diagnosis:

Sebaceoma	Sebaceous Carcinoma
Yellow or flesh-colored circumscribed nodule or an ill-defined plaque	Yellowish firm nodule, a few centimeters in diameter, often ulcerated
Usually on the face or scalp	Usually on the head and neck of elderly patients
Well-circumscribed and symmetric	Asymmetrical and with infiltrative borders
Aggregations do not resemble normal sebaceous lobules and vary markedly in size and shape	Irregular aggregates of neoplastic sebocytes with a great variation in size and shape
An irregular mixture of mature and immature sebocytes with >50% undifferentiated basaloid cells	Neoplastic cells with a different degree of sebaceous differentiation

(*Continued*)

Differential Diagnosis: *Continued*

Sebaceous cells relatively monomorphous and without significant atypia	**Atypical cells with pleomorphic hyperchromatic nuclei and nucleoli**
Mitoses may be numerous but are not atypical	**Numerous mitotic figures, many of which atypical; areas of necrosis**

References:

1. Nelson BR, Hamlet KR, Gillard M, et al. Sebaceous carcinoma. J Am Acad Dermatol 1995; 33:1–15.
2. Moreno C, Jacyk WK, Judd MJ, et al. Highly aggressive extra-ocular sebaceous carcinoma. Am J Dermatopathology 2001; 23:450–455.
3. Rao NA, Hidayat A, McLean IW, Zimmerman LE. Sebaceous carcinomas of the ocular adnexa: a clinicopathologic study of 104 cases with five-year follow-up data. Hum Pathol 1982; 13:113–122.

MUIR–TORRE SYNDROME AND ITS CUTANEOUS MANIFESTATIONS

- Syndrome characterized by the development of sebaceous tumors, often multiple (Fig. 14A), and visceral neoplasms
- Autosomal dominant inheritance
- Sebaceous tumors vary from just one to more than 100 lesions
- Cutaneous tumors may precede or follow the manifestation of the visceral cancer (1)
- Visceral tumors usually of the gastrointestinal tract: polyps of the large bowel and adenocarcinomas
- Other organs may be involved: larynx, the genito-urinary system, ovary, and uterus
- Cutaneous sebaceous neoplasms sometimes difficult to classify (Figs. 14B and 15) (1,2)
- Cystic sebaceous tumors described as marker lesions for the Muir–Torre syndrome (Figs. 14C and D) (2)
- Sebaceous tumors associated with the syndrome (1,3)
  - Sebaceous adenoma
  - Sebaceoma
  - Sebaceous carcinoma
  - Basal cell carcinoma with sebaceous differentiation

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1. Misago N, Narisawa Y. Sebaceous neoplasms in Muir–Torre syndrome. Am J Dermatopathol 2000; 22:155–161.
2. Rutten A, Burgdorf W, Hugel H, et al. Cystic sebaceous tumors as marker lesions for the Muir–Torre syndrome: a histopathologic and molecular genetic study. Am J Dermatopathol 1999; 21:405–413.
3. Banse-Kupin L, Morales A, Barlow M. Torre's syndrome: report of two cases and review of the literature. J Am Acad Dermatol 1984; 10:803–817.

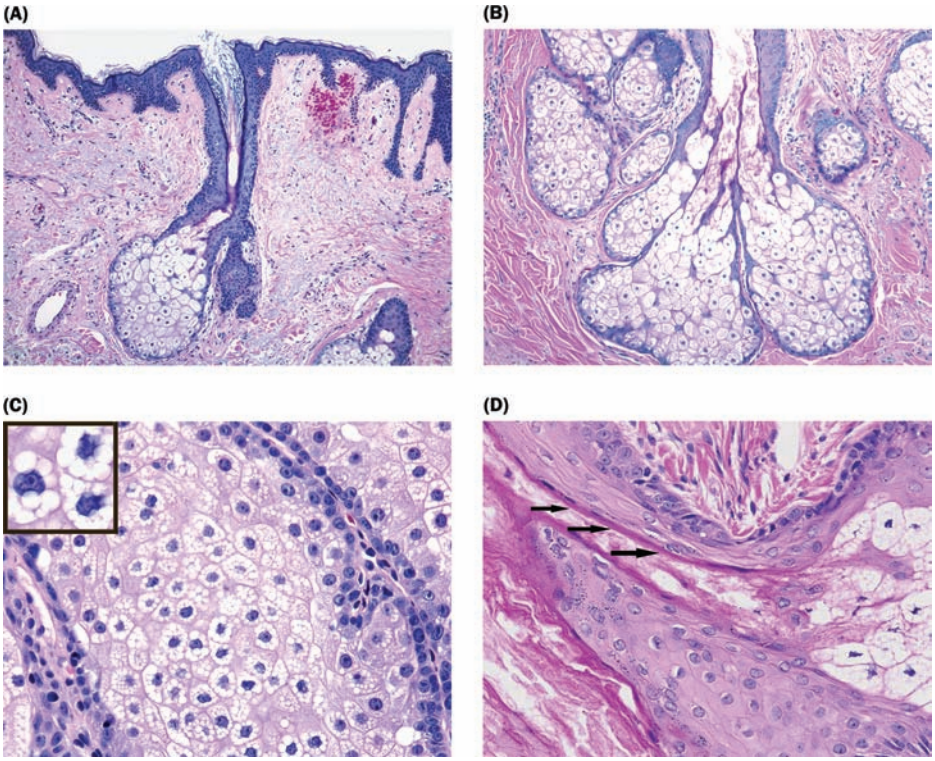

Figure 1 (**A**) A small (vellous) hair follicle and a sebaceous gland forming a folliculosebaceous unit. (**B**) Large sebaceous gland comprised of a few sebaceous lobules and their sebaceous ducts. (**C**) A sebaceous lobule with a row of immature sebocytes at the periphery, with dark nuclei and very little cytoplasm, and mature sebocytes in the center. (*Inset*: Mature sebocytes with scalloped nuclei and vacuolated cytoplasm.) (**D**) Sebaceous duct with eosinophilic crenulated lining containing sebum formed by a nearby sebaceous lobule.

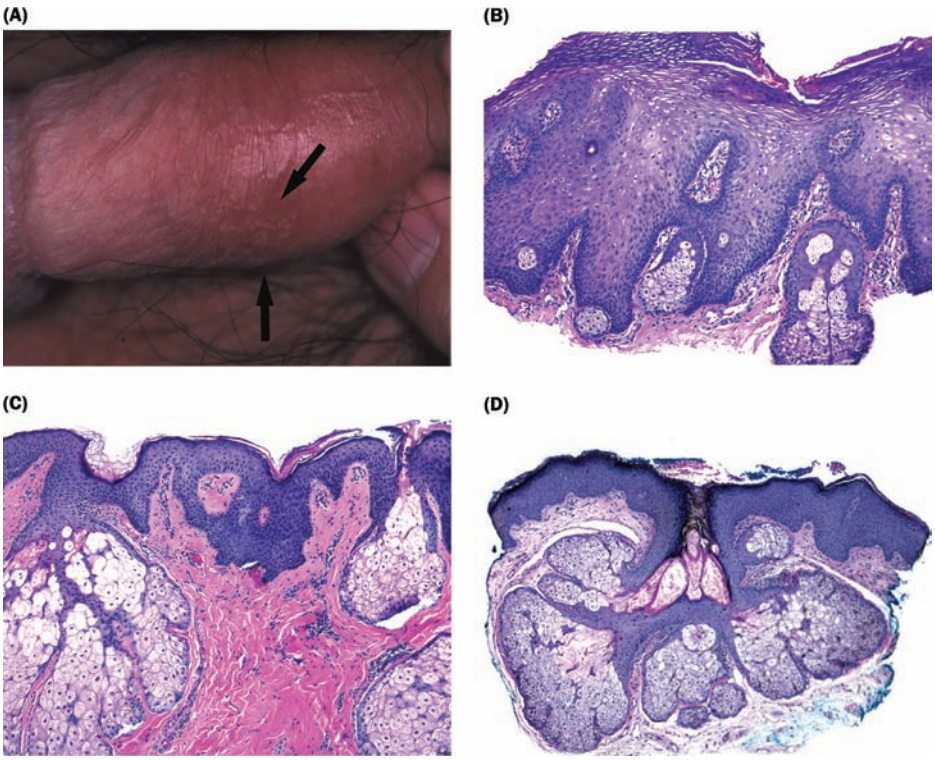

Figure 2 (**A**) Fordyce's spots as tiny white papules on genital skin. (**B**) Mucosa with sebaceous lobules unassociated with hair follicles and situated high in the submucosa. (**C**) Sebaceous lobules with direct opening onto the epidermal surface in a Fordyce's spot. (**D**) A large sebaceous gland containing a few large sebaceous lobules opening within a dilated sebaceous duct leading to the surface epithelium in a Montgomery's tubercle of the nipple.

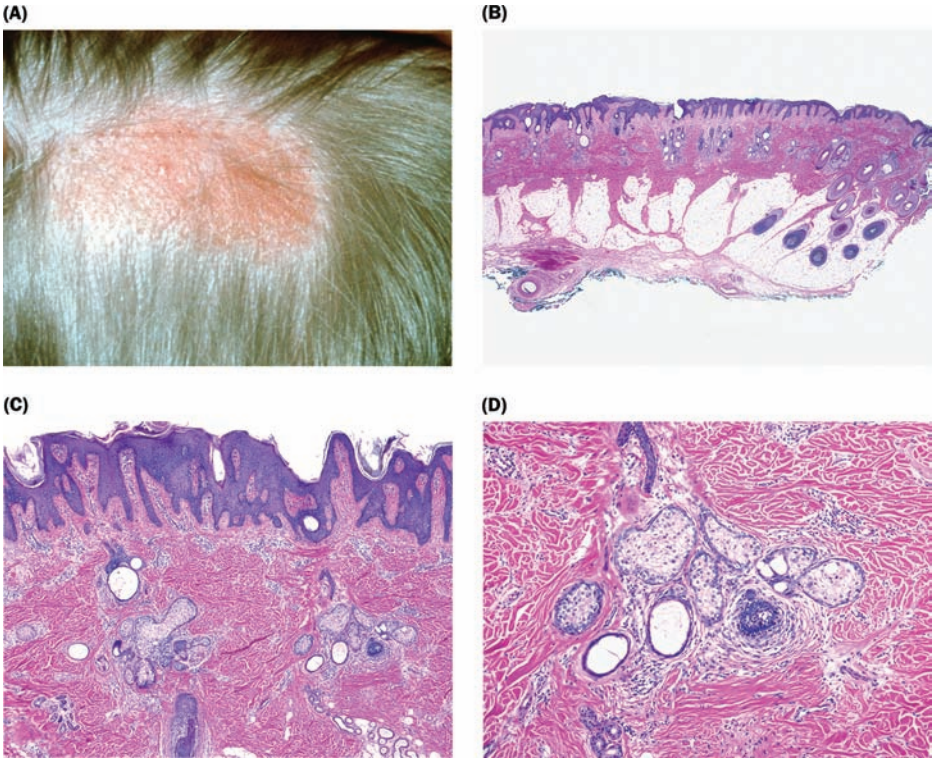

Figure 3 (**A**) Nevus sebaceus in a child presenting as a hairless sebaceus raised patch on the scalp. (**B**) Normal epidermis and mature hair follicles deeply rooted in the subcutis on the right. Slightly hyperplastic epidermis on the left within a lesion of nevus sebaceus in a child with missing mature hair follicles. (**C**) Acanthotic papillomatous epidermis with hyperkeratosis. Immature hair follicles located superficially in the dermis. (**D**) Miniature incompletely differentiated hair follicle with small sebaceous glands.

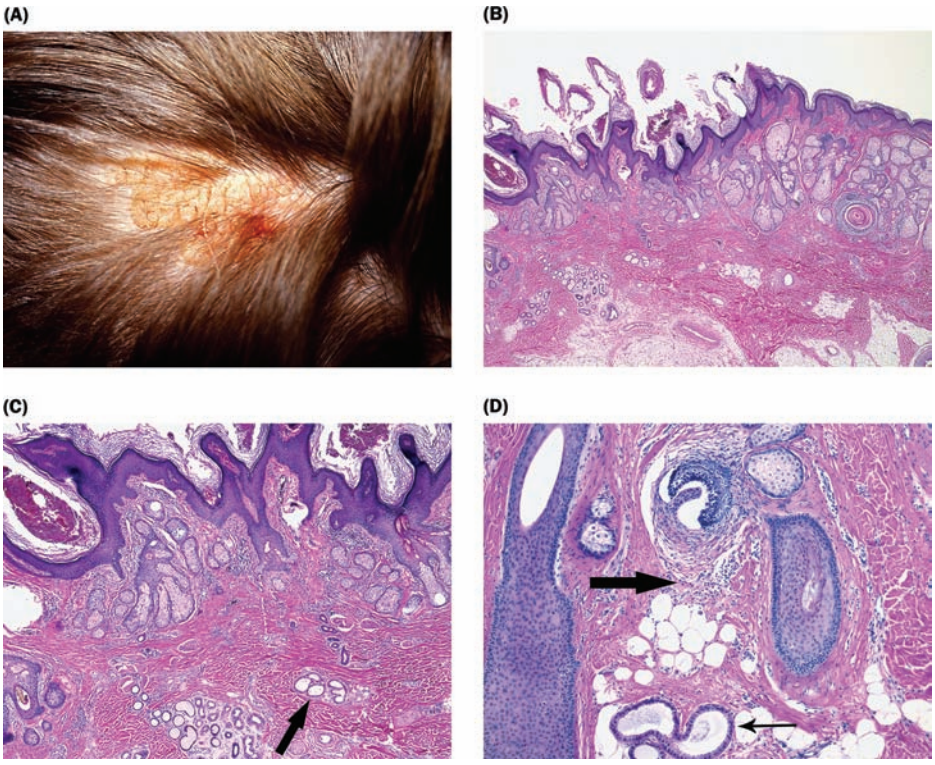

Figure 4 (**A**) Yellow verrucous plaque devoid of hair on the scalp of an adult. (**B**) Epidermis with marked acanthosis, papillomatosis, and hyperkeratosis. Numerous large sebaceous glands. (**C**) Increased number of sebaceous glands with direct opening at the epidermal surface. Apocrine glands in the upper dermis marked by an arrow. (**D**) A normal mature hair follicle on the left next to a small immature one designated by a *thick arrow*. Apocrine glands underneath (*thin arrow*).

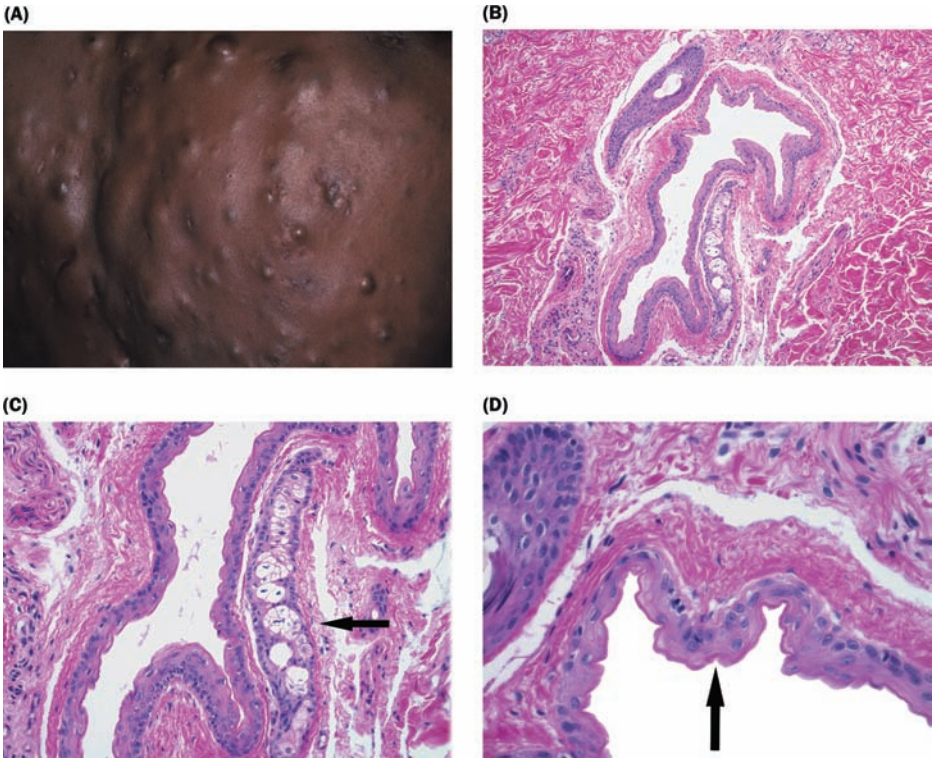

Figure 5 (**A**) Numerous skin-colored papules and nodules on the back of a patient with steatocystoma multiplex. (**B**) Cystically dilated space in the dermis with folded wall lined by stratified squamous epithelium. (**C**) A sebaceous gland (*arrow*) in the vicinity of the cystic space. (**D**) Pink irregular layer identical to the lining of a sebaceous duct covers the epithelium.

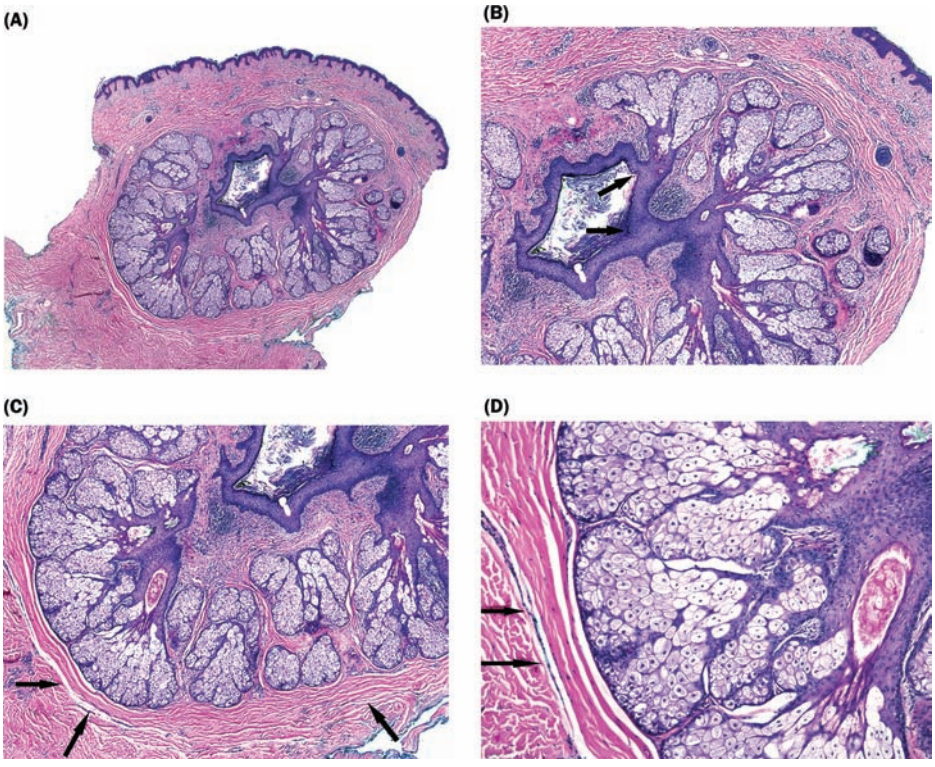

Figure 6 (**A**) Well-circumscribed lesion in the reticular dermis. (**B**) Markedly dilated infundibulum with radiating sebaceous ducts and lobules. (**C**) Dense fibrous stroma encircles the cystic structure and the folliculosebaceous units. (**D**) Clefts between the stroma and the adjacent dermis.

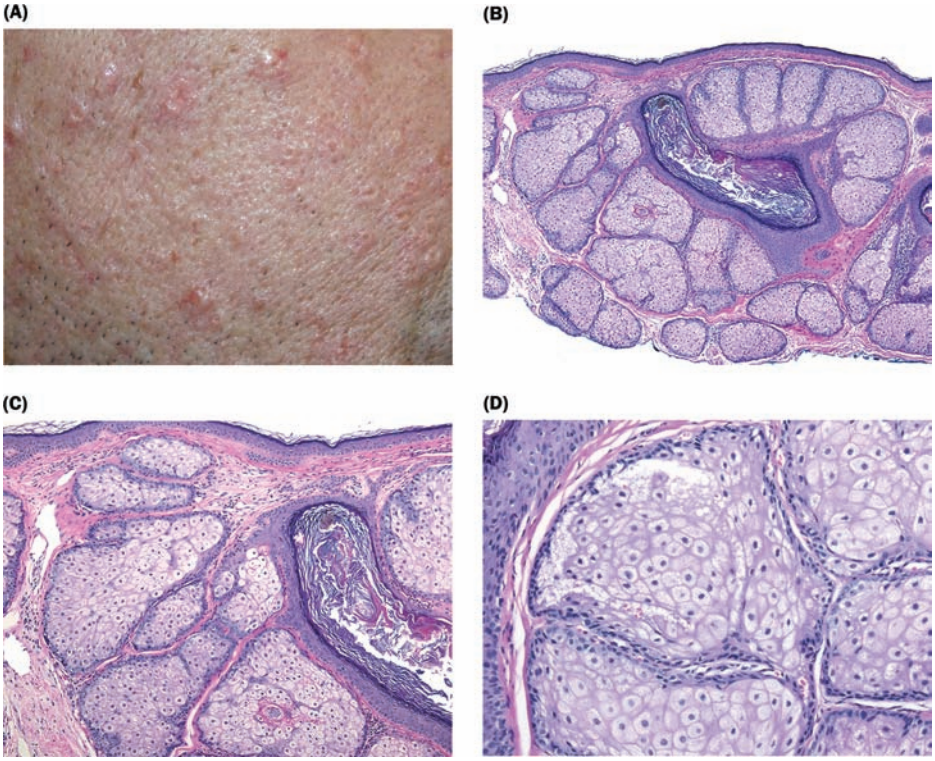

Figure 7 (**A**) Numerous tan to yellowish papules, many of which umbilicated. (**B**) Dilated follicular infundibulum surrounded by numerous large sebaceous lobules. (**C**) Enlarged sebaceous gland in close proximity to the epidermis and adjacent to a cystically dilated infundibulum. (**D**) Large sebaceous lobules with a rim of basaloid cells at the periphery and mature sebocytes in the center are part of the enlarged sebaceous gland.

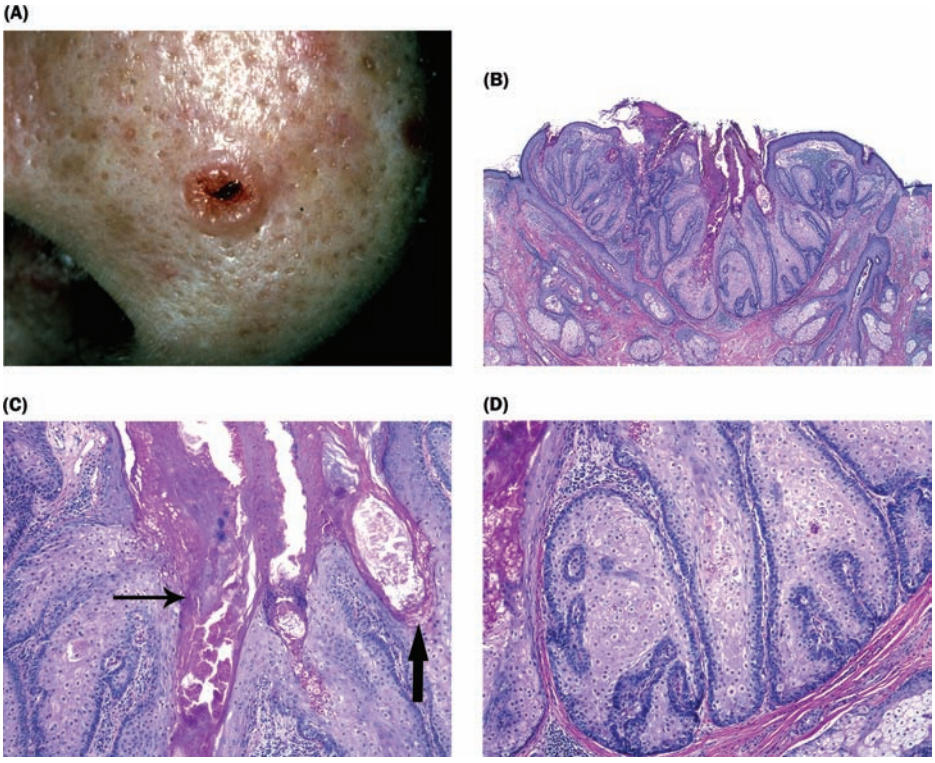

Figure 8 (**A**) Small umbilicated, well-circumscribed yellowish nodule on the nose. (**B**) Well-demarcated exo-endophytic lesion comprised of sebaceous lobules with variation in size and shape. (**C**) Dilated sebaceous ducts filled with sebum connect the sebaceous lobules to the surface. Sometimes, there is a direct opening of the lobules at the surface. (**D**) The sebaceous lobules contain mature sebocytes in the center, which predominate, and immature sebocytes at the periphery.

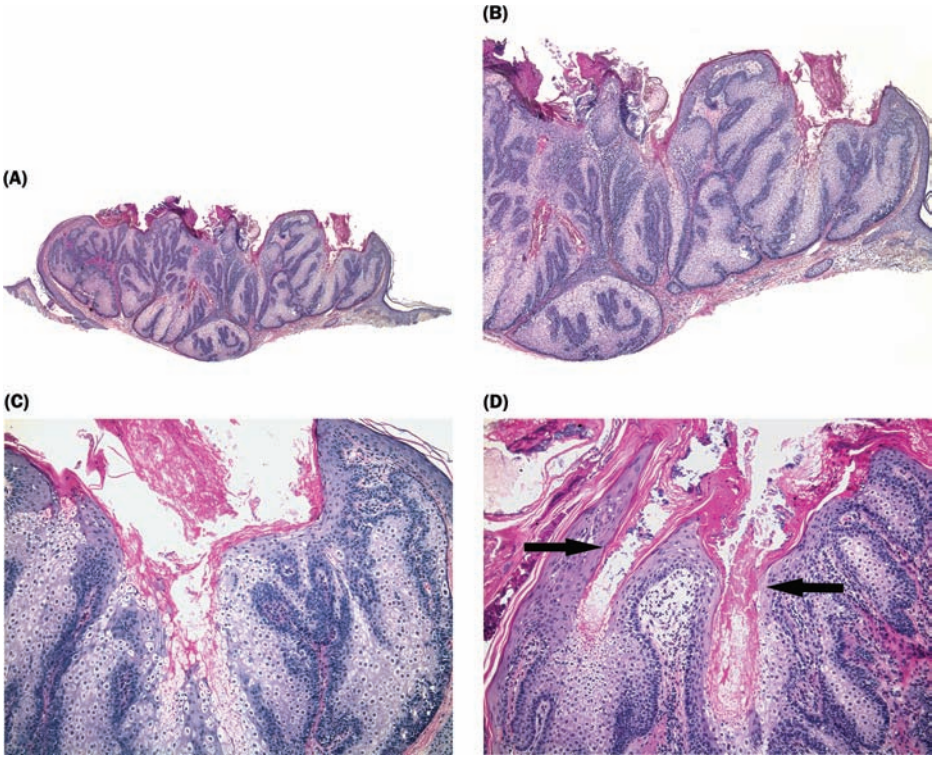

Figure 9 (**A**) Sharply circumscribed sebaceous adenoma containing sebaceous lobules of varying size and shape. (**B**) Some sebaceous lobules are vertically oriented and some have piriform shape. (**C**) Many lobules open directly at the epidermal surface. (**D**) Large dilated sebaceous ducts connect the sebaceous lobules to the surface.

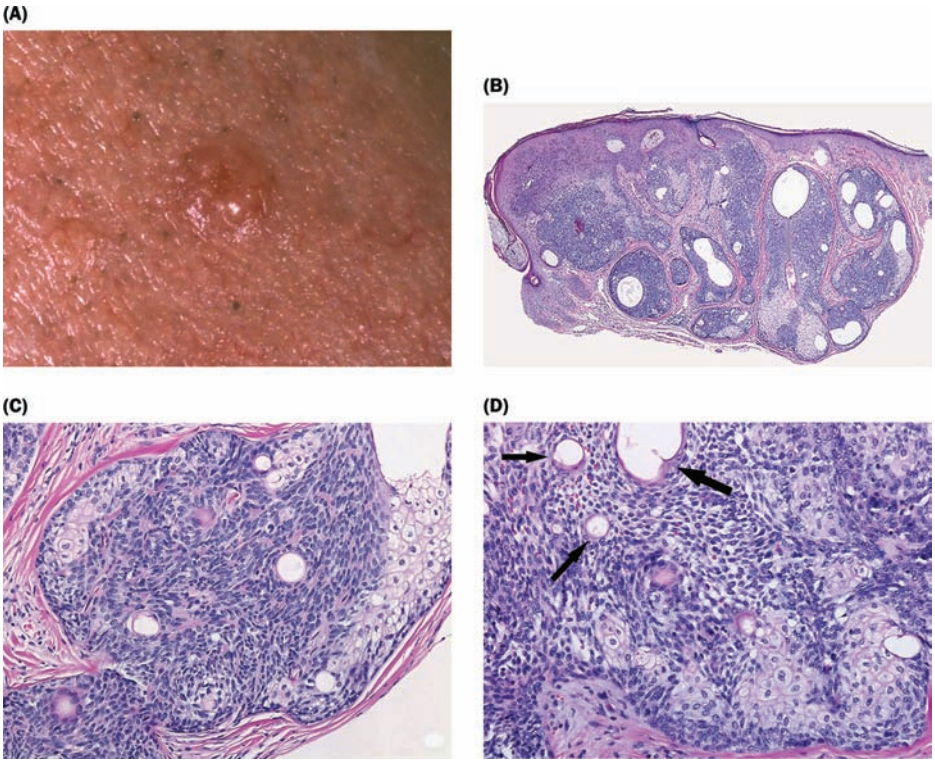

Figure 10 (**A**) Small relatively well-circumscribed umbilicated yellowish nodule. (**B**) Slightly asymmetrical but well-demarcated lesion with smooth borders containing sebaceous aggregates with variation in size and shape. (**C**) Basaloid undifferentiated sebocytes are admixed with single or small clusters of mature vacuolated sebocytes. (**D**) Sebaceous ducts (*arrows*) with pink cuticle-like lining present within this aggregate.

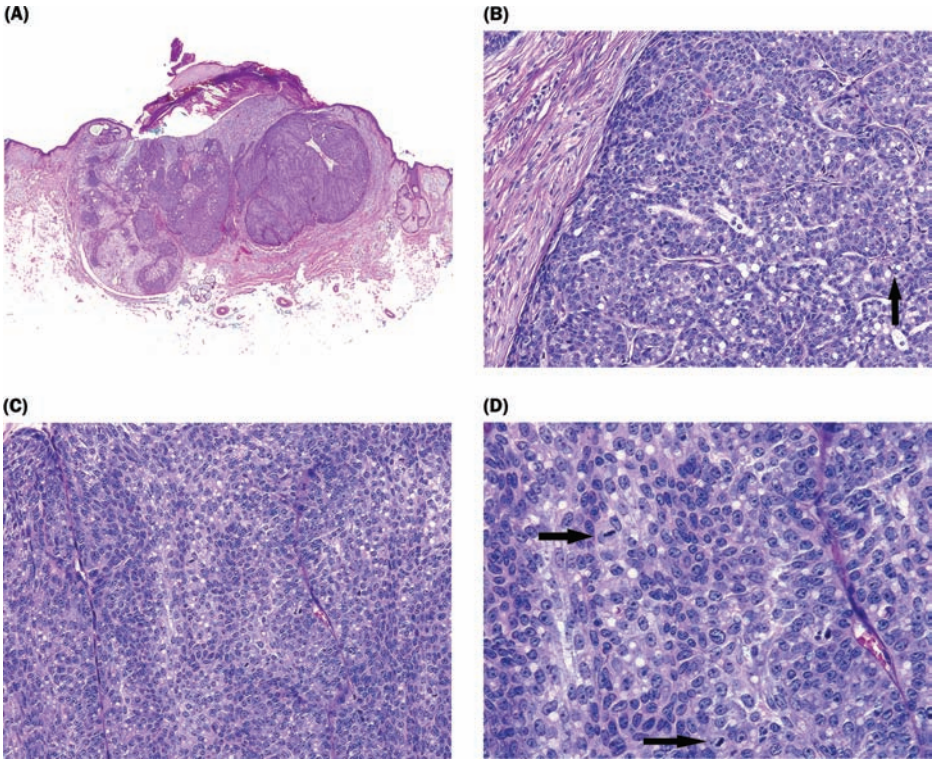

Figure 11 (**A**) Asymmetrical neoplasm showing good circumscription and ulcerated surface covered with a scale-crust. Marked variation in size and shape of aggregations. (**B**) A sebaceous lobule primarily comprised of small basaloid sebocytes with scant cytoplasm. Only rare mature sebocytes are spotted (*arrow*). (**C**) Highly cellular sebaceous lobules containing immature sebocytes that are monomorphous. (**D**) Numerous but not atypical mitotic figures.

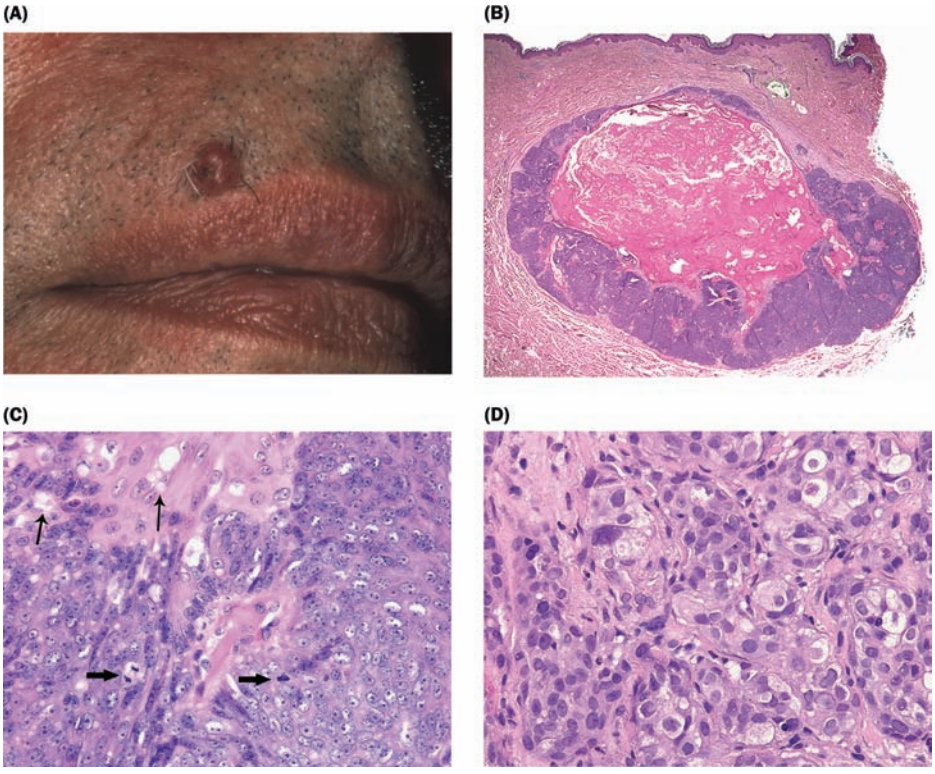

Figure 12 (**A**) Round but slightly asymmetric yellowish nodule. (**B**) Asymmetric cystic neoplasm comprised of large irregular aggregates and central necrosis. (**C**) Crowded-together neoplastic sebocytes with high nuclear-to-cytoplasmic ratio and some in mitosis (*thick arrows*). Occasional mature sebocytes are present (*thin arrow*). (**D**) Markedly pleomorphic neoplastic cells, some with large hyperchromatic irregular nuclei and vacuolated cytoplasm.

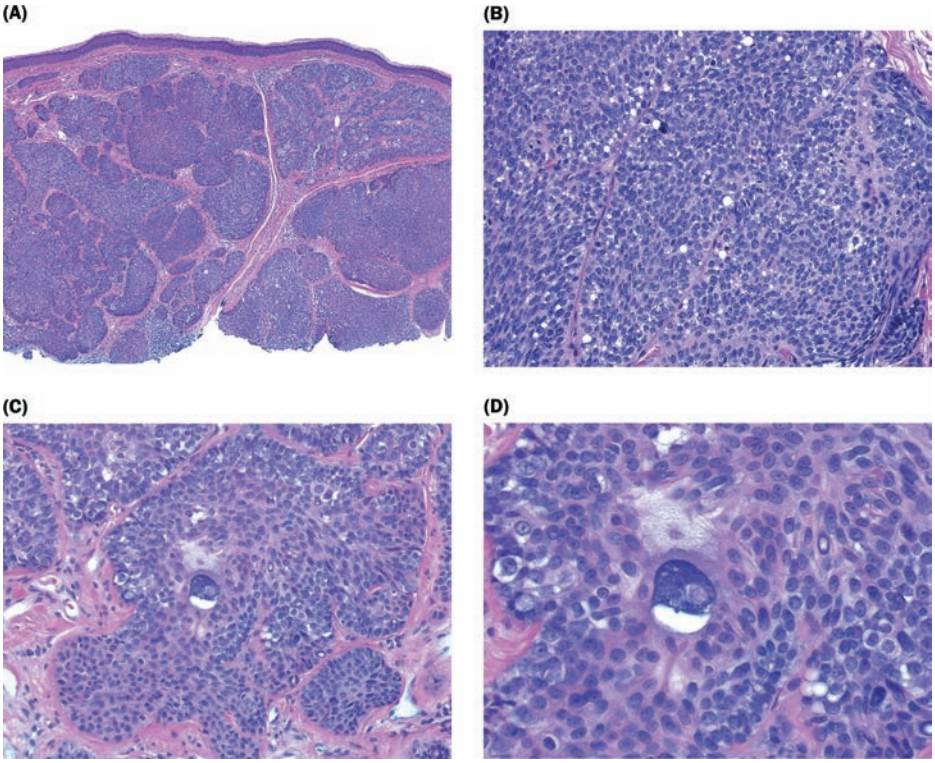

Figure 13 (**A**) Irregular neoplastic aggregates with different shapes in the reticular dermis. (**B**) A mixture of neoplastic sebocytes, majority of which with high nuclear-to-cytoplasmic ratio. Numerous mitotic figures. (**C**) Variation in size and shape of neoplastic sebocytes with different degree of differentiation. (**D**) Large neoplastic cell with hyperchromatic nucleus and prominent nucleolus in the center of an aggregate comprised mostly of immature sebocytes.

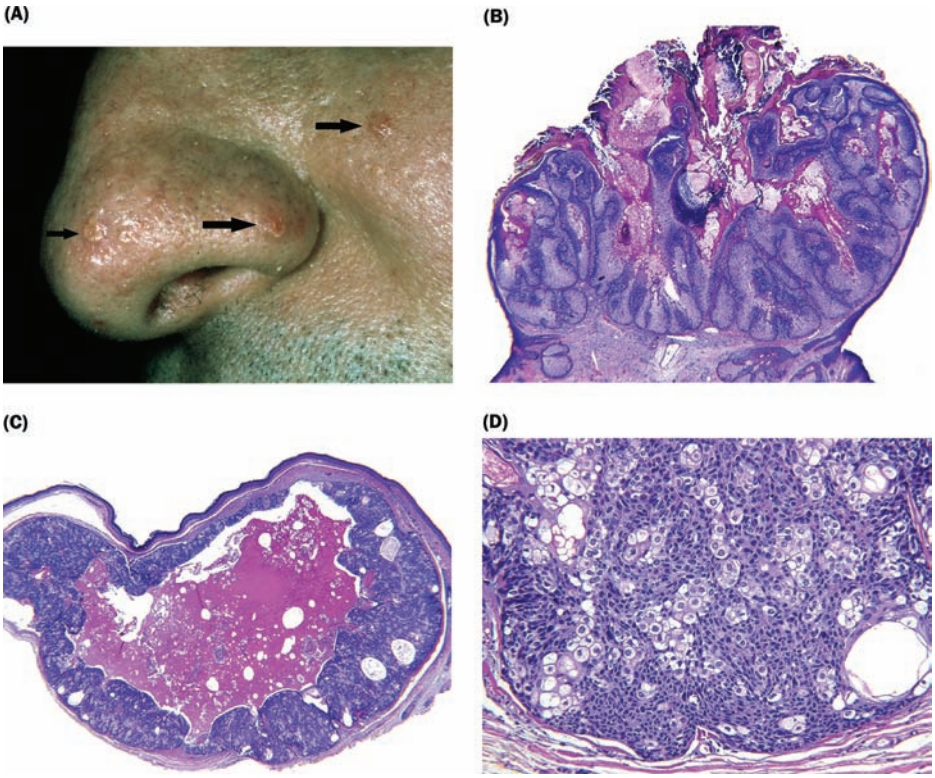

Figure 14 (**A**) Three small umbilicated yellow nodules on the face of a patient with Muir–Torre syndrome. (**B**) A well-demarcated benign sebaceous neoplasm with keratoacanthoma-like architecture and central crater. (**C**) A cystic benign sebaceous neoplasm with irregular sebaceous lobules lining a cystic cavity filled with sebum and cellular debris. (**D**) Mature sebocytes admixed with immature ones within a neoplastic aggregation.

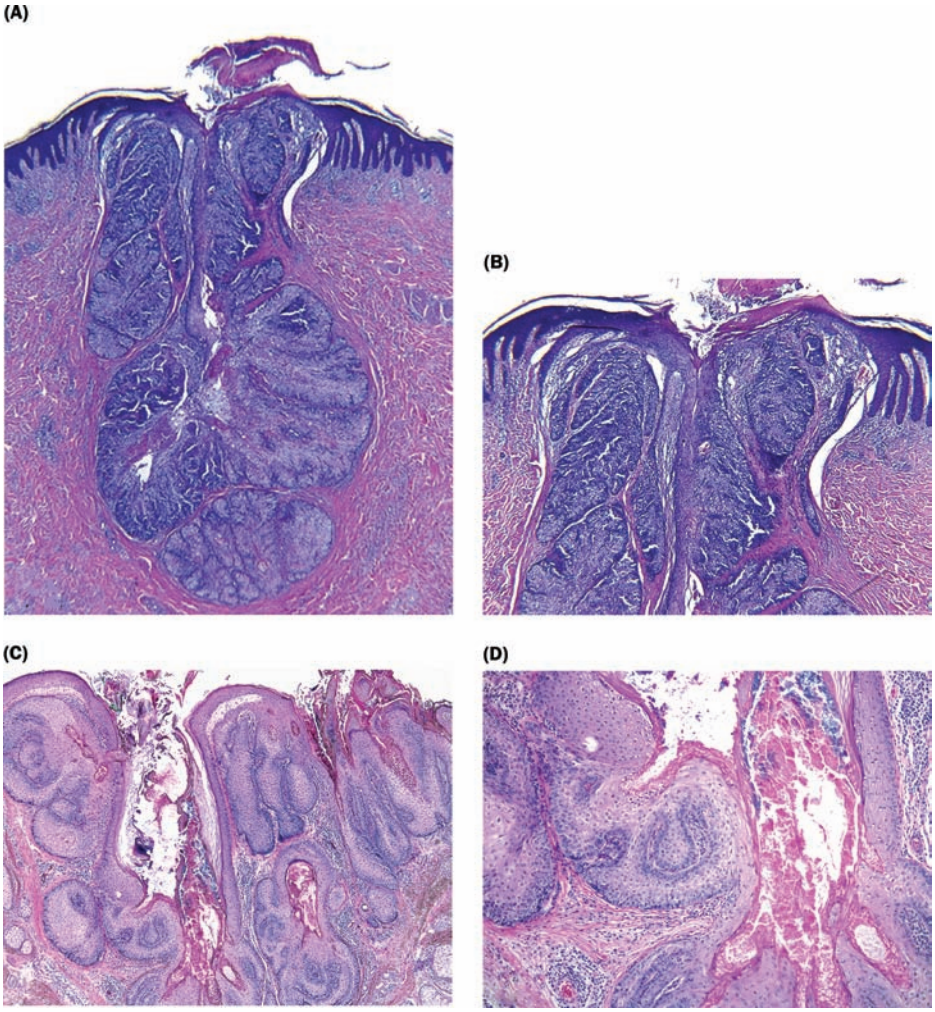

Figure 15 (**A**) Vertically oriented sebaceous neoplasm that is difficult to classify precisely. (**B**) Irregular, vertically oriented sebaceous lobules containing mature and immature sebocytes. (**C**) Asymmetrical but well-circumscribed endophytic sebaceous neoplasm containing sebaceous lobules of different sizes and shapes. (**D**) Mature sebocytes outnumber the immature ones that are seen only at the periphery of the lobules. Large sebaceous ducts join together and lead to the skin surface.

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Glandular Adnexal (Apocrine and Eccrine) Neoplasms

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CONTENTS

The nosology of adnexal neoplasms has been confused and confusing for decades, and much of the mystification of the past was wrought by the lack of logical classification. Classification proposals and inferences regarding lineage from the authorities of the past were often contradictory, and to a lesser extent, this problem persists at the present time. This is in part a consequence of the fact that broad conclusions regarding lineage and classification were based on enzyme histochemical attributes that lacked established specificity and were never properly assessed in the context of controlled trials.

Enzyme histochemistry enjoyed a brief flash of activity in the late 1960s but has proved to be of dubious value over time. Although the number of cases studied by enzymatic analysis was very small and the assessment was based mostly upon uncontrolled qualitative judgments, the results became the basis for conclusions regarding lineage that persisted for decades. The method has not stood the test of time, although it lingers on in the minds of some and in some textbook chapters. Indeed, enzyme histochemistry is no longer generally available as a method of analysis. In short, enzyme histochemistry contributed to the evolution of misguided classification schemes that have persisted in dermatology and dermatopathology. Only recently has the lack of credibility of enzyme analysis led to a rethinking of this field.

Surprisingly, relatively compelling embryological and morphological relationships among adnexal structures were either unrecognized or overlooked by past authorities. It is only in the last decade that some of the subtle clinical and microscopical interrelationships displayed by these fascinating benign growths and the patients that develop them have been more fully appreciated. In the view of this author, the lines of evidence that best guide our thinking regarding the classification of adnexal neoplasms include embryology, combinations of neoplasms and associations between neoplasms, anatomical distribution of neoplasms, and careful microscopical observations.

MICROANATOMICAL AND EMBRYOLOGICAL CONSIDERATIONS

Although we often think of hair follicles, sebaceous glands, and apocrine glands as distinct elements, all three components actually stem from the same structure, which has been termed the folliculosebaceous-apocrine unit. For practical purposes, the terms "follicle," "hair follicle," "folliculosebaceous unit," and "folliculosebaceous-apocrine unit" are used interchangeably. The folliculosebaceous-apocrine unit is a structure that provides insulatory, cosmetic, and pheromonic functions to the mammalian organism. The eccrine unit is a completely independent structure that serves as a thermoregulatory device via secretion of sweat.

The follicle proper consists of an infundibulum, an isthmus, and an underlying stem and bulb. The infundibulum is the superficial most segment, in continuity with the surface epithelium, and is composed mostly of keratinocytes that are microscopically identical to epidermal keratinocytes. Infundibular keratinocytes display pink cytoplasm within a conspicuous layer analogous to the stratum spinosum and mature via a stratum granulosum to form orthokeratin that envelops a hair. The infundibulum forms a tunnel that harbors and shields the projecting hair shaft. The apocrine duct emanates from the lower infundibulum and spirals downward through the dermis to the apocrine secretory unit. Subjacent to the infundibulum, the follicular isthmus is defined superiorly by the origin of the sebaceous duct and inferiorly by the insertion of the leiomyocytes of the arrectores pilorum musculature. The follicular isthmus is characterized microscopically by keratinocytes with dense pink cytoplasm that display abrupt cornification with little intervening stratum granulosum, forming compact orthokeratin that is tightly arrayed around the hair shaft.

Sebaceous and apocrine glands emanate from the primary follicle and reside within the adjacent dermis. Virtually, all follicles sport sebaceous glands, whereas apocrine glands usually involute at most body sites, remaining detectable in genital and axillary sites, in periorbital and periauricular skin, and sometimes in skin of the scalp. The sebaceous duct, distinctive for the corrugated luminal border and compact eosinophilic cuticle lining its canal, courses a

short distance through the adventitial dermis and links to the adjacent sebaceous gland. The sebaceous gland proper consists of a thin peripheral layer of seboblasts with a basaloid appearance, with the bulk of the gland composed of mature sebocytes, characterized by a scalloped nuclear border because of the presence of abundant surrounding coarsely vacuolated cytoplasm.

In areas in which apocrine glands are preserved, the apocrine duct juts from the lower infundibulum just superior to the insertion of the sebaceous duct and spirals downward to join the secretory portion of the apocrine gland, which is situated in the deep reticular dermis and subjacent subcutis. The secretory elements are arranged as tubules lined by cuboidal and columnar cells with ample eosinophilic cytoplasm that often appears finely granular in conventional sections. At the luminal border, a papillated or "decapitation" pattern is often present, reflecting holocrine secretion.

A crucial principle to keep in mind when considering adnexal lesions is the fact that the development of the eccrine apparatus is completely distinct from that of the folliculosebaceous-apocrine unit. In fully developed human skin, eccrine glands and folliculosebaceous-apocrine units are unrelated structures, and their embryogenesis is completely independent. Eccrine glands develop directly from the embryonic epidermis in the early months of fetal development, projecting as a cord of cells that subsequently entubulates to form a gland. Folliculosebaceous units develop directly from the epidermis at much the same time, but the development of follicles differs from the development of eccrine glands in that mesenchymal cells, precursors of the follicular papilla, induce a follicular germ and descend jointly into the dermis with the developing epithelial structure. Subsequently, sebaceous and apocrine glands and their ducts elaborate as secondary structures. The folliculosebaceous unit is a hamartoma-like structure from the start, eventuating with a combination of epithelial cells of different types and perifollicular fibrocytes, whereas the eccrine gland is a strictly epithelial structure.

This ontogenetic principle reflects relationships that can be observed repetitively in dermatological diseases. As one might predict from ontogeny, follicular, sebaceous, and apocrine differentiations are frequently observed conjointly, and combinations of eccrine and folliculosebaceous differentiations probably do not exist. Certainly, authors in the past have described proliferations of putative mixed eccrine and folliculosebaceous differentiation, but in the view of most current authorities, these claims are baseless.

Combinations of adnexal neoplasms also shed light on lineage and provide insight into the development of a logical classification scheme. Although most adnexal neoplasms display a relatively uniform microscopical pattern, it is not uncommon to encounter lesions with biphasic or multiphasic patterns. Excepting the identification of a coincidental "collision" between proliferations of disparate biology, such as syringoma combined with basal cell carcinoma or a melanocytic nevus juxtaposed on desmoplastic trichoepithelioma, the elements that occur conjointly in "combined" adnexal neoplasms can be assumed to be of related lineage. For example, the commingling of spiradenoma and cylindroma is commonplace and suggests a close relationship. Indeed, it has been suggested by some observers that these two separately described lesions represent different patterns of the same entity. Spiradenoma or cylindroma is occasionally captured with trichoepithelioma. Adnexal neoplasms also develop, singly or in combination, in association with nevus sebaceus, which is not an adnexal neoplasm itself but rather a folliculosebaceous-apocrine hamartoma.

It is clear from such combinations that cylindroma and spiradenoma are of the same lineage. The nonsensical historical notion (present in most textbooks of dermatology and dermatopathology) that spiradenoma is "eccrine" and cylindroma is "apocrine" is pure poppycock. This conclusion can be based not only on the fact that the two neoplasms occur intertwined, but also on their relationship in common with both trichoepithelioma and nevus sebaceus.

Although not in direct combination, adnexal neoplasms can also occur jointly (in multiplicity) in the same patient in the context of a genetic disorder, typically a dominantly inherited syndrome. Multiple trichoepitheliomas occurring in concert with multiple cylindromas and/or spiradenomas, the so-called Brooke–Spiegler syndrome, is a common connection. Spiradenoma and cylindroma have also been observed jointly in multiplicity, as has the triad of spiradenoma, cylindroma, and trichoepithelioma. These observations assert that the lineage of cylindroma, spiradenoma, and trichoepithelioma is linked and that cylindroma, spiradenoma, and trichoepithelioma are best classified as folliculosebaceous-apocrine neoplasms.

The topographic distribution of adnexal structures also offers insight into logical classification. There is striking variation in anatomic distribution among adnexal neoplasms, and some of these differences hold implications with respect to logical assignment of lineage. Historically, poroma has been considered so thoroughly eccrine that many dermatologists do not even refer to it as poroma. Rather, the designation "eccrine poroma" is used as its formal name. Poromas are routinely observed on the palms and soles, sites rife with eccrine structures, as one would expect of a neoplasm of eccrine lineage. However, the clinical presentation of poroma is broad and is not limited to glabrous lesions. Poromas present not uncommonly on the scalp and in axillary and inguinal skin, sites where apocrine elements are prominent. Poromas also develop as secondary neoplasms within nevus sebaceus, a folliculosebaceous-apocrine hamartoma. The most parsimonious explanation for the distribution of poroma is not that poroma is eccrine, but rather that poroma may be of either eccrine or apocrine lineage. Similarly, the distribution of syringoma is at odds with historical classification schemes. Purportedly an eccrine neoplasm, syringomata virtually never develop at sites replete with eccrine elements, such as the palm or sole. Acral syringomata are a rarity. Instead, syringomata are found almost exclusively on the periorbital face and genitalia, sites at which apocrine elements are identifiable. This topographic evidence suggests that syringomas are probably apocrine in nature, most of the time.

Microscopy and other morphological tools, including the wide array of available special stains, also play a role in the assessment of lineage. However, if microscopists are to use their observations as the foundation for a system of classification, they must be certain that the microscopical features chosen for tabulation are determinate of a specific line of differentiation. For some lines of differentiation, the meanings attributed to specific microscopical findings are indisputable. The presence of cells with coarsely vacuolated cytoplasm and scalloped nuclei clearly indicates sebaceous differentiation. There is consensus that follicular (germinative) differentiation is established if a proliferation contains basaloid cells resembling the follicular bulb and adjacent mesenchymal cells resembling the papilla. Other unequivocal marks of follicular differentiation include anucleate

matrical cells ("shadow" cells), a palisade of pallid cells with an adjacent thickened basement membrane, an attribute of the follicular outer sheath (trichilemma), and bright pink intracytoplasmic trichohyalin granules, typical of matrical corneocytes of the inner sheath. In contrast to these universally accepted attributes, the features that indicate glandular lineage lack specificity. Decapitation secretion is rightly held as the pathognomonic marker of apocrine differentiation, yet an essentially indistinguishable microscopical pattern can be encountered at times in occluded eccrine glands or in neoplasms of postulated eccrine lineage. Ducts with a compact eosinophilic cuticle have been wrongly interpreted as a specific indicator of eccrine differentiation, as identical structures can reflect apocrine or even sebaceous lineage in the ducts of the folliculosebaceous-apocrine unit.

What then are the specific microscopical features of eccrine glands that, when observed within a neoplasm, confirm eccrine lineage? There are none. Apocrine lineage can be suspected on the basis of recognition of decapitation secretion, but a judgment as to whether a process exhibits eccrine or apocrine differentiation cannot be based on the presence of ducts, as eccrine and apocrine ducts are indistinguishable. In short, microscopical assessment is invaluable in the specific recognition of follicular and sebaceous differentiation and is sometimes sufficient to suspect apocrine differentiation. Microscopy alone is insufficient to establish eccrine lineage, save for the exclusion of other modes of differentiation.

Other morphological tools for assessing lineage, such as electron microscopy and enzyme histochemistry, have been suggested but have been proven to be of little value and will not be addressed further. Immunoperoxidase staining has clarified the classification and lineage of many neoplasms, especially lymphomas, and still holds hope as an arbiter of adnexal lineage. To date, however, immunoperoxidase stains have resolved few, if any, of the conundrums of adnexal classification owing to lack of specificity. Carcinoembryonic antigen (CEA) was among the earliest reagents assessed. Although CEA nimbly labels areas of luminal differentiation, the pattern observed in both eccrine and apocrine ducts (and in eccrine and apocrine lesions) is identical. The situation is much the same for other reagents, including gross cystic disease fluid protein (GCDFP-15), epithelial membrane antigen, and various anti-keratins, all of which have been found at times to stain both eccrine and apocrine elements, whether normal or neoplastic.

CLASSIFICATION OF GLANDULAR ADNEXAL NEOPLASMS

Historically, adnexal neoplasms have been classified into four broad categories, namely follicular, sebaceous, apocrine, and eccrine. In light of the embryological considerations discussed previously, a logical ontogenetic classification yields but two (folliculosebaceous-apocrine and eccrine). This condensation is of no consequence for an established entity with a singular line of differentiation, such as sebaceous adenoma. The classification schemes of the past placed sebaceous adenoma as a tumor of sebaceous lineage, and sebaceous adenoma fits neatly under the rubric of folliculosebaceous-apocrine tumors in a modern classification scheme.

The advantage of ontogenetic classification relates to neoplasms with mixed or allegedly "divergent" differentiation, such as microcystic adnexal carcinoma (MAC). There is no need to debate whether MAC should be classified as a follicular neoplasm or a glandular neoplasm, and there is no need to force it, arbitrarily and uncomfortably, into one category or another. If a classification scheme places MAC as a glandular neoplasm, then what is to be done to acknowledge its follicular attributes? With a broadly conceived classification scheme, MAC can be designated in good conscience as a low-grade form carcinoma of folliculosebaceous-apocrine lineage, a categorization that reflects its heterogeneous differentiation.

In the discussion that follows, proliferations of folliculosebaceous-apocrine lineage will be limited to lesions with apocrine differentiation, as follicular and sebaceous lesions are discussed in other sections. The discussion of proliferations of eccrine lineage will be relatively brief; the fact that there are fewer eccrine proliferations is unsurprising, as eccrine glands lack anatomical complexity and have low proliferative potential.

In most textbooks, adnexal neoplasms with glandular and ductular differentiation have been rigorously separated into eccrine and apocrine neoplasms. Commonly, the distinction was based upon enzyme histochemical data from an imprecise technique that is no longer available. There has also been an illogical desire to lump all adnexal neoplasms of a certain type together and presume that all were of the same lineage. For example, syringoma, which shows distal ductular differentiation, was historically interpreted as exclusively eccrine, although common sense suggests that both apocrine and eccrine syringomata would likely occur. A few authorities have responded to this shortsightedness of the past by grouping apocrine and eccrine neoplasms together in recognition of the fact that it is impossible to determine whether a given lesion, such as a given syringoma, is of apocrine or eccrine lineage. In the presentation that follows, the traditional categorization as "apocrine" or "eccrine" will be maintained, but areas of overlap will be expressly noted. For entities such as syringoma and poroma, which can be of either apocrine or eccrine lineage, the bulk of the presentation will be included in the discussion of apocrine lesions, which is presented first.

EXAMPLES OF ADNEXAL NEOPLASMS

APOCRINE NEOPLASMS

SYRINGOMA

Clinical Presentation:

- Small firm papule with similar coloration to surrounding normal skin (Fig. 1).
- May occur at any site, but prone to occur in the periorbital area.
- Commonly multiple (Fig. 1).
- May occur in "eruptive" fashion, involving the trunk or extremities, including the palms and soles, extensively.

Histopathology:

- Small, symmetrical, and well circumscribed.
- Usually confined to the upper reticular dermis.
- Composed of uniform nests of epithelial cells with pale or pinkish cytoplasm, many with central cuticulated ducts or tubules (Fig. 2).

- Nests may resemble a comma or a tadpole, sometimes (Fig. 2).
- Associated sclerosis (commonly) (Fig. 2).
- Pronounced clear cell change (sometimes) (Fig. 2).
- Squamous metaplasia or cornification, rarely.

Clinicopathologic Correlation:
The firm papular nature of syringoma stems from associated sclerosis.

Pathophysiology:
Syringoma is a benign adnexal neoplasm with negligible proliferative capacity. Clinically, syringomata are small stable papules. Although historically interpreted as a lesion of eccrine lineage, at present, it seems clear that syringomata may be of apocrine or eccrine lineage. Most are probably apocrine, as they occur at "apocrine" sites such as the periorbital area. Acral syringomata also occur and can involve the palm or sole, either singly or in multiplicity.

Differential Diagnosis:
The superficial aspects of a syringoma may be difficult to distinguish from the superficial aspects of an MAC, especially in a shave biopsy. Sometimes, a dermatopathologist will find it necessary to defer to a deeper biopsy for a definitive diagnosis to be rendered. When the interpreter of a superficial biopsy is strongly considering the diagnosis of syringoma in a lesion that shows cornification and involvement of the deep biopsy margin, the clue of the "sesame seed bun" should be considered. To understand this clue, one must consider an analogy between the Big Mac®, a hamburger produced by one of the world's powerhouse fast food chains, and MAC. Just as one cannot deduce that a Big Mac® includes two all-beef patties, special sauce, lettuce, cheese, pickles, and onions merely by gazing at the sesame seed bun on the surface, a dermatopathologist often may also find it difficult to recognize MAC in a superficial biopsy.

Desmoplastic trichoepithelioma may also resemble syringoma. Although both share in common a background of sclerosis, syringoma differs from desmoplastic trichoepithelioma in that it is not composed of basaloid (follicular germinative) cells. Furthermore, the small cystic spaces in a syringoma represent areas of ductular differentiation, whereas the cystic spaces in a trichoepithelioma represent superficial follicular cornification.

Reference:
1. McCalmont TH. A call for logic in the classification of adnexal neoplasms. Am J Dermatopathol 1996; 18:103–109.

POROMA

Synonyms for poroma include hidroacanthoma simplex and dermal duct tumor. The late Elson Helwig of the Armed Forces Institute of Pathology utilized the designation acrospiroma to refer to a broad spectrum encompassing both poroma and hidradenoma.

Clinical Presentation:
- Solitary (almost always); multiple (rarely), known as poromatosis.
- Pigmented (sometimes).
- Highly vascularized (Fig. 3).
- Presents in hyperkeratotic or crusted fashion (sometimes) (Fig. 3).
- Favored sites include palm, sole, and genital or axillary skin.
- Occasionally found as a secondary neoplasm within nevus sebaceous.

Histopathology:
- Circumscribed proliferation of compact cuboidal ("poroid") keratinocytes with monomorphous nuclei and scant eosinophilic cytoplasm (Fig. 4).
- Highly vascularized and inflamed stroma (almost always) (Fig. 4).
- Stromal sclerosis (sometimes).
- Confined to the epidermis (hidroacanthoma simplex) (sometimes).
- Present in broad continuity with the epidermis, with extension into the papillary dermis (juxtaepidermal poroma) (sometimes).
- Present wholly (or nearly so) within the dermis (dermal duct tumor) (sometimes).
- Conspicuous ductal differentiation (almost always) (Fig. 5).
- Intracytoplasmic lumen formation (sometimes).
- Clear cell change (commonly). Necrosis en masse (focal) (commonly).
- Overt apocrine differentiation (sometimes). Focal sebocytic differentiation (sometimes).

Clinicopathologic Correlation:

Clinical Feature	Correlating Microscopic Feature
Vascular (pyogenic granuloma-like) appearance	Highly vasculized stroma and superjacent crust
Firm nodule	Stromal sclerosis
Overlying scale	Intra-epidermal involvement (hidroacanthoma simplex)

Pathophysiology:
Poroma is a benign adnexal neoplasm with low proliferative capacity, and lesions tend to be clinically stable. Rarely, a poroma will undergo malignant transformation with resultant porocarcinoma. Although historically interpreted as a lesion of eccrine lineage, current information clearly indicates that poromata may be of either apocrine or eccrine lineage. Most are probably eccrine, involving glabrous sites. Apocrine poromata may occur at virtually any site, but are prone to occur in axillary, genital, or scalp skin, where apocrine elements can be found. Poromata with sebaceous differentiation are probably best thought of as being lesions of folliculosebaceous-apocrine lineage. In support of this conclusion, this author's experience indicates that sebaceous poromata commonly show apocrine differentiation as well.

Differential Diagnosis:
When intra-epidermal or juxtaepidermal, poroma may closely simulate the configuration of a seborrheic keratosis. Recognizing areas of ductular differentiation and associated highly vascularized stroma are helpful in making the distinction. Hidradenoma is always in the differential diagnosis of poroma and differs in that the epithelial cells that comprise

it tend to be larger and often have ample pale or clear cytoplasm, in contrast to the compact cuboidal cells of poroma. In addition, ductular differentiation tends to be prominent in poroma, yet may be inconspicuous in hidradenoma.

References:
1. Kamiya H, Oyama Z, Kitajima Y. "Apocrine" poroma: review of the literature and case report. J Cutan Pathol 2001; 28:101–104.
2. Harvell JD, Kerschmann RL, LeBoit PE. Eccrine or apocrine poroma? Six poromas with divergent adnexal differentiation. Am J Dermatopathol 1996; 18:1–9.

HIDRADENOMA

Hidradenoma is a close relative of poroma. Some authorities use the broad designation acrospiroma to refer to hidradenoma and poroma jointly.

Clinical Presentation:

- Solitary (almost always).
- Cystic (sometimes) ["solid-cystic" hidradenoma (Fig. 6)].
- Pigmented (rarely) (Fig. 6).
- Highly vascularized (sometimes).
- Favored sites include genital, axillary, or inguinal skin.
- Occasionally found as a secondary neoplasm within nevus sebaceous.

Histopathology:

- Nodular and sharply circumscribed in pattern.
- Solid or cystic or, commonly, a combination of the two (Fig. 7).
- Composed of cells with ample pale or pink cytoplasm (Figs. 7 and 8).
- Overt clear cell change (commonly) ("clear cell" hidradenoma).
- Juxtaepidermal configuration with multifocal attachment to the epidermis (sometimes).
- Ductular/tubular differentiation (often), with varying prominence (Fig. 7).
- Stromal sclerosis (commonly) (Fig. 8).
- Highly vascularized stroma (sometimes).
- Overt apocrine differentiation ("decapitation secretion") (sometimes) (Fig. 8).
- Focal sebocytic differentiation (sometimes).

Clinicopathologic Correlation:

Clinical Feature	Correlating Microscopic Feature
Vascular appearance	Highly vasculized stroma
Firmness	Stromal sclerosis
Cystic appearance ("solid-cystic" hidradenoma)	Cystic dilatation of neoplastic epithelium
Pigmentation	Either lesional hemorrhage or intercalated pigmented dendritic melanocytes

Pathophysiology:

Hidradenoma is a benign adnexal neoplasm with very low proliferative capacity. As a result, lesions tend to be clinically stable. Rarely, a hidradenoma will undergo malignant transformation with resultant hidradenocarcinoma. Although historically interpreted as a lesion of eccrine lineage, current information clearly indicates that hidradenomata may be of either apocrine or eccrine lineage. Most are probably of apocrine lineage. Apocrine hidradenomata may occur at virtually any site, but lesions are prone to occur in axillary, genital, or scalp skin, where apocrine elements can be found. Hidradenomata with sebaceous differentiation are probably best thought of as reflecting folliculosebaceous-apocrine lineage.

Differential Diagnosis:

Hidradenoma and trichilemmoma show overlapping findings in that both commonly display a lobular or nodular profile and are composed of pale or clear cells. Trichilemmoma tends to show verrucous surface changes and a surrounding-thickened basal lamina, as is typical of the follicular outer sheath, whereas hidradenoma lacks those attributes. In contrast, hidradenoma may show focal ductular differentiation or cystic alteration, neither of which is commonly found in trichilemmoma. The cells of poroma tend to be compact with scant cytoplasm, in contrast to the larger pale cells of a hidradenoma.

References:
1. Liu HN, Chang YT, Chen CC, Huang CH. Histopathological and immunohistochemical studies of poroid hidradenoma. Arch Dermatol Res 2006; 297:319–323.
2. Gianotti R, Alessi E. Clear cell hidradenoma associated with the folliculosebaceous-apocrine unit: histologic study of five cases. Am J Dermatopathol 1997; 19:351–357.

APOCRINE ADENOMA

Any benign neoplasm with apocrine differentiation, including poroma and hidradenoma and even spiradenoma and cylindroma, could legitimately be termed an apocrine adenoma in a generic sense. However, on a practical basis, only adenomas with conspicuous apocrine glandular differentiation are included in this category. Entities within this spectrum include tubular adenoma, papillary adenoma, syringocystadenoma papilliferum, and hidradenoma papilliferum.

Clinical Presentation:

- Solitary (virtually always).
- Favored sites include axillary, inguinal, genital, and periauricular skin, as well as the scalp; syringocystadenoma, in particular, favors the head and neck area.
- Surface crust and exudate (sometimes) (especially in association with syringocystadenoma) (Fig. 9).
- Commonly found as a secondary neoplasm within nevus sebaceous.
- Linear configuration, especially when in concert with nevus sebaceous.

Histopathology:

- Nodular and circumscribed from scanning magnification.
- Verrucous surface changes, especially with syringocystadenoma (Fig. 10).
- Tubular, papillary, or tubulopapillary internal structure (Figs. 10 and 11).

- Frond-like internal structure, especially with hidradenoma papilliferum (Figs. 10 and 11).
- Decapitation secretion along lumina border.
- Glands lined by a bilayer of cells with a well-formed myoepithelial layer.
- Mucin-producing cells (sometimes).
- Stromal plasma cells, especially with syringocystadenoma (Fig. 11).

Clinicopathologic Correlation:

Clinical Feature	Correlating Microscopic Feature
Verrucous surface	Glandular crypts in continuity with surface squamous epithelium
Surface crust and exudate	Glandular secretions

Pathophysiology:
Apocrine adenomas represent a group of benign adnexal neoplasms with low proliferative potential. As a result, lesions tend to be clinically stable and do not pose a threat for malignant transformation. Apocrine adenomata may occur at virtually any site, but lesions are prone to occur in the so-called "apocrine" sites such as axillary or genital skin, where apocrine elements are commonly found. Apocrine adenomas are also a common secondary occurrence within nevus sebaceus.

Differential Diagnosis:
Syringocystadenoma differs from hidradenoma papilliferum and tubulopapillary adenoma in that it presents in verrucous or plaque-like rather than nodular fashion. Hidradenoma papilliferum requires distinction from conventional hidradenoma. Although both present in nodular fashion clinically, hidradenoma papilliferum is distinctive for its strikingly papillary internal structure with obvious apocrine glandular differentiation. In contrast, conventional hidradenoma usually has a "solid" microscopical appearance from low magnification and typically demonstrates only focal or inconspicuous glandular or ductular differentiation.

References:
1. Hsu PJ, Liu CH, Huang CJ. Mixed tubulopapillary hidradenoma and syringocystadenoma papilliferum occurring as a verrucous tumor. J Cutan Pathol 2003; 30:206–210.
2. Ishiko A, Shimizu H, Inamoto N, Nakmura K. Is tubular apocrine adenoma a distinct clinical entity? Am J Dermatopathol 1993; 15:482–487.

SPIRADENOMA

Spiradenoma connotes a type of undifferentiated benign adnexal neoplasm that has been historically interpreted as an eccrine lesion, although modern reassessment clearly indicates apocrine lineage.

Clinical Presentation:
- Papular or nodular.
- Rare "giant" lesions may achieve a diameter of several centimeters.
- Bluish coloration (sometimes).
- Painful sometimes.
- Multiple sometimes, especially in the context of Brooke–Spiegler syndrome.
- Present in concert with cylindroma or trichoblastoma, (sometimes).

Histopathology:
- Nodular or multinodular pattern from scanning magnification (Fig. 12).
- Large individual nodules, often positioned within both dermis and subcutis.
- Sharply circumscribed individual nodules (Fig. 12).
- Trabecular internal structure, with compact (dark) cells bordering trabecula and cells with ample pale cytoplasm (pale cells) within trabecular centers (Fig. 13).
- Obvious ductal or apocrine glandular (decapitation) differentiation (sometimes).
- Small lymphocytes scattered throughout trabecular areas (commonly).
- Central cystic degeneration (sometimes).
- Striking-associated vascular ectasia (sometimes).
- Compact eosinophilic periodic acid-Schiff (PAS)-D-positive basement membrane material within or bordering trabecula (sometimes).

Clinicopathologic Correlation:

Clinical Feature	Correlating Microscopic Feature
Blue coloration	Deep location, ectatic vascular spaces in stroma, or intralesional hemorrhage
Nodular morphology	Large collections of undifferentiated adnexal glandular cells
Cystic morphology	Degeneration of adnexal epithelium or stroma or profound vascular ectasia

Pathophysiology:
Spiradenoma is a benign adnexal neoplasm with low proliferative capacity, and recurrence is uncommon after simple enucleation. Rarely, accelerated proliferation with secondary transformation into spiradenocarcinoma may be observed. Although historically interpreted as an "eccrine" lesion based mostly upon long since defunct enzyme histochemical analysis, spiradenoma is now accepted as an apocrine neoplasm that is closely related to cylindroma. Sadly, the designation "eccrine spiradenoma" is entrenched in the language of dermatology and dermatopathology, so much so that spiradenoma is not even indexed under the letter "S" in virtually any textbook of dermatology. Rather, spiradenoma is commonly and wrongly indexed under the letter "E." Stunningly, articles including the term "eccrine" spiradenoma continue to wriggle into the medical literature.

Differential Diagnosis:
Spiradenoma can sometimes be misinterpreted as basal cell carcinoma, although the distinction is typically easily made by an experienced observer. Basal cell carcinoma is enveloped by fibromyxoid stroma and commonly shows necrosis of single cells or areas of necrosis en masse, all of which are lacking in spiradenomata. Cylindroma and spiradenoma are closely related and sometimes occur in synchrony, yet the two lesions remain distinguishable. Spiradenoma is

typically composed of large nodules of undifferentiated "basaloid" cells, while small nests of cylindroma cells are juxtaposed in puzzle-like fashion to form larger nodular collections. In addition, the small nests of cylindroma are often enveloped by a band of periodic acid Schiff after diastase (PAS-D) positive basement membrane material, an attribute that is often absent in spiradenomata.

References:

1. Michal M, Lamovec J, Mukensnabl P, Pizinger K. Spiradenocylindromas of the skin: tumors with morphological features of spiradenoma and cylindroma in the same lesion: report of 12 cases. Pathol Int 1999; 49:419–425.
2. Michal M. Spiradenoma associated with apocrine adenoma component. Pathol Res Pract 1996; 192:1135–1139.

CYLINDROMA

Clinical Presentation:

- Single (sporadic) (sometimes).
- Multiple and confluent (often); multiple lesion may occur in mosaic fashion, a clinical pattern that has been dubbed "turban tumor."
- Favored sites include the head and neck area, especially the scalp and periauricular area, as well as the trunk or genitalia.

Histopathology:

- Nodular or papular at scanning magnification, sometimes with dumbbell-shaped nodules in the dermis and/or subcutis.
- Larger nodules are composed of nests of undifferentiated basaloid cells in close apposition, arrayed in puzzle-like fashion (Fig. 14).
- A rim of densely eosinophilic, PAS-D-positive basement membrane material commonly envelops individual nests (Fig. 14).
- Small dot-like "droplets" of basement membrane material often punctuate the centers of small basaloid (Fig. 14).
- Foci of ductular or apocrine glandular differentiation (sometimes).

Clinicopathologic Correlation:

Clinical Feature	Correlating Microscopic Feature
Nodular morphology	Large collections of undifferentiated adnexal glandular cells
Turban tumor	Confluent array of dermal and subcutaneous nodules

Pathophysiology:

Cylindroma is a benign adnexal neoplasm with low proliferative capacity. Because the nodules of cylindroma are composed of many individual nests, simple enucleation can be difficult and local persistence after biopsy is not uncommon. As a distinct rarity, secondary transformation into cylindrocarcinoma can be observed. With respect to lineage, cylindroma has been generally accepted as an apocrine neoplasm and is viewed as being closely related to cylindroma. Brooke–Spiegler syndrome is an autosomal dominant disease in which multiple cylindromas can occur, as well as multiple spiradenomas and trichoblastomas. The gene has been mapped to 16q, and mutations in the *CYLD* gene have been identified in Brooke–Spiegler families. The *CYLD* gene is believed to be causative of multiple cylindromas, spiradenomas, and trichoblastomas and may represent the underlying cause of solitary sporadic cylindroma as well.

Differential Diagnosis:

Cylindroma and spiradenoma are closely related and sometimes occur conjointly, especially in the context of Brooke–Spiegler syndrome. Despite overlapping features and joint occurrence, the two lesions remain distinguishable. Spiradenoma typically presents as large uniform nodules, whereas cylindroma manifests as a puzzle-like array of small nests that coalesce to form larger nodules. In addition, the small nests of cylindroma are often typically enveloped by a band of PAS-D-positive basement membrane material, an attribute that is only occasionally present in spiradenomata.

References:

1. Lian F, Cockerell CJ. Cutaneous appendage tumors: familial cylindromatosis and associated tumors update. Adv Dermatol 2005; 21:217–234.
2. Oiso N, Mizuno N, Fukai K, Nakagawa K, Ishii M. Mild phenotype of familial cylindromatosis associated with an R758X nonsense mutation in the CYLD tumour suppressor gene. Br J Dermatol 2004; 151:1084–1086.

ADNEXAL CARCINOMA

Adnexal carcinomas (adenocarcinomas) are relatively uncommon, and their rarity has contributed to confusion with respect to diagnosis, classification, and therapy. Because of their infrequency, description of adnexal carcinomas has often come in the form of case reports, and large series that could serve as the foundation for lucid conclusions regarding behavior and therapy has been difficult for investigators to assemble. The literature is probably also skewed by inclusion of extraordinary lesions diagnosed late in their development, which has contributed to a general sense by dermatologists, perhaps unwarranted, that adnexal carcinomas are clinically aggressive. Clearly, additional study, preferably of thoughtfully stratified clinicopathologic entities, is warranted to determine the biological behavior and malignant potential of this group of skin cancers, especially in the early stages of development.

Adnexal carcinomas can develop de novo or can arise in association with an existent benign adnexal neoplasm. For some types of adnexal carcinoma, such as spiradenocarcinoma or cylindrocarcinoma, the adenocarcinomas that develop from the benign neoplasm typically lack a decisive pattern of differentiation and are only specifically diagnosable through recognition of the residual benign lesion. Other forms of adnexal adenocarcinoma, such as porocarcinoma and MAC, display distinctive differentiation that is recognizable whether occurring de novo or developing within a pre-existent benign lesion.

In general, the presentation of adnexal adenocarcinomas is not distinctive. For simplicity, this brief section includes information referencing porocarcinoma and MAC.

Clinical Presentation:

- Plaque-like or nodular, sometimes with ulceration (Fig. 15).
- Often first noted in young or middle-aged adults, commonly women.
- Slow enlargement over years (often).
- Limited mobility (fixed to contiguous structures), (sometimes).
- Often misdiagnosed prior to definitive recognition.
- Left-sided predominance noted in the largest US series (of MAC).

Histopathology:

- Architectural attributes of malignancy include asymmetry, lack of circumscription, and an infiltrative pattern (Fig. 16).
- Associated stromal sclerosis (often) (Fig. 16). Varied cytological atypicality, sometimes pronounced (in porocarcinoma) but often only subtle (in both porocarcinoma and MAC) (Fig. 17).
- Neurotropism (sometimes).
- Muscular invasion (sometimes).
- Superficial follicular differentiation, often with pale collections of outer sheath (trichilemmal) cells or small cornifying cysts (only in MAC).
- Superficial and deep foci of ductular (syringoma-like and poroma-like) differentiation (Fig. 17).

Clinicopathologic Correlation:

Clinical Feature	Correlating Microscopic Feature
Nodular or plaque-like morphology	Collections of neoplastic cells arrayed broadly and deeply in the dermis and/or subcutis
Limited mobility	Deep infiltration (sometimes of fat or muscle or nerve) and associated stromal sclerosis

Pathophysiology:

Adnexal carcinomas are rare lesions that can develop de novo (such as MAC) or in association with a pre-existent benign adnexal neoplasm (such as spiradenocarcinoma or hidradenocarcinoma). The precise genetic or molecular mechanisms that underlie the evolution of various forms of adnexal carcinoma are not yet understood. One large series illustrated that microcystic adnexal shows a left-sided predilection, suggesting that ultraviolet irradiation could play a role in the evolution of some cancers.

Differential Diagnosis:

Desmoplastic trichoepithelioma and MAC show extensive overlap in microscopical findings, as both show a background of reticular dermal sclerosis and both are punctuated by many small superficial cornifying (infundibular) microcysts. Desmoplastic trichoepithelioma differs from MAC in that it is composed mostly of basaloid (follicular germinative) cells, whereas MAC is composed of nests of pale cells with ductal, superficial follicular, or follicular outer sheath differentiation. Porocarcinoma may be misconstrued as poroma, its benign analogue, but is usually differentiable on the basis of parameters such as larger size, infiltrative pattern, and greater nuclear atypicality.

References:

1. Robson A, Greene J, Ansari N, et al. Eccrine porocarcinoma (malignant eccrine poroma): a clinicopathologic study of 69 cases. Am J Surg Pathol 2001; 25:710–720.
2. Chiller K, Passaro D, Scheuller M, Singer M, McCalmont T, Grekin RC. Microcystic adnexal carcinoma: forty-eight cases, their treatment, and their outcome. Arch Dermatol 2000; 136:1355–1359.
3. LeBoit PE, Sexton M. Microcystic adnexal carcinoma of the skin. A reappraisal of the differentiation and differential diagnosis of an underrecognized neoplasm. J Am Acad Dermatol 1993; 29:609–618.

ECCRINE NEOPLASMS

As noted previously, there is extensive overlap between eccrine and apocrine neoplasms. For discussion of common eccrine neoplasms such as syringoma and poroma, please refer to the appropriate segment in the preceding discussion of apocrine neoplasms.

TUBULOPAPILLARY (PAPILLARY) ADENOMA (AND ADENOCARCINOMA)

Clinical Presentation:

- Solitary (almost always).
- Papular or nodular morphology.
- Striking acral predilection; favored sites include fingers, toes, palms, and soles.
- Recent rapid enlargement (not uncommonly).
- Recurrence/persistence after incomplete removal (commonly).

Histopathology:

- Nodular and often asymmetrical from scanning magnification.
- Solid with papillary areas (commonly).
- Cystic, tubular, or cribriform foci (sometimes).
- High cellularity (commonly).
- Nuclear hyperchromatism (often).
- Numerous mitotic figures (commonly).
- Necrosis of single cells or necrosis en masse (sometimes).

Clinical Feature	Correlating Microscopic Feature
Persistence/ recurrence	High cellularity with many mitotic figures
Cystic appearance	Cystic dilatation of neoplastic epithelium

Pathophysiology:

The distinction between papillary adenoma and papillary adenocarcinoma can be challenging. Papillary adenoma of the digit was initially reported as "aggressive digital papillary adenoma" and was deemed "aggressive" because the neoplasms were prone to local recurrence if not completely excised, and some lesions were found to erode bone or infiltrate adjacent soft tissue. Some lesions originally classified as "aggressive papillary adenoma" eventuated with metastasis. Subsequently, such lesions have generally been interpreted

as papillary adenocarcinomas. At present, it is unclear whether there is a spectrum that includes both digital adenomas and adenocarcinomas, or whether virtually all acral papillary lesions represent carcinomas. It seems likely to this author that this spectrum includes both adenomas and adenocarcinomas, but that adenocarcinomas are more common. At best, it is difficult to predict the clinical course of lesions within this spectrum on the basis of the microscopical pattern, and thus a conservative approach to management is warranted.

Differential Diagnosis:

Because of their papillary morphology, papillary adenomas and adenocarcinomas can simulate apocrine adenomas. Apocrine adenomas are typically sharply circumscribed, include a well-formed myoepithelial layer around glands, and show low proliferation, with infrequent mitoses. In contrast, papillary adenomas and adenocarcinomas are cellular lesions in which mitotic figures are commonly found and in which a myoepithelial layer is often lacking. The distinction of digital papillary adenoma/adenocarcinoma from apocrine adenoma is also typically easily made because of differing topography. Because of high cellularity and frequent mitoses, the differential diagnosis of papillary adenoma/adenocarcinoma also includes metastatic adenocarcinoma. In this setting, the exclusion of carcinoma requires careful clinicopathologic correlation.

References:

1. Gorva AD. Digital papillary adenoma and aggressive digital papillary Adenocarcinoma. Am J Dermatopathol 2005; 27: 546–547.
2. Duke WH, Sherrod TT, Lupton GP. Aggressive digital papillary adenocarcinoma (aggressive digital papillary adenoma and adenocarcinoma revisited). Am J Surg Pathol 2000; 24:775–784.
3. Kao GF, Helwig EB, Graham JH. Aggressive digital papillary adenoma and adenocarcinoma. A clinicopathological study of 57 patients, with histochemical, immunopathological, and ultrastructural observations. J Cutan Pathol 1987; 14:129–146.

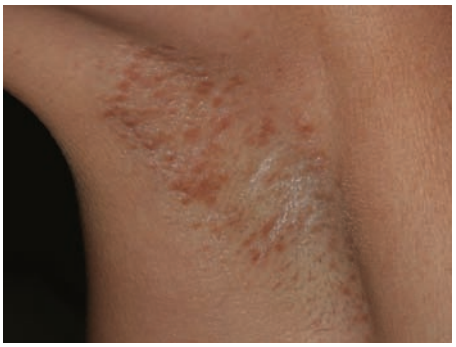

Figure 1 Syringoma. There are multiple, small, firm, skin-colored papules in the axillary vault.

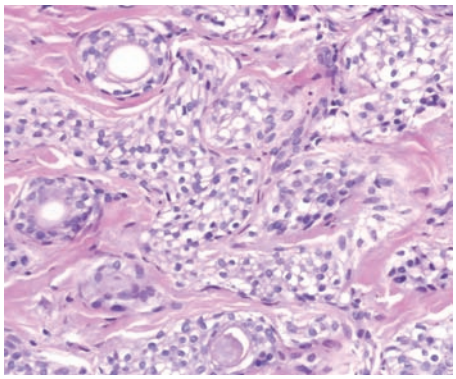

Figure 2 Syringoma. This magnified view shows small nests of cells with clear cytoplasm and small nuclei. Some of the nests are shaped like commas or tadpoles, and some display central ducts lined by a compact eosinophilic cuticle, as is stereotypical of syringoma. There is also associated dermal sclerosis, accounting for the firm clinical quality of a syringoma.

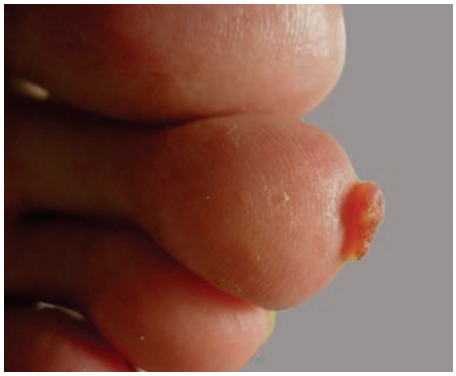

Figure 3 Poroma. This exophytic, scaly papule of the toe assumes a highly vascular and wart-like appearance.

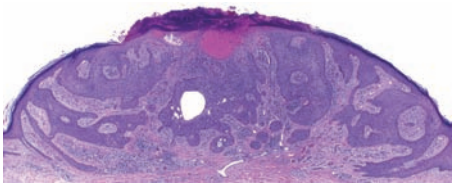

Figure 4 Poroma. At low magnification, this poroma displays an exophytic profile and shows superjacent parakeratosis and crust. The associated stroma is highly vascularized and inflamed.

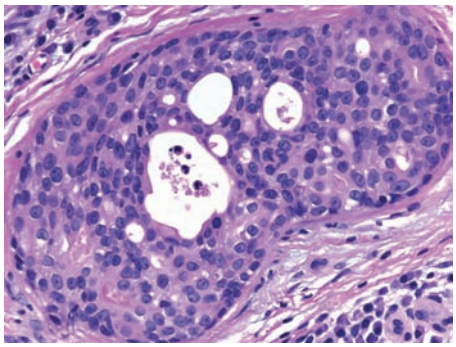

Figure 5 Poroma. This high magnification view demonstrates a nest of poroid cells with monomophous, small, round or ovoid nuclei, and scant eosinophilic cytoplasm. Conspicuous central ductal differentiation is evident.

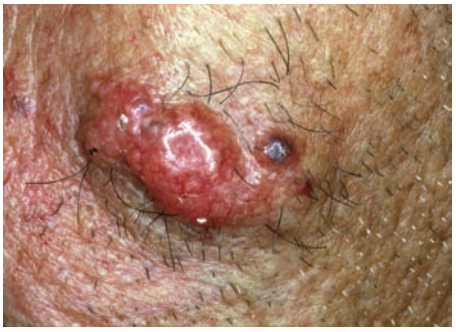

Figure 6 Hidradenoma. This multinodular lesion is partially pigmented and partially cystic and compressible.

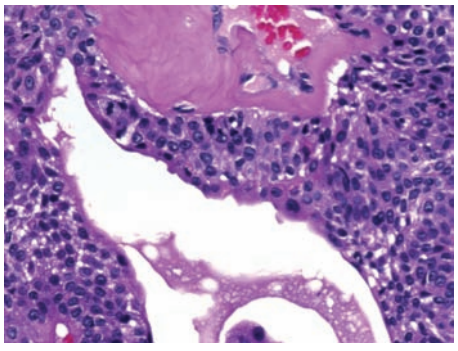

Figure 7 Hidradenoma. At scanning magnification, both solid and cystic areas are clearly evident within a larger circumscribed nodule. Even at low magnification, glandular areas and foci of clear cell change can be seen.

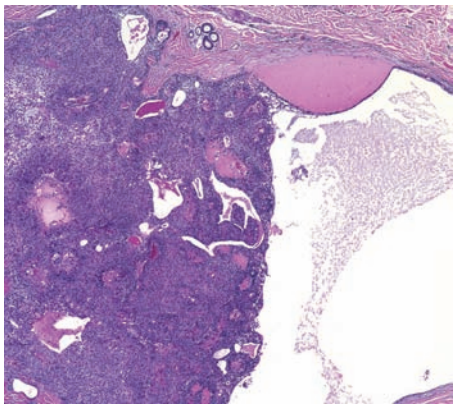

Figure 8 Hidradenoma. This high magnification view highlights keratinocytes with pale or eosinophilic cytoplasm flanking an area of glandular differentiation, with hints of decapitation secretion at the luminal border. The contiguous stroma is sclerotic.

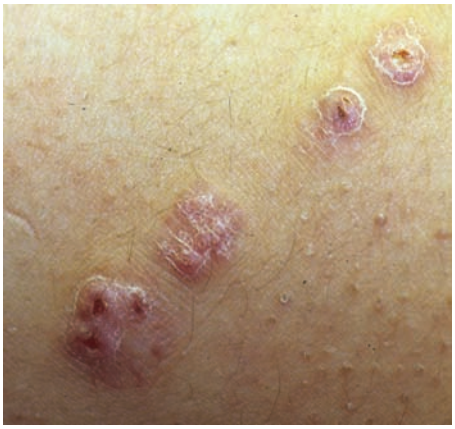

Figure 9 Syringocystadenoma papilliferum. There is a linear array of crusted, slightly verrucous papules on the upper thigh. This linear syringocystadenoma did not occur in concert with nevus sebaceus, but the combination of the two is commonplace.

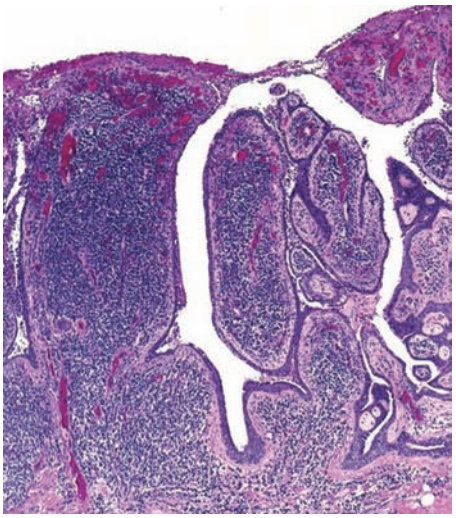

Figure 10 Syringocystadenoma papilliferum. The surface of the biopsy is eroded, with a subjacent papillary array of broad fronds lined by the combination of columnar apocrine epithelium and attenuated squamous epithelium.

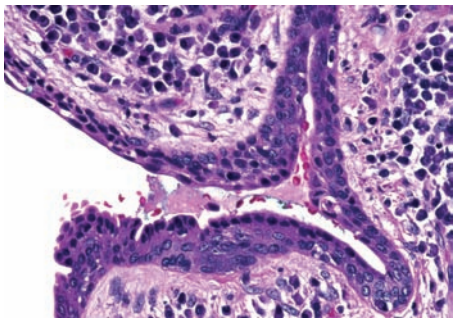

Figure 11 Syringocystadenoma papilliferum. A high magnification view demonstrates obvious apocrine epithelium at the luminal border of a papilla and also highlights many plasma cells within its inflamed "core."

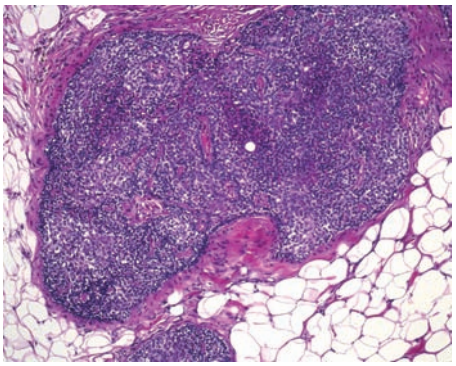

Figure 12 Spiradenoma. Within the subcutis, there is a circumscribed multinodular array of sizable collections of undifferentiated benign (basaloid) glandular cells. Spiradenoma is typified by an oligonodular array of sizable collections of basaloid cells, whereas cylindroma is characterized by numerous small nests of similar cells.

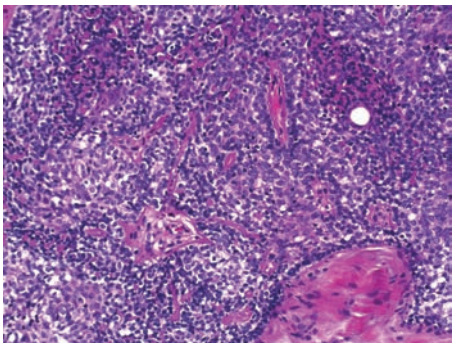

Figure 13 Spiradenoma. At higher magnification, nodules of spiradenoma demonstrate a trabecular internal configuration, with two types of cells present. There are small cells with scant cytoplasm (comprising the so-called "dark" cells) at the borders of trabecula and cells with pale cytoplasm (so-called "light" cells) centrally within trabecula. In actual fact, there are three cell types present, as a sprinkling of superimposed lymphocytes is also a stereotypical finding. Although most spiradenomata show no clear differentiation, foci of apocrine glandular or ductal differentiation can be found at times (a duct is evident in this image).

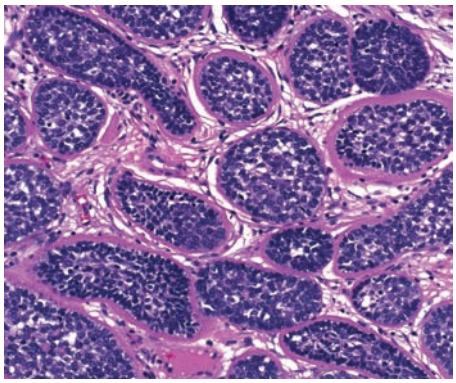

Figure 14 Cylindroma. This magnified view demonstrates many small, closely juxtaposed nests of cylindroma. Most of the nests are encircled by a thickened and [periodic acid Schiff (PAS)-D-positive] basement membrane. A few scattered small dots of PAS-positive material can also be found within the compact nests.

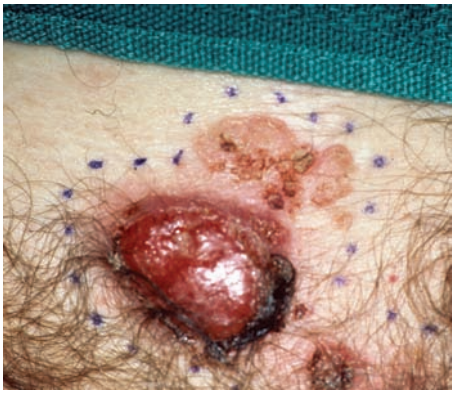

Figure 15 Porocarcinoma. This large asymmetrical ulcerated malignancy was clinically firm and showed limited mobility, reflecting its infiltrative nature.

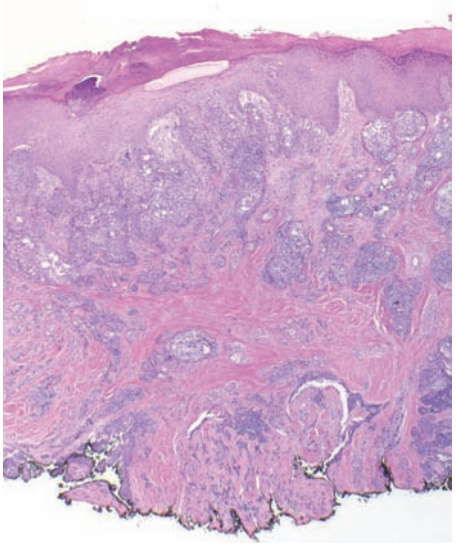

Figure 16 Porocarcinoma. This scanning magnification view demonstrates the deeply infiltrative pattern of this carcinoma and also highlights associated dermal sclerosis. There is overlying crust as a consequence of erosion/ulceration.

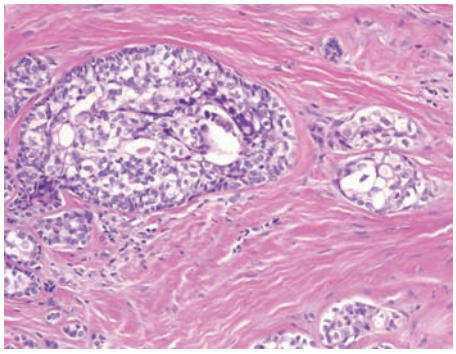

Figure 17 Porocarcinoma. At high magnification, the nests of carcinoma cells vary in size and shape, and areas of distal ductal differentiation (with a cuticulated luminal border) are easily found. Much like microcystic adnexal carcinoma, many examples of porocarcinoma show only modest or slight nuclear atypicality, and thus the distinction from benign lesions must be based upon careful assessment of architectural parameters, including lesional circumscription.

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Benign Melanocytic Neoplasms

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CONTENTS

Benign melanocytic neoplasms constitute an increasingly important and diverse group of cutaneous lesions. Their importance is derived from their relationship to malignant melanoma as simulants, risk markers and precursors to melanoma. As such they pose a significant diagnostic challenge to both clinicians and pathologists because of their profound heterogeneity and capacity to mimic melanoma. There is also evidence that along with cutaneous melanoma melanocytic nevi are increasing in frequency worldwide.

Melanocytic neoplasms originate from melanocytes: neural crest-derived cells defined by their unique property of synthesis of melanin pigments. The melanins are synthesized in unique organelles: the melanosomes, which are also transferred to keratinocytes. Melanocytes seem to originate from pluripotential cells that migrate from the neural crest to the skin via the paraspinal ganglia and their peripheral nerves and become terminally differentiated after migration to the local microenvironment of the dermis and basal layer of the epidermis.

Beyond establishing the embryonic origin of melanocytic nevi from neural crest-derived cells, the histogenesis of these melanocytic proliferations has not been adequately elucidated. The conventional viewpoint is that nevi arise from proliferation of intraepidermal melanocytes within junctional nests or theques. According to this model, nevus cells are considered a morphological variant of melanocytes that have assumed a morphology that is more epithelioid, and less dendritic. With evolution of the lesions, it is held that cells "drop off" (Abtropfung of Unna) into the dermis. The Abtropfung hypothesis derives from cross-sectional observations correlating histological findings in nevi with chronological aging.

Alternative hypotheses regarding the genesis of nevi include the proposal that nevus cells arise from cutaneous nerves, from a pluripotential cell of nerve sheath origin, or by contributions from both neural and non-neural dermal sources. However neural crest cells may phenotypically display both melanocytic and neural differentiation. Whether melanocytic nevi are hamartomas or neoplasms has been subject to long-standing debate. The common finding of other tissue elements in excess within nevi, such as epidermal hyperplasia, hypertrophy of adnexal structures, and connective tissue alterations, indeed suggest that nevi are developmental malformations; thus, the term nevus is often used synonymously with malformation or hamartoma.

On the other hand accumulating data suggest that the melanocytic nevus is clonal, hence a neoplasm and, putatively, the first stage in tumor progression of the melanocytic system. Stages in the putative progression model may not be obligate precursors to the subsequent stages, but rather could represent end stages at any point in the process. In support of this model are the gross morphological and cytological differences between melanocytes and nevus cells; the expression on nevus cells of markers of tumor progression that are not present on intraepidermal basilar melanocytes by immunophenotyping; and the growth advantages of nevus cells over epidermal melanocytes in cell culture.

Both genetic and environmental factors clearly influence the development of melanocytic nevi. Increased numbers of nevi aggregate in some families, and the phenotype of multiple nevi and/or enlarged nevi is linked to melanoma-prone kindreds and, in fact, is the strongest epidemiological risk factor for melanoma. These familial associations indicate a genetic basis for the growth and development of nevi. Quantification of total nevus number and total nevus density in melanoma kindreds has also shown familial (hereditary) correlations, but the nevus phenotype does not readily model genetically as a simple mendelian trait resulting from the transmission of a dominant locus. With respect to environmental factors, sun exposure, especially during early childhood, promotes the initiation and development of nevi in susceptible individuals. This effect is reflected in the observation that nevi have a predilection for sun-exposed sites, especially those sites receiving intermittent, but occasionally intense, ultraviolet exposure. Moreover, nevus counts are higher in tropical than at temperate latitudes. From these empirical

observations, nevi may be viewed as clonal proliferations of initiated cells with a growth advantage over their progenitors, the intraepidermal melanocytes.

A reasonable hypothesis regarding the natural history of melanocytic nevi is that they arise as a lentiginous (i.e., lentigo-like) proliferation of single cell units along the basal zone of elongated and hyperpigmented rete ridges. At some point thereafter, the melanocytes undergo a morphological transition into the epithelioid nevus cells with their propensity to aggregate as junctional nests (junctional nevus). Following this stage of development as a junctional nevus, further cellular development and proliferation results in the migration or "dropping off" of nevus cells and their organization into nests within the papillary dermis (compound nevus). According to this generally accepted model, eventually all intraepidermal proliferation of melanocytes ceases, and the nevus becomes entirely intradermal (dermal nevus). Nevus cells residing within the dermis have reduced proliferative and metabolic activity, except for the formation of melanosomes. With the decline of replication, the nevus cell population is gradually replaced by mesenchymal elements, including fibrous matrix, glycosaminoglycans, and adipose tissue. Most dermal nevi are believed to undergo progressive involution, some eventuating as acrochordons and others shedding. This developmental (or maturational or differentiation) sequence may, presumably, be arrested at any stage, such that a lentigo, junctional nevus, or compound nevus may persist indefinitely. Because the model has been developed from largely cross sectional data, alternative theories of development have been proposed, including a model invoking a reverse order of development.

Table 1 Clinical Criteria Used for the Classification of Benign Melanocytic Neoplasms

Age of onset: congenital or acquired
Size
Small congenital nevus: <1.5 cm
Medium sized congenital nevus: >1.5–20 cm
Large congenital nevus: >20 cm
Garment or bathing trunk nevus
Segmental nevus
Anatomic location
Nonglabrous skin
Glabrous/acral
Mucosal
Genital/flexural
Other sites such as breast, scalp, ear, etc.
Appearance
Border characteristics (symmetry, circumscription)
Surface topography (macular, papular, papillomatous, verrucoid)
Pattern of coloration: variegated or homogeneous
Colors present: flesh, tan, brown, black, blue, gray, white, pink, red
Speckled, targetoid, agminated, zosteriform

Classification and Criteria for Benign Melanocytic Neoplasms:

Benign melanocytic neoplasms constitute a heterogenous spectrum of lesions that are classified according to a number of clinical, histological, and other attributes (Tables 1 and 2). As with any classification there is controversy as to the basis for defining and including the various entities in such a classification. The scheme outlined in Table 3 will be utilized in this chapter. Major considerations for classification include age of onset of the lesion, size, anatomic site, other gross morphologic features, location of melanocytes in the skin, the spatial relationships of melanocytes, cytological features of melanocytes, stromal attributes, and finally abnormal features such as atypical architecture, cytological atypia, and proliferation rate.

In the routine evaluation of melanocytic lesions one is continually faced with the decision as to whether a lesion is benign or malignant. In approaching this problem one has to apply a number of criteria for this interpretation (Table 4) since no single criterion is sufficient. At present there is no universal consensus as to which criteria should be included in this exercise, or the relative importance or relative weight of each criterion. It is certain that this latter exercise should take into consideration clinical information, organizational, cytological, and cell proliferation-related properties of the individual lesion. It must be emphasized that there are exceptions to each criterion, and the failure to consider this may result in both over- and underdiagnosis of melanoma.

An important aspect of the interpretation of melanocytic lesions is recognizing the subjectivity of such evaluation and the imperfect state of knowledge at present. It cannot be overemphasized that despite having criteria for diagnosis a certain percentage of melanocytic lesions cannot be easily interpreted as benign or malignant. Consequently the author utilizes a third or intermediate category reserved for melanocytic lesions occupying the continuum between benign and malignant. An intermediate category avoids overdiagnosis of melanoma and also the under-recognition of abnormal or indeterminate lesions that require additional therapy and close monitoring, rather than being pronounced "benign" without further qualification. The criteria and nomenclature for (and some would argue even the very legitimacy of) such intermediate lesions are presently a source of considerable controversy and debate. The various terms suggested for such intermediate lesions have not as yet been standardized, as evidenced by nomenclature such as "atypical" nevi, "dysplastic" nevi, nevi with architectural disorder and cytological atypia, Spitz tumors with atypical features (atypical Spitz tumors), atypical cellular blue nevi, and so on. The authors believe that additional research and substantial effort are needed to standardize the terminology of benign (and malignant) melanocytic neoplasms. For the time being the authors suggest a provisional terminology (Table 3).

Definition of Terms:

Melanocyte: Melanocytes are the "clear cells" in the basal layer of the epidermis owing to retraction of their cytoplasms. They have dendritic cellular processes and uniform intensely basophilic nuclei slightly smaller than those of nearby keratinocytes. The melanocyte has the unique property of synthesizing the complex molecules, the melanins, in specific organelles, the melanosomes, and transferring them to keratinocytes. Melanocytes seem to originate from pluripotential cells that travel from the neural crest to the skin via the paraspinal ganglia and their peripheral nerves and become terminally differentiated after migration to the local microenvironment of the dermis and basal layer of the epidermis.

Table 2 Histological Criteria for the Classification of Benign Melanocytic Neoplasms

- Location of melanocytes in the skin (depth)
  - Superficial
    - Intraepidermal
    - Papillary dermis
    - Upper half of reticular dermis
  - Deep
    - Lower half of reticular dermis
    - Subcutaneous
    - Fascial
- Disposition of melanocytes
  - Intraepidermal
    - Basilar melanocytes (single cell pattern)
      - Normal numbers
      - Increased frequency
        - – With elongated rete (lentiginous)
        - – Without elongated rete
    - Pagetoid pattern
    - Nested pattern
      - – With lentiginous pattern
      - – Without lentiginous pattern
  - Dermal
    - Diffuse, interstitial
    - Patchy perivascular, periadnexal, perineurial
    - Wedge pattern (deep apex of nests, fascicles of melanocytes extend into reticular dermis or subcutaneous fat)
    - Plexiform pattern (discreet nests, fascicles associated with neurovascular or adnexal structures of reticular dermis with intervening normal dermis)
    - Bulbous aggregates, nodules (cellular nests or fascicles with rounded contours, usually extending into reticular dermis, subcutis)
    - Alveolar pattern
    - Maturation/differentiation
- Stroma
    - Desmoplasia (sclerosis)
- Cell type
    - Small round or oval cell
    - Spindle cell
    - Epithelioid cell (abundant cytoplasm, overall enlarged)
    - Dendritic cell (lengthy, delicate cellular processes)
    - Large spindle cell
    - Large epithelioid cell
    - All with varying degrees of melanization

Table 3 Practical Classification of Benign Melanocytic Neoplasms

- ***Benign melanocytic lesions without clinical or histological atypia*:**
- Circumscribed lentiginous melanocytic proliferations
  - Lentigo simplex
- Common acquired melanocytic nevi and variants
  - Balloon cell nevus
  - Halo nevus
  - Lentiginous junctional and compound nevi
  - Neural nevus (neurotized nevus)
  - Nevus spilus
  - Recurrent/persistent melanocytic nevus
  - Particular anatomic sites:
    - Acral
    - Genital/flexural
    - Breast
    - Scalp
- Congenital melanocytic nevi
  - Small congenital nevus
  - Intermediate congenital nevus
  - Large or giant congenital nevus
- Spitz tumors and variants
  - Desmoplastic Spitz tumor
  - Pigmented spindle cell tumor
- Dermal melanocytoses, blue nevi, and variants
  - Mongolian spot
  - Nevus of Ito and Ota
  - Common blue nevus
  - Epithelioid blue nevus
  - Cellular blue nevus
  - Plexiform pigmented spindle cell nevus/tumor (deep-penetrating nevus)
- Melanocytic nevi with phenotypic heterogeneity (combined nevi)

- ***The clinically and histologically atypical melanocytic nevi/tumors/neoplasms including those with indeterminate biological potential*:**
- Clinically atypical nevi/neoplasms
- Histologically atypical nevi/neoplasms (melanocytic nevus with architectural disorder and cytological atypia; nevus with atypical features) including other melanocytic nevi with atypical features (acral, genital, etc.)
- Congenital nevi with atypical features
  Spitz tumor with atypical features
- Cellular blue nevus with atypical features
- Plexiform pigmented spindle cell nevus/tumor (deep-penetrating nevus) with atypical features
- Melanocytic nevus with phenotypic heterogeneity (combined nevus) with atypical features

***Nevus Cell*:** This somewhat confusing and archaic term refers to the melanocytes present in melanocytic nevi. Although "nevus cells" share properties with melanocytes, they are currently thought to be melanocytes in the initial stage of tumor progression to melanoma. These modified melanocytes are characterized by syncytial aggregation in nests within the epidermis and/or dermis, loss of dendritic processes, and a progressive sequence of differentiation with descent into the dermis termed "maturation."

Type A or epithelioid nevus cells are melanocytes residing in junctional (intraepidermal) or superficial dermal nests. These polygonal cells have the appearance of epithelial cells because of relatively abundant eosinophilic cytoplasms and often the syncytial appearance in aggregate referred to earlier. The nuclei are slight larger than those of basilar melanocytes.

Type B or lymphocytoid nevus cells constitute the next slightly deeper population of dermal melanocytes in this maturational sequence. Thus these cells are commonly small

Table 4 Histopathologic and Clinical Criteria for Melanoma Vs. Benign Melanocytic Lesion

	Melanoma	Benign Lesion
Size	≥6 mm, often ≥10 mm <6 mm small-diameter melanoma, metastatic melanoma	<5 or 6 mm often
Symmetry	Usually asymmetrical with respect to epidermal thickness, melanocytic elements, melanin distribution, host response	Usually symmetrical
Circumscription	Often poorly-circumscribed at peripheries with single-cell intraepithelial patterns	Often well circumscribed with well-defined nests at periphery
Heterogeneity	Often heterogenous with two or more cellular phenotypes, or variable cellular populations	Often homogeneous cellular populations
Intraepidermal patterns	Loss of rete-oriented pattern	Single cells on elongated rete ridges
	Cells scattered in pagetoid patterns above the level of dermal papillae	Little or no pagetoid spread
	Single cells reaching confluence along dermal epidermal junction	Regular, uniform nesting, cohesive, relatively small nests
	Irregular and haphazard nesting	
	Discohesive and large nests	
Dermal patterns	Confluence of cells with little or no maturation (sheet-like patterns of cells)	Regular spacing and maturation with depth
Cellularity, cellular density	High cellular density, crowding of cells	Lower cellular density
Melanin synthesis	Variable or no loss of synthesis with depth	Loss of synthesis with depth
Epidermal reaction	Hyperplasia, thinning ulceration; variable epidermal thickness	Often uniform thickness of epidermis
	Stratum corneum shows alteration: hyperkeratosis, parakeratosis, scale-crust	Stratum corneum basket weave or unaffected
Maturation (differentiation)	Melanoma cells fail to exhibit diminished cellular and nuclear sizes and overall cellular density with depth in dermis	Melanocytes exhibit diminished cellular and nuclear sizes and overall cellular density with depth in dermis;
		Progression from polygonal cells to lymphocyte-like cells to schwannian cells (neurotization) with depth
Mitosis	Likelihood of melanoma increases with absolute number in dermis and depth of mitoses	Usually not present in dermal component
	Atypical mitoses	
Necrosis	Single cells or confluent necrosis	Usually not present
Host response	Often band-like and asymmetrical infiltrates with superficially invasive melanoma	Little or no inflammation, perivascular infiltrates, band-like infiltrates in halo nevi
	Diminished inflammation with increasing tumor thickness	
Regression	Often all stages: early, intermediate, late; multifocal common in thin melanoma; often asymmetrical	Uncommon, often symmetrical

and round, have lesser amounts of cytoplasm, and slightly smaller nuclei hence their resemblance to lymphocytes.

Type C or spindled nevus cells are the final or terminal stage of differentiation or maturation. This population of melanocytes is usually the most deeply situated ones in a nevus and is characterized by schwannian (or neural) differentiation. These are often tapered spindle cells with striking resemblance to Schwann cells. They commonly form nerve-like structures that have been termed neural tubules.

Melanophage: Macrophages, containing coarse melanin pigment, that are present in pigmented melanocytic neoplasms. These macrophages have polygonal morphologies and eccentrically-placed nuclei within the cell.

Lentiginous Melanocytic Proliferation: The proliferative pattern of melanocytes arrayed as single cells in the basal layer of squamous epithelium. The melanocytes are usually most concentrated at the tips of the epidermal rete and least frequent above the dermal papillae. This pattern is observed in lentigines, lentiginous junctional and compound nevi, atypical lentiginous melanocytic proliferations, and lentiginous melanomas.

Pagetoid Melanocytosis (Pagetoid Infiltration; Pagetoid Spread): Single melanocytes and nests of melanocytes scattered throughout the spinous and granular layer of the squamous epithelium in a pattern mimicking Paget's disease of the breast. Pagetoid melanocytosis strictly defined involves only the most superficial spinous layer, that is, the squamous epitheilium above the plane of the most superficial extensions of the dermal papillae. Although a major criterion for melanoma, pagetoid melanocytosis also may occur in the following benign melanocytic

neoplasms: traumatized, solar-irradiated and persistent/recurrent melanocytic nevi; congenital nevi; nevi from children; acral nevi; pigmented spindle cell melanocytic tumors; and Spitz tumors.

Maturation: The sequential cytological alterations (terminal differentiation, or perhaps even senescence) of "nevus cells" or melanocytes (in a melanocytic nevus or Spitz tumor), as outlined earlier under "nevus cells," with progressive descent into the dermis. The assessment of the dermal component of a melanocytic lesion for maturation is often an important exercise in deciding whether the lesion is likely to be benign or malignant. It is important to keep in mind that a given melanocytic nevus may be arrested in only one or two stages of maturation, rather than displaying all three stages. To complicate matters, some proportion of melanomas may show "pseudomaturation."

Melanocytic Nevus: The term nevus historically is a cognate for hamartoma or developmental anomaly, hence melanocytic hamartoma. In common usage the term has come to signify virtually all benign melanocytic lesions, irrespective of whether they are hamartomas (developmental anomalies) or neoplasms. In fact, this distinction has been obscured by increasing the evidence that melanocytic nevi, in general, are clonal and consequently neoplastic.

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LENTIGO SIMPLEX

Lentigo simplex is a circumscribed, uniformly pigmented tan, brown, or dark brown macule usually 1 to 5 mm in diameter occurring either as a solitary lesion or as multiple lesions, possibly in the context of an inherited syndrome, anywhere on the cutaneous or mucocutaneous surface (Fig. 1). These lesions demonstrate regular and well-defined borders. Histologically, they show increased numbers of solitary basilar melanocytes and increased epidermal basal layer and possibly suprabasal layer melanin (Table 5) (Fig. 1B).

Synonyms: Simple lentigo; genital lentiginosis.

Clinical Features:

- Lentigo simplex onsets childhood, adolescence, and in some cases later
- All skin phototypes affected
- Some probably related to sun exposure; persistant
- Usually 1 to 5 mm macules, which are light-, medium-, dark-brown, or black in color
- Homogenous pigment pattern
- Round and oval
- Symmetric
- Regular borders
- Well circumscribed
- Located on any cutaneous surface including sun-protected skin and mucocutaneous sites

Histopathology:

- Elongated, club-shaped epidermal rete ridges
- Basal layer hyperpigmentation, accentuated lower poles of rete
- Increased numbers of basilar melanocytes concentrated on tips of rete ridges
- Melanophages in papillary dermis

Table 5 Differential Diagnosis: Lentigo Simplex

	Lentigo Simplex	Freckle	Café-au-lait Macule	Becker's Nevus	Solar Lentigo	Lentiginous Junctional Nevus
Size	1–5 mm	1–3 mm	2–5 cm	3–12 cm or more	5–15 mm	<5,6 mm
Elongated, club-shaped epidermal rete ridges	Present	Normal configuration usually	Normal configuration usually	Present or absent, sometimes papillomatous epidermal hyperplasia	Often present but may be absent	Present
Basal layer hyperpigmentation, accentuated lower poles of rete	Present	Present	Present	Present	Present	Present
Increased numbers of basilar melanocytes concentrated on tips of rete ridges	Present	Usually absent or slightly increased	Usually absent or slightly increased	Usually absent or slightly increased	Present or absent	Present with junctional nests of melanocytes
Smooth muscle hamartoma	Absent	Absent	Absent	May be present	Absent	Absent
Solar elastosis	Usually absent or slightly increased	Often present	Usually absent or slightly increased	Usually absent or slightly increased	Present	May be present

Clinicopathologic Correlation:

Clinical Feature	Pathologic Feature
Tan to dark brown color	Melanin present in the basal and possibly the suprabasal squamous epithelium, and possibly in dermal melanophages

Differential Diagnosis:

- Freckle
- Café-au-lait macule
- Becker's nevus (melanosis)
- Solar lentigo
- Lentiginous junctional nevus with or without atypia (Table 5)

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COMMON ACQUIRED MELANOCYTIC NEVI

Common acquired melanocytic nevi are the most prevalent benign melanocytic lesions. They are clonal proliferations of melanocytes usually developing in childhood and adolescence but also at any age in adults and defined by their localization to the epidermis (junctional), both epidermis and dermis (compound), or dermis only (dermal or intradermal). In general, common acquired nevi measure about 3 to 6 mm in diameter, are symmetrical, have regular and well-defined borders, and have uniform pink, tan, brown, or dark-brown color (Table 6; Figs. 2 and 3).

A number of subtypes of common acquired nevi have been described and are generally related to a number of factors that may in some way influence or alter the basic morphology of acquired nevi. Some of these determinates include anatomic site, host response, external trauma, and other poorly understood developmental and genetic factors.

Synonym: Common mole.

Clinical Features:

Junctional Nevus	Compound Nevus	Dermal Nevus
Onset childhood, adolescence	Onset childhood, adolescence, third decade	Onset first, second, third decades or later
2 to 5 mm macule	3 to 6 mm papule	3 to 6 mm papule, dome-shaped or papillomatous
Round, oval	Round, oval	Round, oval
Symmetrical	Symmetrical	Symmetrical
Well defined, regular borders	Well defined, regular borders	Well defined, regular borders
Homogeneous brown, dark brown	Homogeneous tan to dark brown	Light brown to flesh tones

Histopathology:

Junctional Nevus	Compound Nevus	Dermal Nevus
Symmetry	Symmetry	Symmetry
Well circumscribed	Well circumscribed	Well circumscribed
Regular junctional nesting	Regular junctional nesting	Dome shaped or papillomatous
Uniform size, shape, and placement of nests	Uniform size, shape, and placement of nests	Orderly arrangement of nevus cells in dermis
Nests often at tips of retia	Nests often at tips of retia	Transition from epithelioid to lymphocytoid to spindled cells with dermal descent
Cohesive nests usually	Cohesive nests usually	
No or little pagetoid scatter	No or little pagetoid scatter	
Lentiginous proliferation common	Nevus cells often confined to papillary or superficial reticular dermis	Nevus cells often confined to papillary or superficial reticular dermis
	Transition from epithelioid to lymphocytoid to spindled cells with dermal descent	Transition from epithelioid to lymphocytoid to spindled cells with dermal descent
	Mitotic figures rare in dermis	Mitotic figures rare in dermis
	Minimal nuclear pleomorphism	Minimal pleomorphism

Clinicopathologic Correlation:

Clinical Feature	Pathologic Feature
Tan or brown color	Junctional nests of melanocytes
Papular appearance	Melanocytes in dermis

Differential Diagnosis:

See Table 6.

- Clinically atypical nevi
- Histologically atypical melanocytic nevi
- Malignant melanoma

Pathophysiology:

Melanocytic nevi are derived from pluripotential cells that migrate from the neural crest and take residence in the basal layer of the epidermis, the dermis, and possibly of sites such as regional lymph nodes. There has been a long-standing debate as to the developmental nature of melanocytic nevi, that is, are they hamartomas or neoplasms, and so on? As already mentioned there is increasing evidence that melanocytic nevi in general are clonal lesions thus supporting a neoplastic basis. However this may not be applicable to all melanocytic nevi.

References:

1. Lund HZ, Stobbe GD. The natural history of the pigmented nevus; factors of age and anatomic location. Am J Pathol 1949; 25:1117–1155.
2. Stegmaier OC, Montgomery H. Histopathologic studies of pigmented nevi in children. J Invest Dermatol 1953; 20:51–62.

Table 6 Differential Diagnosis: Common Acquired Melanocytic Nevi

	Common Acquired Melanocytic Nevi	Histologically Atypical Melanocytic Nevi	Malignant Melanoma
Size	Usually <5, 6 mm	4 to 12 mm or more (any size)	Usually >5, 6 mm, often >10 mm (any size)
Symmetry	Usually present	Often present, may be absent	Often absent
Circumscription	Well circumscribed	Usually poorly circumscribed	Usually poorly circumscribed
Junctional nesting	Regular	Disordered: variation in size, shape, placement of nests on epidermal rete	More disordered often with pagetoid melanocytosis
Lentiginous melanocytic proliferation	May be present	May be present with greater frequency of melanocytes	May be present with contiguous proliferation of melanocytes
Cytological atypia of intra-epidermal melanocytes	Usually absent	Present and variable, ranges from slight to severe	Present, uniform pattern of atypia at least moderate to severe
Maturation	Usually present	Often present, may be diminished	Often absent but "pseudomaturation" may be present
Dermal mitoses	Usually absent, rarely present in small numbers, e.g., 1 to 3/mm^2	Usually absent, rarely present in small numbers, e.g., 1 to 3/mm^2	Commonly present
	Usually superficial and not deep	Usually superficial and not deep	Deeply located mitoses often present

3. Stegmaier OC, Becker SW Jr. Incidence of melanocytic nevi in young adults. J Invest Dermatol 1960; 34:125–129.
4. Maize JC, Foster G. Age-related changes in melanocytic naevi. Clin Exp Dermatol 1979; 4:49–58.

HALO MELANOCYTIC NEVUS

Halo nevi are common nevi exhibiting a peripheral vitiligo-like annulus or "halo" of hypopigmentation or depigmentation surrounding a central nevus (Fig. 4A). Histologically halo nevi demonstrate a dense lymphocytic infiltrate associated with the central nevus and a peripheral zone of hypo- to depigmentation of the epidermis, corresponding to the clinical halo (Fig. 4B). Halo melanocytic nevi may exhibit both clinically and histologically atypical features and thus raise concern for melanoma (Tables 4 and 7).

Synonyms: Suttton's nevus; leukoderma acquisitum centrifugum.

Clinical Features:

- Children, adolescents, and young adults most often affected.
- Multiple or solitary.
- Trunk especially upper back.
- Central nevus 3 to 6 mm in size.
- Symmetry of central nevus and surrounding halo of depigmentation.
- Regular borders.
- Uniform color of central nevus—tan, brown, or pink, and halo—hypo- or depigmentation.

Histopathology:

- More than 5 to 6 mm.
- Symmetry.
- Usually well circumscribed.
- Mononuclear cell infiltrate orderly with well-defined inferior margin.
- Maturation/differentiation of nevus elements.
- Apoptosis of nevus cells common.
- Rete ridges maintained. Low-grade or no cytologic atypia commonly.
- Few mitoses in dermal component (usually <2 to 3/mm^2).
- Atypical mitoses usually absent.

Clinicopathologic Correlation:

Clinical Feature	Pathologic Feature
Halo of hypo- or depigmentation	Diminished or absent epidermal basilar melanocytes and melanin

Differential Diagnosis:

See Table 4, Table 7, and Histopathology under the section "Common Acquired Melanocytic Nevi."

Pathophysiology:

Although poorly understood, the halo phenomenon is thought to represent progressive destruction of nevi by the host immune response, possibly both cell- and antibody-mediated. The infiltrating lymphocytes in halo nevi are predominately T lymphocytes. The presence of both CD8-positive and antigen-presenting cells suggest a cytotoxic destruction of nevus cells. In addition, individuals with halo nevi harbor both activated lymphocytes and antibodies against neoplastic melanocytes in their peripheral blood.

References:

1. Kopf A, Morrill S. I. S. Broad spectrum of leukoderma acquisitum centrifugum. Arch Dermatol 1965; 92:14–35.
2. Wayte DM, Helwig EB. Halo nevi. Cancer 1968; 22:69–90.
3. Mitchell MS, Nordlund JJ, Lerner AB. Comparison of cell-mediated immunity to melanoma cells in patients with vitiligo, halo nevi or melanoma. J Invest Dermatol 1980; 75:144–147.
4. Zeff RA, Freitag A, Grin CM, Grant-Kels JM. The immune response in halo nevi. J Am Acad Dermatol 1997; 37:620–624.

MELANOCYTIC NEVUS OF ACRAL SKIN

Melanocytic nevi involving nonhair-bearing skin of the palms, soles, and digits share characteristics of other acquired nevi but nonetheless manifest properties unique to this portion of the skin (Fig. 4C). Historically, such nevi have often raised concern for melanoma. The increased frequency

Table 7 Differential Diagnosis: Halo Melanocytic Nevus

	Halo Nevi	Histologically Atypical Nevus	Melanoma
Size	Usually <5, 6 mm	4 to 12 mm or more (any size)	Usually >5, 6 mm, often >10 mm (any size)
Symmetry	Usually present	Often present, may be absent	Often absent
Circumscription	Well circumscribed	Usually poorly circumscribed	Usually poorly circumscribed
Junctional nesting	Regular	Disordered: variation in size, shape, placement of nests on epidermal rete	More disordered often with pagetoid melanocytosis
Mononuclear cell infiltrate orderly with well-defined inferior margin	Present	Often present	Greater asymmetry
Cytological atypia of intraepidermal melanocytes	Usually absent, reactive hypertrophy of melanocytes and nuclear variation may be present	Present and variable, ranges from slight to severe	Present, uniform pattern of atypia at least moderate to severe
Maturation	Usually present	Often present, may be diminished	Often absent but "pseudomaturation" may be present
Dermal mitoses	Usually absent, rarely present in small numbers, e.g., 1 to 3/mm^2	Usually absent, rarely present in small numbers, e.g., 1 to 3/mm^2	Commonly present
	Usually superficial and not deep	Usually superficial and not deep	Deeply located mitoses often present

of particular histological characteristics, lentiginous melanocytic proliferation, and pagetoid melanocytosis in acral nevi often suggest melanoma (Fig. 4D). However, other histological features of benign nevi, especially the lack of significant cytological atypia of melanocytes, usually allow distinction from melanoma (Table 8).

Clinical Features:

- All ages
- Size usually 3 to 6 mm
- Macular or only slightly raised
- Uniform brown or dark brown pigmentation
- Symmetry
- Regular and well-defined borders

Histopathology:

- Symmetrical, well demarcated silhouette.
- Regular, evenly spaced nesting at the junctional zone.
- Lentiginous melanocytic proliferation along the basal layer of elongated rete.
- Pagetoid scatter of cells common but orderly.
- Little or no inflammatory reaction within the stroma.
- When of compound type, the dermal nests are well formed and cells mature with dermal descent.

Clinicopathologic Correlation:

Clinical Feature	Pathologic Feature
Parallel rows of pigmentation within nevus	Discrete vertical columns of melanin pigment in stratum corneum

Table 8 Differential Diagnosis: Melanocytic Nevus of Acral Skin

	Acral Melanocytic Nevi	Histologically Atypical Acral Nevi	Acral Melanoma
Size	Usually <7 mm	4 to 12 mm or more (any size)	Usually >6, 7 mm, often >10 mm (any size)
Symmetry	Usually present	Often present, may be absent	Often absent
Circumscription	Well circumscribed	Usually poorly circumscribed	Usually poorly circumscribed
Junctional nesting	Regular	Disordered: variation in size, shape, placement of nests on epidermal rete	More disordered often with pagetoid melanocytosis
Lentiginous melanocytic proliferation	Often present, localized to epidermal rete	May be present with greater frequency of melanocytes	Usually present with contiguous proliferation of melanocytes
Pagetoid melanocytosis	May be present, sparsely cellular density often	May be present, sparsely cellular density often	Often present, greater cellular density compared to nevi and with significant cytological atypia
Cytological atypia of intraepidermal melanocytes	Usually absent	Present and variable, ranges from slight to severe	Present, uniform pattern of atypia at least moderate to severe
Maturation	Usually present	Often present, may be diminished	Often absent but "pseudomaturation" may be present
Dermal mitoses	Usually absent, rarely present in small numbers, e.g., 1 to 3/mm^2	Usually absent, rarely present in small numbers, e.g., 1 to 3/mm^2	Commonly present
	Usually superficial and not deep	Usually superficial and not deep	Deeply located mitoses often present

Differential Diagnosis:
See Table 8.
- Atypical nevi
- Acral lentiginous melanoma

References:

1. McCalmont TH, Brinsko R, LeBoit PE. Melanocytic acral nevi with intraepidermal ascent of cells (MANIACs): a reappraisal of melanocytic lesions from acral sites [abstr]. J Cutan Pathol 1991; 18:378.
2. Boyd AS, Rapini RP. Acral melanocytic neoplasms: a histologic analysis of 158 lesions. J Am Acad Dermatol 1994; 31:740–745.
3. Fallowfield ME, Collina G, Cook MG. Melanocytic lesions of the palm and sole. Histopathol 1994; 24:463–467.
4. Clemente C, Zurrida S, Bartoli C, Bono A, Collini P, Rilke F. Acral-lentiginous naevus of plantar skin. Histopathology 1995; 27:549–555.

RECURRENT/PERSISTENT MELANOCYTIC NEVUS

The recurrent (persistent) nevus is defined as the appearance of macular pigmentation within the confines of the clinical scar of a previously biopsied (usually by shave technique) melanocytic nevus, usually after the passage of about six weeks to six months (Fig. 5A). Histologically regenerative and often irregular single cell and nested intraepidermal melanocytic proliferation, sometimes mimicking melanoma, overlies the dermal scar (Table 9) (Fig. 5B). On occasion, the latter intraepidermal component may show cytological atypia of melanocytes (Fig. 5C) and may extend into the dermal cicatrix. Commonly, a residual dermal nevus (corresponding to the original nevus) involves or resides at the base of the scar. It is important to verify the nature of the lesion originally biopsied and exclude malignant melanoma.

Synonyms: Pseudomelanoma; nevus recurrens.

Clinical Features:
- Onsets approximately six weeks to six months after previous surgery
- Macular pigmentation
- Limited to scar
- 4 to 6 mm (usually <1.5 cm)
- Some irregularity of borders often

Histopathology:
- Effacement of epidermis.
- Dermal scar.
- Intraepidermal melanocytic proliferation limited to area above scar.
- Lentiginous or nested pattern of intraepidermal melanocytes.
- Variable cytologic atypia, usually low-grade.
- Dermal nevus remnant often beneath dermal scar.

Clinicopathologic Correlation:

Clinical Feature	Pathologic Feature
Macular pigmentation within the perimeter of a dermal scar	Intraepidermal (and sometimes dermal) proliferation of often pigmented melanocytes above dermal cicatrix

Differential Diagnosis:
See Table 9.
- Lentigo-like regenerative melanosis overlying dermal scars from biopsy of either melanocytic or nonmelanocytic lesions
- Atypical (dysplastic) nevus
- Melanoma

Pathophysiology:
The regenerative proliferation observed in recurrent melanocytic nevi is poorly understood but has parallels with other traumas incurred by nevi such as ultraviolet irradiation and physical injury not otherwise specified. There is speculation that the intraepidermal melanocytic proliferation originates from the melanocytes in skin appendages.

References:

1. Kornberg R, Ackerman AB. Pseudomelanoma. Arch Dermatol 1975; 111:1588–1590.
2. Park HK, Leonard DD, Arrington JH, Lund HZ. Recurrent melanocytic nevi: Clinical and histologic review of 175 cases. J Am Acad Dermatol 1987; 17:285–292.

Table 9 Differential Diagnosis: Recurrent/Persistent Melanocytic Nevus

	The Recurrent (Persistent) Nevus	Lentigo-Like Regenerative Melanosis Overlying Dermal Scars from Biopsy of Either Melanocytic or Nonmelanocytic Lesions	Histologically Atypical Nevus	Melanoma
Effacement of epidermis	Present	Present	Usually absent	Often present
Dermal scar	Present	Present	Usually absent	Usually absent
Intraepidermal melanocytic proliferation limited to area above scar	Present	Present	May extend beyond scar if present	Usually extends beyond scar if present
Pagetoid melanocytosis	Sometimes present but with little if any cytological atypia	Usually absent	Usually absent	Often present, greater cellular density compared to nevi and with significant cytological atypia
Cytological atypia of intraepidermal melanocytes	Usually absent or slight to moderate (rarely severe)	Usually absent	Present and variable, ranges from slight to severe	Present, uniform pattern of atypia at least moderate to severe
Dermal nevus remnant often beneath dermal scar	Usually present	Absent	Usually absent	Usually absent

GENITAL/FLEXURAL NEVI

These variants of common acquired nevi are largely defined by particular clinical and histological features related to anatomic site, whether this is genitalia (vulva, perineum, and male genitalia), or umbilicus, and other flexural sites such as the axillae. Such nevi may be slightly larger in size and may share some clinical and histological characteristics with other atypical ("dysplastic") nevi such as architectural disorder and cytological atypia (Table 10) (Fig. 6). The relationship of this group of nevi to other "atypical" (so called dysplastic) nevi with respect to nomenclature, melanoma risk, and so on, has not been definitively elucidated.

Synonyms: Atypical melancytic nevi of the genital type; melanocytic nevi of "special" sites.

Clinical Features:

- Occurrence in premenopausal women (range 14–40 years of age)
- Often enlarged, up to 10 mm in diameter
- Other features not well studied

Histopathology:

- Symmetric, occasionally asymmetric
- Well circumscribed usually
- Enlarged junctional nests with diminished cohesion
- Lentiginous melanocytic proliferation
- Confluence of cells, nests along dermal epidermal junction
- Variation in size, shape, and position of junctional nests
- Extension of intraepidermal component along adnexal epithelium
- Generally no pagetoid spread
- Generally no lateral extension
- Fibroplasia common, often lamellar
- Lymphocytic infiltrates
- Cytologic atypia, often slight to moderate
- Somewhat enlarged intraepidermal melanocytes, often abundant cytoplasm
- Multinucleate nevus giant cells
- Maturation of nevus cells common

Clinicopathologic Correlation:

See Clinicopathologic Correlation under the section "Common Acquired Melanocytic Nevi."

Differential Diagnosis:

- Vulvar and other melanomas
- Spitz tumor
- Clinically and histologically atypical nevus

See Table 10.

Pathophysiology:

How the regional cutaneous anatomy influences the histology of melanocytic nevi is poorly understood. Factors such as sun exposure, physical trauma, hormonal influences, type and frequency of skin appendages, and blood and vascular supply would seem operative.

References:

1. Christensen WN, Friedman KJ, Woodruff JD, Hood AF. Histologic characteristics of vulvar nevocellular nevi. J Cutan Pathol 1986; 14:87–91.
2. Clark WH Jr, Hood AJ, Tucker MA, Jampel RM. Atypical melanocytic nevi of the genital type with a discussion of reciprocal parenchymal-stromal interactions in the biology of neoplasia. Hum Pathol 1998; 29(Suppl 1):S1–S24.
3. Rongioletti F, Ball RA, Marcus R, Barnhill RL. Histopathological features of flexural melanocytic nevi: a study of 40 cases. J Cutan Pathol 2000; 27:215–217.

SMALL AND INTERMEDIATE-SIZED CONGENITAL NEVI

In general congenital melanocytic nevi (CMN) are defined by their presence at birth or appearance up to about three

Table 10 Differential Diagnosis: Genital/Flexural Nevi

	Genital/Flexural Nevi	Histologically Atypical Nevus	Vulvar and Other Melanomas
Size	Usually <10 mm, often >5, 6 mm	4 to 12 mm or more (any size)	Usually >5,6 mm, often >10 mm (any size)
Symmetry	Usually present	Often present, may be absent	Often absent
Circumscription	Often well circumscribed	Usually poorly circumscribed	Usually poorly circumscribed
Junctional nesting	Regular but often large hypercellular junctional nests with diminished cohesion; striking horizontal confluence of nests along dermal-epidermal junction	Disordered: variation in size, shape, placement of nests on epidermal rete	More disordered often with pagetoid melanocytosis
Lentiginous melanocytic proliferation	May be present	May be present with greater frequency of melanocytes	May be present with contiguous proliferation of melanocytes
Large "bulky" dermal component	Present commonly in vulvar nevi	Usually absent	Invasive melanoma may be present
Cytological atypia of intraepidermal melanocytes	Often present with enlarged epithelioid melanocytes, atypia often slight to moderate; multinucleate giant cells common	Present and variable, ranges from slight to severe	Present, uniform pattern of atypia at least moderate to severe
Maturation	Usually present	Often present, may be diminished	Often absent but "pseudomaturation" may be present
Dermal mitoses	Usually absent, rarely present in small numbers, e.g., 1 to 3/mm^2	Usually absent, rarely present in small numbers, e.g., 1 to 3/mm^2	Commonly present
	Usually superficial and not deep	Usually superficial and not deep	Deeply located mitoses often present

months of age postpartum (congenital nevus tardive). Clinically and histologically they constitute a continuum; however, they have arbitrarily been classified according to size as small: up to 1.5 cm in diameter and medium: 1.5 to 19.9 cm (Fig. 7A). A proportion of small congenital nevi may show overlap with acquired nevi (some are termed "congenital-pattern" nevi based their involvement of the upper reticular dermis). With increasing size congenital nevi exhibit progressively more distinctive features allowing their definitive recognition (Table 11) (Figs. 7B–D). Increasing evidence suggests that melanoma risk associated with small and medium-sized CMN is not significant, as was previously thought.

Clinical Features:

- May occur anywhere but head and neck is common.
- Symmetry.
- Small congenital nevus: <1.5 cm; medium-sized: >1.5 to 20 cm.
- Round, oval, and elongate in shape.
- Tan, brown, dark brown, often mahogany; or black in color.
- Slightly raised plaque.
- Pebbled or rugose surface.
- Coarse hairs often.

Histopathology:

- Lentiginous melanocytic hyperplasia often
- Junctional, compound or dermal
- Small congenital nevi (<1.5 cm)
- Involvement of upper half of reticular dermis common
  - Interstitial pattern
  - Perivascular, periadnexal pattern
- Medium-sized congenital nevi (1.5–20 cm)
  - Involvement of reticular dermis, particularly lower half
    - Diffuse dermal involvement by nevus cells
    - Interstitial pattern
    - "Inflammatory" pattern
  - Nevus cells within appendages, blood vessels, and nerves

Clinicopathologic Correlation:

Clinical Feature	Pathologic Feature
Tan, brown, or dark brown color	Melanin in epidermis, superficial dermis
Rugose or mamillated topography	Melanocytes in dermis, subcutis or deeper

Differential Diagnosis:

See Table 11.

- Becker's nevus
- Atypical (dysplastic) nevus
- Epidermal nevus
- Congenital lentigo
- Melanoma

LARGE OR GIANT CONGENITAL NEVI

Large or giant congenital nevi have been defined as nevi with diameters of at least 20 cm to those occupying a major portion of the cutaneous surface of an individual. These lesions are clearly distinctive because of their grossly

Table 11 Differential Diagnosis: Small and Intermediate-Sized Congenital Nevi

	Small and Intermediate-Sized Congenital Nevi	Becker's Nevus	Epidermal Nevus	Congenital Lentigo	Histologically Atypical Nevus	Melanoma
Size	Small: <1.5 cm Medium-sized: 1.5–19.9 cm	3–12 cm or more	1–2 cm or more	Any size	3–12 mm or more	Usually >5, 6 mm, often >10 mm
	Rugose or mamillated tan to dark brown slightly raised lesion with well-defined and regular borders	Often unilateral solitary tan to brown patch with serrated borders and prominent coarse hair	Unilateral sometimes linear or systematized verrucoid lesions	Tan to brown macular lesion with well-defined borders	Often irregular and/or ill-defined borders, irregular coloration	Often ABCDEs
Elongated, club-shaped epidermal rete ridges	Often present	Present or absent, sometimes papillomatous epidermal hyperplasia	Papillomatous epidermal hyperplasia	Usually present	Often present	Often absent
Basal layer hyperpigmentation, accentuated lower poles of rete	Often present	May be present	Usually absent	Often present	Often present	Present or absent
Increased numbers of basilar melanocytes concentrated on tips of rete ridges	Often present	Usually absent or slightly increased	Absent	Present	Usually present	Usually contiguous proliferation of atypical melanocytes
Junctional and/or dermal nesting of melanocytes (nevus cells)	Present	Absent	Absent	Absent	Present	Usually nesting of atypical melanocytes

Table 12 Differential Diagnosis: Large or Giant Congenital Nevi

	Large or Giant Congenital Nevi	Becker's Nevus	Neurofibromatosis	Melanoma	Peripheral Nerve Sheath Tumors
Size	>20 cm or major portion of skin surface	3–12 cm or more	Any size	Usually <20 cm	1–20 cm or more
Junctional and/or dermal or deeper nesting of melanocytes (nevus cells)	Present	Absent	Absent (presence of Schwann cells, perineurial fibroblasts, etc.)	Atypical melanocytes	Absent (presence of Schwann cells, perineurial fibroblasts, etc.)

disfiguring appearances and sometimes pose immediate threat to the patient. These lesions also show unique clinical and histological attributes often not shared with smaller congenital nevi (Table 12). Some of these unique properties include: deep tissue involvement (Figs. 7C and 7D), neurocutaneous melanosis (central nervous system involvement), clearly increased melanoma risk, and greater range of other deformities and neoplasia.

Dermal and subcutaneous melanocytic nodules and atypical nodular melanocytic proliferations occurring in congenital nevi may suggest melanoma (Table 13B) (Fig. 8). However, the vast majority of such nodular proliferations are immature or atypical growths and not true biological melanoma, particularly in infants below the age of two. Such proliferative nodules often show transition to the surrounding congenital nevus versus an abrupt interface with the surrounding nevus in melanoma, lack the degree of cytological atypia observed in melanoma, and generally have low mitotic rates (<1 to 3 mitoses/mm^2). However, both biologically indeterminate nodular proliferations and melanoma may be observed. Strikingly, confluent nodules with high-grade cytological atypia and more significant mitotic rates, for example, more than 6 mitoses/mm^2, raise concern for melanoma.

Synonyms: Bathing trunk nevi; garment-type nevi.

Clinical Features:

- Symmetry
- Greater than 20 cm.
- Involvement of major anatomic area, segmental
- Often dorsal involvement
- Occasional congenital deformities
- Well-defined borders
- Brown, dark brown, and black
- "Animal pelt" feature, rugose, doughy
- Soft tissue hypertrophy
- Hypertrichosis
- Scattered satellite nevi distant from giant nevus
- Involvement of meninges common for head and neck nevi

Histopathology:

- Lentiginous melanocytic hyperplasia common
- Usually compound or dermal
- Reticular dermal involvement, superficial and deep, usually
  - Diffuse
  - Interstitial
  - Perivascular, periadnexal
- Subcutaneous involvement, septal≫lobular
- Maturation
- Neural differentiation, neuroid or neurofibroma-like pattern, on occasion
- Wagner-Meissner-like corpuscles
- Fascial or muscle involvement
- Cellular nodules in reticular dermis, on occasion
- Blue nevus component, on occasion
- Spindle and epithelioid cell nevus component, on occasion
- Hamartomatous elements
  - Cartilaginous differentiation
  - Adipose differentiation

Clinicopathologic Correlation:

Clinical Feature	Pathologic Feature
Tan, brown, or dark brown color	Melanin in epidermis, superficial dermis
Rugose or "doughy" texture	Melanocytes in dermis, subcutis or deeper
Palpable nodules	Proliferative nodules of melanocytes in dermis and/or subcutis

Differential Diagnosis:

See Table 12.

- Becker's nevus
- Neurofibromatosis
- Melanoma
- Peripheral nerve sheath tumors

Intraepidermal and Dermal Proliferations Developing in Large/Giant Congenital Nevi:

Benign	Indeterminate/Malignant
Epithelioid cell	
Intraepidermal	
Pagetoid spread in nevi	Pagetoid melanoma
Dermal	
Expansile nodule of epithelioid cells	Melanoma, epithelioid cell type
Epithelioid schwannoma	Malignant epithelioid schwannoma
Pigmented spindle cell	
Dermal	
Expansile nodule of spindle cells	Melanoma, pigmented spindle cell type
Spindle cell with schwannian/perineurial differentiation	
Dermal	
Neurofibroma-like tumor	
Schwannoma	Malignant peripheral nerve sheath tumor
Small round cell	
Dermal	
Expansile nodule of small cells	Small cell melanoma

(*Continued*)

Intraepidermal and Dermal Proliferations Developing in Large/Giant Congenital Nevi: *Continued*

Benign	Indeterminate/Malignant
Specific mesenchymal ("ectomesenchymal") differentiation	
Cartilage	
Lipoma	Rhabdomyosarcoma
Hemangioma	
Neuronal elements	
Ganglioneuroma	Ganglioneuroblastoma
Unclassified or undifferentiated neoplasms	Undifferentiated sarcoma

Pathophysiology:

The biological basis for the development of congenital nevi has not been established. As compared to acquired nevi, the migration of neural crest-derived (pluripotential) cells to their destinations would seem to begin at a much earlier stage in utero. This earlier migration of neurocristic cells may be one reason that may account for the larger sizes of congenital nevi later in life. If the initial end points of migration are comparable in terms of surface area for both congenital and acquired nevi, the enormous expansion in skin surface area from the embryonic stage to that of ex utero could potentially explain the differences in size between congenital and acquired nevi.

References:

1. Mark GJ, Mihm MC, Liteplo MG, Reed RJ, Clark WH. Congenital melanocytic nevi of the small and garment type. Hum Pathol 1973; 4:395–418.
2. Hendrickson MR, Ross JC. Neoplasms arising in congenital giant nevi: morphologic study of seven cases and a review of the literature. Am J Surg Pathol 1981; 5:109–135.
3. Stenn KS, Arons M, Hurwitz S. Patterns of congenital nevocellular nevi. J Am Acad Dermatol 1983; 9:388–393.
4. Rhodes AR, Silberman RA, Harrist TJ, Melski JW. A histologic comparison of congenital and acquired nevomelanocytic nevi. Arch Dermatol 1985; 121:1266–1273.
5. Barnhill RL, Fleischli M. Histologic features of congenital melanocytic nevi in infants less than a year of age. J Am Acad Dermatol 1995; 33:780–785.

SPITZ TUMOR

This unique melanocytic neoplasm developing most commonly in young individuals (but also at birth and in older persons) is defined by a cytologically distinctive large epithelioid and/or spindle-shaped melanocyte in the appropriate clinical and organizational context. Spitz tumors may represent a form of melanocytic neoplasia quite apart from other conventional nevi and melanomas. A number of clinical and histological variants have been described including polypoid, plaque-type, desmoplastic, halo, pagetoid, pigmented, plexiform, combined, and finally atypical variants (Figs. 9 and 10). Of particular note is the frequent difficulty of distinguishing (or not being able to distinguish) atypical variants of Spitz tumor from melanoma (see subsequently).

Synonyms: Spitz nevus; spindle and epithelioid cell nevus; benign juvenile melanoma.

Clinical Features:

- Majority in children, adolescents, young adults but any age
- Location on face and extremities (especially thigh) most common
- Usually solitary; rare multiple or agminated forms occur
- Commonly asymptomatic; rarely pruritic
- History of growth in months; usually less than a year
- Often less than 5 mm, usually less than 10 mm
- Plaque, papule or nodule, often dome-shaped
- Smooth surface topography often
- Pink/red; pigmented forms occur.

Histopathology:

Cytologic features
Spindle and/or epithelioid cell type[a]
Overall monomorphous population of cells[a]
Occasional striking pleomorphism in a minority of cells
Architectural features
Symmetry[a]
Sharp lateral demarcation[a]
Zonation in depth (e.g., "maturation")[a]
Orderly nondisruptive infiltration of collagen by Spitz nevus[a] cells
Other helpful diagnostic features
Absent or rare, but not atypical, mitoses in deep parts[a]
Giant nevus cells
Irregular contours of growth at deep margin[a]
Kamino bodies
Paucity or absence of single-cell upward spread
Junctional clefts
Loss of cohesion between cells (retraction spaces)
Perivascular or diffuse inflammatory infiltrate
Superficial distribution of pigmentation
Telangiectasia and edema
Epidermal hyperplasia

[a]Most helpful features.

Clinicopathologic Correlation:

Clinical Feature	Pathologic Feature
Raised pink nodule	Epidermal hyperplasia, proliferation of epithelioid and or spindle cells in epidermis and/dermis, vascular ectasia, edema

Differential Diagnosis:

- Melanocytic lesions
  - Malignant melanoma
  - Atypical nevi with features of Spitz nevus
  - Variants of nevi with spindle and/or epithelioid cells
    - Pigmented spindle cell nevus
    - Desmoplastic Spitz tumor
    - Plexiform spindle cell nevus/deep penetrating nevus
    - Cellular blue nevus
    - Various "combined" nevi
- Nonmelanocytic lesions
  - Epithelioid cell histiocytoma
  - Reticulohistiocytoma
  - Cellular neurothekeoma

References:
1. Spitz S. Melanomas of childhood. Am J Pathol 1948; 24:591–609.
2. Kernen J, Ackerman L. Spindle cell nevi and epithelioid cell nevi (so called juvenile melanomas) in children and adults: A clinicopathological study of 27 cases. Cancer 1960; 13:612–625.
3. Echevarria R, Ackerman L. Spindle and epithelioid nevi in the adult. Clinicopathologic report of 26 cases. Cancer 1967; 20:175–189.
4. Paniago-Pereira C, Maize J, Ackerman A. Nevus of large spindle and/or epithelioid cells (Spitz's nevus). Arch Dermatol 1978; 114:1811–1823.
5. Weedon D, Little J. Spindle and epithelioid cell nevi in children and adults. A review of 211 cases of the Spitz nevus. Cancer 1977; 40:217–225.

SPITZ TUMOR WITH ATYPICAL FEATURES

A subset of Spitz tumors may be difficult or impossible to distinguish from melanoma and may exhibit one or more atypical features such as large size (often >10 mm), asymmetry, poor circumscription, ulceration, deep involvement, high cellular density, confluent or nodular grow patterns, diminished or absent maturation, cytological atypia beyond what is acceptable for a Spitz tumor, and significant dermal mitotic rates including deep or marginal mitoses (Tables 13 and 14) (Fig. 10). The authors recommend a comprehensive assessment of all such Spitz tumors for risk stratification. Risk stratification permits the general assignment of a risk category of low versus high risk for recurrence and potential regional spread. Some proportion of these lesions are high risk and consequently biologically indeterminate and should be managed with adequate surgical excision and follow-up examinations for recurrence.

Synonym: Atypical Spitz tumor.

Table 13 Assessment of Atypical Spitz Tumors in Children and Adolescents for Risk for Metastasis

Parameter	Score
Age (years)	
0–10	0
11–17	1
Diameter (mm)	
0–10	0
>10	1
Involvement of subcutaneous fat	
Absent	0
Present	2
Ulceration	
Absent	0
Present	2
Mitotic activity (mm^2)	
0–5	0
6–8	2
>9	5

***Note*: Total score and risk for metastasis: 0–2, low risk; 3–4, intermediate risk; 5–11, high risk.**
***Source*: From Ref. 4.**

Clinical Features:
- Individuals of any age
- Often greater than 10mm
- Ulceration may be present
- Asymmetry
- Irregular borders may be present
- Greater frequency of irregular coloration

Histopathology:
- Intraepidermal variant
  - Architectural disorder
    - Disordered intraepidermal melanocytic proliferation:[a]
      - Lentiginous or single-cell pattern[a]
      - Disordered junctional nesting[a]
        - Variation in size, shape, orientation, spacing, cellular cohesion of nests
        - Horizontal confluence and bridging of nests
      - pagetoid spread
    - Asymmetry
    - Poorly circumscribed
    - Lateral extension of intraepidermal component ("shoulder phenomenon")
  - Cytologic atypia[a]
    - Nuclear pleomorphism
    - Variation in nuclear chromatin patterns
    - Nuclear enlargement
    - Variation in nucleoli
  - Host response
    - Patchy to band-like mononuclear infiltrates in papillary dermis
    - Fibroplasia
- Dermal variant
  - Architectural disorder[a]
    - Expansile nodules
    - Increased cellularity
    - Loss of cellular cohesion
    - Asymmetry
    - Deep extension
    - Lack of maturation or orderly infiltration of collagen
    - Ulceration
    - Necrosis
  - Cytologic atypia (as above)
  - Mitotic activity
    - Numerous mitoses, e.g., $>6/mm^2$
    - Mitoses at base of lesion
    - Atypical mitoses
  - Host response
    - Prominent mononuclear cell infiltrates
    - Formation of tumor stroma

[a]Essential criteria for diagnosis.

Differential Diagnosis:
See Table 14.

References:
1. Reed RJ, Ichinose H, Clark WH Jr, Mihm MC Jr. Common and uncommon melanocytic nevi and borderline melanomas. Semin Oncol 1975; 2:119–147.

Table 14 Differential Diagnosis: Spitz Tumor with Atypical Features

	Spitz Tumor	Atypical Spitz Tumor	Malignant Melanoma
Age	Usually <20–30 years, any age	Usually <20–30 years or older, any age	Usually >30 years
Site	Extremities, head	Extremities, head	Usually trunk, distal extremities, any site
Size	Often <5, 6 mm and usually <10 mm	Often >10 mm	Often >10 mm
Symmetry	Present	Often asymmetrical	Usually asymmetrical
Circumscription	Usually well-circumscribed	Less often well-circumscribed	
Epidermal configuration	Usually regular hyperplasia	Effacement may be present	Often effacement
Ulceration	Usually absent	Often present	Often present
Pagetoid melanocytosis	Usually absent, except "pagetoid" variants	Sometimes present, often focal, central portion of lesion	Often present, peripheral
Kamino bodies (dull pink bodies)	Often present, in aggregates	May be present	Usually absent
Maturation	Usually present: diminished cellularity, diminished cellular and nuclear sizes with depth in dermis	Less frequent	Usually absent
Zonation	Morphological characteristics appear uniform from side to side	Less uniformity	Usually absent
Dermal configuration	Often plaque-type, wedge-shaped, or multiple fascicles track along appendageal structures with depth	Cellular plaque or nodule	Often nodular
Depth	Usually does not involve deep dermis or subcutis	Significant depth, may involve subcutis (level V)	
Confluence and high cellular density of melanocytes especially in dermis	Usually not prominent	Often present	Usually present
Dermal mitoses	Often <2–3/mm^2	Usually >2–3, often >6/mm^2	Usually present
Depth of dermal mitoses	Usually superficial	Often superficial and deep (marginal, i.e., near deep margin)	Usually superficial and deep
Cytological atypia of melanocytes	Not significant	Beyond what is acceptable for a Spitz tumor	Significant nuclear pleomorphism, hyperchromatism, prominent nucleoli, high nuclear-to-cytoplasmic ratios

2. Barnhill RL, Flotte T, Fleischli M, Perez-Atayde AR. Childhood melanoma and atypical Spitz-tumors. Cancer 1995; 76:1833–1845.
3. Barnhill RL, Argenyi ZB, From L, et al. Atypical Spitz nevi/tumors: lack of consensus for diagnosis, discrimination from melanoma, and prediction of outcome. Hum Pathol 1999; 30:513–520.
4. Spatz A, Calonje E, Handfield-Jones S, Barnhill RL. Spitz Tumors in Children: A grading system for risk stratification. Arch Dermatol 1999; 135:282–285.
5. Barnhill RL. The Spitzoid lesion: rethinking Spitz tumors, atypical variants, "Spitzoid melanoma" and risk assessment. Mod Pathol 2006; 19:S21–S33.

DESMOPLASTIC SPITZ TUMOR

A variant of Spitz tumor often predominately dermal and characterized by sclerosis of collagen about dermal melanocytes (Table 15). These lesions otherwise show the typical characteristics of Spitz tumors.

Synonym: Desmoplastic nevus

Clinical Features:

- Firm papule or nodule
- Adults (peak incidence in third decade)
- Most commonly located on extremities

Histopathology:

- Spindle and/or epithelioid cells.
- Predominantly intradermal location of melanocytes.
- Sometimes junctional component.
- Dermal stroma with increased collagen.
- Usually circumscribed, but with ill-defined borders.
- Often vaguely wedge shaped.
- Usually diffuse distribution of cells with low cell density.
- Typically small nests and single melanocytes.
- Maturation often present.
- Mitoses absent or rare. Multinucleate giant cells not uncommon (usually superficial).
- Melanin usually sparse or absent.

Clinicopathologic Correlation:

Clinical Feature	Pathologic Feature
Firmness	Sclerosis of dermal collagen

Differential Diagnosis:

See Table 15.

- Desmoplastic melanoma
- Sclerosing blue nevus
- Dermatofibroma

Table 15 Differential Diagnosis: Desmoplastic Spitz Tumor

	Desmoplastic Spitz Tumor	Desmoplastic Melanoma	Sclerosing Blue Nevus	Dermatofibroma
Age	Usually <20–30 years or older, any age	Usually 50–60 years or older	Usually <20–30 years or older, any age	Any age
Site	Extremities, especially proximal arm	Sun-damaged skin, especially head and neck	Dorsal aspects of extremities, head, any site	Lower extremities, any site
Histology	Enlarged spindled and/or epithelioid melanocytes with dermal sclerosis	Spindled melanocytes often small with slight to moderate pleomorphism in variably cellular fascicles in dermis, often neurotropism	Dendritic and/or spindled melanocytes, variably pigmented, embedded in well-defined nodular dermal sclerosis	Spindle cells and "histiocytic" cells in fascicular and storiform patterns, usually forming dermal nodule, typical infiltration of collagen bundles
	S 100+	S 100+	S 100+	S 100−
	Melan-A +	Melan-A−	Melan-A+	Melan-A−
	Gp100/HMB45− usually	Gp100/HMB45− (spindle cells)	Gp100/HMB45+	Gp100/HMB45−Factor 13a+

Pathophysiology:
Although the Spitz tumor has been considered by many to be a variant of melanocytic nevi, there is increasing evidence that they may be a unique subtype of melanocytic neoplasm. In addition to distinctive clinical and histological properties, these lesions and particularly atypical variants demonstrate a number of characteristics that distinguish them from ordinary nevi, for example, DNA tetraploidy, chromosomal 11p amplification, even loss of heterozygosity of genetic material, and involvement of sentinel lymph nodes.

References:

1. Barr R, Morales R, Graham J. Desmoplastic nevus. A distinct histologic variant of mixed spindle and epithelioid cell nevus. Cancer 1980; 46:557–564.
2. MacKie RM, Doherty VR. The desmoplastic melanocytic naevus: A distinct histological entity. Histopathology 1992; 20:207–211.
3. Harris GR, Shea CR, Horenstein MG, Reed JA, Burchette JL, Prieto VG. Desmoplastic (sclerotic) nevus an underrecognized entity that resembles dermatofibroma and desmoplastic melanoma. Am J Surg Pathol 1999; 23(7):786–794.

PIGMENTED SPINDLE CELL MELANOCYTIC TUMOR

The pigmented spindle cell tumor (PSCT) is considered by some to be a pigmented variant of Spitz tumor, and it is clear that clinical and histological overlap occurs between the two lesions. However, the PSCT may show rather distinctive attributes in a large proportion of cases. The lesion usually presents as a small well-defined dark brown to black flat topped papule (Fig. 11A). Histologically, PSCT is a sharply circumscribed mainly intraepidermal proliferation of small heavily pigmented spindle-shaped melanocytes arranged in fascicles or concentric arrays (Figs. 11B–D). A conspicuous feature of PSCT causing considerable confusion with melanoma is pagetoid melanocytosis (Table 16).

Synonyms: Pigmented spindle cell nevus of reed; pigmented spindle cell tumor.

Clinical Features:
- Peak incidence in third decade
- Most often located on extremities (especially thigh)
- Women more than men
- Usually greater than 5, 6 mm
- Symmetric
- Pigmented (usually evenly, often heavily)
- Sharply circumscribed
- Papule or nodule
- History of recent onset

Histopathology:
- Junctional or compound nevus
- Predominantly spindle cells, but occasional epithelioid cells
- Spindle cells more slender and delicate than in Spitz nevi
- Uniform population of cells from side to side
- Symmetrical configuration
- Predominance of junctional nests or fascicles
- Typically ovoid nests with fusiform cells oriented vertically
- Often confluence of nests leading to irregular shapes
- Sharp lateral borders, occasional lentiginous lateral spread
- Usually abundant coarse melanin
- Uniform nuclear features
- Decrease in cell size from top to bottom ("maturation")
- Mitoses not uncommon in intraepidermal component
- Absent or rare dermal mitoses

Clinicopathologic Correlation:

Clinical Feature	Pathologic Feature
Lesion is dark brown to black in color	Melanin in intraepidermal spindle melanocytes, basilar and suprabasilar keratinocytes, and papillary dermal melanophages
Well-defined margins	Sharply demarcated peripheral junctional nests of melanocytes

Differential Diagnosis:
See Table 16.

References:

1. Reed R, Ichinose H, Clark W, Mihm MC. Common and uncommon melanocytic nevi and borderline melanomas. Sem Oncol 1975; 2:119–147.
2. Sagebiel R, Chinn E, Egbert B. Pigmented spindle cell nevus. Clinical and histologic review of 90 cases. Am J Surg Pathol 1984; 8:645–653.
3. Barnhill RL, Barnhill MA, Berwick M, Mihm MC Jr. The histologic spectrum of pigmented spindle cell nevus: a review of 120 cases with emphasis on atypical variants. Human Pathol 1991; 22:52–58.

Table 16 Differential Diagnosis: Pigmented Spindle Cell Melanocytic Tumor

	Pigmented Spindle Cell Melanocytic Tumor	Atypical Pigmented Spindle Cell Tumor	Atypical (Dysplastic) Nevus	Malignant Melanoma
Size	Usually <5, 6 mm	May be >6 mm	4 to 12 mm or more (any size)	Usually >5, 6 mm, often >10 mm (any size)
Symmetry	Usually present	Often asymmetrical	Often present, may be absent	Often absent
Circumscription	Well circumscribed	Less often well-circumscribed	Usually poorly circumscribed	Usually poorly circumscribed
Junctional nesting	Regular often vertically-oriented fascicles or concentric nests of pigmented spindled melanocytes	Less regular, large confluent nests may be present	Disordered: variation in size, shape, placement of nests on epidermal rete	More disordered often with pagetoid melanocytosis
Lentiginous melanocytic proliferation	May be present	May be present	May be present with greater frequency of melanocytes	May be present with contiguous proliferation of melanocytes
Pagetoid melanocytosis	Sometimes present, often involves lower half of epidermis	Often present, may be prominent	Usually absent, may be focal	Usually present
Cytological atypia of intraepidermal melanocytes	Usually absent, small uniform spindle cells, small nuclei with basophilic evenly dispersed chromatin, small nucleoli on occasion	Often present, nuclear enlargement, pleomorphism, some hyperchromatism, larger nucleoli	Present and variable, ranges from slight to severe	Present, uniform pattern of atypia at least moderate to severe
Maturation	Usually present	Often present, may be diminished	Often present, may be diminished	Often absent but "pseudomaturation" may be present
Dermal mitoses	Usually absent, rarely present in small numbers, e.g., 1 to 3/mm^2	Usually absent, rarely present in small numbers, e.g., 1 to 3/mm^2	Usually absent, rarely present in small numbers, e.g., 1 to 3/mm^2	Commonly present
	Usually superficial and not deep	Usually superficial and not deep	Usually superficial and not deep	Deeply located mitoses often present

DERMAL MELANOCYTOSES

The dermal melanocytoses are lesions comprised of dermal dendritic melanocytes with a predilection for certain anatomic sites in persons of color. These conditions often appear at birth or shortly thereafter as gray bluish or brown patches. In some instances papular lesions resembling blue nevi may develop in the Nevi of Ota and Ito. Rare lesions may involve large segments of the skin sometimes with zosteriform distributions and some may develop later in life as acquired dermal melanocytoses.

Clinical Features:

See Table 17.

Clinicopathologic Correlation:

Clinical Feature	Pathologic Feature
Brown color	Epidermal melanin
Bluish gray color	Melanin situated in dermis

Differential Diagnosis:

See Table 18.

- Common blue nevus
- Acquired dermal melanocytoses
- Acquired nevus of Ota like macules
- Malignant melanoma

References:

1. Mishima Y, Mevorah B. Nevus Ota and nevus of Ito in American Negroes. J Invest Dermatol 1961; 36:133–154.
2. Kopf AW, Weidman AI. Nevus of Ota. Arch Dermatol 1962; 85:195–208.
3. Hidano A, Kajima H, Ikeda S, Mizutani, Miyasato H, Niimura M. Natural history of nevus of Ota. Arch Dermatol 1967; 95: 187–195.
4. Hirayama T, Suzuki T. A new classification of Ota's nevus based on histopathological features. Dermatologica 1991; 183: 169–172.

COMMON BLUE NEVUS

Blue nevi (BN) constitute a rather broad clinical and histological spectrum of lesions that is probably far more heterogenous than is reflected by the nomenclature that has developed for these lesions. This group of lesions is principally defined by the clinical property of bluish color (which is not always present) (Fig. 12A) and histologically by a conspicuous cell type the dendritic melanocyte which is present in a large proportion of (but not all) BN (see "Clinicopathologic Correlation" table under the section "Common Blue Nevus" and

Table 17 Clinical Features: Dermal Melanocytoses

	Mongolian Spot	Nevus of Ota	Nevus of Ito
Onset	Birth or soon after	Birth or soon after	Birth or soon after
Size	5 cm	1 to 5 cm	1 to 5 cm
Color	Gray-tan, slate blue	Brown, slate blue	Brown, slate blue
Surface	Macular	Macular, rarely discrete papules	Macular, rarely discrete papules
Distribution	Mid-line	Unilateral	Unilateral
Number	Single, can be multiple	Single	Single
Site	Lumbo-sacral	First and second division trigeminal nerve	Shoulder and upper arm
Racial incidence	Asians and dark-skinned races	Asians and dark-skinned races	Asians and dark-skinned races
Sex	Common	80% in females	80% in females
Clinical course	Usually disappears during first few years of life	Persist; rarely disappear	Persist; rarely disappear
Histopathological features	Scattered dermal melanocytes in lower half of dermis in low concentrations	Moderate number of dermal melanocytes in upper dermis	Moderate number of dermal melanocytes in upper dermis
Ultrastructure	Fully developed melanocytes with only mature melanosomes; virtually no premelanosomes	Fully developed melanocytes with only mature melanosomes; virtually no premelanosomes	Fully developed melanocytes with only mature melanosomes; virtually no premelanosomes

Table 18). The composition of BN commonly includes spindled melanocytes, sclerosis of collagen, and often, significant melanin content usually both in melanocytes and melanophages. The most frequent variant common BN is usually a well-defined dermal aggregate of dendritic melanocytes with varying degrees of dermal fibrosis and an admixture of spindled melanocytes and melanophages (Figs. 12B and C).

Synonym: Dendritic-fibrotic variant of blue nevus.

Clinical Features:

- Onset birth or later
- Women more than men
- Located on face, dorsum of wrist or foot, buttock
- 2 to 10 mm or larger
- Well circumscribed
- Symmetric
- Dome shaped often
- Uniform blue, blue-gray, and blue-black
- No alteration of skin markings
- Regular borders

Histopathology:

- Symmetry
- Alteration of dermis by variable admixture of dendritic melanocytes (usually heavily melaninized), melanophages, and fibrosis
- Dendritic cells often in bundles
- Periadnexal aggregation of dendritic cells often
- Infiltration of smooth muscle, nerves

Clinicopathologic Correlation:

Clinical Feature	Pathologic Feature
Blue-black color	Melanin in dermis
Papule or nodule	Dermal fibrosis and/or dermal proliferation of dendritic/spindled melanocytes

Differential Diagnosis:

See Table 19; also Tables 15 and 18.

Table 18 Differential Diagnosis: Dermal Melanocytoses

	Dermal Melanocytoses	Acquired Dermal Melanocytoses	Acquired Nevus of Ota Like Macules	Common Blue Nevus	Malignant Melanoma
Onset	Birth or soon after	Later in life	Later in life	Birth, later in life	Usually adults
Distribution	Midline, unilateral, dermatomal	Often dermatomal, segmental	Usually bilateral	Dorsal aspects of extremities, any site	Any site
Histology	Sparse numbers of dendritic melanocytes in upper dermis	Sparse numbers of dendritic melanocytes in upper dermis	Sparse numbers of dendritic melanocytes in upper dermis	Alteration of dermis by variable admixture of dendritic melanocytes (usually heavily melaninized), melanophages, and fibrosis	Usually intraepidermal and dermal proliferation of atypical melanocytes

Table 19 Differential Diagnosis: Common Blue Nevus

	Common Blue Nevus	Other Dermal Melanocytoses	Desmoplastic Melanoma	Regressed Melanoma	Metastatic Melanoma
Clinical history		See Tables 16 and 17	See Table 14	Often development of metastases	Documented antecedent primary melanoma
Symmetry	Present			Often asymmetry	Symmetrical or asymmetrical
Histology	Alteration of dermis by variable admixture of dendritic melanocytes (usually heavily melaninized), melanophages, and fibrosis			Admixture of cicatricial fibrosis, melanophages, lymphoplasma cellular infiltrates, and possibly some residual melanoma cells	Dermal aggregate of often heavily pigmented spindled (or other) melanoma cells with fibrosis and melanophages
Cytological atypia	Usually absent			Often absent (no residual melanoma)	Present but may be subtle
Dermal mitoses	Usually absent			Usually absent	Usually present

References:

1. Montgomery H. The blue nevus (Jadassohn-Tieche): Its distinction from ordinary moles and malignant melanomas. Am J Cancer 1939; 36:527–539.
2. Dorsey CS, Montgomery H. Blue nevus and its distinction from Mongolian spot and the nevus of Ota. J Invest Dermatol 1954; 22:225–236.
3. Pittman JL, Fisher BK. Plaque-type blue nevus. Arch Dermatol 1976; 112:1127–1128.

CELLULAR BLUE NEVUS

Cellular blue nevi (CBN) clearly occupy a continuum with the more prevalent common BN. CBN are often larger lesions commonly exhibiting a so called biphasic morphological configuration (Fig. 13A). The latter refers to the presence of a common BN component often superficial that shows transition to a deeper multinodular "cellular" component (Fig. 13B). The principal feature of this deeper component is fairly discrete bundles, concentric aggregates, or sometimes broad sheets of spindled melanocytes often vacuolated, lacking melanin pigment, and partitioned by fibrous tissue (Figs. 13C and 13D). A proportion of CBN may show atypical features such as large size (>1–2 cm), cytological atypia greater that usually observed in a CBN, necrosis, and increased mitotic rate, for example, greater than 2 to 3/mm^2 and may be difficult to differentiate from melanoma (Table 20).

Clinical Features:

- Onset birth, childhood, and adolescence
- Age mean 33 (range 6–85)
- Site buttocks, sacrococcygeal area, forearm/wrist, leg/ankle/foot, scalp, and face
- Gray-blue to blue-black papule, nodule
- Usually well circumscribed
- Regular borders.
- Size 0.3 to 3 cm

Histopathology:

- Symmetry
- Localization to reticular dermis
- Often deep extension with bulging, nodular configuration, rounded, well-demarcated inferior margin
- Heterogeneity of patterns
  - Biphasic pattern most common:
    - Melanin-laden dendritic melanocytes and fibrosis and
    - Bundles of amelanotic fusiform cells
    - Alveolar pattern: fascicles or nests of fusiform cells compartmentalized by fibrous trabeculae
  - Fascicular pattern: fascicles of spindle cells often with clear cytoplasm and prominent schwannian differentiation
  - Cellular blue nevus with atypical features (atypical cellular blue nevus)
  - Large size (>1 to 2 cm)
  - Marked cytologic atypia
  - Increased mitotic rate
  - Necrosis
  - Infiltration of surrounding tissue
- Lacunae containing melanophages
- Cystic degeneration in central part of nevus with loose edematous stroma
- Few or no mitotic figures
- Necrosis absent or uncommon

Clinicopathologic Correlation:

Clinical Feature	Pathologic Feature
Nodule	Dermal/subcutaneous nodule composed of fibrosis and cellular bundles of spindled melanocytes
Blue, blue-gray color	Melanin in dermis

Differential Diagnosis:

See Table 20.

Pathophysiology:

The basis for the development of the dermal melanocytoses and blue nevi has not been elucidated. There is speculation that these lesions may originate from neural-crest derived migratory cells that become arrested in the dermis and thus presumably never reach the epidermis; or possibly they develop from pluripotential cells associated with cutaneous nerves.

Table 20 Differential Diagnosis: Cellular Blue Nevus

	Cellular Blue Nevus	Malignant Melanoma (Malignant Blue Nevus)	Metastatic Melanoma	Clear Cell Sarcoma
Age	Mean age 33 years	Mean age 46 years	Adults	Mean age 30 years
Site	Buttocks, low back region, extremities, scalp	Scalp > other sites	Any site	Distal extremites, especially foot and ankle, deep-seated: tendons, aponeuroses
Size	1–2 cm	1–4 cm	Any size, often <1 cm	1–24 cm, usually >3 cm
Symmetry	Usually present	Usually absent	Often absent, may be present	Often absent
Epidermal involvement	Absent	Absent	Absent or present	Absent
Configuration	Biphasic lobular or multilobular tumor, common blue nevus pattern with deeper fascicle or lobules of amelanotic spindle cells	Often lobular or multilobular tumor, usually cellular blue nevus component and distinct nodular component of malignant epithelioid, or spindle cells, or sheetlike (sarcomatoid) arrangements of atypical spindle cells	Often nodular, aggregates of spindle and/or epithelioid cells	Multilobular, oval or spindle cells in nests and fascicles
Cytological atypia	Absent or low-grade	Usually severe but may be less developed	Usually severe but may be of lesser degree	Moderate to severe
Mitotic rate	Usually <1–2/mm^2	Usually >2/mm^2	Few to many	Usually <3/10 hpf
Necrosis	Usually absent	Often present	Present or absent	May be present
Translocation involving chromosomes 12 and 22	Absent	Absent	Absent	60% to 75%

References:

1. Rodriguez HA, Ackerman LV. Cellular blue nevus. Clinicopathologic study of forty-five cases. Cancer 1968; 21:393–405.
2. Avidor I, Kessler E. "Atypical" blue nevus—a benign variant of cellular blue nevus. Dermatologica 1977; 154:39–44.
3. Temple-Camp CRE, Saxe N, King H. Benign and malignant cellular blue nevus. A clinicopathological study of 30 cases. Am J Dermatopathol 1988; 10:289–296.
4. Tran TA, Carlson JA, Basaca B, Mihm MC Jr. Cellular blue nevus with atypia (atypical cellular blue nevus): a clinicopathologic study of nine cases. J Cutan Pathol 1998; 25:252–258.

COMBINED NEVUS

Combined nevus is a variant of benign melanocytic neoplasm characterized by the presence of two or more distinct populations of melanocytes (Table 21) (Fig. 14). Virtually, any combination of melanocytic components may occur, for example, common acquired nevus and common blue nevus, common nevus and pigmented spindle cell/epithelioid cell dermal component (Figs. 14B–D), Spitz and blue nevus components, congenital nevus and blue nevus and so on.

Synonym: Melanocytic nevus with phenotypic heterogeneity

Clinical Features:

- Any age (birth to old age) but usually more than 40 years
- Women more than men
- Head and neck (especially for blue nevus variants), upper trunk, proximal extremities
- Often component of blue, blue-black
- May have small (1–5 mm) blue, blue-black focus in ordinary nevus
- Size greater than 6 to 7 mm in most instances

Histopathology:

- Symmetrical
- Well-circumscribed
- Orderly arrangements of cells
- Two or more of the following:
  - Ordinary nevus component
  - Pigmented dendritic melanocytes
  - Pigmented spindle/epithelioid cells
  - Amelanotic spindle cells
  - Spitzoid melanocytes.
- Ordinary nevus component often overlies or is adjacent to other component
- Deep involvement occurs often
- Plexiform configuration on occasion

Clinicopathologic Correlation:

Clinical Feature	Pathologic Feature
Blue, blue-black color	Melanin in dermal component
"Black dot" in tan-brown nevus	Melanin in dermal aggregate of epithelioid and/or spindled melanocytes, melanophages

Differential Diagnosis:

See Table 21.

References:
1. Fletcher V, Sagebiel RW. The combined nevus: Mixed patterns of benign melanocytic lesions must be differentiated from malignant melanomas. In: Ackerman AB, ed. Pathology of malignant melanoma. New York: Masson Publishing USA, 1981; 273–283.
2. Rogers GS, Advani H, Ackerman AB. A combined variant of Spitz's nevi. Am J Dermatopathol 1985; 7:61–78.
3. Pulitzer DR, Martin PC, Cohen AP, Reed, RJ. Histologic classification of the combined nevus. Analysis of the variable expression of melanocytic nevi. Am J Surg Pathol 1991; 15:1111–1122.
4. Ball NJ, Golitz LE. Melanocytic nevi (with focal atypical epithelioiid cell components): A review of 73 cases. J Am Acad Dermatol. 1994; 30:724–729.
5. Collina G, Deen S, Cliff S, Jackson P, Cook MG. Atypical dermal nodules in benign melanocytic naevi. Histopathology 1997; 31:77–101.

PLEXIFORM PIGMENTED SPINDLE CELL NEVUS/TUMOR (DEEP-PENETRATING NEVUS)

The plexiform pigmented spindle cell nevus/tumor is a lesion probably closely related to the so called "deep-penetrating nevus," blue nevus, particularly cellular variants, plexiform pigmented spindle and epithelioid cell lesions, and finally Spitz tumor (Table 22) (Fig. 14). Atypical and biologically indeterminate variants of this general group of lesions occur and are characterized by asymmetry, larger size, significant cytological atypia, and increased mitotic rates usually greater than 3 to 4 mitoses/mm^2. The term plexiform pigmented spindle cell nevus is preferred because it is more descriptive of the actual configuration of these lesions.

Clinical Features:
- Age range 10 to 30 years but any age
- Site—face, upper trunk, proximal extremities
- Size greater than 1 cm
- Raised lesions with bluish color

Histopathology:
- Symmetric
- Well circumscribed
- Wedge configuration
- Extension of cellular fascicles into deep dermis or subcutis
- Pigmented spindle cells in fascicles associated with neurovascular bundles
- Occasional junctional nests
- Diffuse involvement of superficial dermis
- Occasional cytologic atypia
- Mitotic figures absent or few in number (<2–3/mm^2)

Clinicopathologic Correlation:
See Clinicopathologic Correlation under the section "Common Blue Nevus" and "Cellular Blue Nevus."

Differential Diagnosis:
See Table 22.
- Spitz tumor
- Cellular blue nevus
- Melanoma

References:
1. Seab JA Jr, Graham JH, Helwig EB. Deep penetrating nevus. Am J Surg Pathol 1989; 13:39–44.
2. Barnhill RL, Mihm MC Jr, Magro CM. Plexiform spindle cell naevus: A distinctive variant of plexiform melanocytic naevus. Histopathology 1991; 18:243–247.
3. Cooper PH. Deep penetrating (plexiform spindle cell) nevus. A frequent participant in combined nevus. J Cutan Pathol 1992; 19:172–180.

Table 21 Differential Diagnosis: Combined Nevus

	Combined Nevus	Cellular Blue Nevus	Malignant Melanoma
Age	Usually <40 years, any age	Usually <40 years, any age	Often >30 to 40 years
Site	Head and neck, upper trunk, proximal extremities	Buttocks, low back region, extremities, scalp	Trunk, extremities, head and neck
Size	Usually <6 mm	Often 1–2 cm	Usually >6 mm, often >10 mm
Symmetry	Usually present	Usually present	Often absent
Circumscription	Well circumscribed	Well circumscribed	Usually poorly circumscribed
Junctional nesting	Regular	Absent	More disordered often with pagetoid melanocytosis
Cytological atypia of melanocytes	Usually absent, may be low-grade in pigmented epithelioid or spindle cell components	Absent or low-grade	Present, uniform pattern of atypia at least moderate to severe
Biphasic pattern	Usually present, often ordinary nevus remnant overlies or adjacent to another distinct component such a blue nevus or plexiform component	Usually present, often "common" blue nevus overlies fascicles or lobules of spindle cells	Usually absent, may be present
Maturation	Usually present, the two or more components show orderly transition	Orderly transition from common to cellular components	Often absent but "pseudomaturation" may be present, abrupt interface with benign component often
Dermal mitoses	Usually absent, rarely present in small numbers, e.g., 1 to 3/mm^2 Usually superficial and not deep	Often <1 to 2/mm^2	Commonly present Deeply located mitoses often present

Table 22 Differential Diagnosis: Plexiform Pigmented Spindle Cell Nevus/Tumor (Deep-Penetrating Nevus)

	Plexiform Pigmented Spindle Cell Nevus/Tumor[a]	Spitz Tumor	Cellular Blue Nevus	Melanoma
Age	Usually <40 years, any age	Usually <20–30 years, any age	Usually <40 years, any age	Often >30 to 40 years
Site	Head and neck, upper trunk, proximal extremities	Extremities, head	Buttocks, low back region, extremities, scalp	Trunk, extremities, head and neck
Size	Usually <6 mm	Often <5, 6 mm and usually <10 mm	Often 1–2 cm	Usually >6 mm, often >10 mm
Symmetry	Usually present	Present	Usually present	Often absent
Circumscription	Well circumscribed	Usually well circumscribed	Well circumscribed	Usually poorly circumscribed
Junctional nesting	Regular	Usually regular	Absent	More disordered often with pagetoid melanocytosis
Cytological atypia of melanocytes	Usually absent, may be low-grade in pigmented epithelioid or spindle cell components	Usually absent	Absent or low-grade	Present, uniform pattern of atypia at least moderate to severe
Biphasic pattern	Usually present, often ordinary nevus remnant overlies or adjacent to another distinct component such a blue nevus or plexiform component	Usually absent	Usually present, often "common" blue nevus overlies fascicles or lobules of spindle cells	Usually absent, may be present
Maturation	Usually present, the two or more components show orderly transition	Usually present: diminished cellularity, diminished cellular and nuclear sizes with depth in dermis	Orderly transition from common to cellular components	Often absent but "pseudo-maturation" may be present, abrupt interface with benign component often
Dermal mitoses	Usually absent, rarely present in small numbers, e.g., 1 to 3/mm^2 Usually superficial and not deep	Often <2 to 3/mm^2 Usually superficial and not deep	Often <1 to 2/mm^2	Commonly present Deeply located mitoses often present
Configuration	Often conventional architecture, plexiform, plaque-type, wedge-shaped	Often plaque-type, wedge-shaped, or multiple fascicles track along appendageal structures with depth	Lobular, multilobular, fascicular	Nodular often
Depth	May involve deep dermis and subcutis	Usually does not involve deep dermis or subcutis	Usually involves deep dermis and subcutis	Any depth

[a]Plexiform spindle cell nevus is similar to deep penetrating nevus but shows a striking plexiform configuration not always present in deep penetrating nevus. Neither does the plexiform nevus always extend as deeply as deep penetrating nevus.

4. Robson A, Morley-Quante M, Hempel H, McKee PH, Calonje E. Deep penetrating naevus: clinicopathological study of 31 cases with further delineation of histological features allowing distinction form other pigmented benign melanocytic lesions and melanoma. Histopathology 2003; 43:529–537.

THE CLINICALLY AND HISTOLOGICALLY ATYPICAL MELANOCYTIC NEVI (THE SO-CALLED "DYSPLASTIC" NEVUS)

For almost thirty years melanocytic nevi seeming to occupy an intermediate position between common banal nevi and melanoma have remained controversial as to their biological nature, significance, and nomenclature. Although considerable research has been conducted on the subject and new important information has emerged, the inability to develop minimal essential clinical and histological criteria for such atypical nevi has encumbered the generation of "clean" data. Furthermore, it seems likely that without a prospective clinical trial, it may not be possible to obtain the necessary data to confirm or refute whether the monitoring of such atypical nevi has any effect on mortality from cutaneous melanoma.

The author acknowledges that significantly increased numbers of melanocytic nevi, both typical and atypical, and other nevus "parameters" (size >5 or 8 mm, irregular borders, variegated color) have been established as risk markers for melanoma beyond question (Fig. 15A). Furthermore there is emerging evidence that a certain degree of histological atypicality (of "moderate to severe" degree) in melanocytic nevi is a risk marker of melanoma.

As a provisional approach the author recommends the use of the following terminology: (*i*) clinically atypical nevus for clinical lesions and (*ii*) melanocytic nevus with architectural disorder and cytological atypia (or nevus with atypical features) for histological lesions (Tables 4 and 6) (Figs. 15B–D).

Synonyms: Dysplastic melanocytic nevi; Clark nevi; atypical nevi; nevi with architectural disorder and cytological atypia.

Clinical Features:

Clinically atypical melanocytic nevus.

***General*:**
- Increased numbers of typical and atypical nevi (e.g., >50 or 100)
- Variation in gross morphologic features among nevi
- Increased numbers of nevi on scalp, female breasts, and buttocks

***Nevus Characteristics*:**
- Increased size (4 to 12 mm usually but exceptions)
- Asymmetry
- Macular component
- Irregular border
- Ill-defined border
- Altered topography, pebbled or cobblestone surface
- Haphazard, variegated or greater complexity of coloration

***Histopathology*:**
Melanocytic nevus with architectural disorder and cytological atypia

***Architectural Features*:**
- Lentiginous melanocytic proliferation[a]
- Variation in size, shape, location of junctional nests with bridging or confluence[a]
- Lack of cellular cohesion of junctional nests
- Lateral extension (the "shoulder" phenomenon) of junctional component

***Cytologic Features*:**
- Spindled cell (with prominent retraction artifact of cytoplasm) pattern
- Epithelioid cell pattern
- Discontinuous nuclear atypia (not all nuclei atypical)[a]:
- Nuclear enlargement
- Nuclear pleomorphism
- Nuclear hyperchromatism
- Prominent nucleoli
- Prominent pale or "dusty" cytoplasm
- Large melanin granules

***Host Response*:**
- Lymphocytic infiltrates
- Fibroplasia
- Concentric eosinophilic pattern
- Lamellar pattern
- Prominent vascularity

Clinicopathologic Correlation:

Clinical Feature	Pathologic Feature
Macular component of nevus	Intraepidermal proliferation of melanocytes
Papular component	Intraepidermal and dermal proliferation of melanocytes
Ill-defined borders	Poor circumscription
Erythema	Lymphocytic infiltrates, prominent vascularity
Irregular pigment pattern	Variable degrees of melanin content epidermis, dermal melocytes, and melanophages

Differential Diagnosis:
See Tables 4 and 6.
- Common acquired nevi
- Spitz tumors
- Pigmented spindle cell melanocytic tumors
- Congenital nevi
- Malignant melanoma

Pathophysiology:
There has been evidence for many years that both genetic and environmental factors probably are relevant to the development of atypical nevi in general. However, it has been difficult to clearly establish thresholds that reliably and reproducibly distinguish the clinically and histologically atypical nevi from ordinary nevi.

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1. Clark WH Jr, Elder DE, Guerry D IV, et al. A study of tumor progression: the precursor lesions of superficial spreading and nodular melanoma. Human Pathol 1984; 15:1147–1165.
2. Elder DE. The dysplastic nevus. Pathology 1985; 17:291–297.
3. Barnhill RL, Roush GC, Duray PH. Correlation of histologic and cytoplasmic features with nuclear atypia in atypical (dysplastic) nevomelanocytic nevi. Hum Pathol 1990; 21:51–58.
4. Piepkorn MW. An appraisal of the dysplastic nevus syndrome concept. Adv Dermatol 1991; 6:35–55; discussion 56.
5. Weinstock MA, Barnhill RL, Rhodes AR, Brodsky GL. Reliability of the histopathologic diagnosis of melanocytic dysplasia. The Dysplastic Nevus Panel. Arch Dermatol 1997; 133:953–958.
6. Piepkorn M. Whither the atypical (dysplastic) nevus? Am J Clin Pathol 2001; 115:177–179.
7. Shors AR, Kim S, White E, et al. Dysplastic naevi with moderate to severe histological dysplasia: a risk factor for melanoma. Br J Dermatol 2006; 155(5):988–993.

[a]Essential features needed for diagnosis. Either lentiginous melanocytic proliferation or variation in junctional nesting is acceptable.

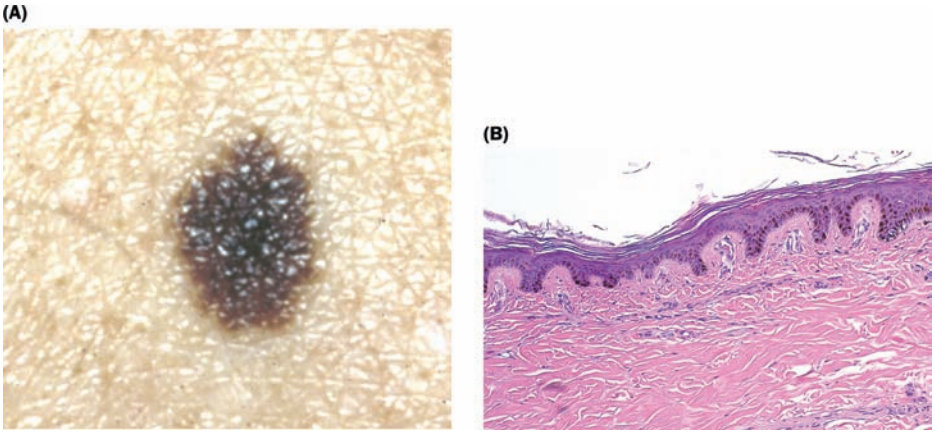

Figure 1 (**A**) Lentigo simplex. Note well-circumscribed borders and uniform dark brown color. (**B**) The lesion demonstrates elongated epidermal rete, basal layer hyperpigmentation, and slightly increased numbers of single basilar melanocytes concentrated on the epidermal rete.

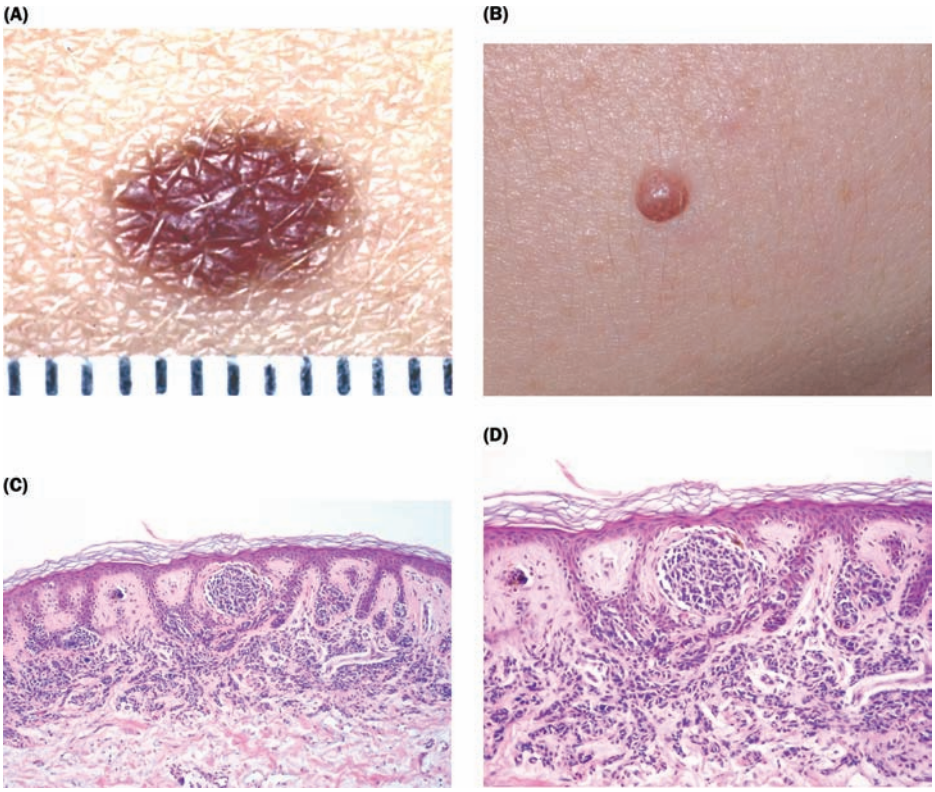

Figure 2 (**A**) Compound nevus. The lesion is symmetrical, well defined, and has uniform brown color. (**B**) Dermal nevus. The lesion is small, symmetrical, well defined, and has regular borders. (**C**) Compound nevus. Note symmetry and regular distribution of melanocytes in junctional and dermal nests. (**D**) Higher magnification showing uniform cytological features of melanocytes.

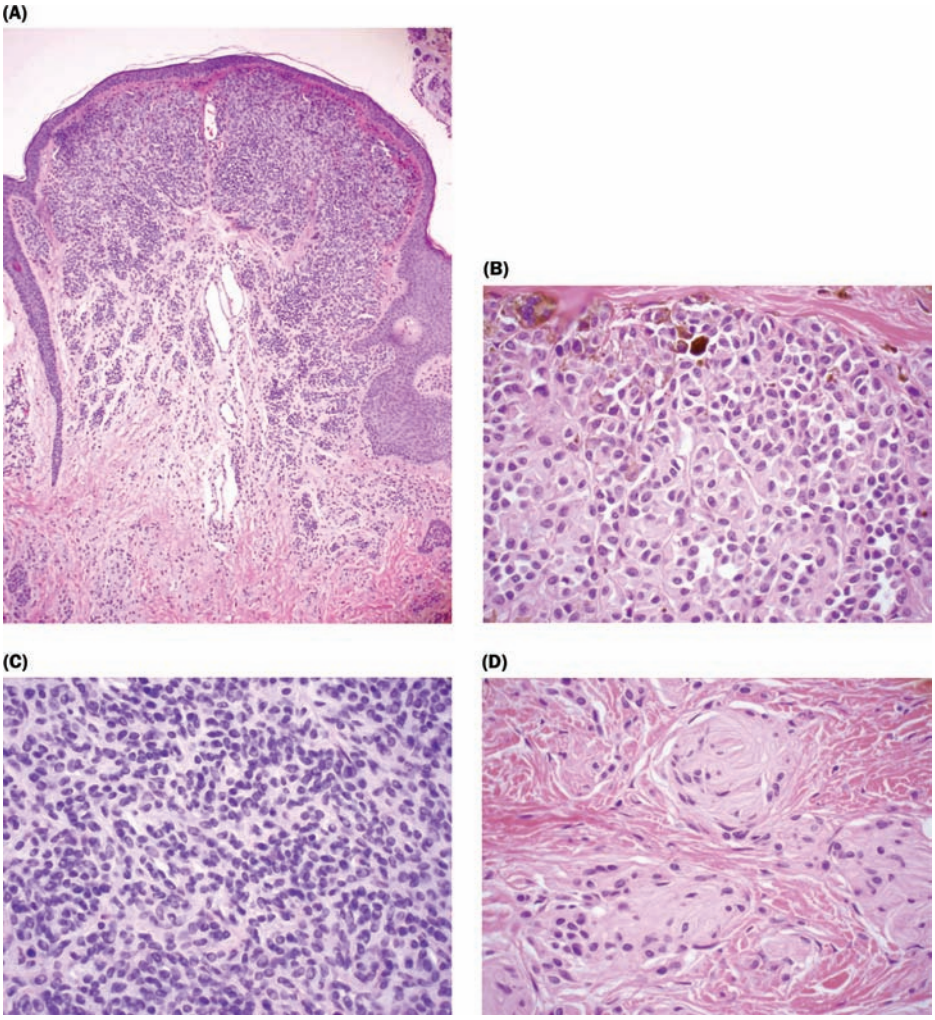

Figure 3 (**A**) Dermal nevus. There is maturation from epithelioid-type cells at the top of the nevus to lymphocytoid cells and finally to cells with schwannian differentiation at the base. (**B**) Epithelioid (or "type A") nevus cells. The melanocytes are present in rounded nests in the superficial dermis. The cells demonstrate abundant eosinophilic cytoplasms, often with syncytial appearances. The nuclei are round or oval and display fairly uniform chromatin. (**C**) Lymphocytoid (or "type B") nevus cells. These nevus cells have little or no demonstrable cytoplasm and contain uniform nuclei that are often slightly smaller than those present in type A cells. (**D**) Spindle (or "type C") nevus cells. These melanocytes commonly have not only spindle-shaped morphologies but also often display neural or schwannian differentiation ("neurotization") in patterns often indistinguishable from a peripheral nerve sheath tumor. These nevus cells are usually sparsely scattered in a delicate fibrous matrix and may form the rather characteristic "neural tubules."

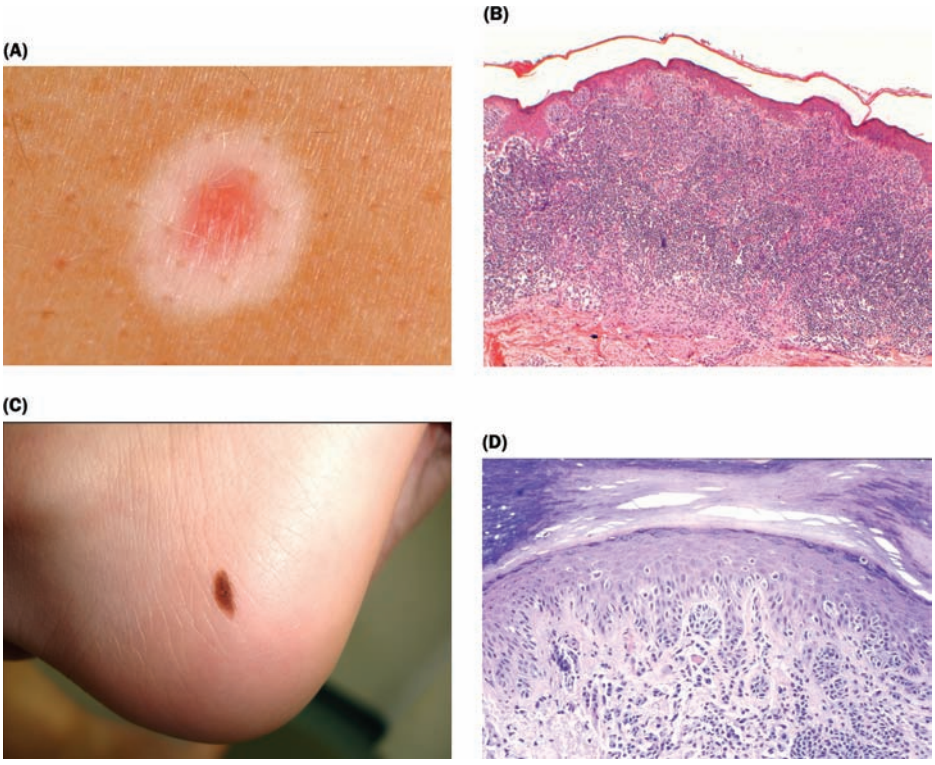

Figure 4 (**A**) Halo melanocytic nevus. Note symmetry and well-delineated nature of the halo and central nevus. (**B**) Halo melanocytic nevus. A compound nevus is obscured by a dense lymphocytic infiltrate. The nevus shows maturation and lacks significant atypia. (**C**) Acral melanocytic nevus. The nevus shows small diameter, symmetry, regular borders, and fairly uniform tan-brown color. (**D**) Acral melanocytic nevus. A compound nevus demonstrating lentiginous melanocytic hyperplasia and noticeable pagetoid melanocytosis—both features raising concern for acral melanoma. However, the lesion has regular nesting of melanocytes and does not show the pronounced cytological atypia of melanoma.

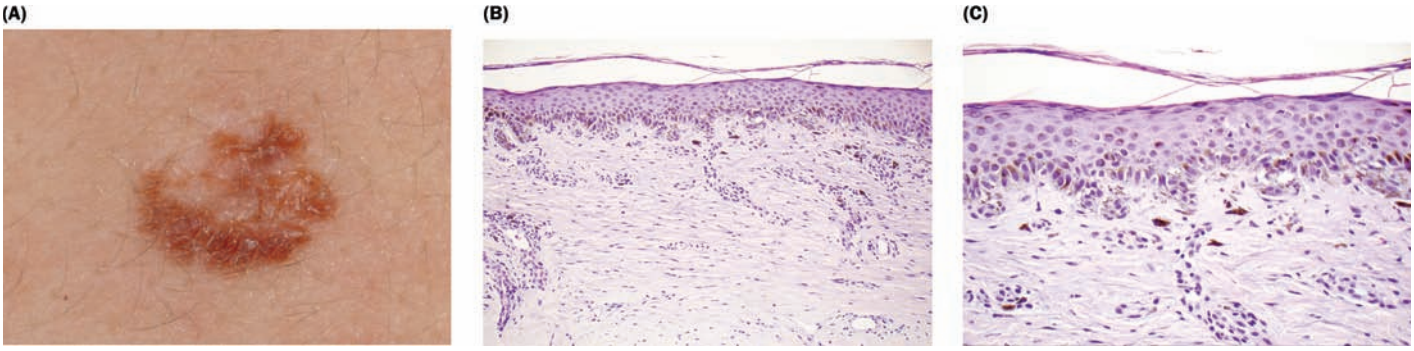

Figure 5 (**A**) Recurrent/persistent melanocytic nevus. The lesion demonstrates somewhat irregular macular pigmentation within the clinical scar of previous biopsy of a nevus. (**B**) Irregular nesting of melanocytes along dermal-epidermal junction and overlying dermal cicatrix from previous biopsy. Residual dermal nevus from the original lesion is present deep to the cicatrix (not observed in this photo). (**C**) Higher maginification of (**B**) shows irregular junctional nesting of melanocytes without significant atypia.

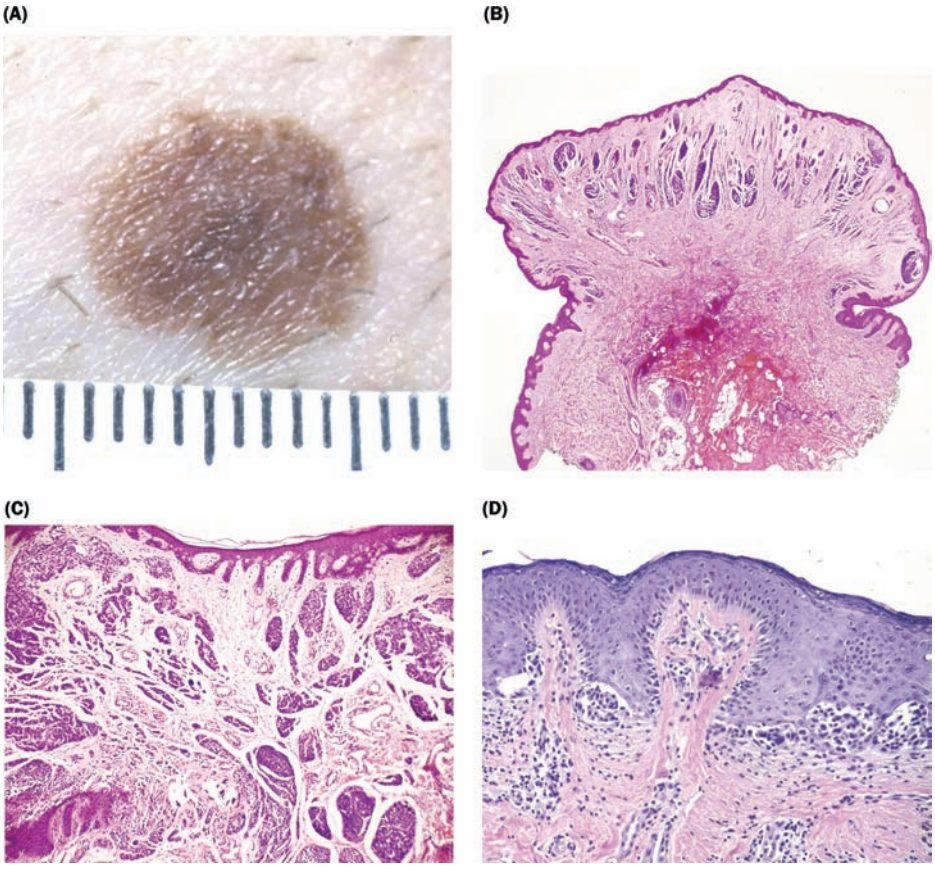

Figure 6 (**A**) Genital melanocytic nevus. The lesion is symmetrical, well defined, has uniform brown color, measures about 1 cm in diameter, and possesses a minimally elevated topography. (**B**) Genital (vulvar) melanocytic nevus. Note symmetrical polypoid profile. (**C**) Genital (vulvar) melanocytic nevus. This compound nevus has an extensive (bulky) dermal component of regularly dispersed nests of nevus cells and shows maturation. (**D**) Genital (vulvar) melanocytic nevus. This lesion exhibits hypercellular, discohesive, and somewhat irregular junctional nesting. The junctional melanocytes are enlarged and contain slightly to moderately atypical nuclei.

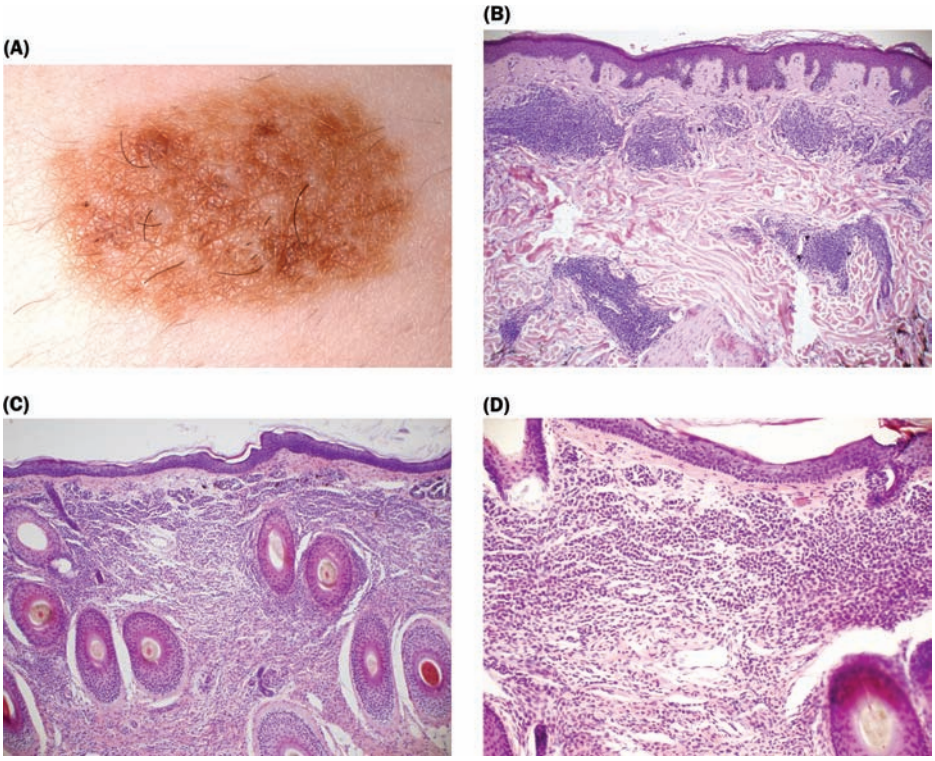

Figure 7 (**A**) Intermediate-sized congenital melanocytic nevus. The lesion is well defined with somewhat speckled brown color. (**B**) Small congenital melanocytic nevus. Note pattern of discreet nesting of melanocytes in reticular dermis that resembles a lymphocytic infiltrate. (**C**) Giant congenital melanocytic nevus. There is diffuse infiltration of the reticular dermis by nevus cells. (**D**) Giant congenital melanocytic nevus. Higher magnification of (**C**) showing orderly pattern of small uniform nevus cells in dermis.

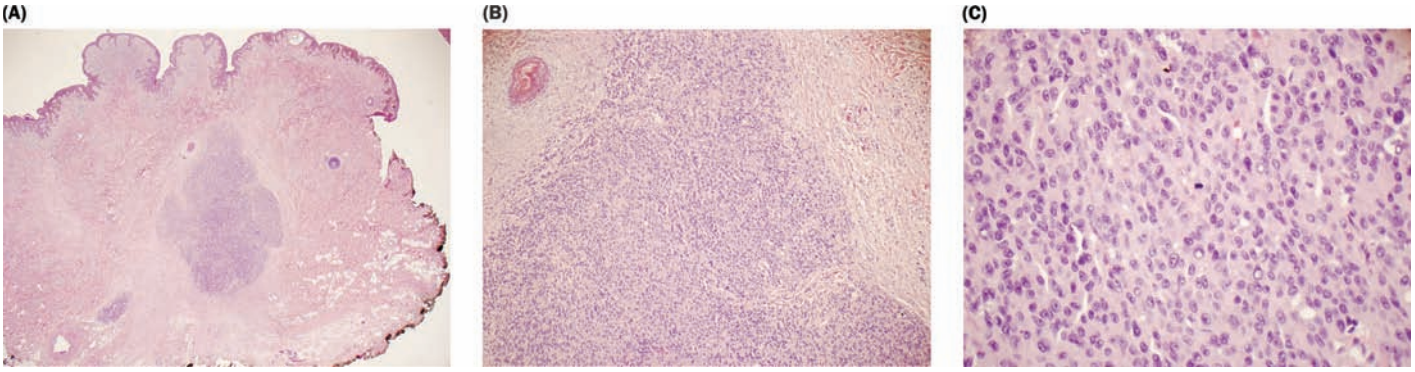

Figure 8 (**A**) Atypical dermal nodular melanocytic proliferation arising in giant congenital melanocytic nevus. The nodular proliferation is present in the mid-dermis and is fairly well circumscribed. (**B**) There is some transition to the surrounding congenital nevus. (**C**) The nodule shows cytological atypia of melanocytes and rare mitoses. The tumor lacks sufficient atypicality for melanoma.

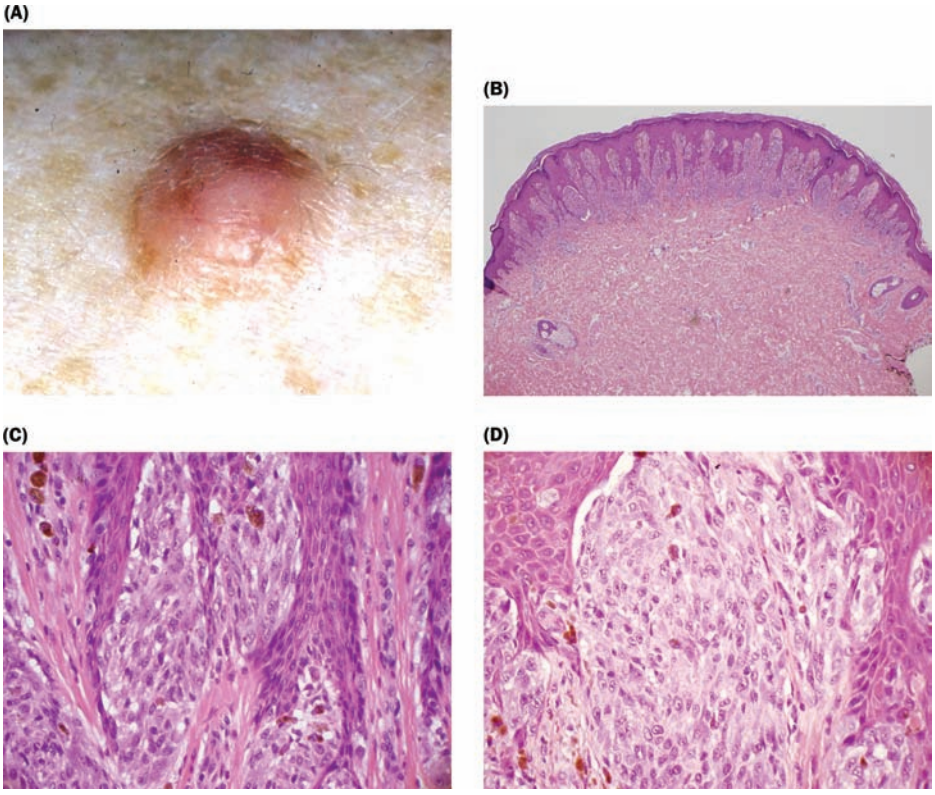

Figure 9 (**A**) Spitz tumor. The lesion is a symmetrical, reddish-pink dome-shaped nodule with uniform smooth surface. (**B**) Compound Spitz tumor. Corresponding symmetrical and well-circumscribed configuration of lesion at scanning magnification. (**C**) Compound Spitz tumor. Characteristic enlarged spindle cells and epithelioid cells arranged in vertically-oriented ("raining down") fascicles and nests, respectively, at the dermal-epidermal junction. (**D**) The melanocytes have eosinophilic "ground glass" cytoplasms and large nuclei with dispersed delicate chromatin.

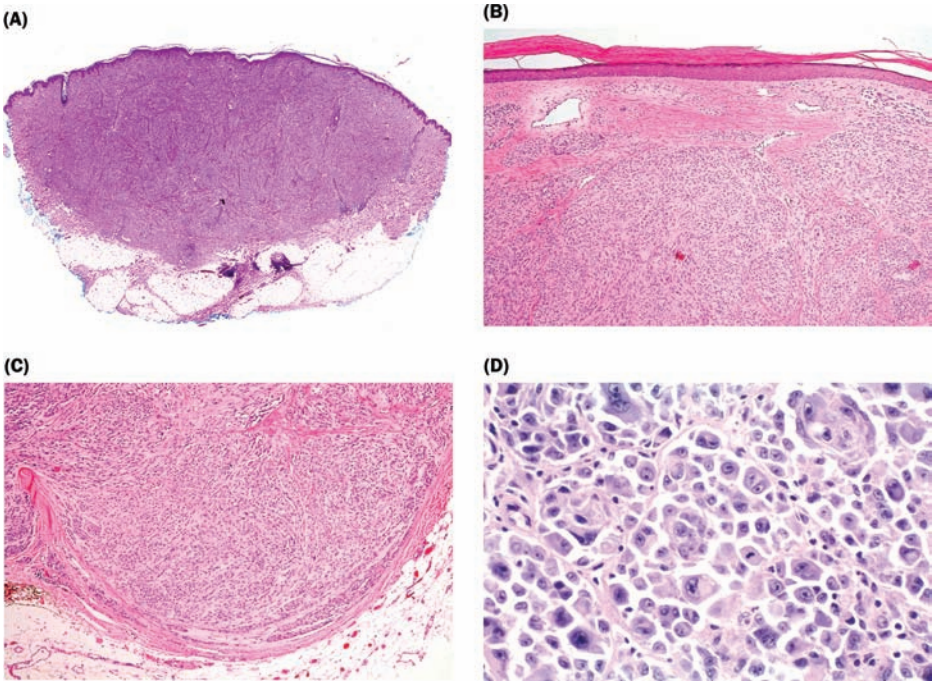

Figure 10 (**A**) Compound Spitz tumor with atypical features. The lesion demonstrates the following abnormal features: "nodule formation" (hypercellularity and confluence of melanocytes), the lack of maturation, and significant depth. (**B**) Higher magnification shows effacement of epidermis and the nodular appearance of the dermal component. (**C**) This lesion demonstrates a nodular growth pattern and dense cellularity at its base, attributes suggesting some risk for an aggressive tumor. (**D**) Markedly atypical compound Spitz tumor. This lesion demonstrates a diffuse infiltration of the dermis without any maturation and pronounced pleomorphism of melanocytes.

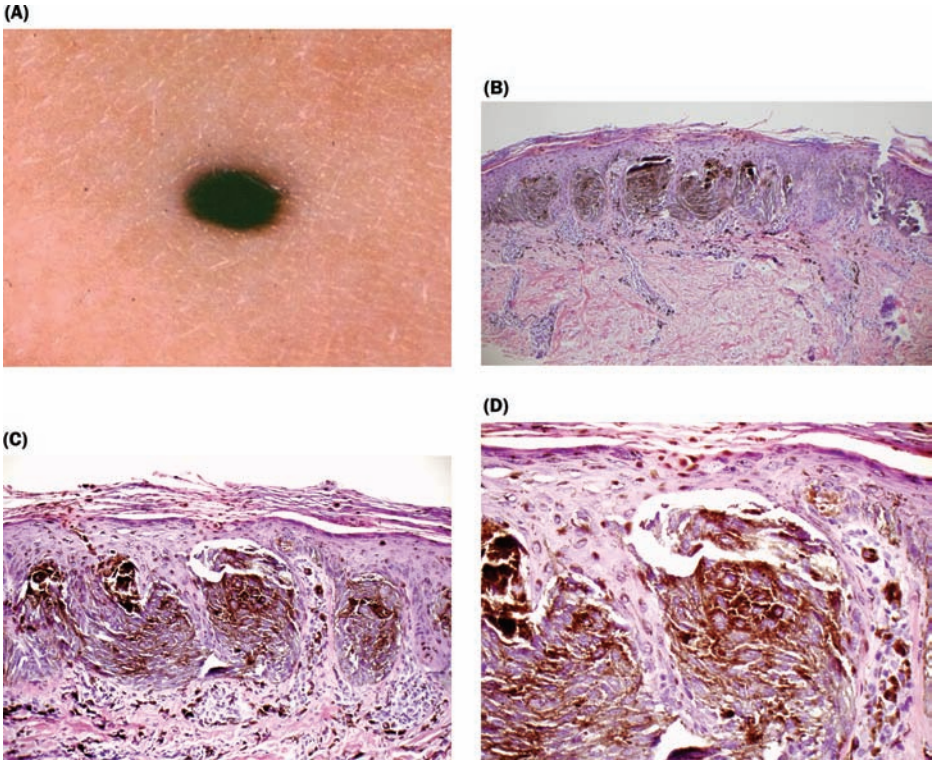

Figure 11 (**A**) Pigmented spindle cell melanocytic tumor. The lesion is small with regular well-defined borders and uniform brown-black color. The tumor also demonstrates a slightly elevated plaque-type topography. (**B**) Pigmented spindle cell melanocytic tumor. Histologically the tumor is a uniform well-circumscribed plaque comprised of hyperplastic epidermis and the junctional aggregates of pigmented spindled melanocytes. (**C**) Intraepidermal nests and vertically-oriented fascicles of spindle cells are regularly and unobstrusively arrayed within the fabric of the epidermis. (**D**) The spindle cells are uniform with delicate basophilic chromatin.

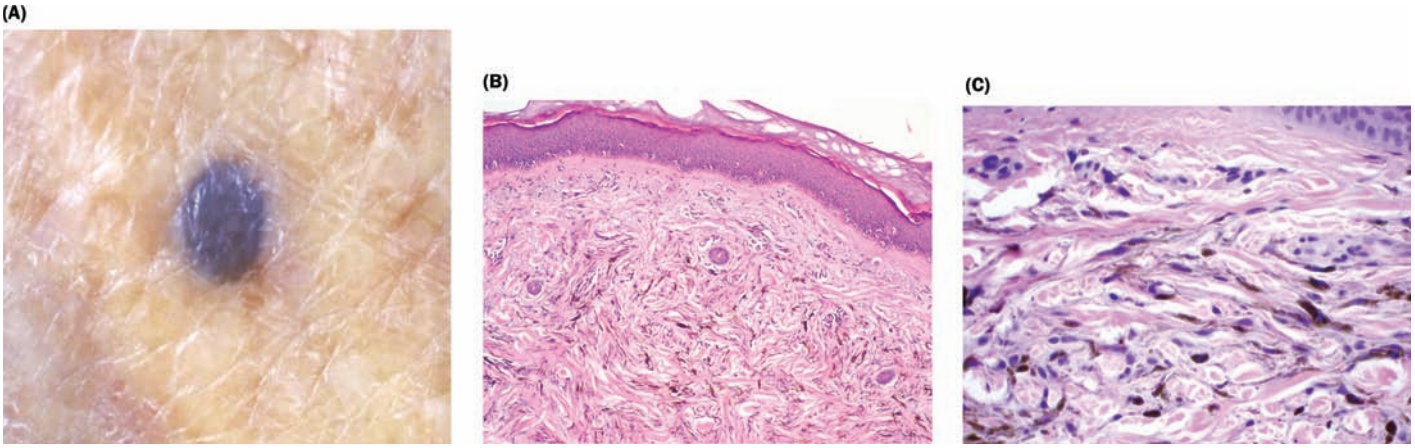

Figure 12 (**A**) Common blue nevus. Note small diameter, striking symmetry, regular and sharply-defined borders, and blue-black coloration. (**B**) Common blue nevus. The lesion exhibits a dermal fibrotic nodule containing dendritic melanocytes and melanophages. (**C**) Higher magnification showing dendritic melanocytes with small uniform nuclei.

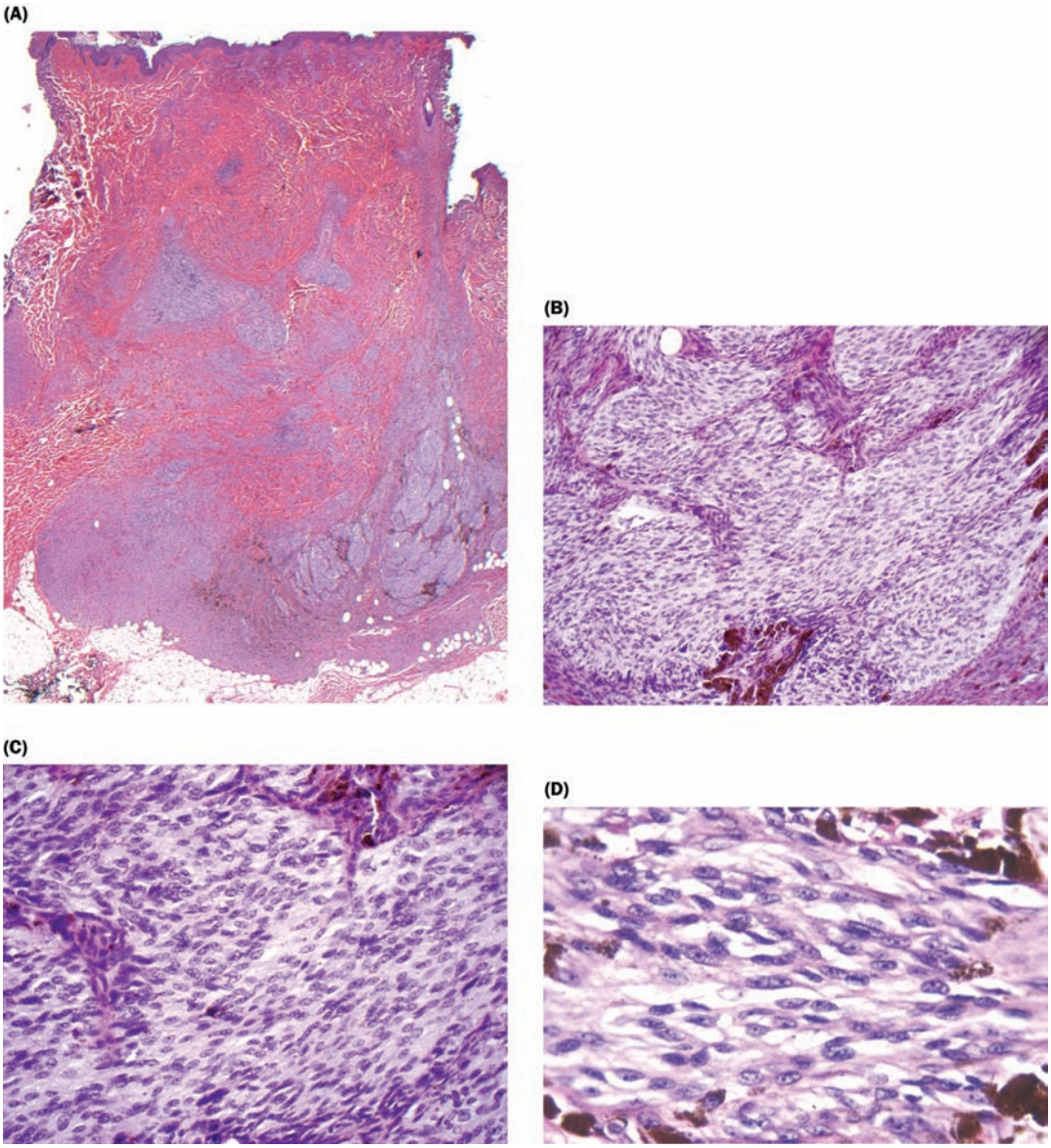

Figure 13 (**A**) Cellular blue nevus. There is a "biphasic" pattern as evidenced by a "common blue nevus" zone superficially giving place to a deeper lobular "cellular" component, which extends into subcutaneous fat. (**B**) The pale-staining lobular component is composed of bundles of generally amelanotic spindle cells. (**C**) Higher magnification showing spindled melanocytes in amelanotic cellular component. (**D**) The spindle cells have eosinophilic to vacuolated cytoplasms and relatively uniform nuclei.

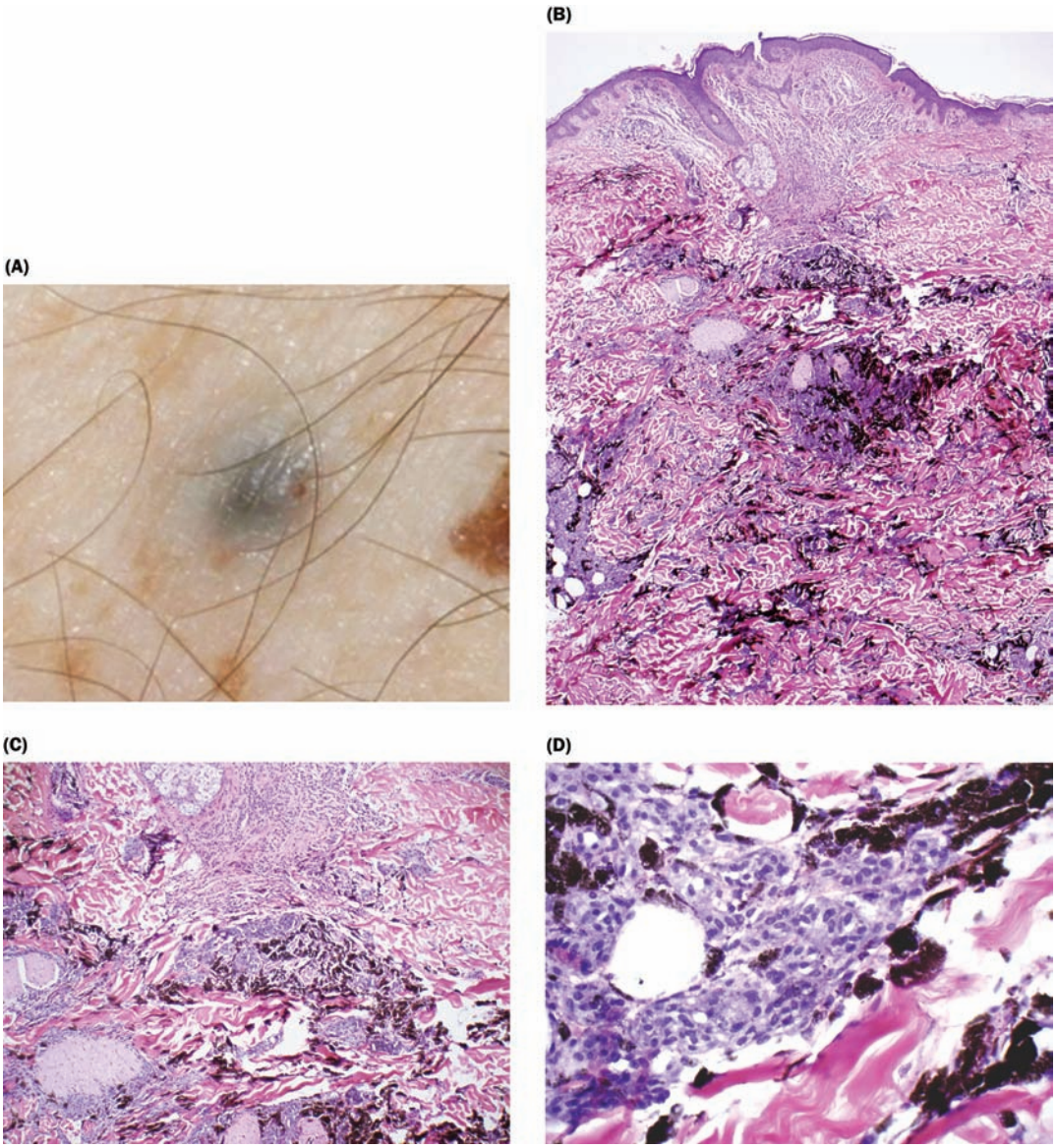

Figure 14 (**A**) Melanocytic nevus with phenotypic heterogeneity (combined nevus). The lesion has bluish color suggesting a blue nevus. (**B**) A conventional dermal nevus is present superficially and gives place to a plexiform pigmented spindle cell component present in the superficial and deep dermis. (**C**) Higher magnification shows transition from dermal nevus to pigmented spindle cell component. (**D**) The latter component is comprised pigmented spindle cells in confluent bundles. The melanocytes display some nuclear enlargement and pleomorphism.

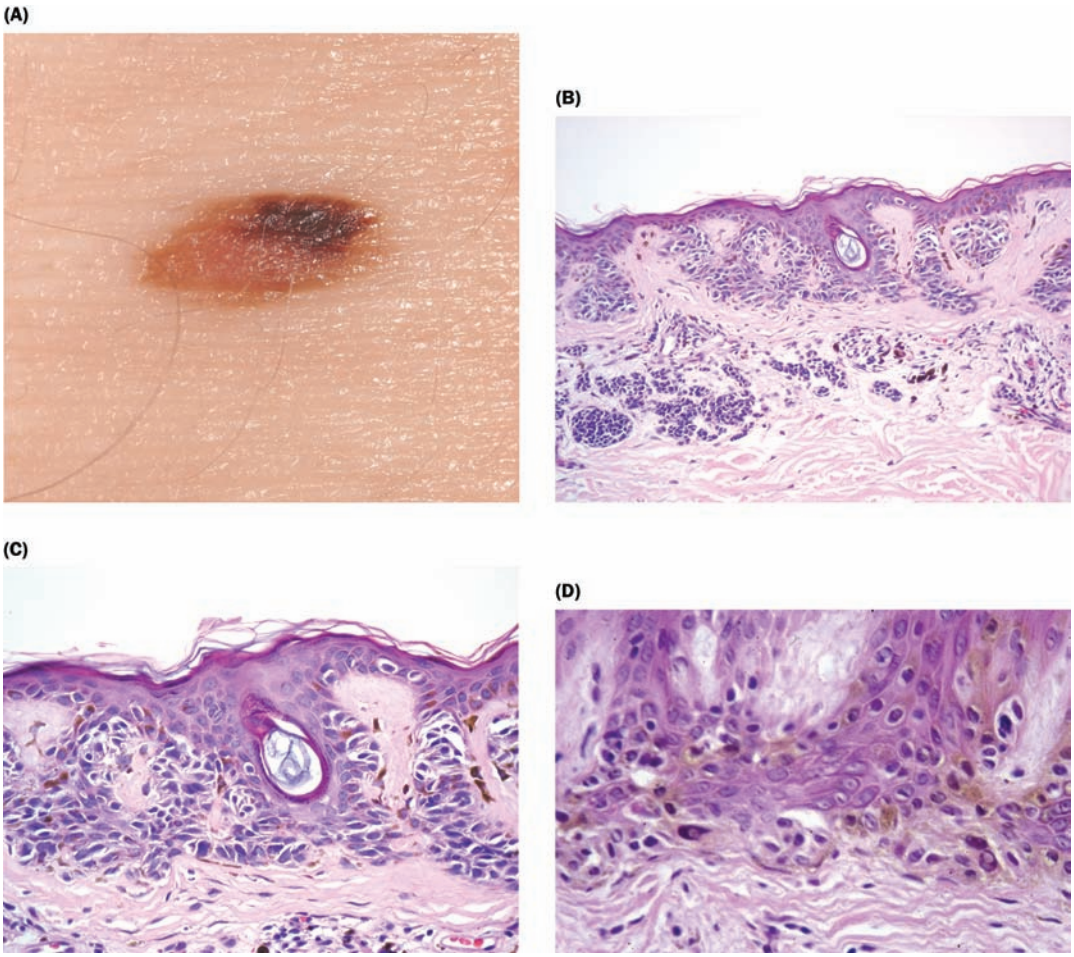

Figure 15 (**A**) Atypical melanocytic nevus. Note asymmetry, slightly irregular borders, and complex coloration with admixture of tan, brown, pink, red, and dark brown. (**B**) Compound nevus with architectural disorder and cytological atypia. The nevus displays irregular patterns of nesting, lentiginous (basilar single-cell) melanocytic proliferation, and variable cytological atypia of intraepidermal melanocytes. (**C**) Compound nevus with architectural disorder and cytological atypia. The intraepidermal melanocytes show confluence along the basal layer. (**D**) The melanocytes striking exhibit nuclear enlargement, nuclear pleomorphism, and some hyperchromatism.

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Malignant Melanocytic Neoplasms

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CONTENTS

Melanocytic neoplasms constitute a spectrum of benign and malignant skin tumors that have distinct clinical, morphological, and molecular genetic profiles. Melanomas are neoplasms of melanocytes that have the potential to metastasize or are on an evolutionary pathway in which the acquisition of that potential is likely. Melanomas may develop within a pre-existing benign melanocytic nevus, but the great majority develop de novo. Intermittent high dose UV radiation is the major environmental risk factor for melanoma, but genetic factors undoubtedly play an important role. Melanomas are the most important group of cutaneous malignancies because of their inherent capability for metastasis.

The most commonly affected anatomic sites are the face in both sexes, the ear, head, neck, back, and shoulders in men, and the legs in women. Melanomas begin as macules that may progress to plaques and tumors. Most begin as faintly uniform brown macules with slightly irregular borders. Over time, they enlarge as they develop variegations in pigmentation and more irregular contours. These features have been associated with the mnemonic ABCD (asymmetry, irregular border, uneven color, diameter greater than 6 mm). Eventually, all or a part of the lesion may become elevated; hence, some have advocated adding "E" to the ABCD mnemonic. Elevated lesions in the form of papules, plaques, nodules, and tumors may develop as malignant melanomas evolve. Nodules and tumors tend to ulcerate. Such ulceration is a consequence of the neoplastic process itself, rather than of external trauma. Pedunculation is a rare type of nodulation of malignant melanoma. Nodules are usually pigmented but occasionally may be devoid of pigment and are then termed amelanotic malignant melanoma. When an amelanotic melanoma ulcerates, it may resemble a pyogenic granuloma.

Classification of Melanoma:

Clark et al. (1) defined four major histogenetic types of melanoma based largely on the growth pattern of their intraepithelial portions. These include superficial spreading melanoma (SSM), nodular melanoma (NM), lentigo maligna melanoma (LMM), and acral lentiginous melanoma (ALM). This classification has been challenged on the grounds that these types of melanoma have a similar prognosis when matched for sex, thickness, and site and that many of the characteristics of each type are, in fact, secondary to the site of the neoplasm or caused by secondary changes such as solar elastosis (2). Although there is general agreement that the Clark classification has neither independent prognostic value nor diagnostic relevance, the Clark nomenclature continues to be widely used in clinical practice. It also is entrenched in the medical literature regarding melanoma and correlates with the epidemiology of the disease. The histopathologic presentations of the four major histogenetic types of melanoma are important because they characterize the important microscopic features of melanoma on the major anatomic sites involved by melanoma, for example, LMM on the head and neck region, SSM on the back and legs, and ALM on the sole and nail unit. ALM has a molecular footprint that is distinctive and suggests a pathogenetic difference from melanomas on other anatomic sites (3).

Clinical Evolution of Melanoma:

Malignant melanomas may arise de novo, that is, in apparently normal skin or in association with a pre-existing melanocytic nevus. When malignant melanomas arise de novo, they begin as a small, lightly pigmented macule that in time is characterized by asymmetry, scalloped borders, poor circumscription, and variations in color of predominantly tan to brown (Fig. 1A). Some such macular lesions become patches that are increasingly asymmetrical, poorly circumscribed, and varied in color (Fig. 1B). Other macular lesions of melanoma eventually become papular or nodular. Some other macular lesions may simply enlarge to become patches, others plaques, and still others combinations of papules or nodules upon patches or plaques (Figs. 2A–C; 3A and B). Some nodules and tumors ulcerate. Some melanomas may undergo partial or complete regression (Fig. 4). The clinical features of malignant melanomas just described apply to malignant melanomas at all anatomic sites of the skin and mucous membranes.

Malignant melanomas that develop in association with the pre-existing acquired melanocytic nevi demonstrate the characteristic features of melanoma including asymmetry, poor circumscription, and variation in color, and these features surround the small, well-circumscribed, evenly pigmented, dome-shaped pre-existing nevus (Fig. 5). Melanomas develop rarely in congenital melanocytic nevi. Clark's (dysplastic) nevi are common, and some malignant melanomas

doubtlessly do arise in association with them. Since Clark's nevi may show some or all of the clinical features that characterize malignant melanomas, changes in size, symmetry, color, or elevation may be clues to evolution of malignant melanoma in association with a Clark's nevus.

Most acquired melanocytic nevi measure less than 6 mm in diameter. Although small melanomas, that is, those less than 6 mm in diameter are being diagnosed more frequently due to increasing awareness of melanoma among physicians and the general public, most melanomas measure greater than 6 mm by the time patients consult a physician. Most melanocytic nevi, other than Clark's nevi, are usually small, symmetrical, well circumscribed, and uniform in color. Conversely, most melanomas are broad, poorly circumscribed, and multicolored.

Histologic Evolution of Melanoma:

A number of histologic features are common to melanoma in most locations and correspond to its evolution. The earliest lesions of most melanomas in situ, small macules clinically, appear microscopically as proliferations of solitary melanocytes at or slightly above the dermal–epidermal junction spaced at irregular intervals (Fig. 6). The nuclei of the melanocytes in these early neoplasms may or may not be cytologically atypical but are almost always larger than those of the non-neoplastic basal melanocytes. As lesions of the melanoma in situ evolve, melanocytes can aggregate to form nests and spread to the upper spinous, granular, and cornified layers. Poor circumscription is a characteristic feature (Fig. 7). Often single neoplastic melanocytes will be visible beyond the last nest on either side of the lesion, and some of these cells may be situated above the basal layer. Melanoma in situ typically involves follicular infundibula with melanocytes distributed in the same pattern as they are within the interadnexal epidermis (Fig. 8). The most common form of melanoma in situ evolves to feature pagetoid upward migration of melanocytes into the upper spinous, granular, and cornified layers and is termed SSM in situ by some. The melanocytes in this form of the disease have more abundant cytoplasm than in the other types, and the cytoplasm is frequently pale and finely vacuolated with or without dusty melanin. Three of the most important criteria for histologic diagnosis of malignant melanoma are breadth (more than 6 mm), asymmetry, and poor circumscription, and of these, asymmetry is by far the most important.

For practical purposes, nearly all melanomas originate in the epidermis or in mucosal epithelium. Melanoma in situ most often occurs de novo but is found above a pre-existent melanocytic nevus in about one-fifth of the cases (Fig. 9). All types of melanocytic nevi, with the exception of Spitz nevi, have been associated with melanoma in situ. Clark's nevus is the type most frequently found in association with melanoma in situ.

As any of the histogenetic types of melanoma in situ evolve, nests enlarge and become confluent with their neighbors, which can result in the formation of odd-shaped nests and dyscohesion between the epidermis and dermis. Lymphocytic infiltrates often accumulate in the papillary dermis at the same time that the nests form in melanoma in situ. The infiltrates are frequently beneath the nests and are distributed asymmetrically with respect to the rest of the neoplasm. Formation of both large nests and dense lymphocytic infiltrates seems to occur just prior to invasion of the papillary dermis (Fig. 10).

The dermal portion of melanoma has a range of histologic appearances. In most invasive melanomas, the dermal cells have an atypical nucleus and abundant cytoplasm and are arranged as single cells or nest. As the cells of an invasive malignant melanoma accumulate in the papillary dermis, nests often become compressed and may be less apparent as melanocytes take on a sheet-like or plaque-like growth pattern. The papillary-reticular dermal interface is often a barrier to expanding melanomas and can become bowed downward before melanoma cells permeate the reticular dermis. Lymphocytes are often present beneath melanoma cells in the papillary dermis but tend to become scant in cases in which the reticular dermis is involved. Other evolutionary changes may include perineural invasion, lymphatic or vascular invasion, regression, and microscopic satellites.

SUPERFICIAL SPREADING MELANOMA

Clinical Presentation:

- SSM occurs most commonly on the back and shoulders in men and on the legs or back in women.
- SSM begins as a small, brown, asymmetric macule. As it grows within the epidermis, it expands centrifugally, but it does not progress at the same rate in all directions, which results in variegation in color and more prominent asymmetry (Figs. 11A and B).
- The color may range from black to brown to blue to pink in different parts of the lesion.
- If regression occurs, the involved focus may appear gray or white (Fig. 11C).
- The lesion often reaches a diameter of more than 1 cm before invasion of the dermis occurs. When invasion occurs, there is usually an eccentrically situated papule, plaque, or nodule within the irregular patch (Fig. 11D).
- Ulceration usually does not occur unless there is a nodule or thick plaque.
- Rarely, SSM may be amelanotic presenting as an erythematous patch or plaque with irregular contours.

Histopathology:

- SSM is defined as having an intra-epidermal component that extends more than a few rete ridges beyond the dermal one and does not show features of either lentigo maligna (LM) or ALM.
- Typically, there is "buckshot" scatter of single atypical melanocytes or small nests of them (pagetoid spread) within the epidermis and epithelial structures of adnexa.
- The neoplastic melanocytes typically have abundant cytoplasm with dusty melanin pigment and vesicular nuclei with prominent nucleoli (Fig. 12).
- The cells of the invasive component are usually large and either round or polygonal (Fig. 13). A common misinterpretation of the histogenetic classification by those who would use it is to diagnose an SSM in which a nodule is present as NM.
- Regression of melanoma is manifested histologically as a zone within the epidermis (and sometimes papillary dermis) in which neoplastic melanocytes are diminished in number compared with the remainder of the lesion and accompanied by a band-like infiltrate of lymphocytes and melanophages, thickening of the papillary dermis, telangiectasias, fibrosis, and loss of the rete ridge pattern in variable proportions (Fig. 14).

NODULAR MALIGNANT MELANOMA

Clinical Presentation:

- All nodules of malignant melanoma begin as macules. The macules extend horizontally to form patches and then vertically to form papules and then nodules. The difference between a nodule of melanoma that develops in an SSM, an LMM, or an ALM and a "nodular" melanoma is that a nodular melanoma has no patch or plaque component detectable by inspection of the lesion.
- The nodules are mostly black in color with fairly uniform pigmentation (Fig. 15A).
- Nodular malignant melanomas (NMs) frequently are eroded or ulcerated by the time the patient consults a physician (Fig. 15B).
- Rarely, nodules of melanoma can be amelanotic (Fig. 15C), but close inspection may sometimes reveal flecks of pigmentation that are asymmetrically situated within the nodule.
- Another rare presentation of NM is as a polypoid lesion with a relatively broad base (Fig. 15D).
- Since the prognosis of melanomas is dependent upon thickness, NMs portend a greater risk for metastasis than other types of melanomas that are patches, plaques, papules, or some combination thereof. However, when corrected for thickness, the prognosis of all four histogenetic types of melanoma is equivalent (4).

Histopathology:

- NM appears as a large protuberant nodule that often attenuates the overlying epidermis (Fig. 16).
- Usually, there are only small foci of intra-epidermal melanoma, but by definition these do not extend laterally much beyond the dermal neoplasm (three rete ridges).
- The cytology of the dermal cells is indistinguishable from that of SSMs of similar depth.
- NMs are thought to have begun as in situ melanoma, but rapid evolution of the dermal component overtook and obscured the in situ portion.

LENTIGO MALIGNA MELANOMA

Clinical Presentation:

- LMM is an invasive melanoma that develops from a precursor lesion termed "lentigo maligna." LM usually occurs on the sun-damaged skin of the head or neck, especially over bony prominences such as the forehead, bald scalp, or malar areas.
- The initial lesion is a faint tan macule. Over time, the macule expands asymmetrically to become a patch that has irregular contours (Figs. 17A and B).
- The range of color is usually less than that occurs in SSM. Typically, the lesions are a combination of tan and brown.
- When invasion occurs, the lesion is often several centimeters in diameter. Invasion can be difficult to detect by inspection or palpation. The author has seen patients with Clark level IV lesions that presented clinically as nonindurated patches. In time, an indurated area or a plaque may develop as a sign of invasion (Fig. 17C).
- Nodules are uncommon but can develop in neglected lesions.
- Some exceptional lesions present as erythematous patches thought to be dermatitis or nonmelanoma skin cancer (Fig. 17D).

Histopathology:

- LM (better termed melanoma in situ of sun-damaged skin of the head or neck) begins as a proliferation of single melanocytes in the basal layer of the epidermis, above the dermis in which there is usually abundant elastotic material (Fig. 18). The neoplastic melanocytes most often have hyperchromatic nuclei, scant cytoplasm, and angulated shapes.
  - Melanocytic giant cells, with scalloped borders and nuclei distributed in a wreath-like configuration, are more commonly found in this setting than in truncal or acral melanomas.
  - Neoplastic melanocytes frequently extend deeply into follicular infundibula and into acrosyringia.
- Only in more fully evolved foci just before invasion are nests, pagetoid upward migration, and lymphocytic infiltrates found (Fig. 19).
- In some examples of LMM, there are only a few invasive melanocytes in the papillary dermis, usually in areas of fibrosis. It can be difficult to identify melanocytes in these subepidermal foci of fibrosis without benefit of immunoperoxidase staining with Mart-1 protein antisera (5). Because the melanocytes can be scattered singly, it would be difficult to distinguish them from fibroblasts, dermal dendroctyes, or macrophages or they may be obscured by lymphocytes and melanophages.
- The invasive component in LMM may be indistinguishable from that seen in other types of melanoma or may consist of spindled melanocytes (Fig. 20). Melanomas whose invasive components are spindled more frequently show neurotropism or exhibit desmoplasia than other subtypes.

ACRAL LENTIGINOUS MELANOMA

Clinical Presentation:

- ALMs occur most commonly on the sole of the foot. They have a predilection for the pressure bearing areas, which include the great toe, the ball, the heel, and the lateral aspect of the sole.
- The initial lesion is an asymmetric brown or black macule (Figs. 21A and B). The borders are usually not sharp. The long axis of the lesion often parallels the direction of the ridges of the volar skin markings.
- The macules will progress over time to irregular plaques. The plaques may ulcerate.
- Nodules may develop in far advanced lesions (Fig. 21C).
- Regression is quite uncommon.
- Melanoma of the nail unit is most common on the great toe, but can affect any digit.
  - The first sign is the appearance of a longitudinal streak of brown pigmentation that begins at the proximal nail fold and then extends distally to the free edge of the nail. It may not be possible to clinically distinguish between benign melanonychia and melanoma in the early evolutionary phase.

- In time, the streak will broaden and may show variegation of pigmentation. There may also be extension of melanoma in situ to involve the proximal nail fold (Hutchinson's sign) (Fig. 21D).
- Late manifestations of subungual melanoma include onycholysis, a subungual mass, and erosion through the nail plate.

Histopathology:
- ALM in situ has, in its beginnings, a basilar pattern of growth in which single melanocytes predominate (Fig. 22).
- These melanocytes are likewise typically angulated in shape and feature hyperchromatic nuclei and scant cytoplasm.
- Melanocytes with prominent branching dendrites are often present (Figs. 23 and 24). The finding of dendritic processes high in spinous layer of the epidermis of acral skin or nail bed epithelium can alert the observer to the possibility of melanoma in situ.
- Scatter of melanocytes in the upper spinous and cornified layers is generally seen in more advanced lesions which can also have nest formation, a lymphocytic infiltrate, and dermal invasion (Fig. 25).
- Spindle dermal melanoma cells, with or without neurotropism and desmoplasia, may also be seen in ALM.

DESMOPLASTIC MELANOMA

Clinical Presentation:
- Desmoplastic melanoma (DM) is a type of spindle cell melanoma that stimulates fibroplasia in the dermis.
- The incidence of DMs is not known with certainty, but they comprise only a few percent of all melanomas.
- DM may develop at many anatomic sites, but most commonly, they are situated on the head and neck region.
- These lesions usually lack pigmentation and may be mistaken for nonmelanoma skin cancers or scars (Fig. 26).
- They present as firm papules, plaques, or nodules.
- Although usually asymptomatic, those that are neutropic can present with localized pain or anesthesia.

Histopathology:
- Proliferation of typical and atypical melanocytes is commonly associated with fibroplasia as in lamellar fibroplasia, concentric fibroplasia, fibrosing types of blue nevi, and in desmoplastic Spitz's nevi and malignant melanomas.
- DMs most often develop on the head or neck.
- They show features of melanoma in situ of the LM type in approximately half of cases.
- Characteristically, the tumors are invasive into the reticular dermis or subcutis at presentation (Fig. 27).
- The atypical melanocytes in the dermis usually have a spindle shape. It is often difficult to differentiate between atypical spindle-shaped melanocytes of malignant melanoma and large, plump fibroblasts of the desmoplastic component. The melanocytes often are randomly arranged among the thickened collagen bundles, but sometimes the cells are in parallel array forming fascicles.
- The spindle cells often extend into the subcutaneous fat producing widened septa.
- Large melanocytes with atypical nuclei and prominent nucleoli are usually detectable but sometimes the neoplastic melanocytes have only mild nuclear atypia.
- Although the majority of DMs are amelanotic, the finding of numerous melanophages among the thickened collagen bundles of the reticular dermis is sometimes a clue to search for atypical melanocytes. A more frequent clue is the presence of nodules of lymphocytes and plasma cells at the deep aspect of the lesion.
- Neurotropism is a frequent occurrence. The atypical spindle-shaped melanoma cells wrap around nerve bundles and may extend into the nerve sheath causing thickening of the nerves (Fig. 27D). Sometimes the melanoma cells may form fascicles resembling nerves, which are termed neural differentiation.
- Immunohistochemistry is often necessary to establish the diagnosis and to differentiate DMs from spindle-cell desmoplastic squamous cell carcinoma and atypical fibroxanthoma. S-100 protein is consistently demonstrable in the atypical melanocytes. Mart-1 (Melan-A) and HMB-45 are frequently not detectable and therefore are not reliable markers.

NEVOID MELANOMA

Definition:
The term nevoid melanoma has been used to describe papular, predominantly intradermal proliferations of deceptively banal-appearing atypical melanocytes that are small and fairly symmetric thus resembling the architecture of a benign nevus. The concept is in evolution and is not universally accepted. Nevoid melanomas are rare and often are diagnosed retrospectively after metastases have occurred. It is likely that many so-called nevoid melanomas represent early NMs (6). Others are made up of large epithelioid melanocytes that resemble the cells of a Spitz's nevus. Since only a minority of such lesions actually behave in a malignant fashion, it is likely that many such lesions actually are Spitz's nevi that have been misdiagnosed.

Clinical Presentation:
- Nevoid melanomas are dome-shaped papules that vary from the size of ordinary acquired nevi, that is, less than 6 mm, to the size of Spitz's nevi, which can range up to 1 cm in diameter.
- They generally are symmetric and have even rather than scalloped borders and fairly uniform pigmentation.
- The color usually is a shade of brown from tan to dark brown (Fig. 28).
- Most have a smooth surface but some are papillated.
- Some such lesions are removed primarily because the patient noted growth in a mole.

Histopathology:
- Nevoid melanomas usually show a symmetric silhouette (Fig. 29).
- The diameter of a standard low-power field is about 5 mm, and therefore, most of the lesion, if not all of it, often fits in one field.
- Features of melanoma in situ are not present. In fact, the junctional component is minimal or undetectable.

- Within the dermis is a proliferation of atypical melanocytes in sheets or as nests that tend to be confluent.
- The melanocytes usually are not blatantly atypical but there is no tendency for them to decrease in size with increasing depth in the dermis.
- The nests also may remain large at the base of the lesion.
- Mitotic figures and apoptotic cells are usually found.
- Large cohesive nests of melanocytes in the deep aspect of the lesion and melanogenesis in the deep portion and lymphocytes at the base of the lesion are clues that should alert the microscopist to the possibility of nevoid melanoma (Fig. 29C). Sometimes, the cells may resemble the cells of a Spitz's nevus but fail to demonstrate maturation in the deep portion of the lesion.
- Immunohistochemistry may be helpful in differentiating these tumors from benign nevi.
  - Staining for HMB-45 is helpful for gaging maturation (Fig. 29D). Dermal nevus cells other than those in blue nevi usually do not label for HMB-45. However, immature melanocytes and melanoma cells often do label. A symmetrical labeling of dermal melanocytes is also a finding in some nevoid melanomas.
  - MIB-1 (Ki-67) may also be helpful, especially if mitoses are not found. This proliferation is not usually detectable in the nuclei of benign melanocytes. If more than a few percent of melanocytes within the dermis label for MIB-1, melanoma should be suspected (Fig. 29E).
- Small cutaneous metastases of melanoma may be confused with primary nevoid melanoma since they, too, may be symmetric, lack involvement of the epidermis, show confluence of atypical melanocytes arranged as nests or as sheets in the dermis, and lack signs of maturation. If melanoma cells are found in endothelium-lined spaces or if the patient has a past history of melanoma, the lesion most likely is a metastasis.

METASTATIC MELANOMA

Clinical Presentation:

Local metastases of malignant melanoma include microsatellites, macrosatellites, and in-transit lesions.

- Microsatellites are not clinically apparent. They are discrete tumor nests greater than 0.05 mm in diameter that are separated from the main body of the tumor by normal reticular dermis or subcutaneous adipose tissue.
- The macrosatellites and in-transit lesions present clinically as papules close to the primary melanoma (macrosatellites) or between the regional lymph nodes (in-transit metastases) (Fig. 30). They usually are black or bluish in color, but sometimes are amelanotic, particularly if they are situated in the subcutaneous fat.
- Distant cutaneous metastases have the same clinical appearance as local metastases.

Histopathology:

- Satellite metastases can be identified microscopically by the presence of an aggregation of atypical melanocytes that is separated from the primary malignant melanoma by a zone of normal dermis or subcutaneous fat (Fig. 31).
  - The cells of a single lesion of metastatic melanoma are generally of a single cytologic type.
  - Usually, the neoplastic melanocytes are arranged as discrete nests, but sometimes they are interposed between collagen bundles in starburst configuration in the reticular dermis.
  - In some instances, atypical melanocytes can be demonstrated within the lumina of endothelium-lined spaces, that is, lymphatics or blood vessels.
  - Satellite metastasis may regress completely, leaving melanophages in the reticular dermis as residua.
- Distant cutaneous metastases of malignant melanoma show the same histopathologic features (Fig. 32).
- Most cutaneous metastases of malignant melanomas do not involve the epidermis; however, some metastases show epidermotropism of atypical melanocytes (Fig. 33).
  - Whereas most cutaneous metastases involve the reticular dermis, epidermotropic metastases usually involve the papillary dermis.
  - The combination of atypical melanocytes proliferating within the epidermis and papillary dermis simulates primary malignant melanoma. Features that can aid in the differentiation of epidermotropic metastases from primary melanomas include:
    - Small size, sometimes 3 mm or less
    - Atypical melanocytes within intradermal endothelium-lined spaces
    - Elongation of inwardly turned rete ridges (collarettes) at the periphery of the specimen, and
    - A zone of atypical melanocytes within the dermis broader than that within the epidermis.

Clinicopathologic Correlation:

The most important architectural criteria for histopathologic diagnosis of malignant melanoma are breadth (more than one standard 40× field in diameter), asymmetry, and poor circumscription, and of these, asymmetry is the most important. These microscopic features are reflected clinically in the diameter of malignant melanomas that is greater than that of acquired melanocytic nevi, the asymmetry of melanomas compared to the symmetry of banal nevi, and poor circumscription of malignant melanoma compared to the sharp

Clinical Feature	Pathologic Feature
Broad, asymmetrical lesion, poorly circumscribed	Histologically the lesion is broad, asymmetrical, and poorly circumscribed
Variegation in color, particularly many hues of brown	Melanocytes haphazardly scattered throughout the epidermis
Whitish or ivory discoloration	Fibrosis in thickened papillary dermis
Focal whitening of lesion	Loss of melanin in the epidermis due to destruction of melanocytes and/or fibrosis
Focal blue or gray color	Abundant melanophages within a zone of fibrosis in the papillary dermis
Elevation of the melanoma in the form of plaques, papules, or nodules	Proliferation of atypical melanocytes in the papillary and reticular dermis
Ulceration	Result of proliferation of atypical melanocytes within the epidermis in confluence which may cause consumption of keratinocytes and loss of integrity of the dermoepidermal junction zone

circumscription of most acquired melanocytic nevi. Because the atypical melanocytes of malignant melanomas are haphazardly scattered throughout the epidermis, sometimes within the stratum corneum, melanomas tend to have variegation in color. In contrast, junctional and compound types of nevi have nests of melanocytes that are limited to the dermoepidermal junction and, consequently, these lesions tend to be mostly uniform in color.

Prognostic Factors:

- So long as atypical melanocytes are confined to the epidermis and epithelial structures of adnexal (melanoma in situ), the neoplasm is biologically benign, that is, there is no possibility of metastasis. When atypical melanocytes of malignant melanoma descend into the dermis, there is the potential for metastasis. There is a direct relationship between thickness of malignant melanoma, as measured by an ocular micrometer from the top of the granular layer of the epidermis to the base of the neoplasm, and potential for metastasis (7).
- Thin melanomas, that is, malignant melanomas less than 1.0 mm, rarely metastasize, whereas thicker melanomas are more prone to metastasize.
- When thin melanomas do metastasize, they usually have the following characteristics:
  - Neoplastic melanocytes in the dermis differ cytologically from those in the epidermis
  - More than one cytologic type of atypical melanocytes in the dermis
  - Nests of atypical melanocytes in the dermis tend to be relatively large
  - The aggregations of atypical melanocytes in the dermis tend to be confluent and, in doing so, form small nodules (so-called "vertical" or "tumorigenic" growth phase) (Fig. 34).
- Ulceration, defined histologically as the absence of an intact epidermis overlying a significant portion of the primary tumor, is also a powerful predictor of survival. The presence of ulceration decreases survival in all melanoma tumor thickness categories.
- Microstaging of melanoma includes the determination of thickness and ulceration. The American Academy of Dermatology has developed evidence-based guidelines of care for malignant melanoma (8). The guidelines emphasize the importance of tumor thickness and ulceration. The Clark level has been widely used to describe the extent of involvement by the tumor of cutaneous and subcutaneous structures.
  - Level I is intraepidermal growth without breach of the basement membrane
  - Level II is invasion of the papillary dermis
  - Level III is tumor filling the papillary dermis and bowing down the papillary dermis-reticular dermis interface
  - Level IV is invasion of the reticular dermis by neoplastic melanocytes, and
  - Level V is growth of neoplastic melanocytes within the subcutaneous fat.

The evidence-based guidelines of the American Academy of Dermatology state that the evidence for the Clark levels as indictors of prognosis is inconsistent. The American Joint Committee on Cancer melanoma staging system utilizes the Clark level only for subcategorizing thin melanomas less than 1 mm in thickness (9,10).

Summary of Histologic Features of Melanomas:

Architectural Pattern

Relatively broad lesion (more than one low-power field in greatest diameter)

Asymmetry

Poor circumscription

Single melanocytes predominate over nests of melanocytes in the epidermis

Nest of melanocytes variable in sizes, irregular in shapes, and tending toward confluence

"Buckshot" scatter of melanocytes throughout the epidermis

Melanocytes extending far down the epithelial structures of adnexa

Failure of maturation of melanocytes with progressive descent into the dermis

Cytological Features

Atypical melanocytes

Melanocytes in mitosis

Necrotic melanocytes

Adjunctive Clues

Signs of severe solar elastosis

Melanocytes in mitosis near the base of the neoplasm

Abundant melanin in melanocytes near the base of a neoplasm

Signs of regression of parts of the lesion, that is, fibrosis and/or marked melanosis in a thickened papillary dermis

Patchy, uneven distribution of melanin within the neoplasm

Satellite neoplastic melanocytes (a sign of local metastasis)

Melanocytes within vascular lumina

Presence of plasma cells

Presence of melanocytes with pagetoid morphology (abundant cytoplasm containing dusty melanin)

If these criteria and adjunctive clues are properly read and interpreted in satisfactory biopsy specimens, malignant melanomas may be differentiated with near certainty from melanocytic nevi of all kinds, including Spitz's nevi.

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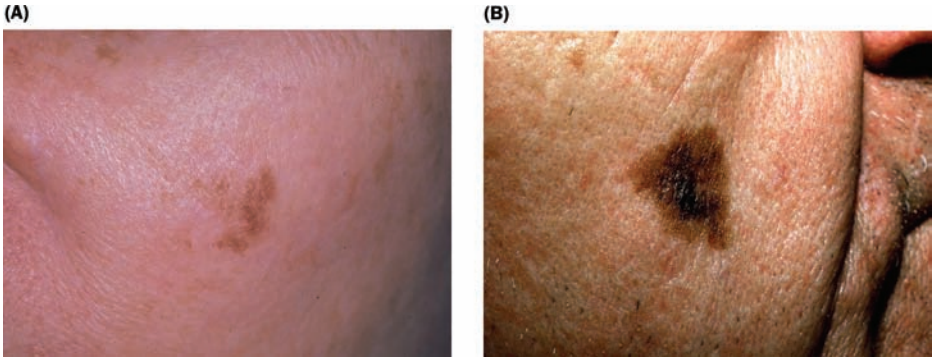

Figure 1 Melanoma in situ on chronically sun-damaged skin of the face. (**A**) This early lesion shows scalloped borders and variegated pigmentation with shades of tan and brown. (**B**) This lesion is characteristic of fully evolved melanoma in situ showing features that may be noted on any body site. The lesion is broad, asymmetric, and has irregular borders and variegated pigment.

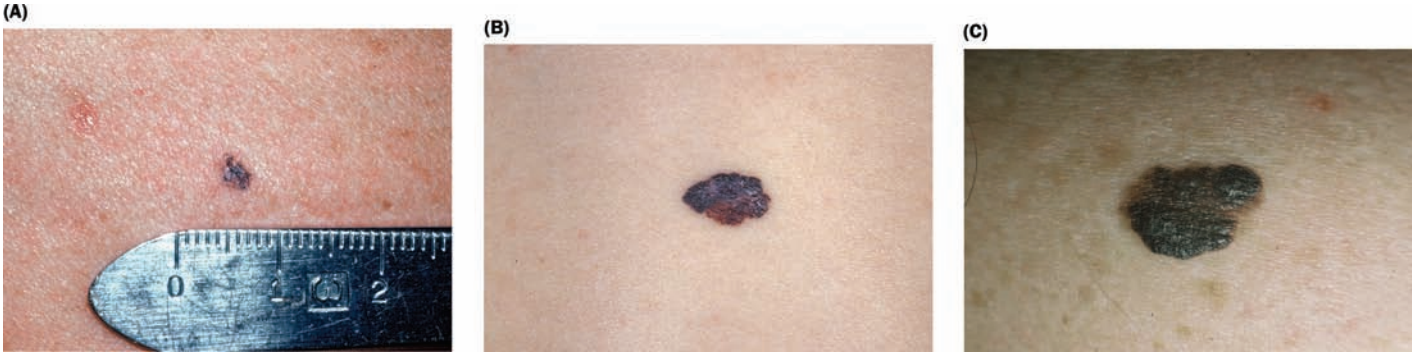

Figure 2 (**A**) Melanoma in situ on the torso. This very early lesion is only approximately 3 mm in diameter. However, even at this early stage in its development, it shows variegated pigmentation and asymmetry. (**B**) Melanoma in situ on the back. This melanoma in situ is considerably broader than the lesion in (**A**). As it has grown, it has become more asymmetric and shows scalloped borders and variegated pigmentation with hues of brown and dark brown. (**C**) Melanoma on the upper back. This melanoma is slightly elevated forming a plaque. Although it is fairly uniform in its color, it shows scalloped borders and an uneven surface contour. It also is asymmetric. The elevation implies invasion of the dermis.

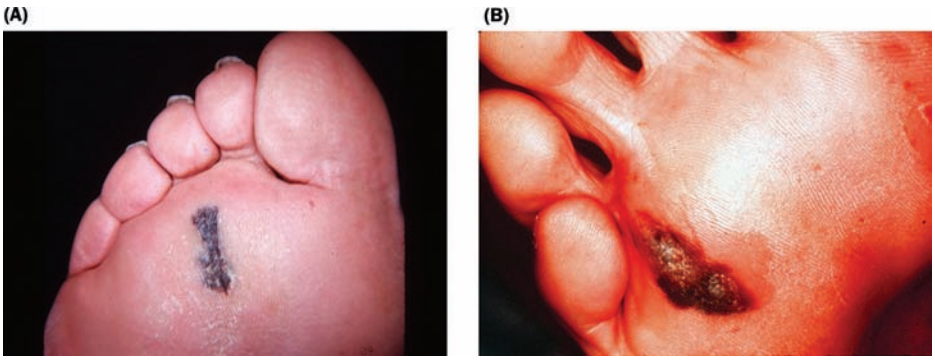

Figure 3 (**A**) Melanoma in situ on the sole of the foot. This early lesion shows all the hallmarks of melanoma in situ. It is greater than 6 mm in its largest dimension, it is irregular in shape with angulated and escalloped borders, and it has some variation in pigmentation. (**B**) Melanomas on volar skin, just as melanomas on other body sites, begin as macules that enlarge to form patches upon which papules or plaques may develop and eventually nodulation may occur if left untreated. This lesion is more advanced than the lesion shown in (**A**). It shows a papule and a small plaque developing upon the markedly irregular patch of pigmentation that is irregular in contour and asymmetric.

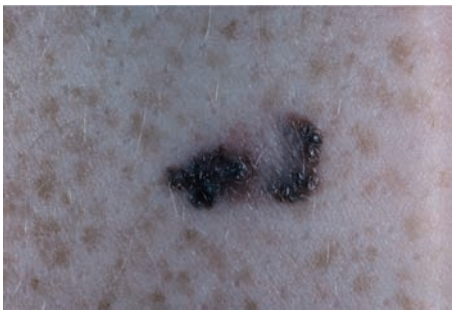

Figure 4 Melanoma on the back with focal regression. This lesion is broad and asymmetric. Even as it continues to expand in size, the host immune response has been successful in destroying a portion of the lesion resulting in focal regression. The regressed area has a grayish-white appearance.

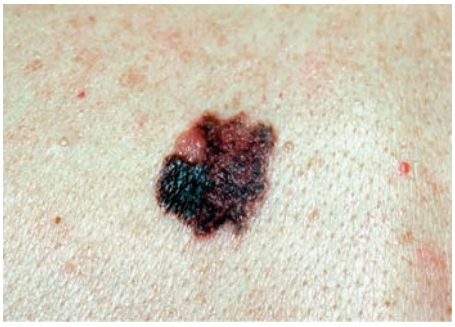

Figure 5 Malignant melanoma in situ arising in association with a pre-existing melanocytic nevus. At the left upper pole, there is a pink papule that had been present for many years. The patient noted the development of an irregular pigmented patch that developed asymmetrically in regard to the pre-existing nevus. This lesion shows all the hallmarks of melanoma in situ being broad, irregular in color, asymmetric, and with escalloped borders.

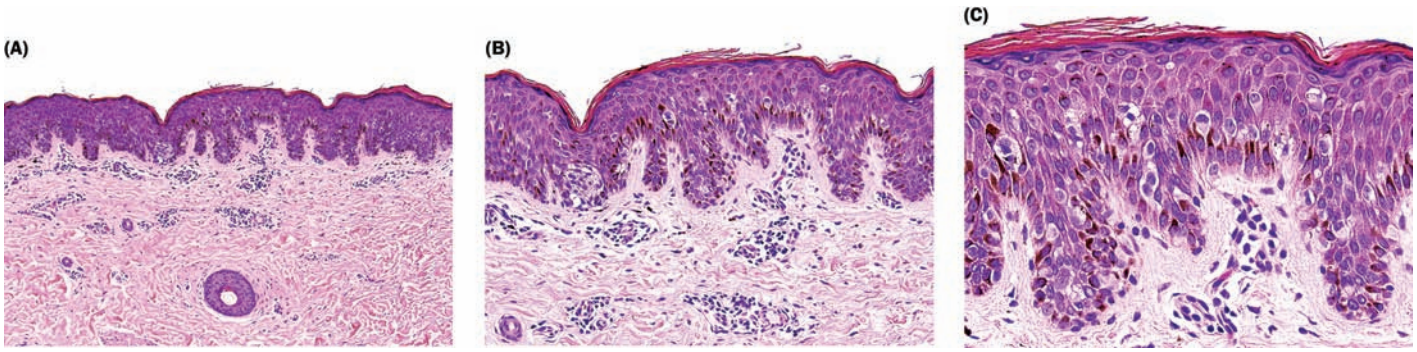

Figure 6 Early evolving melanoma in situ on skin of the trunk. (**A**) This early evolving melanoma in situ shows a proliferation of melanocytes predominantly as solitary units in the basal zone of the epidermis and slightly above it. The epidermis shows irregular acanthosis. Within the dermis is a host response of mononuclear cells. (**B**) At higher magnification, the melanocytes are easily detected. They are large, many having abundant, pale-staining cytoplasm and nuclei that are larger than the nuclei of the keratinocytes. There is an asymmetrically situated nest of similar large melanocytes at the dermoepidermal junction. (**C**) At high magnification, the large melanocytes are found mainly at the dermoepidermal junction, but many are present within the spinous layer. The cells are irregular in size, shape, and spacing. Many have hyperchromatic and pleomorphic nuclei. At this early stage in its development, no atypical melanocytes are present in the upper reaches of the epidermis.

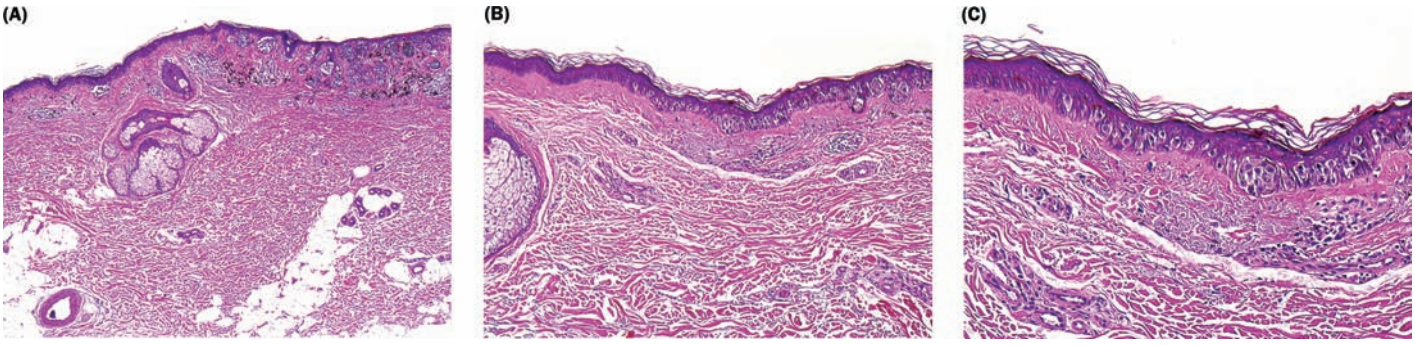

Figure 7 Melanoma in situ demonstrating poor circumscription. (**A**) At scanning magnification, the lesion is broad and demonstrates asymmetry. The melanocytes are present at the dermoepidermal junction as nests and as solitary units. Within the dermis is a host response of lymphocytes and macrophages. The edge of the lesion is to the left of center. (**B**) At higher magnification, the proliferation of melanocytes gradually diminishes near the lateral border of the lesion. (**C**) At high magnification, it is evident that melanocytes as solitary units extend laterally far beyond the last detectable nest. This is the characteristic feature of poor circumscription. In addition to the extension as solitary units, it is evident that some are above the basal layer, which is not a feature of benign melanocytic proliferations.

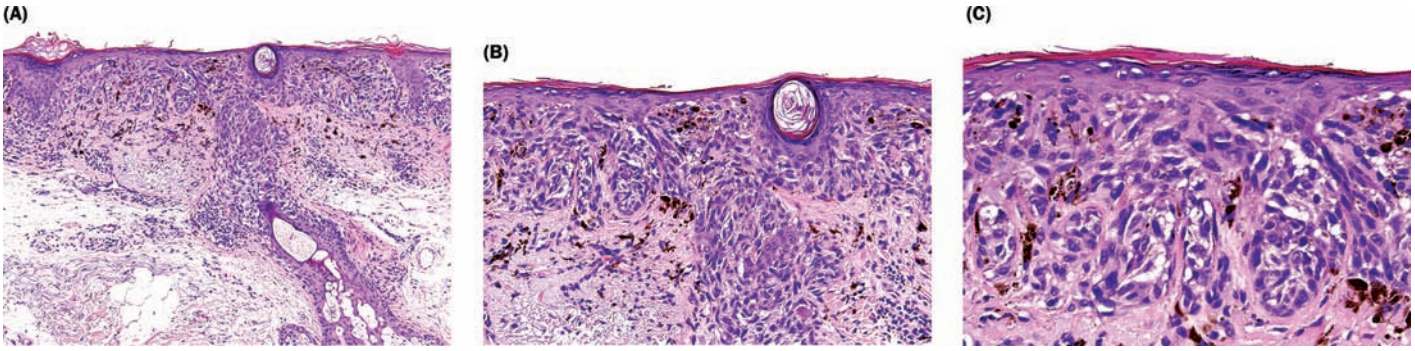

Figure 8 Melanoma in situ on chronically sun-damaged skin of the face with follicular involvement. (**A**) At low magnification, it is evident that there is a melanocytic proliferation arranged as solitary units and as nests that involves not only the surface epidermis, but also the follicular infundibulum in the middle of the field. Melanomas on every body site have a tendency to extend down epithelial structures of adnexa. This is most easily and most frequently detected in melanomas on the face because of the prominent hair follicles on the face. Melanoma may also extend down eccrine ducts. (**B**) At higher magnification, there is confluence of atypical melanocytes as nests and as solitary units in the epidermis and in the follicular infundibulum. (**C**) At higher magnification, the atypical melanocytes are easily detectable. On the sun-damaged skin of the face, the atypical melanocytes tend to be smaller than those on the trunk and have hyperchromatic, elongated, and angulated nuclei. Because of retraction artifact, they often appear to be surrounded by a cleft or halo.

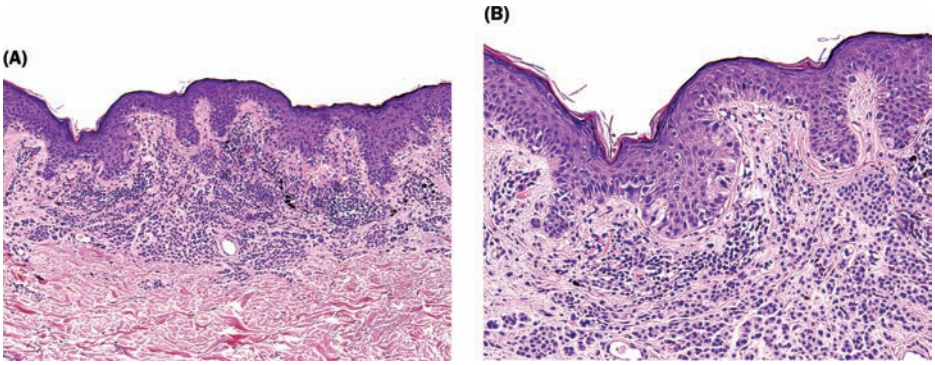

Figure 9 Melanoma in situ arising in association with a pre-existing nevus. (**A**) Within the dermis, there are orderly nests and single melanocytes that show maturation with increase in depth typical of melanocytic nevi. The epidermis shows acanthosis and a poorly-circumscribed and poorly-organized proliferation of melanocytes as solitary units predominantly. (**B**) At higher magnification, the atypical features of evolving melanoma in situ are evident. There is confluence of solitary unit melanocytes in the basal zone that show nuclear hyperchromasia and pleomorphism and there is pagetoid spread above the basal zone. On the other hand, the nevus cells within the dermis are small and uniform in size. The features of melanoma in situ arising in association with a pre-existent nevus are no different than the features of melanoma in situ that arises de novo.

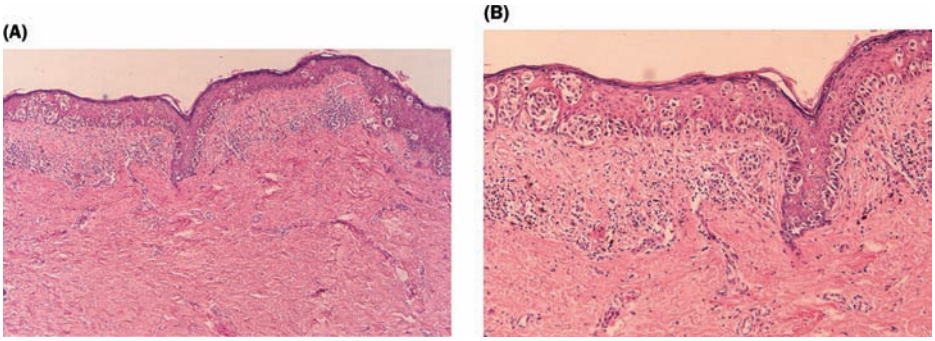

Figure 10 Early invasive melanoma on the skin of the trunk. (**A**) There are certain features that are often noted in the epidermis before invasion of the dermis occurs. In addition to melanocytes as solitary units, there are nests of atypical melanocytes and the nests are present not only at the dermoepidermal junction, but also in the middle and upper levels of the epidermis. There also is a prominent host response of lymphocytes and macrophages in the thickened papillary dermis. In this lesion, there is a nest of large atypical melanocytes just to the left of the hair follicle in the middle portion of the field. (**B**) At higher magnification, the pagetoid spread of atypical melanocytes through the full thickness of the epidermis is evident as is the transepidermal migration of nests of atypical melanocytes. Similar changes are found in the hair follicle epithelium. Within the thickened papillary dermis, there is a nest of atypical melanocytes that have the same cytologic features as those present in the epidermis.

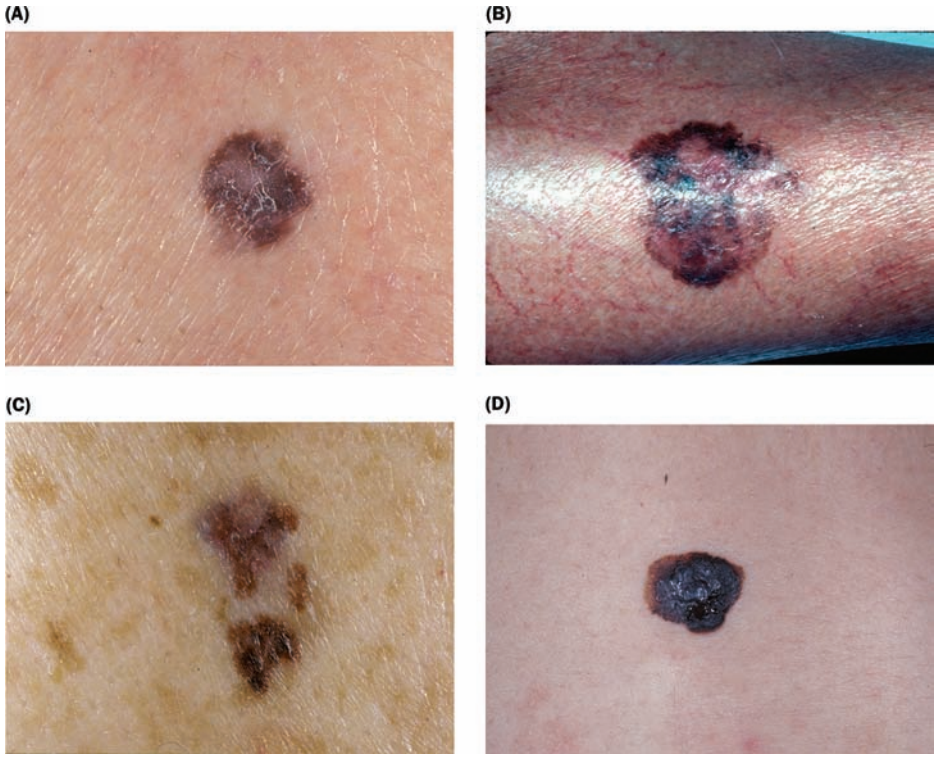

Figure 11 Superficial spreading melanoma (SSM). (**A**) This early melanoma is asymmetric, poorly circumscribed, the border is irregular, and the color varies from pink to tan to brown. (**B**) SSMs may become very broad before they invade the dermis. This lesion has areas of regression but also shows papular foci of invasive melanoma.(**C**) This melanoma shows extensive regression in the center, but continues to expand asymmetrically and has papular areas of invasion. (**D**) There is a small nodule of melanoma at the inferior pole of this mostly plaque-like melanoma.

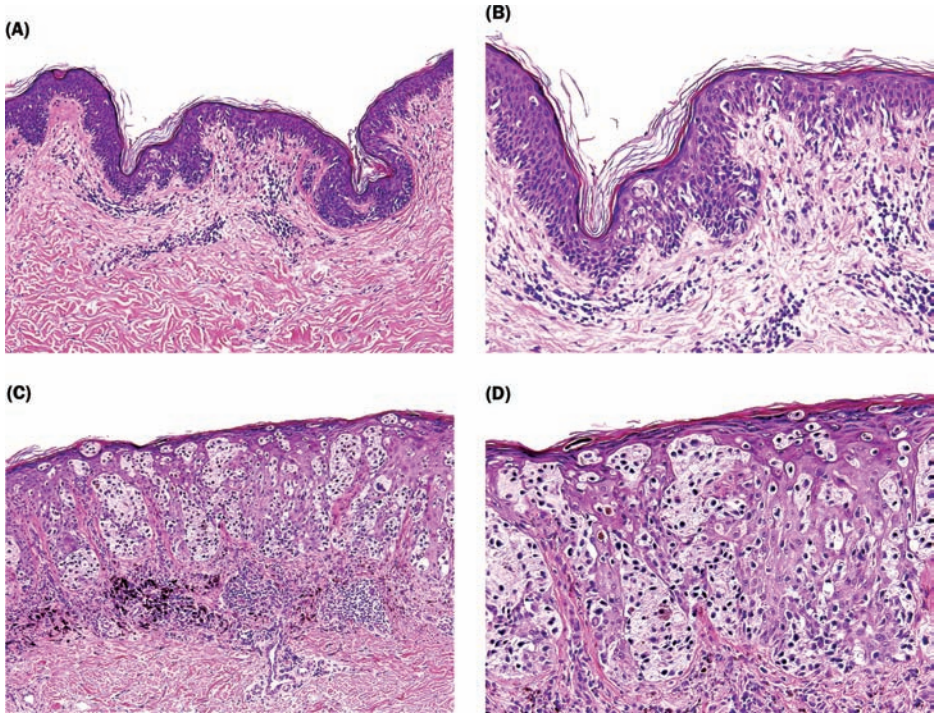

Figure 12 Superficial spreading melanoma (SSM) in situ. (**A** and **B**) Early evolving SSM in situ. There is a poorly circumscribed and asymmetric proliferation of large, pale-staining melanocytes predominantly as solitary units, but also as nests within the basal zone and at higher levels within the epidermis. (**C** and **D**) Fully evolved SSM in situ characterized by full thickness growth of large atypical melanocytes as solitary units and nests. Note the dense host response of lymphocytes in the papillary dermis.

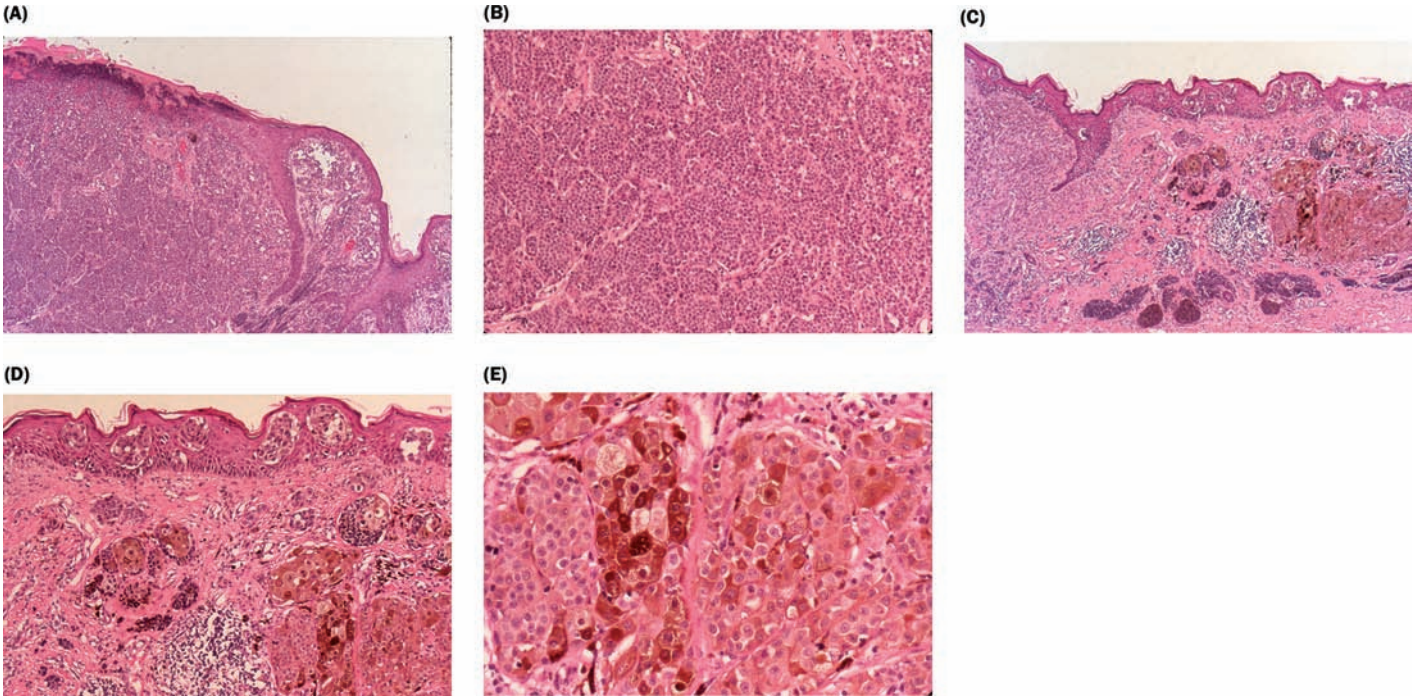

Figure 13 Superficial spreading melanoma with a nodule. (**A** and **B**) This nodule of melanoma is ulcerated. Within the dermis, there is confluence of nests of large, atypical melanocytes. There is no decrease in size of the melanocytes with increasing depth in the dermis, that is, no maturation. (**C**–**E**) Adjacent to the nodule is a plaque. The epidermis shows prototypical melanoma in situ. The dermal component consists of two different populations of atypical melanocytes. One population consists of large pale cells with dispersed dusty melanin, and the other of smaller cells with hyperchromatic nuclei and heavily pigmented cytoplasm.

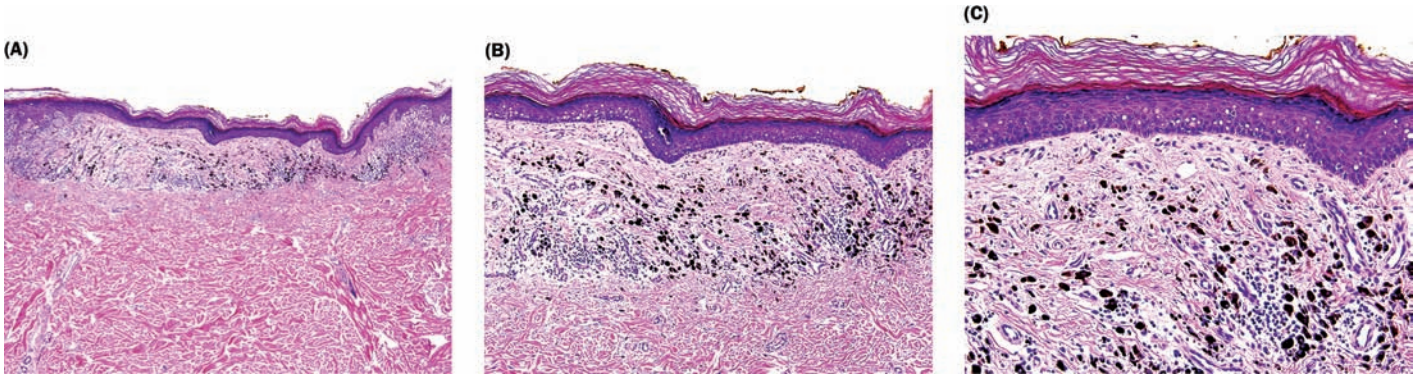

Figure 14 Superficial spreading melanoma with regression. (**A**) In the center, there is a broad focus of regression. At both sides of this zone, there is proliferation of atypical melanocytes in the epidermis and papillary dermis. (**B** and **C**) In the zone of regression, the epidermis is effaced. No melanocytes are detectable in the epidermis or dermis. The papillary dermis is expanded by fibrosis and contains myriad melanophages.

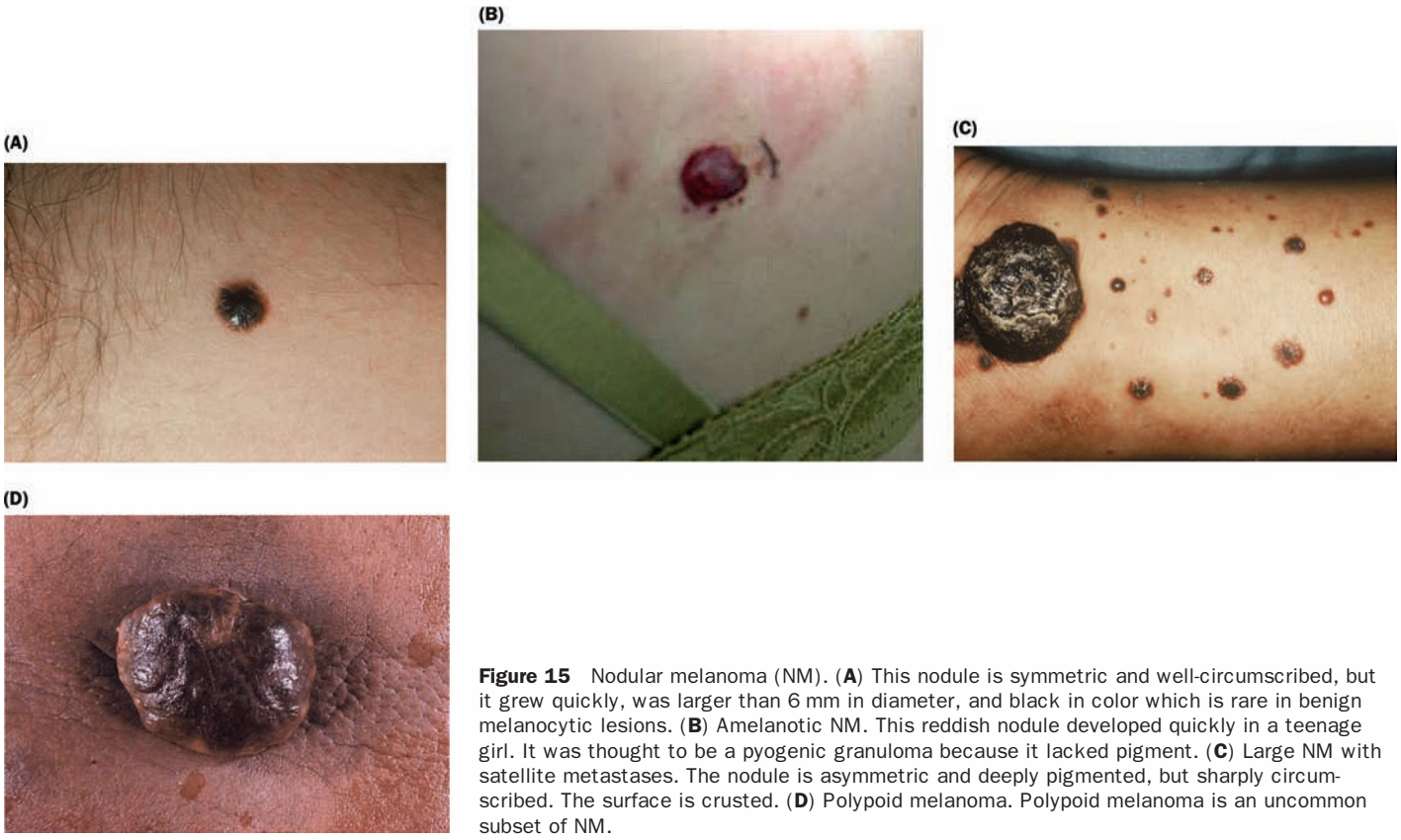

Figure 15 Nodular melanoma (NM). (**A**) This nodule is symmetric and well-circumscribed, but it grew quickly, was larger than 6 mm in diameter, and black in color which is rare in benign melanocytic lesions. (**B**) Amelanotic NM. This reddish nodule developed quickly in a teenage girl. It was thought to be a pyogenic granuloma because it lacked pigment. (**C**) Large NM with satellite metastases. The nodule is asymmetric and deeply pigmented, but sharply circumscribed. The surface is crusted. (**D**) Polypoid melanoma. Polypoid melanoma is an uncommon subset of NM.

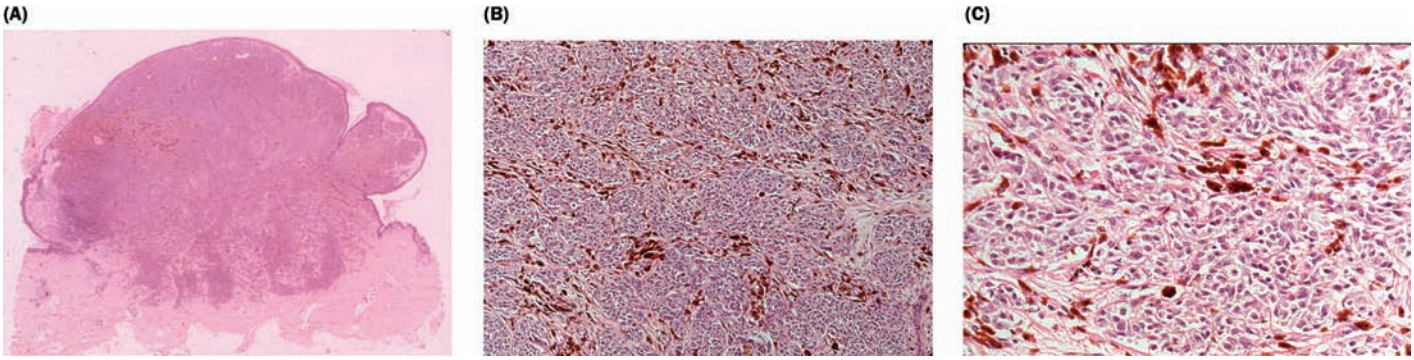

Figure 16 Nodular melanoma (NM). (**A**) At scanning magnification, the nodule is predominantly exophytic. It is asymmetric. There is no melanoma in situ in the contiguous epidermis. (**B** and **C**) The dermal component of this NM cannot be distinguished from the nodular phase of superficial spreading melanoma seen in Figure 13B. The phenotypic cells are atypical epithelioid melanocytes with pale-staining cytoplasm, which are arranged in confluent nests with no signs of maturation. Lymphocytic infiltration usually is sparse or absent.

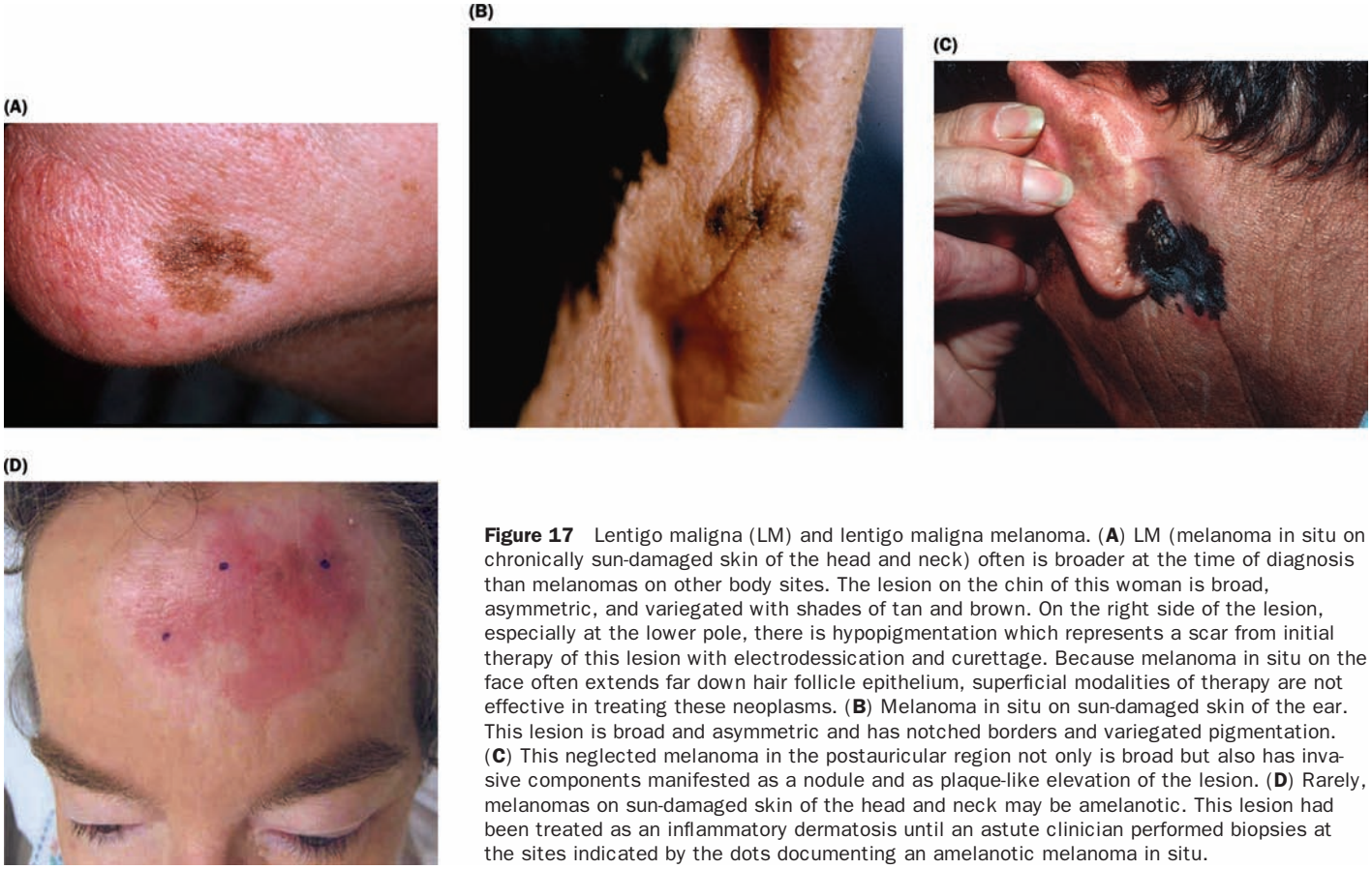

Figure 17 Lentigo maligna (LM) and lentigo maligna melanoma. (**A**) LM (melanoma in situ on chronically sun-damaged skin of the head and neck) often is broader at the time of diagnosis than melanomas on other body sites. The lesion on the chin of this woman is broad, asymmetric, and variegated with shades of tan and brown. On the right side of the lesion, especially at the lower pole, there is hypopigmentation which represents a scar from initial therapy of this lesion with electrodessication and curettage. Because melanoma in situ on the face often extends far down hair follicle epithelium, superficial modalities of therapy are not effective in treating these neoplasms. (**B**) Melanoma in situ on sun-damaged skin of the ear. This lesion is broad and asymmetric and has notched borders and variegated pigmentation. (**C**) This neglected melanoma in the postauricular region not only is broad but also has invasive components manifested as a nodule and as plaque-like elevation of the lesion. (**D**) Rarely, melanomas on sun-damaged skin of the head and neck may be amelanotic. This lesion had been treated as an inflammatory dermatosis until an astute clinician performed biopsies at the sites indicated by the dots documenting an amelanotic melanoma in situ.

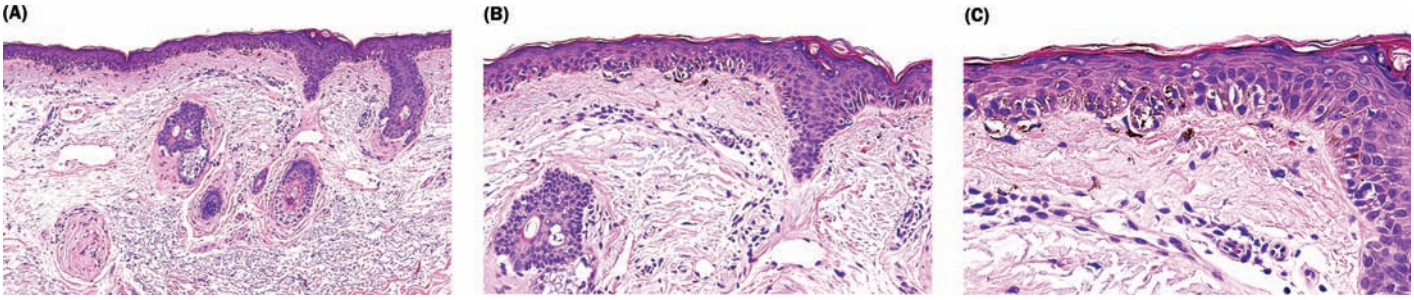

Figure 18 Lentigo maligna (melanoma in situ on chronically sun-damaged skin of the head and neck). (**A**) There is a broad and poorly circumscribed proliferation of melanocytes at the dermoepidermal junction predominantly as solitary units but also as nests. The dermis characteristically shows severe solar elastosis. (**B**) At higher magnification, the melanocytes can be seen at the dermoepidermal junction surrounded by retraction artifacts. The melanocytes are hyperchromatic and angulated. There almost always is involvement of the follicular units. There is a sparse host response of lymphocytes and macrophages around the vessels of the superficial plexus. (**C**) At higher magnification, the hyperchromasia and pleomorphism of the melanocytes is evident. Atypical melanocytes are also present in the basal zone in the vellus hair follicle at the right.

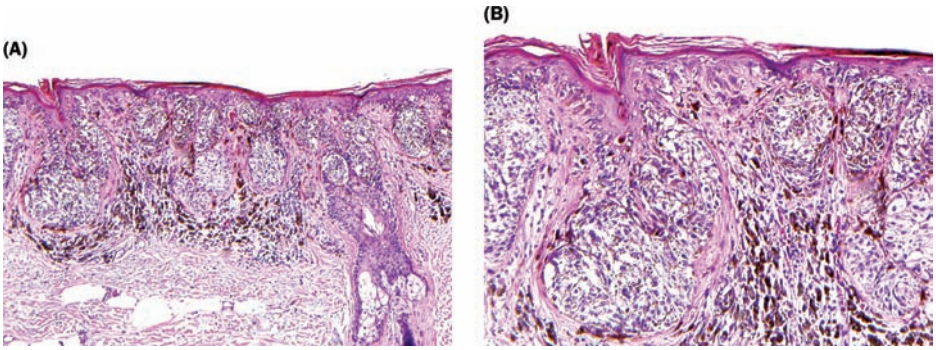

Figure 19 Fully evolved lentigo maligna (melanoma in situ on chronically sun-damaged skin of the head and neck). (**A**) Over time, there is a progressive development of nests in addition to solitary unit melanocytes at the dermoepidermal junction of the surface epidermis and the follicular epithelium. When nested up, there is almost always a more dense host response of lymphocytes and macrophages in the dermis. (**B**) Extensive replacement of the hair follicle epithelium by atypical melanocytes is evident. In addition to the involvement of dermoepidermal junction of the hair follicles and surface epidermis, there is also pagetoid spread at this phase in the development of the lesion.

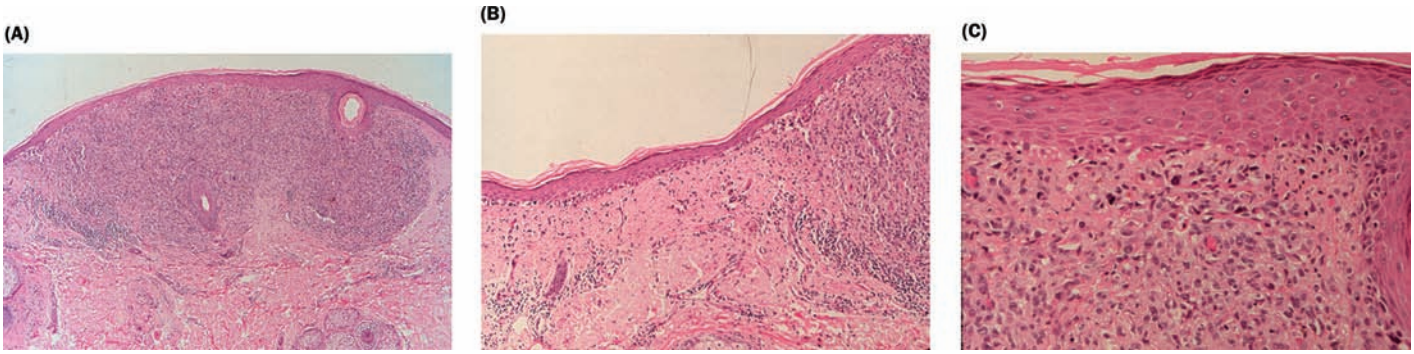

Figure 20 Lentigo maligna melanoma (malignant melanoma of the chronically sun-damaged skin of the head and neck). (**A**) At scanning magnification, there is a broad nodule with sheet-like arrangement of atypical melanocytes extending downward from the dermoepidermal junction into the underlying dermis. (**B**) Adjacent to the nodule, there is a proliferation of atypical melanocytes predominantly as solitary units at the dermoepidermal junction above solar elastosis typical of the in situ phase of melanoma on chronically sun-damaged skin of the head and neck. (**C**) This higher power photomicrograph of the summit of the nodule shows the sheet-like arrangement of relatively small but atypical melanocytes extending downward from the dermoepidermal junction into the dermis of this invasive melanoma. It is common on the head and neck region for the neoplastic melanocytes to invade the dermis in the form of a diffuse sheet rather than as nests as commonly occurs on other body sites.

Figure 21 Acral lentiginous melanoma (ALM). (**A**) ALMs are most common on the weight-bearing areas of sole. This lesion on the plantar aspect of the great toe is an example. This lesion has a uniform black color, but it is very large and has a geographic outline. Histologically, the entire lesion was confined to the epidermis and acrosyringia, that is, it was an in situ lesion. (**B**) ALM is not common on the hands but may occur. This lesion on the volar aspect of the fifth digit exhibits a breadth greater than 6 mm, asymmetry and irregular borders. (**C**) Advanced ALM. This extensive lesion involves the majority of the forefoot. It extended through the toe length to plantar aspect of the toes and the ball of the foot. This patient had extensive regional and distant metastases at the time of presentation. (**D**) ALM involving nail unit and proximal nail fold (Hutchinson's sign). Melanomas of the nail unit often begin as pigmented streaks in the nail. The streaks may become progressively broader and pigmentation may develop on the posterior nail fold. In some instances such as this example, the entire nail unit is involved.

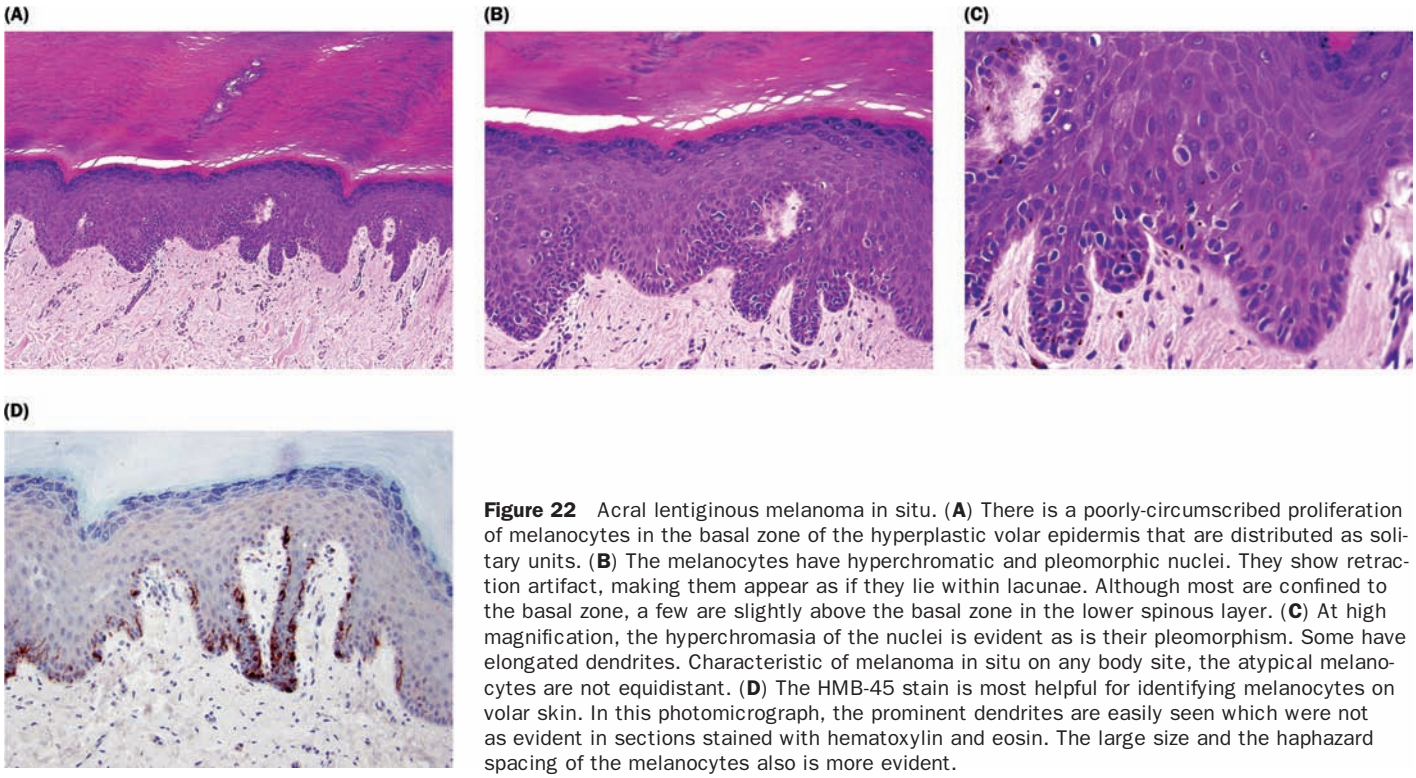

Figure 22 Acral lentiginous melanoma in situ. (**A**) There is a poorly-circumscribed proliferation of melanocytes in the basal zone of the hyperplastic volar epidermis that are distributed as solitary units. (**B**) The melanocytes have hyperchromatic and pleomorphic nuclei. They show retraction artifact, making them appear as if they lie within lacunae. Although most are confined to the basal zone, a few are slightly above the basal zone in the lower spinous layer. (**C**) At high magnification, the hyperchromasia of the nuclei is evident as is their pleomorphism. Some have elongated dendrites. Characteristic of melanoma in situ on any body site, the atypical melanocytes are not equidistant. (**D**) The HMB-45 stain is most helpful for identifying melanocytes on volar skin. In this photomicrograph, the prominent dendrites are easily seen which were not as evident in sections stained with hematoxylin and eosin. The large size and the haphazard spacing of the melanocytes also is more evident.

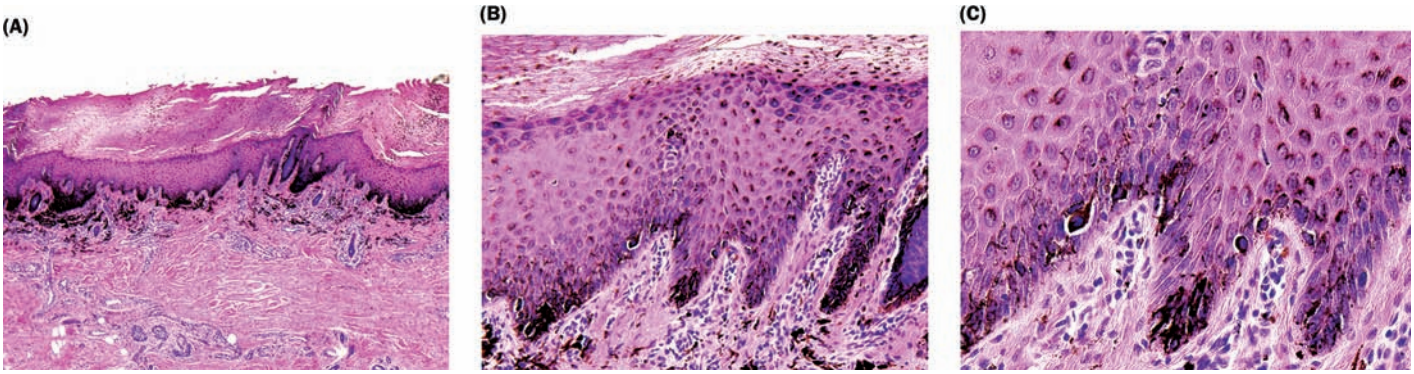

Figure 23 Acral lentiginous melanoma in situ with abundant melanin pigment. These photomicrographs show the histologic features of the melanoma in situ of the great toe clinically illustrated in Figure 21A. (**A**) The epidermis shows irregular acanthosis. There is abundant melanin pigment even in the cornified layer. It has been said that columns of pigment in the cornified layer correlate with benign lesions on volar skin, but this is an exception. (**B**) The large size of the melanocytes an the very long prominent dendrites are easily seen. (**C**) The nuclei of the melanocytes are large and hyperchromatic. The dendrites extend well above the basal layer.

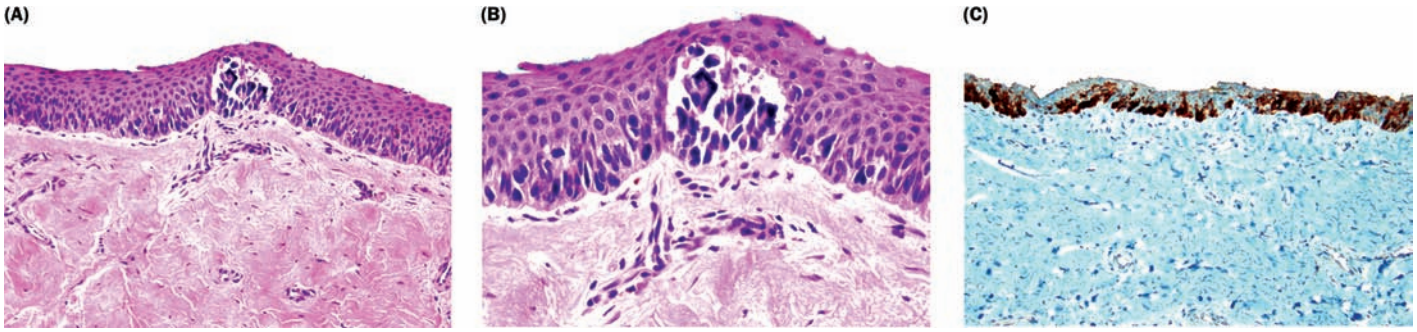

Figure 24 Acral lentiginous melanoma (ALM) in situ of a nail unit. (**A**) The atypical melanocytes in the center are arranged as a nest, but there are solitary unit melanocytes in the basal and parabasal layers of the epidermis flanking the nest. (**B**) At higher magnification, the atypical melanocytes within the basal and parabasal layer can be seen. They are hyperchromatic and have retraction artifact around them characteristic of ALM. They are similar in size and staining to the melanocytes in the nest. (**C**) Sections stained with the immunoperoxidase technique for HMB-45 show a proliferation of large melanocytes mainly as solitary units that are confluent across a broad stretch of the epidermis. Dendrites can be seen extending through the full thickness of the epidermis of the nail matrix.

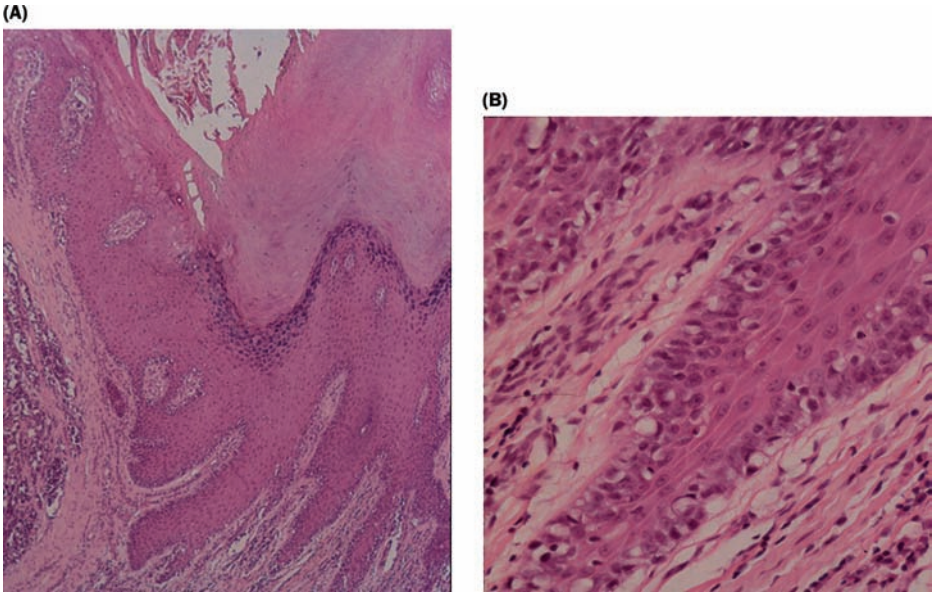

Figure 25 Invasive acral lentiginous melanoma (ALM) of the sole. (**A**) On the left-hand side of the photomicrograph is the edge of a nodule of invasive melanoma. The nodular component of ALM is not in any way different than the nodular component of melanomas on other body sites. There is confluence of nests of atypical melanocytes and they usually do not show the prominent dendrites that they do when they are in the epidermis of acral skin. On the right-hand side of the photograph, there is ALM in situ. (**B**) This is the in situ component of the invasive melanoma. The melanocytes appear to lie within lacunae due to retraction from the adjacent keratinocytes. They have hyperchromatic nuclei and prominent dendrites. Note that melanocytes are present not only along the sides of the rete, but also in the basal layer over the top of the dermal papilla. Benign melanocytic proliferations on volar skin usually do not show involvement of the basal zone over the tops of the dermal papillae.

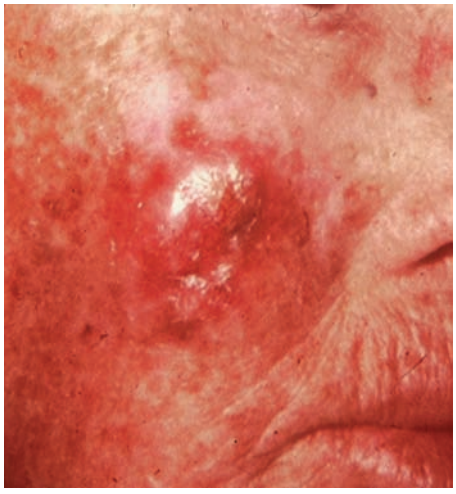

Figure 26 Desmoplastic malignant melanoma. Desmoplastic malignant melanoma is often difficult to diagnose clinically. The melanocytes usually do not produce melanin pigment, so the lesions are pink to red in color depending on their vascular supply. They are usually very firm to palpation and are poorly circumscribed.

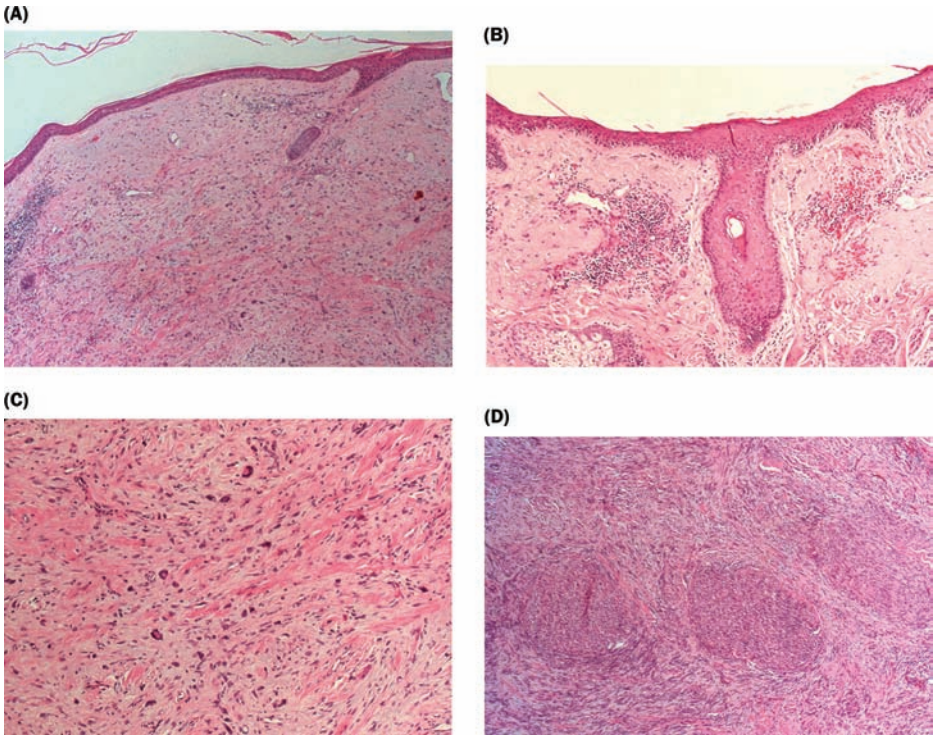

Figure 27 Desmoplastic malignant melanoma. (**A**) At scanning magnification, the lesion appears as a poorly circumscribed nodule that shows a proliferation of spindle cells within a densely collagenized stroma. At the left-hand side of the lesion is a collection of lymphocytes. Collections of lymphocytes at the sides and at the bottom of a spindle cell proliferation is a clue to the diagnosis of desmoplastic melanoma. (**B**) As many as 50% of the desmoplastic melanomas on the head and neck do not show an in situ component of melanoma. Adjacent to the nodule shown in Figure 1, there was a lentiginous junctional proliferation of small, spindle-shaped melanocytes above solar elastosis. There is a host response of mononuclear cells in the dermis. These features are consistent with an early developmental phase of lentigo maligna (melanoma in situ on chronically sun-damaged skin of the head and neck). (**C**) Higher magnification of the dermal nodule shows spindle cells in more or less parallel array among thickened collagen bundles. In this lesion, there also are multinucleated melanocytic giant cells. These are not found in desmoplastic melanomas usually and caused possible confusion with atypical fibroxanthoma in this case. Immunohistochemical staining is necessary to distinguish desmoplastic melanoma from desmoplastic spindle cell squamous cell carcinoma and atypical fibroxanthoma. Desmoplastic melanomas are positive for S-100 protein in almost all instances, whereas squamous cell carcinomas and atypical fibroxanthomas are not. (**D**) Desmoplastic melanoma often is associated with neurotropism. In this lesion, there was extensive neurotropism. The spindle cells surround the nerves and the nerves are expanded by the infiltration of spindle-shaped melanocytes.

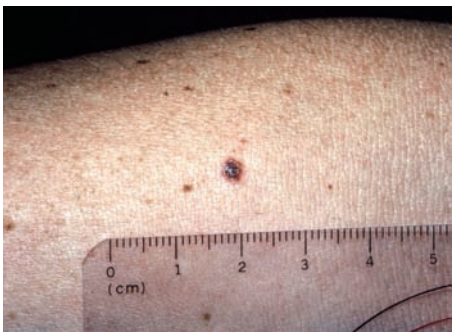

Figure 28 Nevoid melanoma. Nevoid melanomas may not be recognized clinically as melanomas because of their small size and relative uniformity. This small lesion is only approximately 3 to 4 mm in diameter. It also is relatively well circumscribed. The so-called nevoid melanomas in actuality probably represent early nodular melanomas.

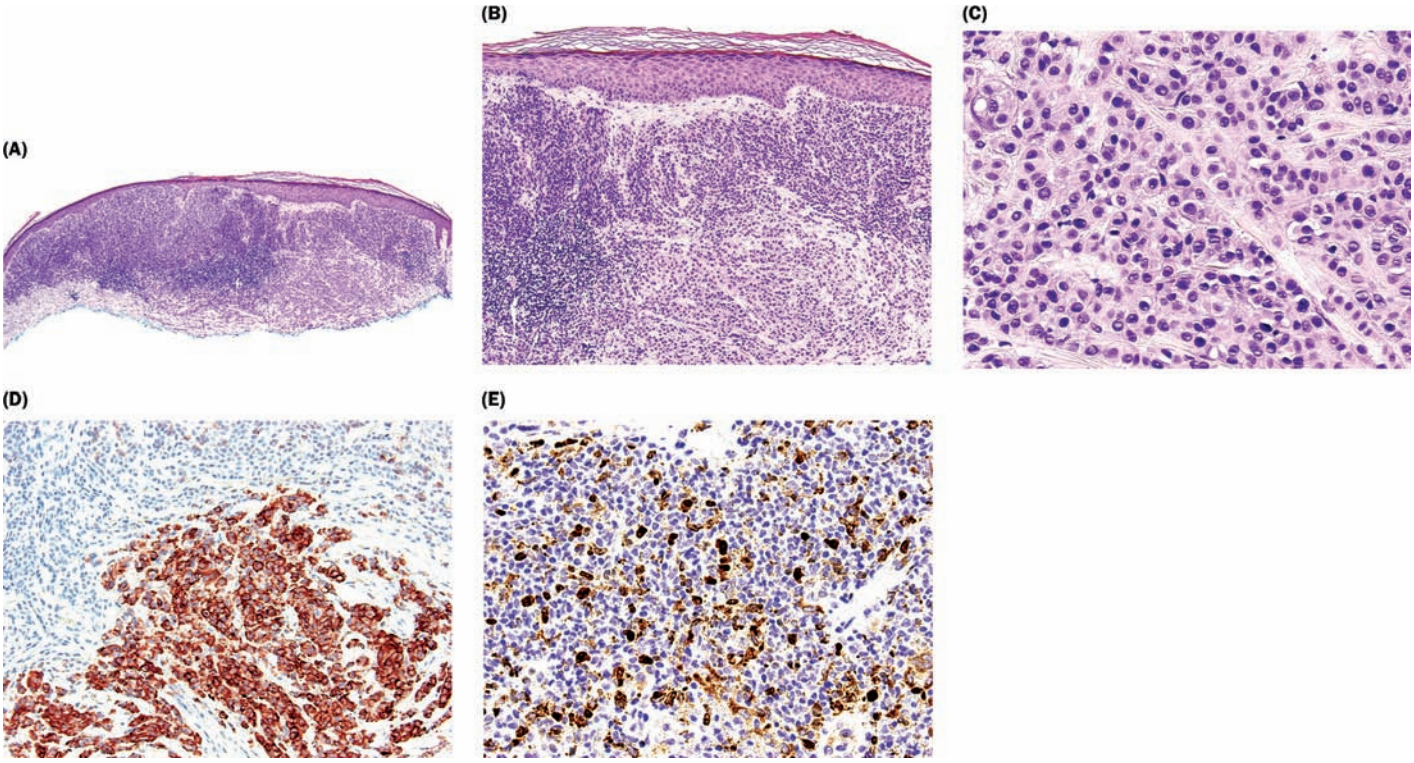

Figure 29 Nevoid melanoma. (**A**) At scanning magnification, the silhouette of this nevoid melanoma is that of a symmetric, dome-shaped papule with a smooth surface contour. In actuality, the dermal component shows asymmetry. The right half of the lesion shows a population of larger melanocytes in the middle and deep dermis, which is not evident in the remainder of the lesion. (**B**) At higher magnification, the two populations of melanocytes can be seen. The superficial population consists of small, darkly staining melanocytes resembling nevus cells and the deeper population consists of larger melanocytes having more abundant cytoplasm and larger nuclei. In melanocytic nevi, the tendency is for cells to become smaller with increase in depth, not larger as in this lesion. (**C**) At higher magnification, the cytologic detail of the large atypical melanocytes becomes evident. They have hyperchromatic and pleomorphic nuclei and they are in a disorderly arrangement. (**D**) Staining with immunoperoxidase technique for HMB-45 can be helpful in gaging maturation. In melanocytic nevi, HMB-45 may label the junctional component and sometimes the nevus cells in the most superficial aspect of the lesion that are still capable of producing melanin pigment, but the more deeply situated nevus cells do not label. In this lesion, there is strong labeling of the large atypical cells in the deep part of the lesion, but there is also labeling of many of the smaller, more nevoid-appearing cells in the upper dermis. The strong staining for HMB-45 implies an immature phenotype. (**E**) Labeling of the nuclei for MIB-1 (Ki-67) can also be helpful in determining the proliferation rate of melanocytes. In this nevoid melanoma, there is a high index of nuclear labeling which is helpful in corroborating the diagnosis.

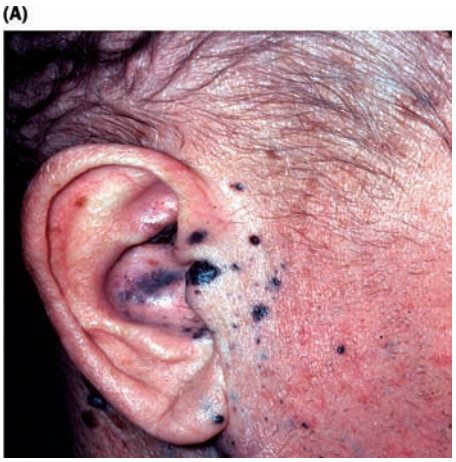

Figure 30 Metastatic malignant melanoma. This patient shows varying-sized papules of bluish-black pigmentation in the skin of the face and ear and extending onto the neck. He had a primary melanoma of the scalp.

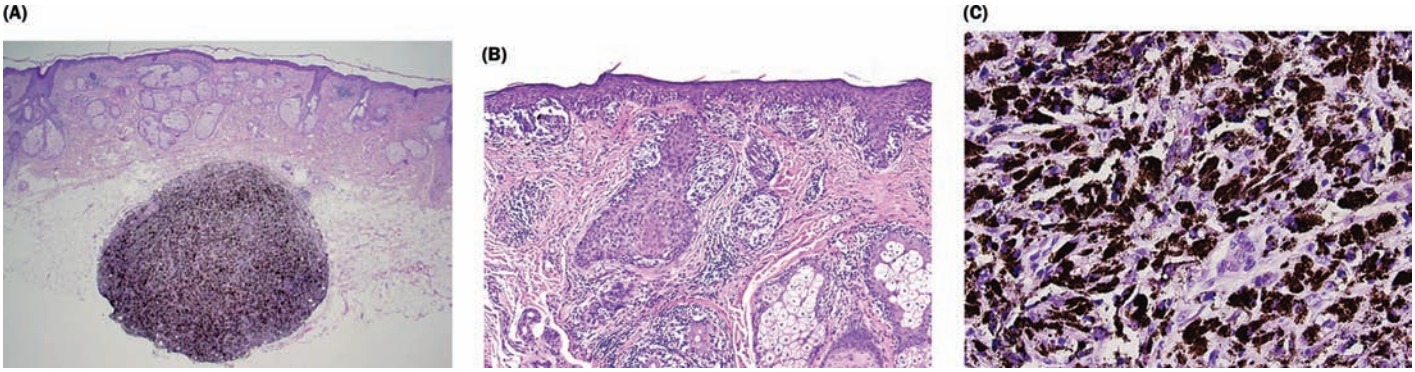

Figure 31 Microscopic satellite metastasis. (**A**) At scanning magnification, there is a nodule of melanocytes and melanophages in the subcutaneous tissue that is separated from the melanoma that is present in the epidermis and superficial dermis. (**B**) Higher magnification of the superficial aspect of this malignant melanoma shows typical features of melanoma in situ in the epidermis and pilosebaceous apparatus and invasive melanoma in the superficial dermis. (**C**) High magnification of the subcutaneous nodule shows atypical melanocytes in clusters and as single units. Within the stroma, there are innumerable melanophages containing large, coarse melanoma granules.

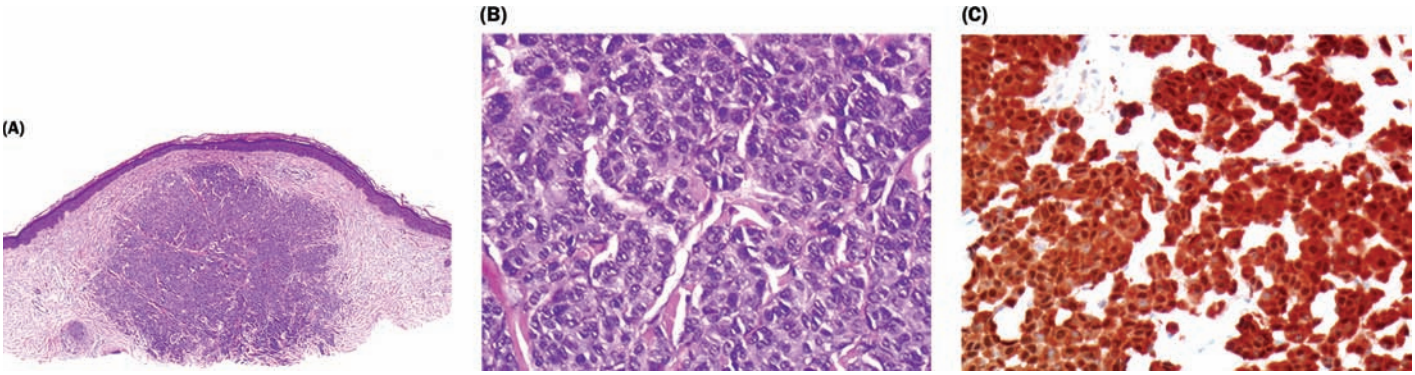

Figure 32 Melanoma metastatic to the skin. (**A**) At scanning view, there is a nodule of atypical melanocytes as nests and solitary units among collagen bundles in the reticular dermis. There is a zone of uninvolved dermis that separates the nodule from the epidermis. There is no detectable proliferation of melanocytes within the epidermis. When a nodule of melanoma is found with no in situ component, then it most likely is a metastatic lesion. As is the case in most metastatic lesions to skin, there is no host inflammatory response. (**B**) At higher magnification, the atypical nuclear features of the neoplastic melanocytes are evident. The cells are large and hyperchromatic and pleomorphic. Often mitotic figures are easily detected and apoptotic cells also are usually found. (**C**) Immunoperoxidase staining can be helpful in distinguishing metastatic melanoma from other metastatic neoplasms. In this case, antisera to Mart-1 (Melan-A) was used and showed strong labeling of the atypical cells. Mart-1 is highly sensitive and specific for melanocytes.

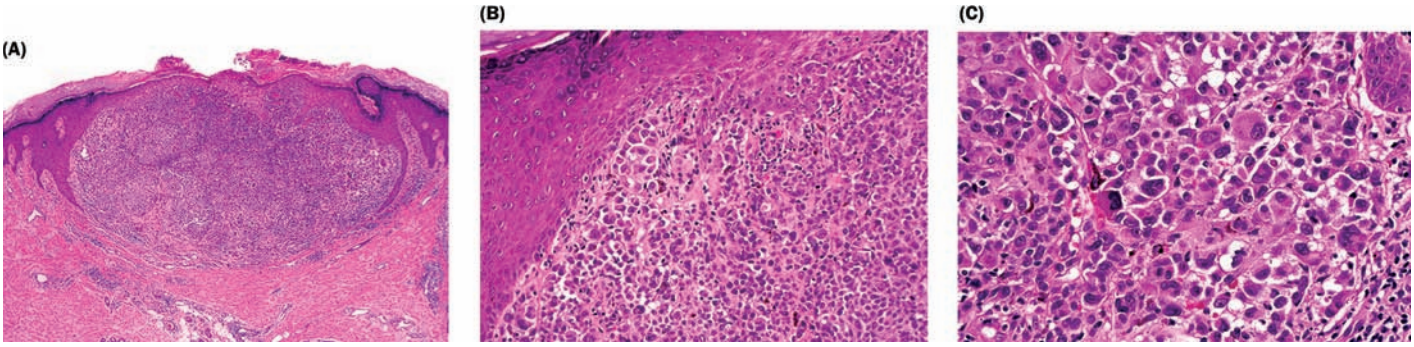

Figure 33 Epidermotropic metastatic melanoma. (**A**) In rare instances, the melanoma cells will be confined to the expanded papillary dermis instead of the reticular dermis. In such cases, the melanoma cells abut the epidermis and may actually grow into the epidermis simulating the epidermal features of a primary melanoma. However, at low magnification, the epithelial buttresses at the edges of this lesion are a helpful clue that this is a metastatic lesion. (**B**) At higher magnification, it is evident that there are melanocytes proliferating not only in the dermis, but also along the dermoepidermal junction and slightly above it. (**C**) The melanocytes have large, bizarre, hyperchromatic, and pleomorphic nuclei. Some are multinucleated and resemble Spitz's nevus cells, but the lack of maturation and the prominent pleomorphism of the melanocytes side-by-side at any level of the dermis are not features of Spitz's nevus.

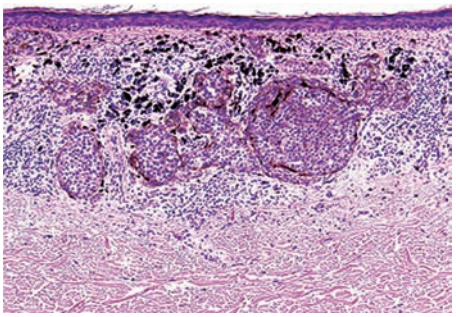

Figure 34 The so-called "tumorigenic" growth phase melanoma. Thin melanomas, less than 1 mm in thickness, rarely metastasize. When thin melanomas do metastasize, they often show small nodules in the superficial dermis. It is rare to see nests of melanocytes the size of those shown in the dermis in this figure in thin melanomas. When present, they indicate an increased risk for metastasis.

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Fibrohistiocytic Lesions

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CONTENTS

HISTIOCYTIC LESIONS

The constellation of histiocytic neoplasms of the skin encompass a wide array of lesions with diverse etiologies. The histiocyte, in the strict sense of the definition is a resident tissue macrophage responsible for phagocytosis of host and foreign material and antigen presentation. Some histiocytic neoplasms, such as xanthomas, represent true lesions comprised of tissue macrophages, which aggregate within the dermis. Others, such as dermatofibromas or fibrous histiocytoma, are classified as histiocytic tumors in a more loosely defined sense. Some entities, although previously classified as histiocytoses, are now recognized to have no relation to histiocytic cellular lineages and are, in fact, derived from entirely different origins. These tumors include atypical fibroxanthomas, dermatofibrosarcoma protuberans, fibromatosis, nodular fasciitis, soft fibroma, and pleomorphic fibroma, some of which are most likely derived from myofibroblastic cells. In this section, we intend to convey, where possible, the basic elements of the above-listed tumors with focus on the prototypic clinical and histologic characteristics.

EXAMPLES OF HISTIOCYTIC LESIONS

JUVENILE XANTHOGRANULOMA

Synonym: None.

Clinical Presentation:
- Most common non-Langerhans cell histiocytosis
- Median age of onset is two years
- Present as solitary or multiple reddish-brown or yellowish papules or nodules 1 to 2 cm in diameter (Fig. 1A)
- Four percent of patients may have systemic involvement of
  - Liver
  - Spleen
  - Lungs
  - Central nervous system
  - Eyes; may develop spontaneous hyphema
- Benign self-limited course with spontaneous gradual involution over months to years
- May resolve with scars or pigmentary alteration
- Morbidity and mortality are increased in systemic disease

Histopathology:
- Circumscribed nodular infiltrate of the papillary and reticular dermis
- Composed predominantly of histiocytes with rare lymphocytes, plasma cells, and neutrophils (Fig. 1B)
- Touton giant cells predominate in younger lesions and may be less prominent in older lesions (Fig. 1C)

Special Studies:
- Positive for factor XIIIa, CD68, CD163, CD14, and fascin
- Negative for S100 and CD1a

Immunohistochemistry:

	Immunohistochemistry				
Diagnosis	**CD68**	**CD1a**	**S100**	**FXIIIa**	**CD31**
Juvenile xanthogranuloma (JXG)	(+)	(−)	(+/−)	(+)	(+/−)
Spitz nevus	(+/−)	(−)	(+)	(−)	(−)
LCH	(+/−)	(+)	(+)	(−)	(−)
Hemangioendothelioma	(−)	(−)	(−)	(−)	(+)

Clinicopathologic Correlation:
- Rare association with neurofibromatosis type 1 and juvenile myelomonocytic leukemia

Differential Diagnosis:

Clinical	Histologic
Lipoma	**Reticulohistiocytoma**
Dermatofibroma	**Langerhans cell histiocytosis**
Xanthoma	**Hemangioendothelioma**
Reticulohistiocytoma	**Spitz nevus**
	Lipoblastoma
	Dermatofibroma

Pathophysiology:
- Likely represents a part of the spectrum of non-Langerhans cell histiocytoses including benign cephalic histiocytosis, generalized eruptive histiocytoma, and progressive nodular histiocytosis
- True etiopathogenesis is unknown

References:

1. Weitzman S, Jaffe R. Uncommon histiocytic disorders: the non-Langerhans cell histiocytoses. Pediatr Blood Cancer 2005; 45:256–264.
2. Zvulunov A, Barak Y, Metzker D. Juvenile xanthogranuloma, neurofibromatosis, and juvenile chronic myelogenous leukemia. Arch Dermatol 1995; 131:904–908.
3. Freyer DR, Kennedy R, Bostrom BC, et al. Juvenile xanthogranuloma: forms of systemic disease and their clinical implications. J Pediatr 1996; 129:227–237.
4. Janssen D, Harms D. Juvenile xanthogranuloma in childhood and adolescence: a clinicopathologic study of 129 patients from the Kiel pediatric tumor registry. Am J Surg Pathol 2005; 29:21–28.

ATYPICAL FIBROXANTHOMA

Synonym: None.

Clinical Presentation:
- Sun exposed areas of head and neck
- Older individuals, sixth to seventh decade
- Rapidly growing nodules with occasional ulceration (Fig. 2A)
- May represent a superficial, indolent form of malignant fibrous histiocytoma
  - Occasionally, may be locally aggressive
  - Rare instances of systemic and limited local skin metastasis

Histopathology:
- Spindle cell neoplasm arising in the superficial dermis (Fig. 2B)
- Dramatic pleomorphic hyperchromatic nuclei "monster cells" (Fig. 2C)
- Numerous atypical mitotic figures

Special Studies:
- Immunohistochemistry is variable and nondiagnostic
- CD68, CD99, vimentin typically positive
- Must perform immunohistochemical panel to exclude
  - Melanoma
  - Spindle squamous cell carcinoma
  - Leiomyosarcoma
  - Angiosarcoma
  - Malignant peripheral nerve sheath tumor

Immunohistochemistry:

	Immunohistochemistry					
Diagnosis	**SMA**	**S100**	**CD31**	**CD68**	**CK 5/6**	**VIM**
Atypical fibroxanthoma	**Focal (+)**	(−)	(−)	(+)	(−)	(+)
Spindle squamous cell carcinoma	(−)	(−)	(−)	(−)	(+)	(+/−)
Melanoma	(−)	(+)	(−)	(+/−)	(−)	(+)
Leiomyosarcoma	(+)	(−)	(−)	(−)	(−)	(+)
Angiosarcoma	(−)	(−)	(+)	(−)	(−)	(+)

Clinicopathologic Correlation:
- May occur in areas of prior radiation
- May occur in the setting of immunosuppression
- Reported in patients with xeroderma pigmentosa

Differential Diagnosis:

Clinical	Histologic
Squamous cell carcinoma	**Melanoma**
Basal cell carcinoma	**Malignant peripheral nerve sheath tumor**
Melanoma	**Leiomyosarcoma**
	Spindle squamous cell carcinoma
	Angiosarcoma
	Malignant granular cell tumor

Pathophysiology:
- Unknown.

References:

1. Perrett CM, Cerio R, Proby CM, Harwood CA. Atypical fibroxanthoma in a renal transplant recipient. Histopathology 2005; 47(3):326–327.
2. Diaz-Cascajo C, Weyers W, Borghi S. Pigmented atypical fibroxanthoma: a tumor that may be easily mistaken for malignant melanoma. Am J Dermatopathol 2003; 25(1):1–5.
3. Monteagudo C, Calduch L, Navarro S, Joan-Figueroa A, Llombart-Bosch A. CD99 immunoreactivity in atypical fibroxanthoma: a common feature of diagnostic value. Am J Clin Pathol 2002; 117(1):126–131.

4. Crowson AN, Carlson-Sweet K, Macinnis C, et al. Clear cell atypical fibroxanthoma:a clinicopathologic study. J Cutan Pathol 2002; 29(6):374–381.
5. Huether MJ, Zitelli JA, Brodland DG. Mohs micrographic surgery for the treatment of spindle cell tumors of the skin. J Amer Acad Dermatol 2001; 44(4):656–659.

DERMATOFIBROMA

Synonyms: Benign fibrous histiocytoma; sclerosing hemangioma.

Clinical Presentation:

- Hyperpigmented to erythematous firm nodule 0.5 to 1.0 cm in diameter (Fig. 3A)
- Lower extremity
- Female predominance
- May be preceded by history of local trauma
- Exhibit dimpling when squeezed between fingers "dimple sign"
- Benign process without malignant potential
- Local excision or cryotherapy is typically curative

Histopathology:

- Poorly circumscribed dermal proliferation of spindle cells (Fig. 3B)
- Collagen trapping at the periphery of the lesion
- Collagen bundles may become more dense and coarse (Fig. 3C)
- Mixed inflammatory infiltrates may be appreciated
- Vascular ectasia, hemorrhage, and hemosiderin may be observed
- Overlying epidermal hyperplasia and hyperpigmentation of the rete tips

Special Studies:

- Spindle cells stain positive for factor XIIIa
- No staining with CD34

Immunohistochemistry:

	Immunohistochemistry			
Diagnosis	**CD34**	**CD31**	**FXIIIa**	**S100**
Dermatofibroma	(−)	(−)	(+)	(−)
Neurofibroma	(+/−)	(−)	(−)	(+)
DFSP	(+)	(−)	(−)	(−)
Kaposi's sarcoma	(+)	(+)	(−)	(−)

Clinicopathologic Correlation

Clinical Feature	Pathologic Feature
Hyperpigmentation	**Overlying epidermal hyperplasia/hyperpigmentation**
"Dimple Sign"	**Delicate interlacing fascicles which surround and trap collagen fibrils**

- May be associated with local trauma
- Multiple eruptive dermatofibromas have been reported in systemic lupus erythematosus (SLE) and HIV infection

Differential Diagnosis:

Clinical	Histologic
Dermatomyofibroma	**Dermatomyofibroma**
Melanoma (in cases of aneurysmal DF)	**Dermatofibrosarcoma protuberans**
Leiomyoma	**Hypertrophic scar**
Arteriovenous malformation (in cases of aneurysmal DF)	**Hemangioma**
Xanthoma (in cases of heavily lipidized DF)	**Perineurioma**
Dermatofibrosarcoma protuberans	

Pathophysiology:

- Benign proliferation of dermal dendocytic cells
- Unknown whether DFs represent a true neoplastic lesion or a reactive process
- Inflammatory cells such as mast cells may play a role in pathophysiology

References:

1. Zelger B, Zelger BG, Burgdorf WH. Dermatofibroma—a critical evaluation. Int J Surg Pathol 2004; 12(4):333–344.
2. Yamamoto T, Katayama I, Nishioka K. Role of mast cells in dermatofibroma: recent viewpoints into the pathogenesis. Eur J Dermatol 2003; 13(5):419–423.
3. Niiyama S, Katsuoka K, Happle R, Hoffmann R. Multiple eruptive dermatofibromas: a review of the literature. Acta Derm Venereol 2002; 82(4):241–244.
4. McCalmont TH. Sclerotic fibroma: a fossil no longer. J Cutan Pathol 1994; 21(1):82–85.

DERMATOFIBROSARCOMA PROTUBERANS

Synonym: None.

Clinical Presentation:

- Variable depending upon stage
  - Plaque stage presents with an erythematous plaque-like dermal nodule (Fig. 4A)
  - Tumor stage presents with a large, fixed firm multinodular nonpainful tumor, which may ulcerate (Fig. 4B)
- Locally aggressive with 10% local recurrence after wide local excision
- Recurrence rate is 50% in positive margin excisions
- Rare distant metastasis associated with long-standing tumors and incomplete excision
- Moh's micrographic surgery has been applied to these lesions with improvement in recurrence rates
- Adjuvant therapies include local radiation to tumor excision sites
- New therapy imatinib mesylate
  - Monoclonal antibody designed to inhibit the function of PDGF-β tyrosine kinase

Histopathology:

- Dermal proliferation of bland monomorphic spindle cells arranged in whorled and storiform pattern (Fig. 4C)
- Significant nuclear atypia, mitoses, and necrosis are not common features
- Malignant cells dissect through subcuticular fat

- May be associated with a proliferation of melanin containing spindle cells "Bednar tumor"
- Ten to fifteen percent of dermatofibrosarcomas protuberans may have fibrosarcomatous and malignant fibrous histiocytoma-like areas

Special Studies:
- Eighty to ninety percent of tumors stain positive for CD34
- Tumors stain negative for factor XIIIa
- Loss of CD34 positivity may be associated with fibrosarcomatous changes

Immunohistochemistry:

	Immunohistochemistry			
Diagnosis	**CD34**	**FXIIIa**	**S100**	**CD68**
Dermatomyofibrosarcoma protuberans	(+)	(−)	(−)	(−)
Dermatofibroma	(−)	(+)	(−)	(+/−)
Desmoplastic melanoma	(−)	(−)	(+)	(+/−)

Clinicopathologic Correlation:

Clinical Feature	Pathologic Feature
Fixed dermal tumor nodule	**Interlacing fascicles of spindle cells dissecting and infiltrating through subjacent and surrounding tissues**
Reddish brown pigmentation	**May reflect presence of melanin within tumor**

- Isolated cases of nuchal-type fibromas, spindle cell lipomas, and breast carcinoma have been reported in association with dermatofibrosarcoma protuberans

Differential Diagnosis:

Clinical	Histologic
Dermatomyofibroma	**Spindle melanoma (in cases of pigmented DFSP)**
Leiomyosarcoma	**Dermatofibroma**
Nodular fasciitis	**Hypertrophic scar**
Dermatofibroma	**Diffuse neurofibroma**
Metastatic neoplasm	**Low-grade fibrosarcoma**

Pathophysiology:
- Malignant cell is though to be of fibroblastic origin
- Cytogenetic analysis may reveal supernumerary ringed chromosome with t(17;22)(q22;q13) translocation
  - Generates a fusion protein linking the PDGF-β gene to the COL1A1 gene promoter

References:

1. Haycox CL, Odland PB, Olbricht SM, Piepkorn M. Immunohistochemical characterization of dermatofibrosarcoma protuberans with practical applications for diagnosis and treatment. J Amer Acad Dermatol 1997; 37(3 Pt 1):438–444.
2. Mendenhall WM, Zlotecki RA, Scarborough MT. Dermatofibrosarcoma protuberans. Cancer 2004; 101(11):2503–2508.
3. Goldblum JR, Reith JD, Weiss SW. Sarcomas arising in dermatofibrosarcoma protuberans: a reappraisal of biologic behavior in eighteen cases treated by wide local excision with extended clinical follow up. Am J Surg Pathol 2000; 24(8):1125–1130.
4. Billings SD, Folpe AL. Cutaneous and subcutaneous fibrohistiocytic tumors of intermediate malignancy: an update. Am J Dermatopathol 2004; 26(2):141–155.

DERMATOMYOFIBROMA

Synonym: Plaque-like dermal fibromatosis.

Clinical Presentation:
- Upper trunk, neck, and proximal extremities of young adult females
- Red-brown dermal nodules and plaques ranging 1 to 2 cm in size (Fig. 5A)
- May clinically resemble keloids
- Lesions follow a benign limited course
- Local excision is typically curative
- No reported cases of local recurrence or metastasis

Histopathology:
- Bland uniform spindle cells in parallel and intersecting fascicles (Fig. 5B and C)
- Lesions are broader and less well circumscribed compared to dermatofibromas
- Preserve adnexal structures
- Features of collagen trapping and overlying epidermal hyperplasia seen in dermatofibromas are not appreciated in dermatomyofibromas

Special Studies:
- Spindle cells are positive for muscle specific actin and vimentin
- Spindle cells are negative for CD34, smooth muscle actin, desmin, and S100
- Rare interspersed dermal dendrocytes are positive for factor XIIIa

Immunohistochemistry:

	Immunohistochemistry			
Diagnosis	**MSA**	**SMA**	**S100**	**Desmin**
Dermatomyofibroma	(+)	(−)	(−)	(−)
Dermatofibroma	(−)	(+/−)	(−)	(−)
Leiomyoma	(+)	(+)	(−)	(+)
Neurofibroma	(−)	(−)	(+)	(−)

Clinicopathologic Correlation:

Clinical Feature	Pathologic Feature
Keloid-like plaques	**Broad horizontal fascicles of spindle cells**

Differential Diagnosis:

Clinical	Histologic
Plaque stage DFSP	Dermatofibroma
Leiomyoma	Extra-abdominal fibromatosis
Nodular fasciitis	Hypertrophic scar
Dermatofibroma	
Keloid	
Neurofibroma	
Adult myofibromatosis	
Extra-abdominal fibromatosis	
Hypertrophic scar	
Plaque-stage Kaposi's sarcoma	

Pathophysiology:
- Neoplastic cells are likely of myofibroblastic origin

References:

1. Kamino H, Reddy VB, Gero M, Greco MA. Dermatomyofibroma. A benign cutaneous, plaque-like proliferation of fibroblasts and myofibroblasts in young adults. J Cutan Pathol 1992; 19(2):85–93.
2. Mentzel T, Kutzner H. Haemorrhagic dermatomyofibroma (plaque-like dermal fibromatosis): clinicopathological and immunohistochemical analysis of three cases resembling plaque-stage Kaposi's sarcoma. Histopathology 2003; 42(6):594–598.
3. Mortimore RJ, Whitehead KJ. Dermatomyofibroma: a report of two cases, one occurring in a child. Australas J Dermatol 2001; 42(1):22–25.
4. Tani M, Komura A, Ichihashi M. Dermatomyofibroma (Plaque-formige dermale fibromatose). J Dermatol 1997; 24(12):793–797.

EPITHELIOID HISTIOCYTOMA

Synonyms: Epithelioid benign fibrous histiocytoma; epithelioid cell fibroblastoma; epithelioid cell fibrocytoma; histiocytoid dermal dendrocytoma; adventitial cellular myxofibroblastoma.

Clinical Presentation:
- Raised to pedunculated erythematous to brown minimally scaling nodule with surrounding epidermal collarette
- Lower extremity of middle-aged individuals
- May represent an uncommon variant of benign fibrous histiocytoma
- Local excision is typically curative
- Recurrence after incomplete excision has been reported

Histology
- Well circumscribed, superficial papillary dermal proliferation of angulated epithelioid cells with eosinophilic cytoplasm (Figs. 6A and B)
- Typically occur in an exophytic papule or sessile polyp
- Overlying epidermis may be effaced and melanocytic hyperplasia at the tips of the rete, characteristic of dermatofibromas, is not seen
- Other features of dermatofibromas, including foamy histiocytes, and hemosiderin-laden macrophages, are not seen
- Coarse or keloid-like collagen at the periphery of the tumor may or may not be evident
- May be associated with a proliferation of benign appearing angulated vascular spaces with flat endothelial cells
  - This has lead some investigators to postulate a vascular origin for the tumor

Special Studies:
- Fifty percent of cases express factor XIIIa
- CD31 and factor VIII highlight reactive endothelial cells, but typically not the main body of the tumor

Immunohistochemistry:

	Immunohistochemistry		
Diagnosis	FXIIIa	S100	CD68
Epithelioid histiocytoma	(+)	(−)	(+)
Spitz nevus	(−)	(+)	(+/−)
DF	(+)	(−)	(+/−)

Clinicopathologic Correlation:

Clinical Feature	Pathologic Feature
Nodule/pedunculated lesion with surrounding collarette	Tumor cells arise high in the superficial papillary and reticular dermis and push upward on the epidermis

Differential Diagnosis:

Clinical	Histologic
Pyogenic granuloma	Spitz nevus
Intradermal nevus	Pyogenic granuloma
Glomus tumor	Cutaneous perineuroma
Angioma	Juvenile xanthogranuloma
Basal cell carcinoma	Recticulohistiocytoma
Poroma	Langerhans cell histiocytosis
Dermatofibroma	

Pathophysiology:
- Likely similar to dermatofibroma/benign fibrous histiocytoma
- Epithelioid morphology may be associated with the location in which the histiocytic proliferation occurs
- Histiocytic cells proliferating in the superficial papillary dermis may have a more epithelioid quality whereas those in the deeper reticular dermis develop a more spindle morphology

References:

1. Jones EW, Cerio R, Smith NP. Epithelioid cell histiocytoma: a new entity. Br J Dermatol; 120(2):185–195.
2. Mehregan AH, Mehregan DR, Broecker A. Epithelioid cell histiocytoma. A clinicopathologic and immunohistochemical study of eight cases. J Am Acad Dermatol 1992; 26(2 Pt 1):243–246.
3. Glusac EJ, Barr RJ, Everett MA, Pitha J, Santa Cruz DJ. Epithelioid cell histiocytoma. A report of 10 cases including a new cellular variant. Am J Surg Pathol 1994; 18(6):583–590.

4. Singh Gomez C, Calonje E, Fletcher CD. Epithelioid benign fibrous histiocytoma of skin: clinico-pathological analysis of 20 cases of a poorly known variant. Histopathology 1994; 24(2): 123–129.

FIBROMATOSIS

Synonyms: Extra-abdominal desmoid tumor; aggressive fibromatosis; musculoaponeurotic fibromatosis.

Clinical Presentation:
- Firm fixed skin colored to erythematous solitary dermal nodule originating from the shoulder or pelvic girdle musculature
- Incidence and site of occurrence may be affected by age and sex of patient.
- Follows a course of rapid evolution and subsequent stabilization
- Spontaneous resolution has been documented in women after menopause

Histopathology:
- Characterized by broad interlacing fascicles of plump spindle cells embedded in a collagenous stroma (Figs. 7A and B)
- Fascicles may infiltrate into surrounding tissues
- Cytologic atypia and mitoses are not seen
- A sparse, peripherally located inflammatory infiltrate may be seen in association with the tumor

Special Studies:
- Tumor cells are reactive for factor XIIIa, smooth muscle actin, and vimentin
- Tumor cells are negative for CD34, S100, and desmin
- Cases associated with familial adenomatosis polyposis syndrome and Gardner's syndrome have elevated expression of nuclear beta-catenin
- Occurrence may be linked to pregnancy, local trauma, and familial adenomatosis polyposis syndrome

Immunohistochemistry:

	Immunohistochemistry				
Diagnosis	**FXIIIa**	**SMA**	**CD34**	**S100**	**Desmin**
Fibromatosis	(+/−)	(+)	(−)	(−)	(−)
DFSP	(−)	(−)	(+)	(−)	(−)
DF	(+)	(+/−)	(−)	(−)	(−)
Spindle melanoma	(−)	(−)	(−)	(+)	(−)
Nodular fasciitis	(−)	(+)	(−)	(−)	(+)

Clinicopathologic Correlation:

Clinical Feature	Pathologic Feature
Fixed dermal nodule	**Deep seated fibroblastic proliferation interlacing between surrounding structures**
May occur over flexor surfaces	**Tumor cells originating from the fascial plane**

Differential Diagnosis:
- Hypertrophic scar
- Juvenile hyaline fibromatosis
- Nodular fasciitis
- Myofibromatosis
- Cranial fasciitis

Pathophysiology:
- Tumors result from a clonal proliferation of myofibroblastic cells arising from the fascial or musculoaponeurotic structures
- Tumors undergo initial phase of growth followed by a stabilization phase
- Hormonal status may affect tumor growth as tumor cells often express estrogen receptors
- Heredity and prior history of local trauma may play a role in pathogenesis of lesions

References:
1. Pereyo NG, Heimer WL II. Extraabdominal desmoid tumor. J Am Acad Dermatol 1996; 34(2 Pt 2):352–356.
2. Mendenhall WM, Zlotecki RA, Morris CG, Hochwald SN, Scarborough MT. Aggressive fibromatosis. Am J Clin Oncol 2005; 28(2):211–215.
3. Oh CK, Son HS, Kwon YW, Jang HS, Kwon KS. Intralesional fluorouracil injection in infantile digital fibromatosis. Arch Dermatol 2005; 141(5):549–550.

NODULAR FASCIITIS

Synonyms: Postoperative/post-traumatic spindle cell neoplasm, pseudosarcomatous fasciitis/fibromatosis, proliferative fasciitis, infiltrative fasciitis.

Clinical Presentation:
- Benign reactive fibroblastic tumor
- Rapidly growing, tender, skin colored to erythematous, well-circumscribed, firm, fixed dermal nodule
- Equal sex distribution, peak age of onset is the fourth decade
- Common antecedent history of trauma
- When occurring in skin most commonly affects the trunk and extremities
- Follows a course of rapid evolution and subsequent stabilization
  - Rare cases of self-regressing lesions are reported
  - Morbidity may be associated with rapid growth and compression of adjacent structures

Histopathology:
- Proliferation of cytologically bland, immature appearing fibroblasts, and myofibroblastic cells in loose fascicles on a background of myxoid stroma (Figs. 8A and B)
- Delicate capillaries and red cell extravasation are common (Fig. 8A)
- Accompanying mixed inflammatory infiltrate composed of neutrophils, histiocytes, and lymphocytes
- Mitoses are numerous but of normal morphology

Special Studies:
- Tumor cells stain positive for vimentin, SMA, CD68, Factor XIIIa, and desmin
- Rare cytokeratin expression has been documented
- History of local trauma in 5% to 15% of cases

Immunohistochemistry:

	Immunohistochemistry			
Diagnosis	**SMA**	**CD68**	**FXIIIa**	**Desmin**
Nodular fasciitis	(+)	(+)	(+)	(+)
Fibrosarcoma	(−)	(−)	(−)	(−)

Clinicopathologic Correlation:

Clinical Feature	Pathologic Feature
Fixed dermal nodule	**Deep seated fibroblastic proliferation interlacing between surrounding structures**
Warmth, tenderness, and erythema	**Proliferation of capillaries with red cell extravasation with associated inflammatory infiltrates**

Differential Diagnosis:

Clinical	Histologic
Fibromatosis	**Low-grade fibrosarcoma**

Pathophysiology:
- Exhuberant response to local injury
- Reports of a reciprocal translocation on chromosome 15 resulting in aberrant expression of fibroblast growth factor 7 and possibly neurotrophic tyrosine kinase receptor, type 3

References:

1. Gelfand JM, Mirza N, Kantor J, et al. Nodular fasciitis. Arch Dermatol 2001; 137(6):719–721.
2. Zuber TJ, Finley JF. Nodular fasciitis. Southern Med J 1994; 87(8):842–845.
3. Graham BS, Barrett TL, Goltz RW. Nodular fasciitis: response to intralesional corticosteroids. J Am Acad Dermatol 1999; 40(3):490–492.
4. Velagaleti GV, Tapper JK, Panova NE, Miettinen M, Gatalica Z. Cytogenetic findings in a case of nodular fasciitis of subclavicular region. Cancer Genet Cytogenet 2003; 141(2):160–163.

PLEOMORPHIC FIBROMA

Synonym: None.

Clinical Presentation:
- Asymptomatic dome shaped to polypoid firm flesh colored nodule on the trunk, extremities, or face
- Size ranges from 1 to 2 cm
- Age ranges from 30 to 70 years old
- Equal sex distribution
- Benign tumor with little or no malignant potential
  - One case of malignant degeneration of a myxoid pleomorphic fibroma into myxofibrosarcoma has been reported

Histopathology:
- Structural features of a soft fibroma
  - Papillary/reticular dermal hypocellular fibrous process (Fig. 9A)
  - Increased and thickened collagenous stroma
  - Overlying epidermal papillomatosis may be present
- Distinguished by presence of plump, stellate, and multinucleated cells with nuclear atypia (Fig. 9B)

Special Studies:
- Atypical cells stain positive for vimentin
- Rare sparse staining for factor XIIIa, CD34, and SMA
- Atypical cells fail to stain with S100 or CD68

Immunohistochemistry:

	Immunohistochemistry				
Diagnosis	**FXIIIa**	**CD34**	**SMA**	**S100**	**CD68**
Pleomorphic fibroma	(+/−)	(+/−)	(+/−)	(−)	(−)
Dermatofibroma	(+)	(−)	(+/−)	(−)	(+/−)
Dermatomyofibroma	(−)	(−)	(+/−)	(−)	(+/−)
Soft fibroma	(−)	(−)	(−)	(−)	(+/−)

Clinicopathologic Correlation:
- None.

Differential Diagnosis:

Clinical	Histologic
Acrochrodon/skin tag/ fibroepithelial papilloma/ soft fibroma	**Acrochrodon/skin tag/ fibroepithelial papilloma/ soft fibroma**
Dermatofibroma	**Dermatofibroma**

Pathophysiology:
- Pleomorphic cells may be of myofibroblastic origin
- May share some common etiopathogenesis with dermatofibromas

References:

1. Kamino H, Lee JY, Berke A. Pleomorphic fibroma of the skin: a benign neoplasm with cytologic atypia. A clinicopathologic study of eight cases. Am J Surg Pathol 1989; 13(2):107–113.
2. Garcia-Doval I, Casas L, Toribio J. Pleomorphic fibroma of the skin, a form of sclerotic fibroma: an immunohistochemical study. Clin Exp Dermatol 1998; 23(1):22–24.
3. Rudolph P, Schubert C, Zelger BG, Zelger B, Parwaresch R. Differential expression of CD34 and Ki-M1p in pleomorphic fibroma and dermatofibroma with monster cells. Am J Dermatopathol 1999; 21(5):414–419.
4. Dore A, Robertson I, Williamson R, Weedon D. Progression of a myxoid pleomorphic fibroma to myxofibrosarcoma. Australas J Dermatol 2003; 44(4):287–290.

SOFT FIBROMA

Synonyms: Acrochordon; fibroepithelial papilloma; fibroma pendulum; skin tag.

Clinical Presentation:
- Most common benign skin tumor
- Asymptomatic flesh colored soft papules ranging in size from 0.2 to 2 cm

- Larger lesions may be pedunculated
- Predominantly occur in the axilla, neck, and groin
- May also occur on the proximal extremities and face
- Forty-six percent of general adult population possess at least one
- Benign course
  - One case of incidental basal cell carcinoma in soft fibroma
  - Negligible incidence of unanticipated malignancy in biopsies of soft fibromas

Histopathology:
- Clinical and histopathologic features are characteristic
- Loose fibro-collagenous vascular stalk projecting above the epidermis (Fig. 10A)
- Epidermis displays slight acanthosis and papillomatosis (Fig. 10B)
- Thrombosis with associated edema, vascular congestion, and ulceration may be seen

Special Studies:
- No significant immunoperoxidase studies have been published regarding skin tags

Clinicopathologic Correlation:
- Positive association with peripheral glucose intolerance and obesity
- No correlation with the occurrence of colonic polyps
- Numerous rare conditions may be associated with soft fibromas
  - Birt-Hogg-Dube syndrome
  - Acromegaly
  - Goldenhar-Gorlin syndrome
  - Oculocerebrocutaneous syndrome

Differential Diagnosis:

Clinical	Histologic
Neurofibroma	Pleomorphic fibroma
Intradermal nevus	Verruca vulgaris
Pedunculated seborrheic keratosis	Acquired digital fibrokeratome Pedunculated seborrheic keratosis

Pathophysiology:
- Unknown

References:

1. Banik R, Lubach D. Skin tags: localization and frequencies according to sex and age. Dermatologica 1987; 174(4):180–183.
2. Eads TJ, Chuang TY, Fabre VC, Farmer ER, Hood AF. The utility of submitting fibroepithelial polyps for histological examination [see comment]. Arch Dermatol 1996; 132(12):1459–1462.
3. Hayes AG, Berry AD III. Basal cell carcinoma arising in a fibroepithelial polyp [see comment]. J Am Acad Dermatol 1993; 28(3):493–495.

LANGERHANS CELL HISTIOCYTOSIS

Synonym: Histiocytosis X.

Clinical Presentation:
- Multisystem disease affecting skin, bones, lymph nodes, liver, spleen, lungs, and hypothalamus

Three Variants:
- Letterer-Siwe
  - Follows acute and progressive course
  - Clinically resembles seborrheic dermatitis (Fig. 11A)
  - Involves inguinal and flexural areas of infants
  - Systemic involvement is common
- Hand-Schuller-Christian
  - Follows more chronic course
  - Clinically similar to Letterer-Siwe
  - Occurs in older children
  - May present with triad of osteolytic defects, diabetes insipidus, and exophthalmos
- Eosinophilic granuloma
  - Most common form of Langerhans cell histiocytosis
  - Bone lesions predominate, skin lesions are less common
  - Occurs in children, typically over the age of six years
  - Follows an indolent course rarely requiring systemic chemotherapy
- Less common variants
  - Congenital self-healing reticulohistiocytosis
  - Langerhans cell granulomatosis

Histopathology:
- Nodular to lichenoid infiltrate of bland appearing epithelioid cells with abundant pale eosinophilic cytoplasm
- Nuclear features are described as reniform or kidney shaped and have a vesicular appearance (Fig. 11B)
- Associated infiltrate of lymphocytes, neutrophils, and eosinophils often present
- Exocytosis of Langerhans cells may be evident (Fig. 11C)
- Significant nuclear atypia and mitoses are not evident except in cases of malignant Langerhans cell histiocytosis

Special Studies:
- Cells are positive for CD1a, S100 and variably positive for CD68 (Fig. 11D)
- Electron microscopy demonstrates the presence of Birbeck granules (Fig. 11E)
- Sporadic cases of Langerhans cell histiocytosis preceding or following acute leukemias have been reported
- One reported case of Langerhans cell histiocytosis occurring in association with basal cell carcinoma in a patient with chronic coal tar exposure

Immunohistochemistry:

	Immunohistochemistry			
Diagnosis	CD1a	CD4	S100	CD68
LCH	(+)	(+)	(+)	(+)
Melanoma	(−)	(−)	(+)	(−)
Mycosis fungoides	(−)	(+)	(−)	(−)

Clinicopathologic Correlation:

Clinical Feature	Pathological Feature
Scaling erythematous plaques	Epidermotropic Langerhans cells with associated acanthosis and spongiosis

Differential Diagnosis

Clinical	Histologic
Seborrheic dermatitis	Spitz nevus
Tinea capitis	Non-X histiocytosis
Diaper dermatitis	

Pathophysiology

- May be related to deranged stimulatory paracrine intercellular signaling loop between Langerhans cells and T lymphocytes

References:

1. Shaffer MP, Walling HW, Stone MS. Langerhans cell histiocytosis presenting as blueberry muffin baby. J Am Acad Dermatol 2005; 53(2):S143–S146.
2. Caldemeyer KS, Parks ET, Mirowski GW. Langerhans cell histiocytosis. J Amer Acad Dermatol. 2001; 44(3):509–511.
3. Misery L, Godard W, Hamzeh H, et al. Malignant Langerhans cell tumor: a case with a favorable outcome associated with the absence of blood dendritic cell proliferation. J Amer Acad Dermatol 2003; 49(3):527–529.
4. Stefanato CM, Andersen WK, Calonje E, et al. Langerhans cell histiocytosis in the elderly: a report of three cases. J Am Acad Dermatol 1998; 39(2 Pt 2):375–378.
5. Steiner M, Matthes-Martin S, Attarbaschi A, et al. Improved outcome of treatment-resistant high-risk Langerhans cell histiocytosis after allogeneic stem cell transplantation with reduced-intensity conditioning. Bone Marrow Transplant 2005; 36(3):215–225.

XANTHOMAS

Synonyms: None.

Clinical Presentation:

- General term for wide array of entities with dermal deposition of lipid substance and histiocytes
- Present as single or multiple firm, white to yellow dermal papules or nodules with variably associated erythema (Figs. 12A and B)

Table 1 Features of Various forms of Xanthomas

Subtype	Location	Clinical Appearance	Gene Defect	Hyperlipidemia	Histologic Characteristics	Associated Conditions
Xanthelasma (planar xanthoma)	Eyelids	Waxy yellow papules	None	Variable (most commonly hyperlipoproteinemia type III)	Nonspecific	None
Verruciform xanthoma	Areas of trauma: Oral mucosa and genitalia	Verrucous yellow to grey papules and plaques	Possible association with 3 beta-hydroxysteroid dehydrogenase mutation	Absent	Papillomatous epidermis with foamy histiocytes concentrated in dermal papillae	One reported case of association with HHV-6
Eruptive xanthoma	Pressure points of extensor surfaces and buttocks	Yellow papules with erythematous base which wax and wane	None	Present (most commonly hyperlipidemia types I, IV, and V)	Foamy histiocytes may be admixed with lymphocytes and neutrophils	Hyperlipidemia may result in pancreatitis
Palmoplantar xanthoma (planar xanthoma)	Palmar creases	Waxy firm papules	Homozygous ApoE2/E2	Present (most commonly familial dysbetalipoproeinemia)	Nonspecific	Strong association with atherosclerotic disease
Tuberous xanthoma	Extensor aspects of knees, elbows, and buttocks	Yellow to erythematous dermal papules and nodules, not associated with underlying tendon	None	Present (most commonly familial dysbetalipoproteinemia type III, also homozygous familial hypercholesterolemia, cerebrotendinous xanthomatosis, beta-sitosterolemia, and type IV hyperlipoproteinemia)	Nonspecific	Peripheral vascular disease
Cerebrotendinous xanthoma	Tendons of the hands, knees, elbows and Achilles	Slow growing tendinous tumors	Sterol 27-hydroxylase deficiency	Absent	Nonspecific	Achilles tendon xanthomas, mental impairment, cerebellar dysfunction, cataracts, atherosclerotic disease
Xanthoma disseminatum	Flexural	Numerous red to yellow papules and plaques	None	Absent	Nonspecific	Diabetes insipidus
Intertriginous xanthoma (planar xanthoma)	Intertriginous most commonly web spaces	Yellow cobblestone-like papules and plaques	None	Present (most commonly homozygous and heterozygous familial hypercholesterolemia)	Nonspecific	Strong association with atherosclerotic disease

- Onset may be rapid or gradual
- Distribution determined by subtype and can range from eyelids to palmo-plantar to diffuse
- Most common form on bilateral eyelids, termed xanthelasma
  - Present as waxy yellow dermal papules coalescing into plaques
  - Fifty percent of cases associated with underlying hyperlipidemia
- Typically indolent course and benign prognosis
  - Morbidity and mortality may be related to sequelae of underlying hyperlipidemia (Table 1)

Histopathology:

- Findings may be subtle
  - Lipid substance is often poorly preserved in routine fixation
- Early lesions may present with more inflammatory infiltrates
- Mature lesions contain large areas infiltrated by foamy histiocytes (Figs. 12C and D)
- Long-standing lesions often have numerous multinucleate giant cells with a Touton morphology

Special Studies:

- Lipid stains highlight deposits in frozen section
- Deposits composed of cholesterol may be polarizable
- Xanthomas may or may not be associated with underlying hyperlipidemia
- Table 1 outlines the specific associations reported with particular types of xanthomatosis

Immunohistochemistry:

	Immunohistochemistry		
Diagnosis	**CD1a**	**CD68**	**S100**
Xanthoma	(−)	(+)	(−)
Langerhans cell histiocytosis	(+)	(+)	(+)

Clinicopathologic Correlation:

Clinical Features	Pathological Features
Yellow coloration	**Reflects deposition of lipid material within the dermis**
Halo of erythema (seen in eruptive xanthomas)	**Associated inflammatory infiltrate**

Differential Diagnosis:

Clinical	Histologic
Dermatofibromas	**Langerhans cell histiocytosis**
Sarcoidosis	**Granular cell tumor**
Verruca	
Molluscum contagiosum	
Neurofibroma	

Pathophysiology:

- May be idiopathic or related to acquired or heritable hyperplasia

Acquired Hyperlipidemia:

- Diabetes mellitus
- Obesity
- Nephrotic syndrome
- Thyroid disease
- Cholestatic liver disease
- Medications, for example, estrogens and retinoids

References:

1. Bel S, Garcia-Patos V, Rodriguez L, et al. Cerebrotendinous xanthomatosis. J Am Acad Dermat 2001; 45(2):292–295.
2. Bergman R. The pathogenesis and clinical significance of xanthelasma palpebrarum. J Am Acad Dermat 1994; 30(2 Pt 1):236–242.
3. Connolly SB, Lewis EJ, Lindholm JS, Zelickson BD, Zachary CB, Tope WD. Management of cutaneous verruciform xanthoma. J Am Acad Dermatol 2000; 42(2 Pt 2):343–347.
4. Maize JC, Burgdorf WH, Hart MA. Cutaneous Pathology. Churchill Livingstone, 1998:407, 763–771.

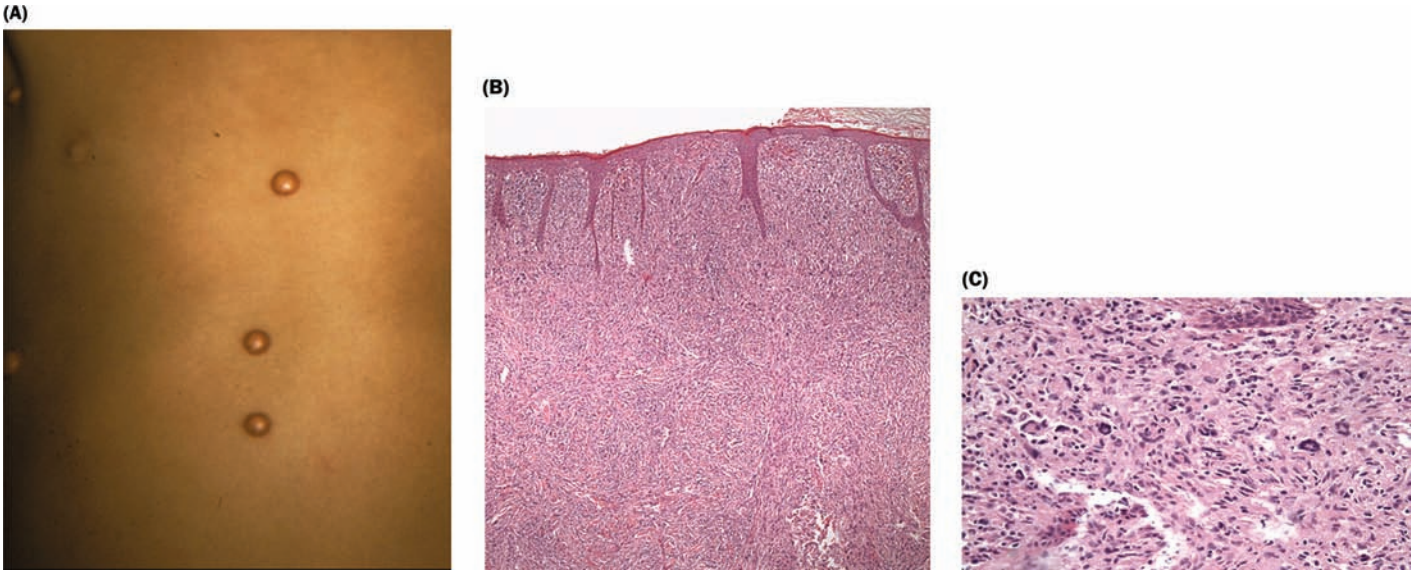

Figure 1 (**A**) Clinical image of juvenile xanthogranuloma. (**B**) Juvenile xanthogranuloma, 20×. (**C**) Juvenile xanthogranuloma, 200×, Touton giant cells.

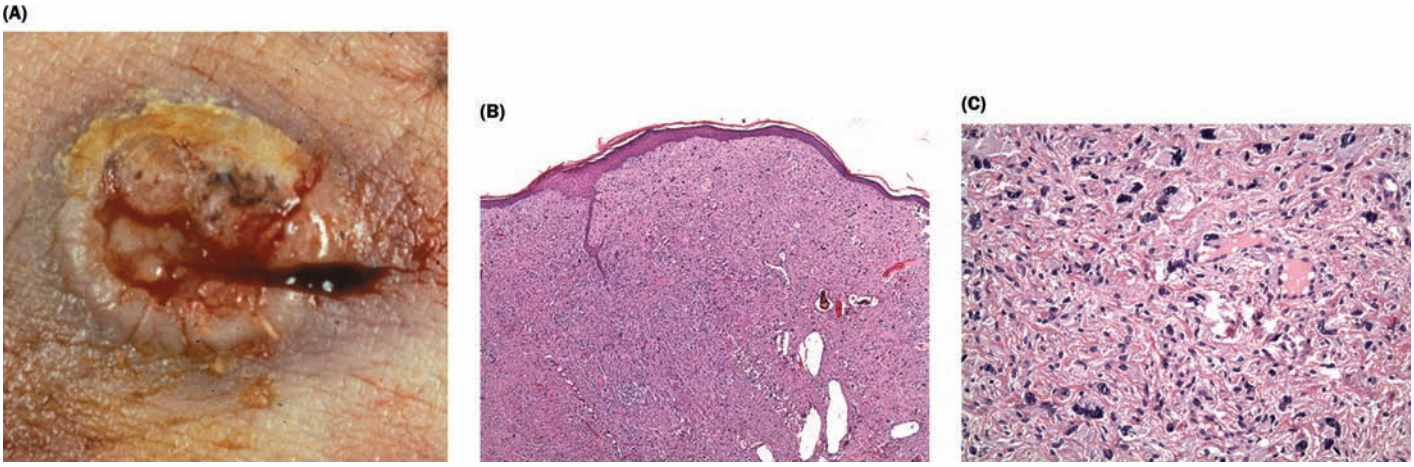

Figure 2 (**A**) Clinical image of ulcerated atypical fibroxanthoma. (**B**) Atypical fibroxanthoma 100× and (**C**) 400×.

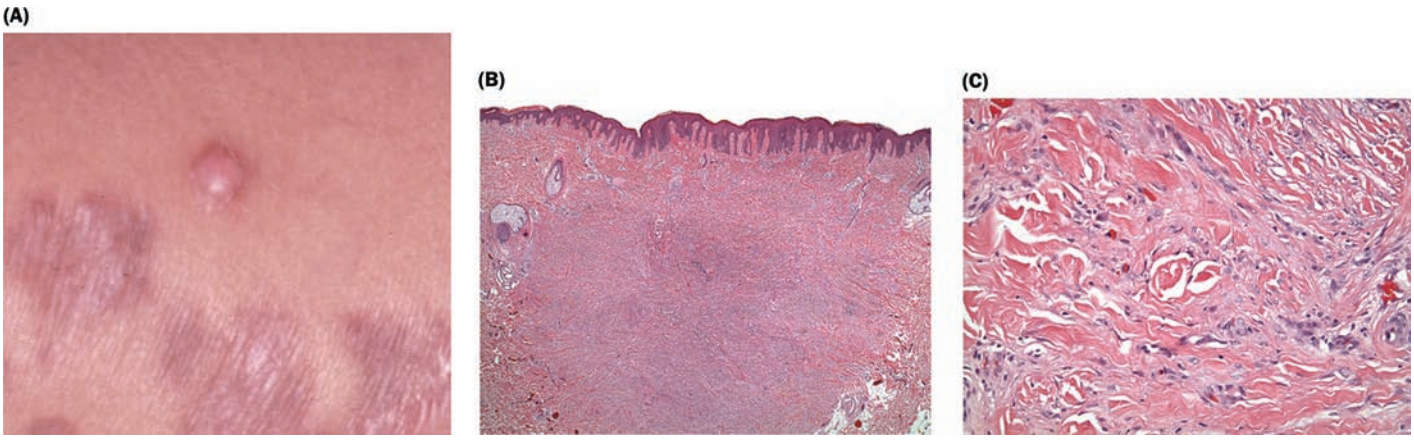

Figure 3 (**A**) Dermatofibroma occurring adjacent to scar. (**B**) Dermatofibroma histology 20× and (**C**) 200×.

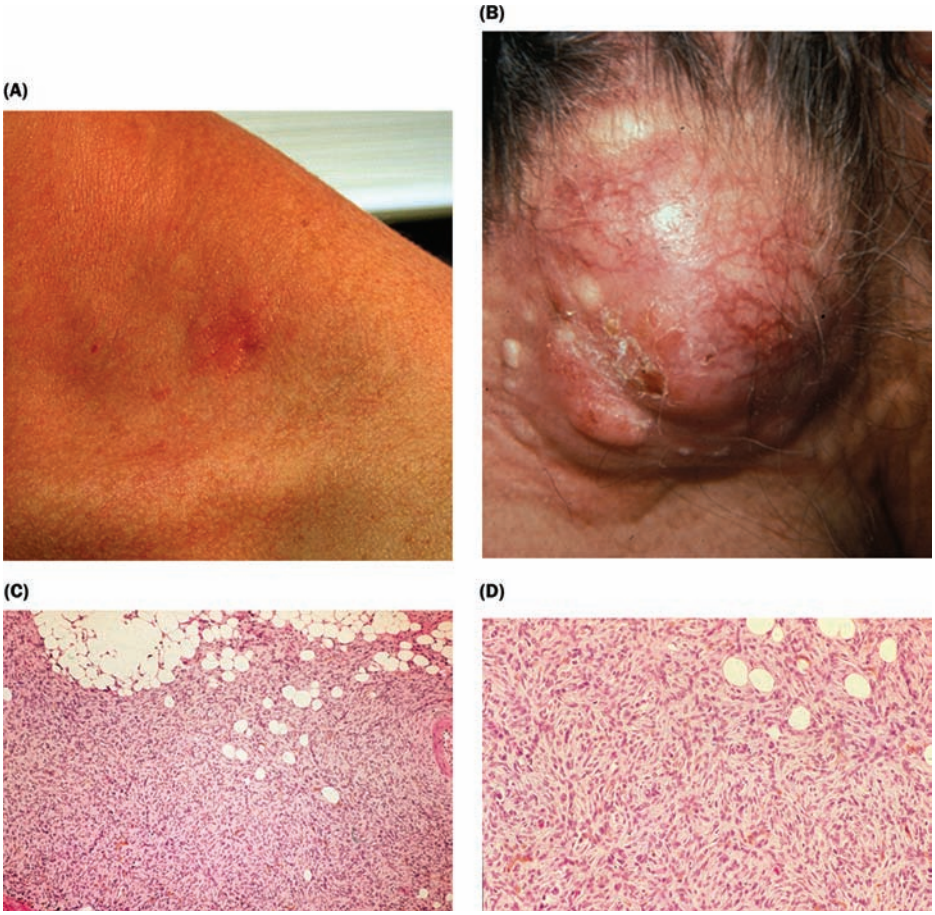

Figure 4 Dermatofibrosarcoma protuberans: (**A**) plaque stage, (**B**) tumor stage, (**C**) histology 100×, and (**D**) histology 200×.

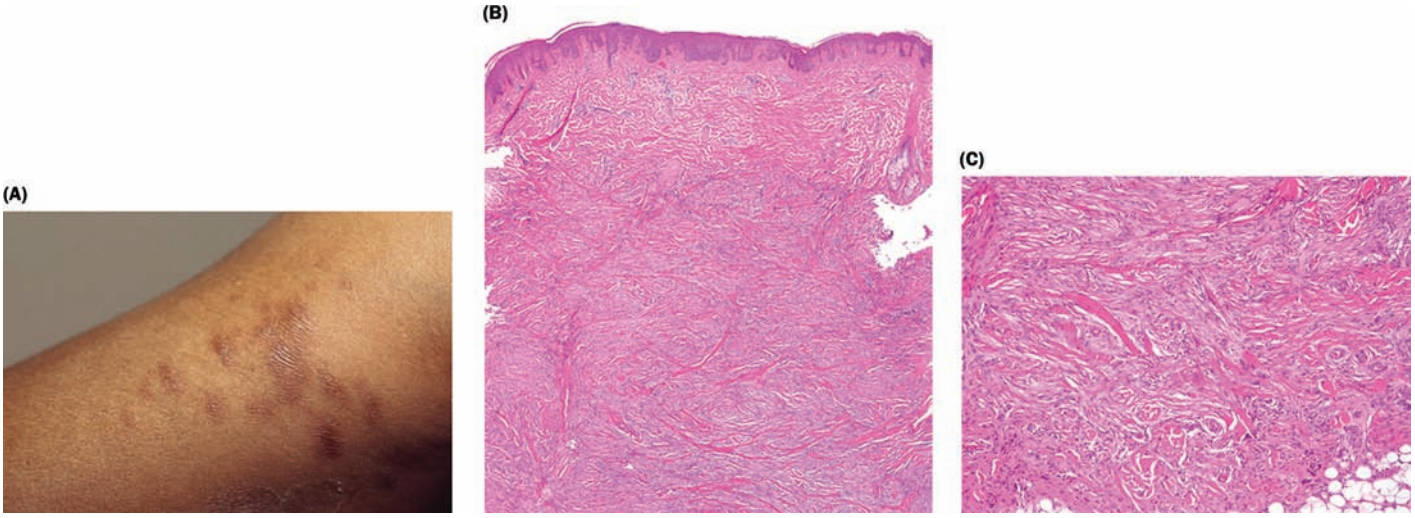

Figure 5 (**A**) Dermatomyofibromas on upper extremity. (**B**) Dermatomyofibroma histology 20× and (**C**) 200×.

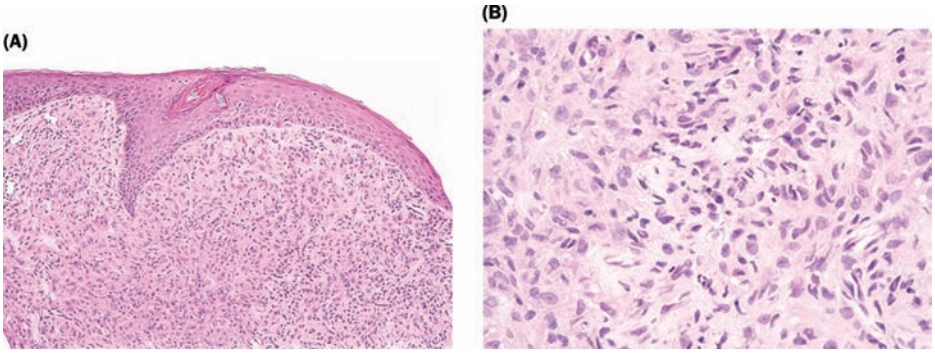

Figure 6 Epithelioid histiocytoma histology: (**A**) 100× and (**B**) 200×.

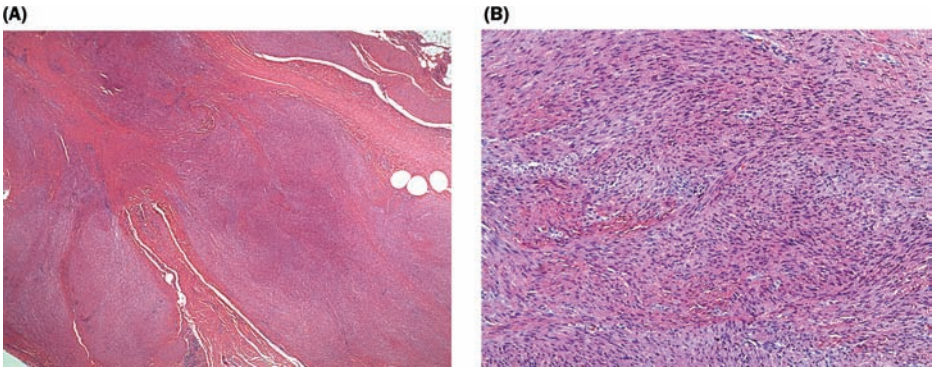

Figure 7 Fibromatosis histology: (**A**) 20× and (**B**) 200×.

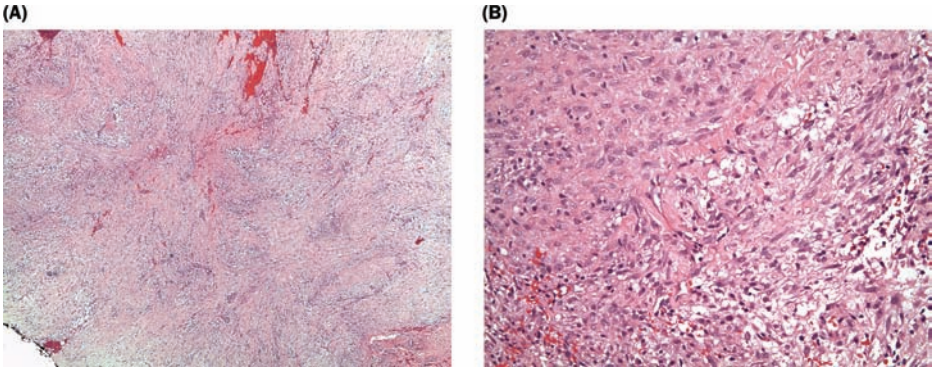

Figure 8 Nodular fasciitis histology: (**A**) 20× and (**B**) 200×.

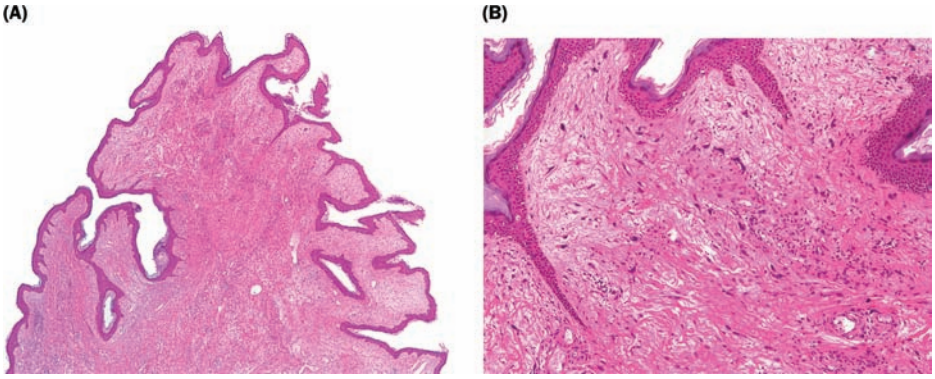

Figure 9 Pleomorphic fibroma: (**A**) 20× and (**B**) 200×.

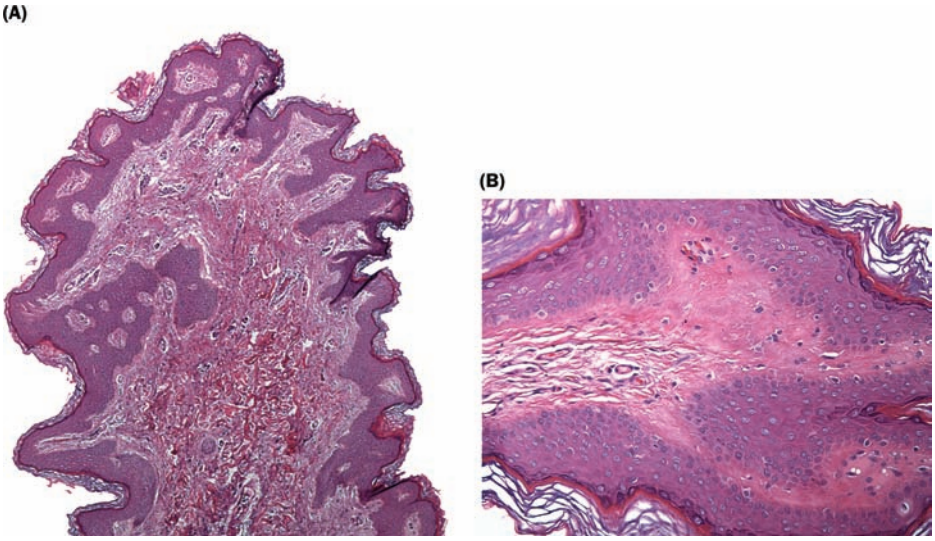

Figure 10 Soft fibroma: (**A**) 20× and (**B**) 200×.

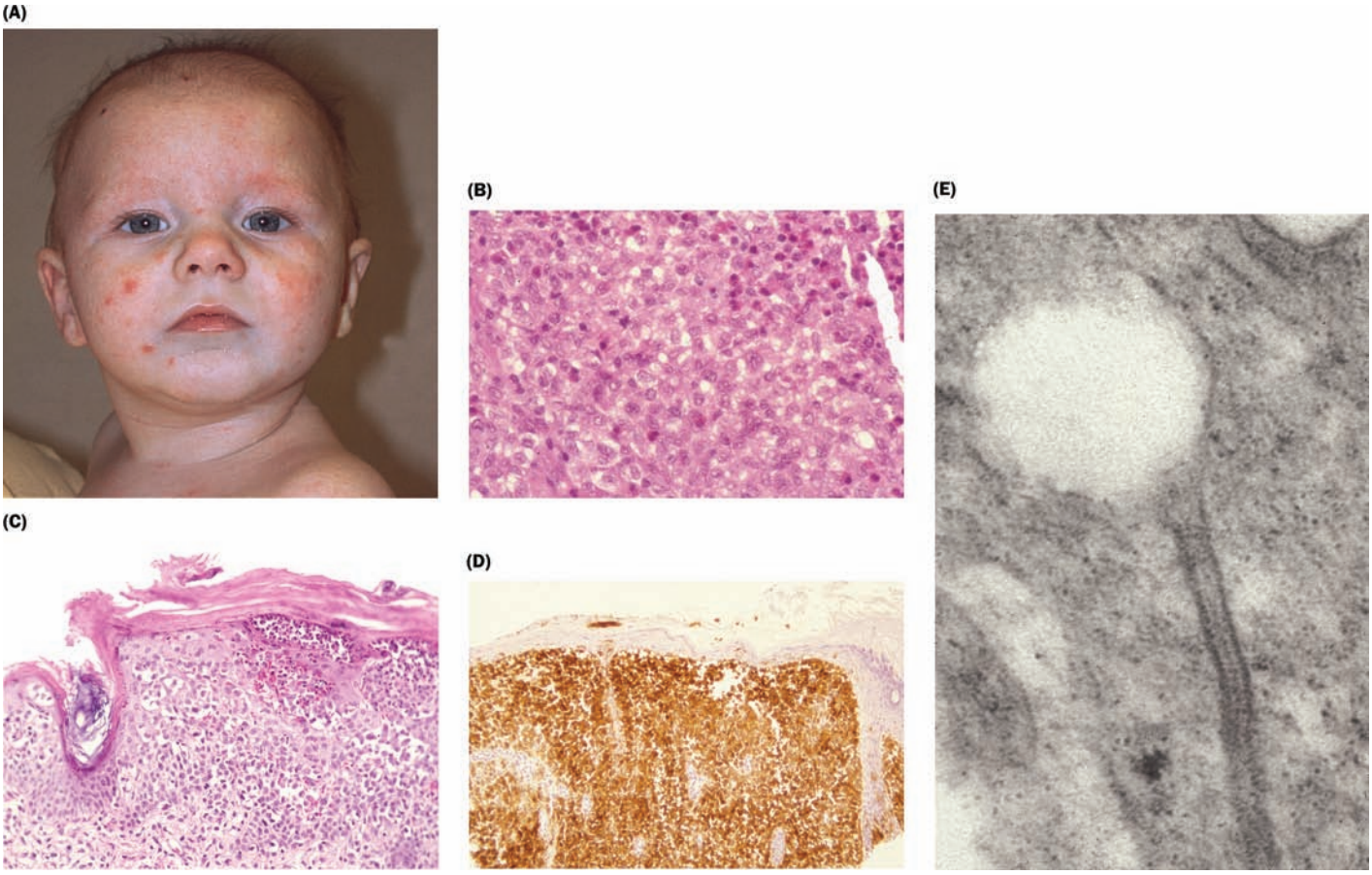

Figure 11 (**A**) Cutaneous Langerhans cell histiocytosis, Letterer-Siwe variant. Langerhans cell histiocytosis histology: (**B**) 400× and (**C**) 200×. (**D**) CD1a positivity in Langerhans cell histiocytosis. (**E**) Electron microscopy of Birbeck granule.

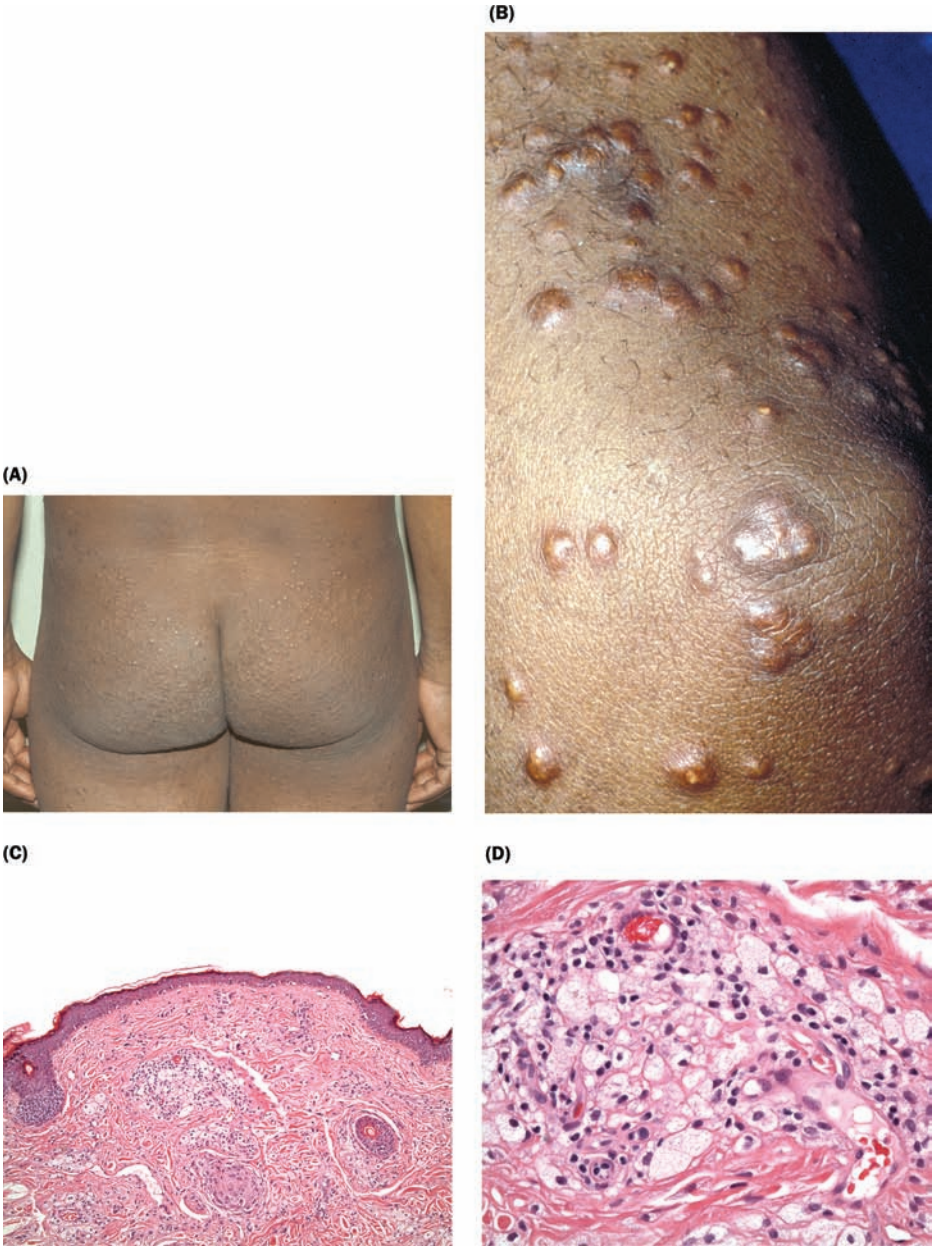

Figure 12 Eruptive xanthoma (**A**); close-up (**B**). Xanthelasma histology: (**C**) 100× and (**D**) 400×.

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Vascular Proliferations

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CONTENTS

Proliferations of blood and lymphatic vessels are notoriously difficult to classify. This chapter presents the vascular proliferations that are most commonly sampled by biopsy, or ones in which understanding the histopathologic features is helpful to dermatologists or pathologists trying to make sense of this field.

A useful exercise is to identify normal capillaries, venules, lymphatic vessels, arterioles, and veins in skin biopsies of nonvascular lesions. Capillaries are small vessels, best seen in dermal papillae, having round lumens and thin walls. Lymphatic vessels have even thinner walls, flattish endothelial cells, and angulated lumens. Venules are best seen around the superficial plexus (at the base of the papillary dermis) and have slightly thicker walls than do capillaries. Arterioles have a round periphery and a small round lumen more narrower than the vessel wall. A cross-section of an arteriole will show concentric bands of smooth muscle. Arterioles also have internal and external elastic laminae. Veins have oblong shapes, oval lumens, and a more haphazard arrangement of smooth muscle in their walls.

Vascular differentiation can be inferred by lumen formation. Not all spaces that contain erythrocytes are vascular lumens—traumatized epithelial or even melanocytic proliferations can have erythrocytes between cells. If clear cut lumens are not present, immunohistochemical studies may be helpful. The most specific antibody in general use for identifying endothelial cells is that directed against CD31. Less specific is CD34. An antibody against factor VIIIRag (von Willebrand's factor) is also relatively specific, but less sensitive. *Ulex europeus* agglutinin binds to endothelial and epithelial cells; in the context of a keratin negative neoplasm, it can be useful. Many vascular proliferations have endothelial cells that lie on a basement membrane, which can be identified by staining with antisera to laminin and type IV collagen.

A superb monograph on vascular proliferations of the skin is referenced below. .

References:

1. Dalton SR, Fillman EP, Ferringer T, Tyler W, Elston DM. Smooth muscle pattern is more reliable than the presence or absence of an internal elastic lamina in distinguishing an artery from a vein. J Cutan Pathol 2006; 33(3):216–219.
2. Sangueza O, Requena L. Pathology of Vascular Skin Lesions: Clinicopathologic Correlations. Totowa, NJ: Human Press, 2003.

INFANTILE HEMANGIOMA

Synonym: Juvenile hemangioma.

Clinical Presentation:

- Relatively common (almost 10% of infants by age 1)
- Onset shortly after birth
- Usually single
- Involution spontaneously in most cases (except noninvoluting congenital hemangioma, which is present at birth)
- Raised, smooth surfaced lobulated light to bright red or blue plaques and nodules (Fig. 1A)
- Some have dilated vessels (veins or capillaries) visible on their surface.
- Rapid onset, and a long stable period, followed by involution in most cases by age 7 (except noninvoluting congenital hemangioma)
- Kassabach–Merritt syndrome (platelet consumption) can occur, but is more common with kaposiform hemangioendothelioma and tufted hemangiomas.

Histology:

- Dermis and/or subcutis diffusely involved depending on the depth of hemangioma
- Compact masses of capillaries and venules (Figs. 1B and C)
- High cellularity in early lesions with inconspicuous lobules
- Density of vessels decrease, and lumens become more conspicuous with time, as endothelial cells flatten
- Fibrosis and adipocytes with involution
- A lobular pattern is more pronounced in noninvoluting congenital hemangioma.

Immunohistochemistry:
- Endothelial cells are positive for Glut-1 (Fig. 1D), a glucose transport protein in common infantile hemangiomas, but not in noninvoluting congenital hemangioma.

Clinicopathologic Correlation:

Clinical Feature	Pathologic Feature
Pallor preceding onset of lesions	Many mast cells, which may degranulate in early lesions
Involution of lesions	Thick rings of collagen around residual vessels
Possible origin from placental vessels	Glut-1 positivity

Differential Diagnosis:

Infantile Hemangioma	Vascular Malformation
Small vessels (mostly)	Large muscular vessels (mostly)
High cellularity, compact arrangement, lumens inconspicuous	Lower cellularity, loose arrangement, lumens conspicuous
Capillaries and venules	Dilated thin walled vessels and muscular walled veins

References:

1. Dadras SS, North PE, Bertoncini J, Mihm MC, Detmar M. Infantile hemangiomas are arrested in an early developmental vascular differentiation state. Mod Pathol 2004; 17(9):1068–1079.
2. North PE, Waner M, James CA, Mizeracki A, Frieden IJ, Mihm MC Jr. Congenital nonprogressive hemangioma: a distinct clinicopathologic entity unlike infantile hemangioma. Arch Dermatol 2001; 137(12):1607–1620.

LYMPHANGIOMA

Synonym: Superficial cutaneous lymphatic malformation.

Clinical Features:
- Onset in some cases at birth
- Clear papules, sometimes clustered in "lymphangioma circumscriptum" (Fig. 2A)
- Livid skin between papules (sometimes)
- Pink to pale blue color
- Spongy texture in deep lymphatic malformations
- Rarely, deep tissue has lymphatic malformation also

Histology (Figs. 2B–E):
- Very thin delicate vessel walls
- Irregularly shaped; sometimes angulated lumens
- Perivascular lymphoid infiltrates
- Deep vessels can have smooth muscle in their walls
- Dilated superficial vessels can appear to touch the undersurface of epidermis
- With superficial dermal involvement, epidermis can be hyperplastic or papillated

Clinicopathologic Correlation:

Clear Papules at Surface	Lack of Erythrocytes in Lumens
Spongy texture	Dilated vessels
Lesions can suddenly turn red	Bleeding to lesions, with erythrocytes in lumens

Immunohistochemistry:
- Endothelial cells positive for D2-40 and Lyve-1 (lymphatic markers)

Differential Diagnosis:
- Both lymphangioma and Kaposi's sarcoma have vessels with angulated lumens that can envelope pre-existent structures (promontory sign).

Lymphangioma	Lymphangioma-Like Kaposi's Sarcoma
Lumens all markedly dilated	Lumens narrow
No spindle cells between collagen bundles	Spindle cells between collagen bundles
Lymphocytes only	Lymphocytes, plasma cells, and siderophages

References:

1. Whimster IW. The pathology of lymphangioma circumscriptum. Br J Dermatol 1976; 94(5):473–486.
2. Fukunaga M. Expression of D2-40 in lymphatic endothelium of normal tissues and in vascular tumours. Histopathology 2005; 46(4):396–402.

ANGIOKERATOMA

Synonym: None.

Clinical Features:
- Small red to black papules and nodules; usually solitary (Fig. 3A)
- Skin surface variably elevated, papillated, and hyperkeratotic
- Multiple angiokeratomas are localized to
  - Genitalia (Fordyce)
  - Acral skin (Mibelli)
  - Disseminated (Fabry's disease)
- Fabry's disease features glucosylceramide accumulation in multiple organs

Histology:
- Dilated vessels with round lumens in papillary dermis (Figs. 3B and C)
- Lumens contain erythrocytes and almost touch the undersurface of epidermis
- Epidermal hyperplasia and hyperkeratosis (less in Fordyce and angiokeratoma corporis diffusum of Fabry's disease)
- Thrombi in lumens (sometimes) (Fig. 3D)
- Intravascular papillary endothelial hyperplasia in lumens (sometimes)

Clinicopathologic Correlation:

Raised Scaly Surface	Epidermal Hyperplasia and Hyperkeratosis
Deep red color	Vessels nearly touch the undersurface of epidermis
Thrombi in lumens (sometimes)	Lesions can turn from dark red to black, simulating melanoma

Reference:

1. Schiller PI, Itin PH. Angiokeratomas: an update. Dermatology 1996; 193(4): 275–282.

CHERRY HEMANGIOMA

Synonym: Campbell de Morgan spots.

Clinical Features:
- Onset in young adults and middle age
- Bright red; round slightly elevated firm papules; less than 5 mm in diameter
- Torso most commonly affected

Histopathology:
- Dome shaped surface
- Small thin walled vessels with round lumens in expanded papillary dermis
- Fibrosis between vessels in older lesions

ARTERIOVENOUS HEMANGIOMA

Synonyms: Cirsouid aneurysm; acral arteriovenous tumor.

Clinical Features:
- Small pink to blue; sometimes tan papule; solitary
- Face and hands most commonly affected

Histology:
- Domed surface
- Muscular walled vessels in haphazard cluster in the dermis (Figs. 4A and B)
- More vessels have features of veins than of arteries (and lack internal elastic lamina with an elastic stain)
- Elastic tissue stains show features intermediate between arteries and veins in some vessels

Reference:
1. Connelly MG, Winkelmann RK. Acral arteriovenous tumor. A clinicopathologic review. Am J Surg Pathol 1985; 9(1):15–21.

MICROVENULAR HEMANGIOMA

Clinical Features:
- Round red patch; solitary
- Adults usually affected
- Can occur in POEMS syndrome

Histology:
- Small oval vessels with elongated, thin lumens (Figs. 5A–C)
- Entire thickness of reticular dermis involved
- Pericytes present around vessels

Differential Diagnosis:
- Both conditions feature small vessels interposed between collagen bundles in the reticular dermis

Microvenular Hemangioma	Kaposi's Sarcoma
Lumens oval or round; simple	Most lumens angulated; can be complex
No inflammatory cells	Lymphocytes, plasma cells, and siderophages
Promontory sign	No promontory sign
Few spindled cells apart from vessels	Spindle cells apart from vessels

Reference:
1. Hunt SJ, Santa Cruz DJ, Barr RJ. Microvenular hemangioma. J Cutan Pathol 1991; 18(4):235–240.

TARGETOID HEMOSIDEROTIC HEMANGIOMA

Synonym: Hobnail hemangioma.

Clinical Features:
- Red papule in center (Fig. 6A)
- Red brown to tan round macule around it, which can regress
- Onset following trauma in some cases

Histology:
- Upper papillary dermis involved centrally (Fig. 6B)
- Upper reticular dermis involved at periphery
- Central papules have dilated vessels with round lumens containing erythrocytes (Fig. 6C).
- "Hobnail" endothelial cells (nuclei protrude into lumens with stalks of cytoplasm) in central vessels; sometimes with small papillations
- Angulated vessels with thin walls at periphery (Fig. 6D)
- Extravasated erythrocytes and siderophages in peripheral component

Targetoid Hemosiderotic Hemangioma	Kaposi's Sarcoma
Upper dermis (mostly)	Upper and lower dermis
Few spindled cells outside vessels	Many spindled cells outside vessels
Few or no plasma cells	Plasma cells
Characteristic central and peripheral zones	No characteristic zonation
"Hobnail" endothelial cells in dilated vessels	Flattish endothelial cells in dilated vessels

References:
1. Franke FE, Steger K, Marks A, Kutzner H, Mentzel T. Hobnail hemangiomas (targetoid hemosiderotic hemangiomas) are true lymphangiomas. J Cutan Pathol 2004; 31(5):362–367.
2. Carlson JA, Daulat S, Goodheart HP. Targetoid hemosiderotic hemangioma—a dynamic vascular tumor: report of 3 cases with episodic and cyclic changes and comparison with solitary angiokeratomas [Review]. J Am Acad Dermatol 1999; 41(2 Pt 1): 215–224.
3. Guillou L, Calonje E, Speight P, Rosai J, Fletcher CD. Hobnail hemangioma: a pseudomalignant vascular lesion with a reappraisal oftargetoid hemosiderotic hemangioma. Am J Surg Pathol 1999; 23(1):97–105.
4. Santa Cruz DJ, Aronberg J. Targetoid hemosiderotic hemangioma. J Am Acad Dermatol 1988; 19(3):550–558.

PYOGENIC GRANULOMA

Synonyms: Lobular capillary hemangioma; granuloma pyogenicum.

Clinical Features:
- Solitary (usually)
- Glistening dark red papule or nodule (Fig. 7A)

- Scaly collarette
- Lips, nailfolds, face most common sites
- Satellite lesions may follow attempted ablation
- Deep dermal, subcutaneous, and intravascular variants may appear as skin colored papules.

Histology:
- Protuberant rounded mass in papillary dermis (Figs. 7B–D)
- Ulceration in young lesions
- Neutrophils in ulcerated lesions
- Lobules of capillaries and venules
- Lobules have a few vessels with dilated lumens, irregular shapes, and many with small round lumens
- Many small oval cells (pericytes) between vessels
- Lobules separated by bands of fibrosis

Pyogenic Granuloma	Bacillary Angiomatosis	Kaposi's Sarcoma, Nodule
Fibrous bands separate lobules	Few fibrous bands	Few fibrous bands
Neutrophils only near ulcer	Neutrophils beneath ulcer around bacterial clusters	Lymphocytes and plasma cells
No fascicles of spindled cells	No fascicles of spindled cells	Fascicles of spindled cells
No or few globules	No or few globules	Eosinophilic globules
No purplish clumps inbetween vessels	Purplish clumps (bacteria) inbetween vessels	No purplish clumps inbetween vessels

References:

1. Mills SE, Cooper PH, Fechner RE. Lobular capillary hemangioma: the underlying lesion of pyogenic granuloma. A study of 73 cases from the oral and nasal mucous membranes. Am J Surg Pathol 1980; 4(5):470–479.
2. LeBoit PE. Lobular capillary proliferation: the underlying process in diverse benign cutaneous vascular neoplasms and reactive conditions. Semin Dermatol 1989; 8(4):298–310.

BACILLARY ANGIOMATOSIS

Clinical Features:
- Immunosuppressed patients (mostly)
  - Few to thousands of lesions
  - Red papules to nodules (Fig. 8A)
  - Some larger, deep lesions skin colored
  - Lesions concentrated around mucous membranes
  - Skin lesions can be accompanied by internal involvement
    - Bone lesions
    - Lymphadenopathy
    - Peliosis hepatis (blood filled cysts in liver)
    - Peliosis splenis

Histology:
- Rounded masses of small vessels in superficial dermis, deep dermis, or both (Fig. 8B)
- Superficial lesions often surrounded by collarette of epithelium
- Endothelial cells have enlarged vesicular nuclei; abundant pink cytoplasm
- Vessels may not be recognizable
- Granular purple clusters of bacteria
- Neutrophils and nuclear dust around bacteria (Fig. 8C)
- Organisms stain with Warthin–Starry silver stain, but not with Gomori methanamine silver, Brown–Brenn (gram), or PAS-D stains (Fig. 8D)

Pathophysiology:
The clusters of bacteria in bacillary angiomatosis are *Bartonella*, in most cases *B. henselae,* but also *B. quintana*. In immunocompetent hosts, these bacilli produce cat scratch disease and trench fever, respectively. The bacilli produce an angiogenic factor(s) that stimulates endothelial cell proliferation and activation.

References:

1. Koehler JE, Sanchez MA, Garrido CS, et al. Molecular epidemiology of bartonella infections in patients with bacillary angiomatosis-peliosis. N Engl J Med 1997; 337(26):1876–1883.
2. LeBoit PE, Berger TG, Egbert BM, Beckstead JH, Yen TS, Stoler MH. Bacillary angiomatosis. The histopathology and differential diagnosis of a pseudoneoplastic infection in patients with human immunodeficiency virus disease. Am J Surg Pathol 1989; 13(11):909–920.

EPITHELIOID HEMANGIOMA

Synonyms: Histiocytoid hemangioma; angiolymphoid hyperplasia with eosinophilia; papular angioplasia; epithelioid angiomatous nodule.

Clinical Features:
- Can occur anywhere, but head most commonly involved; predilection for ear
- Red to red brown papules and nodules (Fig. 9A)
- Rarely, renin-producing lesions associated with hypertension
- Kimura's disease is a different condition, but was formerly thought to be related

Histology:
- Large endothelial cells with abundant eosinophilic cytoplasm and vesicular nuclei (Figs. 9B–D)
- Endothelial cells may have a large intracytoplasmic vacuole
- Endothelial cells can be present in identifiable vessels, or for sheets without discrete vessels.
- Dense lymphoid infiltrates, even lymphoid follicles and eosinophils in stroma in cases designated angiolymphoid hyperplasia with eosinophilia
- Distorted muscular vessels (arterioles or veins) can be present

Differential Diagnosis:

Epithelioid Hemangioma	Bacillary Angiomatosis	Epithelioid Angiosarcoma
Nuclei typical	Nuclei typical or atypical	Nuclei atypical
Lymphocytes and eosinophils	Neutrophils	Lymphocytes, but not eosinophils
Malformed arterioles and veins (sometimes)	No malformed arterioles or veins	No malformed arterioles or veins
No purplish granular clumps (bacilli)	Purplish granular clumps (bacilli)	No purplish granular clumps (bacilli)

Pathophysiology:
The finding of distorted arterioles and veins at the bases of some lesions suggests that they can begin in arteriovenous malformations

References:

1. Brenn T, Fletcher CD. Cutaneous epithelioid angiomatous nodule: a distinct lesion in the morphologic spectrum of epithelioid vascular tumors. Am J Dermatopathol 2004; 26(1): 14–21.
2. Fetsch JF, Weiss SW. Observations concerning the pathogenesis of epithelioid hemangioma (angiolymphoid hyperplasia). Mod Pathol 1991; 4(4):449–455.
3. Urabe A, Tsuneyoshi M, Enjoji M. Epithelioid hemangioma versus Kimura's disease. A comparative clinicopathologic study. Am J Surg Pathol 1987; 11(10):758–766.
4. Olsen TG, Helwig EB. Angiolymphoid hyperplasia with eosinophilia. A clinicopathologic study of 116 patients. J Am Acad Dermatol 1985; 12(5 Pt 1):781–796.

KAPOSI'S SARCOMA

Clinical Features:
- Due to infection by human herpes virus 8 (HHV-8), also known as Kaposi's sarcoma virus
- Older men of Mediterranean descent affected in classic form
- Young Africans affected in African epidemic form
- Associated with immunosuppression in most cases in younger patients (HIV infection, transplant patients)
- Lesions begin as flat pink to red discolorations (macules or patches) (Fig. 10A)
- Later lesions are plaques or nodules (Fig. 11A)
- Lesions few to hundreds

Histology:
The histopathologic features vary so significantly with respect to the development of lesions that they will be considered in terms of patches, plaques, and nodules. There are no significant differences in histopathologic findings between lesions of Kaposi's sarcoma in the different clinical forms listed earlier.

Patch Stage:
- Increased numbers of small spindled cells in reticular dermis, concentrated around pre-existent vessels and adnexa (Figs. 10 B and C)
- Papillary dermis often spared
- Thin walled vessels with angulated lumens
- Spindled cells and thin vessels between collagen bundles in reticular dermis
- Vessel lumens can surround pre-existent structures (promontory sign)
- Few erythrocytes in some early lesions
- Infiltrates of lymphocytes and plasma cells around vessels
- Extravasated erythrocytes, but usually few of them

Plaque Stage:
- Spindled cells more numerous, predominating in areas
- Many extravasated erythrocytes and siderophages
- Eosinophilic globules (small pink intracytoplasmic globules) present often

Nodular Stage:
- Spindle cells form solid masses (Fig. 11B)
- Slit-like spaces between them containing erythrocytes
- Surface rounded and elevated
- Eosinophilic globules (small pink intracytoplasmic globules, Fig. 11C) present almost invariably

Immunohistochemistry:
- Spindle cells are CD31+, Ulex europeus+, variably factor VIIIRAg+, D2-40+
- Nuclei of spindle cells stain for Kaposi's sarcoma virus latent nuclear antigen-1 (Fig. 11D)
- Vessels in patch stage outlined by laminin, type IV collagen

Differential Diagnosis: Patch Stage Kaposi's Sarcoma

Kaposi's Sarcoma	Microvenular Hemangioma	Targetoid Hemosiderotic Hemangioma
Spindle cells outside of recognizable vessels	Few spindle cells outside of recognizable vessels	Few spindle cells outside of recognizable vessels
Promontory sign	No promontory sign	No promontory sign
Angulated lumens	Oval lumens	Angulated lumens
Reticular dermis affected (usually)	Reticular dermis affected (usually)	Papillary and upper reticular dermis affected

Pathophysiology:
Infection with Kaposi's sarcoma virus leads to the production of a viral homolog of human interleukin-6 and other angiogenic factors.

References:

1. Klouche M, Carruba G, Castagnetta L, Rose-John S. Virokines in the pathogenesis of cancer: focus on human herpesvirus 8. Ann NY Acad Sci 2004; 1028:329–339.
2. Ackerman AB. Subtle clues to diagnosis by conventional microscopy. The patch stage of Kaposi's sarcoma. Am J Dermatopathol 1979; 1(2):165–172.
3. Hong A, Davies S, Lee CS. Immunohistochemical detection of the human herpes virus 8 (HHV8) latent nuclear antigen-1 in Kaposi's sarcoma. Pathology 2003; 35(5):448–450.

ANGIOSARCOMA

Clinical Features:
- Almost always occurs in stereotypic settings
  - Head and face of elderly most common (Fig. 12A)
  - Lymphedematous limbs
  - Postmastectomy
  - Postradiation
- Pink patches to red plaques and nodules
- Appears especially on face and head and can extend far beyond obvious skin discoloration
- Treatment wide excision; radiation when possible
- High fatality rate unless detected early

Rare Low Grade Forms:
- Epithelioid hemangioendothelioma
- Retiform hemangioendothelioma
- Dabska's tumor

Histology:

Early Lesions:

- Angulated vessels positioned between collagen bundles in reticular dermis
- Endothelial cells have hyperchromatic nuclei
- Papillations of endothelial cell extend into vessel lumens
- Erythrocytes in vessel lumens (often)

Fully Developed Lesions:

- Solid masses of spindled or epithelioid neoplastic cells (Figs. 12B–D)
- Lumens may be inapparent
- Lymphoid nodules (often)

Epithelioid Hemangioendothelioma:

- Dermis diffusely infiltrated by nests and strands of neoplastic endothelial cells
- Constituent cells have abundant pale cytoplasm, sometimes with prominent cytoplastic vacuoles.
- Epidermal hyperplasia variable
- Mucinous stroma

Retiform Hemangioendothelioma:

- Large dermal and/or subcutaneous mass
- Branching, elongated lumens lined by plump to cuboidal endothelial cells (similar in pattern to rete testis)
- Variable fibrosis and lymphocytic infiltrates

Immunohistochemistry:

- Factor VIIIRag, Ulex europeus agglutinin, CD31, CD34 usually positive, D2-40 sometimes positive in conventional angiosarcoma. Loss of one or more endothelial markers is relatively frequent.

Clinicopathologic Correlation:

Subclinical extension of the edges of the neoplasm corresponds to dilated vessels with subtle atypia of endothelial cells.

Differential Diagnosis:

Angiosarcoma	Kaposi's Sarcoma
Endothelial cells hyperchromatic	Endothelial cells euchromatic
Papillations in vascular lumens	No papillations in vascular lumens
Spindle cells randomly positioned in early lesions	Spindle cells around vessels and adnexa in early lesions
KSV latent nuclear antigen negative	KSV latent nuclear antigen positive

References:

1. Morgan MB, Swann M, Somach S, Eng W, Smoller B. Cutaneous angiosarcoma: a case series with prognostic correlation. J Am Acad Dermatol 2004; 50(6):867–874.
2. Quante M, Patel NK, Hill S, et al. Epithelioid hemangioendothelioma presenting in the skin: a clinicopathologic study of eight cases. Am J Dermatopathol 1998; 20(6):541–546.
3. Calonje E, Fletcher CD, Wilson-Jones E, Rosai J. Retiform hemangioendothelioma. A distinctive form of low-grade angiosarcoma delineated in a series of 15 cases. Am J Surg Pathol 1994; 18(2): 115–125.

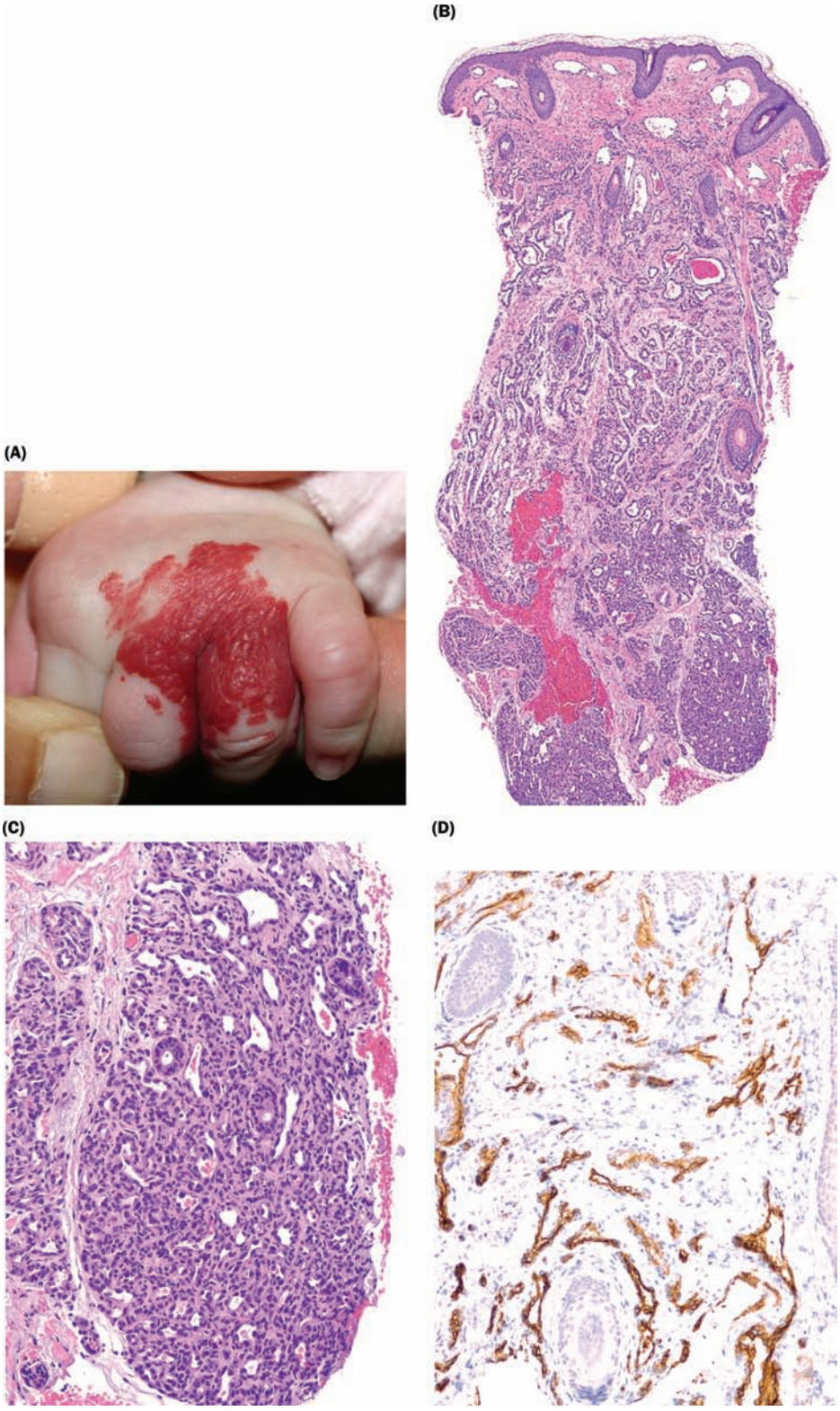

Figure 1 (**A**) An infantile hemangioma on a hand. (**B**) Infantile hemangioma, showing a lobular proliferation of small vessels in both the superficial and deep dermis. (**C**) Infantile hemangioma. The vessels in actively growing or stable lesions are closely packed. (**D**) Infantile hemangioma. A Glut-1 stain marks the endothelial cells.

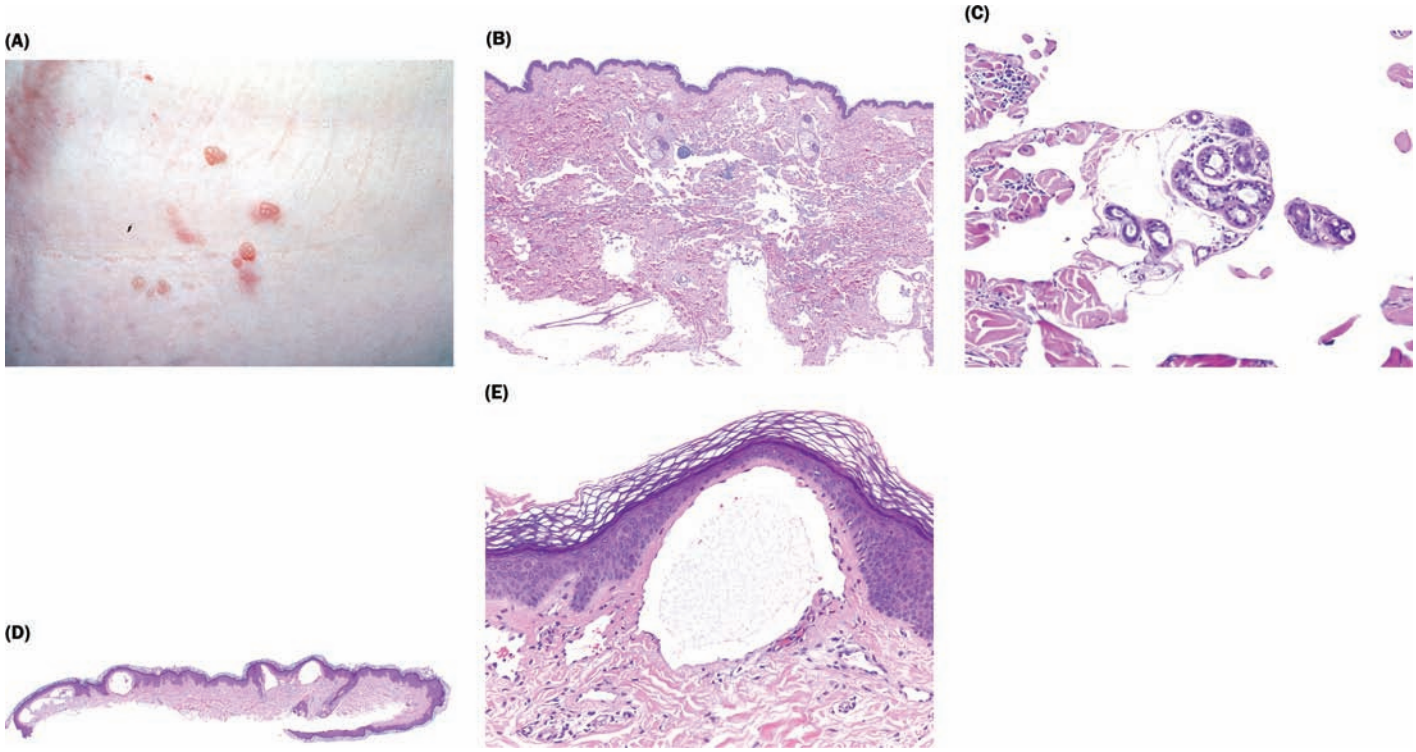

Figure 2 Lymphangioma. (**A**) Small vesicle-like blebs are present on the surface of the lesion in lymphangioma circumscriptum. (**B**) Dilated thin walled vessels with irregularly shaped lumens are present in both the superficial and deep dermis. (**C**) Note that pre-existent structures, here an eccrine coil, can protrude into vascular lumens. (**D**) Lesions in which vessels approach the surface evoke epidermal hyperplasia. (**E**) A dilated lumen containing pale pink material, lymph, appears to almost touch the undersurface of the epidermis.

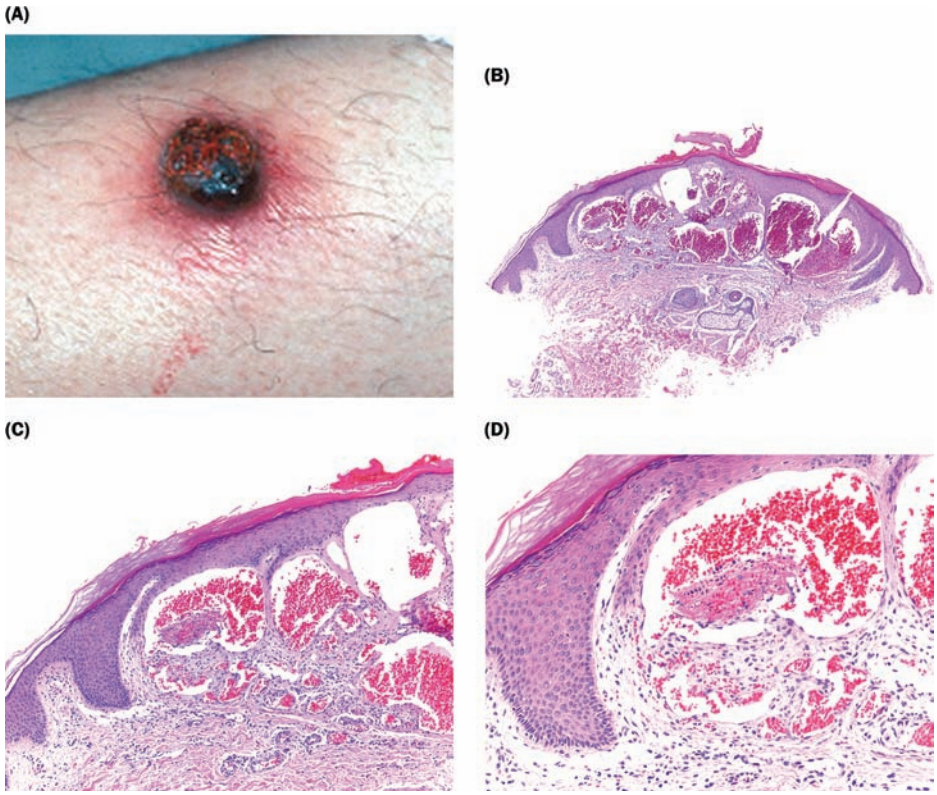

Figure 3 Angiokeratoma. (**A**) A raised, dark red papule protrudes from a leg. (**B**) A domed surface is present, with subjacent dilated thin walled vessels that contain erythrocytes. (**C**) The dilated vessels nearly touch the epidermal undersurface. (**D**) A thrombus is present in a vascular lumen.

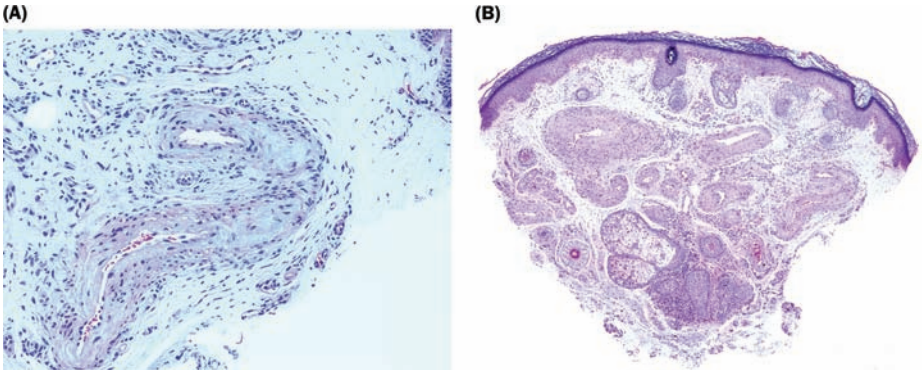

Figure 4 Arteriovenous hemangioma. (**A**) There are thick walled vessels with muscular walls in the reticular dermis. (**B**) The constituent vessels have both oblong and oval lumens, and are not all easily classifiable as either arterioles or veins.

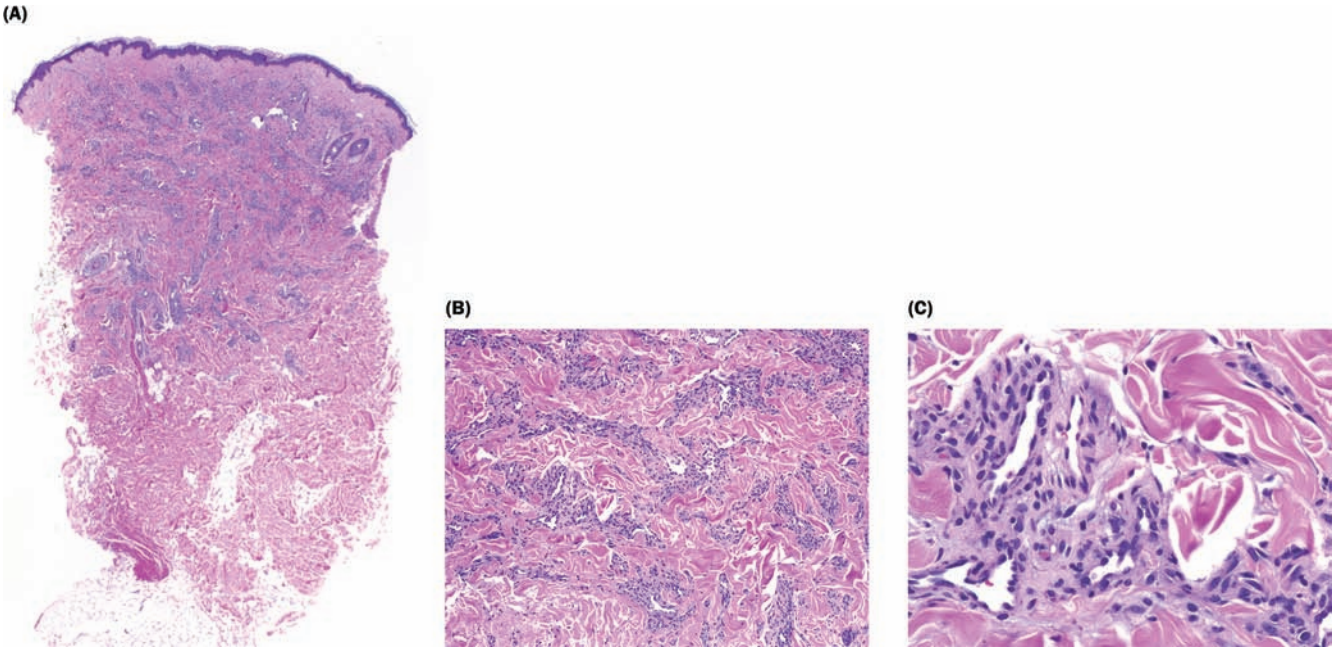

Figure 5 Microvenular hemangioma. (**A**) The reticular dermis is permeated by small caliber vessels, diffusely distributed. (**B**) There are few spindled cells between the small vessels. (**C**) The vessels have oval lumens.

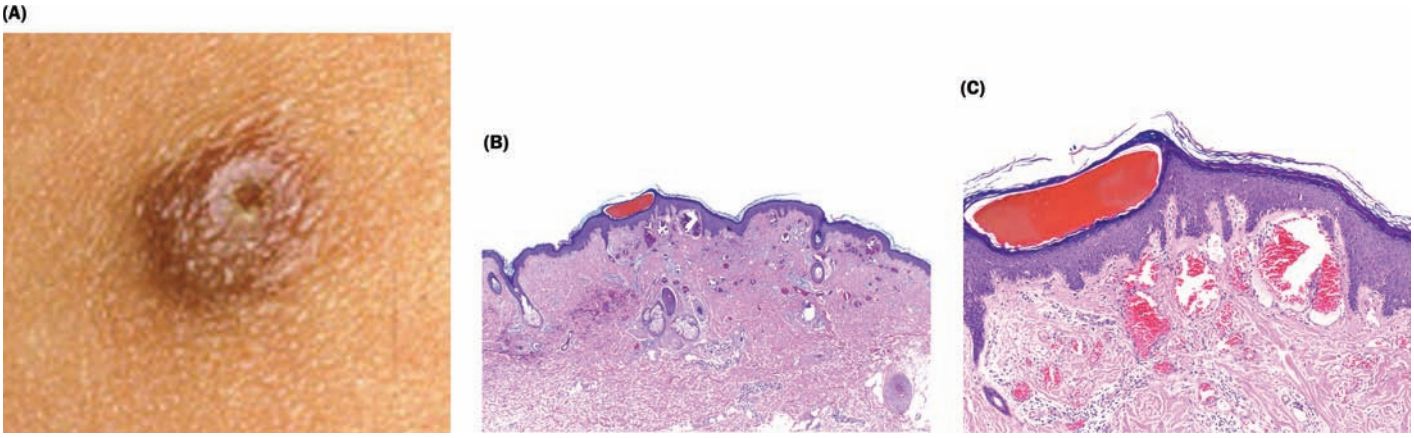

Figure 6 Targetoid hemosiderotic hemangioma. (**A**) There is a reddish-brown papule with a faint rust colored macule around it. (**B**) The center of the lesion is raised, and contains dilated erythrocyte filled thin walled vessels. (**C**) Some of the central, superficial vessels come close to the undersurface of the epidermis, resembling an angiokeratoma. (**D**) Peripheral vessels with small lumens positioned between collagen bundles can simulate Kaposi's sarcoma. (*Continued*)

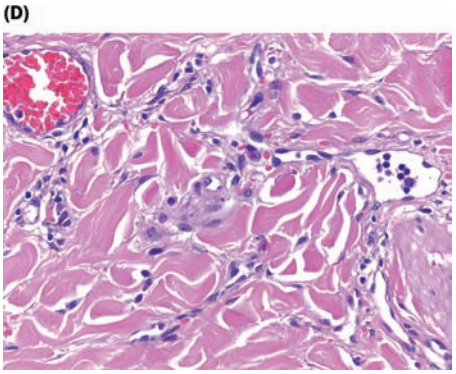

Figure 6 *Continued.*

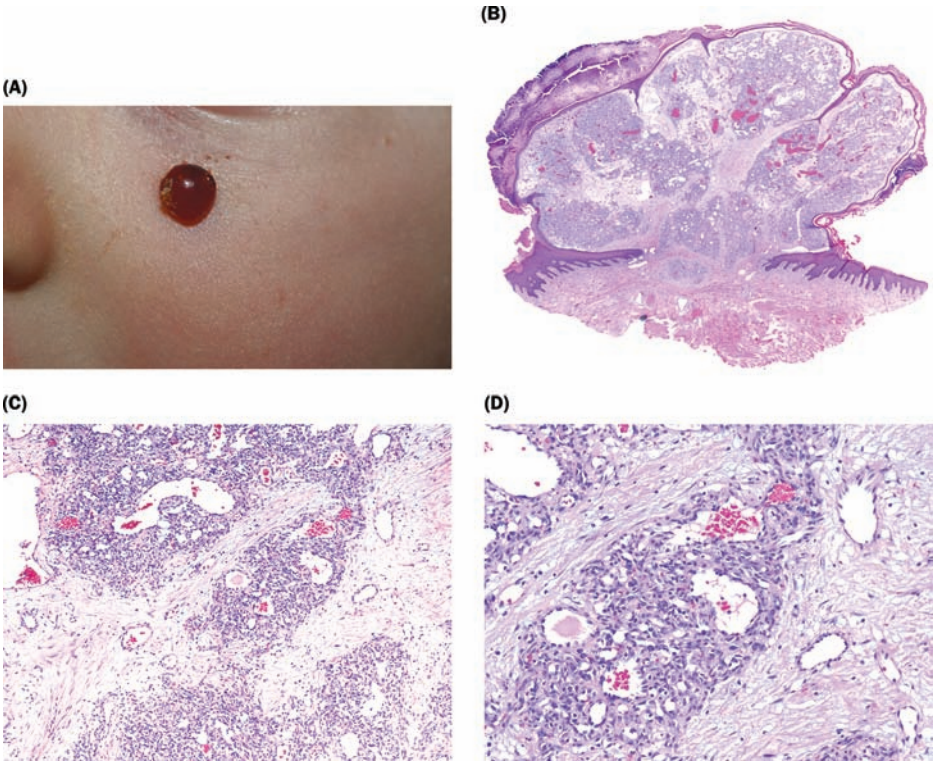

Figure 7 Pyogenic granuloma. (**A**) A typical exophytic papule on the face. (**B**) The protuberant vascular proliferation is surrounded by an epithelial collarette. (**C**) The lobules of the pyogenic granuloma are separated from one another by bands of fibrous tissue. (**D**) Within the lobules are vessels with narrow lumens, many pericytes (seen only as small bland spindled cells) and vessels with more capacious lumens containing erythrocytes.

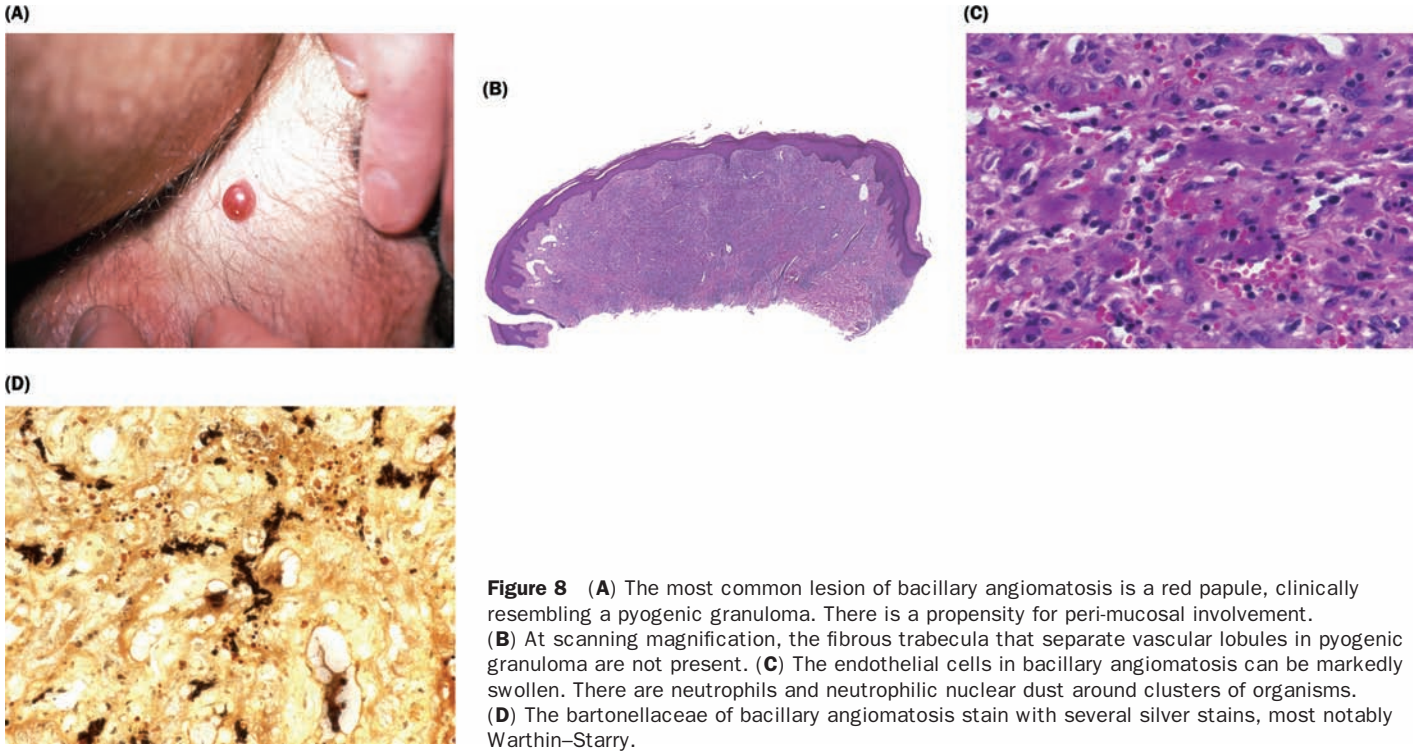

Figure 8 (**A**) The most common lesion of bacillary angiomatosis is a red papule, clinically resembling a pyogenic granuloma. There is a propensity for peri-mucosal involvement. (**B**) At scanning magnification, the fibrous trabecula that separate vascular lobules in pyogenic granuloma are not present. (**C**) The endothelial cells in bacillary angiomatosis can be markedly swollen. There are neutrophils and neutrophilic nuclear dust around clusters of organisms. (**D**) The bartonellaceae of bacillary angiomatosis stain with several silver stains, most notably Warthin–Starry.

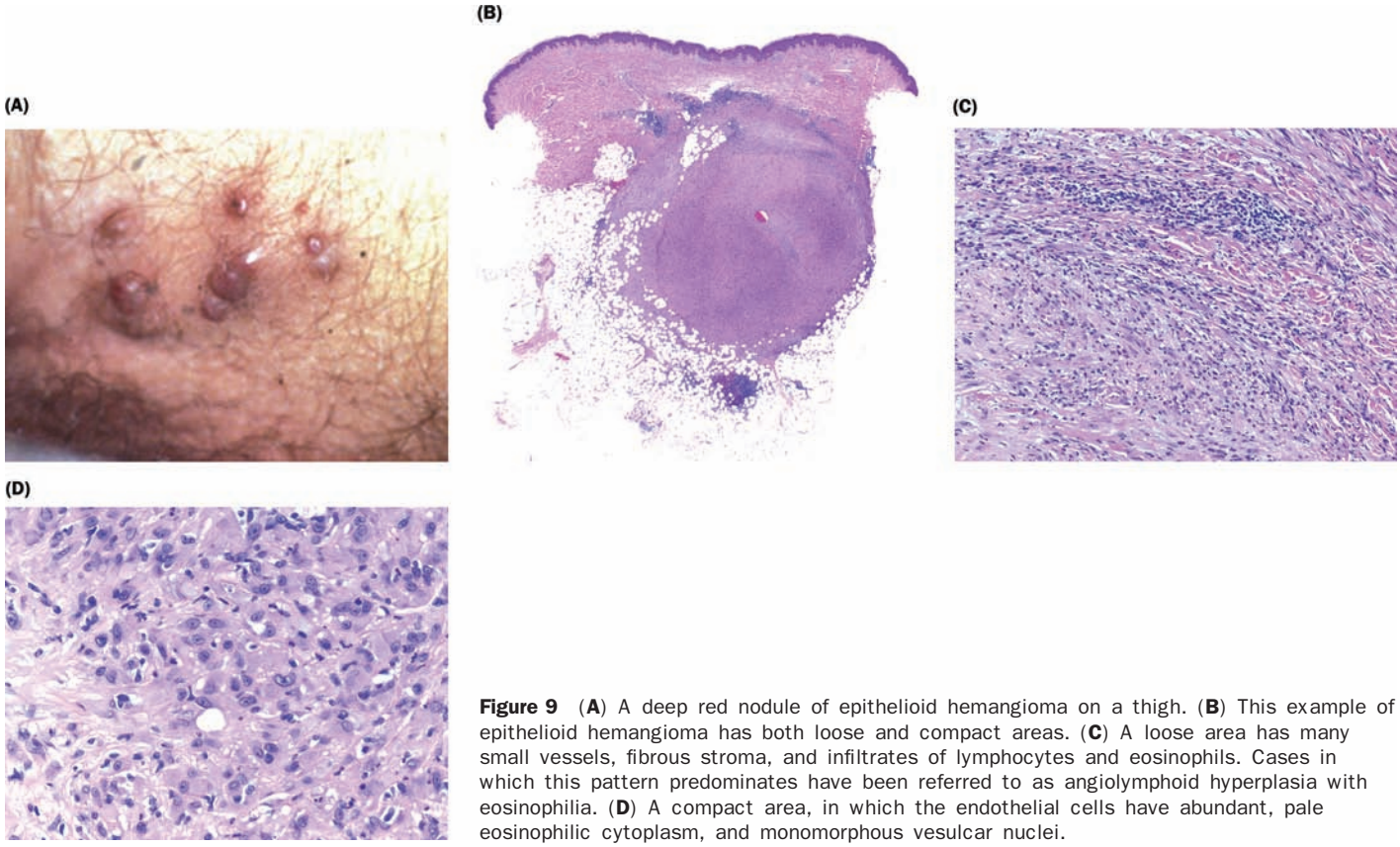

Figure 9 (**A**) A deep red nodule of epithelioid hemangioma on a thigh. (**B**) This example of epithelioid hemangioma has both loose and compact areas. (**C**) A loose area has many small vessels, fibrous stroma, and infiltrates of lymphocytes and eosinophils. Cases in which this pattern predominates have been referred to as angiolymphoid hyperplasia with eosinophilia. (**D**) A compact area, in which the endothelial cells have abundant, pale eosinophilic cytoplasm, and monomorphous vesulcar nuclei.

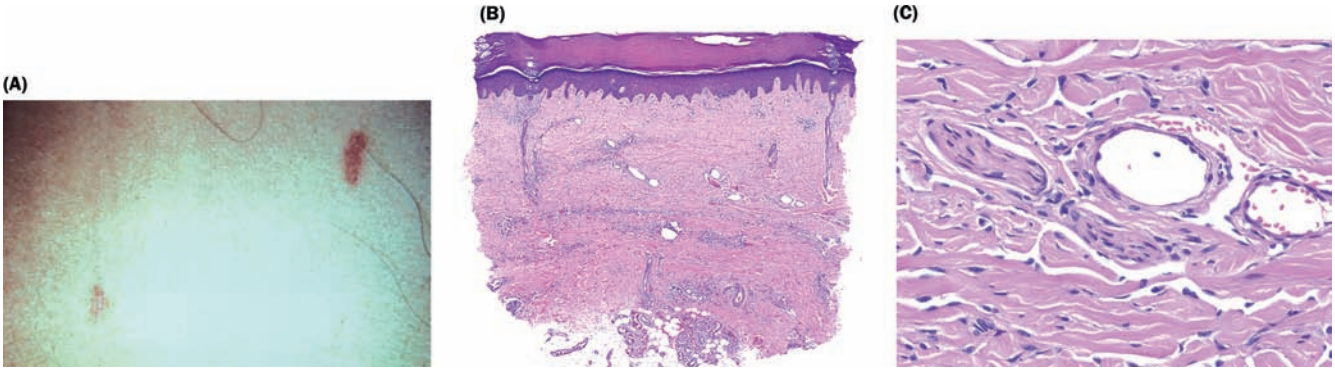

Figure 10 (**A**) Macules and patches of Kaposi's sarcoma are flat pink to red lesions. (**B**) The patch stage of Kaposi's sarcoma can be difficult to recognize at scanning magnification. Clues to diagnosis include an increase in cellularity around pre-existent vascular and epithelial adnexal structures. (**C**) Spindled cells, now recognized as endothelial intercalate between collagen bundles in the reticular dermis in the patch of Kaposi's sarcoma. Some newly formed vessels surround pre-existent round vessels and nerve fascicles.

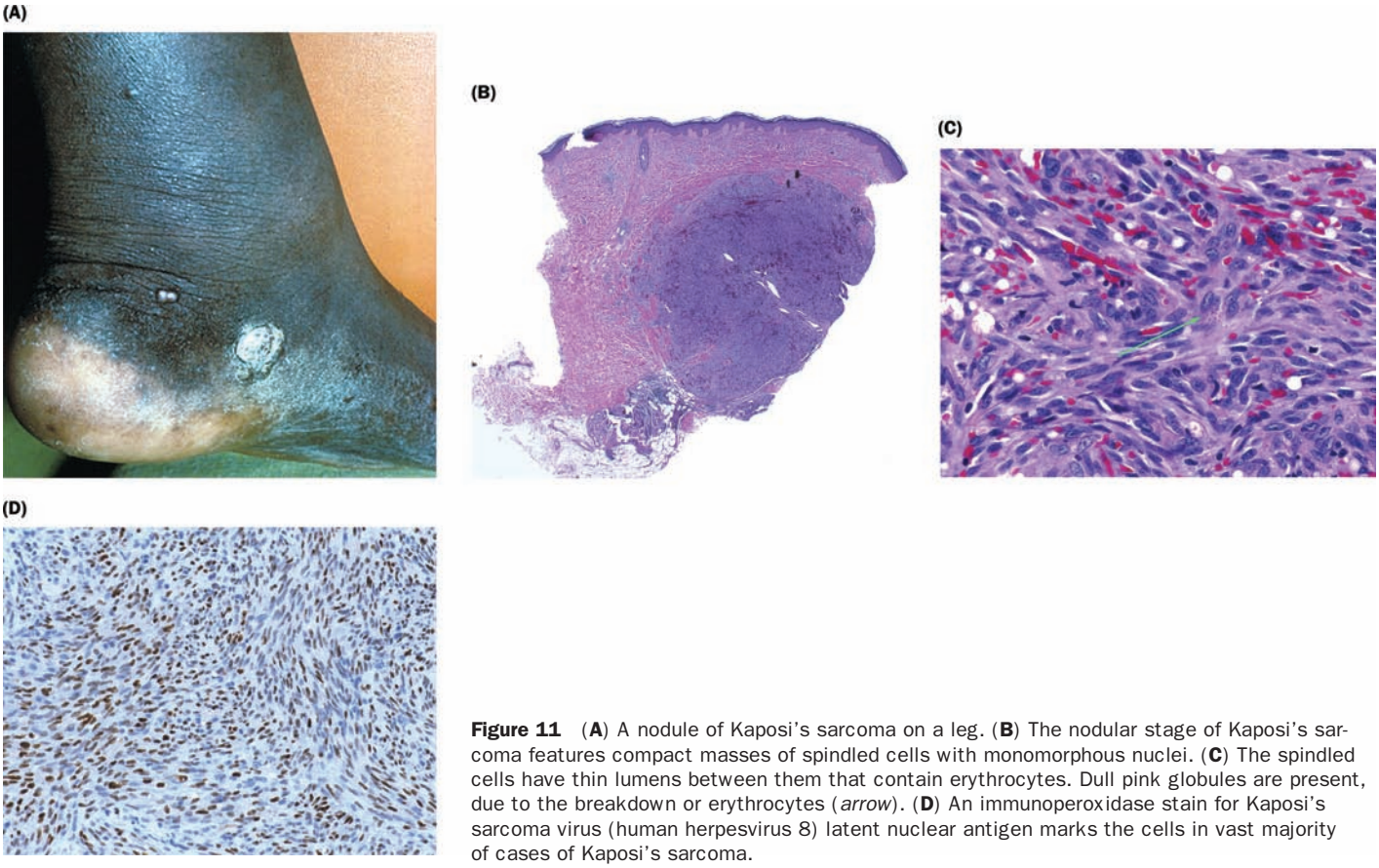

Figure 11 (**A**) A nodule of Kaposi's sarcoma on a leg. (**B**) The nodular stage of Kaposi's sarcoma features compact masses of spindled cells with monomorphous nuclei. (**C**) The spindled cells have thin lumens between them that contain erythrocytes. Dull pink globules are present, due to the breakdown or erythrocytes (*arrow*). (**D**) An immunoperoxidase stain for Kaposi's sarcoma virus (human herpesvirus 8) latent nuclear antigen marks the cells in vast majority of cases of Kaposi's sarcoma.

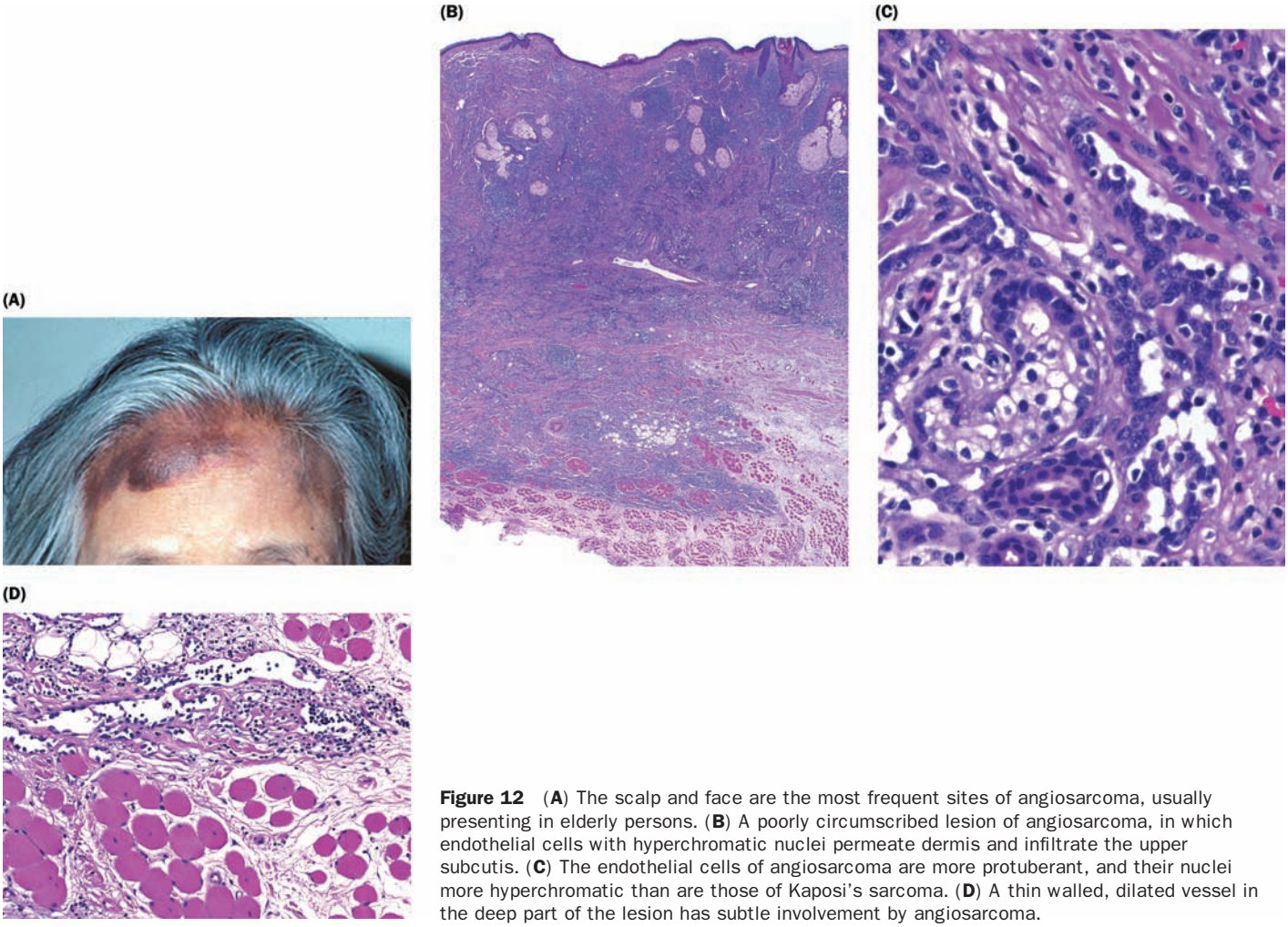

Figure 12 (**A**) The scalp and face are the most frequent sites of angiosarcoma, usually presenting in elderly persons. (**B**) A poorly circumscribed lesion of angiosarcoma, in which endothelial cells with hyperchromatic nuclei permeate dermis and infiltrate the upper subcutis. (**C**) The endothelial cells of angiosarcoma are more protuberant, and their nuclei more hyperchromatic than are those of Kaposi's sarcoma. (**D**) A thin walled, dilated vessel in the deep part of the lesion has subtle involvement by angiosarcoma.

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Neural Neoplasms

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CONTENTS

The term "neural neoplasms" is somewhat deceptive because most common tumors of the peripheral nervous system consist not only of nerves, but also of a variety of other cellular elements such as Schwann cells and fibroblasts. An understanding of the basic structure of peripheral nerves will aid in understanding the classification of these tumors. Nerves are composed of bundles of both sensory and motor nerve fibers surrounded by connective tissue. Individual nerve fibers are enveloped by myelin produced by Schwann cells. The nerve fibers and Schwann cells are housed within connective tissue called endoneurium. Another layer of connective tissue called perineurium surrounds these packages of nerves, myelin, and endoneurium. Tumors of the peripheral nervous system may arise from any of the tissue types within a nerve bundle. The most common of these tumors are discussed below.

NEUROFIBROMA

Synonyms: Plexiform neurofibroma; elephantiasis neuromatosis (large neurofibroma, often plexiform, in subcutis); Von Recklinhausen's disease (classic type I neurofibromatosis).

Clinical Presentation:

Solitary Neurofibromas:

- Common sporadic tumors
- Nondescript soft pink-brown papules or nodules (up to 3 cm in diameter) (Fig. 1A)
- Any site and any age, most common in second and third decades

Multiple Neurofibromas:

- May be sporadic or associated with neurofibromatosis (eight clinical subtypes)
- Type I (classic) neurofibromatosis: autosomal dominant, features multiple café au lait macules, axillary freckling, Lisch nodules (Figs. 1B and 2C)
- Plexiform neurofibromas nearly pathognomonic for neurofibromatosis, resemble "bag of worms" in soft tissue (Fig. 2A), pendulous skin referred to as "elephantiasis neuromatosa"
- Diffuse and segmental neurofibromas also markers for neurofibromatosis (Fig. 1C)

Histopathology:

- Well-circumscribed but nonencapsulated dermal lesions (Fig. 1D)
- Bland spindle cell tumors haphazardly placed in myxoid stroma, interspersed with variable amounts of collagen (Figs. 3A–D)
- Nuclei of spindle cells "S" shaped, with tapered ends (Fig. 3B)
- Mixture of cell types: Schwann cells, fibroblasts, residual nerve fibers and mast cells
- Staining patterns: Bodian stain and neurofilament + (axons), S100 + (Schwann cells and axons), Type IV collagen + (fibroblasts), epithelial membrane antigen may be + (perineural cells), Giemsa + mast cells are abundant (Figs. 4A–D)
- Plexiform neurofibroma: hypertrophied nerve bundles in deep dermis and subcutis (Fig. 2B)
- Diffuse neurofibroma: diffuse infiltration of the dermis and subcutis by spindle cells typical of neurofibroma; about 10% patients have neurofibromatosis

Clinicopathologic Correlation:

Clinical Feature	Pathologic Feature
Soft papules that invaginate on pressure then return to level of skin ("buttonhole sign")	Delicate spindle cells in loose myxoid stroma
Folds of skin feeling like bag of worms on palpation (plexiform neurofibroma)	Expanded nerves in plexiform bundles in deep dermis and/or subcutis
Flat pigmented patch (café au lait macule)	Increased melanin in basal layer, epidermis
Pigmented spots in iris (Lisch nodules)	Hamartoma containing melanin in iris

Pathophysiology:
In classic Type I neurofibromatosis, mutations of chromosome 17 cause inactivation of the protein product "neurofibromin," and are related to the development of multiple neurofibromas. The cause of sporadic solitary neurofibromas is not known. A small proportion of patients with neurofibromatosis (2–5%) develop malignant nerve sheath tumors.

References:

1. Tsao H. Update on familial cancer syndromes and the skin. J Am Acad Dermatol 2000; 42:939–969.
2. Requena L, Sangueza OP. Benign neoplasms with neural differentiation: a review. Am J Dermatopathol 1995; 17:75–96.

SCHWANNOMA

Synonyms: Neurilemmoma; acoustic neuroma; neurinoma; "schwannomatosis" if multiple.

Clinical Presentation:
- Isolated nodules in deep soft tissue or dermis, may be tender
- Any site and age; head and extremities most common

Histopathology:
- Encapsulated collection of spindle cells in subcutis or dermis (Fig. 5A)
- Biphasic growth pattern: dense aggregates of spindle cells ("Antoni A areas") (Figs. 5B and C) and paucicellular myxoid areas with bland stellate cells ("Antoni B areas") (Fig. 5D)
- Spindle cells tend to palisade, and may form "Verocay bodies" where nuclei line up around less cellular areas of matrix (Fig. 5C)
- Staining pattern: S-100 protein and CD57 + (Schwann cells), collagen Type IV + (stroma), Bodian stain and neurofilament − (neurons/axons absent) (Figs. 6A and B)
- Cystic degeneration may occur, vessels may be hyalinized (Fig. 6C)
- Usually few mitotic figures; when numerous, may indicate malignant change

Numerous Histologic Variants:
- Ancient schwannomas: degenerative changes, bizarre cytology (Fig. 6D)
- Plexiform schwannomas: intersecting fascicles throughout dermis (but not typically associated with classic Type I neurofibromatosis)
- Psammomatous melanotic schwannomas contain melanin and calcified psammoma bodies (associated with Carney's syndrome)

Differential Diagnosis:

Neurofibroma	Schwannoma
Unencapsulated	Encapsulated by perineurium
Usually no underlying nerve	Attached to underlying nerve
Usually centered in dermis	Usually centered in subcutis

(*Continued*)

Differential Diagnosis: *Continued*

Neurofibroma	Schwannoma
Haphazard lattice of spindle cells without palisaded nuclei or verocay bodies	Palisaded nuclei and verocay bodies alternate with hypocellular areas
Composed of axons, Schwann cells, fibroblasts	Contain Schwann cells, fibroblasts; no axons
Plexiform variant associated with classic neurofibromatosis	Plexiform variant rare, not associated with classic neurofibromatosis

Pathophysiology:
Schwannomas result from proliferation of Schwann cells within the perineurium, forming an encapsulated tumor. The explanation for Schwann cell proliferation is not clear, although abnormalities of the gene product of neurofibromatosis type 2 on chromosome 22 have been implicated in some cases.

References:

1. Argenyi ZB, Balough K, Abraham AA. Degenerative ("ancient") changes in benign cutaneous schwannoma. A light microscopic, histochemical and immunohistochemical study. J Cutan Pathol 1993; 20:148–153.
2. Megahed M. Plexiform schwannoma. Am J Dermatopathol 1994; 16:288–293.

NEUROMA

PALISADED ENCAPSULATED NEUROMA

Synonym: Solitary circumscribed neuroma.

Clinical Features:
- Small tan-pink papules
- Usually on face of adults, without gender predilection

Histopathology:
- Centered in the mid dermis, encapsulated or nearly so (Fig. 7A)
- Intersecting fascicles of bland spindle cells show nuclear palisades (Fig. 7B)
- Scattered axons and Schwann cells present
- Staining pattern: neurofilament + (axons), S100 protein + (Schwann cells), epithelial membrane antigen + (perineurial capsule) (Figs. 7C and D)

TRAUMATIC NEUROMA

Synonyms: Rudimentary supernumerary digit; rudimentary polydactyly; Morton's neuroma.

Clinical Features:
- Nonspecific firm nodule typically on extremities (sites of trauma), may be painful
- Rudimentary supernumerary digit (ulnar base of the 5th finger): traumatic neuroma from postnatal or in utero destruction of true supernumerary digit (Fig. 8A)
- Morton's neuroma: non-neoplastic fibrosis of the plantar digital nerve.

Histopathology:

- Haphazard collections of small nerves in sclerotic stroma (Fig. 9A)
- Hypertrophic nerves trapped in dense fibrous tissue (Fig. 9B)

Pathophysiology:

Traumatic neuromas are not true neoplasms; they represent aberrant reinnervation after trauma.

MUCOSAL NEUROMA

Clinical Features:

- Papules on mucosa of lips, mouth, eyelids (Fig. 10A). Seen in patients with multiple endocrine neoplasia Type IIb/III (with pheochromocytoma, C-cell hyperplasia, medullary carcinoma of thyroid and parathyroid hyperplasia).

Histopathology:

- Hypertrophic nerve bundles scattered in submucosa (Fig. 10B)
- Nerves surrounded by thickened perineurium

Differential Diagnosis:

Palisaded Encapsulated Neuroma	Traumatic Neuroma	Mucosal Neuroma
Benign neoplasm	Nonneoplastic	Nonneoplastic
Encapsulated	Nonencapsulated	Nonencapsulated
Solid circumscribed lesion, fascicles of nerve fibers	Separate nerves trapped in collagen	Hypertrophied nerves in submucosa

References:

1. Fletcher CDM. Solitary circumscribed neuroma of the skin (so called palisaded encapsulated neuroma). Am J Surg Pathol 1989; 13:574–580.
2. Argenyi ZB, Santa Cruz D, Bromley C. Comparative light-microscopic and immunohistochemical study of traumatic and palisaded encapsulated neuromas of the skin. Am J Dermatopathol 1992; 14:504–510.

NEUROTHEKEOMA

Synonyms: Nerve sheath myxoma; myxoma of nerve sheath; cutaneous lobular myxoma; perineural myxoma; plexiform myxoma.

TYPE I: CLASSIC NEUROTHEKEOMA (NERVE SHEATH MYXOMA)

Clinical Features:

- Nontender soft tan nodule of head and neck, sometimes upper extremities
- Patients typically woman under 30 years old

Histopathology:

- Sharply circumscribed lobules of myxoid tissue in dermis (Fig. 11A)
- Scantly cellular, nuclei may be spindled or epithelioid, but are bland (Fig. 11B)
- Typically S100+, may be tumor of Schwann cells or perineurium; axons are absent (Bodian and neurofilament stains) (Fig. 11C).

TYPE II: CELLULAR NEUROTHEKEOMA

Clinical Features:

- Nonspecific dermal nodule
- Trunk, extremities, or head and neck of young adults

Histopathology:

- Ill-defined nodular growth pattern in dermis (Fig. 12A)
- Cells are large, epithelioid, with oval nuclei and abundant cytoplasm (Fig. 12B)
- Cytologic atypia and occasional mitoses may be seen, minimal myxoid stroma
- Staining pattern: S100−, neuroectodermal marker protein gene product (PGP) 9.5+, actin± (Figs. 12C and D)

Differential Diagnosis:

Classic Myxoid Neurothekeoma	Cellular Neurothekeoma
Well-circumscribed, lobular	Ill-defined, infiltrative
Abundant mucin	Scant mucin
Spindled or stellate cells	Epithelioid or polygonal cells
Scant cytoplasm	Abundant cytoplasm
Mitoses few in number	Mitoses may be numerous
Stain + for S-100 protein and Type IV collagen	Stain—for S-100 protein and neural markers

Pathophysiology:

The histogenesis of cellular neurothekeoma is unclear. Some neurothekeomas, labeled "Type III," show mixed features of both myxoid and cellular variants. Nonetheless, insufficient evidence exists to date to enable classification of purely cellular tumors.

References:

1. Argenyi ZB, LeBoit PE, Santa Cruz D, Swanson PE, Kutzner H. Nerve sheath myxoma (neurothekeoma) of the skin: light microscopic and immunohistochemical reappraisal of the cellular variant. J Cutan Pathol 1993; 20:294–303.
2. Barnhill RL, Mihm MC. Cellular neurothekeoma. A distinctive variant of neurothekeoma mimicking nevomelanocytic tumors. Am J Surg Pathol 1990; 14:113–120.
3. Fetsch JF, Laskin WB, Miettinen M. Nerve sheath myxoma. Am J Surg Pathol 2005; 29:1615–1624.

GRANULAR CELL TUMOR

Synonyms: Granular cell myoblastoma; granular cell neuroma; granular cell neurofibroma; granular cell schwannoma; Abrikossoff tumor.

Clinical Features:

- Solitary painless tan dome-shaped nodule, may be brown-red (Fig. 13A)
- Any age, often head and neck including tongue, multiple lesions in about 10%

Histopathology:

- Poorly circumscribed proliferation of epithelioid cells through the dermis (Fig. 13B)
- Eosinophilic granular periodic acid-Schiff + (PAS+) cytoplasm, round to oval uniform nuclei (Fig. 13C)
- May have verrucous epidermal hyperplasia
- Cells often associated with capsules of small cutaneous nerves (Fig. 13C)
- Immunostaining: S-100 protein+, CD57+, neurofilament—(Fig. 13D)
- Atypical mitoses, necrosis, ulceration are clues to malignant granular cell tumor, which are large, grow rapidly, and frequently metastasize

Clinicopathologic Correlation:

Clinical Feature	Pathologic Feature
Dome shaped	Dermis filled with granular cells
Hyperkeratotic, resembling wart or squamous cell carcinoma	Marked pseudoepitheliomatous hyperplasia and/or ulceration

Differential Diagnosis:

Granular Cell Tumor	Cellular Neurothekeoma	Leiomyoma	Spitz Nevus
Poorly circumscribed	Poorly circumscribed	Poorly circumscribed	Poorly circumscribed
Round cells with prominent granules	Round cells without granules	Usually spindle cells	Round and spindle cells, no granules
S-100 protein+	S-100 protein−	S-100 protein−	S-100 protein+
PAS + granules	PAS−	PAS−	PAS−

Pathophysiology:

Presumed to be tumor of nerve sheath origin, although precise cell of origin not clear. Granules are composed of lysosomes, and may be giant in size.

References:

1. Ordonez NG. Granular cell tumor: a review and update. Adv Anat Pathol 1999; 6:186–203.
2. Miracco C, Andreassi A, Laurini L, De Santi MM, Taddeucci P, Tosi P. Granular cell tumour with histological signs of malignancy: report of a case and comparison with 10 benign and 4 atypical cases. Br J Dermatol 1999; 141:573–575.

RUDIMENTARY MENINGOCELE

Synonyms: Cutaneous meningioma; heterotopic meningeal tissue.

Clinical Features:

- Solitary nodule on scalp or over vertebral column (Fig. 14A)
- Usually alopecic, may be surrounded by "hair collar."
- Radiologic studies necessary to rule out communication with underlying central nervous system (CNS)
- Other variants of cutaneous meningioma include meningiomas of sensory organs (eye, ear) that secondarily invade skin, and meningiomas of the CNS that metastasize to skin (both are true tumors, rather than congenital malformations)

Histopathology:

- Islands of meningothelial cells in sclerotic dermis with dilated vessels (Fig. 14B)
- Cells form sheets, oval nuclei with pale cytoplasm (Fig. 14C)
- Calcified psammoma bodies and other glial elements may be present
- Meningothelial cells stain for epithelial membrane antigen and vimentin (Fig. 14D)

Differential Diagnosis:

True Meningioma	True Meningocele	Rudimentary Meningocele	Glial Heterotopia (Nasal Glioma)
Often connected to underlying meninges, involves skin by continuity	Connection to underlying meninges, congenital malformation	No connection to meninges, although fibrous stalk may be present	Connection to underlying central nervous system in 20%
Tumor of meninges of central nervous system	Defect of neural tube closure	Ectopic meningothelial rests in skin and subcutis	Ectopic glial tissue in skin, typically nasal sidewall
Neoplasm involves skin secondarily	Non-neoplastic	Non-neoplastic	Non-neoplastic

Pathophysiology:

Cases of rudimentary meningocele tend to occur along sites of neural tube closure, suggesting that failure to achieve complete fusion of the neural tube during development allows for persistence of meningothelial and sometimes glial elements in the skin.

References:

1. Shabrawi-Caelen LE, White WL, Soyer HP, Kim BS, Frieden IJ, McCalmont TH. Rudimentary meningocele: remnant of a neural tube defect? Arch Dermatol 2001; 137:45–50.
2. Berry AD, Patterson JW. Meningoceles, meningomyeloceles, and encephaloceles: a neuro-dermatopathologic study of 132 cases. J Cutan Pathol 1990; 18:164–177.

MERKEL CELL CARCINOMA

Synonyms: Cutaneous neuroendocrine carcinoma; trabecular carcinoma.

Clinical Features:

- Sun-exposed skin of elderly Caucasians (head, neck, extremities) (Fig. 15A)
- Usually solitary, may be multiple
- Aggressive behavior, recurrence rate 36%, metastatic rate 50%

Microscopic features:

- Sheets of small blue tumor cells in dermis, mitoses numerous (Fig. 15B)
- Cells have scanty cytoplasm and ill-defined borders (Fig. 15C)
- Vesicular nuclei tend to mold around one another (Fig. 15C)
- Rare cases show pagetoid scatter of Merkel cells in epidermis, may mimic melanoma
- Characteristic perinuclear dot-like staining with cytokeratins 20, cam5.2, mnf116, and vimentin (Fig. 15D)
- Diffuse staining for cluster designation (CD) 56 (neural cell adhesion molecule)
- No staining for thyroid transcriptase 1 (TTF-1); neuroendocrine carcinoma of lung metastatic to skin usually TTF-1 positive

Differential Diagnosis:

Merkel Cell Carcinoma	Metastatic Neuroendocrine Carcinoma	Melanoma	Lymphoma
Salt and pepper chromatin	Salt and pepper chromatin	Large nucleoli	Smooth chromatin or prominent nucleoli
Nuclear molding	Nuclear molding	No nuclear molding	No nuclear molding
CK20 +	Most CK20−	CK20−	CK 20−
CD56 +	CD56 +	CD56−	CD56 ±
TTF-1−	TTF-1 +	TTF ±	TTF-1−
S-100−	S-100−	S-100 +	S-100−
LCA−	LCA −	LCA−	LCA+

***Abbreviation*: LCA, leukocyte common antigen.**

References:

1. Scott MP, and Helm KF. Cytokeratin 20: a marker for diagnosing Merkel cell carcinoma. Am J Dermatopathol 1999; 21:16–20.
2. Hanly AJ, Elgart GW, Jorda M, Smith J, Nadji M. Analysis of thyroid transcription factor-1 and cytokeratin 20 separates Merkel cell carcinoma from small cell carcinoma of lung. J Cutan Pathol 2000; 27:118–120.
3. Mott RT, Smoller GR, Morgan MB. Merkel cell carcinoma: a clinicopathologic study with prognostic implications. J Cutan Pathol 2004; 31:217–223.

MALIGNANT PERIPHERAL NERVE SHEATH TUMOR

Synonyms: Malignant schwannoma; malignant neurilemmoma; neurofibrosarcoma.

Clinical Features:

- Seen in the setting of neurofibromatosis (>50% cases) but also occurs sporadically
- Deeply situated mass typically on lower extremity, may be associated with pain

Microscopic Features:

- Associated with underlying nerve, usually in deep soft tissue. In skin, typically in subcutis but may occur in dermis.
- Highly cellular with necroses and abnormal mitoses (Figs. 16A and B).
- May show nuclear palisading or differentiation toward neural structures (Fig. 16C).
- Differentiation toward skeletal muscle called "Triton tumor" (Fig. 16D).

Clinicopathologic Correlation:

Clinical Feature	Pathologic Feature
New firm growing deep soft tissue mass in patient with neurofibromatosis	Large mass of atypical spindle cells, mitoses and necrosis, S-100 protein positive

References:

1. Sangueza OP, Requena L. Neoplasms with neural differentiation. Part II: Malignant neoplasms. Am J Dermatopathol 1998; 20:89–102.
2. Misago N, Ishii Y, Kohda H. Malignant peripheral nerve sheath tumor of the skin: a superficial form of this tumor. J Cutan Pathol 1996; 23:182–188.

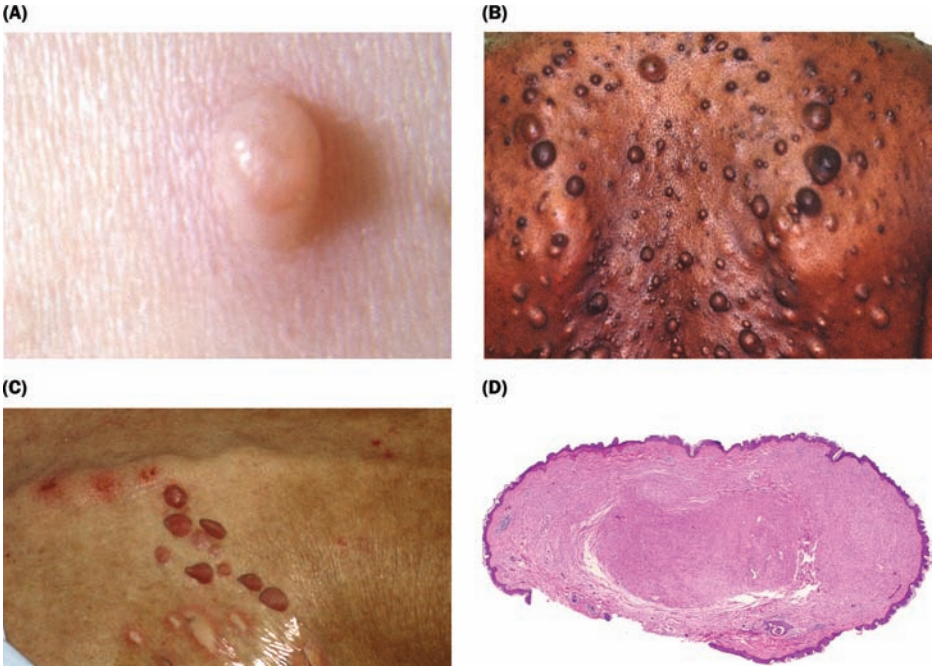

Figure 1 Soft papular solitary neurofibroma (**A**), multiple neurofibromas of Von Recklinhausen's disease (**B**), and linear papules of segmental neurofibromatosis (**C**) all show similar histologic findings (**D**).

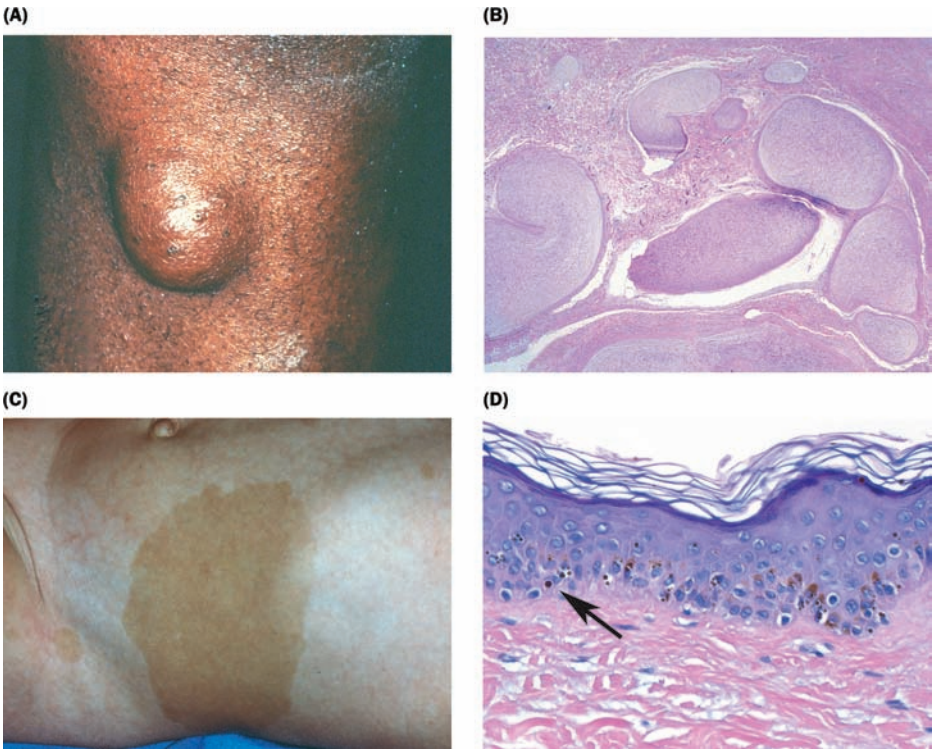

Figure 2 This large soft cutaneous nodule (**A**) contains expanded nerves in the deep dermis and subcutis, typical of plexiform neurofibroma. (**B**) Café au lait macules seen in neurofibromatosis are flat pigmented patches (**C**) characterized by increased epidermal melanin (**D**) and large melanosomes (**D**, *arrow*).

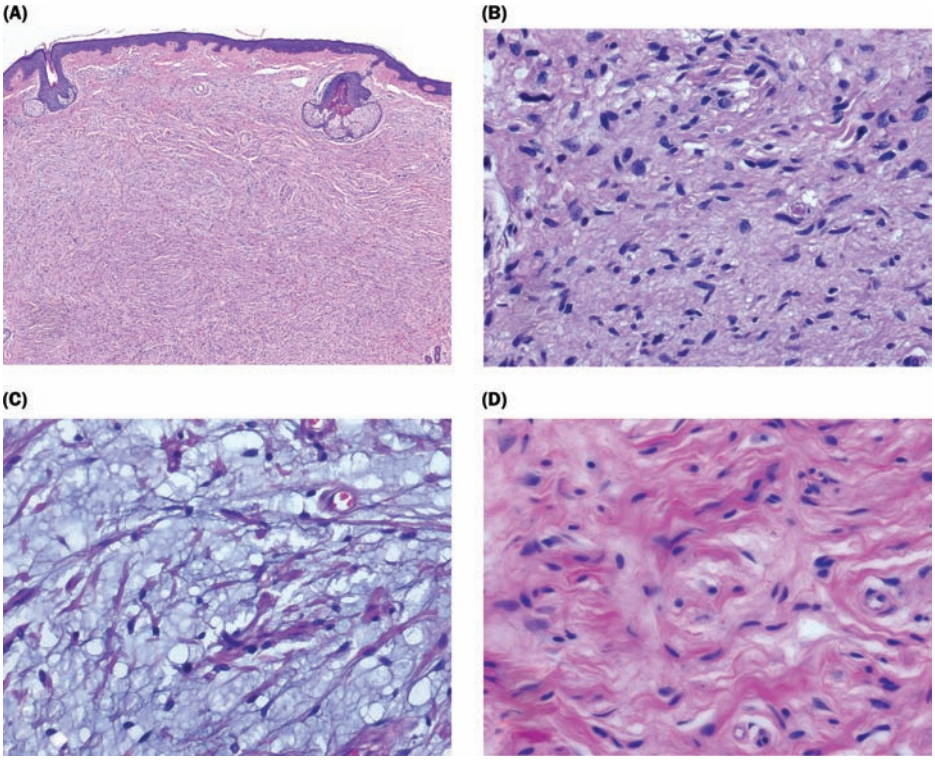

Figure 3 Histologically, neurofibromas feature diffuse collections of spindle cells in the dermis (**A**) with tapered curved nuclei (**B**) in a stroma that varies from highly myxoid (**C**) to collagenous (**D**).

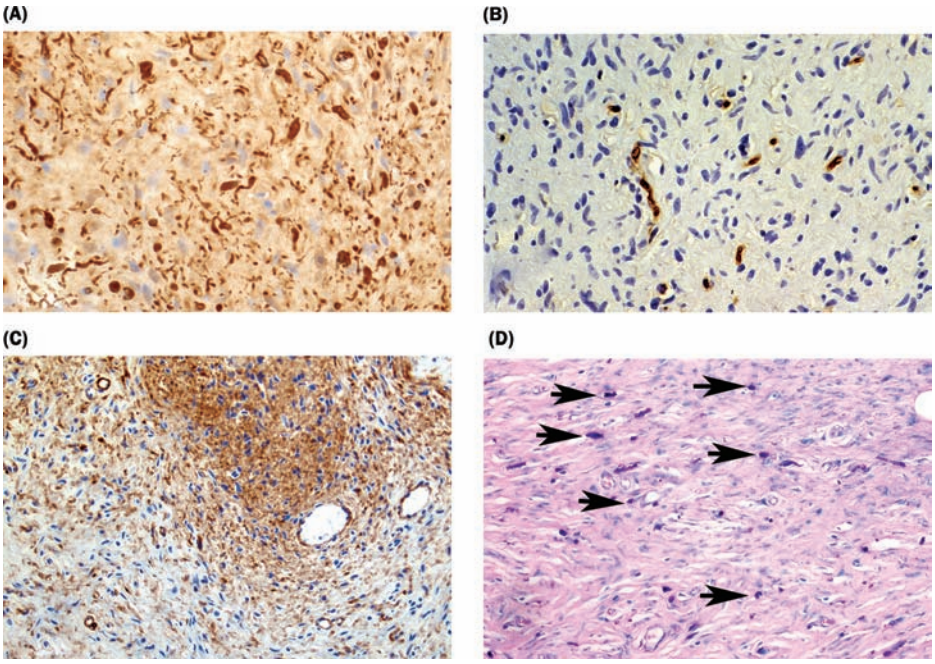

Figure 4 Neurofibromas are composed of several different cells types. Brown immunostaining with S-100 protein highlights both Schwann cells and nerve fibers (**A**), while stains for neurofilament reveal neurons in neurofibromas (**B**, single brown cells). There is strong positivity for Type IV collagen produced by fibroblasts in these tumors (**C**, areas of brown staining). Staining with Giemsa accentuates the purple granules in the cytoplasm of the many mast cells present in neurofibromas (**D**, *arrows*).

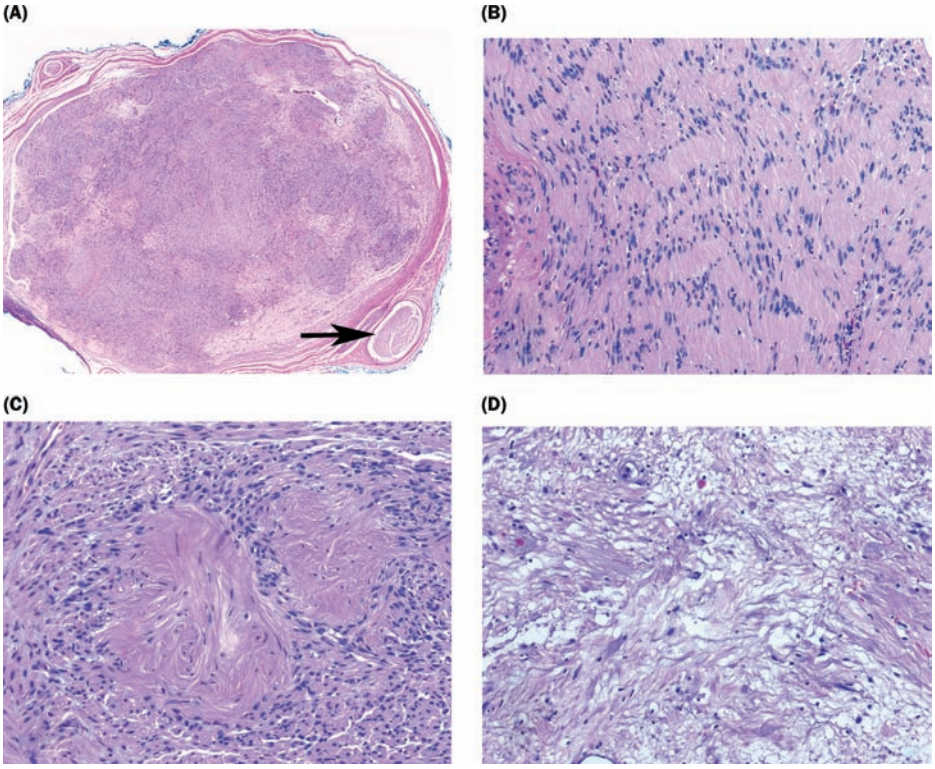

Figure 5 Schwannomas are encapsulated (**A**) and are often attached to an underlying nerve (**A**, *arrow*). In the cellular Antoni A areas of schwannomas, nuclei palisade (**B**) and form Verocay bodies around acellular stroma (**C**), in contrast to the loose myxoid haphazard arrays in the Antoni B areas of these lesions (**D**).

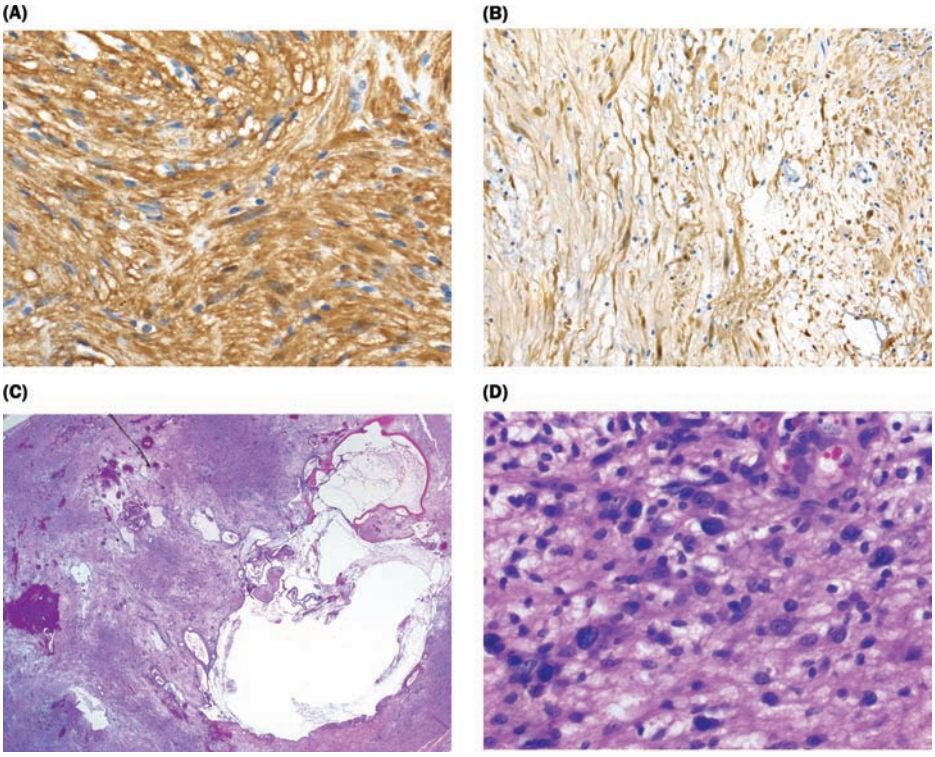

Figure 6 The cells in both the cellular and hypocellular myxoid areas of schwannomas stain strongly for S-100 protein (**A**,**B**, brown cells). "Ancient schwannomas" show cysts and hemorrhage (**C**) and enlarged atypical nuclei (**D**), but behave in a benign fashion.

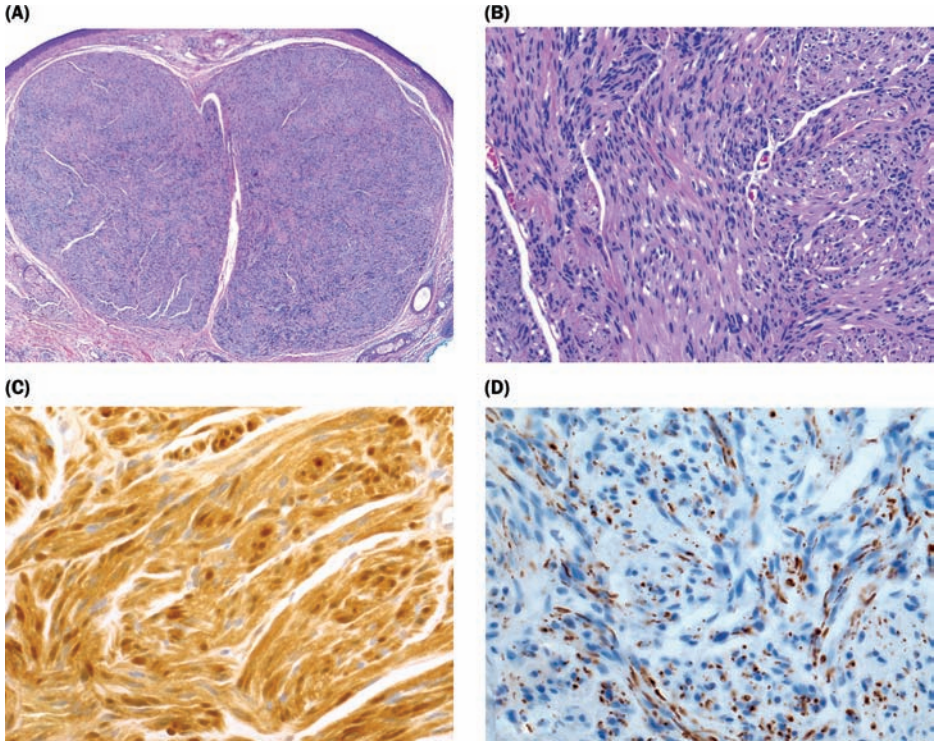

Figure 7 Palisaded encapsulated neuromas are sharply circumscribed tumors of the superficial dermis (**A**) featuring densely cellular fascicles of spindle cells in palisaded arrays (**B**). The lesions are diffusely S-100 protein positive (**C**, brown cells), and are composed predominantly of Schwann cells, but also contain nerve fibers and axons that can be labeled immunohistochemically with neurofilament (**D**, brown spindle cells).

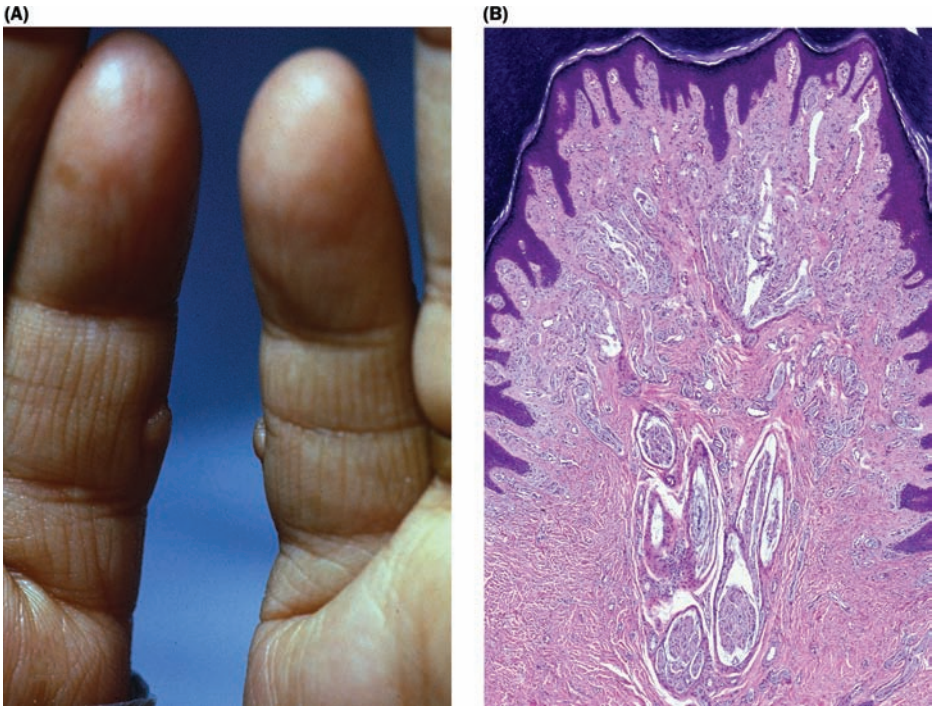

Figure 8 Clinically, rudimentary supernumerary digits are located at the ulnar side of the 5th digit (**A**, bilateral lesions) and are composed of bundles of small nerves trapped in collagen (**B**).

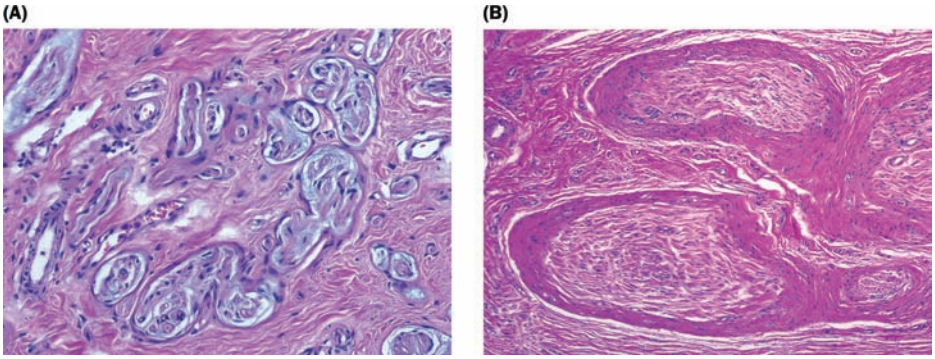

Figure 9 A higher power microscopic view of rudimentary supernumerary digit shows multinodular collections of nerves in dense connective tissue (**A**). In contrast, Morton's neuroma represents hyperplastic plantar nerves encased in dense fibrosis (**B**).

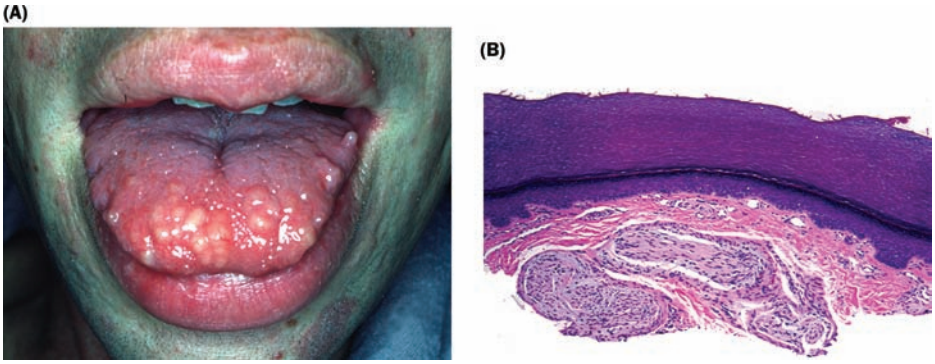

Figure 10 (**A**) Soft pale papules on the mucosa typify the mucosal neuromas seen in multiple endocrine neoplasia type IIb/III. (**B**) Histologically, there are nonencapsulated hypertrophic nerves in the submucosa.

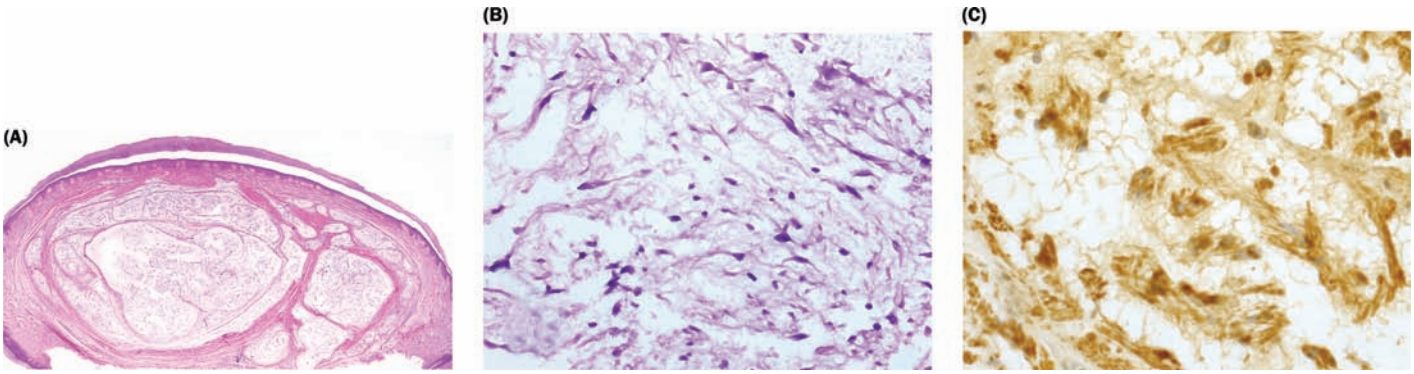

Figure 11 At low power, nerve sheath myxomas demonstrate multiple nodules of hypocellular myxoid stroma (**A**, **B**) containing a few scattered S-100 protein positive brown spindle cells (**B**).

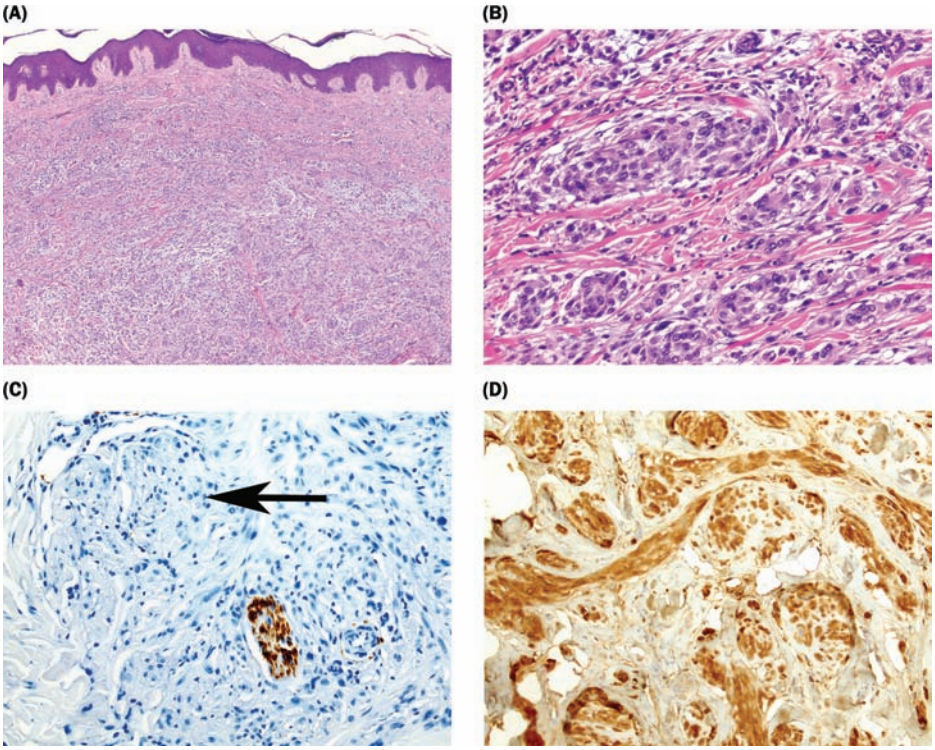

Figure 12 Cellular neurothekeomas extend diffusely through the dermis (**A**) and are characterized by epithelioid cells with minimal mucin (**B**). Unlike classic neurothekeomas, they fail to label with S-100 protein (**C**: absence of staining of tumor indicated by arrow, normal nerve stains brown with S-100 protein). Brown staining (**D**) indicates immunohistochemical positivity for PGP 9.5, a marker of neuroectodermal tissue that is usually present in cellular neurothekeomas.

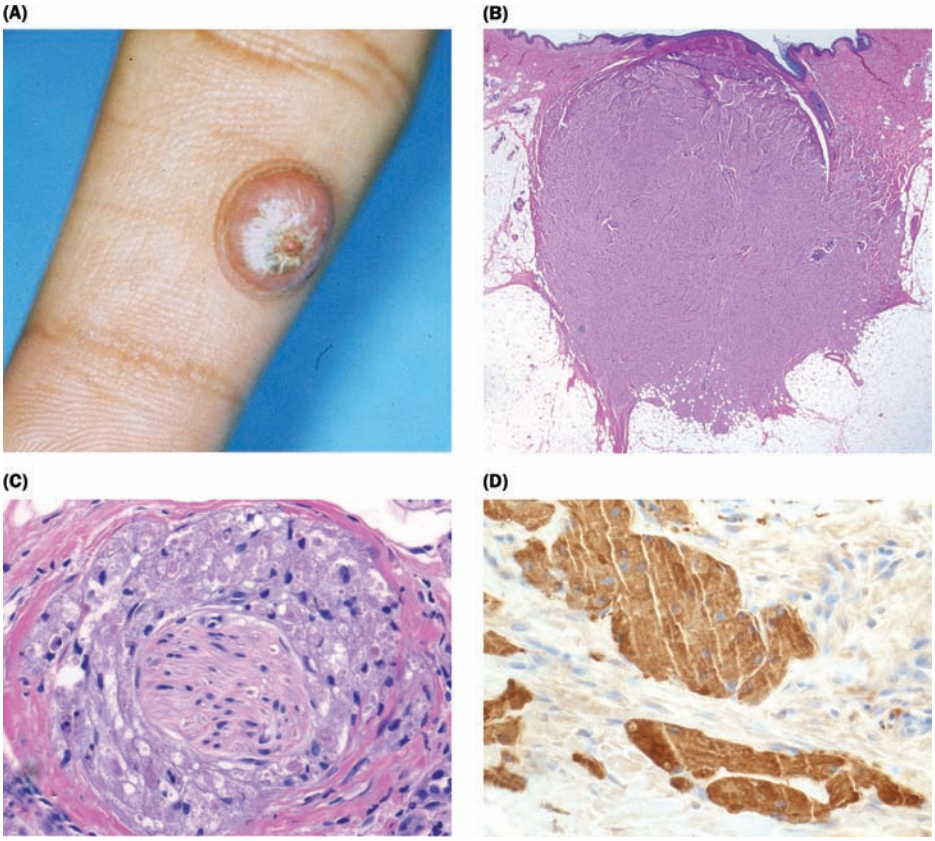

Figure 13 Clinically, granular cell tumors are solitary dome-shaped nodules that may be hyperkeratotic (**A**). Histologically, they are poorly circumscribed (**B**). The characteristic round cells contain granular cytoplasm and are frequently associated with small cutaneous nerves (**C**). The granular cells stain strongly with S-100 protein (**D**, brown cells).

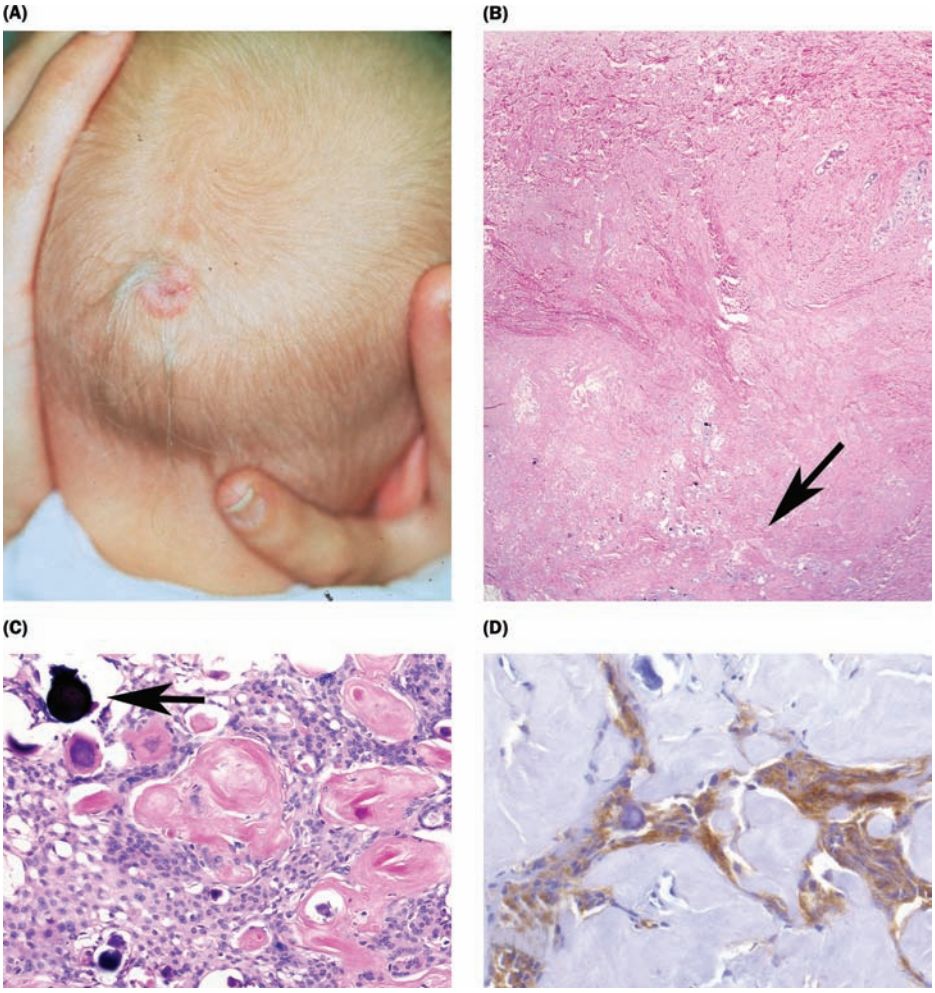

Figure 14 Rudimentary meningoceles are nodules typically located on the scalp or over the spine (**A**). In the deep dermis, there sclerosis (**B**, *arrow*) and an infiltrate of uniform oval cells (**C**) with calcified deposits called psammoma bodies (**C**, *arrow*). The meningothelial cells stain brown for epithelial membrane antigen (**D**).

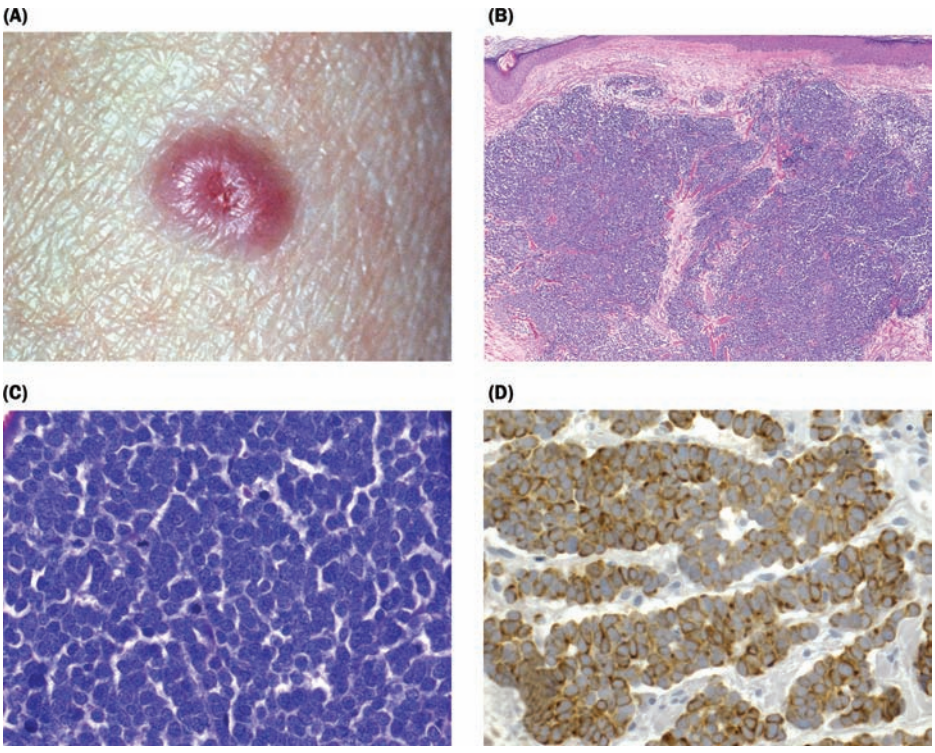

Figure 15 Merkel cell carcinoma presents clinically as a nondescript nodule on sun exposed skin (**A**). Microscopically, sheets of undifferentiated blue cells show a high mitotic rate, nuclear molding, and stippled chromatin (**C**). Cytokeratin 20 labels the cells with a brown perinuclear dot of positivity (**D**).

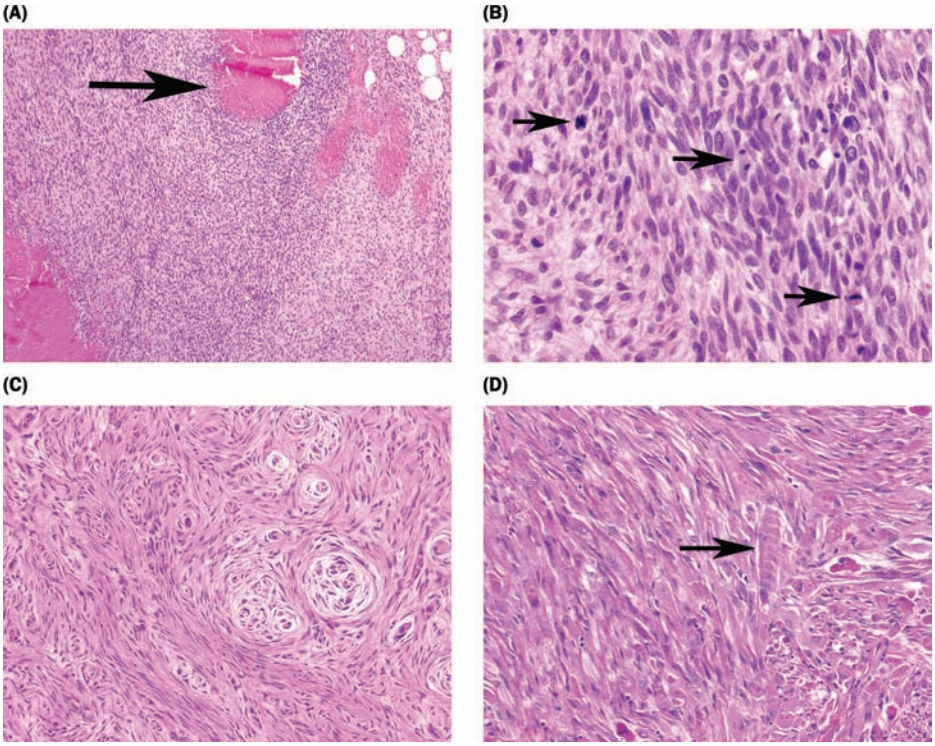

Figure 16 Malignant peripheral nerve sheath tumors are large and cellular (**A**), with areas of pink necrosis (**A**, *arrow*). There are dense sheets of atypical spindle cells (**B**) with numerous mitoses (**B**, *arrows*). The malignant cells sometimes differentiate to resemble nerve end organs such as Wagner-Meissner bodies (**C**) and may show features resembling skeletal muscle (**D**), such as cross striations within dense eosinophilic cytoplasm (**D**, *arrow*).

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Muscle Neoplasms

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CONTENTS

Smooth muscle is present in normal skin as muscle of hair erection (arrector pili muscle), in the walls of blood vessels, nipple, and in genital skin, for example, vulva and scrotum. Histologic features of smooth muscle differentiation include spindle-shaped cells with eosinophilic cytoplasm and elongated blunt-ended ("cigar" shaped) nuclei. Perinuclear vacuolization, more prominent on transversely cut sections, is also characteristic. By immunohistochemical studies, the smooth muscle cells are characteristically positive for intermediate filaments—vimentin and desmin. Both benign and malignant proliferations with smooth muscle differentiation can occur in skin. The more common of these will be presented in this chapter. In addition, glomus tumors that are considered to be of modified smooth muscle differentiation are also included. Tumors of skeletal muscle and myofibroblastic differentiation are briefly addressed.

TUMORS WITH SMOOTH MUSCLE DIFFERENTIATION

SMOOTH MUSCLE HAMARTOMA AND BECKER'S NEVUS

Clinical Presentation:
- Smooth muscle hamartoma presents at birth as single, large patch or indurated plaque on trunk, especially lumbosacral area or proximal extremities (Fig. 1A)
- Becker's nevus presents in childhood or early adulthood as large patch or plaque on upper half of trunk or shoulder (Fig. 2A)
- Male preponderance
- Follicular papules may be present
- Hyperpigmentation and hypertrichosis are more prominent in Becker's nevus
- Transient piloerection or elevation of a lesion induced by rubbing (pseudo-Darier sign)

Histopathology:

Smooth Muscle Hamartoma:
- Discrete, hyperplastic smooth muscle bundles within the reticular dermis (Fig. 1B)
- Smooth muscle bundles oriented in varying directions (Fig. 1C)
- Some smooth muscle bundles connect to hair follicles

Becker's Nevus:
- Hyperkeratosis, acanthosis, and hyperpigmentation of the overlying epidermis (Fig. 2B)
- The rete ridges have flat bases and rectangular shapes
- Increased bundles of smooth muscle in the dermis (Fig. 2C)

Differential Diagnosis:

Features	Congenital Smooth Muscle Hamartoma	Becker's Nevus
Clinical	Present at birth	Onset in childhood or adolescence
	Trunk and proximal extremities	Upper half of trunk and shoulder
Histopathologic	Epidermal changes and hyperpigmentation may be absent	Epidermal changes, hyperpigmentation, and hypertrichosis prominent
	Increase in smooth muscle bundles prominent	Increase in smooth muscle bundles variable

Features	Smooth Muscle Hamartoma	Pilar Leiomyoma
Clinical	Single large patch or plaque	Multiple, small, reddish-brown nodules
Histopathologic	Discrete bundles of smooth muscle extending in different directions	Interlacing bundles of smooth muscle

Clinicopathologic Correlation:
Congenital smooth muscle hamartoma and Becker's nevus may be considered as a spectrum with varying amounts of smooth muscle hyperplasia, variable hyperpigmentation, and hypertrichosis.

Clinical Feature	Pathologic Feature
Follicular papules	Smooth muscle bundles centered around follicles
Transient piloerection (pseudo-Darier sign)	Some smooth muscle bundles connect to hair follicles
Hyperpigmentation	Increased melanin in the epidermis

References:

1. Holst V, Junkins-Hopkins J, Elenitsas R. Cutaneous smooth muscle neoplasms: clinical features, histologic findings and treatment options. J Am Acad Dermatol 2002; 46(4):477–494.
2. Zvulunov A, Rotem A, Merlob P, et al. Congenital smooth muscle hamartoma. Prevalence, clinical findings, and follow-up in 15 patients. Am J Dis Child 1990; 144:782–784.
3. Alfadley A, Hainau B, Alrobaee A, Banka N. Becker's melanosis: a report of 12 cases with atypical presentation. Int J Dermatol 2005; 44:20.

LEIOMYOMA

Clinical Presentation:

Pilar Leiomyoma:

- Multiple or solitary forms—multiple form more common
- Small (usually <1 cm), firm, reddish-brown nodules on trunk, extensor surface of extremities, and face and neck (Fig. 3A)
- Tender and painful—pain can be spontaneous or triggered by exposure to cold, pressure, or trauma
- Solitary pilar leiomyomas are typically larger than multiple pilar leiomyomas (>2 cm) and show a predilection for involvement of extremities.

Genital Leiomyomas:

- Typically occur on scrotum, labia majora, or nipple, as solitary asymptomatic dermal nodule (Fig. 3B)

Angioleiomyoma:

- Painful, subcutaneous nodules, up to 4 cm in size; occur on lower extremities
- Solid subtype—more common in females on extremities and painful
- Venous subtype—show slight male preponderance; occur frequently on head and are painless

Angiolipoleiomyoma:

- Adults—men
- Head and neck or upper extremities
- Dome-shaped deep dermal or subcutaneous nodules

Histopathology:

Pilar Leiomyoma:

- Essentially similar histology for multiple and solitary forms
- Poorly demarcated dermal proliferation of interlacing bundles of smooth muscle cells, with eosinophilic cytoplasm and cigar-shaped nuclei (Figs. 4A–C)
- Mitotic figures rare

Genital Leiomyoma:

- Similar histology as pilar leiomyoma

Angioleiomyoma:

- Well-circumscribed subcutaneous nodule composed of interlacing bundles of smooth muscle cells, with varying admixture size of vascular channels (Fig. 5A)
- Patterns—cavernous, capillary or solid, and venous (Figs. 5B–D)
- Intravascular variant (rare)

Angiolipoleiomyoma:

- Well-circumscribed dermal nodule (Fig. 6A)
- Well-defined fibrous capsule
- Varying proportion of smooth muscle cells, vascular channels, and adipose tissue (Fig. 6B)
- Smooth muscle fascicles are connected to the vascular walls (Fig. 6C)
- Adipocytes intimately admixed with smooth muscle cells and vessels (Fig. 6C)

Immunohistochemical Studies:

- Positive for vimentin, smooth muscle actin (SMA), and desmin

Differential Diagnosis: Painful Cutaneous Nodule

Diagnosis	Clinical	Histopathology	Immuno-histochemistry
Pilar leiomyoma	Multiple, trunk face	Fascicles of smooth muscle cells	Vimentin, SMA, Desmin
Angioleiomyoma	Solitary; extremities	Smooth muscle cells closely associated with blood vessels	Vimentin, SMA, Desmin
Glomus tumor	Solitary, hand	Sheets or nests of monomorphous cells surrounding blood vessels	Vimentin, SMA, muscle specific actin
Angiolipoma	Multiple, forearm	Well-encapsulated mature adipose tissue, admixture of blood vessels with fibrin thrombi	S-100 protein in the adipocytes
Eccrine spiradenoma	Solitary mass, extremities	Two types of epithelial cells, duct formation	Cytokeratin
Neuroma	Solitary skin-colored nodule, sites of trauma	Bundles of spindle-shaped cells with wavy nuclei	S-100 protein

***Abbreviation*: SMA, smooth muscle actin.**

References:

1. Raj S, Calonje E, Kraus M, Kavanagh G, Newman PL, Fletcher CDM. Cutaneous pilar leiomyoma: clinicopathologic analysis of 53 lesions in 45 patients. Am J Dermatopathol 1997; 19:2–9.
2. Ragsdale BD. Tumors with fatty, muscular, osseous and cartilaginous differentiation. In: Elder DE, ed. Lever's Histopathology of Skin. Philadelphia: Lippincott Williams and Wilkins, 2005:1078–1086.
3. Mehregan DA, Mehregan DR, Mehregan AH. Angiomyolipoma. J Am Acad Dermatol 1992; 27:331–333.

SUPERFICIAL LEIOMYOSARCOMA

Clinical Presentation:
- Solitary cutaneous or subcutaneous nodule
- Most common on hair bearing surfaces of extremities, especially lower extremity
- Typically <2 cm in diameter
- Overlying skin discolored or depressed

Histopathology:
Cutaneous Leiomyosarcoma:
- Poorly defined nodular proliferation of densely packed, interlacing bundles of atypical smooth muscle cells (Figs. 7A and B)
- Necrosis and hemorrhage (Fig. 7C)
- Cytologic atypia and mitotic figures (Fig. 7D)
- Morphologic similarity to pilar leiomyoma

Subcutaneous Leiomyosarcoma:
- Well-circumscribed subcutaneous mass (Fig. 8A)
- Densely packed aggregates of atypical smooth muscle cells (Fig. 8B)
- Cytologic atypia and mitotic figures (Fig. 8C)
- Necrosis and hemorrhage
- Morphologic similarity of angioleiomyoma

Immunohistochemistry:
- Positive for vimentin, SMA, and desmin (Fig. 8D)
- Higher grade tumors and subcutaneous leiomyosarcomas show less consistent staining

Differential Diagnosis:

Superficial Leiomyosarcoma	Leiomyoma
Cellularity—dense	Not dense
Nuclear pleomorphism present	Variable
Mitotic figures common	Rare
Necrosis and hemorrhage may be present	Absent

Superficial Cutaneous Leiomyosarcoma	Atypical Fibroxanthoma (Superficial Malignant Fibrous Histiocytoma)
Spindle-shaped cells with blunt-ended (cigar-shaped) nuclei	Spindle-shaped cells with pleomorphic nuclei and multinucleated giant cells
Immunohistochemistry: positive for vimentin and smooth muscle markers	Positive for vimentin, but negative for smooth muscle markers

Clinicopathologic Correlation:

	Cutaneous Leiomyosarcoma	Subcutaneous Leiomyosarcoma
Prognosis	Generally good	More aggressive
Local recurrence	30–50%	Up to 70%
Metastases	Uncommon	30–40%

References:

1. Stout AP, Hill WT. Leiomyosarcoma of the soft tissues. Cancer 1958; 11:844–854.
2. Spencer JM, Amonette RA. Tumors with smooth muscle differentiation. Dermatol Surg 1996; 22:761–768.
3. Lange J. Leiomyosarcoma. In: Miller SJ, Maloney ME, editors. Cutaneous Oncology: Pathophysiology, Diagnosis, and Management. Malden (MA): Blackwell Science, 1998:, 893–896.
4. Jegasothy BV, Gilgor RS, Hull DM. Leiomyosarcoma of the skin and subcutaneous tissue. Arch Dermatol 1981; 117:478–481.

GLOMUS TUMOR

Clinical Presentation:
- Young adults between third and fourth decades
- Common sites: hand, especially subungual region and palm, foot, and forearm
- Presents as a solitary, small, bluish red nodule that is painful (Fig. 9A)
- Multiple in about 10% of patients
  - May be hereditary; autosomal dominant pattern
  - Children are affected
  - Asymptomatic; small reddish-blue papules (Fig. 10A)
  - Typically not subungual
  - Glomangioma pattern

Histopathology:
Solid Type:
- Well-circumscribed nodule composed of small vascular spaces surrounded by sheets or nests of uniform round cells with eosinophilic cytoplasm; round to oval nuclei (Figs. 9B–D)
- Minimal cytologic pleomorphism

Vascular Type (Glomangioma):
- Numerous dilated thin-walled vascular spaces surrounded by one to few layers of glomus cells (Figs. 10B–D)

Glomangiomyoma:
- Spindle-shaped, smooth muscle cells near the vascular spaces that blend with adjacent glomus cells (Figs. 11A–C)

Immunohistochemistry:
Glomus cells are positive for SMA, muscle-specific actin, and only rarely and focally for desmin

Differential Diagnosis:

Solid Glomus Tumor	Eccrine Spiradenoma
Sheets of monomorphous cells	Two types of cells with ductal differentiation
Immunohistochemistry—positive muscle markers	Positive epithelial markers

Glomangioma	Blue Rubber Bleb Nevus
Vascular spaces surrounded by glomus cells	Vascular spaces lined by single endothelial cell layer; no glomus cells

References:
1. Carroll RE, Berman AT. Glomus tumors of the hand. Review of the literature and report on twenty-eight cases. J Bone Joint Surg 1972; 54A:691–703.
2. Happle R, Konig A. Type 2 segmental manifestation of multiple glomus tumors: a review and reclassification of 5 case reports. Dermatology 1999; 198:270–272.
3. Pepper MC, Laubenheimer R, Cripps DJ. Multiple glomus tumors. J Cutan Pathol 1977; 4:244–257.
4. Calduch L, Monteagudo C, Martinez-Ruiz E, et al. Familial generalized multiple glomangiomyoma: report of a new family, with immunohistochemical and ultrastructural studies and review of the literature. Pediatr Dermatol 2002; 19:402–408.

TUMORS WITH SKELETAL MUSCLE DIFFERENTIATION

RHABDOMYOMA

Clinical Presentation:
- Uncommon generally deep-seated tumors
- Fetal type
  - Face and neck area of infants and children
  - Presents as a subcutaneous mass
- Adult type
  - Head and neck area of elderly males
  - Presents as deep-seated mass
- Genital
  - Vagina and vulva of middle-aged women
  - Polypoid mass

Histopathology:

Fetal Type:
- Immature round to spindle-shaped cells in a myxoid stroma; some cells with more eosinophilic cytoplasm and occasional cross striations

Adult Type:
- Large, round or polygonal cells or strap cells with abundant eosinophilic cytoplasm (Figs. 12A–B)
- Minimal nuclear pleomorphism
- Readily identifiable cross-striations
- Rod-like inclusions

Genital Type:
- Polypoid mass covered by epithelium (Fig. 12C)
- Polymorphous cell population; some cells are polygonal and others are elongated; many with cross striations (Figs. 12D–E)

Immunohistochemistry:
- Positive for muscle-specific actin, myogenin, and desmin

References:
1. Willis J, Abdul-Karim FW, Di Sant'Agnese PA. Extracardiac rhabdomyomas. Semin Diagn Pathol 1994; 11:15–25.
2. Kapadia SB, Meis JM, Frisman DM, et al. Adult rhabdomyoma of the head and neck: a clinicopathologic and immunophenotypic study. Hum Pathol 1993; 28:608–617.
3. Kapadia SB, Meis JM, Frisman DM, et al. Fetal rhabdomyoma of the head and neck. A clinicopathologic and immunophenotypic study of 24 cases. Hum Pathol 1993; 24:754–765.

RHABDOMYOSARCOMA

Clinical Features:
- Involvement of skin by primary rhabdomyosarcoma is rare.
- Occasional metastasis may occur in skin
- Young patients are affected
- Predilection for face
- Sarcoma botryoides subtype—common in genitourinary tract

Histopathology:
- Embryonal, alveolar, and pleomorphic subtypes
- Alveolar subtype—more common in skin
  - Relatively large cells recognizable as "rhabdomyoblasts" arranged as nests separated by fibrous septa (Fig. 13A)
  - In the center of nests, there is cellular dissociation resulting in "alveolar" pattern (Fig. 13B)
- Embryonal
  - Small round or spindle-shaped cells loosely arranged in a myxoid stroma (Figs. 13C–D)
  - Varying numbers of rhabdomyoblasts (Figs. 13E)
- Pleomorphic
  - Virtually never presents in skin
  - Highly atypical cells with scattered recognizable rhabdomyoblasts

Immunohistochemistry:
- Positive for desmin, muscle-specific actin, myogenin, and MyoD
- Most useful in differentiating rhabdomyosarcoma from other round blue cell tumors

References:
1. Wiss K, Solomon AR, Raimer SS, et al. Rhabdomyosarcoma presenting as a cutaneous nodule. Arch Dermatol 1988; 124:1687–1690.
2. Schmidt D, Fletcher CDM, Harms D. Rhabdomyosarcomas with primary skin presentation. Pathol Res Pract 1993; 189: 422–427.

TUMORS WITH MYOFIBROBLASTIC DIFFERENTIATION

SOLITARY CUTANEOUS MYOFIBROMA

Solitary cutaneous myofibroma is a benign neoplasm with myofibroblastic differentiation. Myofibroblasts are cells that show features of both smooth muscle differentiation and fibroblastic differentiation.

Clinical Presentation:
- Solitary
- Well circumscribed
- 0.5 to 3 cm in size
- Dermal/subcutaneous nodule with predilection for head and neck and shoulder girdle area
- Adolescents and adults

Histopathology:
- Well circumscribed; unencapsulated
- Nodular or lobulated (Fig. 14A)

- Biphasic growth pattern
- Central hemangiopericytoma-like area with round to oval cells arranged around blood vessels (Fig. 14B)
- Peripheral nodules composed of short fascicles of spindle-shaped cells, resembling smooth muscle (Figs. 14C–D)
- Areas of central hyalinization within the peripheral nodules

Differential Diagnosis:

Diagnosis	Myofibroma	Leiomyoma	Hemangio-pericytoma
Clinical	Solitary	Multiple	Solitary
Histopathology	Biphasic pattern with pericytoma-like areas surrounded by fascicles of smooth muscle–like cells	Fascicles of smooth muscle cells	Irregularly branching blood vessels surrounded by round to oval cells without pericytes
Immunohisto-chemistry	Positive SMA, MSA, and vimentin	Positive SMA, MSA, vimentin and desmin	Positive vimentin

Abbreviations: MSA, muscle-specific actin; SMA, smooth muscle actin.

Reference:

1. Guitart J, Ritter JH, Wick MR. Solitary cutaneous myofibromas in adults: report of six cases and discussion of differential diagnosis. J Cutan Pathol 1996; 23:437–444.

DERMATOMYOFIBROMA

Clinical Presentation:

- Solitary, plaque-like cutaneous lesion
- Tan to red surface discoloration
- Predilection for shoulder girdle

Histopathology:

- Plaque-like dermal proliferation of spindle-shaped cells, resembling smooth muscle cells (Fig. 15A)
- Cells arranged in fascicles parallel to the surface of the skin (Fig. 15B)
- Proliferation surrounds the blood vessels and adnexa without obliterating them (Fig. 15C)
- Uniform spindle-shaped cells with eosinophilic cytoplasm and elongated nuclei (Fig. 15D)

Differential Diagnosis:

Diagnosis	Dermatomy-ofibroma	Dermatofibroma	Leiomyoma
Clinical	Solitary plaque-like shoulder	Solitary dermal nodules lower extremity	Multiple dermal nodules, trunk, face, and neck
Histopathology	Myofibroblasts and fibroblasts oriented parallel to surface	Fibroblasts and in a haphazard array; thickened bundles of collagen and foamy histiocytes	Fascicles of smooth muscle in a pattern reminiscent of normal muscle of hair erection
	Reticular dermis and upper subcutaneous fat	Mostly dermal	Mostly dermal
	No obliteration of adnexa	Adnexa obliterated	Adnexa obliterated
Immunohisto-chemistry	SMA, negative desmin	Factor XIIIa	SMA, desmin

Abbreviation: SMA, smooth muscle actin.

References:

1. Kamino H, Reddy VB, Gero M, Greco MA. Dermatomyofibroma. J Cutan Pathol 1992; 19:85–93.
2. Mentzel T, Calonje E, Fletcher CDM. Dermatomyofibroma: additional observation on a distinctive cutaneous myofibroblastic tumor with emphasis on differential diagnosis. Br J Dermatol 1993; 129:69–73.

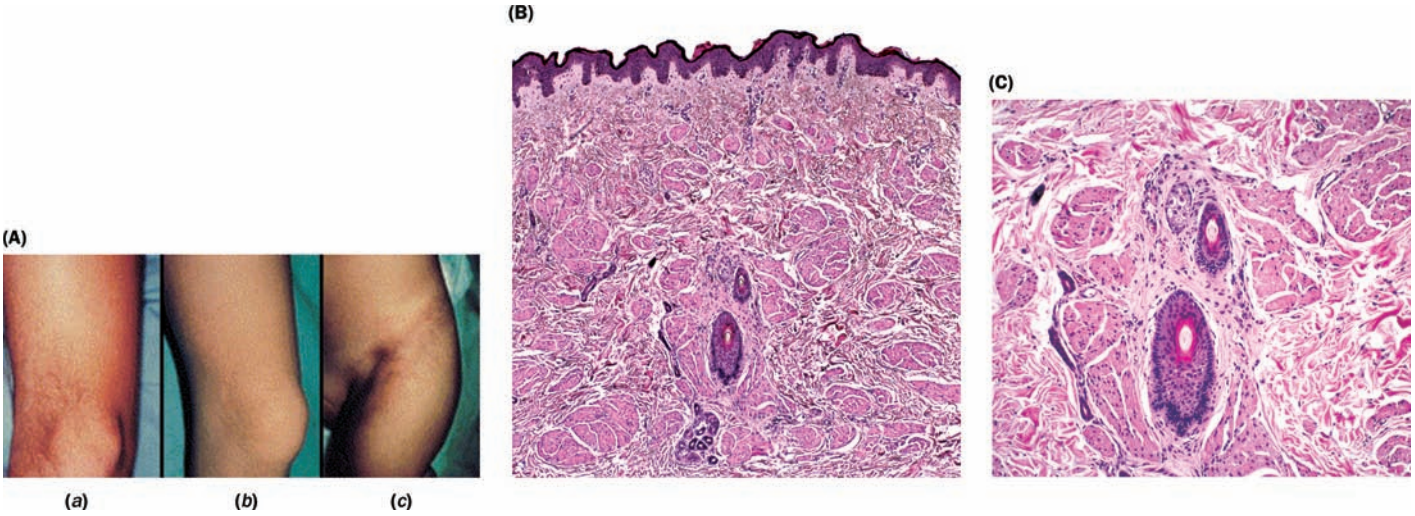

Figure 1 (**A**) Congenital smooth muscle hamartoma/Becker's nevus. *Source*: From Ref. 1 (Holst V, et al., 2002). Plaques with hypertrichosis (*a–c*), hyperpigmentation (*c*), and follicular centered papules (*b*). (**B**) Discrete bundles of smooth muscle in the reticular dermis. (**C**) Well-defined bundles of monomorphous smooth muscle cells arranged haphazardly; some are connected to the hair follicles.

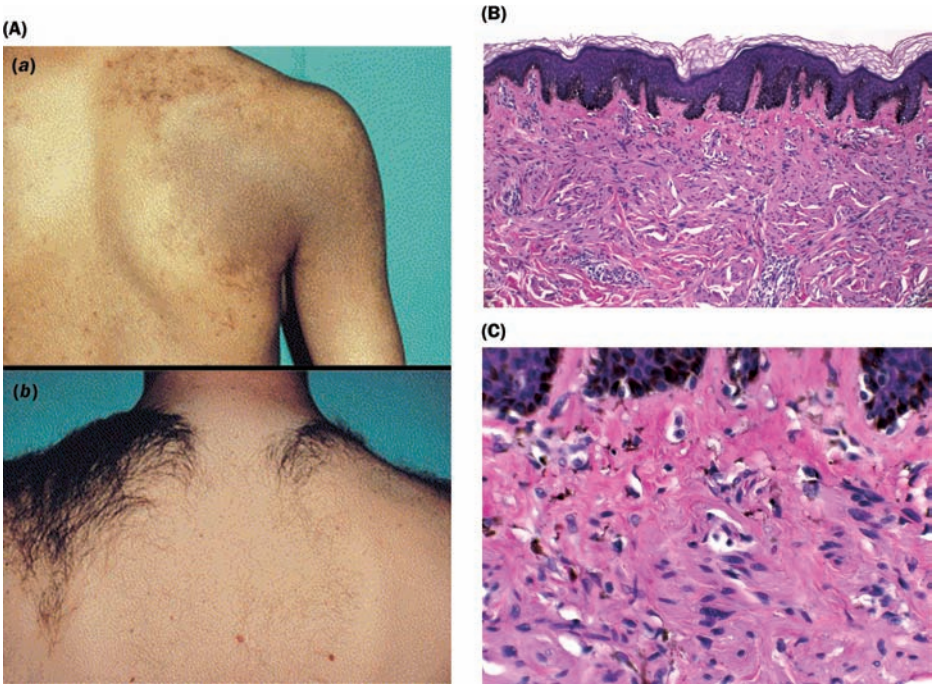

Figure 2 (**A**) Becker's nevus on the shoulder: a patch with hyperpigmentation (*a*) and hypertrichosis (*b*). *Source*: From Ref. 1 (Holst V, et al., 2002). (**B**) Becker's nevus—mild hyperkeratosis; epidermal hyperplasia with flat bases of the rete and hyperpigmentation. (**C**) Increased smooth muscle bundles in the dermis.

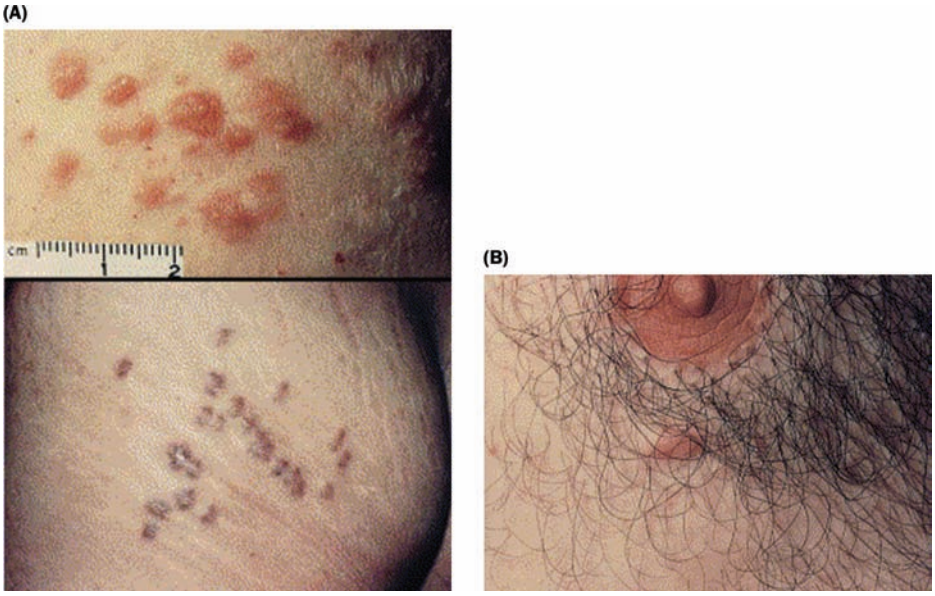

Figure 3 (**A**) Pilar leiomyoma. Multiple firm red to brown dermal nodules. *Source*: Reprinted from Holst VA et al. J Am Acad Dermatol 2002; 480, with permission from Elsevier). (**B**) Solitary/genital leiomyoma. Solitary, pink papule near the areola of the breast. *Source*: Reprinted from Holst VA, et al. J Am Acad Dermatol 2002; 481, with permission from Elsevier.

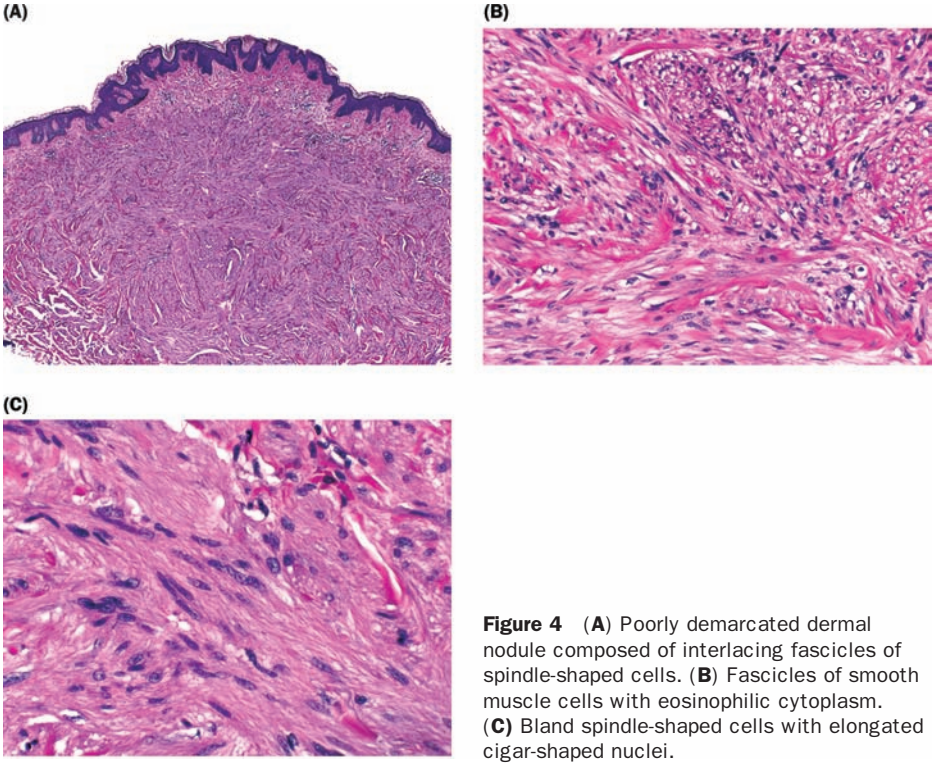

Figure 4 (**A**) Poorly demarcated dermal nodule composed of interlacing fascicles of spindle-shaped cells. (**B**) Fascicles of smooth muscle cells with eosinophilic cytoplasm. (**C**) Bland spindle-shaped cells with elongated cigar-shaped nuclei.

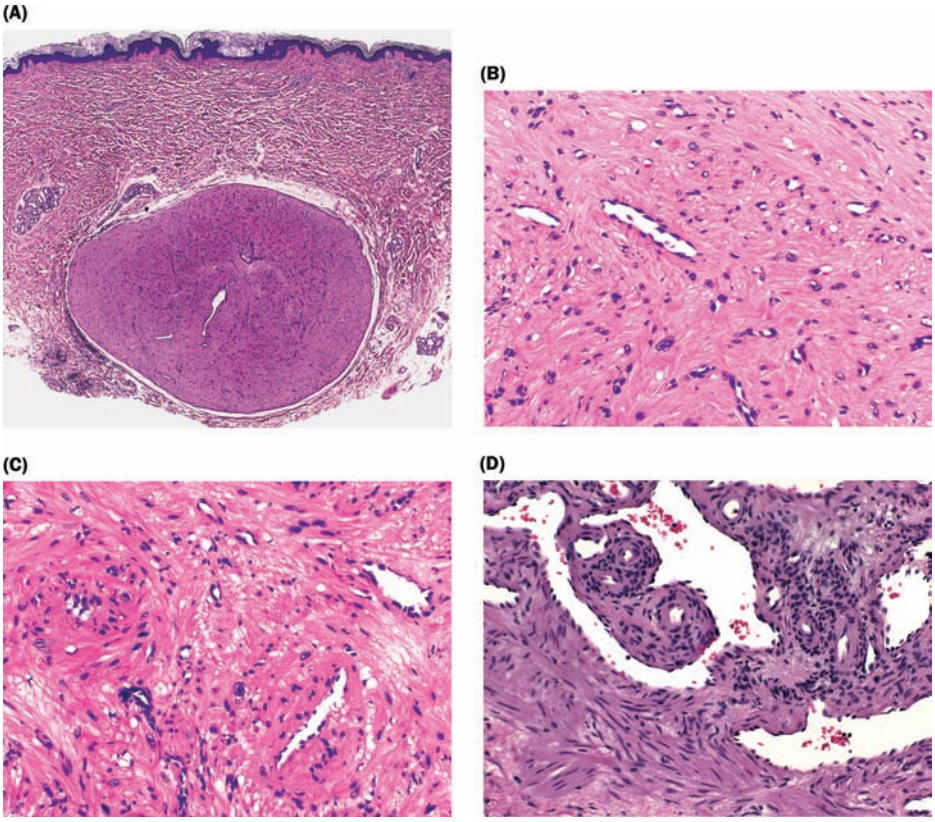

Figure 5 (**A**) Angioleiomyoma. Low power view shows a well-circumscribed subcutaneous nodule characteristic of angioleiomyomas of all histologic subtypes. (**B**) Capillary/solid type. Closely compacted smooth muscle cells and small slit-like vascular channels. (**C**) Cavernous type. Smooth muscle cells blending with the wall of dilated vascular channels. (**D**) Venous type. Smooth muscle cell proliferation and distinct vascular channels within the subcutaneous nodule.

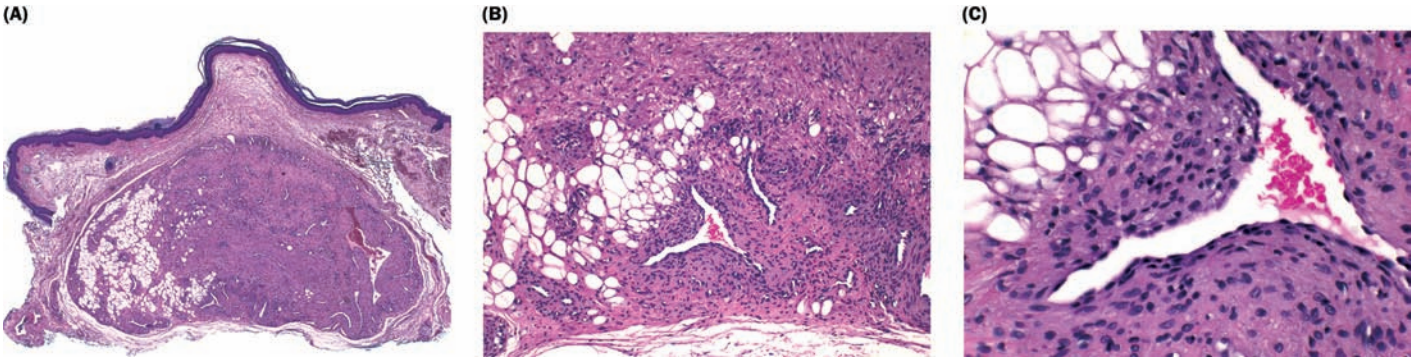

Figure 6 Angiolipoleiomyoma. (**A**) Well-circumscribed, deep dermal/subcutaneous nodule surrounded by a fibrous capsule. (**B**) Intimate admixture of smooth muscle cells, vascular channels, and adipose tissue. (**C**) Fascicles of smooth muscle cells imperceptibly merge with the vascular walls.

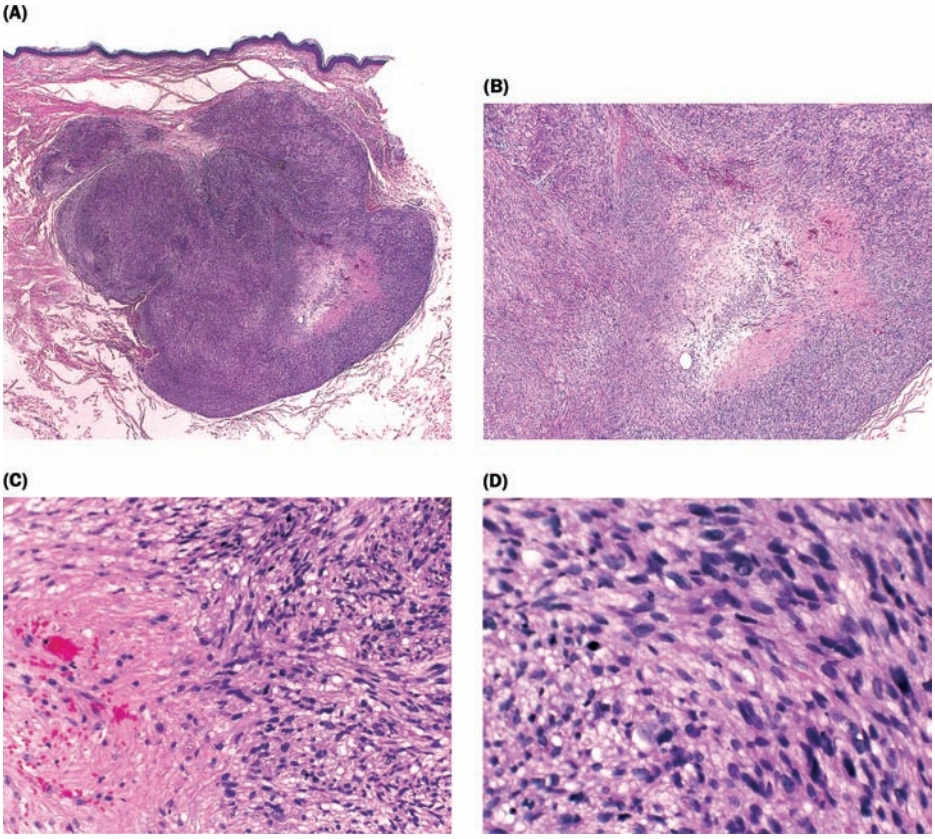

Figure 7 Cutaneous leiomyosarcoma. (**A**) Large poorly defined dermal nodule. (**B**) Densely packed interlacing bundles of pleomorphic spindle-shaped cells. (**C**) Areas of necrosis and hemorrhage. (**D**) Nuclear atypia and mitotic figures.

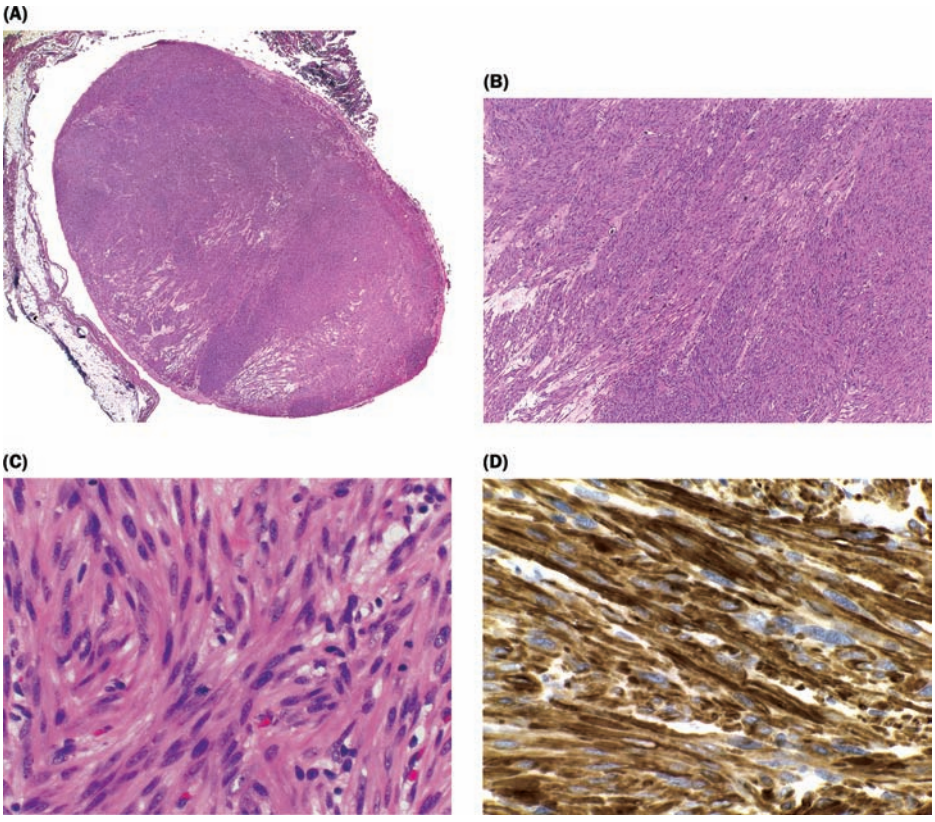

Figure 8 Subcutaneous leiomyosarcoma. (**A**) Large, relatively well-circumscribed subcutaneous mass. (**B**) Irregular fascicles of atypical spindle-shaped cells. (**C**) Nuclear atypia and mitotic figures. (**D**) The atypical spindle-shaped cells are positive for desmin.

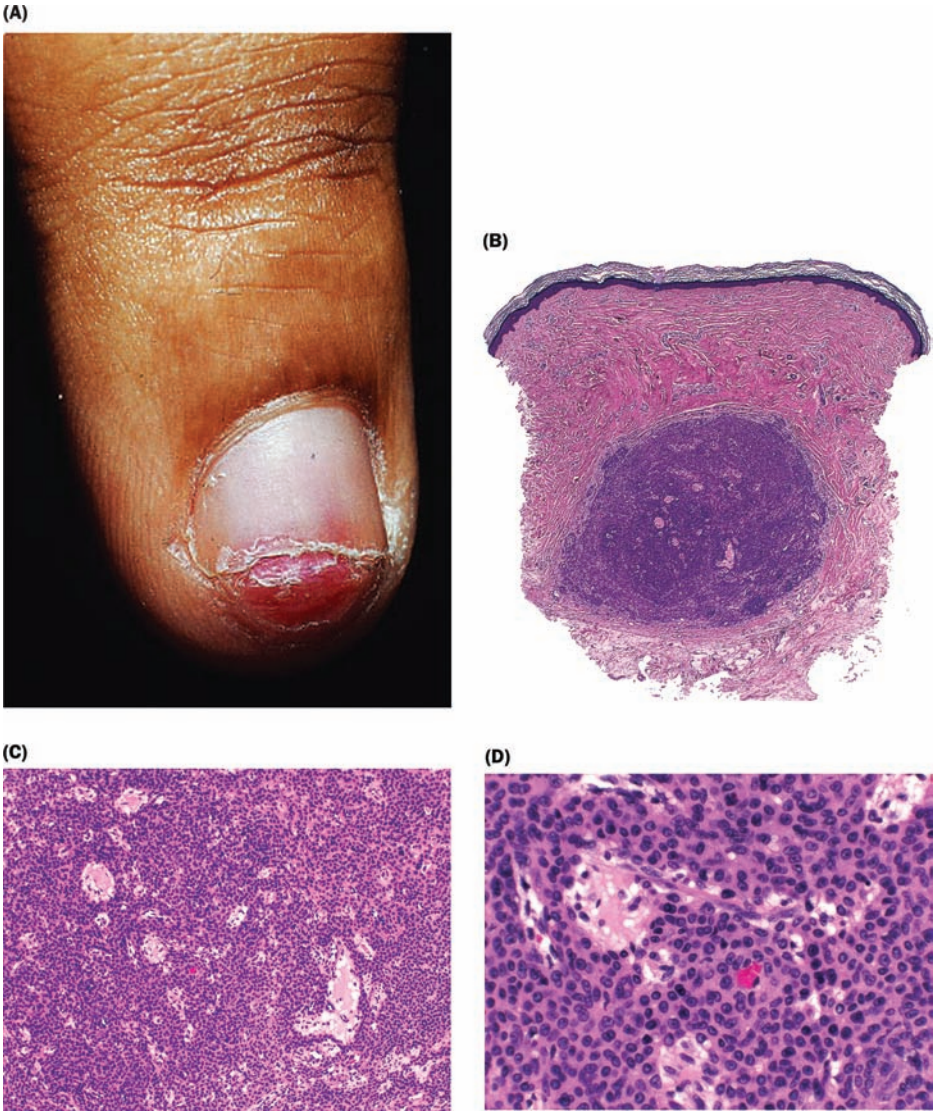

Figure 9 Glomus tumor. (**A**) Reddish subungual nodule. *Source*: Reprinted from Fitzpatrick's Color Atlas of Dermatology, 2004–2005, Fig. 9–18, with permission from the McGraw-Hill companies. (**B**) Well-circumscribed dermal nodule with inconspicuous vascular spaces. (**C**) Solid sheets of uniform round cells surrounding vascular spaces. (**D**) Round to oval cells with eosinophilic cytoplasm and monomorphic nuclei lining and surrounding the vessels.

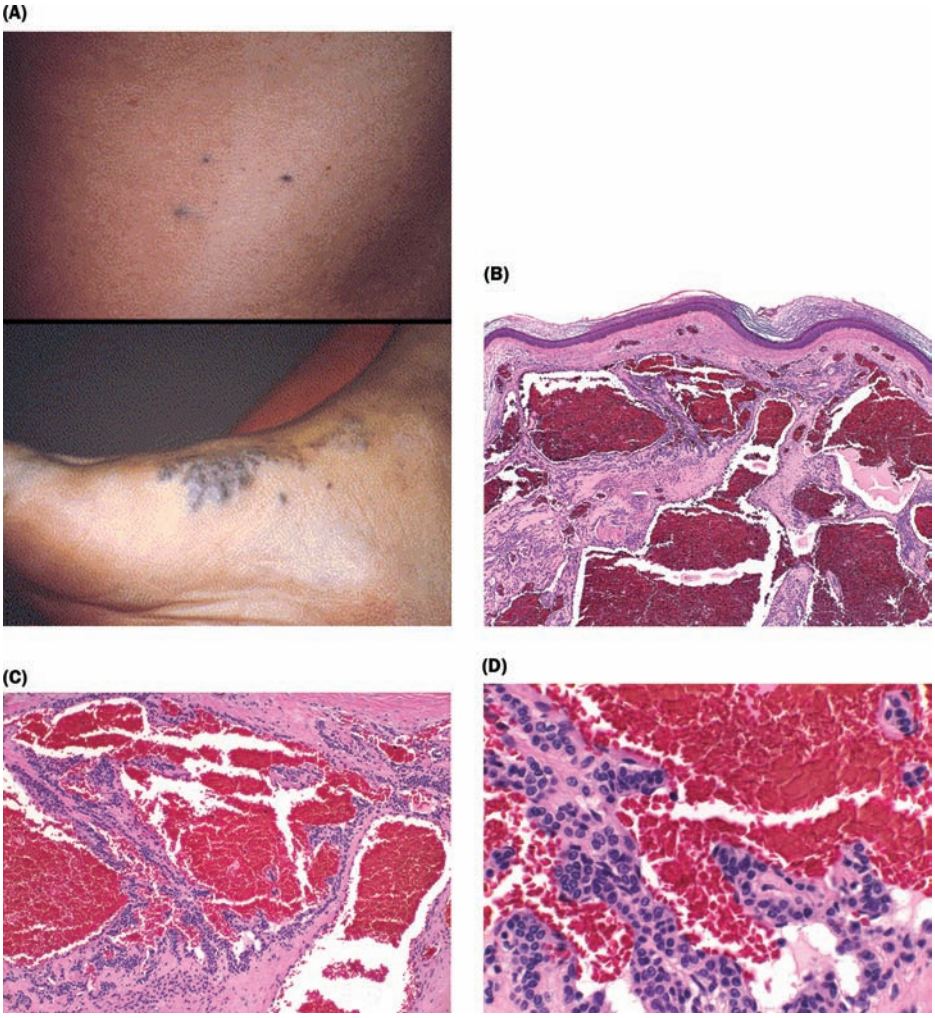

Figure 10 Glomangioma. (**A**) Multiple small reddish-blue papules on the trunk (*top*) and Multiple blue papules on the foot (*bottom*). *Source*: Reprinted from J Am Acad Dermatol 2001; 153 (Figs. 2 and 3), with permission from Elsevier. (**B**) Dermal proliferation of widely dilated vascular spaces. (**C**) Dilated vascular spaces surrounded by two to three layers of cells. (**D**) Vascular spaces surrounded by uniform round cells.

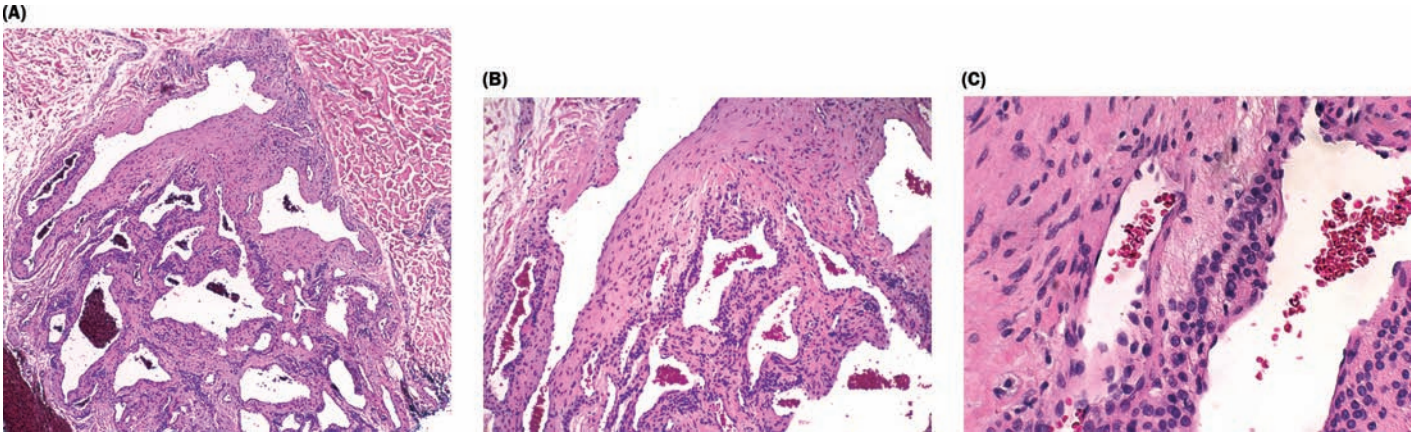

Figure 11 Glomangiomyoma. (**A**) Deep dermal nodule of vascular proliferation with a prominent spindle cell component. (**B**) Spindle-shaped cell proliferation separating the vascular spaces, some of which are surrounded by glomus cells. (**C**) Spindle-shaped cells merge imperceptibly with the round glomus cells.

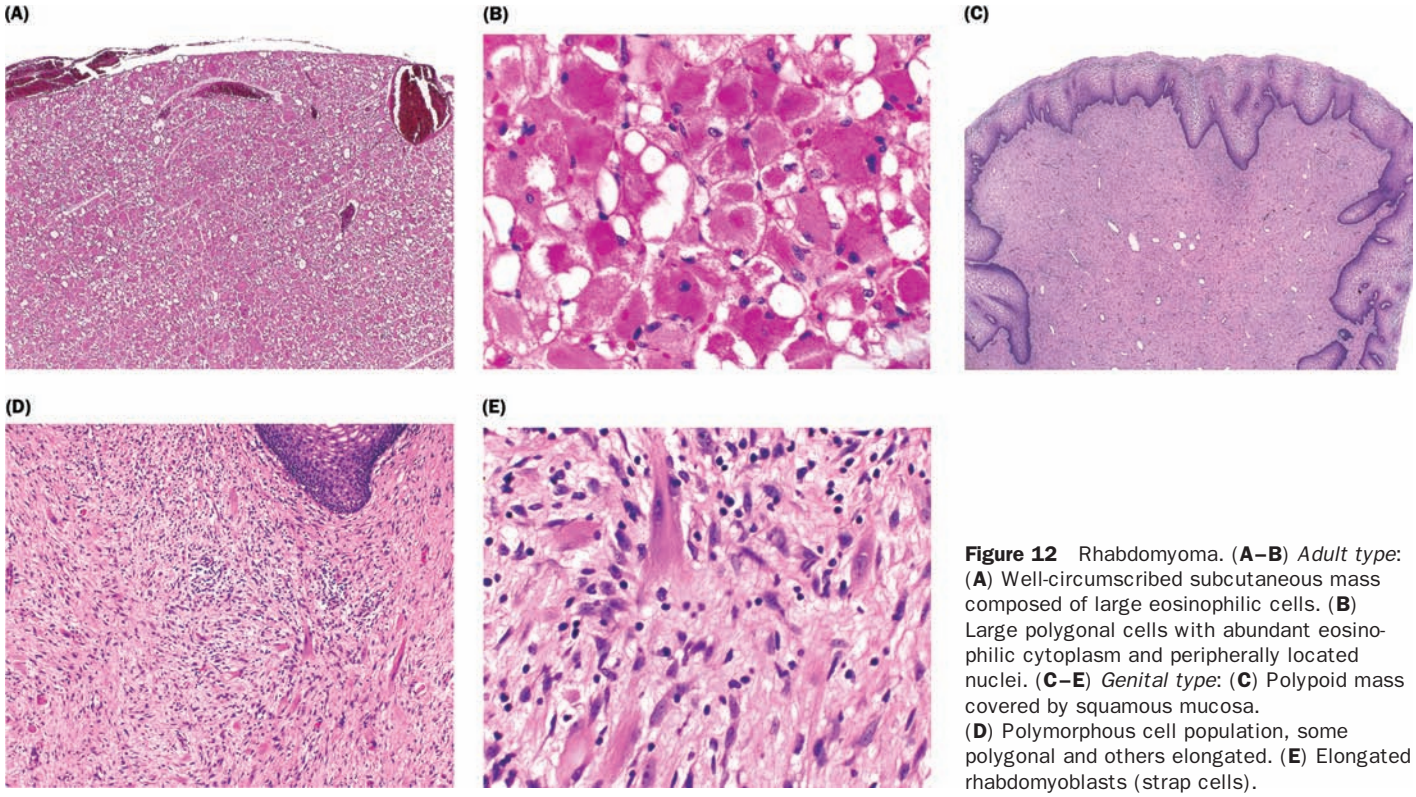

Figure 12 Rhabdomyoma. (**A–B**) *Adult type*: (**A**) Well-circumscribed subcutaneous mass composed of large eosinophilic cells. (**B**) Large polygonal cells with abundant eosinophilic cytoplasm and peripherally located nuclei. (**C–E**) *Genital type*: (**C**) Polypoid mass covered by squamous mucosa. (**D**) Polymorphous cell population, some polygonal and others elongated. (**E**) Elongated rhabdomyoblasts (strap cells).

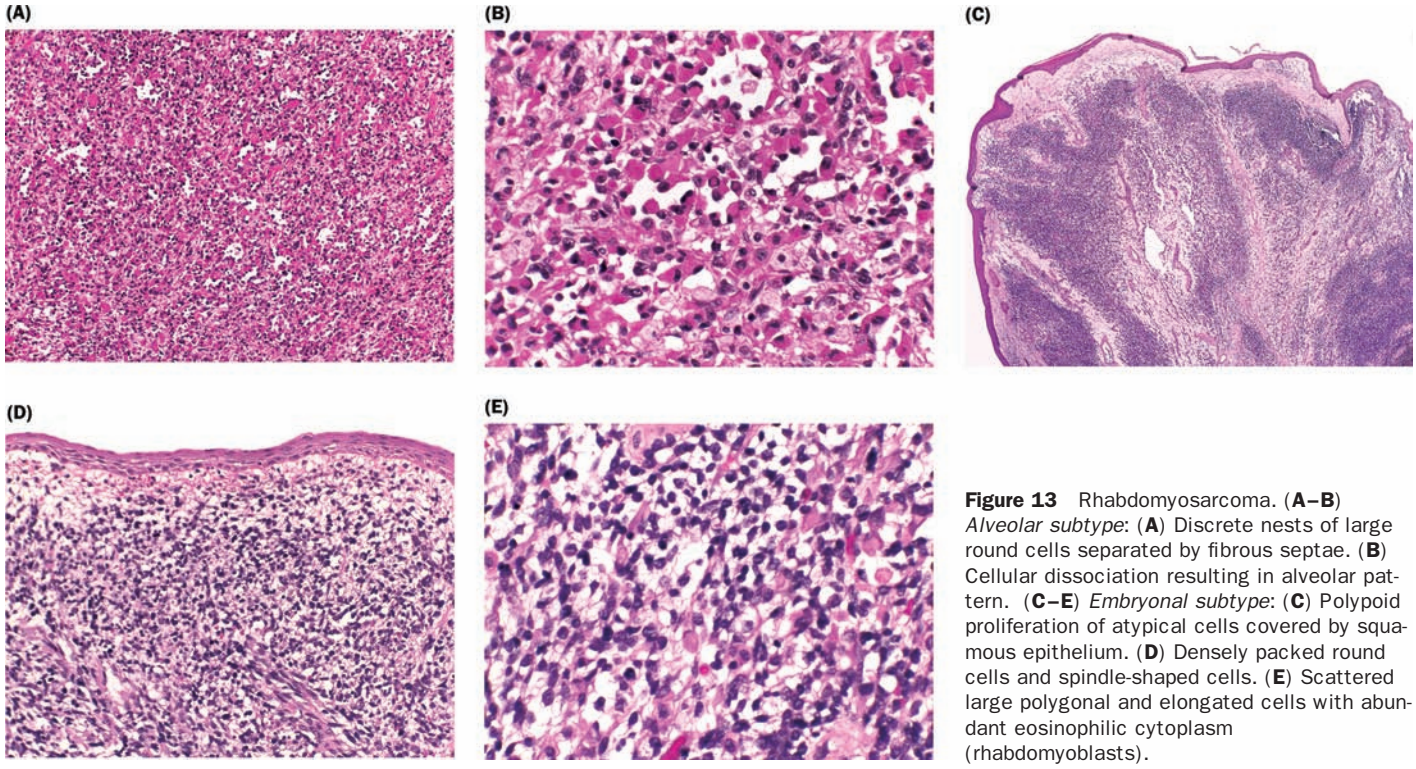

Figure 13 Rhabdomyosarcoma. (**A–B**) *Alveolar subtype*: (**A**) Discrete nests of large round cells separated by fibrous septae. (**B**) Cellular dissociation resulting in alveolar pattern. (**C–E**) *Embryonal subtype*: (**C**) Polypoid proliferation of atypical cells covered by squamous epithelium. (**D**) Densely packed round cells and spindle-shaped cells. (**E**) Scattered large polygonal and elongated cells with abundant eosinophilic cytoplasm (rhabdomyoblasts).

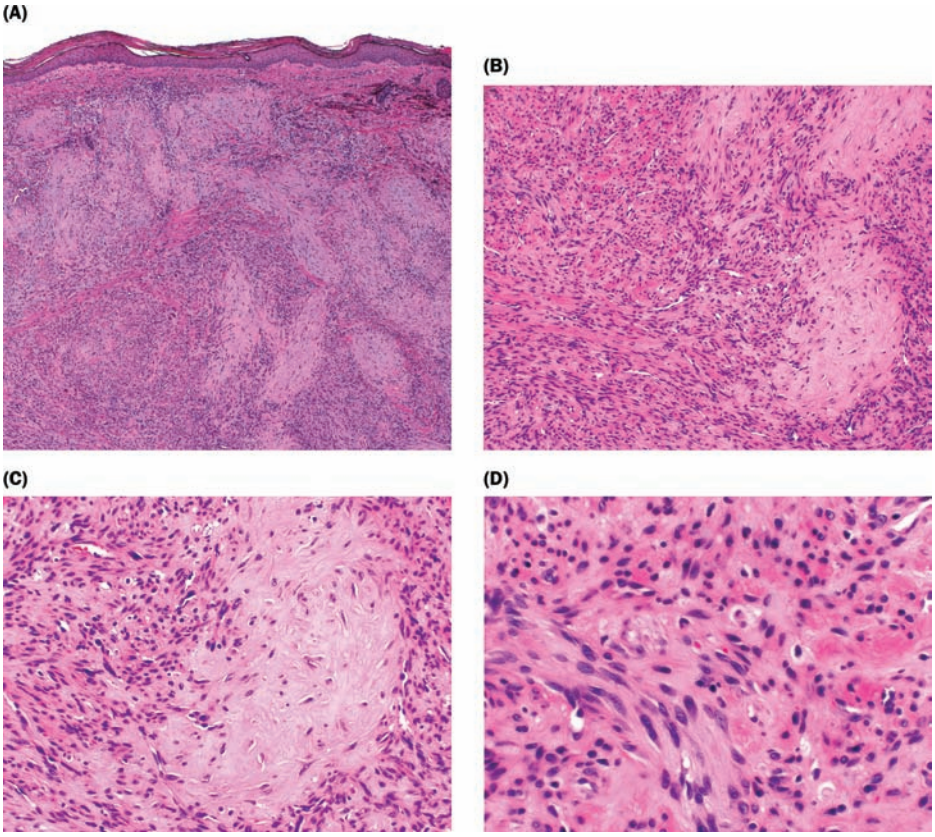

Figure 14 Solitary cutaneous myofibroma. (**A**) Nodular dermal proliferation with a biphasic pattern. (**B**) Central areas with vascular spaces surrounded by small round to oval cells (hemangiopericytomalike), and peripheral nodules composed of short fascicles of spindle shaped cells. (**C**) Spindle-shaped cells blend with oval cells surrounding the vascular spaces. (**D**) Spindle-shaped cells with elongated nuclei, resembling smooth muscle cells.

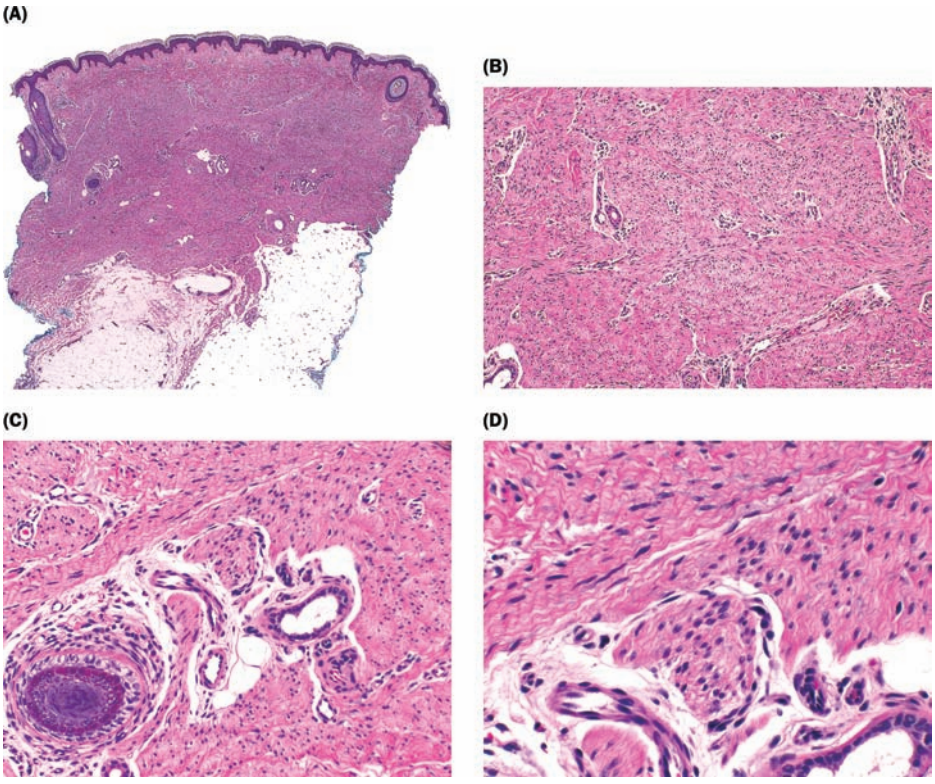

Figure 15 Dermatomyofibroma. (**A**) Plaque-like proliferation of spindle-shaped cells in the dermis. (**B**) Fascicles of spindle-shaped cells arranged parallel to the surface of skin. (**C**) Cells surround the blood vessels and adnexa, without obliterating them. (**D**) Spindle-shaped cells with eosinophilic cytoplasm and elongated nuclei, resembling smooth muscle.

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Depositions and Dermal Disorders

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CONTENTS

This chapter covers the disorders that primarily affect the dermis. These include depositions of substances such as amyloid and monosodium urate, as well as alterations to the various constituents of the dermis, such as collagen, elastic tissue, fibroblasts, and dermal mucin (hyaluronic acid).

SCLERODERMA AND MORPHEA

Synonyms: Progressive systemic sclerosis (scleroderma); localized scleroderma (morphea).

Clinical Presentation:

Scleroderma:

- Systemic connective tissue disease affecting skin, intestinal tract, kidneys, lungs, and heart
- Hyper- or hypopigmented, indurated and tightened skin of face and trunk (Fig. 1A)
- Raynaud's phenomenon
- Sclerodactyly
- Telangiectasias

Morphea:

- Skin-limited disease, without internal organ involvement
- Firm, ivory-colored plaque with hyperpigmented or erythematous border (Fig. 1B)

Histology:

- Same for both scleroderma and morphea
- Increased and thickened dermal collagen that involves entire reticular dermis (Fig. 1C)
- Loss of cutaneous appendages
- Thickened and closely apposed collagen bundles (Fig. 1D)
- Superficial and deep perivascular and interstitial infiltrate of lymphocytes and plasma cells in early, inflammatory phase (Fig. 1E)

Clinicopathologic Correlation:

Clinical Feature	Pathologic Feature
Firm induration with tight skin	Increased and thickened collagen bundles
Erythematous/hyperpigmented border	Superficial and deep lymphocytes and plasma cells

Differential Diagnosis:

Scleroderma	Scleredema	Scleromyxedema
Dermal thickness normal or slightly increased	Dermis markedly thickened	Dermal thickness normal or slightly increased
No mucin	Mucin in early phase only	Increased dermal mucin
Normal number of fibroblasts	Normal number of fibroblasts	Increased dermal fibroblasts
Loss of adnexal structures	No loss of adnexae	No loss of adnexae

Pathophysiology:

- Increased collagen production and deposition by activated fibroblasts
- Reasons for heightened fibroblast activity are incompletely understood

Reference:

1. Young EM Jr, Barr RJ. Sclerosing dermatoses. J Cutan Pathol 1985; 12:426.

LICHEN SCLEROSUS

Synonyms: Lichen sclerosus et atrophicus; kraurosis vulvae; balanitis xerotica obliterans (term for penile disease).

Clinical Presentation:
- Firm, indurated ivory-colored plaque, with erythematous or hyperpigmented border (Fig. 2A)
- Atrophic epidermis, sometimes with lichen-like surface hyperkeratosis
- Anogenital region, usually
- Well-recognized clinical and pathologic overlap with morphea

Histology:
- Hyperkeratosis, usually
- Epidermal atrophy, usually (Fig. 2B)
- Sclerosis (usually) or edema (less often) of papillary and upper reticular dermis (Fig. 2B)
- Lichenoid, band-like, lymphocytic infiltrate with interface alteration in early inflammatory phase (Fig. 2C)

Clinicopathologic Correlation:

Clinical Feature	Pathologic Feature
Lichen-like appearance	Hyperkeratosis
Firm induration	Dermal sclerosis
Epidermal atrophy	Thinned epidermis

Pathophysiology:
- Ultimate causes of fibrosis and sclerosis are incompletely understood, but altered fibroblast activity appears to play a role.

References:
1. Meffert JJ, Davis BM, Grimwood RE. Lichen sclerosus. J Am Acad Dermatol 1995; 32:393.
2. Fung MA, LeBoit PE. Light microscopic criteria for the diagnosis of early vulvar lichen sclerosus: a comparison with lichen planus. Am J Surg Pathol 1998; 22:473.

SCLEROMYXEDEMA

Synonyms: Lichen myxedematosus; papular mucinosis.

Clinical Presentation:
- Scleromyxedema and lichen myxedematosus represent the same disorder with different clinical expressions
- Multiple waxy papules (lichen myxedematosus) (Fig. 3A)
- Diffuse induration and thickening of skin (scleromyxedema)
- Hands, forearms, upper trunk, and face
- Most cases associated with IgG λ paraproteinemia
- Rare cases associated with multiple myeloma or Waldenström's macroglobulinemia

Histology:
- Increased dermal fibroblasts (Fig. 3B)
- Increased dermal collagen, which may be subtle (Fig. 3C)
- Increased dermal mucin (hyaluronic acid), highlighted with Hale's colloidal iron or Alcian blue stains (Fig. 3D)

Clinicopathologic Correlation:

Clinical Feature	Pathologic Feature
Waxy papules with indurated and thickened skin	Increased mucin (hyaluronic acid), fibroblasts, and collagen

Differential Diagnosis:

Scleromyxedema	Scleroderma	Scleredema
Dermal thickness normal or slightly increased	Dermal thickness normal or slightly increased	Dermis markedly thickened
Increased dermal mucin	No mucin	Mucin in early phase only
Increased dermal fibroblasts	Normal number of fibroblasts	Normal number of fibroblasts
No loss of adnexae	Loss of adnexal structures	No loss of adnexae

Pathophysiology:
- Dermal fibroblasts stimulated to produce increased amounts of hyaluronic acid (mucin) and collagen.
- Most patients also have an IgG λ paraprotein, but relationship of this paraprotein to increased fibroblast activity is not clearly known.

Reference:
1. Dinneen AM, Dicken CH. Scleromyxedema. J Am Acad Dermatol 1995; 33:37.

SCLEREDEMA

Clinical Presentation:
- Symmetrical, diffuse, thickening and induration of skin (Fig. 4A)
- Upper trunk and neck

Other Clinical Patterns:
- Postinfectious (usually Streptococcal)
- Diabetes-associated
- Idiopathic

Histology:
- Normal epidermis
- Greatly thickened dermis, due to increased dermal collagen (Fig. 4B)
- Retained, but entrapped adnexal structures (Fig. 4C)
- Increased dermal mucin, in early phase only

Clinicopathologic Correlation:

Clinical Feature	Pathologic Feature
Thickened and indurated skin of upper back	Greatly thickened dermis, with increased collagen deposition

Differential Diagnosis:

Scleredema	Scleroderma	Scleromyxedema
Dermis markedly thickened	Dermal thickness normal or slightly increased	Dermal thickness normal or slightly increased
Mucin in early phase only	No mucin	Increased dermal mucin
Normal number of fibroblasts	Normal number of fibroblasts	Increased dermal fibroblasts
No loss of adnexae	Loss of adnexal structures	No loss of adnexae

Pathophysiology:
- Not well understood

Reference:
1. Venencie PY, Powell FC, Su WPD, et al. Scleredema: a review of 33 cases. J Am Acad Dermatol 1984; 11:128.

PSEUDOXANTHOMA ELASTICUM

Clinical Presentation:
- "Chicken flesh-like," yellowish, coalescent, papules and plaques (Fig. 5A)
- Neck, axillae, antecubital, and popliteal fossae
- Later, affected skin becomes lax and wrinkled
- Angioid streaks of retina
- Hypertension, cerebrovascular accidents, and intestinal hemorrhage

Histology:
- Basophilic, short, curled, fragmented, and calcified dermal elastic fibers (Figs. 5B and C)

Clinicopathologic Correlation:

Clinical Feature	Pathologic Feature
Yellowish, "chicken flesh-like" skin	Calcification of dermal elastic fibers
Lax and wrinkled skin	Destruction of dermal elastic fibers
Tendency to intracerebral and intestinal hemorrhage	Calcification of elastic tissue within blood vessels, with decreased vascular integrity

Pathophysiology:
- Multisystem disease with calcification of elastic fibers within skin, eyes, and cardiovascular system
- Causes underlying elastic fiber calcification are not understood
- 90% of cases autosomal recessive inheritance

Reference:
1. McKee PH, Cameron CHS, Archer DB, Logan WC. A study of four cases of pseudoxanthoma elasticum. J Cutan Pathol 1977; 4:146.

ELASTOSIS PERFORANS SERPIGINOSA

Clinical Presentation:
- Pruritic, grouped keratotic papules in annular or serpigenous configurations (Fig. 6A)
- Papules are umbilicated with central plug of debris
- Neck, face, and upper extremities
- Associated with disorders of connective tissue, including Ehlers-Danlos syndrome, Marfan syndrome, osteogenesis imperfecta, pseudoxanthoma elasticum

Histology:
- Epidermal perforation filled with degenerated elastic fibers and basophilic debris
- At edge of perforation, hyperplastic epidermis envelops the fragmented elastic fibers and basophilic debris, originating from dermis below (Figs. 6B and C)

Clinicopathologic Correlation:

Clinical Feature	Pathologic Feature
Keratotic, umbilicated papule	Epidermal hyperplasia, surrounding perforation
Plug of debris	Degenerated elastic fibers and basophilic debris, within epidermal perforation

Differential Diagnosis:

Elastosis Perforans Serpiginosa	Reactive Perforating Collagenosis	Kyrle's Disease	Perforating Folliculitis
Patients with inherited disorders of connective tissue	Childhood or patients with chronic renal failure	Patients with diabetes mellitus and/or chronic renal failure	None
Elimination through epidermis	Elimination through epidermis	Elimination through epidermis or hair follicle	Elimination through hair follicle
Perforating altered elastic tissue	Perforating altered collagen	Perforating keratin, parakeratin, and inflammatory debris	Perforating altered collagen and elastic tissue

Pathophysiology:
- Expulsion of altered elastic fibers transepidermally
- Reasons underlying the elastic fiber alteration are not clearly known

Reference:
1. Patterson JW. The perforating disorders. J Am Acad Dermatol 1984; 10:561.

Table 1 Differential Diagnosis: Pretibial and Generalized Myxedema

Pretibial Myxedema	Generalized Myxedema	Reticular Erythematous Mucinosis	Scleromyxedema (Lichen Myxedematosus)	Focal Mucinosis
Epidermal hyperplasia and hyperkeratosis	± Epidermal hyperplasia and hyperkeratosis	No epidermal hyperplasia	No epidermal hyperplasia	Epidermal hyperplasia with collarettes
Diffuse mucin	Diffuse mucin, sometimes subtle	Diffuse mucin	Diffuse mucin	Localized mucin, fairly well circumscribed
No inflammation	No inflammation	Superficial and deep perivascular lymphocytes	Sparse perivascular lymphocytes	No inflammation
Normal number of dermal fibroblasts	Normal number of dermal fibroblasts	Normal number of dermal fibroblasts	Increased dermal fibroblasts	Increased dermal fibroblasts, some stellate

ANETODERMA

Clinical Presentation:
- Soft, flesh-colored, wrinkled papules and plaques (Fig. 7A)
- Papules and plaques herniate inwards when palpated
- Associations include sarcoidosis, varicella zoster, penicillamine, as well as chronic infectious diseases such as syphilis, leprosy, HIV, and tuberculosis

Histology:
- H&E sections usually have appearance of normal or unaltered skin (Fig. 7B)
- Early cases may exhibit mild mononuclear or acute inflammatory infiltrate (Fig. 7C)
- Elastic tissue stains (Verhoeff van Gieson stain) show loss of elastic fibers from superficial and mid-dermis (Fig. 7D)

Clinicopathologic Correlation:

Clinical Feature	Pathologic Feature
Soft papules that herniate inwards with palpation	Loss of dermal elastic fibers

Pathophysiology:
- Localized loss of dermal elastic tissue fibers (elastolysis)
- Reasons for elastolysis are not clearly known

Reference:
1. Venencie PY, Winkelmann RK, Moore BA. Anetoderma: clinical findings, associations, and long-term follow-up evaluations. Arch Dermatol 1984; 120:1032.

PRETIBIAL AND GENERALIZED MYXEDEMA

Clinical Presentation:
Pretibial Myxedema:
- Indurated plaques and nodules (Fig. 8A)
- Anterior shins
- Hyperthyroidism

Generalized Myxedema:
- Puffy, edematous appearing skin
- Face, hands, and ankles
- Hypothyroidism

Histology:
- Increased dermal mucin (hyaluronic acid) that splays collagen bundles apart (Fig. 8B)
- Mucin highlighted with Hale's colloidal iron or Alcian blue stains (Fig. 8C)
- Epidermal hyperkeratosis with pretibial myxedema
- Generally, no epidermal changes with generalized myxedema.

Clinicopathologic Correlation:

Clinical Feature	Pathologic Feature
Puffy and indurated skin	Increased mucin (hyaluronic acid) deposition

Differential Diagnosis:
See Table 1.

Pathophysiology:
- Dermal fibroblasts stimulated to produce increased amounts of hyaluronic acid (mucin)
- Mechanisms for increased fibroblast activity are not completely understood, but in pretibial myxedema, autoantibodies (i.e., LATS) may be responsible

Reference:
1. Heymann WR. Advances in the cutaneous manifestations of thyroid disease. Int J Dermatol 1997; 36:641.

AMYLOIDOSIS

Clinical Presentation:
- *Primary systemic amyloidosis*: Periorbital, waxy, papules and plaques, which exhibit intralesional hemorrhage ("pinch hemorrhages" of the eyelid) (Fig. 9A)
- *Nodular amyloidosis*: Solitary or multiple nodules
- *Macular amyloidosis*: Hyperpigmented, rippled, patches and plaques
- *Lichen amyloidosis*: Pruritic, hyperkeratotic papules, usually on shins

Histology:
- All subtypes exhibit deposition of eosinophilic amyloid within dermis.

- Primary systemic and nodular amyloidosis show similar features with relatively large nodular aggregates of amyloid which involve the entire dermis, often extending into subcutaneous fat. Amyloid is also deposited within blood vessel walls and around eccrine glands (Figs. 9B and C).
- Macular and lichen amyloidosis exhibit much smaller, globular, deposits of amyloid which are confined to the papillary dermis. Lichen amyloidosis exhibits epidermal hyperplasia and hyperkeratosis, whereas macular amyloidosis usually lacks epidermal changes (Fig. 9D).
- Amyloid highlighted by various stains, including Congo red, thioflavine T, and crystal violet.

Clinicopathologic Correlation:

Clinical Feature	Pathologic Feature
Pinch hemorrhages of primary amyloidosis	Amyloid deposition within dermis and blood vessels, leading to impaired vascular integrity with hemorrhage

Differential Diagnosis:

Adult Colloid Milium	Nodular Amyloidosis
Sun-exposed sites only	Sun-exposed and non-sun-exposed sites
Congo red positive	Congo red positive
Fissures and clefts divide eosinophilic deposits	Fissures and clefts divide eosinophilic deposits
Fibroblasts line fissures and clefts	No fibroblasts lining fissures and clefts
Deposits limited to upper dermis	Deposits involve upper and lower dermis
Grenz zone of papillary dermal sparing	May or may not have Grenz zone

Pathophysiology:

- All types of amyloidosis are secondary to extracellular deposition of insoluble fibrillar proteins, known generically as amyloid. The various subtypes of amyloidosis are associated with specific types of amyloid protein.
- Primary systemic and nodular amyloidosis are associated with light chain amyloid, whereas macular and lichen amyloidosis are associated with keratin amyloid.

Reference:

1. Breathnach SM. Amyloid and amyloidosis. J Am Acad Dermatol 1988; 18:1.

GOUT

Clinical Presentation:

- Painful, solitary, or multiple white–yellow nodules (tophi), which may discharge chalky white material (Fig. 10A)
- Fingers and toes, especially around joints
- Occasionally, helix of ear

Histology:

- In alcohol-fixed specimens, collections of brown needle-shaped crystals (monosodium urate) deposited within dermis
- In routine, formalin-fixed specimens, remnants of crystals appear as fan-shaped sheaths, surrounded by foreign body-type multinucleated giant cells (Figs. 10B and C)

Clinicopathologic Correlation:

Clinical Feature	Pathologic Feature
Chalky white–yellow material	Crystals of monosodium urate

Pathophysiology:

- Overproduction of uric acid leads to deposition of monosodium urate crystals within the dermis and subcutaneous tissue

Reference:

1. Palmer DG, Highton J, Hessian PA. Development of the gout tophus. An hypothesis. Am J Clin Pathol 1989; 91:190.

CALCINOSIS CUTIS

Clinical Presentation:

- *Tumoral calcinosis*: Large, firm nodules overlying joints, especially elbows
- *Scrotal calcinosis*: Single or multiple firm nodules on scrotal skin
- *Subepidermal calcified nodule*: Single hyperkeratotic, firm nodule on head or extremities of children
- *Calciphylaxis*: Single or multiple, firm, tender plaques, sometimes with necrosis. Patients usually have underlying chronic renal failure, or hyperparathyroidism, and the condition is often fatal (Fig. 11A)

Histology:

- *Tumoral calcinosis*: Large basophilic calcium aggregates within dermis, often surrounded by foreign body giant cell reaction (Fig. 11B)
- *Scrotal calcinosis*: Same as tumoral calcinosis
- *Subepidermal calcified nodule*: Variably sized basophilic calcium aggregates within papillary and upper dermis, with overlying epidermal hyperplasia and hyperkeratosis (Fig. 11C)
- *Calciphylaxis*: Fine, particulate basophilic calcium aggregates within blood vessels and surrounding adipocytes of subcutaneous fat. Affected blood vessels usually exhibit luminal narrowing or occlusion (Fig. 11D)

Clinicopathologic Correlation:

Clinical Feature	Pathologic Feature
Firm, tender nodules	Nodular aggregates of calcium salts within dermis
Tender plaques, sometimes with necrosis (calciphylaxis)	Calcium deposition within blood vessels, leading to luminal narrowing or occlusion with subsequent ischemic necrosis (calciphylaxis)

Table 2 Differential Diagnosis: Calcinosis Cutis

Tumoral Calcinosis	Scrotal Calcinosis	Subepidermal Calcified Nodule	Calciphylaxis
Joints, especially elbows	Scrotal skin	Head/neck and extremities	Most often lower extremities, but can occur anywhere
No epidermal changes	No epidermal changes	Epidermal hyperplasia and hyperkeratosis	±Epidermal necrosis
Calcium deposits within dermis and subcutaneous tissue	Calcium deposits within dermis	Calcium deposits within papillary and reticular dermis	Calcium deposits within blood vessels and surrounding adipocytes

Differential Diagnosis:

See Table 2.

Pathophysiology:

- Deposition of calcium salts within skin
- In calciphylaxis, deposition is due to overt primary or secondary hyperparathyroidism or elevation of calcium–phosphorus product (often in association with chronic renal failure)
- In other forms of calcinosis cutis, exact pathogenesis is not well understood

References:

1. Walsh JS, Fairley JA. Calcifying disorders of the skin. J Am Acad Dermatol 1995; 33:693.
2. Khafif RA, Delima C, Silverberg A, et al. Calciphylaxis and systemic calcinosis: collective review. Arch Intern Med 1990; 150:956.

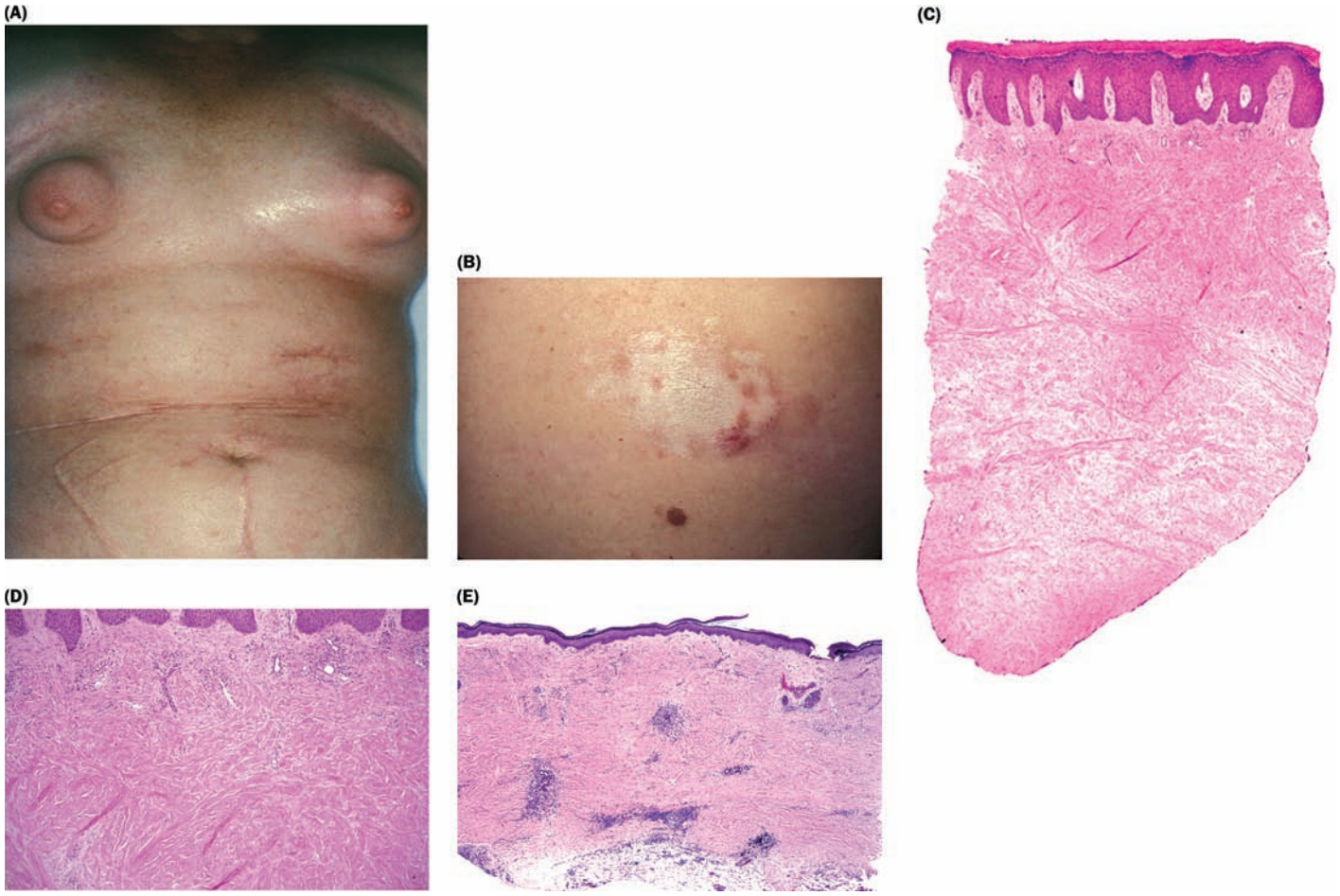

Figure 1 (**A**) Hyperpigmented, indurated, and tightened skin of trunk. (**B**) Firm, ivory-colored plaque with hyperpigmented border. (**C**) Increased and thickened dermal collagen that involves entire reticular dermis with loss of cutaneous appendages. (**D**) Thickened and closely apposed collagen bundles. (**E**) Superficial and deep perivascular and interstitial infiltrate of lymphocytes and plasma cells in early, inflammatory phase. *Source*: Fig. 1A—Courtesy of Elsevier; Slide Set for Color Atlas of Dermatology, Callen et al. 1993; 805.

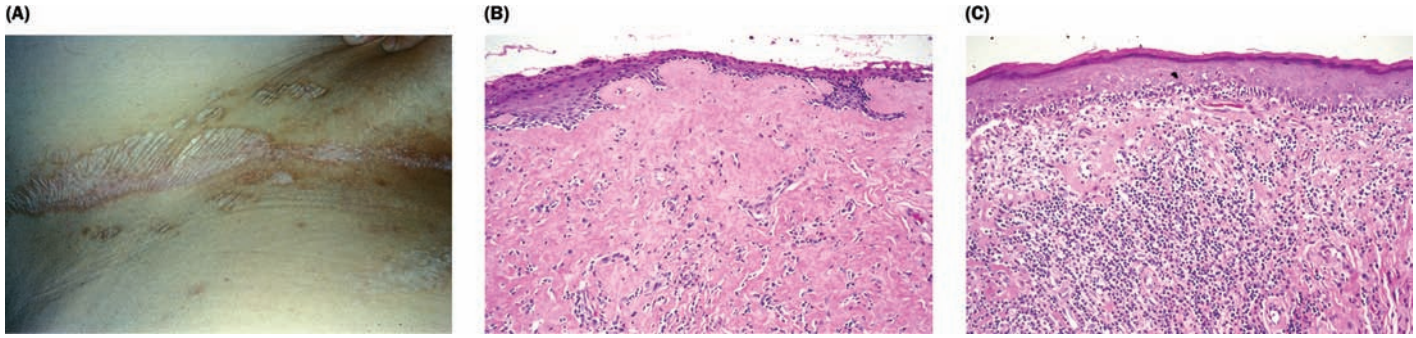

Figure 2 (**A**) Firm, indurated ivory-colored plaques, with hyperpigmented borders. (**B**) Sclerosis of papillary and upper reticular dermis with epidermal atrophy. (**C**) Lichenoid, band-like, lymphocytic infiltrate with interface alteration in early inflammatory phase. *Source*: Fig. 2A—Courtesy of Elsevier; Slide Set for Color Atlas of Dermatology, Callen et al. 1993; 785.

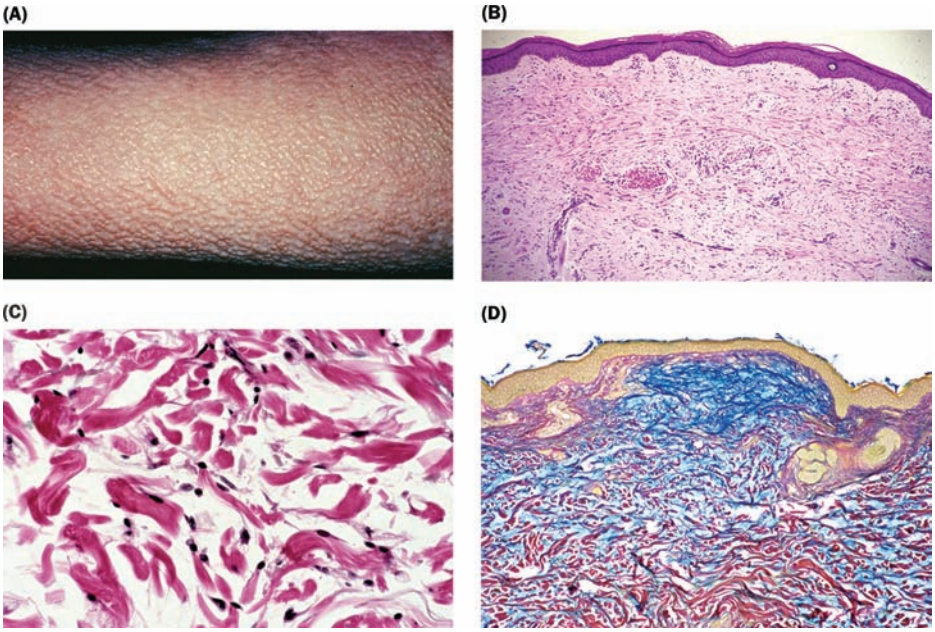

Figure 3 (**A**) Multiple waxy papules of lichen myxedematosus (scleromyxedema). (**B**) Increased dermal fibroblasts. (**C**) Increased dermal collagen. (**D**) Increased dermal mucin (hyaluronic acid), highlighted with Hale's colloidal iron stain. *Source*: Fig. 3A—Courtesy of Elsevier; Slide Set for Color Atlas of Dermatology, Callen et al. 1993; 881.

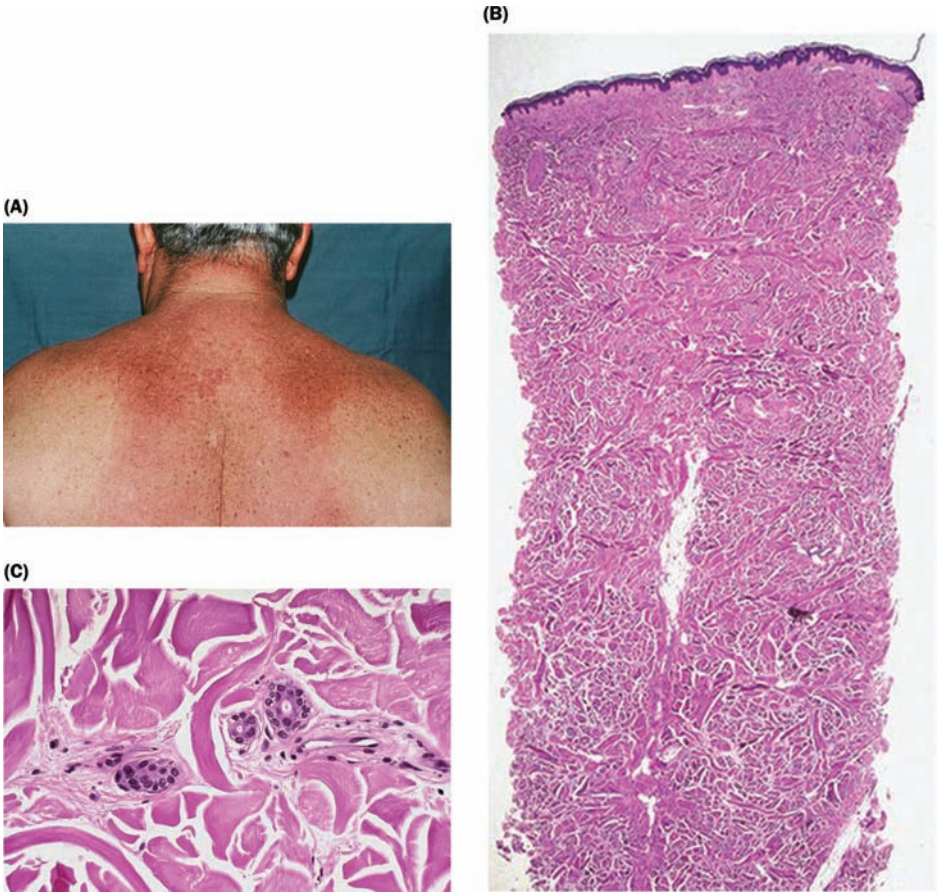

Figure 4 (**A**) Symmetrical, diffuse, thickening and induration of skin of the back in scleredema. (**B**) Greatly thickened dermis, due to increased dermal collagen. (**C**) Sweat glands entrapped by increased dermal collagen. *Source*: Fig. 4A—Courtesy of Elsevier; Slide Set for Color Atlas of Dermatology, Callen et al. 1993; 810.

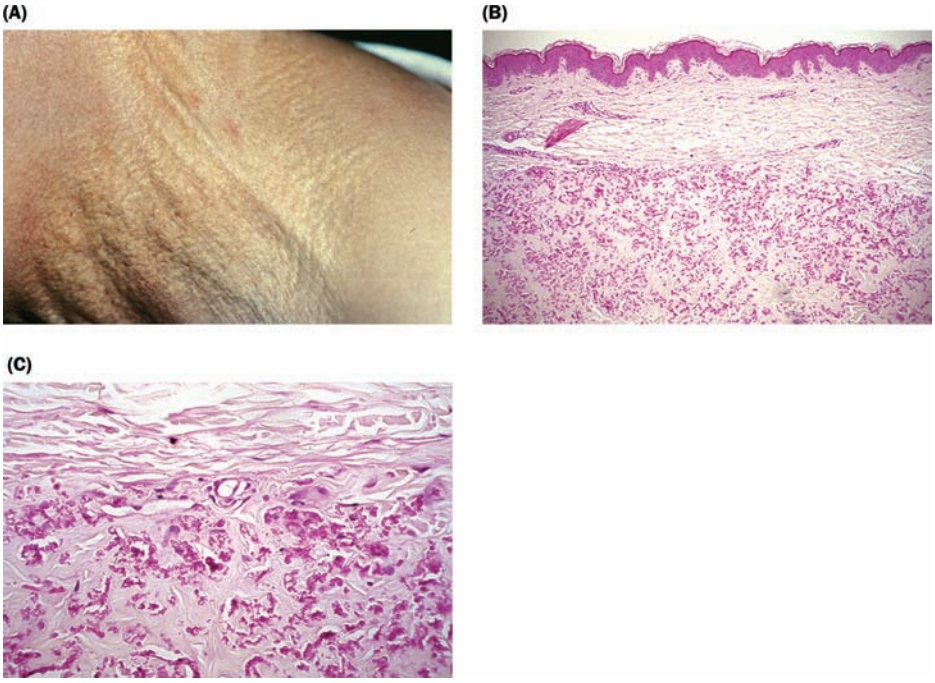

Figure 5 (**A**) ''Chicken flesh-like,'' yellowish plaque of pseudoxanthoma elasticum. (**B**) Calcified elastic fibers within lower reticular dermis. (**C**) Basophilic, short, curled, fragmented, and calcified dermal elastic fibers. *Source*: Fig. 5A—Courtesy of Elsevier; Slide Set for Color Atlas of Dermatology, Callen et al. 1993; 308.

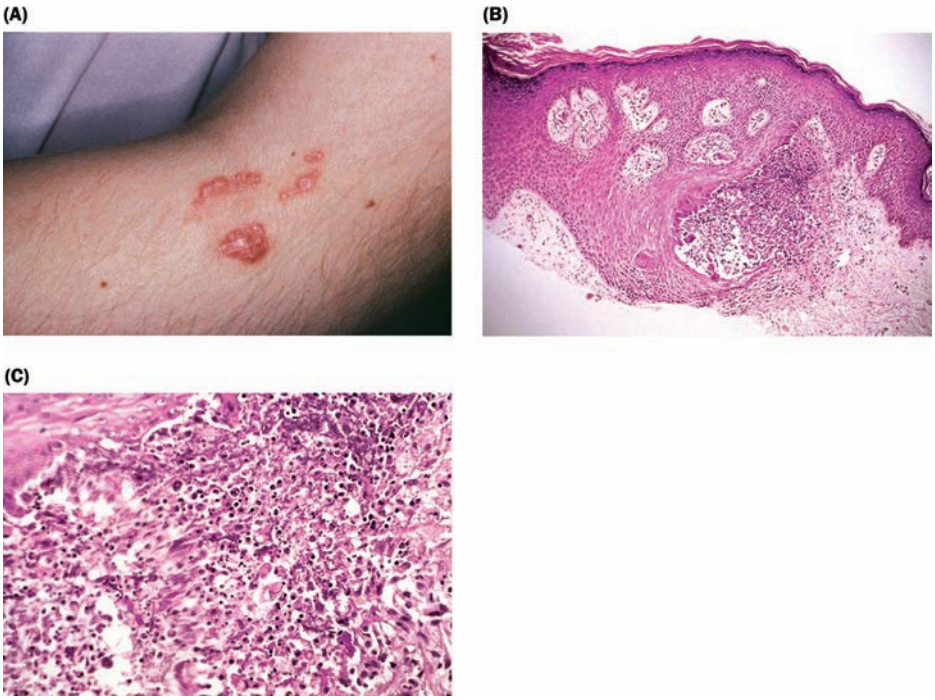

Figure 6 (**A**) Pruritic, grouped keratotic papules in annular configuration. (**B**) Edge of perforation, with hyperplastic epidermis enveloping altered dermal elastic fibers. (**C**) Fragmented and degenerated elastic fibers with accompanying basophilic debris. *Source*: Fig. 6A—Courtesy of Elsevier; Slide Set for Color Atlas of Dermatology, Callen et al. 1993; 879.

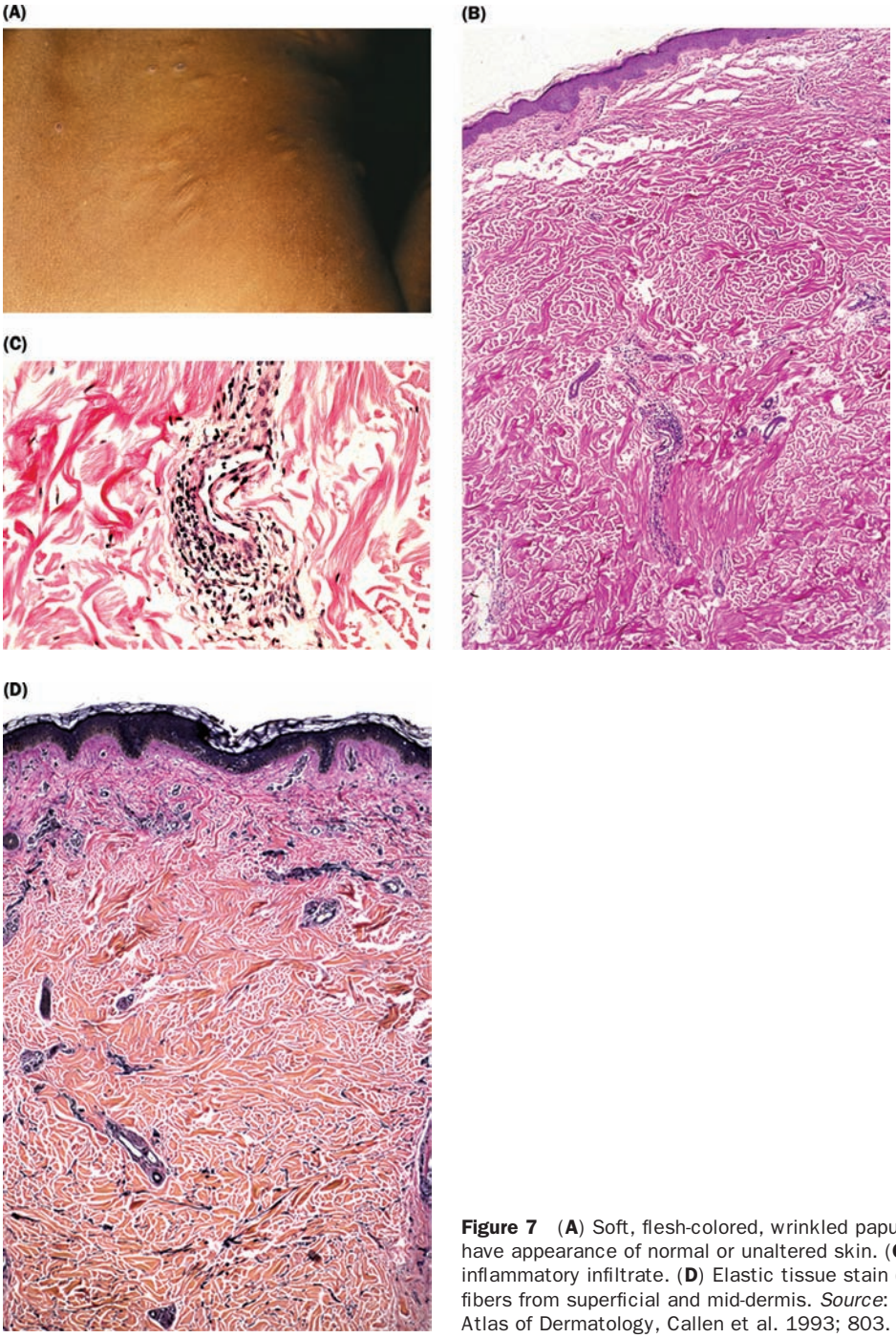

Figure 7 (**A**) Soft, flesh-colored, wrinkled papules. (**B**) H&E sections of anetoderma usually have appearance of normal or unaltered skin. (**C**) Early cases may exhibit mild mononuclear inflammatory infiltrate. (**D**) Elastic tissue stain (Verhoeff van Gieson stain) shows loss of elastic fibers from superficial and mid-dermis. *Source*: Fig. 7A—Courtesy of Elsevier; Slide Set for Color Atlas of Dermatology, Callen et al. 1993; 803.

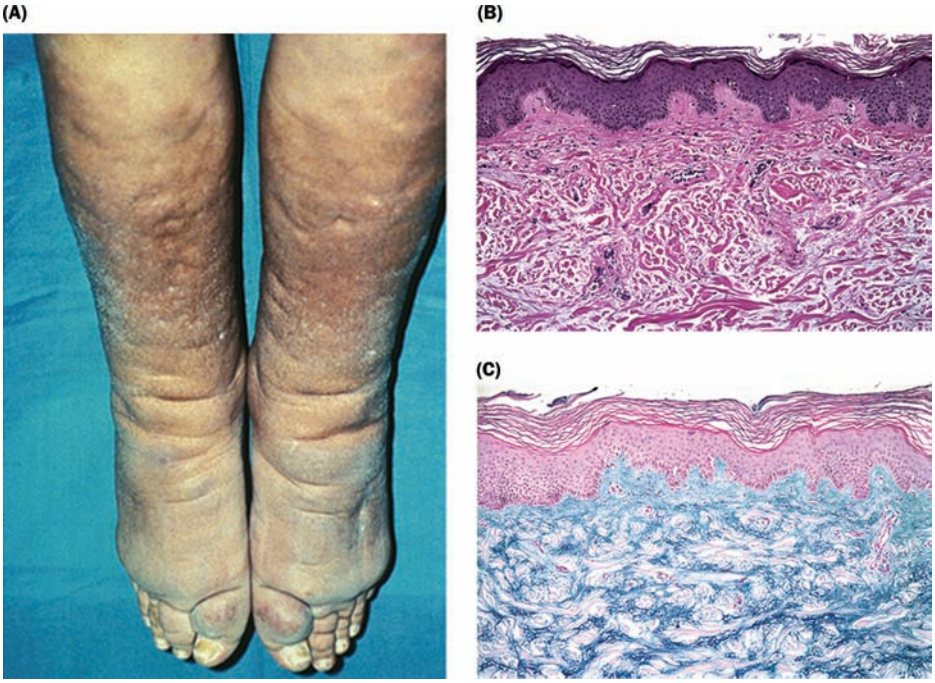

Figure 8 (**A**) Indurated plaques and nodules of pretibial myxedema. (**B**) Increased dermal mucin (hyaluronic acid) which pushes collagen bundles apart. (**C**) Dermal mucin highlighted with Hale's colloidal iron stain. *Source*: Fig. 8A—Courtesy of Elsevier; Slide Set for Color Atlas of Dermatology, Callen et al. 1993; 815.

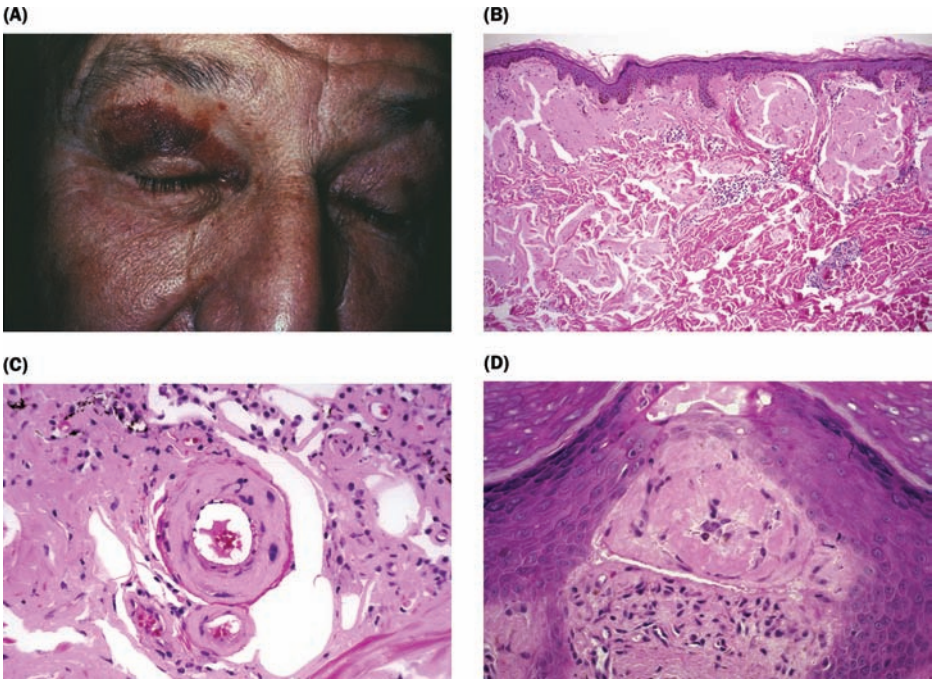

Figure 9 (**A**) "Pinch hemorrhages" of the eyelid in primary systemic amyloidosis. (**B**) In primary systemic amyloidosis, relatively large nodular aggregates of amyloid involve the entire dermis. (**C**) In primary systemic amyloidosis, amyloid is also deposited within blood vessel walls. (**D**) In lichen amyloidosis, the deposits of amyloid are small and confined to the papillary dermis. *Source*: Fig. 9A—Courtesy of Elsevier; Slide Set for Color Atlas of Dermatology, Callen et al. 1993; 679.

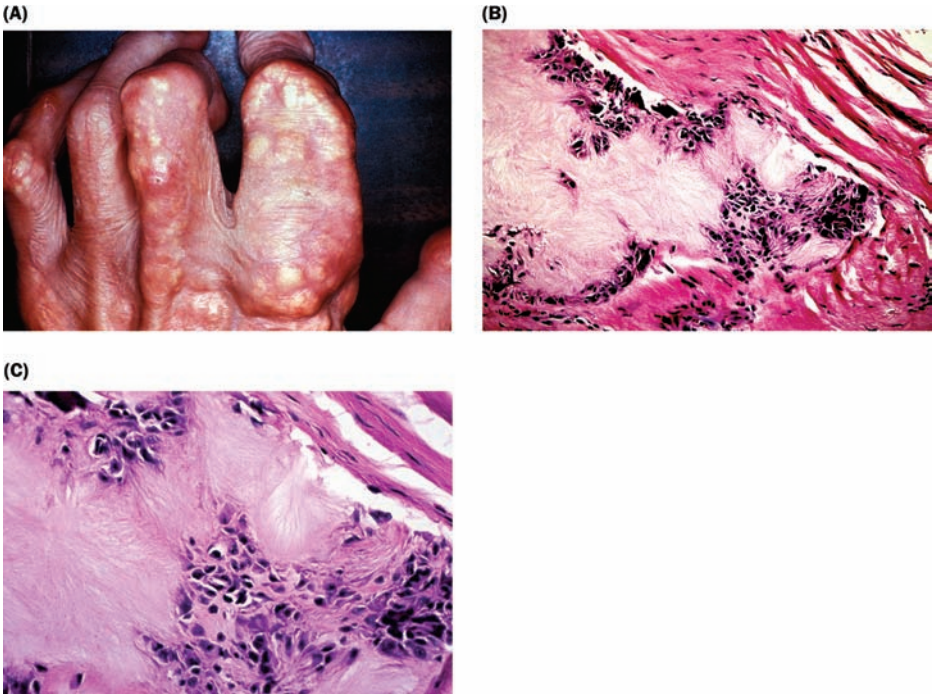

Figure 10 (**A**) Multiple, white–yellow nodules (tophi) of gout. (**B**) Monosodium urate crystals deposited within the dermis. (**C**) In routine, formalin-fixed specimens, remnants of crystals appear as fan-shaped sheaths, surrounded by foreign body-type multinucleated giant cells. *Source*: Fig. 10A—Courtesy of Elsevier; Slide Set for Color Atlas of Dermatology, Callen et al. 1993; 474.

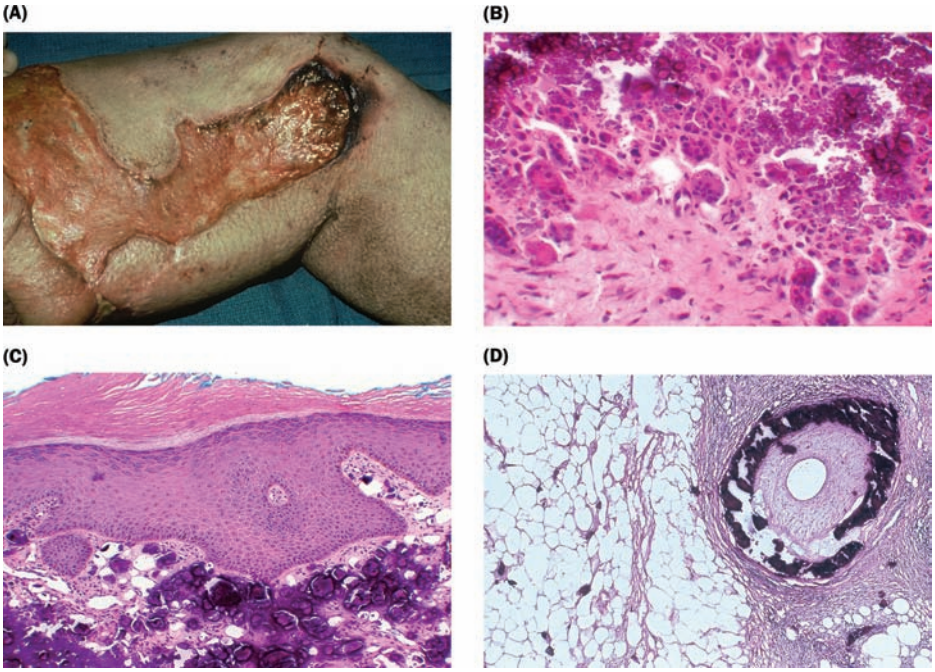

Figure 11 (**A**) A dramatic example of calciphylaxis with extensive necrosis of skin and subcutaneous tissue. (**B**) In tumoral calcinosis, irregularly shaped aggregates of calcium are surrounded by foreign body type giant cells. (**C**) In subepidermal calcified nodule, basophilic aggregates of calcium are found in the papillary and reticular dermis, with associated epidermal hyperplasia and hyperkeratosis. (**D**) In calciphylaxis, deposits of basophilic calcium are found within blood vessel walls, with associated luminal narrowing.

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Fat and Osseous Neoplasms

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CONTENTS

BENIGN FAT NEOPLASMS

Benign fat neoplasms comprise more than half of all benign soft tissue tumors. They outnumber their malignant counterparts (liposarcomas) by a margin of over 100:1. They show various degrees of fatty differentiation manifested by adipocytes with vacuolated clear cytoplasm that bulge against or distort its nucleus. Caution should be rendered in differentiating some simulators of adipocytes including vacuolated histiocytes, metastatic signet ring carcinoma cells, clear cell melanoma, and mesenchymal cells producing cytoplasmic acid mucopolysaccharide.

Clinically most benign fat neoplasms are represented by a single mass that is located in the superficial soft tissue. Fat neoplasms located in deep soft tissues, and particularly the ones located in the retroperitoneal area, should be differentiated from well-differentiated liposarcomas.

Immunohistochemistry has some use in the diagnosis of adipose tissue tumors. Normal fat cells and neoplastic fat cells express S-100 protein. Spindle cell lipomas show positivity for CD34 antigen. Electron microscopy practically never has a role in the diagnosis of fatty tumors. Cytogenetics alterations have been reported in some fatty tumors and may prove to be of diagnostic importance in the future.

The classification of benign fat neoplasm is achieved by identification of heterologous elements that it may show (smooth muscle, cartilage, bone, bone marrow) or specific histological differentiation of other elements including fibrous tissue, vascular component, or myxoid component, etc. The classification and key clinicopathological features of benign fatty tumors are summarized in the Table 1.

LIPOMA

Synonyms: Typical lipoma; simple lipoma.

Clinical Presentation:
- Lipomas are the most common connective tissue tumor in adults
- Represented by asymptomatic subcutaneous mobile mass located on the trunk, upper extremities, thighs, and posterior neck (Fig. 1A)
- Usually slow growing, well circumscribed and encapsulated mass. The size is less than 5cm in 80% of cases; however, it can reach a size of over 20cm.

Histopathology:
- Encapsulated tumor comprised of lobules of mature adipose tissue divided by thin incomplete fibrous septa with few blood vessels (Fig. 1B).
- Neoplastic mature fat cells are morphologically indistinguishable from normal adult fat cells; therefore, a diagnosis of lipoma cannot be made unless a mass has been identified.
- Variants of typical lipomas are classified by the presence of heterologous elements such as smooth muscle (myolipoma), cartilage (chondrolipoma), bone (osteolipoma), and bone marrow elements (myelolipoma) or by histological differentiation of specific elements including fibrous tissue (fibrolipoma) (Fig. 1C) or myxoid matrix (myxolipoma) (Fig. 1D). Finally, typical lipomas seated deeply in skeletal muscle are classified as intra/intermuscular lipomas (Table 1).
- Infarcted lipomas show areas of fat necrosis, foreign body reaction, and mitotic activity may be evident.

Clinicopathologic Correlation:
See Table 1.

Differential Diagnosis:
See Table 2.

Table 1 Classification and Key Clinicopathologic Features of Benign Fatty Tumors

Tumor Type	Key Clinical Features	Key Histological Features
Lipoma (typical lipoma) and variants Intramuscular lipoma Fibrolipoma Myxolipoma	Typical lipomas and its variants are represented by asymptomatic subcutaneous mobile mass Deeply seated in skeletal muscle	All are composed of mature adipose tissue that is histologically indistinguishable from non-neoplastic (normal) mature fat Lipomas within skeletal muscle Prominent fibrous septa Myxoid matrix
Lipomas with heterologous elements Myolipoma Chondrolipoma Osteolipoma Myelolipoma	Found usually at the adrenal gland or retroperitoneum	Foci of mature smooth muscle Island of mature cartilage Foci of metaplastic bone Foci of bone marrow elements
Angiolipoma	Deeply seated often multiple firm tender or painful nodules. Occurs in young adults	Encapsulated, small size, multiplicity, and subcutaneous location. Presence of mature fat, peripheral streaks of thick-walled capillaries filled with erythrocytes and often microthrombi
Angiomyolipoma	Renal and retroperitoneal primary tumor. Rare in skin manifested as deeply seated solitary asymptomatic nodule	Various amounts of mature fat, thick-walled blood vessels and irregularly arranged smooth muscle bundles. Smooth muscle actin (SMA) and human melanoma black (HMB) 45 (+)
Spindle cell lipoma	Occurs in older males. Slow growing, well-circumscribed soft solitary tumor located on posterior shoulders, neck, and back	Mature adipocytes and spindle cells in a fibrous stroma with focal myxoid changes. CD34 (+) and S-100 protein (−)
Pleomorphic lipoma	Same as spindle cell lipoma	Same as spindle cell lipoma plus multinucleated floret-like giant cells
Chondroid lipoma	Subcutaneous or intramuscular firm yellow nodule. Usually located on the shoulder, arm, and thigh	Epithelioid cartilage-like differentiation. Alternating ordinary white fat cells, epithelioid-appearing tumor cells, chondroid cells, and myxoid matrix.
Hibernoma	Subcutaneous tumor often increased warmth over tumor. Usually back (interscapular)	Three cell types: large multivacuolated adipocytes, large univacuolated fat, and small cells with granular eosinophilic cytoplasm
Lipoblastoma	Occurs exclusively in infants and children up to seven years	Immature fat cells separated by a myxoid matrix and admixed with a variable number of adult fat cells
Atypical lipoma	Predominantly occur in older age groups. Wide variety of subcutaneous locations	Presence of significant nuclear atypia detectable by low magnification (4–10× objective)
Nevus lipomatosus superficialis	Characterized by multiple papular, polypoid, or plaque like-lesions. Usually in children. In adults a localized form exists	Deposition of lobules of mature fat in the superficial dermis. Increased small blood vessels. Areas of loose fibrous tissue and diminished elastic fibers and appendages
Hemosiderotic fibrohistiocytic lipomatous lesion	Slow-growing asymptomatic nodule on the foot (ankle) in females	Abundant mature fat tissue and focal bundles of plump spindle cells. Prominent hemosiderin deposition in spindle cell areas. Mild cytological atypia
Piezogenic pedal papules	Multiple small skin-colored papules and nodules on the heels	Loss of septa and enlargement of fat lobules with herniation into dermis. Mature fat cell identical to normal mature fat cells

Table 2 Differential Diagnosis: Lipoma

	Location	Histopathology
Typical lipoma	Subcutaneous mass	Mature fat cell identical to normal mature fat cells
Normal fat	No mass is evident	Mature fat cells identical to neoplastic mature fat cells
Atypical lipoma	Subcutaneous mass	Presence of significant adipocyte atypia (4–10×)
Well-differentiated liposarcoma	Deep mass	Presence of adipocyte atypia, lipoblasts, myxoid, and fibrous tissue with atypical cells
Myxoid liposarcoma	Deep mass	Presence of adipocyte atypia, lipoblast, and myxoid stroma with arborizing vascular pattern
Pseudolipomatosis cutis	No mass is evident	Presence of dermal superficial vacuoles without nuclei. Consider an artifact of tissue fixation
Infarcted lipoma	Subcutaneous mass	Presence of fat necrosis, foreign body reaction, and mitosis
Intramuscular hemangioma	Deep mass	Predominance of vascular proliferation compare to mature fat

Pathophysiology:
- Recent genetic findings support the neoplastic versus hyperplastic nature of most lipomas and the separation of several lipoma types as specific disease entities
- Seventy-five percent of lipomas show kariotype abnormalities, usually rearrangement on 12q13–15 and 6p

References:

1. Connective tissue tumors. McKee PH, Calonje JE, Granter SR, eds. Pathology of the Skin with Clinical Correlations. 3rd ed. Philadelphia: Elsevier Mosby, 2005:1684–1865.
2. Mandahl N, Hoglund M, Mertens F, et al. Cytogenetic aberrations in 188 benign and borderline adipose tissue tumors. Genes Chromosomes Cancer 1994; 9(3):207–215.
3. Tumors of fat. Weedon D, ed. Skin Pathology. 1st ed. Edinburgh: Churchil Livingstone, 1997:787–795.

ANGIOLIPOMA

Synonym: None.

Clinical Presentation:
- Angiolipomas are relatively common; they represent about 10% of adipose tumors.
- Deeply seated often multiple firm and tender or painful nodules, 1 to 4cm in diameter.
- Usually in young adults, lesions can be found anywhere on trunk and extremities, especially upper limbs (Fig. 2A).

Histopathology:
- Encapsulated tumor consisting of lobules of mature adipocytes and irregular anastomosing small blood vessels that comprise 5% to 50% of tumor mass (Fig. 2B).
- Blood vessels are mainly located on the periphery of the tumor; they have prominent pericytes, no endothelial atypia and lumina with erythrocytes and thrombi (Fig. 2C).
- Numerous mast cells can be present.
- Very rarely blood vessels constitute most of the lesion; the tumor is then called cellular angiolipoma.

Clinicopathologic Correlation:
See Table 1.

Differential Diagnosis:
The differential diagnosis of this lesion in part depends on the density of the vessels. The hypovascular lesion may be mistaken for typical lipomas.

	Histopathology
Angiolipoma	Encapsulated, small size, multiplicity, and subcutaneous location. Presence of mature fat, peripheral streaks of thick-walled capillaries filled with erythrocytes and often microthrombi
Cellular angiolipoma	Presence of a dominant vascular component in lobular configuration and prominent fibrin thrombosis. Scattered fat cells are seen. Mitotic activity can be present. No endothelial atypia is evident
Kaposi sarcoma	Irregular slit-like vascular spaces, extravasated red cells. Periodic acid Schiff (PAS)-positive intracytoplasmic globules. Presence of spindle cells, plasma cells, and hemosiderin deposition. Lacks microthrombi

(*Continued*)

Differential Diagnosis: ***Continued***

	Histopathology
Spindle cell hemangioma	Poorly circumscribed, thin-walled cavernous vascular spaces intermixed with spindle to epithelioid cells. Bland endothelial cells
Spindle cell lipoma	Presence of mature fat and bland spindled mesenchymal cells in various amounts. Mast cells and myxoid stroma can be present
Intramuscular hemangioma	Deep seated with a combination of vascular (capillary or cavernous) elements and lipomatous elements

Pathophysiology:
- Angiolipomas have normal kariotype, suggesting that they may be reactive rather then neoplastic

References:

1. Connective tissue tumors. McKee PH, Calonje JE, Granter SR, eds. Pathology of the Skin with Clinical Correlations. 3rd ed. Philadelphia: Elsevier Mosby, 2005:1684–1865.
2. Sciot R, Akerman M, Dal Cin P, et al. Cytogenetics analysis of subcutaneous angiolipomas: further evidence supporting its difference from ordinary pure lipomas. A report of the CHAMP Study Group. Am J Surg Pathol 1997; 21:441–444.
3. Tumors of fat. Weedon D, ed. Skin Pathology. 1st ed. Edinburgh: Churchil Livingstone, 1997:787–795.

ANGIOMYOLIPOMA

Synonym: None.

Clinical Presentation:
- Rare mesenchymal tumor that primarily occurs in the kidney and retroperitoneum. Less frequent in the liver, abdominal, and extra-abdominal sites.
- Bilateral and multiple angiomyolipomas are associated with tuberous sclerosis complex.
- Rarely encountered in the skin as a deeply seated solitary asymptomatic nodule, usually in females (Fig. 3A).

Histopathology:
- Well-circumscribed subcutaneous neoplasm comprised of various amounts of mature fat, thick-walled blood vessels, and irregularly arranged smooth muscle bundles (Figs. 3B and C)
- The smooth muscle component is reactive to smooth muscle actin, desmin, HMB45, and MelanA, and is negative for CD34 antigen

Clinicopathologic Correlation:
See Table 1.

Differential Diagnosis:

	Histopathology
Angiomyolipoma	Various amounts of mature fat, thick-walled blood vessels, and irregularly arranged smooth muscle bundles. SMA and HMB45 (+)
Angiolipoma	Presence of mature fat, peripheral streaks of thick-walled capillaries filled with erythrocytes and often microthrombi

(*Continued*)

Differential Diagnosis: *Continued*

	Histopathology
Leiomyoma (vascular)	Fascicles of bland smooth muscle and thin-walled blood vessels
Renal cell carcinoma	Clear cells nested, with network of small vessels. Reactive for epithelial membrane antigen and cytokeratins
Well-differentiated lipoma-like liposarcoma	Presence of significant adipocyte atypia. Deep location

The differential diagnosis depends upon the predominance differentiation of its components of this neoplasm.

Pathophysiology:
- Angiomyolipomas show kariotype abnormalities, usually rearrangement on 12q, 16p13

References:

1. Connective tissue tumors. McKee PH, Calonje JE, Granter SR, eds. Pathology of the Skin with Clinical Correlations. 3rd ed. Philadelphia: Elsevier Mosby, 2005:1684–1865.
2. Del Sordo R, Colella R, Leite S, et al. Cutaneous angiomyolipoma: a case report and literature review. Pathologica 2005; 97(3):137–140.
3. Val-Bernal JF, Mira C. Cutaneous angiomyolipoma. J Cutan Pathol 1996; 23:364–368.

SPINDLE CELL LIPOMA

Synonym: None.

Clinical Presentation:
- Occurs in older men (median age of 55 years)
- Slow growing, well-circumscribed soft solitary tumor located on posterior shoulders, neck, and back (Fig. 4A)

Histopathology:
- Tumor is located in dermis and subcutis, well-circumscribed, but without a capsule
- Tumor consists of mature adipocytes and spindle cells in a fibrous stroma with focal myxoid changes (Fig. 4B)
- Spindle cells can be palisaded, fasciculated, or they can be found haphazardly throughout the tumor. They have pale eosinophilic cytoplasm, without nuclear atypia or mitotic activity (Fig. 4C)
- Large numbers of mast cells and coarse collagen bundles are often seen between the spindle cells
- The myxoid stromal change may be a dominant feature in some cases
- Immunohistochemistry studies show reactivity to CD34 antigen. They are S100 protein, desmin, and smooth muscle actin negative

Clinicopathologic Correlation:
See Table 1.

Differential Diagnosis:

	Histopathology
Spindle cell lipoma	Mature adipocytes and spindle cells in a fibrous stroma with focal myxoid changes. CD34 (+) and S-100 (−)

(*Continued*)

Differential Diagnosis: *Continued*

	Histopathology
Pleomorphic lipoma	Same as spindle cell lipoma, plus multinucleated floret-like giant cells. CD34 (+) and S100 (−)
Neurofibroma	Mixture of elongated spindled Schwann cells and fibroblast in a background of wavy collagenous fibers. Mast cells present. S-100 (+)
Leiomyoma	Radially or haphazardly arranged, poorly circumscribed clusters of mature smooth muscle. SMA (+)
Myxoid liposarcoma	Presence of adipocyte atypia, lipoblasts, myxoid stroma with arborizing vascular pattern
Hemosiderotic fibrohistiocytic lipomatous lesion	Abundant mature fat tissue and focal bundles of plump spindle cells. Prominent hemosiderin deposition in spindle cell areas. Mild cytological atypia.

Most spindle cell lipomas contain all three elements, and when present in near equal proportions the appearance is distinctive and not easily confused with other entities. Those with spindle cell predominance may resemble neurofibroma or leiomyomas.

Pathophysiology:
- The 16q losses with partial monosomy are typical of spindle cell and pleomorphic lipoma and differ from the changes seen in other lipomas. Recurrent involvement of chromosome 13q has also been reported.

References:

1. Connective tissue tumors. McKee PH, Calonje JE, Granter SR, eds. Pathology of the Skin with Clinical Correlations. 3rd ed. Philadelphia: Elsevier Mosby, 2005:1684–1865.
2. Dal Cin P, Sciot R. Fletcher CD, et al. Lesions of 13q may occur independently of deletion of 16q in spindle cell/pleomorphic lipomas. Histopathology 1997; 31:222–225.
3. Fletcher CDM, Martin-Bates E. Spindle cell lipoma: a clinicopathological study with some original observations. Histopathology 1987; 11:803–817.

PLEOMORPHIC LIPOMA

Synonym: Giant cell lipoma.

Clinical Presentation:
- Usually manifests as soft painless solitary tumor on posterior neck or shoulders of elderly men.

Histopathology:
- Pleomorphic lipoma is a variant of spindle cell lipoma, therefore, shares the same histological features with the addition of multinucleated floret-like giant cells with radially arranged nuclei, like petals of flowers (Figs. 5A and B)
- Some of these tumors have prominent nuclear atypia with hyperchromasia and even occasional atypical mitosis. In such cases, for instance the border between pleomorphic lipoma and atypical lipoma is arbitrary.

Clinicopathologic Correlation:
See Table 1.

Differential Diagnosis:
See Differential Diagnosis in the section "Angiomyolipoma" (p. 373).

Pathophysiology:
- Kariotype abnormalities are the same as spindle cell lipoma.

References:

1. Connective tissue tumors. McKee PH, Calonje JE, Granter SR, eds. Pathology of the Skin with Clinical Correlations. 3rd ed. Philadelphia: Elsevier Mosby, 2005:1684–1865.
2. Schmookler BM, Enzinger EM. Pleomorphic lipoma: a benign tumor simulating liposarcoma. A clinicopathologic analysis of 48 cases. Cancer 1982; 47:126–133.

CHONDROID LIPOMA

Synonym: None.

Clinical Presentation:
- Young adults with female predominance
- Subcutaneous or intramuscular firm yellow nodule (average diameter 3–4cm)
- Usually located on the shoulder, arm, and thigh

Histopathology:
- The lesions are lobulated and consist of alternating ordinary white fat cells, epithelioid-appearing tumor cells, chondroid cells, and myxoid matrix
- Univacuolated, multivacuolated lipoblasts, and hibernoma-like cells with granular eosinophilic cytoplasm in chondromyxoid matrix. Hemorrhage and fibrosis are often present
- Immunohistochemically is reactive to the S-100 protein, CD68, keratins, and vimentin
- Lipomas with true cartilaginous differentiation do not belong to this category and are classified as chondrolipoma

Clinicopathologic Correlation:
See Table 1.

Differential Diagnosis:

	Histopathology
Chondroid lipoma	**Alternating ordinary white fat cells, epithelioid-appearing tumor cells, chondroid cells, and myxoid matrix**
Myxoid liposarcoma	**Presence of adipocyte atypia, lipoblasts, myxoid stroma with arborizing vascular pattern**
Extraskeletal myxoid chondrosarcoma	**Presence of prominent lobulation, mature fat is not present, and the matrix is myxoid rather than hyaline-like or chondroid**

Pathophysiology:
- Balance translocation t(11;16)(q13;p12–13) has been described

References:

1. Connective tissue tumors. McKee PH, Calonje JE, Granter SR, eds. Pathology of the Skin with Clinical Correlations. 3rd ed. Philadelphia: Elsevier Mosby, 2005:1684–1865.
2. Kindblom LG, Meis-Kindblom JM. Chondroid lipoma: an ultrastructural and immunohistochemical analysis with further observations regarding its differentiation. Hum Pathol 1995; 26:706–715.

HIBERNOMA

Synonym: Brown fat tumor.

Clinical Presentation:
- Usually young adults, it occurs most commonly in the thigh, shoulder, and back (interscapular region)
- Slow-growing subcutaneous tumor often increased warmth over the area of tumor

Histopathology:
- Large tumor, encapsulated and lobulated, with three cell types.
  - Large multivacuolated adipocytes ("mulberry cells") are predominant cell population.
  - Large univacuolated fat cells with peripheral nucleus (resemble mature adipocytes).
  - Small cells with granular eosinophilic cytoplasm (Figs. 6A and B)..
- The cells have prominent nucleoli, but lack mitotic activity.
- Lobules are divided by thin fibrous septa with abundant blood vessels.
- Immunohistochemically are S-100 protein positive.

Clinicopathologic Correlation:
See Table 1.

Differential Diagnosis:

	Histopathology
Hibernoma	**Three cell types: large multivacuolated adipocytes, large univacuolated fat, and small cells with granular eosinophilic cytoplasm**
Granular cell tumor	**Cytoplasm is not vacuolated, is granular**
Liposarcoma with hibernoma-like areas	**Atypical adipocytes, arborizing vascular pattern, presence of lipoblasts**

Pathophysiology:
- Rearrangements found on chromosome 11q13

References:

1. Tumors of fat. Weedon D, ed. Skin Pathology. 1st ed. Edinburgh: Churchil Livingstone, 1997:787–795.
2. Connective tissue tumors. McKee PH, Calonje JE, Granter SR, eds. Pathology of the Skin with Clinical Correlations. 3rd ed. Philadelphia: Elsevier Mosby, 2005:1684–1865.
3. Furlong MA, Farnburg-Smith JC, Mettinen M. The morphologic spectrum of hibernoma: a clinicopathologic study of 170 cases. Am J Surg Pathol 2001; 25:809–814.

LIPOBLASTOMA

Synonym: None.

Clinical Presentation:
- Occurs exclusively in infants and children up to seven years of age.
- Manifests as subcutaneous mass usually on the extremities, there are two forms
  - Localized
  - Diffuse (lipoblastomatosis)
  - Benign tumor may recur especially if diffuse

Histopathology:
- It is composed of small, immature fat cells separated by a myxoid matrix and admixed with a variable number of adult fat cells
- Tumor consisting of lobules of different types of lipoblasts (univacuolar, multivacuolar, granular) as well as mature adipocytes, and stellate, spindle mesenchymal cells
- There are no atypical mitoses or nuclear polymorphism.
- Stroma is often patchy myxoid with plexiform capillaries

Clinicopathologic Correlation:
See Table 1.

Differential Diagnosis:

	Age	Histopathology
Lipoblastoma	Children	Immature fat cells separated by a myxoid matrix and admixed with a variable number of adult fat cells
Myxoid liposarcoma	Adults	Presence of adipocyte atypia, lipoblasts, myxoid stroma with arborizing vascular pattern. Cytogenetics studies show t(12;16)(q13;11)
Fibrolipoma	Young adults	Mature fat with prominent fibrous septa

Pathophysiology:
- Characteristic rearrangement 8q11–q13 that leads to activation of PLAG1 oncogene

References:

1. Connective tissue tumors. McKee PH, Calonje JE, Granter SR, eds. Pathology of the Skin with Clinical Correlations. 3rd edition. Philadelphia: Elsevier Mosby, 2005:1684–1865.
2. Harrer J, Hammon G, Wagner T, et al. Lipoblastoma and lipoblastomatosis: a report of two cases and review of the literature. Eur J Pediatr Surg 2001; 11:342–349.
3. Dal Cin P, Sciot R, De Wever I, et al. New discriminative chromosomal marker in adipose tissue tumors. The chromosome 8q11–q13 region in lipoblastoma. Cancer Genet Cytogenet 1994; 78:232–235.
4. Hibbard MK, Kozakewich HP, Dal Cin P, et al. PLAG1 fusion oncogenes in lipoblastoma. Cancer Res 2000; 60:4869–4872.

ATYPICAL LIPOMA

Synonym: None.

Clinical Presentation:
- Predominantly occur in older age groups.
- They are located in a wide variety of subcutaneous locations, most commonly the shoulders, back, arm, and buttock.
- These tumors may recur locally, but transformation to high-grade sarcoma is rare.
- Similar tumors in intramuscular and retroperitoneal locations are by convention designated well-differentiated liposarcomas. Also tumors whose cellularity and atypia are equal to that of pleomorphic liposarcoma are classified as such regardless of location.

Histopathology:
- Atypical lipoma and well-differentiated liposarcoma are histologically and genetical identical
- The atypical nuclei are seen at low magnification (4–10× objective). Mitotic activity is absent

Clinicopathologic Correlation:
See Table 1.

Differential Diagnosis:

	Location	Histopathology
Atypical lipoma	Subcutaneous tissue	Presence of significant nuclear atypia detectable by low magnification (4–10× objective)
Well-differentiated liposarcoma	Intramuscular or retroperitoneal area	Presence of significant nuclear atypia detectable by low magnification (4–10× objective)

Pathophysiology:
- Similar chromosomal rearrangements in 12q involving the gene encoding HMGIC have been found in atypical lipoma as seen in lipoma and in well-differentiated liposarcoma

References:

1. Evans HL, Soule EH, Winkelmann RK. Atypical lipoma, atypical intramuscular lipoma, and well differentiated retroperitoneal liposarcoma: a reappraisal of 30 cases formerly classified as well differentiated liposarcoma. Cancer 1979; 43(2):574–584.
2. Weiss SW, Rao VK. Well-differentiated liposarcoma (atypical lipoma) of deep soft tissue of the extremities, retroperitoneum, and miscellaneous sites. A follow-up study of 92 cases with analysis of the incidence of "dedifferentiation." Am J Surg Pathol 1992; 16(11):1051–1058.

NEVUS LIPOMATOSUS SUPERFICIALIS

Synonym: None

Clinical Presentation:
- Uncommon connective tissue nevus. Characterized by multiple papular, polypoid, or plaque-like lesions (Fig. 7A)
- Occurs usually in children and young adults, pelvic girdle is the most common location
- Its diffuse form is labeled "Michelin tire appearance."
- Solitary forms in adults may occur and is more likely to represent a variant of fibroepithelial polyp

Histopathology:
- Collections of mature adipocytes in dermis, mature fat comprises 10% to 70% of the lesion (Fig. 7B)
- Other connective tissue abnormalities may be present—thickening of the collagen bundles, increased elastic tissue, increased number of fibroblasts, mononuclear cells, and blood vessels, and reduced folliculosebaceous units
- Epidermal changes including papillomatosis, acanthosis, and hyperpigmentation of the basal cell layer
- Sometimes dilated follicular ostia can be present

Clinicopathologic Correlation:
See Table 1.

Differential Diagnosis:

	Histopathology
Nevus lipomatosus superficialis	Deposition of lobules of mature fat in the superficial dermis. Increased small blood vessels. Areas of loose fibrous tissue and diminished elastic fibers and appendages
Fibroepithelial polyp	Normal to hyperplastic epidermis surrounded by a core of fibrovascular tissue with loose or dense collagen. Fat cells can be present and if abundant it overlaps with nevus lipomatosus superficialis
Fibrolipoma	Mature fat with prominent fibrous septa
Focal dermal hypoplasia	Histologically indistinguishable from nevus lipomatosus superficialis. Goltz syndrome involves both the ectoderm and mesoderm and is found only in females

References:

1. Tumors of fat. Weedon D, ed. Skin Pathology. 1st ed. Edinburgh: Churchil Livingstone, 1997:787–795.
2. Connective tissue tumors. McKee PH, Calonje JE, Granter SR, eds. Pathology of the Skin with Clinical Correlations. 3rd ed. Philadelphia: Elsevier Mosby, 2005:1684–1865.
3. Dotz W, Prioleau PG. Nevus lipomatosus cutaneus superficialis. A light and electron microscopic study. Arch Dermatol 1984; 120:376–379.

HEMOSIDEROTIC FIBROHISTIOCYTIC LIPOMATOUS LESION

Synonym: None.

Clinical Presentation:
- Slow-growing asymptomatic nodule on the foot (ankle) in females

Histopathology:
- Well-circumscribed lesion consisting of abundant mature fat tissue and focal bundles of plump spindle cells. Cytological atypia is mild and mitotic figures are rare.
- Prominent hemosiderin deposition in the spindle cell areas.

Clinicopathologic Correlation:
See Table 1.

Differential Diagnosis:
See Differential Diagnosis in the section "Spindle Cell Lipoma" (p. 374).

Pathophysiology:
- Result of trauma

References:

1. Connective tissue tumors. McKee PH, Calonje JE, Granter SR, eds. Pathology of the Skin with Clinical Correlations. 3rd ed. Philadelphia: Elsevier Mosby, 2005:1684–1865.
2. Marshall-Taylor C, Fanburg-Smith JC. Hemosiderotic fibrohistiocytic lipomatous lesion: ten cases of a previously undescribed fatty lesion of the foot/ankle. Mod Pathol 2000; 13:1192–1199.

PIEZOGENIC PEDAL PAPULES

Synonym: None.

Clinical Presentation:
- Multiple small skin-colored papules and nodules on the heels, usually asymptomatic
- Similar lesions have been reported on the wrist

Histopathology:
- Loss of septa and enlargement of fat lobules with herniation into dermis

Clinicopathologic Correlation:
See Table 1.

Differential Diagnosis:

	Histopathology
Piezogenic pedal papules	Loss of septa and enlargement of fat lobules with herniation into dermis. Mature fat cell identical to normal mature fat cells
Typical lipoma	Mature fat cell identical to normal mature fat cells

Pathophysiology:
- Pressure-induced herniations of fat through defects of connective tissue.

References:

1. Tumors of fat. Weedon D, ed. Skin Pathology. 1st ed. Edinburgh: Churchil Livingstone, 1997:787–795.
2. Connective tissue tumors. McKee PH, Calonje JE, Granter SR, eds. Pathology of the Skin with Clinical Correlations. 3rd ed. Philadelphia: Elsevier Mosby, 2005:1684–1865.
3. Laing VB, Fleischer AB. Piezogenic wrist papules: a common and asymptomatic finding finding. J Am Acad Dermatol 1991; 24:415–417.

LIPOMATOSES

Synonym: Multiple lipoma syndromes.

Introduction:
This designation is used for a heterogeneous group of conditions all of which manifest as a diffuse regional collection of adipose tissue without a well-defined tumor mass. Table 3 summarizes the lipomatosis syndromes. Some lipomatosis are part of a hereditary syndrome (diffuse symmetric lipomatosis, Madelung disease), and others may be based on acquired metabolic changes (steroid lipomatosis).

Table 3 Lipomatosis Syndromes

Type	Clinical Highlights	Histopathology
Diffuse lipomatosis	Lipomatous growth involving an entire region (extremity) in different tissue planes	For all lipomatosis, the fat does not differ from normal adipose tissue; therefore, the distinction is made on clinical grounds
Symmetrical lipomatosis (Madelung disease, Launois-Bensaude syndrome)	Prominent symmetrical fat collection in the neck, upper trunk, and arm	
Pelvic lipomatosis	Pelvic fat collection, including urinary tract and colorectum. Most common in African Americans	
Encephalocraniocutaneous lipomatosis	Congenital hamartomatous condition with skin lesion, lipomas, and ipsilateral oculocerebral malformations	
Steroid lipomatosis	Lipomatous masses caused by excessive corticosteroid stimulation. A variety of sites can be affected, including the spinal epidural space	
Folded skin with lipomatous nevus (Michelin-tire baby)	Generalized folding of the skin in newborns. Microcephaly, foot bone abnormalities, hemiplegia, hemihypertrophy, chromosomal abnormalities, abnormal ears, and neural defects	
Adiposis dolorosa: Dercum's disease	Multiple tender to painful plaque-like lipomas in the pelvic region and lower extremities. Postmenopausal females	Presence of mature adipose tissue with focal fat necrosis

Clinical Presentation:
Lipomatoses are extremely rare; there are several forms, but only two affect subcutaneous fat:
1. Multiple symmetrical lipomatosis has two variants
   - Diffuse form affects mostly children, has association with diabetes and autosomal dominant inheritance
   - Localized form (Madelung's disease) affects primarily middle-aged man with increased alcohol uptake and manifests as multiple lipomas in posterior neck and shoulder girdle ("horse-collar" appearance) (Fig. 8A)
2. Multiple asymmetric lipomatosis can affect any site and has no association (Fig. 8B)

Histopathology:
- Lipomas in multiple lipoma syndromes are histologically indistinguishable from common lipomas and normal fat

Clinicopathologic Correlation:
See Table 3.

Differential Diagnosis:
Although these conditions are clinically distinctive, they are rarely seen as surgical specimens. Histologically, the fat does not differ from normal adipose tissue.

Pathophysiology:
- Point mutations in codon 8344 in mitochondrial DNA encoding the transfer RNA gene for lysine have been detected in some patients with multiple symmetric lipomatosis

References:

1. Tumors of fat. Weedon D, ed. Skin Pathology. 1st ed. Edinburgh: Churchil Livingstone, 1997:787–795.
2. Connective tissue tumors. McKee PH, Calonje JE, Granter SR, eds. Pathology of the Skin with Clinical Correlations. 3rd ed. Philadelphia: Elsevier Mosby, 2005:1684–1865.
3. Ruzicka T, Vieluf D, Landthaler M, et al. Benign symmetric lipomatosis Launois-Bensaude. Report of ten cases and review of the literature. J Am Acad Dermatol 1987; 17:663–674.

FOLDED SKIN WITH LIPOMATOUS NEVUS

Synonym: Michelin-tire baby.

Clinical Presentation:
- Generalized folding of the skin in newborns, during childhood gradually diminishes
- Other abnormalities: microcephaly, foot bone abnormalities, hemiplegia, hemihypertrophy, chromosomal abnormalities, abnormal ears, and neural defects

Histopathology:
- Some areas with dermal fat lobules, others with excessive subcutaneous adipose tissue

Clinicopathologic Correlation:
See Table 3.

Differential Diagnosis:
The differential diagnosis is as with the other lipomatoses and it is made on clinical grounds (Table 3).

References:

1. Connective tissue tumors. McKee PH, Calonje JE, Granter SR, eds. Pathology of the Skin with Clinical Correlations. 3rd ed. Philadelphia: Elsevier Mosby, 2005:1684–1865.
2. Burgdorf WH. Doran CK, Worret WI. Folded skin with scarring: Michelin tire baby syndrome? J Am Acad Dermatol 1982; 7: 90–93.
3. Kharfi M, Zaraa I, Chaouechi S, et al. Michelin tire syndrome: a report of two siblings. Pediatr Dermatol 2005; 22(3):245–249.

ADIPOSIS DOLOROSA

Synonym: Dercum's disease.

Clinical Presentation:
- Multiple tender to painful plaque-like lipomas in the pelvic region and lower extremities

- Predominantly in postmenopausal females
- Associated with weakness, fatigability, and depression

Histopathology:
- Presence of mature adipose tissue with focal fat necrosis and rarely granulomatous inflammation

Clinicopathologic Correlation:
See Table 3.

Differential Diagnosis:
The differential diagnosis is as with the other lipomatoses and it is made on clinical grounds (Table 3).

References:
1. Connective tissue tumors. McKee PH, Calonje JE, Granter SR, eds. Pathology of the Skin with Clinical Correlations. 3rd ed. Philadelphia: Elsevier Mosby, 2005:1684–1865.
2. Palmer ED. Dercum's disease: adiposis dolorosa. Am Fam Phys 1981; 24:155–157.

MALIGNANT FAT NEOPLASMS

Liposarcoma is the designation for a group of histologically and genetically distinct sarcomas with fatty differentiation. Together these tumors are among the most common sarcomas (25–35%). Most liposarcomas occur in deep soft tissues, whereas lipomas are usually subcutaneous. Two types are histologically and genetically distinct (well-differentiated liposarcoma and myxoid-round cell liposarcoma). All four types of liposarcomas present in different ages and sites and have peculiar clinicopathological features (Table 4). The diagnosis of liposarcoma is based on recognition of the typical histological pattern of any specific type of liposarcoma. Adipocytic atypia is present by definition. Although multivacuolated lipoblasts are often found in all types of liposarcoma, they are not required for diagnosis and are uncommon in well-differentiated tumors.

WELL-DIFFERENTIATED LIPOSARCOMA

Synonym: None.

Clinical Presentation:
- Most common variant (50%). Present in adults (fifth to eighth decade)
- Deep soft tissue of extremities, buttocks, shoulder, and retroperitoneal area (Fig. 9A). Occurrence in distal extremities is rare
- High local recurrence up to 10 to 15 years but has very low disease-related mortality
- Often generate large tumors

Histopathology:
- Show greatest resemblance to normal adipose tissue
- Five histological patterns are recognized and may overlap each other
  - *Lipoma-like*: Simulate lipoma, show focal widened fibrous septa with hypercellularity and cytological atypia (4–10× objective). Multivacuolated lipoblasts may be present (Fig. 9B).
  - *Sclerosing*: Atypical cells embedded in a dense collagenous stroma. Prominent nuclear pleomorphism and mild mitotic activity. Vascular smooth muscle proliferation with mild atypia in medium-size tumoral vessels.
  - *Myxoid*: Atypical cells embedded in a dense myxoid matrix. Prominent nuclear pleomorphism and mild mitotic activity.
  - *Inflammatory*: Lymphoid cells sometime with germinal center formation. Myxoid-sclerosing stroma is also present.

Table 4 Key Clinicopathologic Features of Liposarcomas

Type	Incidence	Age at presentation	Location	Histopathology	Genetics
Well differentiated	>50%	Middle age to old	Deep soft-tissue extremities and retroperitoneum	Five patterns: lipoma-like, sclerosing, myxoid, inflammatory, and spindle cell. Widened fibrous septa with cytological atypia. Lipoblast may be present	12q amplification
Myxoid-round cell	30–40%	Young adults	Exclusively intramuscular: extremities (thigh)	Small cells with scant cytoplasm in myxoid matrix. Prominent arborizing thin-walled capillary vessels (chicken-wire) configuration Round cell liposarcoma show focal or diffuse round blue cells with few areas of adipocytic differentiation. Cytological atypia, lipoblasts, and mitotic activity are present	t(12;16)
Pleomorphic	<5%	Old age	Extremities retroperitoneum	Sheets of highly pleomorphic bizarre multivacuolated lipoblasts with one or more hyperchromatic nuclei and numerous mitoses	Unknown
Dedifferentiated	5%	Middle age to old	Extremities retroperitoneum	Low-grade differentiation: cellular fibromatosis, fibrosarcoma. High-grade differentiation: pleomorphic MFH and fibrosarcoma	Unknown

- *Spindle cell*: More in the retroperitoneal tumors, showing increase cellularity and pleomorphism.
- Presence of lymphoid infiltration, adipocyte cell size variation, and single-cell fat necrosis.
- Mitotic activity is very low and not required for diagnosis.

Clinicopathologic Correlation:
See Table 4.

Differential Diagnosis:

	Histopathology
Well-differentiated liposarcoma	Five patterns: lipoma-like, sclerosing, myxoid, inflammatory, and spindle cell. Widened fibrous septa with cytological atypia. Lipoblast may be present
Spindle cell lipoma	Presence of mature fat and bland spindled mesenchymal cells in various amounts. Mast cells and myxoid stroma can be present
Pleomorphic lipoma	Same as spindle cell lipoma, plus multinucleated floret-like giant cells. CD34 (+) and S100 (−)
Chondroid lipoma	Alternating ordinary white fat cells, epithelioid-appearing tumor cells, chondroid cells, and myxoid matrix
Fat necrosis	Presence of fat necrosis, foreign body reaction, and mitosis

Pathophysiology:
- Gene rearrangements of 12q are found in well-differentiated liposarcomas.

References:

1. Tumors of fat. Weedon D, ed. Skin Pathology. 1st ed. Edinburgh: Churchil Livingstone, 1997:787–795.
2. Connective tissue tumors. McKee PH, Calonje JE, Granter SR, eds. Pathology of the Skin with Clinical Correlations. 3rd ed. Philadelphia: Elsevier Mosby, 2005:1684–1865.
3. Dei Tos AP, Mentzel T, Fletcher CDM. Primary liposarcoma of the skin: a rare neoplasm with unusual high-grade features. Am J Dermatopathol 1998; 20:332–338.
4. Allen PW, Strungs I, MacCormac LB. Atypical subcutaneous fatty tumors. A review of 37 reffered cases. Pathology 1998; 30:123–125.

MYXOID AND ROUND CELL LIPOSARCOMA

Synonym: None.

Clinical Presentation:
- Round cell liposarcoma, originally considered a type of its own, is now considered a high-grade variant of myxoid liposarcoma.
- Myxoid liposarcoma is the second most common type (30–40%).
- Occurs in young adults (median age 44 years). It is almost exclusively intramuscular in the deep soft tissues of the extremity (thigh). Other sites are popliteal fosa, calf, and upper extremity.
- They prone to locally recur and approximately 20% to 30% develop metastasis. Round cell tumor behaves more aggressively.

Histopathology:
- Evenly dispersed small oval or plump cells with scant cytoplasm in myxoid matrix. Prominent arborizing thin-walled capillary vessels (chicken-wire) configuration (Fig. 10A).
- Areas of adipocytic differentiation are present. Lipoblasts are usually present. Prominent cystic spaces filled with mucus material may be noted.
- Round cell liposarcoma show focal or diffuse round blue cells with few areas of adipocytic differentiation. Cytological atypia, lipoblasts, and mitotic activity are present (Fig. 10B).

Clinicopathologic Correlation:
See Table 4.

Differential Diagnosis:

	Histopathology
Myxoid and round cell liposarcoma	Small cells with scant cytoplasm in myxoid matrix. Prominent arborizing thin-walled capillary vessels (chicken-wire) configuration
Intramuscular myxoma	Paucicellular tumor with a scant vascular pattern
Myxoid MFH	Prominent vascular pattern of thick-wall vessels, focal fibrous matrix, variable cellular pleomorphism
Lipoblastoma	Deep lipoblastoma show lobulation
Extraskeletal myxoid chondrosarcoma	Tumor cells with a rim of eosinophilic cytoplasm arranged in cords or rounded clusters in a hypovascular background

Pathophysiology:
- The typical, most common cytogenetic change in myxoid as well as round cell liposarcoma is the translocation t(12;16)(q13;p11) supporting the genetic identity of these histological types

References:

1. Tumors of fat. Weedon D, ed. Skin Pathology. 1st ed. Edinburgh: Churchil Livingstone, 1997:787–795.
2. Connective tissue tumors. McKee PH, Calonje JE, Granter SR, eds. Pathology of the Skin with Clinical Correlations. 3rd ed. Philadelphia: Elsevier Mosby, 2005:1684–1865.
3. Dei Tos AP, Mentzel T, Fletcher CDM. Primary liposarcoma of the skin: a rare neoplasm with unusual high-grade features. Am J Dermatopathol 1998; 20:332–338.
4. Allen PW, Strungs I, MacCormac LB. Atypical subcutaneous fatty tumors. A review of 37 reffered cases. Pathology 1998; 30:123–125.

PLEOMORPHIC LIPOSARCOMA

Synonym: None.

Clinical Presentation:
- Rare (5%). Occur in older individuals, predominantly in the deep muscles of the extremities and retroperitoneum. Ulceration is common (Fig. 11A).
- High-grade tumor with tendency to metastasize to lungs. Cutaneous pleomorphic liposarcomas are indolent tumor if completely excised.

Histopathology:
- Sheets of highly pleomorphic bizarre multivacuolated lipoblasts with one or more hyperchromatic nuclei and numerous mitoses (Fig. 11B)
- Histological variants include: pleomorphic MFH-like and epithelioid variant

Clinicopathologic Correlation:
See Table 4.

Differential Diagnosis:

	Histopathology
Pleomorphic liposarcoma	**Sheets of highly pleomorphic bizarre multivacuolated lipoblasts with one or more hyperchromatic nuclei and numerous mitoses. S100 protein +/− reactivity**
Pleomorphic MFH	**Displays bizarre tumor giant cells admixed with conventional MFH areas. CD68 and Factor XIIIa positive**
Dedifferentiated liposarcoma	**Low to high-grade areas of sarcomatous dedifferentiation greater to 1 cm in diameter within well-differentiated liposarcoma**

Pathophysiology:
- The specific genetic changes of pleomorphic liposarcoma are not known.

References:

1. Tumors of fat. Weedon D, ed. Skin Pathology. 1st edition. Edinburgh: Churchil Livingstone, 1997:787–795.
2. Connective tissue tumors. McKee PH, Calonje JE, Granter SR, eds. Pathology of the Skin with Clinical Correlations. 3rd ed. Philadelphia: Elsevier Mosby, 2005:1684–1865.
3. Dei Tos AP, Mentzel T, Fletcher CDM. Primary liposarcoma of the skin: a rare neoplasm with unusual high-grade features. Am J Dermatopathol 1998; 20:332–338.
4. Allen PW, Strungs I, MacCormac LB. Atypical subcutaneous fatty tumors. A review of 37 reffered cases. Pathology 1998; 30:123–125.

DEDIFFERENTIATED LIPOSARCOMA

Synonym: None.

Clinical Presentation:
- Most commonly occurs in retroperitoneal well-differentiated liposarcomas, but it may also occur in deep extremity liposarcomas. Rarely in subcutaneous atypical lipomas.
- This term refers to the presence of solid sheets (at least 1 cm in diameter) of undifferentiated, nonlipogenic areas in a well-differentiated liposarcomas.

Histopathology:
- The dedifferentiated components often have an abrupt transition from the well-differentiated areas
- They can have low-grade dedifferentiation (hypercellular fibromatosis or fibrosarcoma) or high-grade dedifferentiation (pleomorphic MFH or fibrosarcoma)
- Heterologous elements are occasionally seen, and are high-grade components representing extraskeletal osteosarcoma, chondrosarcoma, leiomyosarcoma, or rhabdomyosarcoma

Clinicopathologic Correlation:
See Table 4.

Differential Diagnosis:
See "Differential Diagonis" table of section "Pleomorphic Liposarcoma."

Pathophysiology:
- The genetic aspects of dedifferentiated liposarcoma are poorly understood.

References:

1. Tumors of fat. Weedon D, eds. Skin Pathology. 1st edition. Edinburgh: Churchil Livingstone, 1997:787–795.
2. Connective tissue tumors. McKee PH, Calonje JE, Granter SR, eds. Pathology of the Skin with Clinical Correlations. 3rd ed. Philadelphia: Elsevier Mosby, 2005:1684–1865.
3. Dei Tos AP, Mentzel T, Fletcher CDM. Primary liposarcoma of the skin: a rare neoplasm with unusual high-grade features. Am J Dermatopathol 1998; 20:332–338.
4. Allen PW, Strungs I, MacCormac LB. Atypical subcutaneous fatty tumors. A review of 37 reffered cases. Pathology 1998; 30:123–125.

BONE NEOPLASMS

Primary benign (osteoma cutis) or malignant (extraskeletal osteosarcoma) bone-forming lesions arising in the skin are extremely rare. Secondary metaplastic cutaneous ossification associated with a wide range of inflammatory, traumatic, and neoplastic processes are by far more common. The most common tumors showing this features are pilomatrixoma, melanocytic nevi (osteonevus of Nanta), basal cell carcinomas, hemangiomas, schwannomas, lipomas, chondroid syringomas, epidermal and dermoid cysts, dermatofibromas, and ossifying fibromyxoid tumor. It may also develop in sites of infection, trauma, scarring, injection sites, hematomas, and in chronic cutaneous depostis or be a component of malignant neoplasms including extraskeletal chondrosarcomas, liposarcomas, and malignant fibrous histiocytomas.

OSTEOMA CUTIS

Synonym: Cutaneous ossification.

Clinical Presentation:
- Osteoma cutis can present as a solitary or multiple lesions
- It can be present on birth or develop later in life
- Mutliple osteoma cutis are found in
  - Congenital plaque-like osteomatosis: present at birth, showing a large mass of bone in the lower dermis or subcutaneous tissues affecting the thigh, scalp, back, and calf
  - Multiple osteomas: multiple foci of cutaneous ossification are present at birth or develop in childhood. Albright's hereditary osteodystrophy should be included
  - Albright's hereditary osteodystrophy: cutaneous ossification at an early age, hypocalcemia, round

facies, defective dentition, mental retardation, calcification of basal ganglia, cataracts, and stubby hands with short fingers
- Solitary osteoma cutis is manifested as single small osteomas arising later in life in various locations (Fig. 12A)

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Histopathology:
- Bone tissue usually develops by mesenchymal (membranous) ossification without a cartilage precursor.
- Well-circumscribed nodule of mature lamellar bone in dermis without osteoblastic or osteoclastic activity. Fatty stromal component with occasional hemopoietic cells (Fig. 12B).
- Occasional osteoblastic activity is seen in Albright's hereditary osteodystrophy.

Clinicopathologic Correlation:
See Table 5.

Differential Diagnosis:
Osteoma cutis should be differentiated with its own different types (solitary, multiple, and metaplastic), as well as with extraskeletal osteosarcoma and subungual exostosis (Table 5).

Pathophysiology:
- Albright's hereditary osteodystrophy is an X-linked dominant disorder producing pseudohypoparathyroidism and pseudopseudohypoparathyroidism syndromes. The osteoblasts that form bone in primary cutaneous ossification originate in pre-existing fibrous connective tissue, and thus their product is termed intramembranous rather than enchondral bone.
- The pathogenesis of metaplastic ossification is given by appropriate stimulation where indigenous fibroblasts have the ability to modulate into osteoblastic cells.

References:
1. Connective tissue tumors. McKee PH, Calonje JE, Granter SR, eds. Pathology of the Skin with Clinical Correlations. 3rd ed. Philadelphia: Elsevier Mosby, 2005:1684–1865.
2. Thielen AM, Stucki L, Braun RP, et al. Multiple cutaneous osteomas of the face associated with chronic inflammatory acne. J Eur Acad Dermatol Venereol 2006; 20(3):321–326.

EXTRASKELETAL OSTEOSARCOMA

Synonym: Osteogenic sarcoma

Clinical Presentation:
- Very rare (1–5% of all osteosarcomas). Can arise de novo or from heterotopic bone
- Represented by ill-defined deeply seated soft tissue tumor of elderly individuals, usually located on the limbs (Fig. 13A)
- High mortality (75%), frequent metastases (lungs)

Histopathology:
- The histologic appearance is similar to that of conventional osteosarcoma, showing high degree of atypia associated with at least some osteoid formation with hyperchromatic osteoblasts (Fig. 13B)
- The cellular spindle cells areas show scant eosinophilic cytoplasm and elongated hyperchromatic nuclei and may have condroblastic, fibroblastic, or osteoclast-like giant cells differentiation
- Tumor cells are vimentin and osteocalcin positive, S100 and cytokeratin negative

Clinicopathologic Correlation:
See Table 5.

Table 5 Clinicopathologic Correlation: Extraskeletal Osteosarcoma

	Clinical	Histopathology
Solitary osteoma cutis	Single small osteomas arising later in life in various locations	Well-circumscribed nodule of mature lamellar bone in dermis without osteoblastic or osteoclastic activity. Fatty stromal component with occasional hemopoietic cells
Multiple osteoma cutis Albright's hereditary osteodystrophy	Cutaneous ossification at an early age, hypocalcemia, round facies, defective dentition, mental retardation, calcification of basal ganglia, cataracts, and stubby hands with short fingers	Mature lamellar bone in dermis with occasional osteoblastic activity
Congenital plaque-like osteomatosis	Present at birth, showing a large mass of bone in the lower dermis or subcutaneous tissues affecting the thigh, scalp, back, and calf	Mature lamellar bone in dermis extending around the dermal appendages
Multiple osteomas	Multiple foci of cutaneous ossification are present at birth or develop in childhood without systemic involvement	Well-circumscribed nodule of mature lamellar bone in dermis without osteoblastic or osteoclastic activity
Metaplastic ossification	Associated with a wide range of inflammatory, traumatic, and neoplastic processes	Well-circumscribed nodule of mature lamellar bone in dermis without osteoblastic or osteoclastic activity. Fatty stromal component with occasional hemopoietic cells
Extraskeletal osteosarcoma	Rare, ill-defined deeply seated soft-tissue tumor of elderly, usually on the limbs	Cellular spindle cells areas with scant eosinophilic cytoplasm and elongated hyperchromatic nuclei with foci of osteoid formation
Subungual exostosis	Painful verrucous nodule that causes elevation and dystrophy of overlying nail plate. History of trauma	Trabecular bone with impaired calcification, covered distally with fibrocartilage

Differential Diagnosis:
The differential diagnosis is as with other ossifying dermatoses (Table 5).

References:

1. Connective tissue tumors. McKee PH, Calonje JE, Granter SR, eds. Pathology of the Skin with Clinical Correlations. 3rd ed. Philadelphia: Elsevier Mosby, 2005:1684–1865.
2. Lidang Jenssen M, Schumacher B, Myhre Jenssen O, et al. Extrasceleteal osteosarcomas: a clinicopathologic studies of 25 cases. Am J Surg Pathol 1998; 22:588–594.
3. Santos-Juanes J, Galache C, Miralles M, et al. Primary cutaneous extraskeletal osteosarcoma under a previous electrodessicated actinic keratosis. J Am Acad Dermatol 2004; 51(6): 1040.

SUBUNGUAL EXOSTOSIS

Synonym: None.

Clinical Presentation:
- Reactive tumor-like condition where there is outgrowth of bone, arising from the distal phalanx
- Painful verrucous nodule that causes elevation and dystrophy of overlying nail plate (Fig. 14A)
- History of trauma is evident is 64% of cases

Histopathology:
- Mature exostoses show trabecular bone with impaired calcification, covered distally with fibrocartilage (Fig. 14B)
- They are cartilage derived (endochondral ossification)

Clinicopathologic Correlation:
See Table 5.

Differential Diagnosis
The differential diagnosis is as with other ossifying dermatoses (Table 5).

Pathophysiology:
- Trauma results in inflammation and fibroblastic proliferation that undergoes chondroid metaplasia, calcification and endochondral ossification to from mature trabecular bone.

References:

1. Diseases of nails. McKee PH, Calonje JE, Granter SR, eds. Pathology of the Skin with Clinical Correlations. 3rd ed. Philadelphia: Elsevier Mosby, 2005:1127–1152.
2. Shulze KE, Herbert AA. Diagnostic features, differential diagnosis, and treatment of subungual osteochondroma. Pediatr Dermatol 1994; 11:39–41.
3. Grisafi PJ, Lombardi CM, Sciarrino AL, et al. Three select subungual pathologies: subungual exostosis, subungual osteochondroma, and subungual hematoma. Clin Podiatr Med Surg 1989; 6:355–364.

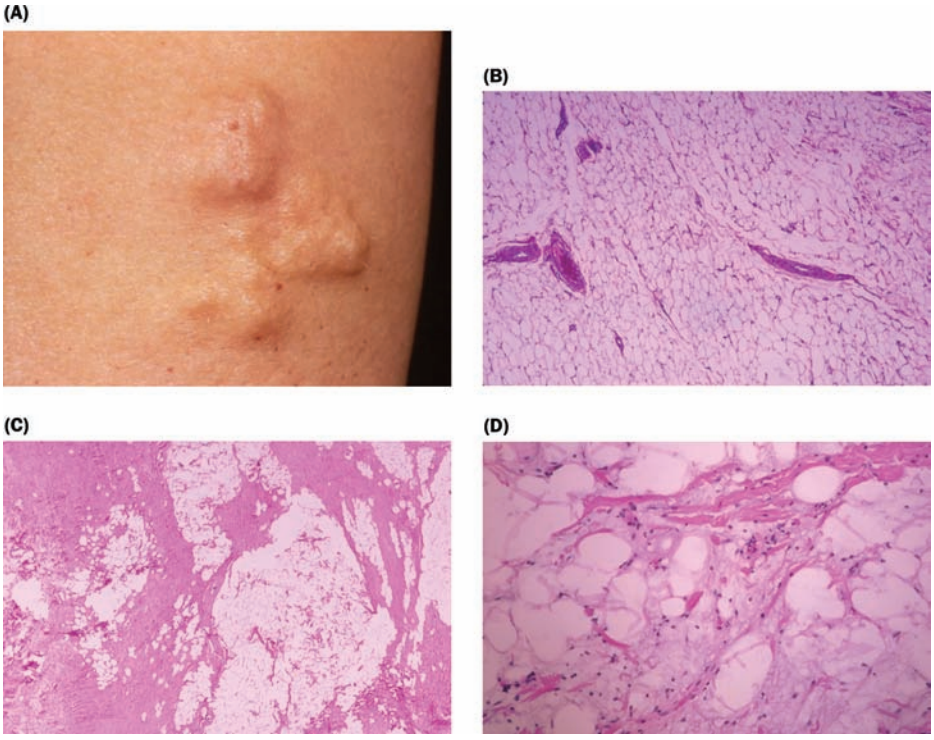

Figure 1 Lipoma. (**A**) Multilobulated subcutaneous lipoma, (**B**) mature adipose tissue and incomplete thin fibrous septa, (**C**) thick fibrous septa in fibrolipoma, and (**D**) prominent myxoid matrix in myxolipoma.

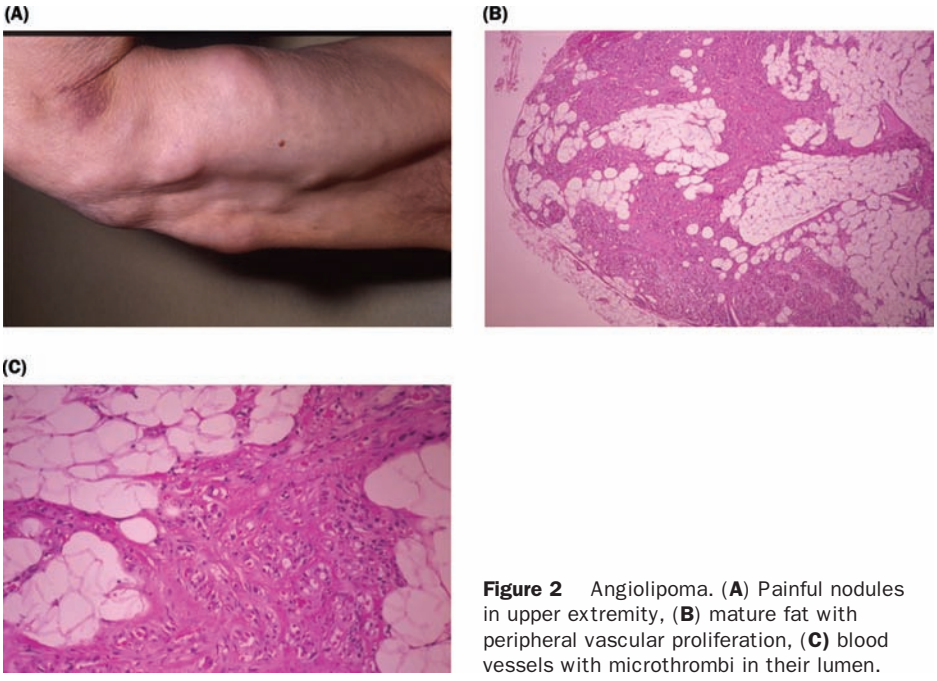

Figure 2 Angiolipoma. (**A**) Painful nodules in upper extremity, (**B**) mature fat with peripheral vascular proliferation, (**C**) blood vessels with microthrombi in their lumen.

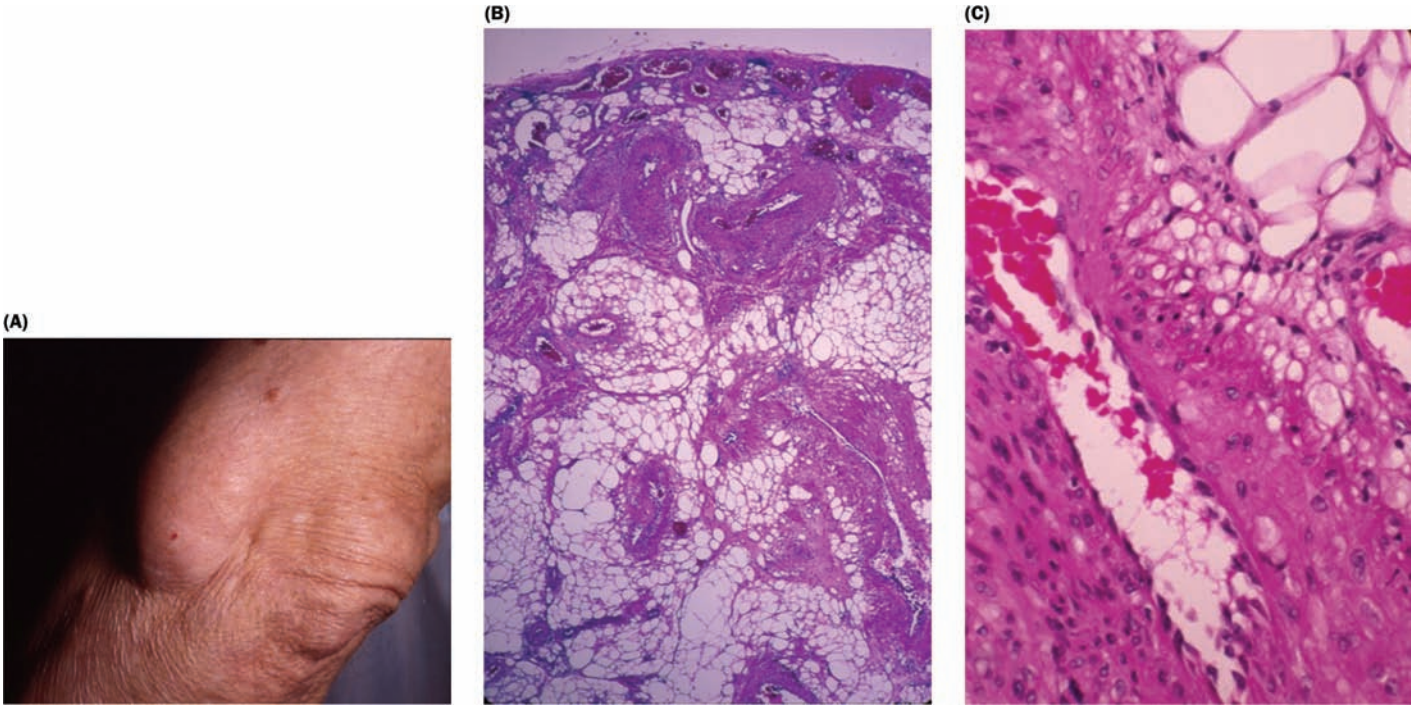

Figure 3 Angiomyolipoma. (**A**) Deeply seated asymptomatic nodule, (**B**) mature fat, thick-wall blood vessels, and smooth muscle bundles, and (**C**) thick-wall blood vessels.

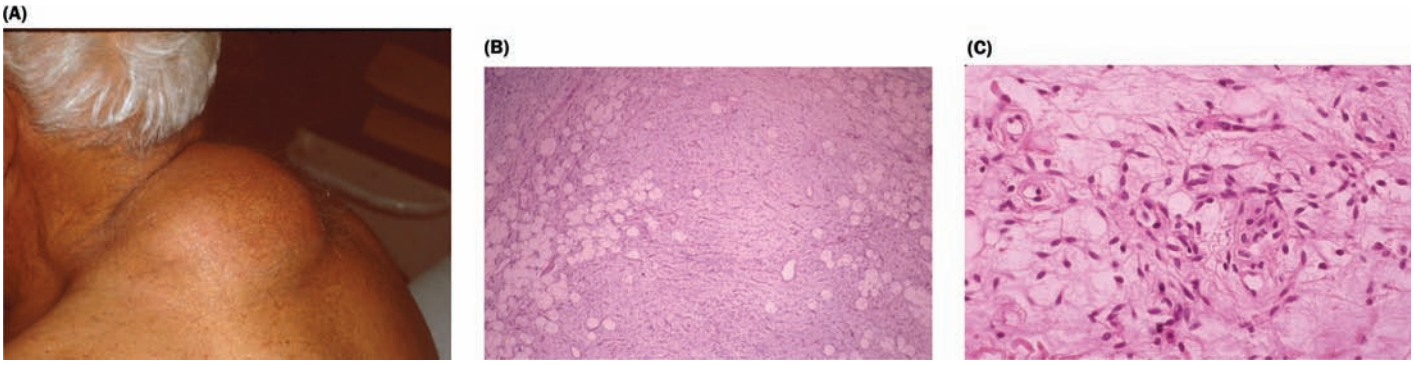

Figure 4 Spindle cell lipoma. (**A**) Slow growing mass on the back, (**B**) mature fat and spindle cells in a fibromyxoid stroma, and (**C**) spindle cells with eosinophilic cytoplasm arranged haphazardly.

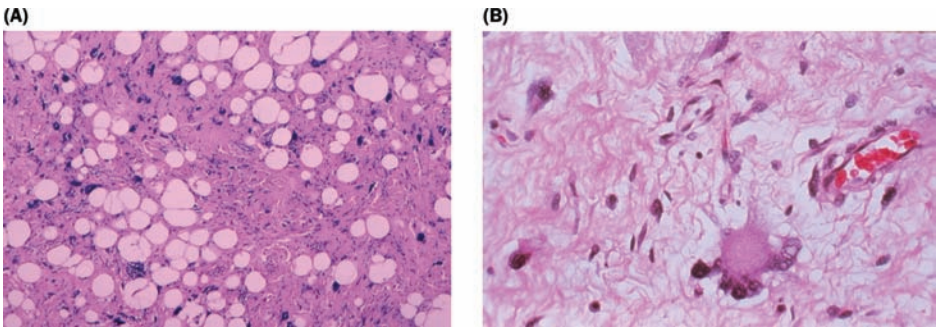

Figure 5 Pleomorphic lipoma. (**A**) Spindle cells in a fibromyxoid stroma with focal mature fat and giant cells, (**B**) multinucleated floret-like giant cells.

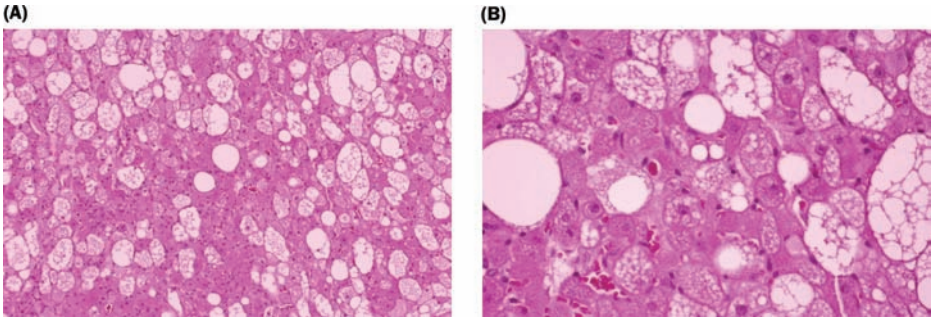

Figure 6 Hibernoma. (**A**) Multivacuolated adipocytes (brown fat) and (**B**) small cells with granular eosinophilic cytoplasm.

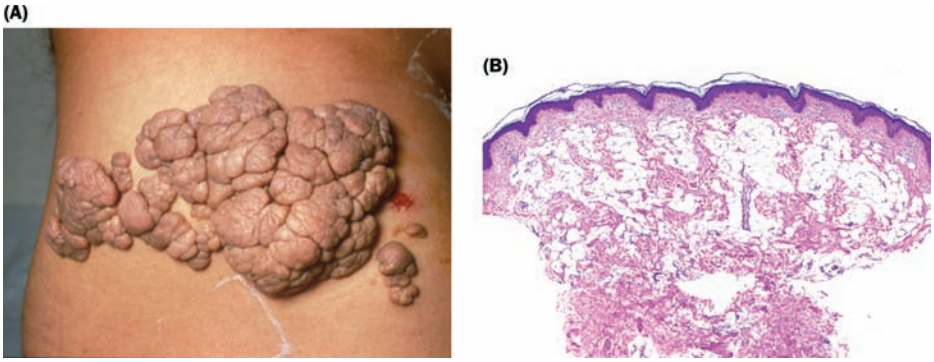

Figure 7 Nevus lipomatosus superficialis. (**A**) Multiple polypoid nodules with broad base and (**B**) collection of mature fat in the dermis.

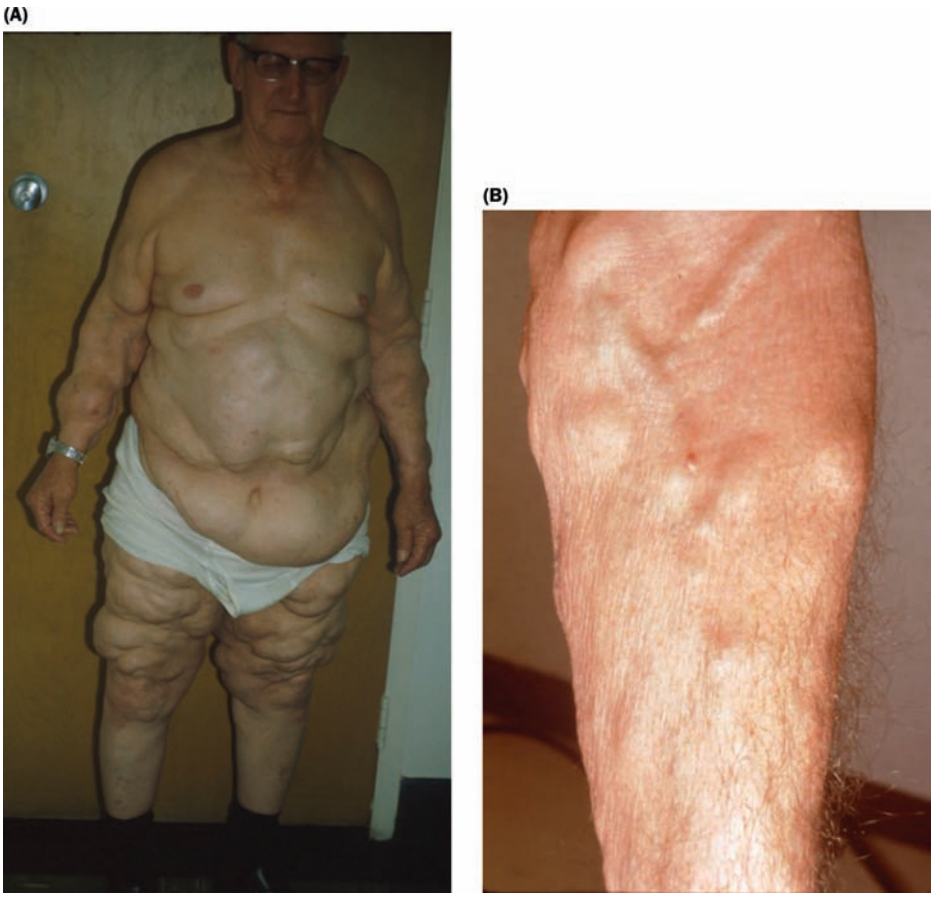

Figure 8 Lipomatoses. (**A**) Symmetrical diffuse lipomatosis and (**B**) asymmetrical localized lipomatosis.

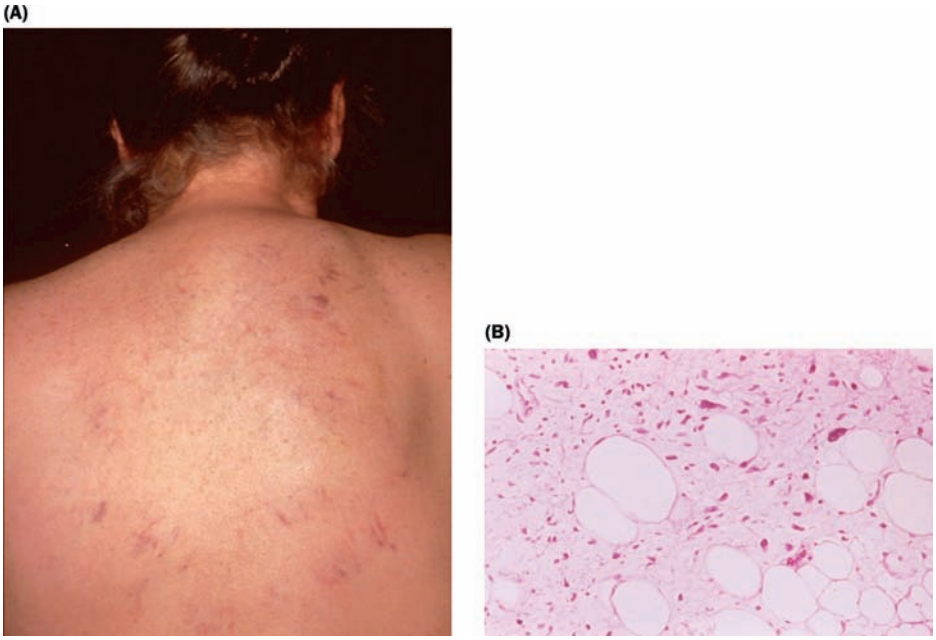

Figure 9 Well-differentiated liposarcoma. (**A**) Deep soft tissue mass and (**B**) mature fat, focal widened fibrous septa with hypercellularity and cytological adipcytic atypia.

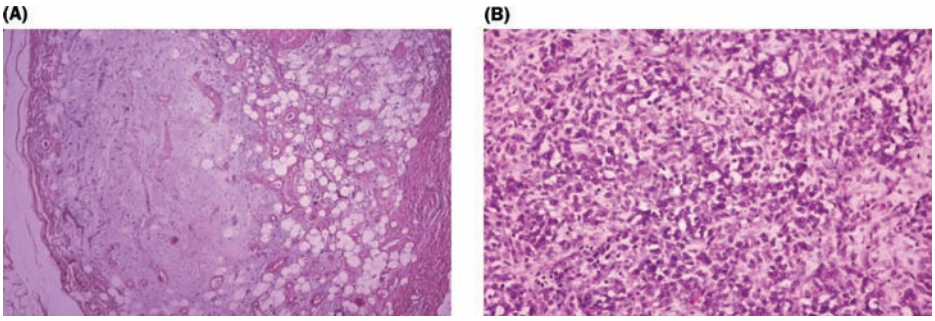

Figure 10 Myxoid and round cell liposarcoma. (**A**) Small to plump spindle cells in myxoid matrix with arborizing capillary vessels and (**B**) round blue cells with significant atypia, and lipolblasts.

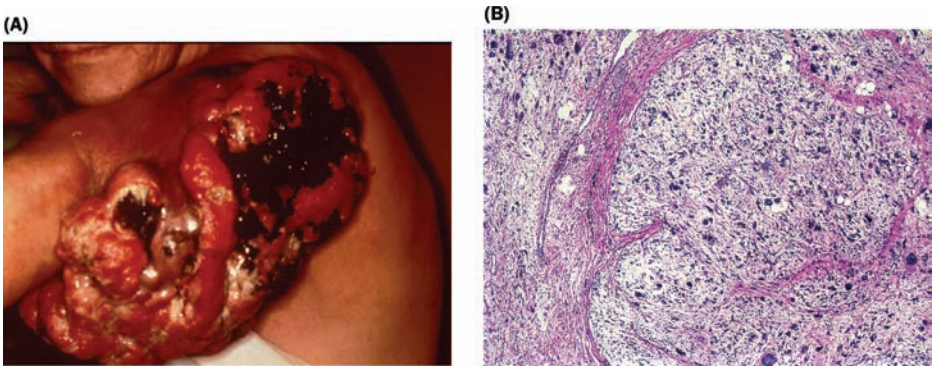

Figure 11 Pleomorphic liposarcoma. (**A**) Ulcerated deep large mass on upper extremity and (**B**) pleomorphic bizarre multivacuolated lipoblast with numerous mitotic activity.

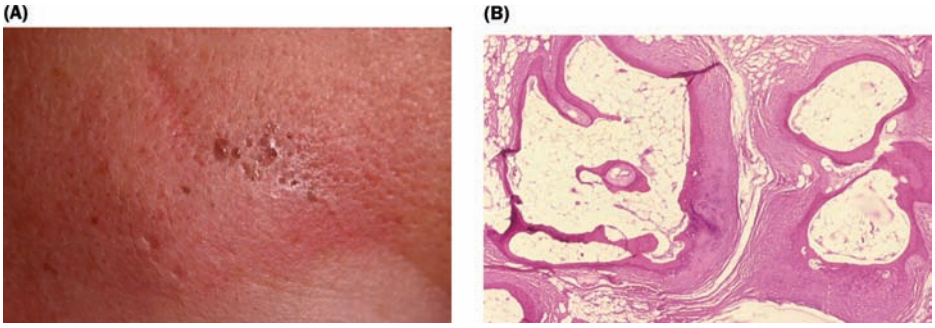

Figure 12 Osteoma cutis. (**A**) Solitary indurated lesion and (**B**) mature lamellar bone in dermis without osteoblastic or osteoclastic activity. Fatty stromal component with occasional hemopoietic cells.

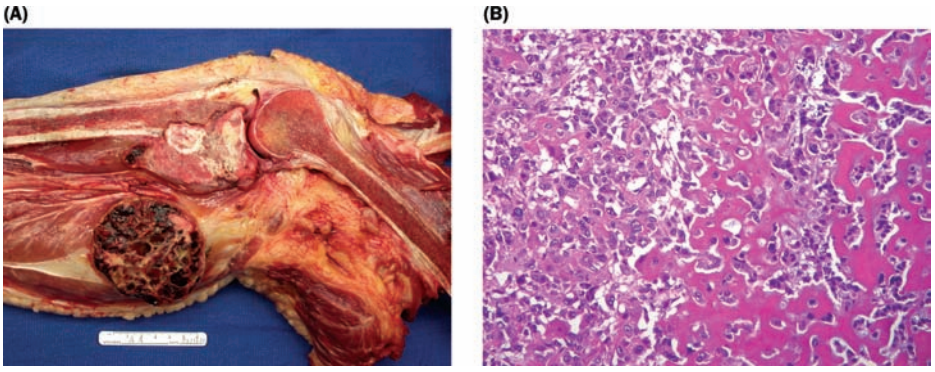

Figure 13 Extraskeletal osteosarcoma. (**A**) Deeply seated osseous tumor (intramuscular) on lower extremity and (**B**) atypical hyperchromatic osteoblasts with osteoid formation.

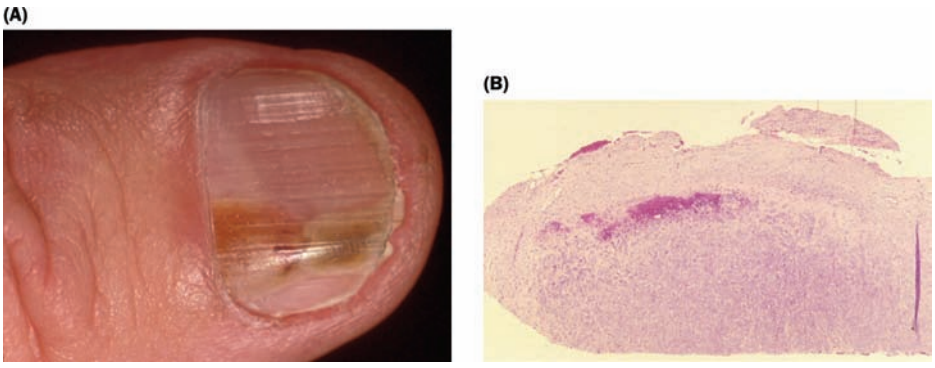

Figure 14 Subungual exostosis. (**A**) Painful papule with elevation and dystrophy of nail plate and (**B**) trabecular bone with impaired calcification, covered distally with fibrocartilage.

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Metastatic Neoplasms

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CONTENTS

This chapter focuses mainly on varied manifestations of metastatic malignancy in the skin. Skin offers a unique opportunity in the management of malignant disorders. Many significant human cancers are limited in their therapy because of the tendency for delay in diagnosis due to their hidden nature. Based on these delays, presentation may be delayed and outcome or management is often dramatically different among patients. Malignancies with skin involvement are often noticed immediately by the patient and hence are generally quickly evaluated and diagnosed. This speeds therapy, and generally changes it, as metastasis alters staging and therapy. Dermatologists and dermatopathologists play a vital role in this pathway to the rapid diagnosis of affected patients.

In the past, careful evaluation of histologic sections allowed for an informed guess on the cell of origin for a given tumor. Although electron microscopy was the "gold standard" for diagnosis in challenging cases, there have been major advances in the past 20 years with regard to immunohistochemistry. Immunohistology is in daily use in most modern laboratories and has led to unprecedented insight into tumor origin. In addition, the use of newer markers such as tests for *Her*2 allow for safer and highly effective molecular therapies in selected cases. Dermatopathologists must be well schooled in evaluation of metastatic disease, one of the truly critical diagnostic challenges facing us.

METASTASES (FIG. 1)

Metastatic tumors include all types and grades, and, therefore any discussion of the subject is really a condensed version of malignant pathology. Certain diagnoses are vastly more common, and appreciation of the likelihood of metastasis for a given clinical setting is important for proper diagnosis.

The first critical issue for the evaluator is the question of carcinoma versus sarcoma. Many cases may be evaluated simply on the basis of the presence or absence of epithelial elements except few cases which are especially challenging. Indeed, metastatic carcinomas outnumber skin involvement by sarcomas in most series by more than three to one. Immunohistochemically, the vast majority of metastatic carcinomas easily demonstrate keratin. Most laboratories employ a keratin "cocktail" of antibodies as a first test to assure the diagnosis. Specific keratins are then often evaluated to further identify the lesion.

Although it is unfair to generalize, it is often also important to obtain staining for S-100 protein and epithelial membrane antigen (EMA) early in the evaluation. Individual tumors commonly require more specific antibody profiles as will be discussed in association with those tumors.

References:

1. Azoulay S, Adem C, Pelletier FLE, et al. Skin metastases from unknown origin: the role of immunohistochemistry in the evaluation of cutaneous metastases of unknown origin. J Cutan Pathol 2005; 32:561–566.
2. Saeed S, Keehn CA, Morgan MB. Cutaneous metastasis: a clinical, pathological, and immunohistochemical appraisal. J Cutan Pathol 2004; 31(6):419–430.

BREAST CARCINOMA (FIG. 2)

In all published series, breast cancer is the most common metastatic tumor. There are five major types. Common presentations include (*i*) tumor cells that "track" among collagen bundles (the so-called "Indian-file" pattern as seen in Fig. 3), (*ii*) intravascular collections referred to as inflammatory carcinoma, (*iii*) carcinomas that aggregate as nodules of carcinoma, (*iv*) dense fibrotic collections (carcinoma en cuirasse), and (*v*) subcutaneous nodular collections. Once carcinoma is suspected, it is important to clarify the diagnosis and highlight the presence of vascular involvement. Most cases stain positively with the antibody directed at cytokeratin 7. In addition, many cases stain with stains to epithelial membrane antigen (EMA) and hybridization to estrogen receptor. In some cases, it is important to perform immunohistochemistry or fluorescence in situ hybridization to identify the presence of *HER2* since current evidence indicates that these patients may be uniquely sensitive to therapy with trastuzumab.

Clinical Presentation:

- There are several different patterns of clinical presentation with distinct histology
  - Nodular metatstases present clinically as firm pink to red nodules frequently localized to the chest wall
  - Carcinoma en cuirasse: a fibrotic presentation of widespread chest wall metastases
  - An inflammatory presentation in breast cancer suggests infection (cellulitis) but is more long lasting and often painful

Histology:

- *Nodular metastases.* Demonstrate linear collections of carcinoma between collagen bundles, the so-called Indian-file pattern
- *Carcinoma en cuirasse.* Often demonstrates broad zones of carcinoma but can mimic nodular metastases
- *Inflammatory carcinoma* (Fig. 4). Demonstrates intralymphatic involvement with cancerous aggregates

Immunohistochemistry:

- Once carcinoma is suspected, immunohistochemistry can clarify the diagnosis and highlight the presence of vascular involvement
  - Most cases stain with cytokeratin 7 antibody
  - Many cases stain EMA antibody
  - Estrogen receptor *in* in situ hybridization is common
  - Immunohistochemistry or fluorescence in situ hybridization to identify the presence of *HER2* since these patients may be uniquely sensitive to therapy with trastuzumab

Clinicopathologic Correlation:

Clinical Feature	Pathologic Feature
Inflammatory cellulites like feature	Involvement of tumor in lymphatics
Carcinoma en cuirasse	Collections of tumor aggregates with surrounding cicatrix and fibrosis
Ulcerated nodular carcinoma	Small collections of tumor cells with absent epidermis

References:

1. Tot T. Patterns of distribution of cytokeratins 20 and 7 in special types of invasive breast carcinoma: a study of 123 cases. Ann Diagn Pathol 1999; 3(6):350–356.
2. Pritchard KI, Shepherd LE, O'Malley FP, et al. N Engl J Med 2006; 354:2103–2111.

PAGET'S DISEASE (FIG. 5)

Paget's disease occurs in two forms: (*i*) associated with breast carcinoma and (*ii*) the extramammary form which may be associated with other internal malignancies or apparently on its own. The two forms associated with internal malignancy of breast or other site can be considered a local form of intraepidermal metastasis. In particular, immunohistochemistry is used to separate the various associated malignancies.

Clinical Presentation:

- Cases of Paget's disease present similarly regardless of primary pathology
  - Macular erythema usually with a very sharply defined border
  - Many lesions appear partially eroded or crusted and may simulate an eczematous dermatitis.
  - The tumor extends to associate with the primary source of the tumor and thus represents contiguous spread rather than a lymphatic metastasis
  - Mammary Paget's disease represents extension from ductal carcinoma of the breast and extends directly to the involved duct, and thus includes the areola
  - This feature can help to distinguish it from other causes of eczematous reactions.

Histology:

- Despite the multiple sources of carcinoma, the histology of the various forms of Paget's disease are remarkably similar.
  - All examples include epidermis that is infiltrated by neoplastic cells of the extending tumor.
  - Offending cells are larger than keratinocytes and include a pale, expanded cytoplasm.
  - In Paget's disease associated with adenocarcinoma, these cells contain abundant mucin.
  - Mucicarmine and other epithelial mucin stains are positive.

Immunohistochemistry:

- Immunohistochemistry play a vast role in the setting of Paget's disease, since the various primary causes can often be analyzed by the use of keratin antibodies.
  - Most cases of mammary Paget's disease are positive for cytokeratin 7.
  - Many cases express EMA or low molecular weight keratins.
  - Similar features are often seen in extramammary Paget's disease of adnexal origin.
  - Cytokeratin 20 is positive (whereas cytokeratin 7 is generally negative) in cases of urothelial or anal or rectal carcinoma origin.
  - Urothelial cases can be further identified with the use of stains for Uroplakin III.

Clinicopathologic Correlation:

Clinical Feature	Pathologic Feature
Sharp margination	Histology limited to epidermis
Red eczematous appearance	Stratum corneum often absent
Clinical site localized to site of primary tumor	Direct extension of malignant cells from tumor

References:

1. Sakoforas GH, Blanchard DK, Sarr MG, Farley DR. Paget's disease of the breast: a clinical perspective. Langenbeck's Arch Surg 2001; 386:444–450.
2. Brown HM, Wilkinson EJ. Uroplakin-III to distinguish primary vulvar Paget disease from Paget disease secondary to urothelial carcinoma. Hum Pathol 2002; 33(5):545–548.

COLON CARCINOMA

Colon cancer is one among the most common carcinomas, and often metastasizes to the skin (Fig. 6).

Clinical Presentation:
- Most cases show extension to adjacent areas of the abdomen or groin.
- There are reports of seeding of the tumor to surgical sites.
- Usual lesion is a faint to strikingly red firm nodule on the abdomen.

Histology:
- Frequently demonstrates large gland-like spaces similar to primary colon carcinoma (Fig. 7)
- Often well differentiated in appearance
- Cases may show goblet cells and crypts
- Generally demonstrates a high mitotic rate
- May include markedly atypical cells or bizarre mitoses

Immunohistochemistry:
- Generally express cytokeratin 20 and carcinoembryonic antigen
- Negative with cytokeratin 7 antibodies

Clinical Feature	Pathologic Feature
Red firm nodule	Extensive vascularity with thin epidermis
Frequent ulceration	Epidermis absent or distorted

Reference:
1. Chu P, Wu E, Weiss LM. Cytokeratin 7 and cytokeratin 20 expression in epithelial neoplasms: a survey of 435 cases. Mod Pathol 2000; 13(9):962–972.

THYROID CARCINOMA (FIG. 8)

Clinical Presentation:
- Relatively nonspecific presentation in many cases
- Typical examples metastasize to the head or neck with the scalp as a favored site
- Prior history of thyroid carcinoma is common since skin metastasis is rare
- Scalp lesions are often dull and skin colored

Histology:
- Histology may differ depending on the original tumor type. More often than in other metastases, review of the primary lesion can be illuminating, as the metastatic tumor often recapitulates the histology with remarkable fidelity.
  - Papillary thyroid tumors can be difficult to separate from adnexal tumors, as they may produce mucin and their papillary architecture may recapitulate apocrine tumors.
  - Most well-differentiated examples contain at least some thyroglobulin.
  - Eosinophilic pools of thyroglobulin are most striking in cases of follicular thyroid carcinoma metastatic to skin.
  - Nuclear histology is not particularly revealing and mitotic figures may be hard to identify.
  - However, many cases show abundant, pale cytoplasm and at least some nuclear variability.

Immunohistochemistry:
- Most demonstrate staining for thyroglobulin
- Many cases are decorated with the antibody to TTF-1

Clinical Feature	Pathologic Feature
Indistinct dermal firm nodule	Histology limited to dermis
Frequently observed to be slow growing	High level of differentiation in many cases

References:
1. Quinn TR, Duncan LR, Zembowicz A, Faquin WC. Cutaneous metastasis of follicular thyroid carcinoma: a report of four cases and a review of the literature. Am J Dermatopathol 2005; 27:306–312.
2. Elgart GW, Patterson JW, Taylor R. Cutaneous metastasis from papillary carcinoma of the thyroid gland [review]. J Am Acad Dermatol 1991; 25(2 Pt 2):404–408.

MELANOMA (FIG. 9)

Besides being the most common fatal malignancy in skin as a primary tumor, melanoma also spreads in skin as cutaneous metastases.

Clinical Presentation:
- Most present as a blue, tan, brown, or black firm skin nodule
- Solitary or multiple lesions are seen
- Metastatic melanoma may demonstrate the unusual propensity to spread to only one side of the body, ipsilateral to the primary tumor
- Most cases demonstrate only individual or few metastatic tumors adjacent to the primary tumor or in the same extremity

Histology:
- Most metastatic melanomas recapitulate those features in the primary tumor.
- Variably shaped and sized melanocytic cells with nuclear variability, prominent eosinophilic nucleoli, and frequent mitotic figures are expected in these tumors.
- Most studies confirm that the mitotic index is generally high in metastatic melanoma.
- Most examples lack significant lymphocytic inflammation, a feature almost never seen in primary malignant melanoma.
- Most metastases are dermal nodules separated from the epidermal surface and lack a connection to it.
- Dense melanin in the dermis in melanophages, referred to as "tumoral melanosis."
- Many examples demonstrate a fibrotic host response.

Immunohistochemistry:
- S-100 protein is generally present on tumor cells
- Many also express other common melanoma markers (MART-1, HMB-45 antigen, Melan A)

Clinical Feature	Pathologic Feature
Blue, black, or brown appearance	Correlates with melanization of the tumor
Commonly observed as very firm	Dense associated fibrosis in many cases
Usually minimal erythema surrounding metastatic cases	Essentially absent inflammation in skin metastases

References:

1. Sondak VK, Taylor JM, Sabel MS, et al. Mitotic rate and younger age are predictors of sentinel lymph node positivity: lessons learned from the generation of a probabilistic model. Ann Surg Oncol 2004; (3):247–258.
2. Cochran AJ, Bhuta S, Paul E, Ribas A. The shifting patterns of metastatic melanoma [vii. review]. Clin Lab Med 2000; 20(4):759–783.

RENAL CELL CARCINOMA

Cutaneous metastases from renal cell carcinoma occur only in advanced cases, and in that situation appear to arise uncommonly. Diagnosis can usually be confirmed by histology alone.

Clinical Presentation:

- Head and neck are most common
- Reddish- or skin-colored nodules, which may ulcerate, predominate in clinical reviews

Histology:

- Most cases demonstrate features consistent with the usual findings of the primary tumor.
- There are nests of clear cells with extensive vasculature extending within the dermis.
- Mitoses are not common except in advanced cases.

Immunohistochemistry:

- Most cases of renal cell carcinoma express keratins and a cocktail for AE1/AE3 decorates most cases.
- Many examples are also highlighted with the CD10 antibody (also known as common lymphocytic leukemia antigen).
- A relatively newly described protein, g250 is identified in 85% of renal cell carcinoma cases as the renal cell carcinoma antigen.

Clinical Feature	Pathologic Feature
Commonly red or plum colored	Marked vascular proliferation in most cases
Frequent ulceration	Many examples show thrombosed vessels and histological necrosis

References:

1. Childs RW, Clave E, Tisdale J, et al. Successful treatment of metastatic renal cell carcinoma with non-myeloablative allogenic peripheral-blood-progenitor-cell transplant: evidence for a graft vs. tumor effect. J Clin Oncol 1999; 17:2044–2049.
2. Perna AG, Smith MJ, Krishna B, Reed JA. CD10 is expressed in cutaneous clear cell lesions of different histogenesis. J Cutan Pathol 2005; 32(5):348–351.

PULMONARY ADENOCARCINOMA

Adenocarcinoma of pulmonary origin metastasizes to skin somewhat more rarely than small cell carcinoma.

Clinical Presentation:

- As is typical of many metastatic lesions, metastasis from the lung favors the adjacent region of the chest and back.

Histology:

- Pulmonary adenocarcinoma demonstrates many of the features of other adenocarcinomas.
- There are gland-like spaces with prominent mucin in the center of the collections of tumor.
- Cytology does not separate pulmonary cases from those with primary tumors of other sites.

Immunohistochemistry:

- Immunohistology is the centerpiece of diagnosis of metastatic pulmonary adenocarcinoma.
- The vast majority of pulmonary adenocarcinoma cases are CK7 positive and negative for CK 20, similar to the keratin profile of breast carcinomas.
- The addition of TTF-1, which is positive in lung cancer cases, but negative in most breast cancers, is also very helpful.

PULMONARY SMALL (OAT) CELL CARCINOMA (FIG. 10)

Small cell carcinoma of the lung is an uncommon source of cutaneous metastasis, but is important to separate from primary neuroendocrine carcinomas including Merkel cell carcinoma.

Clinical Presentation:

- Although a rare source of metastasis, the lip appears to represent a common site of skin metastasis.
- Most are smooth or eroded firm nodules.

Histology:

- Very dark small cells with little appreciable cytoplasm and prominent nuclear molding.
- Most examples are deeply basophilic and include many mitotic figures and dyskeratotic cells.
- Separation from Merkel cell carcinoma on histologic grounds is often impossible.
- Thus, all cases require immunohistochemistry.
- It is important to recognize that other tumors of small blue cells including lymphomas and some melanomas should be excluded.

Immunohistochemistry:

- Pulmonary small cell carcinoma includes positive staining for cytokeratin 20 and TTF-1.
- The TTF-1 stain is typically negative in Merkel cell carcinoma, although it is relatively common in other nonpulmonary sources of small cell carcinoma.

Clinical Feature	Pathologic Feature
Ulceration common	Tumor necrosis with absent epidermis

References:
1. Su YC, Hsu YC, Chai CY. Role of TTF-1, CK20, and CK7 immunohistochemistry for diagnosis of primary and secondary lung adenocarcinoma. Kaohsiung J Med Sci 2006; 22(1):14–19.
2. Yang DT, Holden JA, Florell SR. CD117, CK20, TTF-1, and DNA topoisomerase II-alpha antigen expression in small cell tumors. J Cutan Pathol 2004; 31(3):254–261.

BLADDER CARCINOMA

Although squamous cell carcinoma and adenocarcinoma occur, the vast majority of bladder carcinoma cases are transitional cell carcinoma. In general, distant metastasis must be differentiated from local extension to the abdominal wall, as this may affect prognosis.

Clinical Presentation:
- Patients typically present with an erythematous nodular or multinodular eruption
- Cases are frequently misdiagnosed as an inflammatory process
- One reported case demonstrated a "zosteriform" presentation on the chest

Histology:
- Most cases demonstrate dermal nests of pale cells with an eosinophilic cytoplasm.
- Occasional cases demonstrate a pattern of Paget's disease.

Immunohistochemistry:
- Most studies identify a majority of cells that stain positively with both cytokeratins 7 and 20.
- However, a minority of cases are negative for cytokeratin 20.
- Recent studies suggest that positive staining for Uroplakin III (UroIII) is diagnostic for a urothelial origin, but present in only about half of cases.
- Some cases demonstrate reactivity for E-cadherin that was correlated with early recurrence.

Clinical Feature	Pathologic Feature
Sharp margination in Pagetoid cases	Histology limited to epidermis
Clinical site localized to site of primary tumor	Direct extension of malignant cells from tumor

References:
1. Kalajian AH, Piparo GF, Scalf CA, et al. A baffling basaloid blain. Am J Dermatopathol 2005; 27(2):168–170.
2. Mueller TJ, Wu H, Greenberg RE. Cutaneous metastases from genitourinary malignancies [review]. Urology 2004; 63(6): 1021–1026.
3. Brown HM, Wilkinson EJ. Uroplakin-III to distinguish primary vulvar Paget disease from Paget disease secondary to urothelial carcinoma. Hum Pathol 2002; 33(5):545–548.

PROSTATE CARCINOMA (FIG. 11)

Carcinoma of the prostate is extremely common, but rarely metastasizes. Reports suggest that less than one half percent of cases metastasize to skin.

Clinical Presentation:
- Several reported cases demonstrate an exanthematous appearance.
- Some of these cases demonstrate intravascular extension (carcinoma erysipylotoides).
- Nodular presentations are also observed.

Histology:
- Gland-like structures are prominent in some cases.
- Most demonstrate sheets or cords of cells with an expanded faintly eosinophilic cytoplasm with hyperchromatic nuclei.
- Mitotic figures are common.

Immunohistochemistry:
- Positive staining for prostate specific antigen is seen in more than 85% in reported cases.
- Additional staining for prostatic acid phosphatase may identify other affected cases.

Clinical Feature	Pathologic Feature
Exanthem-like appearance	Lymphatic spread
Firm nodules	Dermal tumor

Reference:
1. Pique Duran E, Paradela A, Farina MC, et al. Cutaneous metastases from prostatic carcinoma. J Surg Oncol 1996; 62(2): 144–147.

ESOPHAGEAL CARCINOMA (FIG. 12)

Carcinoma of the esophagus rarely metastasizes to the skin.

Clinical Presentation:
- Most cases probably represent local extension.
- Cases present in the neck or upper chest.
- A single report highlighted the painful nature of a scalp metastasis.

Histology:
- A dermal collection of atypical squamous epithelium is appreciated and may demonstrate substantial necrosis
- There is a high mitotic rate
- Eosinophilic staining of the cytoplasm is common

Immunohistochemistry:
- Expect staining for both cytokeratins 7 and 20 in cases of metastatic esophageal adenocarcinoma.
- c erb b and p53 are highly expressed.

Reference:
1. Smith KJ, Williams J, Skelton H. Metastatic adenocarcinoma of the esophagus to the skin: new patterns of tumor recurrence and alternate treatments for palliation. J Cutan Pathol 2001; 8:425–431.

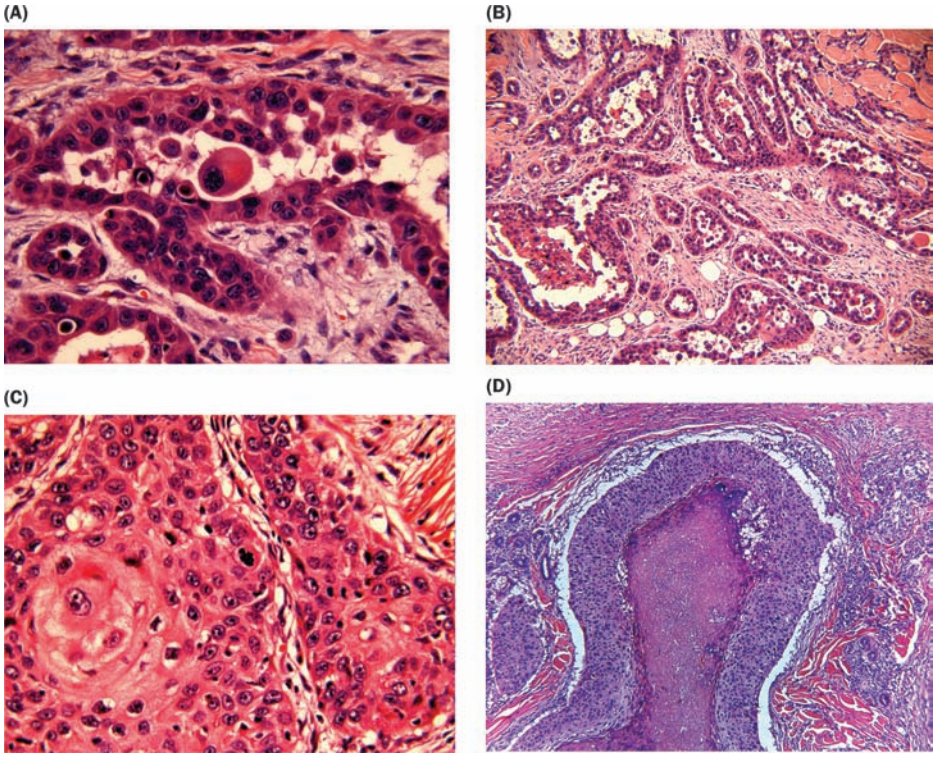

Figure 1 Squamous cell carcinoma demonstrates a varied appearance in metastatic cases. (**A** and **B**) Examples of a metastatic squamous cell carcinoma demonstrating a pseudoglandular or acantholytic appearance which must be separated from adenocarcinoma by histochemistry or immunohistochemistry. (**C**) Squamous eddy with prominent mitoses. (**D**) Example of metastatic squamous cell carcinoma with central necrosis.

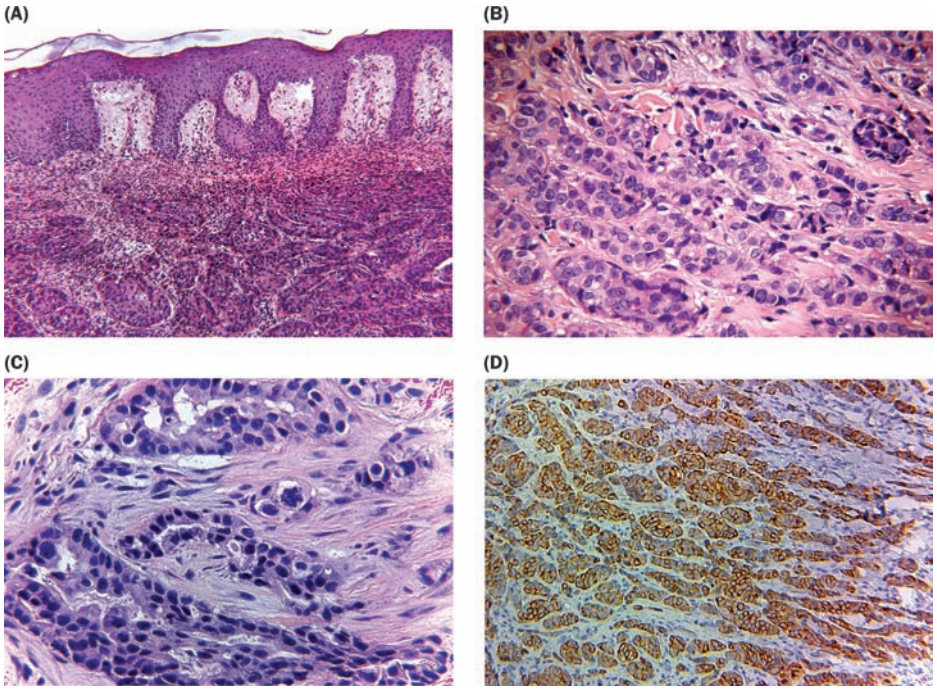

Figure 2 Breast carcinoma is the most common primary tumor for metastases. On a routine case as shown on the (**A**) there is an eroded surface with a dense infiltrate of metastatic cells extending among the dermal collagen bundles. This interstitial pattern is typical of metastatic breast carcinoma. Higher power can demonstrate gland formation as seen in the (**B**) panel or a purely interstitial pattern as seen in the bottom left. Many immunostains are useful in breast carcinoma including CEA as seen on the lower right panel.

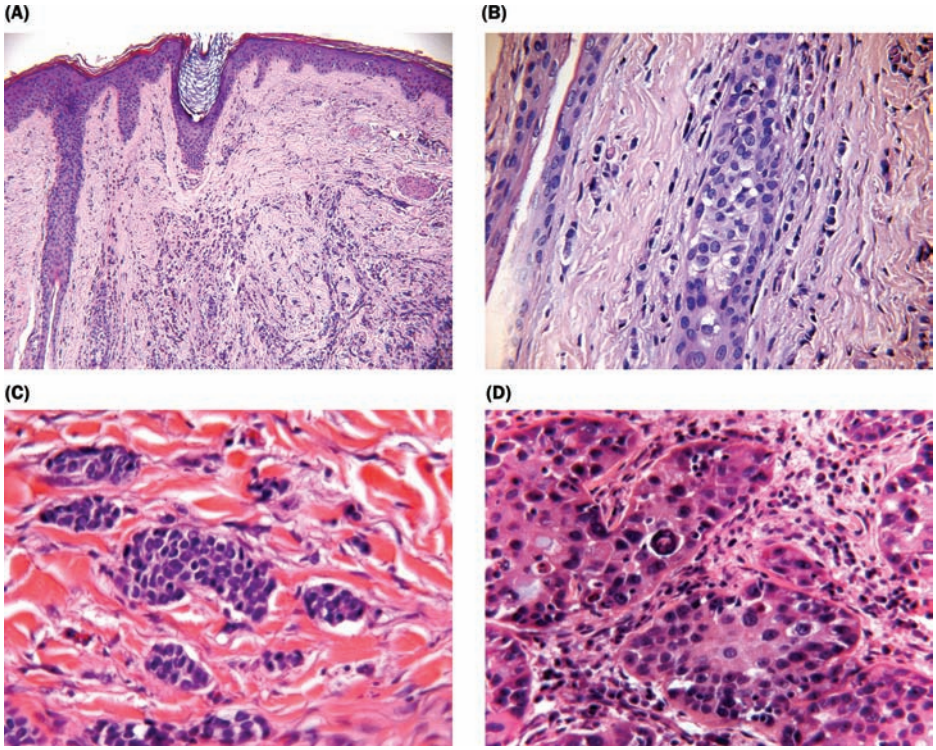

Figure 3 The classic description of linear elements of metastatic carcinoma forming an "Indian file" arrangement is seen in (**A**) and at higher power on (**C**). (**B**) Metastatic carcinoma is seen extending around a follicle. (**D**) Shows a focus of squamatized epithelium in an example of metastatic breast adenocarcinoma.

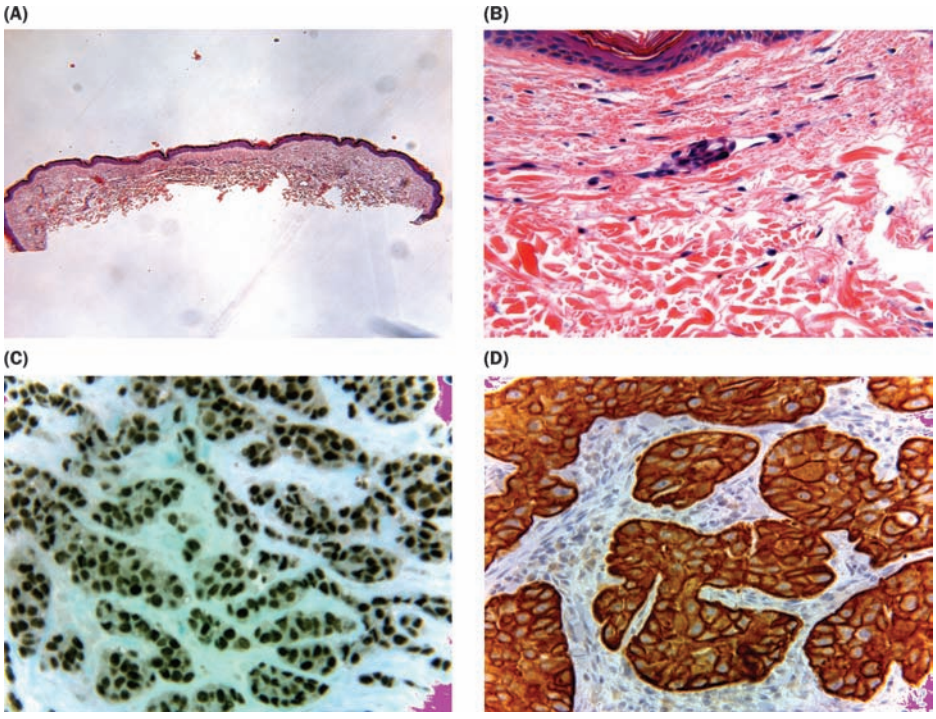

Figure 4 Scanning magnification of a case of inflammatory carcinoma reveals little as seen in (**A**) but high power as seen (**B**) highlights involvement of lymphatic vessels with tumor aggregates. Many cases of breast carcinoma demonstrate nuclear staining for estrogen receptor (**C**) and most cases are positive with antibody to cytokeratin 7 (CK7) (**D**).

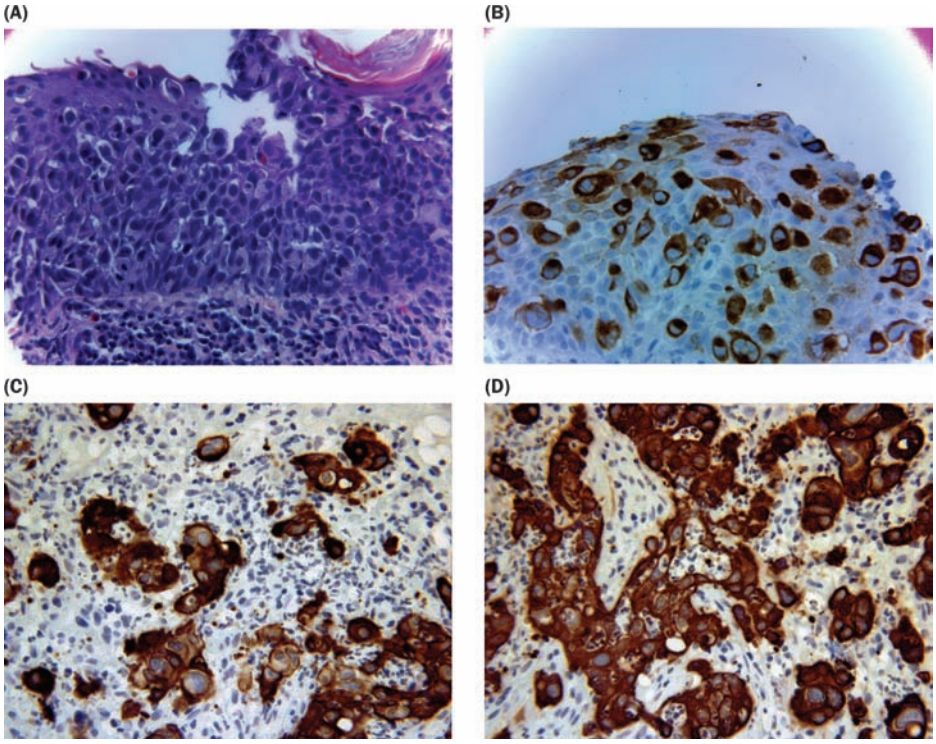

Figure 5 Urothelial extramammary Paget's disease is shown in (**A**) with positive staining for cytokeratin 7 shown on (**B**). Cytokeratin 20 is often frequently positive. In this case the invasive componenet stained with both antibodies (**C** and **D**).

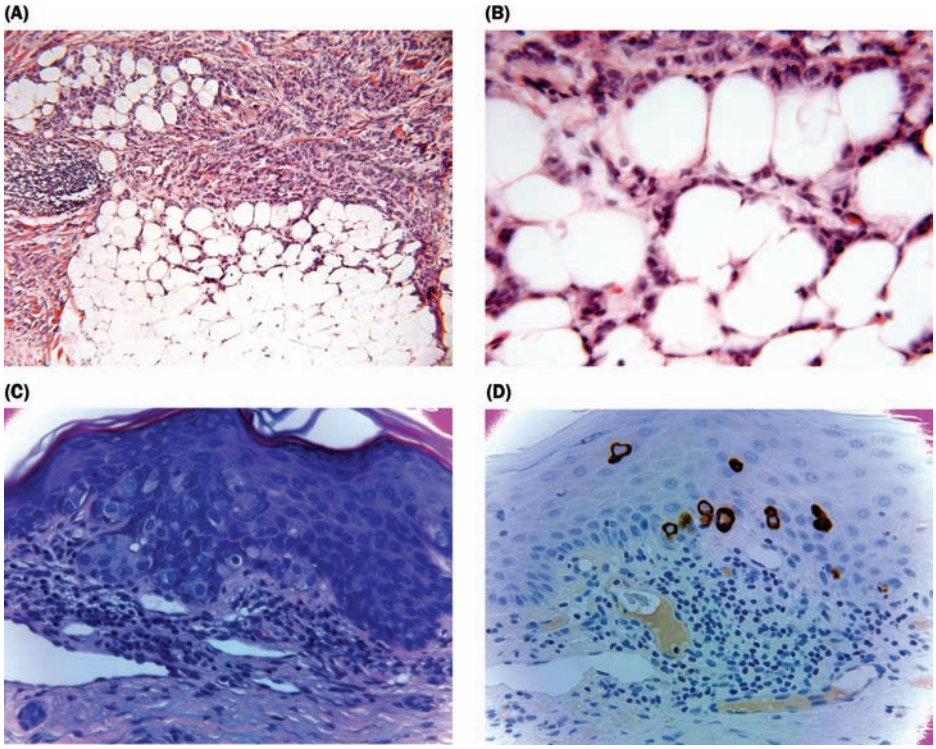

Figure 6 Metastatic adenocarcinoma can fill the dermis to the subcutaneous border demonstrating "carcinomatous panniculitis" (**A** and **B**). Overlying collections of intraepidermal spread of ductal carcinoma account for the appearance of Paget's disease [H&E (**C**) and cytokeratin 7 (**D**)].

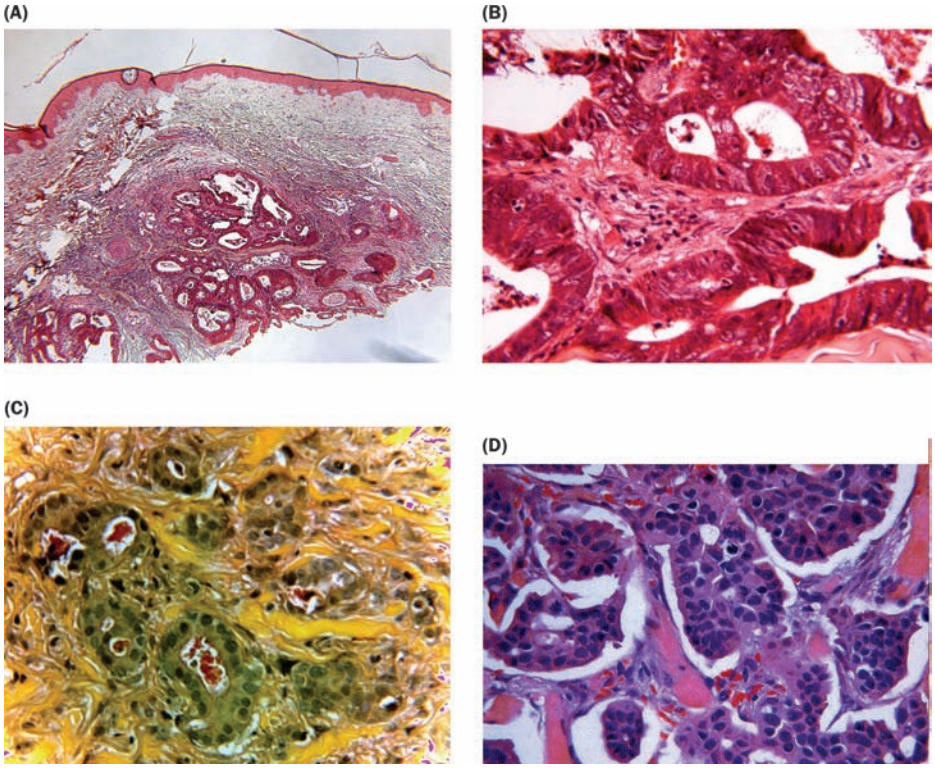

Figure 7 Metastatic colonic adenocarcinoma may demonstrate distinctive gland-like spaces (**A** and **B**). Some cases demonstrate more subtle glandular features (**C**). Mucicarmine staining is generally positive in cases with at least moderate differentiation (**D**) as would be staining for cytokeratin 20.

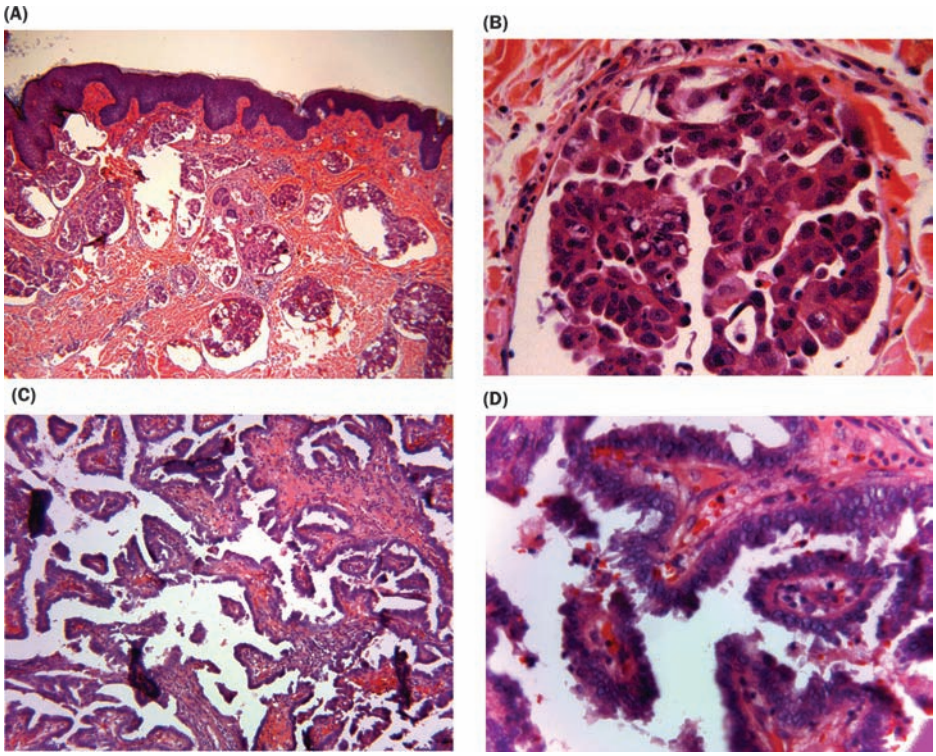

Figure 8 Thyroid metastases often recapitulate the appearance of the primary tumor. (**A** and **B**) demonstrate intravascular extension of a case of follicular thyroid carcinoma. (**C** and **D**) demonstrate papillary thyroid cancer metastases.

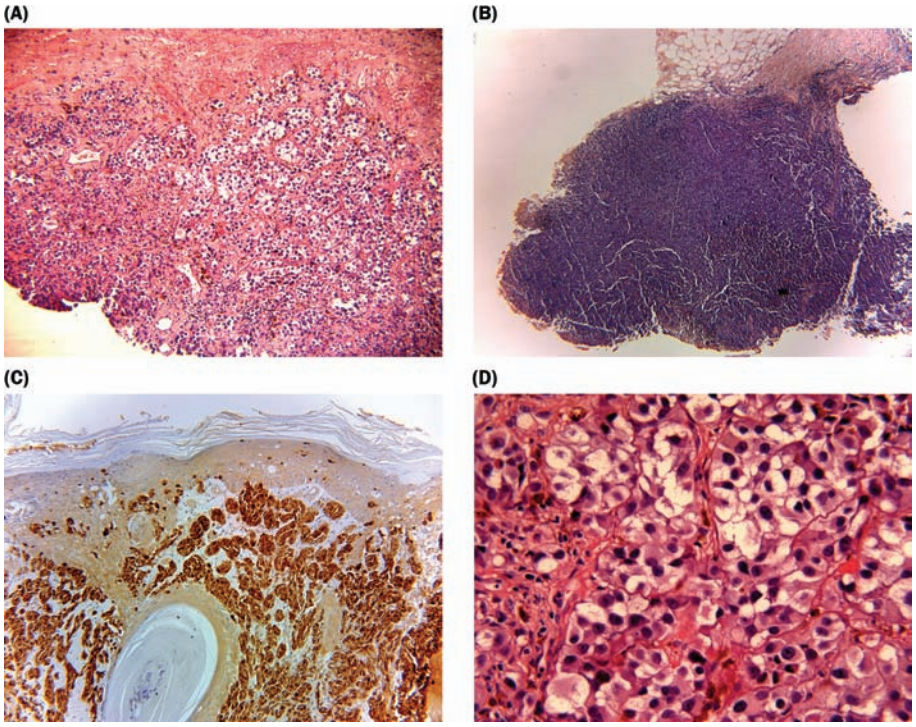

Figure 9 Melanoma is often a challenging diagnosis in cases of metastasis. Valuable tips to a metastatic case include zones of necrosis (**A**) and lack of association with the overlying epidermis (**B**). Immunohistochemistry is often of great help in cases of malignant melanoma as demonstrated in the S-100 stain shown (**C**). High power view of the cells in metastatic melanoma simulates those of primary melanoma (**D**).

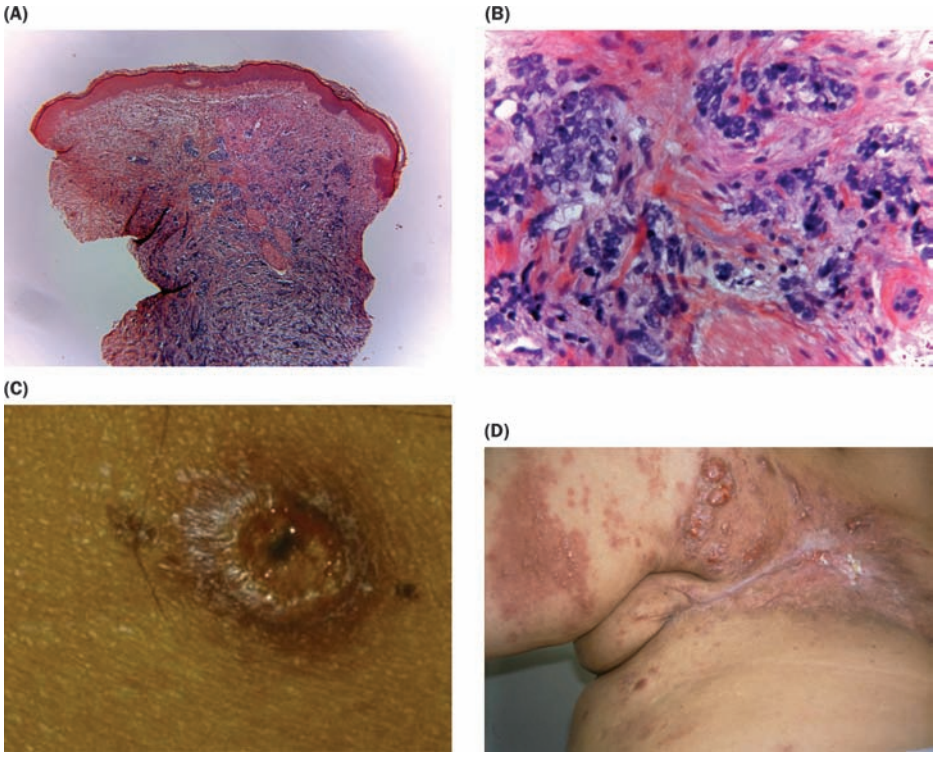

Figure 10 Metastatic small cell carcinoma of the lung seen at scanning and high power. There is frequent crush artifact present. (**A** and **B**). Clinical appearance is rarely helpful in metastatic disease. Lesions such as this solitary metastasis from pancreatic carcinoma (**C**). Clinically quite similar to the multiple axillary metastases from breast carcinoma (**D**).

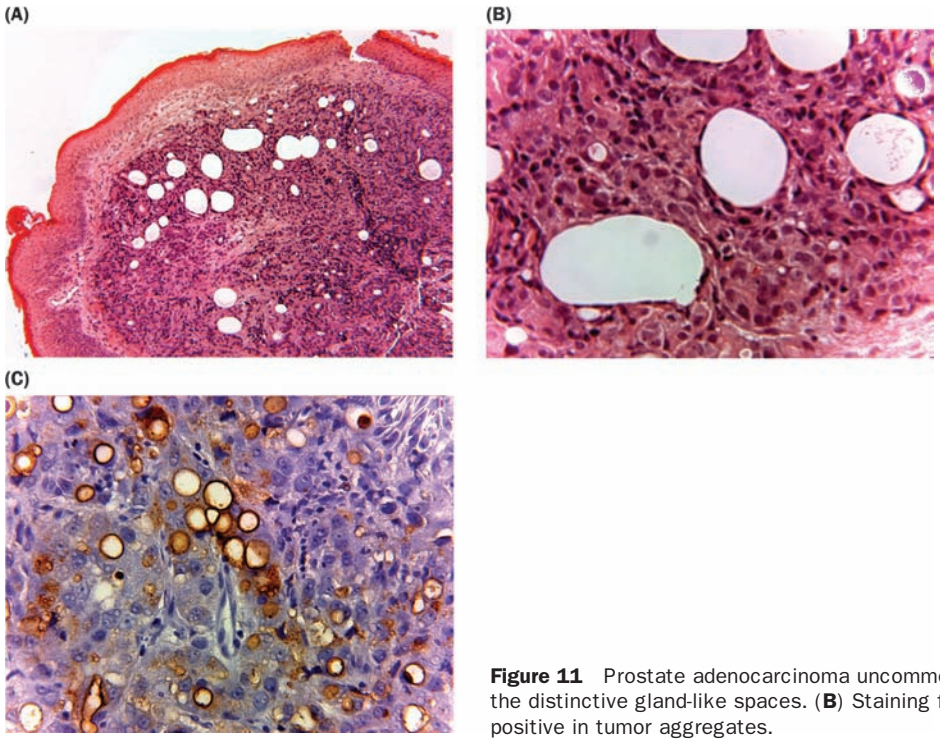

Figure 11 Prostate adenocarcinoma uncommonly metastasizes to the skin. (**A**) Show the distinctive gland-like spaces. (**B**) Staining for prostate specific antigen (PSA) is positive in tumor aggregates.

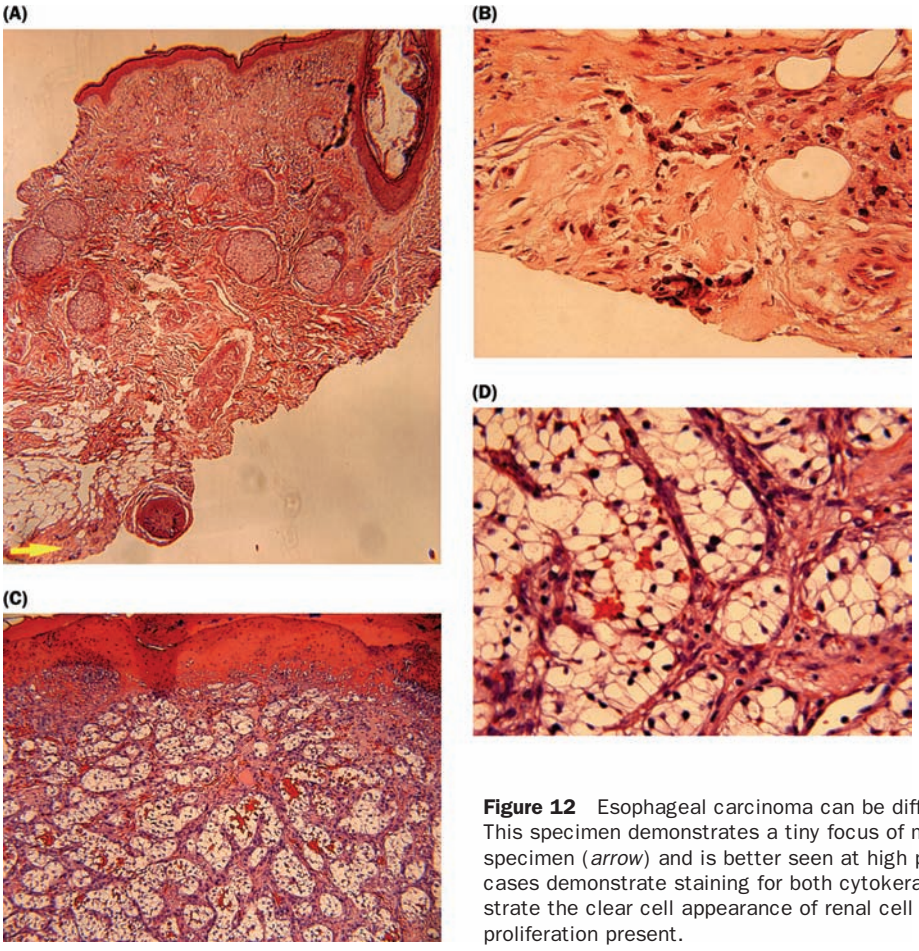

Figure 12 Esophageal carcinoma can be difficult to appreciate in routine sections. This specimen demonstrates a tiny focus of metastasis which was at the base of the specimen (*arrow*) and is better seen at high power. (Top left and right panels) These cases demonstrate staining for both cytokeratins 7 and 20. The bottom panels demonstrate the clear cell appearance of renal cell carcinoma. Note the extensive vascular proliferation present.

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Cutaneous Lymphomas

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CONTENTS

Cutaneous lymphoproliferative disorders are a heterogeneous group of diseases and represent one of the most challenging areas in dermatopathology. Several types of T-and B-cell lymphomas can involve the skin, either primarily or secondarily. After the gastrointestinal tract, the skin is the second most common site of extranodal non-Hodgkin lymphoma.

Careful correlation of clinical and histopathologic findings is essential for accurate diagnosis and proper classification. In some cases, close follow-up of the patient and sequential biopsy sampling over time may be necessary for a definitive diagnosis.

Primary cutaneous lymphomas often have a different clinical behavior, prognosis, and treatment from similar systemic/nodal counterparts, which may also involve the skin secondarily.

Important advances in immunology, molecular biology, and immunohistochemistry have led to a better understanding of cutaneous lymphomas. A list of the most useful immunophenotypic markers in the evaluation of lymphoid infiltrates is provided in Table 1.

Classification schemes for lymphomas have frequently changed over time and recent consensus efforts have culminated in the current WHO–EORTC classification for cutaneous lymphomas (Table 2, Fig. 1). An extensive review of all diagnostic categories is beyond the scope of this text; the main types of primary cutaneous lymphomas are discussed below.

Table 1 Immunohistochemical Stains Used in the Diagnosis of Lymphoproliferative Disorders

Antibody	Predominant Cells Labeled
CD1a	Langerhans cells, precursor T-cells
CD2	T-cells
CD3	T-cells
CD4	T-helper cells
CD5	T-cells, B-CLL, mantle cell lymphoma
CD7	T-cells
CD8	T-cytotoxic cells
CD10	(CALLA: common acute lymphoblastic leukemia antigen), germinal center B-cells, follicular lymphoma, B-ALL, Burkitt lymphoma
CD15	Neutrophils, Reed-Sternberg cells (classical Hodgkin lymphoma)
CD20	B-cells
CD21	Follicular dendritic cells
CD30	Activated lymphocytes, ALCL, LyP (types A and C), Reed-Sternberg cells (classical Hodgkin lymphoma)
CD34	Endothelial cells, precursor cells
CD43	T-cells, myeloid cells, mast cells, T-cell lymphomas, some B-cell lymphomas
CD45	(LCA: leukocyte common antigen), hematolymphoid cells, most B- and T-cell lymphomas
CD45RO	T-cells
CD56	(NCAM: neural cell adhesion molecule), NK cells, NK-cell lymphomas, some T-cell lymphomas, gamma-delta T-cell lymphoma, neuroendocrine tumors
CD68	Histiocytes/macrophages, mast cells
CD79a	Immature and mature B-cells, plasma cells
CD117	(c-kit), mast cells
CD138	Plasma cells
TIA-1	T-cytotoxic cells, cytotoxic T/NK-cell lymphomas
Granzyme B	T-cytotoxic cells, cytotoxic T/NK-cell lymphomas
Perforin	T-cytotoxic cells, cytotoxic T/NK-cell lymphomas
BCL-2	T-cells, non-germinal center B-cells, subset of follicular lymphomas
BCL-6	Germinal center B-cells, B-cell lymphomas of germinal center origin
Myeloperoxidase	Myeloid cells
TdT	Precursor cells, B- and T-ALL (acute lymphoblastic leukemia/lymphoma)

Abbreviations: ALCL, anaplastic large cell lymphoma; ALL, acute lymphoblastic leukemia/lymphoma; CLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; LyP, lymphomatoid papulosis.

MYCOSIS FUNGOIDES

Synonym: Cutaneous T-cell lymphoma (CTCL).

Mycosis fungoides (MF) is the most common cutaneous lymphoma. It is notorious for mimicking a wide variety of other disorders, both clinically and histopathologically.

Table 2 WHO–EORTC Classification of Cutaneous Lymphomas with Primary Cutaneous Manifestations

Cutaneous T-cell and NK-cell lymphomas
MF
MF variants and subtypes
Folliculotropic MF
Pagetoid reticulosis
Granulomatous slack skin
Sezary syndrome
Adult T-cell leukemia/lymphoma
Primary cutaneous CD30+ lymphoproliferative disorders
Primary C-ALCL
LyP
Subcutaneous panniculitis-like T-cell lymphoma
Extranodal NK/T-cell lymphoma, nasal type
Primary cutaneous peripheral T-cell lymphoma, unspecified
Primary cutaneous aggressive epidermotropic CD8+ T-cell lymphoma (provisional)
Cutaneous (gamma-delta) T-cell lymphoma (provisional)
Primary cutaneous CD4+ small/medium-sized Pleomorphic T-cell lymphoma (provisional)
Cutaneous B-cell lymphomas
PCMZL
PCFCL
Primary cutaneous DLBCL, leg type
Primary cutaneous DLBCL, other
Intravascular large B-cell lymphoma
Precursor hematologic neoplasm
CD4+/CD56+ hematodermic neoplasm (blastic NK-cell lymphoma)

Abbreviations: **C-ALCL, cutaneous anaplastic large cell lymphoma; DLBCL, diffuse large B-cell lymphoma; MF, mycosis fungoides; PCFCL, primary cutaneous follicle center lymphoma; PCMZL, primary cutaneous marginal zone B-cell lymphoma.**

Any of the histopathologic criteria listed below may or may not be present in any given biopsy of MF. The final diagnosis rests upon clinicopathologic correlation, and in some cases, T-cell receptor gene rearrangement studies.

Clinical Presentation:

- Initial lesions are patches with discoloration, sometimes with scale.
- Involvement of doubly sun-protected areas (undergarment regions) is typical, though any site may be involved.
- With progression, palpable plaques of variable thickness may evolve from patches.
- With further progression, some patients develop expansile tumors, which may ulcerate.

Histopathology:

Patch and Plaque Stage:

- Patch-stage lesions show an infiltrate of lymphocytes within the epidermis and papillary dermis.
  - Lymphocytes within the epidermis larger than those within the dermis.
  - Pautrier's microabscesses (well-defined collections of intraepidermal lymphocytes).
  - Intraepidermal lymphocytes, associated with a relative paucity of spongiosis.
  - Lymphocytes aligned within the basal layer of the epidermis.
  - Lymphocytes may be small or "medium-large" (approximating the width of basilar keratinocyte nuclei).
  - Convoluted lymphocyte nuclei.
  - Haloed lymphocytes (lymphocytes within the epidermis, with vacuoles around them, which are prominent enough to be seen at relative low power).
  - Thickened, wiry collagen bundles within the papillary dermis.
  - Plaque-stage lesions are similar to patch-stage lesions but show, in addition, reticular dermal involvement.

Tumor Stage:

- Diffuse dermal infiltration by lymphocytes.
- Cells may be small-to-medium size convoluted lymphocytes or larger transformed cells.
- Epidermotropic features may be present or absent.

Postulated Cell of Origin: Peripheral epidermotropic T-cell, usually of CD4+ phenotype.

References:

1. Smoller BR, Bishop K, Glusac EJ, Kim YH, Hendrickson M. Reassessment of histologic parameters in the diagnosis of mycosis fungoides. Am J Surg Pathol 1995; 19:1423–1430.
2. Santucci M, Biggeri A, Feller AC, Massi D, Burg G. Efficacy of histologic criteria for diagnosing early mycosis fungoides. An EORTC Cutaneous Lymphoma Study Group investigation. Am J Surg Pathol 2000; 24:40–50.
3. Glusac EJ. Criterion by criterion, mycosis fungoides. Am J Dermatopathol 2003; 25:264–269.

PRIMARY CUTANEOUS CD30-POSITIVE LYMPHOPROLIFERATIVE DISORDERS

This category represents the second most common group of cutaneous T-cell lymphoma. LyP and primary C-ALCL are part of the spectrum of primary cutaneous CD30-positive lymphoproliferative disorders. There are also borderline cases with overlapping clinical and histopathologic findings. Histologic criteria alone are often insufficient to differentiate between these two ends of the spectrum, and careful clinical correlation and follow-up are generally necessary for appropriate classification (Table 3).

PRIMARY CUTANEOUS ANAPLASTIC LARGE CELL LYMPHOMA

Synonyms/Previous Related Terms: Anaplastic large cell CD30-positive lymphoma; cutaneous Ki-1 lymphoma; regressing atypical histiocytosis.

Primary C-ALCL is a T-cell lymphoma presenting in the skin and composed of large atypical cells, the majority of which express CD30. There is no evidence or history of another CTCL at the time of presentation. C-ALCL affects adults predominantly, with a male-to-female ratio of 2:1.

Table 3 Clinicopathologic Correlation of Primary Cutaneous CD30-Positive Lymphoproliferative Disorders

	LyP	C-ALCL
Clinical findings	Multiple recurrent self-regressing papules	Solitary or localized nodules or tumors
Histopathologic findings	Variable findings depending on the histologic subtype (Table 5)	Dense diffuse infiltrate of large atypical CD30+ lymphoid cells Usually scant background inflammation
Differential diagnosis (correlation of clinical and pathologic findings usually necessary)	C-ALCL Reactive inflammatory infiltrates with activated CD30+ lymphocytes (reactions to drugs, arthropod bites, and viral infections)	LyP Secondary cutaneous involvement by systemic/nodal CD30+ ALCL Large cell transformation of MF with CD30 expression

Abbreviations: C-ALCL, cutaneous anaplastic large cell lymphoma; LyP, lymphomatoid papulosis.

Clinical Presentation:

- Most patients present with solitary or localized nodules or tumors (Fig. 6A), and the disease is usually limited to the skin at the time of diagnosis. Ulceration is common.
- Partial or complete spontaneous regression may be observed, but cutaneous relapses are frequent.
- Extracutaneous dissemination usually involves regional lymph nodes and may be observed in up to 10% of cases.

Histopathology:

- Dense diffuse dermal infiltrate composed of cohesive sheets of large atypical CD30-positive cells. The cells generally exhibit anaplastic features with round, oval, or irregularly-shaped nuclei, prominent nucleoli, and abundant cytoplasm (Fig. 6C).
- Pleomorphic or immunoblastic features may be observed.
- Ulceration and epidermal hyperplasia may be seen, but epidermotropism is usually absent.

Table 4 Comparison of Primary Cutaneous Anaplastic Large Cell Lymphoma and Systemic/nodal Anaplastic Large Cell Lymphoma (Patterns of Expression Observed in Majority of Cases)

	Primary Cutaneous ALCL	Systemic ALCL
EMA	Negative	Positive
CLA, HECA-452	Positive	Negative
ALK	Negative	Positive in subset of cases (60–85%)
Translocations involving ALK (most common: t(2;5)/NPM-ALK/ nucleophosmin-ALK)	Absent	Present in subset of cases

Abbreviations: ALCL, anaplastic large cell lymphoma; ALK, anaplastic lymphoma kinase; CLA, cutaneous lymphocyte antigen; EMA, epithelial membrane antigen; NPM, nucleophosmin.

- A prominent background inflammatory infiltrate is usually not seen but may be present in ulcerated lesions.

Immunophenotype:

- The large atypical cells usually show an activated CD4-positive T-cell phenotype with CD30 expression (>75% of cells) and variable loss of T-cell markers (CD2, CD5, and/or CD3).
- There is frequent expression of cytotoxic granule-associated proteins (TIA-1, granzyme B, perforin).
- Unlike systemic/nodal ALCL, (epithelial membrane antigen (EMA) is usually negative. Staining for the (anaplastic lymphoma kinase (ALK) protein is negative in the vast majority of cases (Table 4).

Postulated Cell of Origin: Activated skin-homing T-lymphocyte

LYMPHOMATOID PAPULOSIS

Lymphomatoid papulosis (LyP) is a chronic recurrent cutaneous disease characterized by self-regressing papulonecrotic or papulonodular lesions. LyP itself has an excellent

Table 5 Histologic Subtypes of Lymphomatoid Papulosis

Histologic Subtypes	LyP Type A (Fig. 7)	LyP Type B	LyP Type C
	Classic	Resembles MF Uncommon	Resembles ALCL
Histology	Scattered small clusters of large atypical CD30+ cells, which may be Reed-Sternberg-like or multinucleated Prominent mixed inflammatory infiltrate with small lymphocytes, neutrophils, eosinophils, and/or histiocytes	Epidermotropic infiltrate of small atypical lymphocytes with cerebriform nuclei	Monotonous population or large clusters of large atypical CD30+ cells Relatively few admixed inflammatory cells
Immunophenotype	CD30+ CD4+ Variable loss of CD2, CD5, and/or CD3 Frequent expression of cytotoxic proteins (TIA-1, granzyme B, perforin)	CD30 − CD3+ CD4+ CD8−	Similar to type A

Abbreviation: LyP, lymphomatoid papulosis.

prognosis; however, in a small subset of patients (4–20%), LyP may be preceded by, concurrent with, or followed by, a lymphoma. LyP affects mainly adults but may occur in children.

Clinical Presentation:

- Papular, papulonecrotic, and/or papulonodular lesions at different stages of development (Fig. 7A). Lesion occurs predominantly on the trunk and limbs.
- There is spontaneous regression within 3 to 12 weeks, often leaving behind superficial scars.

Histopathology:

The histologic findings are quite variable and may correlate with the age of the lesion. Three histologic subtypes have been described but lesions may show overlapping features (Table 5).

***Postulated Cell of Origin*:** Activated skin-homing T-lymphocyte

References:

1. Bekkenk MW, Geelen FA, van Voorst Vader PC, et al. Primary and secondary cutaneous CD30(+) lymphoproliferative disorders: a report from the Dutch Cutaneous Lymphoma Group on the long-term follow-up data of 219 patients and guidelines for diagnosis and treatment. Blood 2000; 95(12):3653–3661.
2. el-Azhary RA, Gibson LE, Kurtin PJ, Pittelkow MR, Muller SA. Lymphomatoid papulosis: a clinical and histopathologic review of 53 cases with leukocyte immunophenotyping, DNA flow cytometry, and T-cell receptor gene rearrangement studies. J Am Acad Dermatol 1994; 30:210–218.
3. Willemze R, Jaffe ES, Burg G, et al. WHO–EORTC classification for cutaneous lymphomas. Blood 2005; 105(10):3768–3785.

FOLLICULAR LYMPHOMA

Synonym: Primary cutaneous follicle center lymphoma (PCFCL).

PCFCL is a neoplasm of follicle center B-cells (mixture of centrocytes/cleaved cells and variable numbers of centroblasts/noncleaved cells) with a follicular, follicular and diffuse, or a diffuse growth pattern. The clinical behavior and prognosis of primary cutaneous follicular lymphoma are significantly more favorable than systemic/nodal follicular lymphoma. Cutaneous follicular lymphoma should be differentiated from other forms of cutaneous B-cell lymphoma (Table 6).

Clinical Presentation:

Solitary or grouped plaques and tumors, usually on the scalp/forehead or on the trunk (Fig. 8A). Tumors may be surrounded by erythematous papules and plaques. Multifocal lesions are uncommon.

Histopathology:

- Moderate to dense, nonepidermotropic lymphocytic infiltrate with follicular, follicular and diffuse, or a diffuse growth pattern (Fig. 8B).
- Admixture of centrocytes (cleaved follicle center cells) and variable numbers of centroblasts (large noncleaved follicle center cells).

Table 6 Characteristic Clinical and Histopathologic Features of Cutaneous Follicular Lymphoma and Diffuse Large B-Cell Lymphoma

	Primary Cutaneous Follicular Lymphoma (Fig. 8)	Primary Cutaneous DLBCL, Leg Type (Fig. 10)
Clinical features	Middle-aged adults with lesions on the head or neck	Elderly patients with lesions on the leg(s) (rare cases may occur elsewhere)
Morphology	Admixture of centrocytes and centroblasts with variable growth pattern (follicular, follicular and diffuse, diffuse)	Confluent sheets of large lymphocytes resembling centroblasts or immunoblasts Diffuse growth pattern
Bcl-2	Usually negative	Positive
Mum-1	Negative	Positive

Abbreviation: DLBCL, diffuse large B-cell lymphoma.

- Follicles with abnormal morphologic features, reduced/absent mantle zone, and lack of tingible body macrophages.

Immunophenotype:

- The neoplastic follicular cells express CD20, CD79a, and bcl-6. CD10 expression is variable. CD5 and CD43 are negative.
- The proliferation rate with Ki-67/MIB-1 is reduced compared to normal/reactive lymphoid follicles. Although the vast majority of systemic/nodal follicular lymphomas express bcl-2, primary cutaneous follicular lymphomas are usually bcl-2-negative.
- The presence of extrafollicular clusters of CD10/bcl-6-positive cells outside CD21-positive follicular dendritic cell networks is a useful diagnostic finding (Figs. 8E, and F).

***Postulated Cell of Origin*:** Germinal center B-cell

References:

1. de Leval L, Harris NL, Longtine J, Ferry JA, Duncan LM. Cutaneous B-cell lymphomas of follicular and marginal zone types: use of Bcl-6, CD10, Bcl-2, and CD21 in differential diagnosis and classification. Am J Surg Pathol 2001; 25(6):732–741.
2. Leinweber B, Colli C, Chott A, Kerl H, Cerroni L. Differential diagnosis of cutaneous infiltrates of B lymphocytes with follicular growth pattern. Am J Dermatopathol 2004; 26(1):4–13.
3. Willemze R, Jaffe ES, Burg G, et al. WHO–EORTC classification for cutaneous lymphomas. Blood 2005; 105(10):3768–3785.

MARGINAL ZONE B-CELL LYMPHOMA

Synonym: Primary cutaneous marginal zone B-cell lymphoma (PCMZL)

PCMZL is an indolent extranodal B-cell lymphoma composed of a morphologically heterogeneous infiltrate of small lymphocytes and a variable plasma cell component. Most cases of apparent primary cutaneous plasmacytoma are actually examples of marginal zone B-cell lymphoma with prominent plasma cell differentiation. Plasmacytoma

differs from marginal zone lymphoma by the sparseness/absence of lymphocytes and the presence of cytologic atypia of plasma cells.

Clinical Presentation:
- Red to violaceous papules, plaques, and nodules on the trunk or arms (Fig. 9A). Presentation with multifocal skin lesions is common.
- Dissemination to extracutaneous sites is rare, but cutaneous recurrences may be observed. The prognosis is excellent.

Histopathology:
- Nodular to diffuse, nonepidermotropic lymphocytic infiltrate (Fig. 9B).
- Admixture of small lymphocytes, marginal zone B cells, lymphoplasmacytoid cells, plasma cells, and small reactive T-cells. Plasma cells often located at the periphery of the infiltrates and in the superficial dermis.
- Reactive (non-neoplastic) lymphoid follicles with germinal centers may be observed.

Immunophenotype:
- The neoplastic cells are immunoreactive with CD20, CD79a, and Bcl-2.
- Expression of CD5, CD10, or bcl-6 by neoplastic cells is not observed. However, associated reactive germinal centers are CD10/bcl-6-positive and bcl-2-negative.
- Unlike other B-cell lymphomas, monotypic immunoglobulin light chain expression is demonstrable on paraffin sections in the majority of cases (Figs. 9E and F).

***Postulated Cell of Origin*:** Postgerminal center, marginal zone B-cell

References:
1. Hoefnagel JJ, Vermeer MH, Jansen PM, et al. Primary cutaneous marginal zone B-cell lymphoma: clinical and therapeutic features in 50 cases. Arch Dermatol 2005; 141(9):1139–1145.
2. Willemze R, Jaffe ES, Burg G, et al. WHO–EORTC classification for cutaneous lymphomas. Blood 2005; 105(10):3768–3785.

DIFFUSE LARGE B-CELL LYMPHOMA

Synonym: Primary cutaneous diffuse large B-cell lymphoma (DLBCL), leg-type.

Primary cutaneous DLBCL is an uncommon cutaneous B-cell lymphoma composed of large lymphocytes. Lesions predominantly affect elderly patients and occur characteristically on the lower legs.

Clinical Presentation:
- Patients usually present with rapidly growing red or bluish-red tumors on one or both legs (Fig. 10A).
- Unlike other primary cutaneous B-cell lymphomas, extracutaneous dissemination is common, and the prognosis is unfavorable.

Histopathology:
Dense diffuse infiltrate composed of monomorphous, confluent sheets of large atypical lymphocytes (centroblasts or immunoblasts) in the dermis and often in the panniculus (Figs. 10B and C). A significant component of centrocytes/cleaved cells is not observed. Mitotic figures are frequently seen. The epidermis is usually spared.

Immunophenotype:
The large lymphocytes express CD20 and CD79a. Bcl-6 expression is frequent. Unlike primary cutaneous follicle center lymphoma (PCFCL), there is a strong expression of bcl-2 and MUM-1/IRF4 (Table 6, Fig. 10E).

***Postulated Cell of Origin*:** Peripheral B-cell

References:
1. Vermeer MH, Geelen FA, van Haselen CW, et al. Primary cutaneous large B-cell lymphomas of the legs. A distinct type of cutaneous B-cell lymphoma with an intermediate prognosis. Dutch Cutaneous Lymphoma Working Group. Arch Dermatol 1996; 132(11):1304–1308.
2. Willemze R, Jaffe ES, Burg G, et al. WHO–EORTC classification for cutaneous lymphomas. Blood 2005; 105(10):3768–3785.

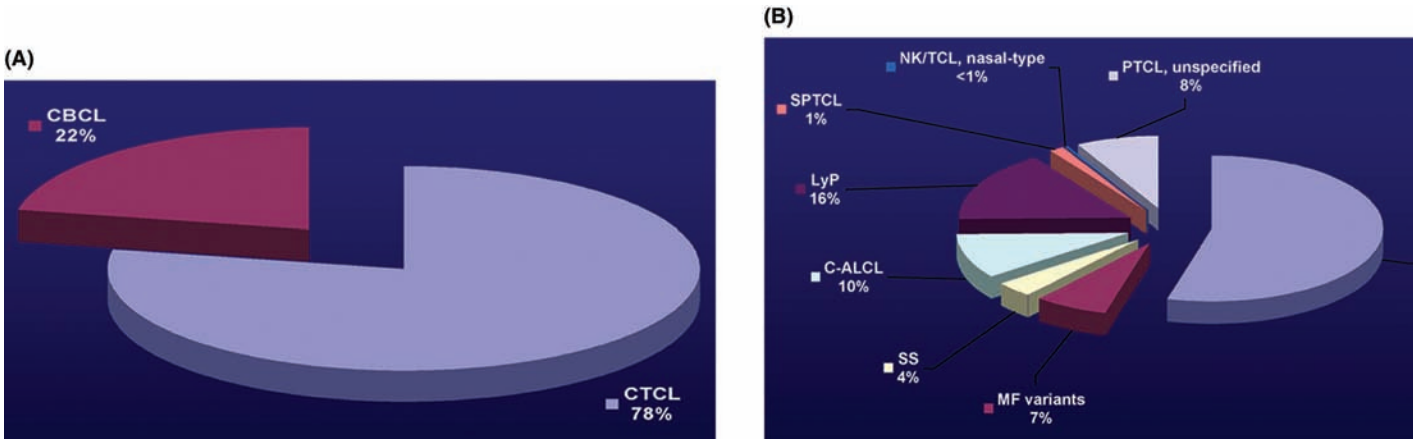

Figure 1 Relative frequency of cutaneous lymphomas. (**A**) Relative frequency of primary cutaneous T-cell lymphoma and B-cell lymphoma. (**B**) Relative frequency of different types of cutaneous T/NK-cell lymphomas. *Source*: 1905 patients with a primary cutaneous lymphoma registered at the Dutch and Austrian Cutaneous Lymphoma Group 1986–2002. Blood 2005; 105(10):3768–3785.

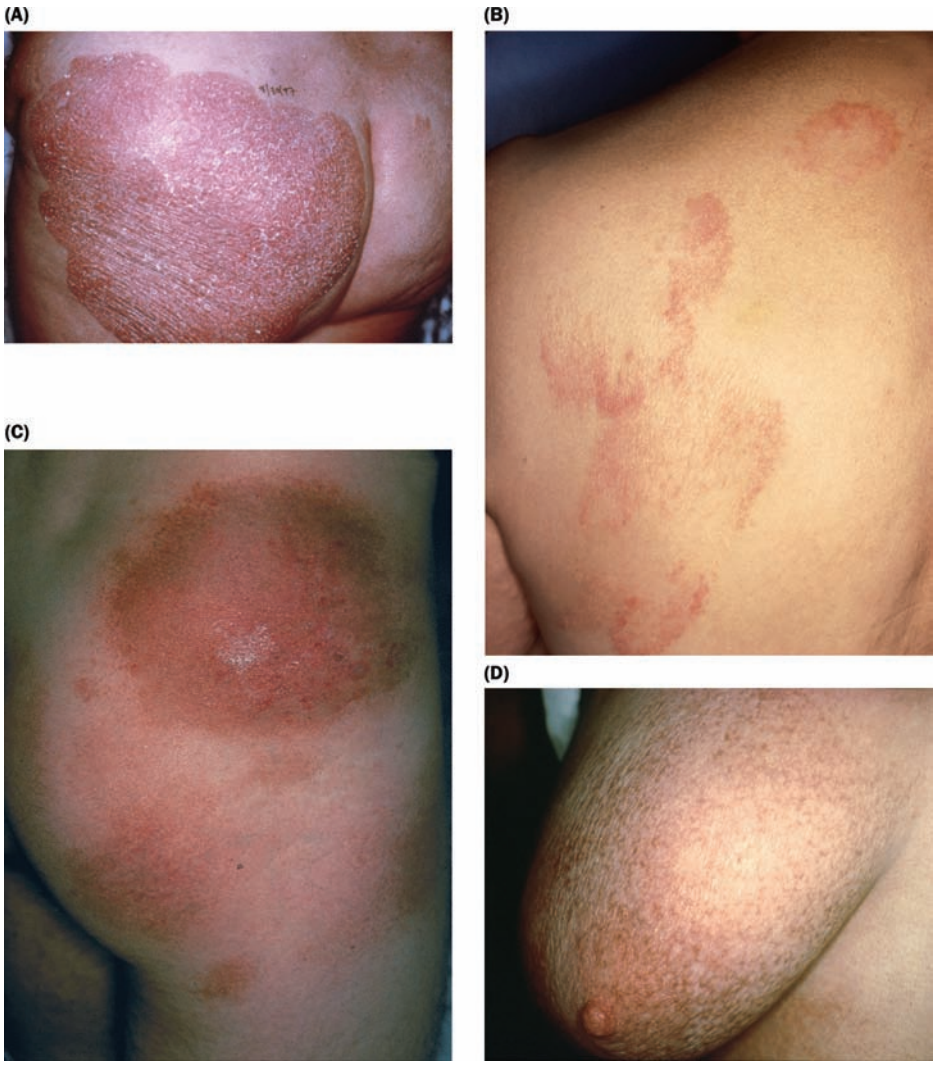

Figure 2 Mycosis fungoides (MF), patch-stage clinical lesions. (**A**) Large erythematous scaly patch of buttock. (**B**) Annular lesions of patch-stage MF. (**C**) Patch-stage MF with purpuric appearance. (**D**) Poikilodermatous change is a feature of MF.

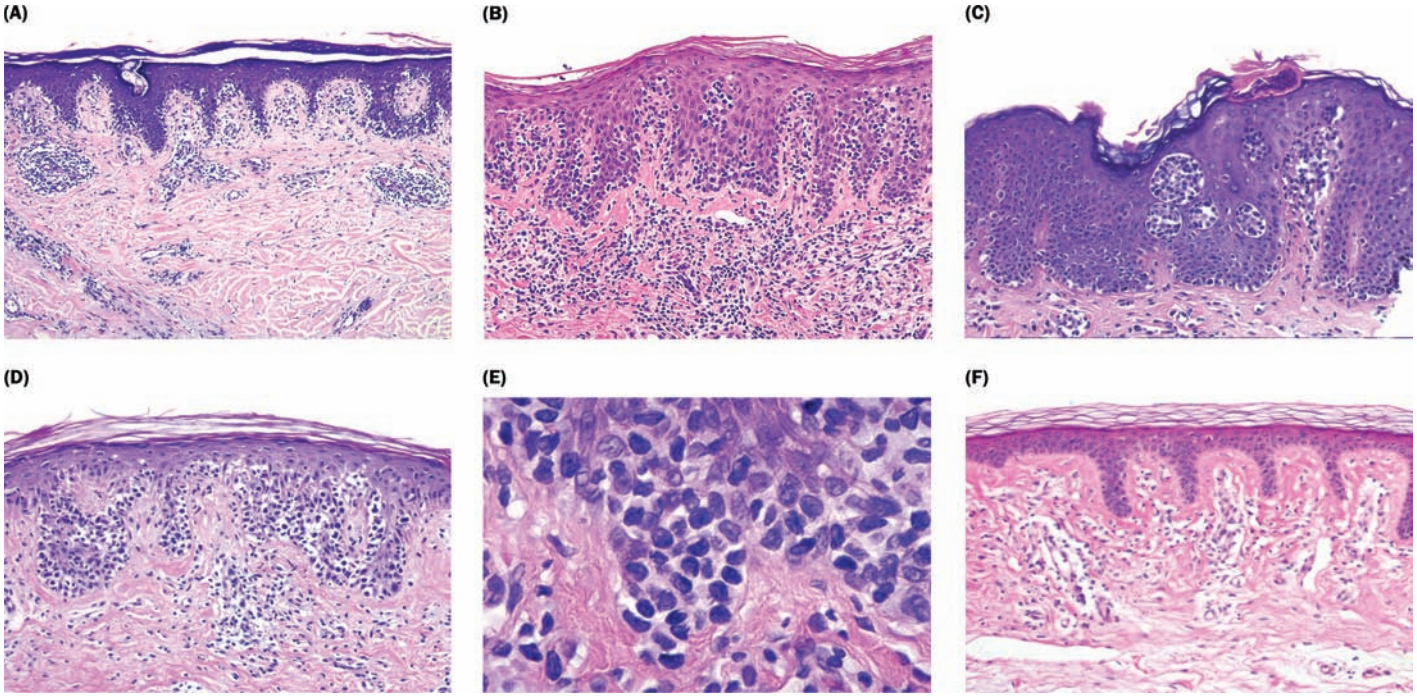

Figure 3 Mycosis fungoides (MF), patch-stage histopathology. (**A**) Superficial lymphocytic infiltrate with "disproportionate exocytosis" (lymphocytes in the epidermis associated with relative paucity of spongiosis). (**B**) Prominent basilar lymphocytes. (**C**) Pautrier's microabscesses (well-defined collections of lymphocytes within the epidermis). (**D**) Lymphocytes present within the epidermis are larger than those in the dermis and exhibit "halos." (**E**) Medium-large convoluted lymphocytes that approximate the width of basilar keratinocytes. (**F**) Thickened, wiry collagen bundles within the papillary dermis (late patch state MF).

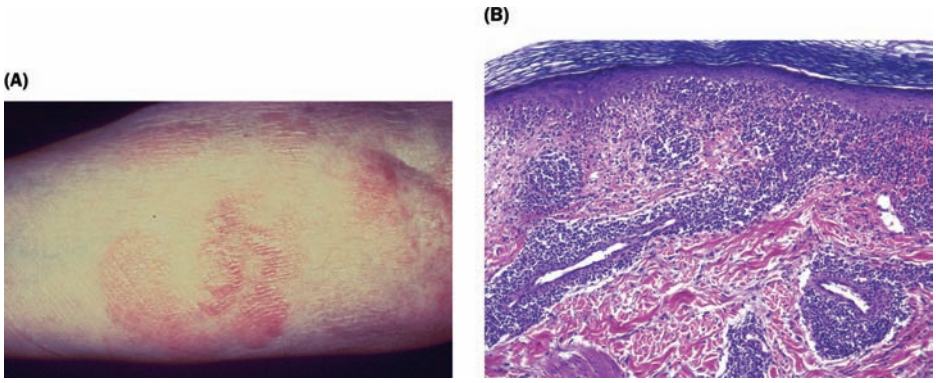

Figure 4 Mycosis fungoides MF, plaque stage. (**A**) Plaque-stage MF. (**B**) Plaque-stage MF with intra-epidermal lymphocytes and reticular dermal involvement.

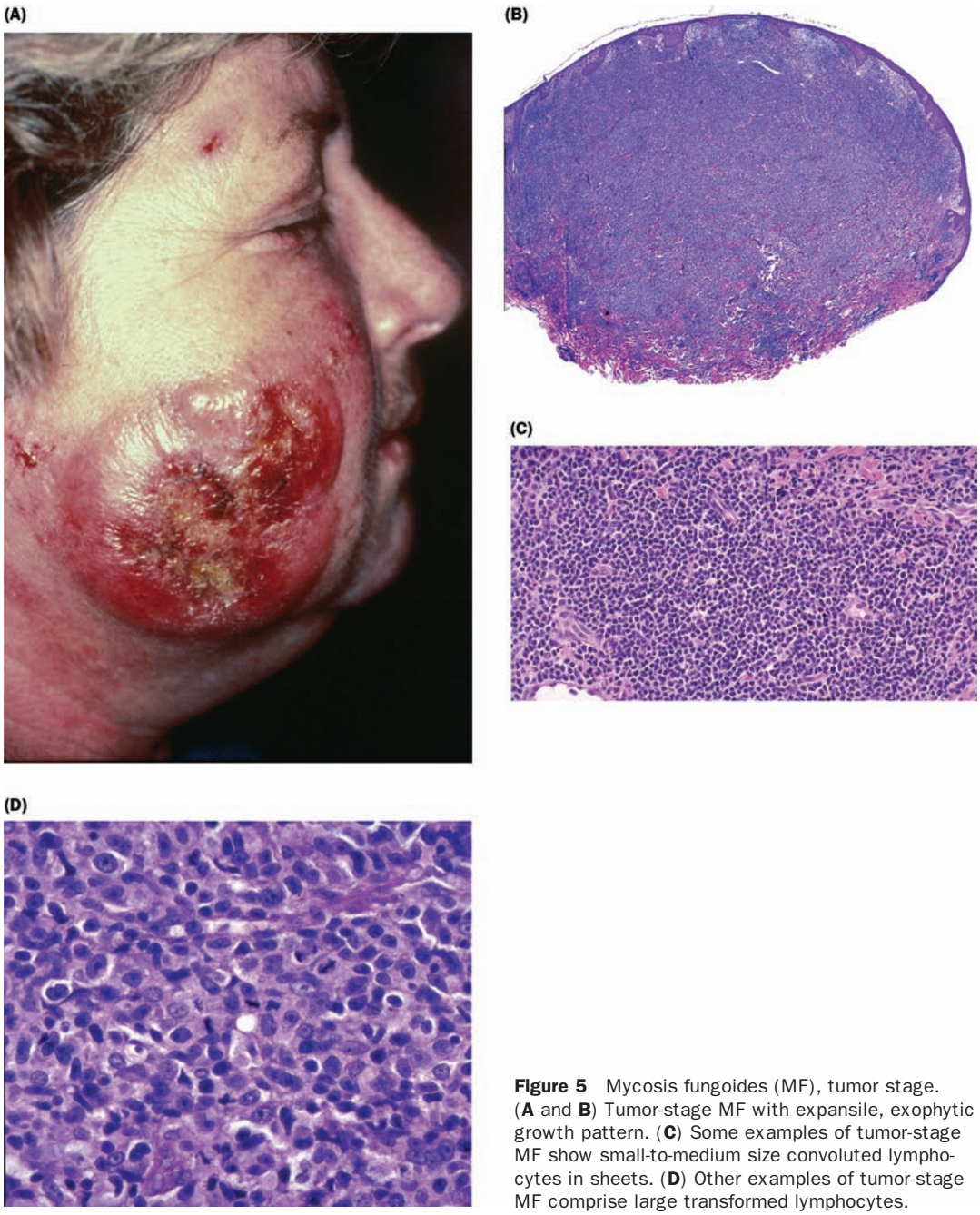

Figure 5 Mycosis fungoides (MF), tumor stage. (**A** and **B**) Tumor-stage MF with expansile, exophytic growth pattern. (**C**) Some examples of tumor-stage MF show small-to-medium size convoluted lymphocytes in sheets. (**D**) Other examples of tumor-stage MF comprise large transformed lymphocytes.

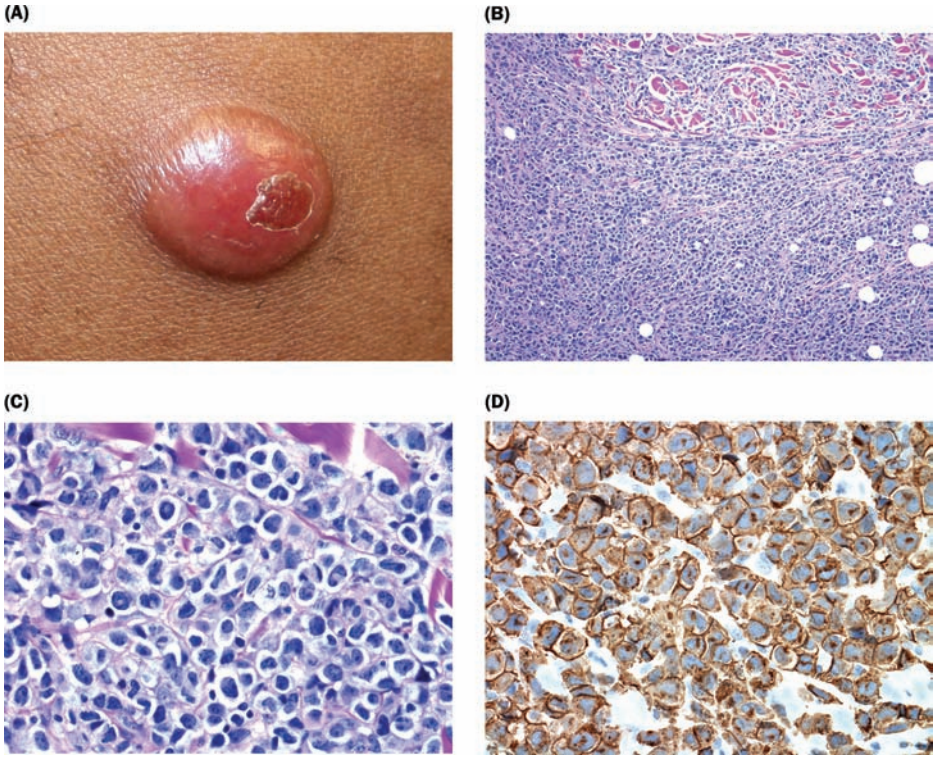

Figure 6 Cutaneous anaplastic large cell lymphoma. (**A**) Solitary tumor on the right shoulder (**B**) Diffuse lymphoid infiltrate in the dermis and superficial panniculus. (**C**) Confluent sheets of large atypical lymphocytes with round and irregularly shaped nuclei and abundant cytoplasm. (**D**) Strong expression of CD30 by the vast majority of neoplastic lymphocytes.

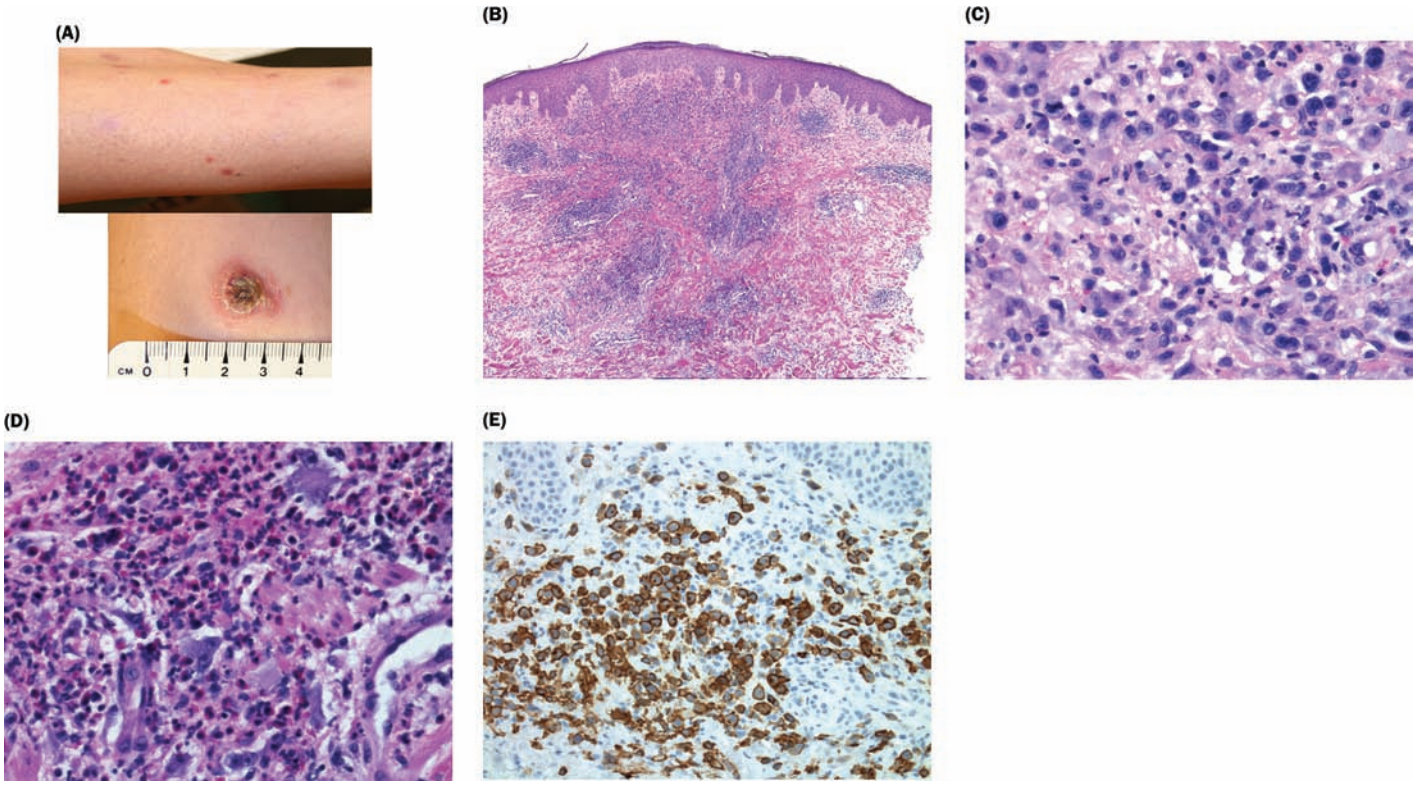

Figure 7 Lymphomatoid papulosis. (**A**) Clinical presentation with multiple papules and papulonecrotic lesions. (**B**) Wedge-shaped dermal infiltrate. (**C**) Small clusters and scattered large atypical lymphocytes and mixed inflammatory infiltrate of neutrophils, histiocytes, and small lymphocytes. (**D**) Scattered Reed-Sternberg-like atypical lymphocytes and mixed inflammatory infiltrate of neutrophils, eosinophils, histiocytes, and small lymphocytes. (**E**) CD30 expression by large lymphocytes, which are arranged as single cells and in small clusters.

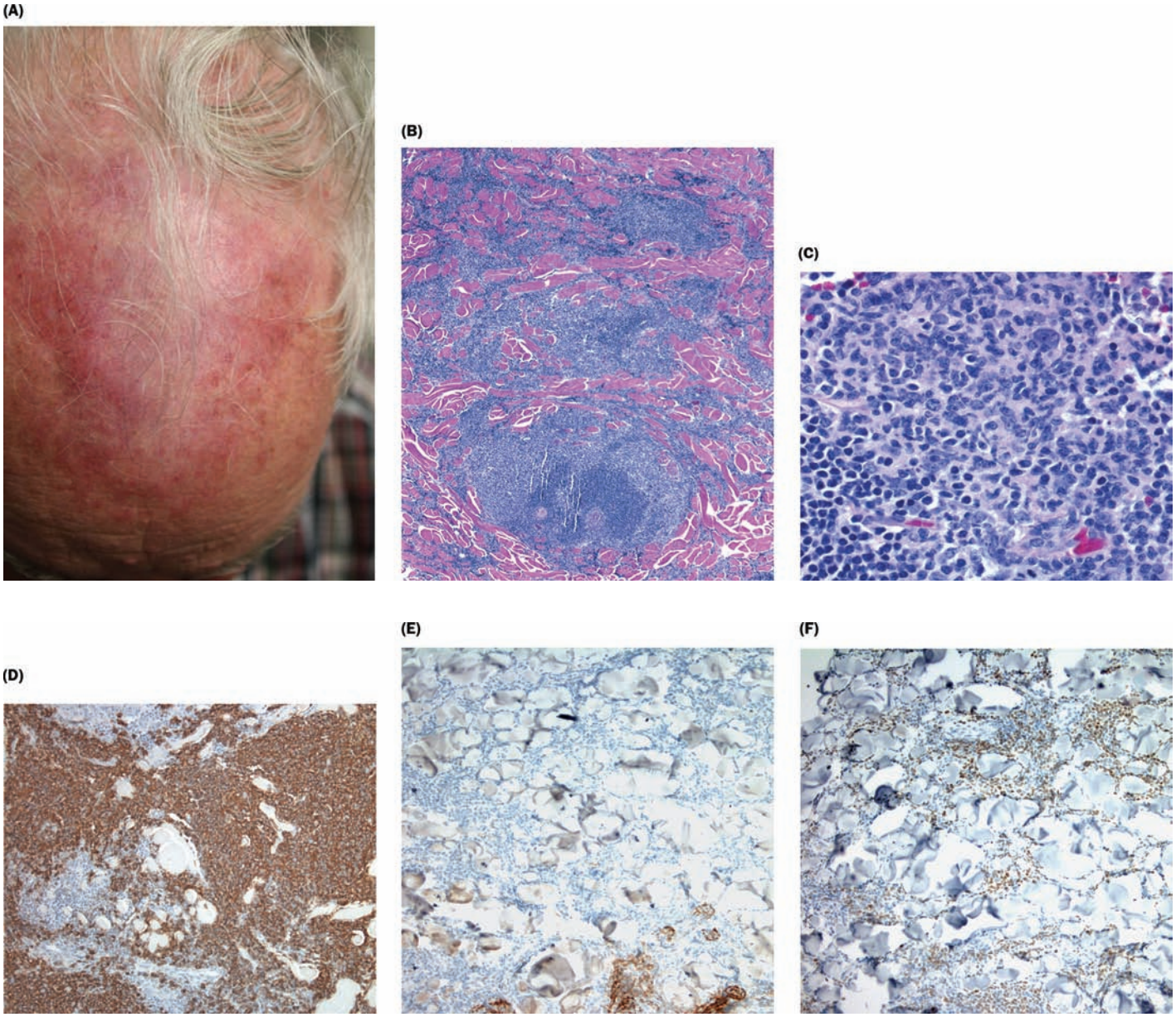

Figure 8 Cutaneous follicular lymphoma. (**A**) Clinical presentation with grouped erythematous lesions and plaques on the scalp. (**B**) Moderately dense dermal lymphocytic infiltrate with follicular and focally diffuse growth pattern. (**C**) Predominance of centrocytes (small cleaved cells) admixed with centroblasts (noncleaved cells). (**D**) CD20 expression by the majority of the lymphoid infiltrate. (**E**) Irregularly shaped lymphoid follicles highlighted by CD21-positive follicular dendritic cell networks. (**F**) Extrafollicular clusters of Bcl-6-positive neoplastic cells outside lymphoid follicles (compare with Fig. 8E).

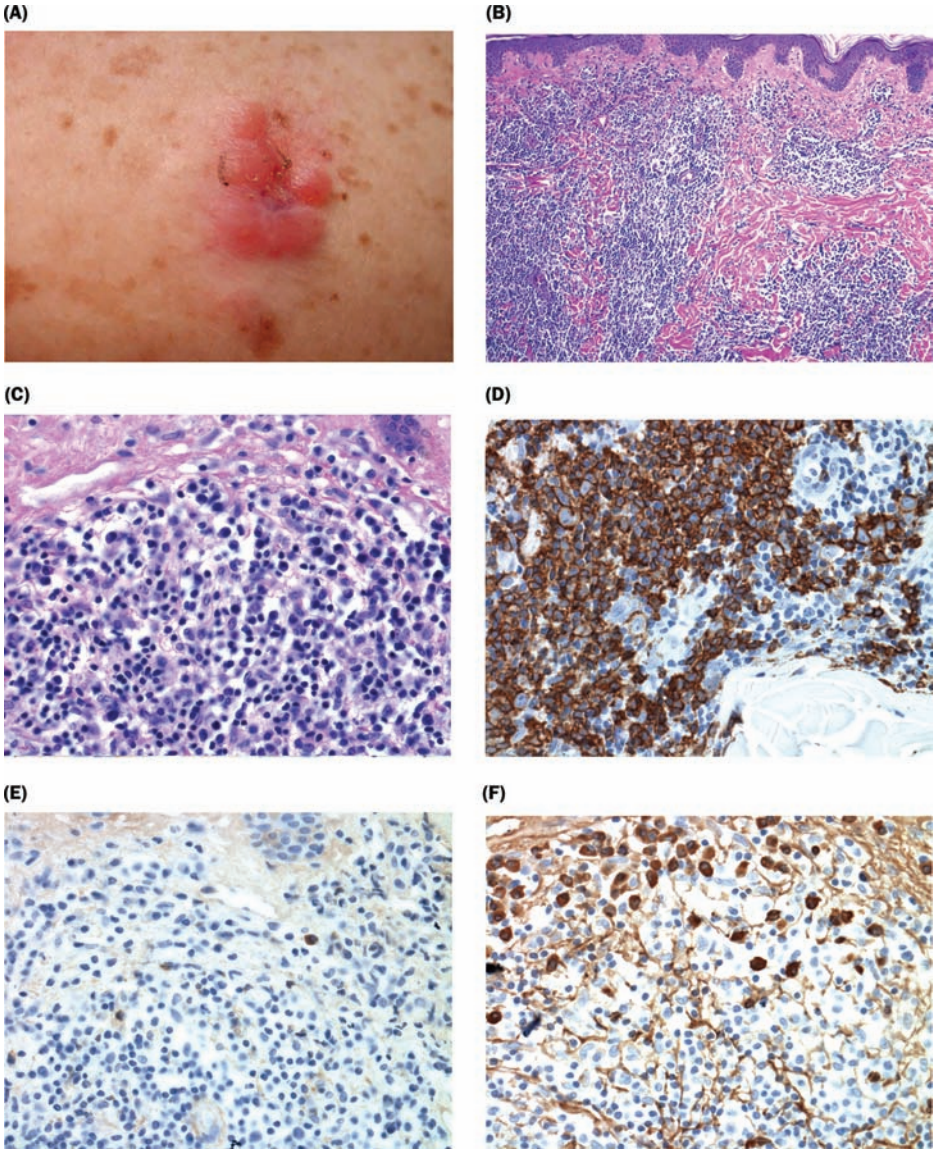

Figure 9 Cutaneous marginal zone B-cell lymphoma. (**A**) Clinical presentation with multiple erythematous papules and plaques on the back. (**B**) Non-epidermotropic, nodular, and diffuse lymphocytic infiltrate in the dermis. (**C**) Admixture of small lymphocytes and plasma cells. (**D**) CD20 expression by neoplastic lymphocytes. (**E** and **F**) Monotypic expression of immunoglobulin light chain by plasma cells (E, kappa; F, lambda).

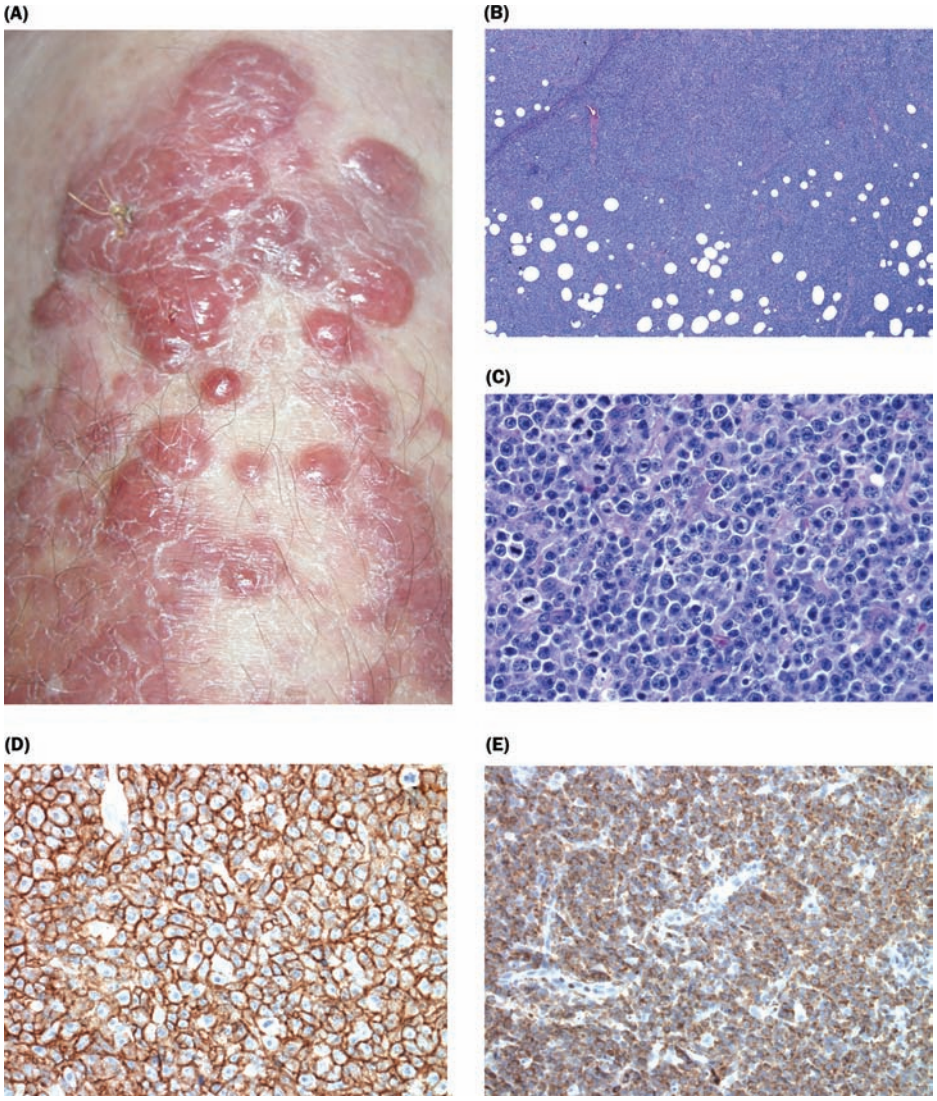

Figure 10 Cutaneous diffuse large B-cell lymphoma (DLBCL). (**A**) Multiple erythematous tumors on the leg. (**B**) Dense diffuse lymphoid infiltrate in the dermis and panniculus. (**C**) Confluent sheets of large atypical lymphocytes with prominent nucleolus and vesicular chromatin. Scattered mitotic figures are present. (**D**) Strong expression of CD20 by neoplastic lymphocytes. (**E**) Bcl-2 expression by neoplastic lymphocytes.

28

Practical Immunohistochemistry in Dermatopathology

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What Is Immunohistochemistry?

Immunohistochemistry (IHC) is the use of immunologic techniques to identify cellular antigens (proteins) that are not visible on routine hematoxylin and eosin stained sections.

Role of Immunohistochemistry in Diagnostic Dermatopathology:

- Most commonly, to identify tissue of origin/differentiation
- Less commonly to determine B-cell clonality in cutaneous B-cell infiltrates
- Rarely determine biologic behavior of tumors and identify infectious agents

Markers (Antibodies) for Tissue Origin/Differentiation:

- Epithelial
- Melanocytic
- Mesenchymal (including muscle and endothelium)
- Neuroendocrine
- Hematopoietic

Markers of Epithelial Differentiation:

Epithelial Membrane Antigen (EMA):

- Stains variety of normal glandular (eccrine/apocrine) and sebaceous epithelium and their tumors; primary cutaneous and metastatic carcinomas; perineurioma and Paget's disease/extramammary Paget's disease (PD/EMPD)—*low specificity*

Carcinoembryonic Antigen (CEA):

- Detect glandular differentiation in primary cutaneous (eccrine/apocrine) tumors and metastatic adenocarcinomas to the skin; and PD/EMPD

Sex-Hormone Receptors: Estrogen Receptor (ER)/Progesterone (PR):

- Primary cutaneous eccrine tumors and metastatic carcinoma (i.e., breast)

Cytokeratins:

- Intermediate filament in epithelial cells. Expression is generally conserved in poorly differentiated epithelial neoplasms
- Group of more than 19 subtypes, divided into two subfamilies based on isoelectric points

Commonly Used Cytokeratins (CK):

- AE1/AE3 (pan-CK cocktail)—used to differentiate carcinomas from other tumors
- Cam 5.2
  - Stains eccrine glands well, apocrine/sebaceous glands variably
  - Does not stain normal epidermis, rarely squamous cell carcinoma (SCC) and one-third of basal cell carcinomas
- CK5/6: useful in spindle cell/sarcomatoid SCC
- CK7: stain of choice for PD/EMPD
- CK20: stain of choice for Merkel cell carcinoma (+/−characteristic perinuclear "dot")

Markers of Melanocytic Differentiation:

S-100:

- Family of calcium channel binding proteins. *High sensitivity* for melanocytic tumors, but *low specificity* as found in other nonmelanocytic tissues—must be combined with another melanocytic marker.
  - *Neuroectodermal*: Schwann cells, neurons, and glia
  - *Epithelial*: Ducts and myoepithelial cells of eccrine, apocrine, salivary, and mammary glands
  - *Mesenchymal*: Chondrocytes, adipocytes, endothelial cells, and smooth and skeletal muscle
  - *Hematologic*: Langerhans cells

MART-1, HMB-45, Tyrosinase, and NKI/C3:

- *Lower sensitivity* and *higher specificity* markers for melanocytic neoplasms compared to S-100
- Desmoplastic melanomas may not be reactive

Markers of Mesenchymal Differentiation:

Vimentin:

- Intermediate filament; expressed in all mesenchymal cells; variety of other cells
- *High sensitivity*, but *low specificity*—typically used to assess antigen preservation

Factor XIIIa:

- Marker of subgroup of dermal dendrocytes/antigen presenting cells
- Positive in dermatofibroma; may also be seen in angiofibroma, atypical fibroxanthoma, juvenile xanthogranuloma, and other xanthomas

CD34:

- Marker for endothelial cells and different subgroup of dermal dendrocytes
- *High sensitivity*, but *low specificity*—positive in dermatofibrosarcoma protuberans, vascular tumors, leukemia cutis, and wide range of spindle cell neoplasms

Muscle Markers:
- *Actin*: Both broad spectrum and smooth muscle-specific antibodies
- *Desmin*: Intermediate filament expressed in both smooth and skeletal muscle

Vascular Markers:
- *CD31*: Reported as overall *most sensitive* and *most specific* vascular marker
- *CD34*: Most sensitive marker for Kaposi's sarcoma
- *Factor VIII* (*von Willebrand factor*): Less sensitive than CD34 or CD31

Markers of Neuroendocrine Differentiation:
Neuron-Specific Enolase:
- Expressed by neuroendocrine carcinomas, melanocytic and neural tumors—*high sensitivity*, but *low specificity*

Synaptophysin and Chromogranin:
- May be expressed by different cell populations within the same tumor

CD56 and CD57:
- Neuroendocrine carcinomas, neural and nerve sheath tumors, and natural killer cells (NK-cells)

Markers of Hematopoietic Differentiation:

T-Cell Lymphoma Markers	B-Cell Lymphoma Markers
CD3-pan T-cell	CD10-FCCL
CD4-T helper	CD20-pan B-cell
CD5-pan T-cell	CD21-follicular dendritic cells
CD7-pan T-cell	CD79a-pan B-cell
CD8-T suppressor	bcl-2-marker of FCCL
CD43-pan T-cell	bcl-6-marker of FCCL
CD45RO-pan T-cell CD56/CD57-NK-cell	κ and λ light chains-monotypic plasma cells
Histiocytic Markers	**Activation Marker**
CD1a-Langerhans cells HAM56 MAC387 CD68	CD30-lymphomatoid papulosis, anaplastic large cell lymphoma, Hodgkin dz.

Abbreviation: FCCL, follicular center cell lymphoma.

An in-depth review of the use of immunohistochemistry in the diagnosis of cutaneous lymphomas is beyond the scope of this chapter. However, a number of basic principles are important.

T-Cell Lymphoma:
- Typically predominance of T-cells, with predominance of either CD4 or CD8 positive cells
- Loss of expression of pan T-cell antigens (i.e., CD5 and CD7)
- There is no immunohistochemical marker for T-cell clonality (as in B-cells)

B-Cell Lymphoma:
- Typically predominance of B-cells
- B-cells may show gain of expression of pan T-cell antigens (i.e., CD5 and CD43)
- κ and λ light chain restriction identifies monotypic plasma cells ("clonality")
- May express bcl-2 and bcl-6 (particularly FCCL)

Practical Uses for IHC in Diagnostic Dermatopathology:
Important Considerations:
- Some antibodies are *not specific* for a certain cell type—use panel of antibodies
- *Differential diagnosis* must be constructed prior to antibody panel
- Positive and negative *controls* are necessary—many antibodies have *positive internal control* in skin tissue
- IHC does *not* distinguish benign versus malignant lesions

Differential Diagnoses in which IHC Is Helpful:
- Pagetoid cells
- Small blue cells
- Spindle cells
- Dermatofibroma versus dermatofibrosarcoma protuberans
- Epithelioid cells

Differential Diagnosis of Pagetoid Cells:

	Cam 5.2	AE1/AE3	EMA	S-100	CD3
Paget's disease	+ (and CK7)	−	+	− / +	−
Bowen's (SCC in situ)	−	+	− / +	−	−
Melanoma in situ	−	−	−	+	−
Mycosis fungoides	−	−	−	−	+

Abbreviations: EMA, epithelial membrane antigen; SCC, squamous cell carcinoma.

Case 1: Paget's Disease:
See Figures 1A and B.

Case 2: Bowen's Disease:
See Figure 2.

Case 3: Melanoma In Situ:
See Figure 3.

Case 4: Mycosis Fungoides:
See Figure 4.

Differential Diagnosis of Small Blue Cells:
See Table 1.

Case 5: Merkel Cell Carcinoma:
See Figure 5.

Case 6: Metastatic Small Cell Carcinoma (Lung):
See Figure 6.

Case 7: Metastatic Melanoma:
See Figure 7.

Table 1 Differential Diagnosis: Small Blue Cells

	Cam 5.2	CK20	NSE	S-100	CD markers	Actin	ER/PR
Merkel cell carcinoma	+	+	+	−	−	−	−
Small cell carcinoma of lung	+	−	+	−	−	−	−
Melanoma	−	−	+ / −	+	−	−	−
Lymphoma/leukemia	−	−	−	−	+	−	−
Lobular carcinoma of breast	+	−	−	−	−	−	+ / −

Abbreviations: ER, estrogen receptor; PR, progesterone receptor, NSE, neuron-specific enolase.

Table 2 Differential Diagnosis: Spindle Cells

	AE1/AE3	S-100	MART-1	CD68	CD34	Actin
Squamous cell carcinoma	+	−	−	−	−	−
Neural tumor	−	+	−	−	+ / −	−
Melanocytic tumor	−	+	+	+ / −	−	−
Atypical fibroxanthoma	−	−	−	+	−	− / +
Kaposi's sarcoma	−	−	−	−	+	−
Leiomyoma/sarcoma	−	−	−	−	−	+

Case 8: Leukemia Cutis:
See Figure 8.

Case 9: Metastatic Breast Carcinoma (Lobular Type):
See Figure 9.

Differential Diagnosis of Spindle Cells:
See Table 2.

Case 10: Squamous Cell Carcinoma (Spindle Variant):
See Figure 10.

Case 11: Neurofibroma:
See Figure 11.

Case 12: Blue Nevus:
See Figure 12.

Case 13: Atypical Fibroxanthoma:
See Figure 13A and B.

Case 14: Kaposi's Sarcoma:
See Figure 14.

Case 15: Leiomyoma:
See Figure 15.

DF vs. DFSP

	Factor XIIIa	CD34
DF	+	−
DFSP	−	+

Case 16: Dermatofibroma:
See Figure 16.

Case 17: Dermatofibrosarcoma Protuberans:
See Figure 17.

Differential Diagnosis of Epithelioid Cells:
See Table 3.

Case 18: Spitz Nevus:
See Figure 18.

Table 3 Differential Diagnosis: Epithelial Cells

	S-100	MART-1	CD1a	CD68	Factor XIIIa	AE1/AE3
Melanocytic tumor	+	+	−	+ / −	−	−
Langerhans cell histiocytosis	+	−	+	+ / −	−	−
Epithelioid cell histiocytoma	−	−	−	+ / −	+	−
Lymphoma	−	−	−	−	−	−
Squamous cell carcinoma	−	−	−	−	−	+

Case 19: Langerhans Cell Histiocytosis:
See Figure 19.

Case 20: Epithelioid Cell Histiocytoma:
See Figure 20.

Case 21: Lymphoma-Large Cell Type:
See Figure 21.

Case 22: Squamous Cell Carcinoma (Poorly Differentiated):
See Figure 22.

Case 23: Malignant Melanoma (With Pseudo-Carcinomatous Hyperplasia):
See Figure 23.

Tumor Biology:
See Figure 24.

Infections:
See Figure 25.

References:

1. Hudson AR, Smoller BR. Immunohistochemistry in diagnostic dermatopathology. Dermatol Clin 1999; 17:667–689.
2. Smoller BR, ed. Practical Immunopathology of the Skin. Totawa, NJ: Human Press, 2002.
3. Immunoquery website (http://www.ipox.org).

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I would like to thank Diana Rozenski and Joe Beauchemin for their technical support.

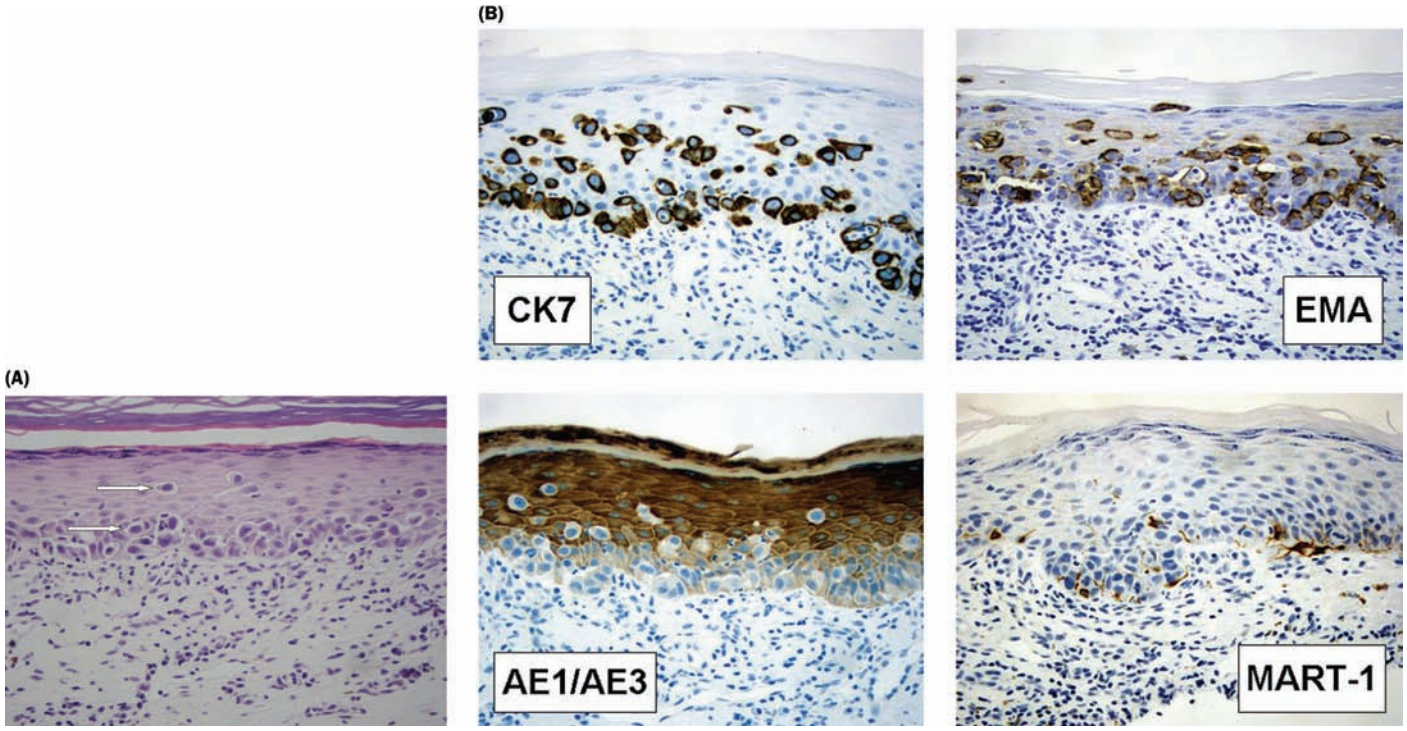

Figure 1 Paget's disease. (**A**) Atypical cells within the lower to mid layers of the epidermis (*arrows*). (**B**) Tumor cells are positive for CK7 and EMA, and negative for AE1/AE3 and MART-1. *Abbreviations*: CK, cytokeratin; EMA, epithelial membrane antigen.

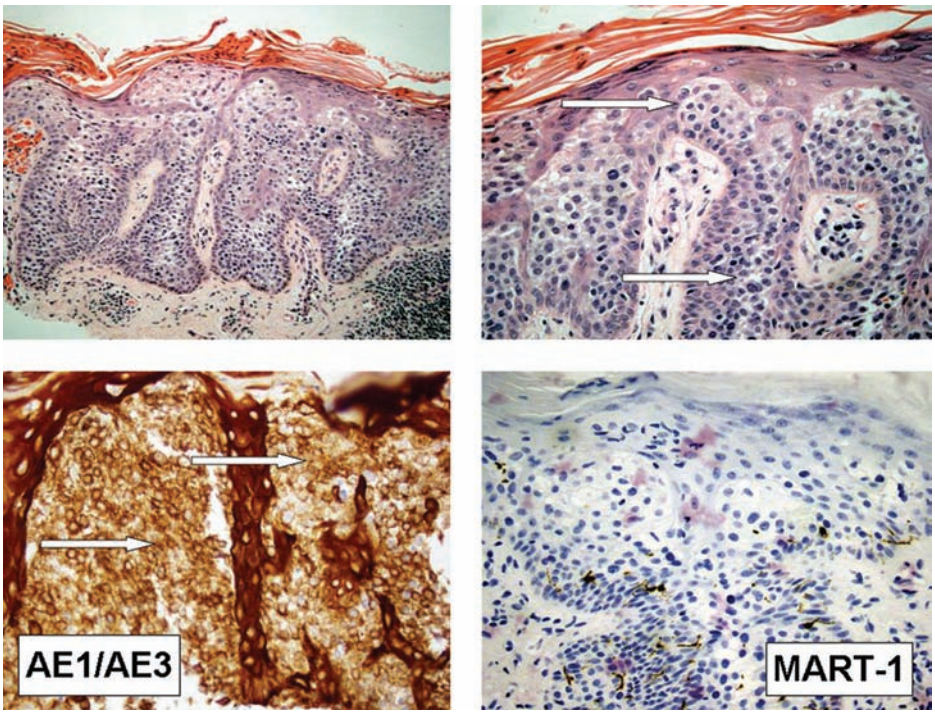

Figure 2 Bowen's disease. "Clonal" proliferation of single and nested atypical cells within all layers of the epidermis (*arrows*). Tumor cells are positive for AE1/AE3 and negative for MART-1.

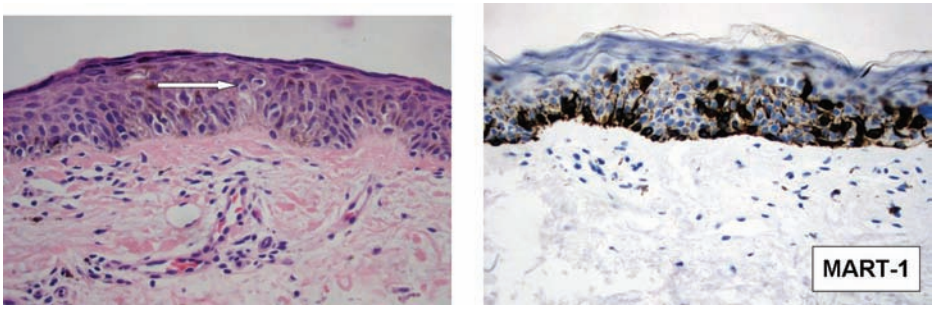

Figure 3 Melanoma in situ. A typical cells within the lower to mid layers of the epidermis (*arrow*). Tumor cells are positive for MART-1.

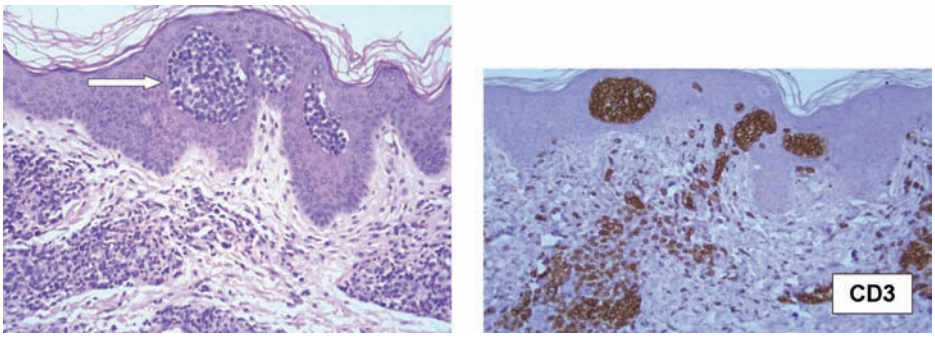

Figure 4 Mycosis fungoides. Nests of hyperchromatic cells in the epidermis (*arrow*). Tumor cells are positive for CD3.

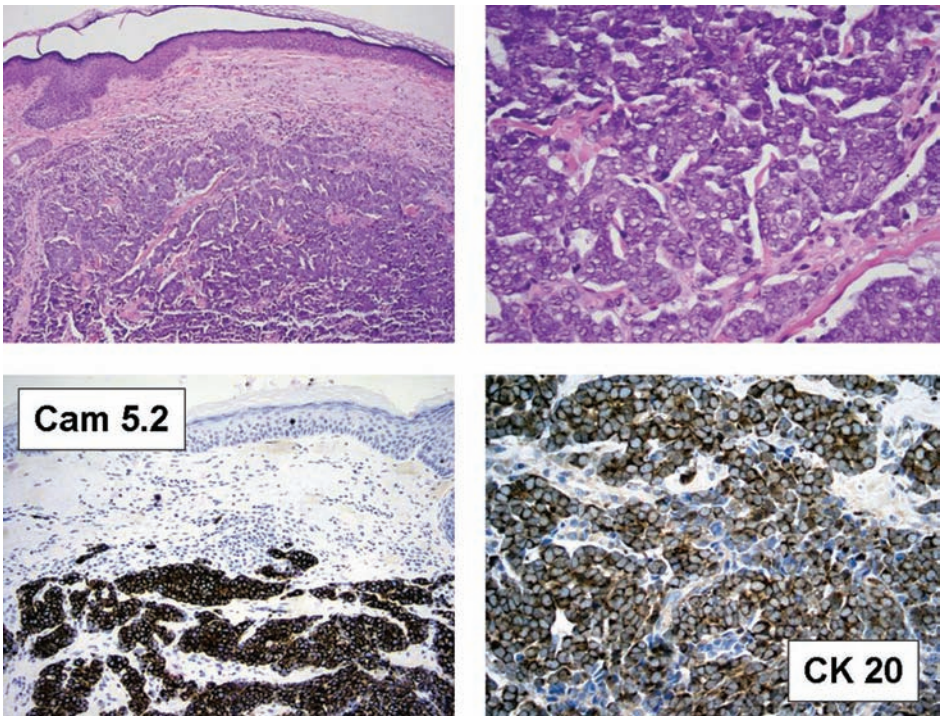

Figure 5 Merkel cell carcinoma. Intradermal tumor composed of monomorphous "small round blue cells." Tumor cells are positive for both Cam 5.2 and cytokeratin 20. *Abbreviation*: CK, cytokeratin.

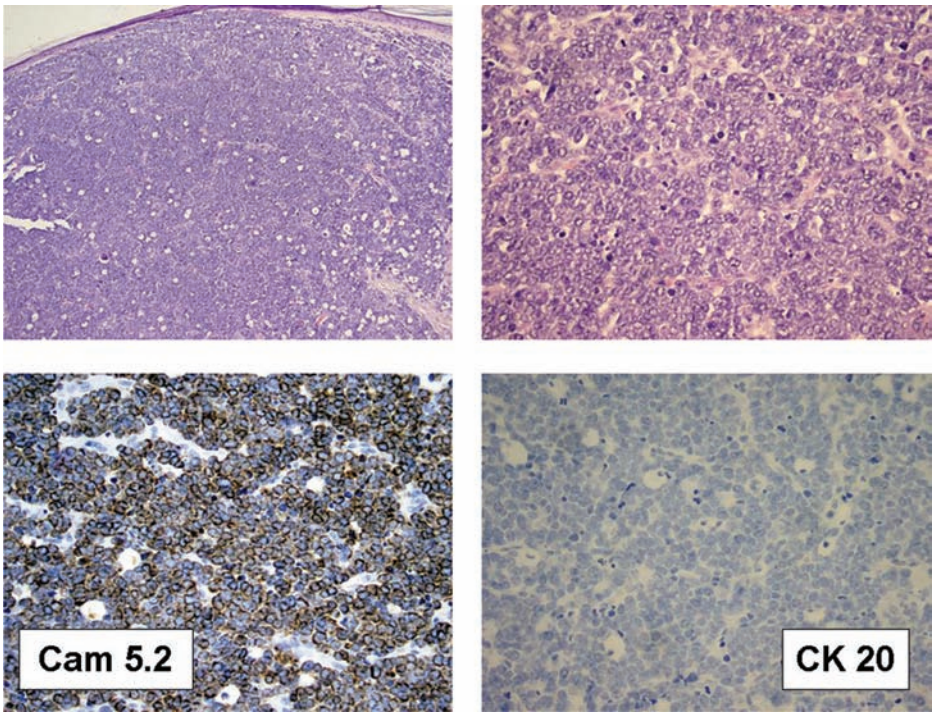

Figure 6 Metastatic small cell carcinoma. Intradermal tumor composed of monomorphous "small round blue cells." Tumor cells are positive for Cam 5.2, but negative for CK20. *Abbreviation*: CK, cytokeratin.

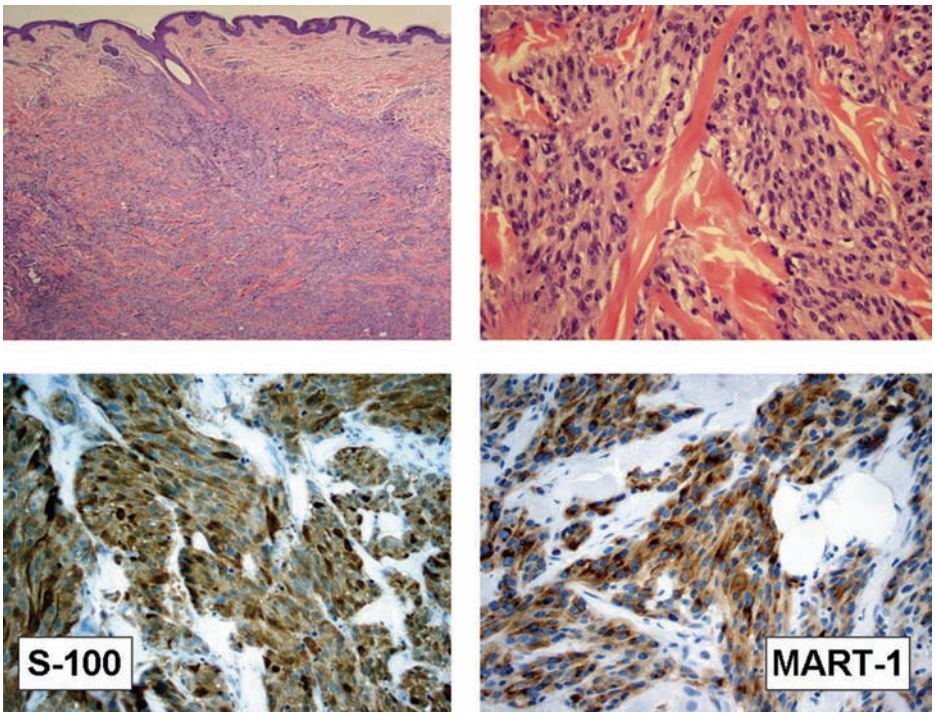

Figure 7 Metastatic melanoma. Intradermal infiltrate of small round and spindle blue cells. Tumor cells are positive for S-100 and MART-1.

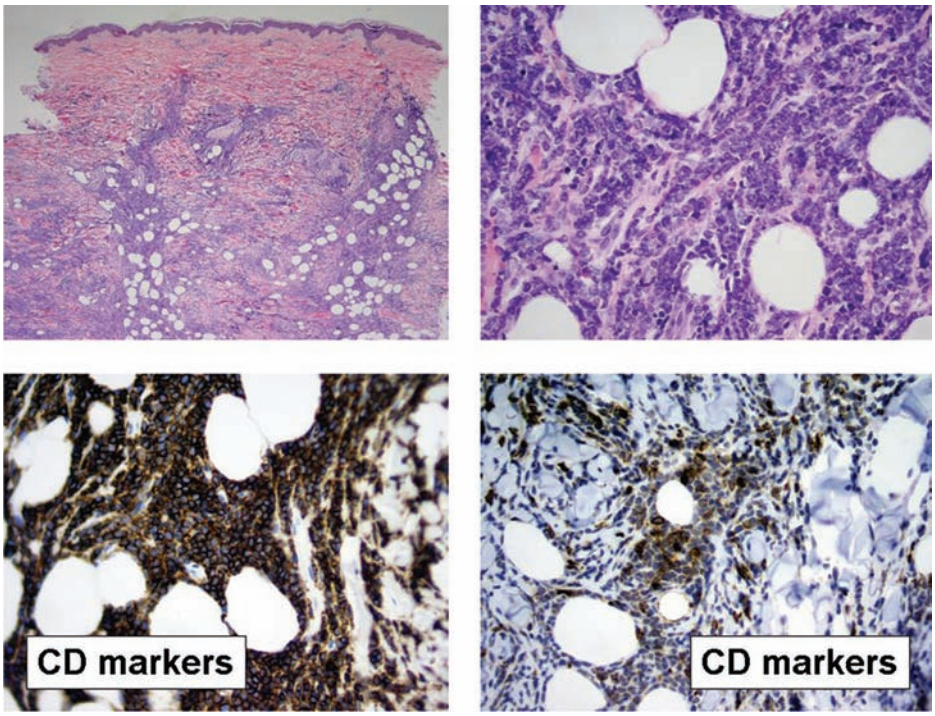

Figure 8 Leukemia cutis. Intradermal infiltrate of small round blue cells, which show variable staining for CD markers, depending on subtype of disease.

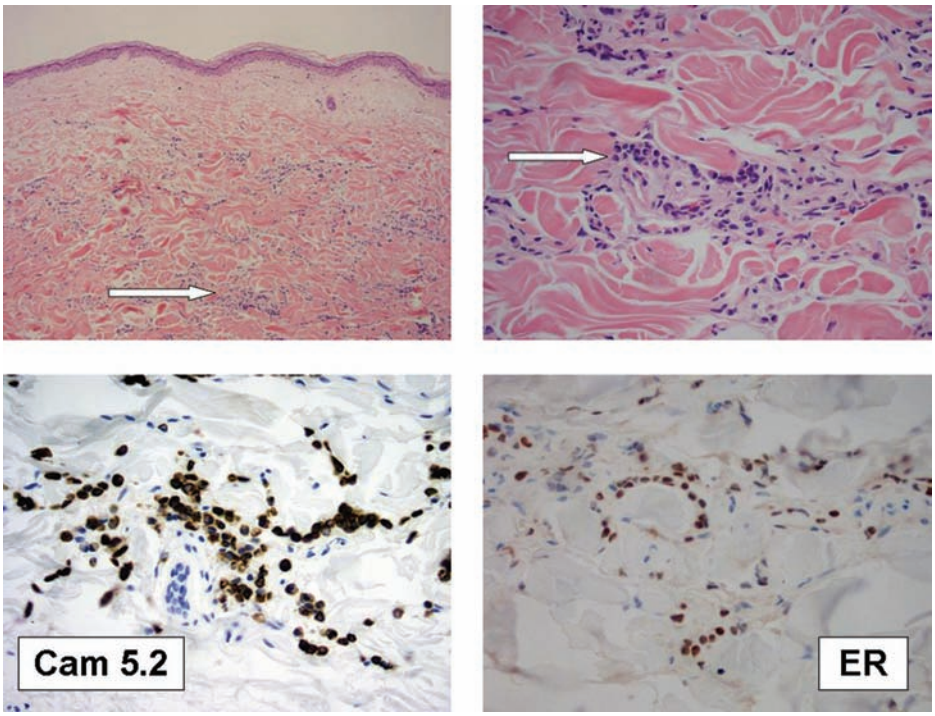

Figure 9 Lobular breast carcinoma. Intradermal interstitial infiltrate of small round blue cells (*arrow*). Tumor cells are positive for Cam 5.2 and ER.
Abbreviation: ER, estrogen receptor.

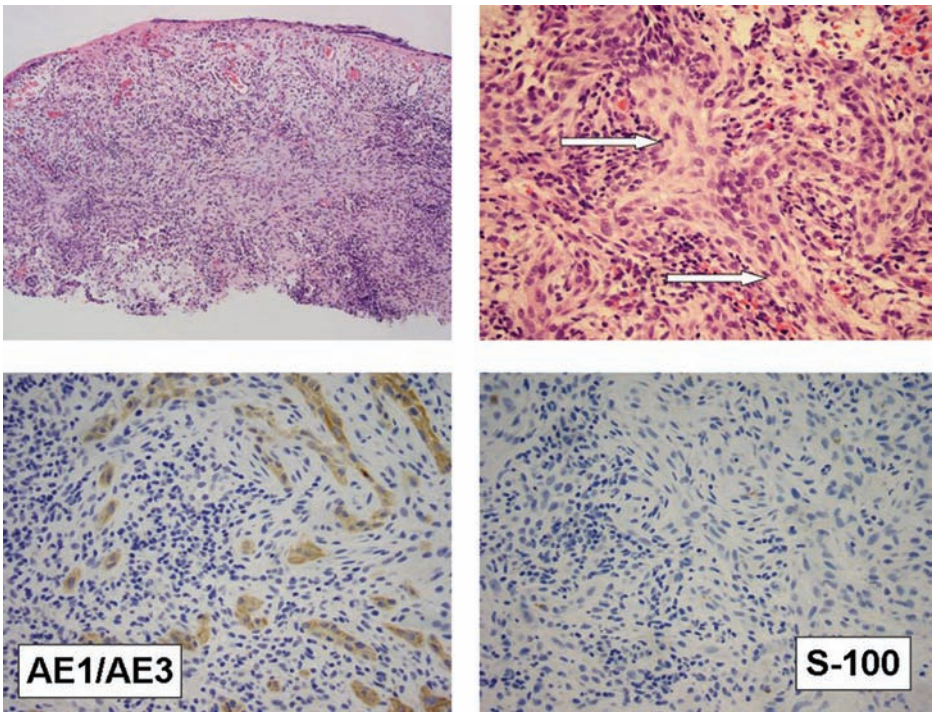

Figure 10 Squamous cell carcinoma. Ulcerated tumor with infiltrating nests and cords of spindle and polygonal tumor cells (*arrows*). Tumor cells are positive for AE1/AE3 and negative for S-100.

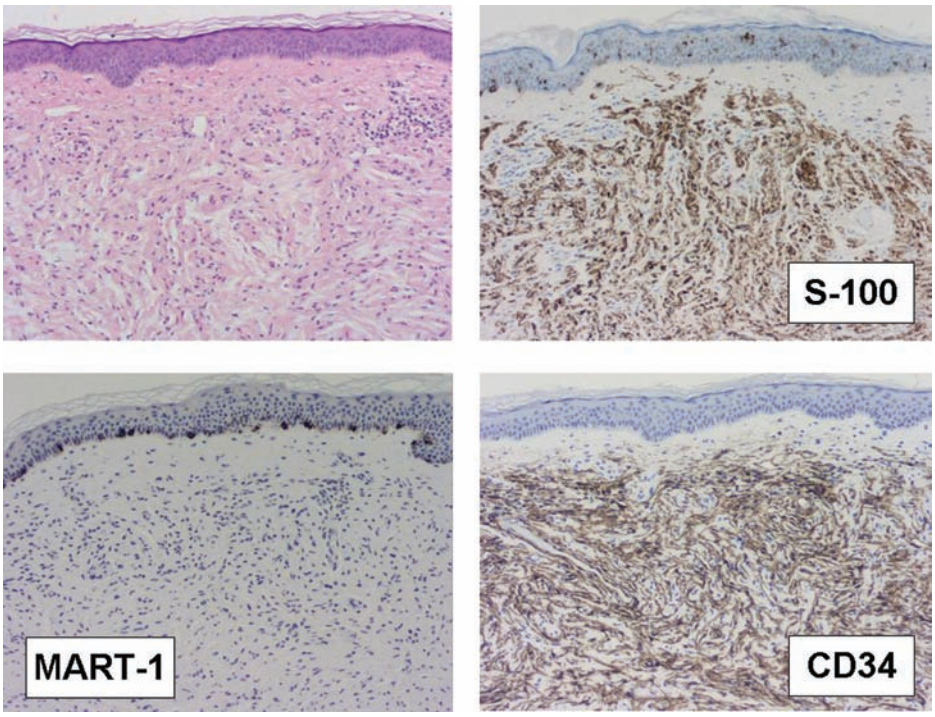

Figure 11 Neurofibroma. Intradermal proliferation of spindle and S-shaped cells in short intersecting fascicles. Spindle cells are positive for S-100 and negative for MART-1. Note reactivity for CD34.

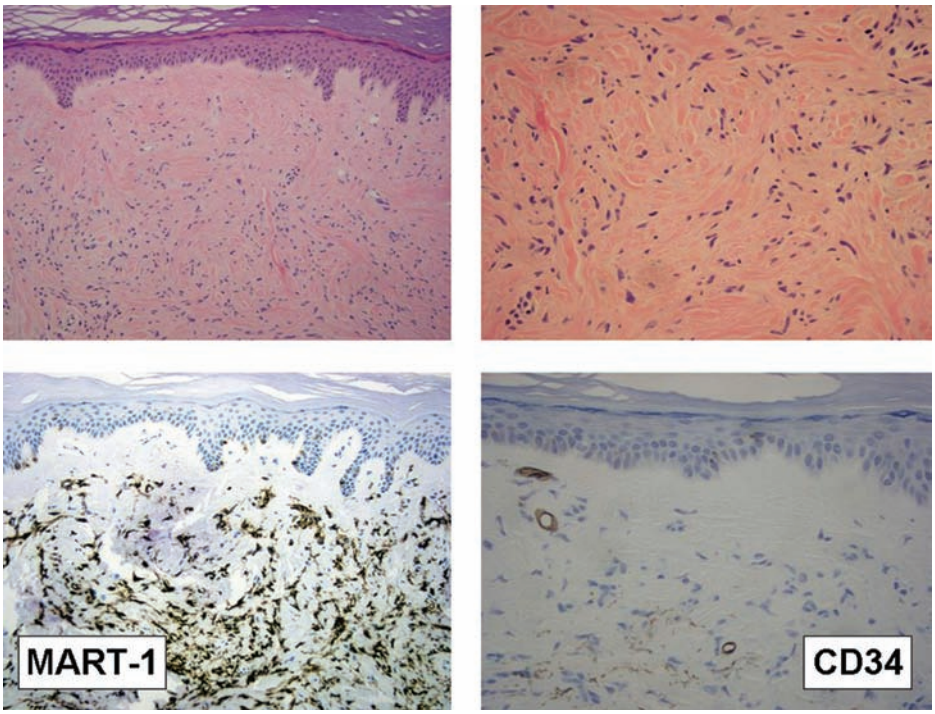

Figure 12 Blue nevus. Proliferation of MART-1 positive and CD34 negative spindle cells within a fibrotic dermis.

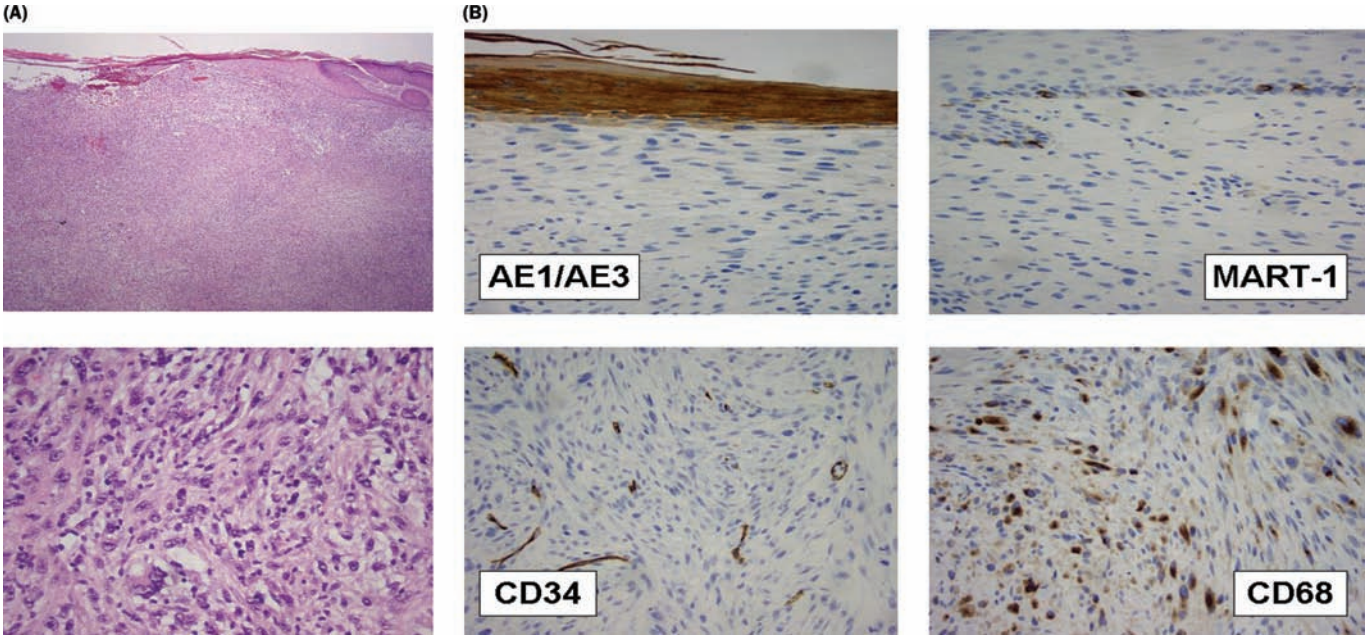

Figure 13 Atypical fibroxanthoma. (**A**) Ulcerated tumor composed of hyperchromatic and pleomorphic, spindle and epithelioid cells with focal giant cell formation. (**B**) Tumor cells are negative for AE1/AE3, MART-1, and CD34, but positive for CD68. *Note*: CD34 outlines intra-tumoral blood vessels (*internal positive control*).

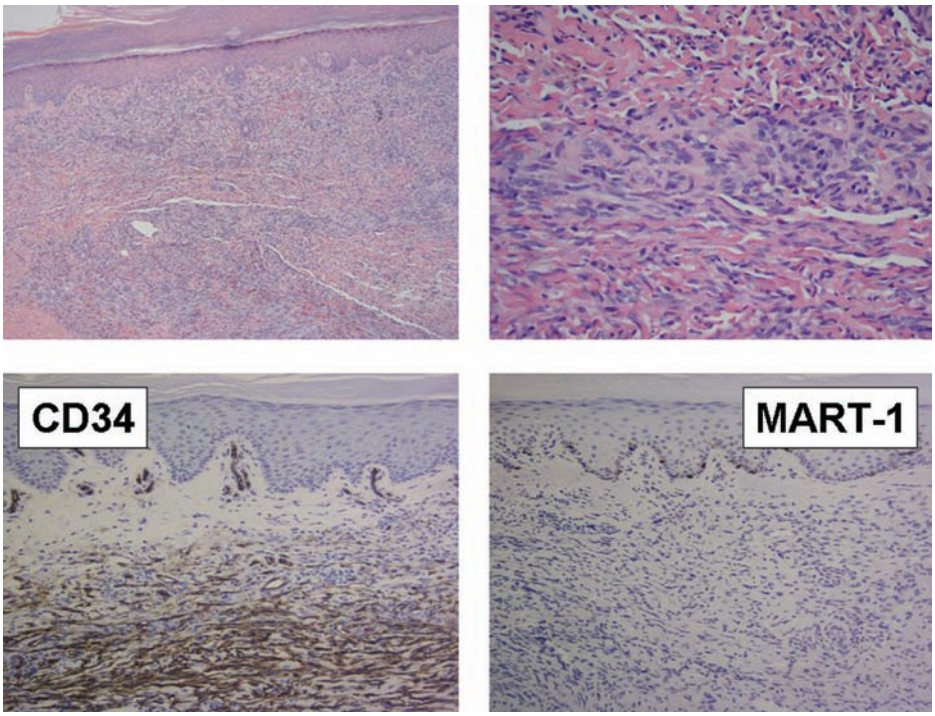

Figure 14 Kaposi's sarcoma. Intradermal tumor composed of spindle cells with slit-like spaces containing erythrocytes. Spindle cells are positive for CD34 (and other vascular markers) and negative for MART-1.

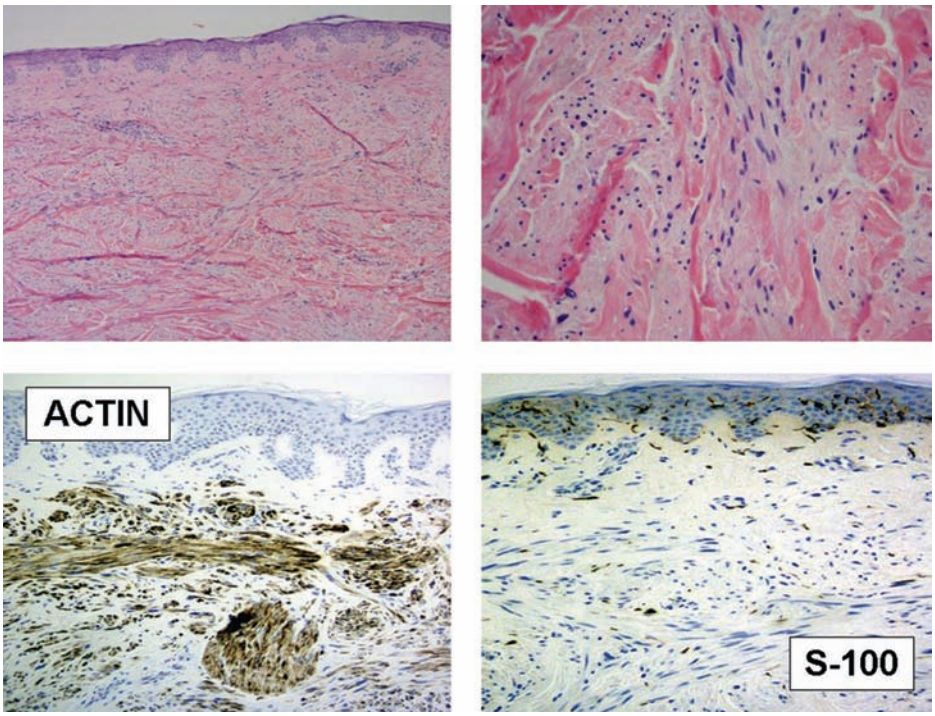

Figure 15 Leiomyoma. Intradermal proliferation of spindle cells in intersecting fascicles. Spindle cells are positive for actin and negative for S-100.

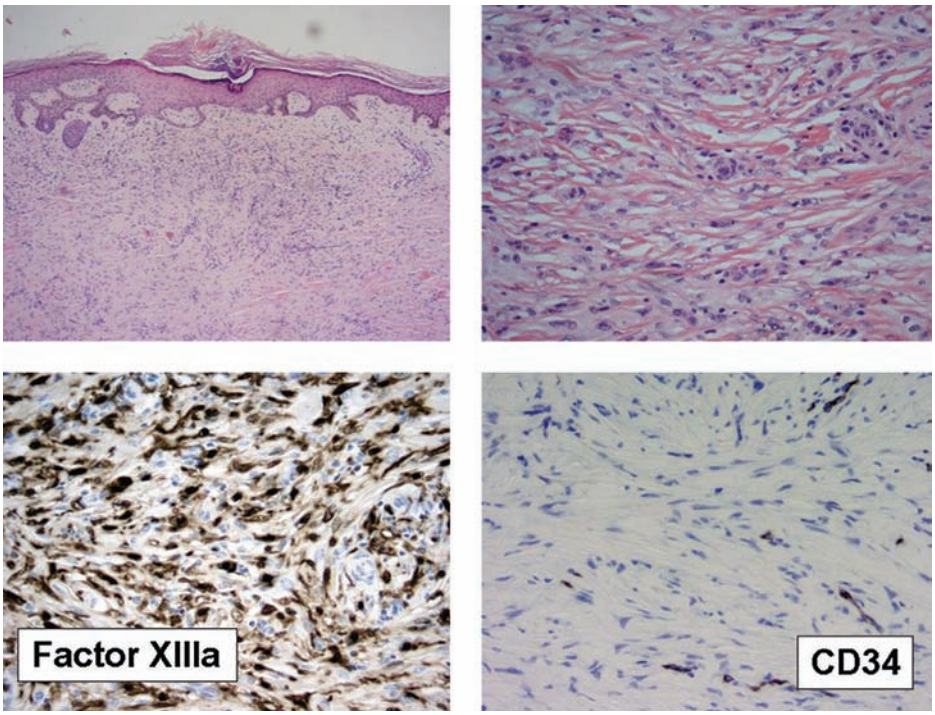

Figure 16 Dermatofibroma. Intradermal spindle cell proliferation with characteristic epidermal hyperplasia and basilar hyperpigmentation. Spindle cells are positive for Factor XIIIa and negative for CD34. CD34 outlines intra-tumoral blood vessels.

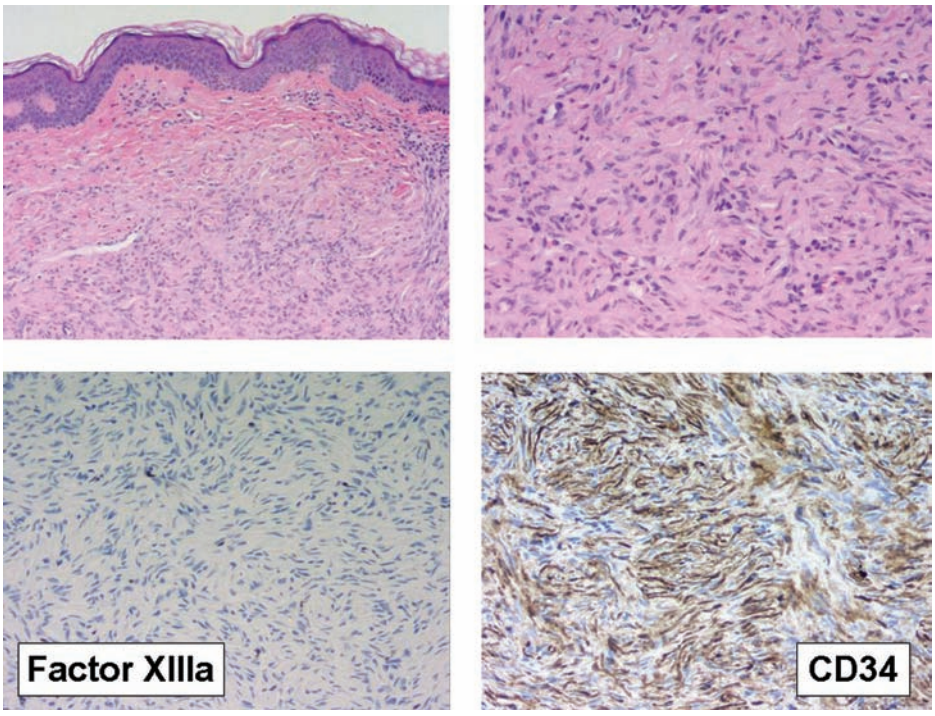

Figure 17 Dermatofibrosarcoma protuberans. Deep dermal tumor composed of spindle cells in a storiform pattern. Tumor cells are positive for CD34 and negative for Factor XIIIa. Factor XIIIa focally outlines background "dermal dendrocytes."

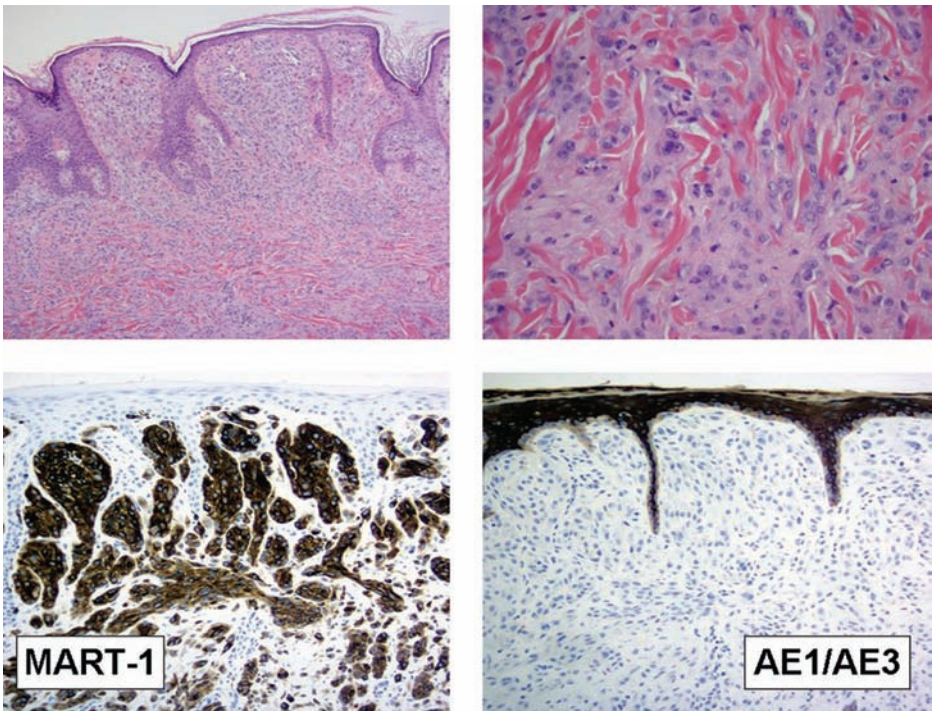

Figure 18 Spitz nevus. Intradermal proliferation of epithelioid cells, which are positive for MART-1 and negative for AE1/AE3.

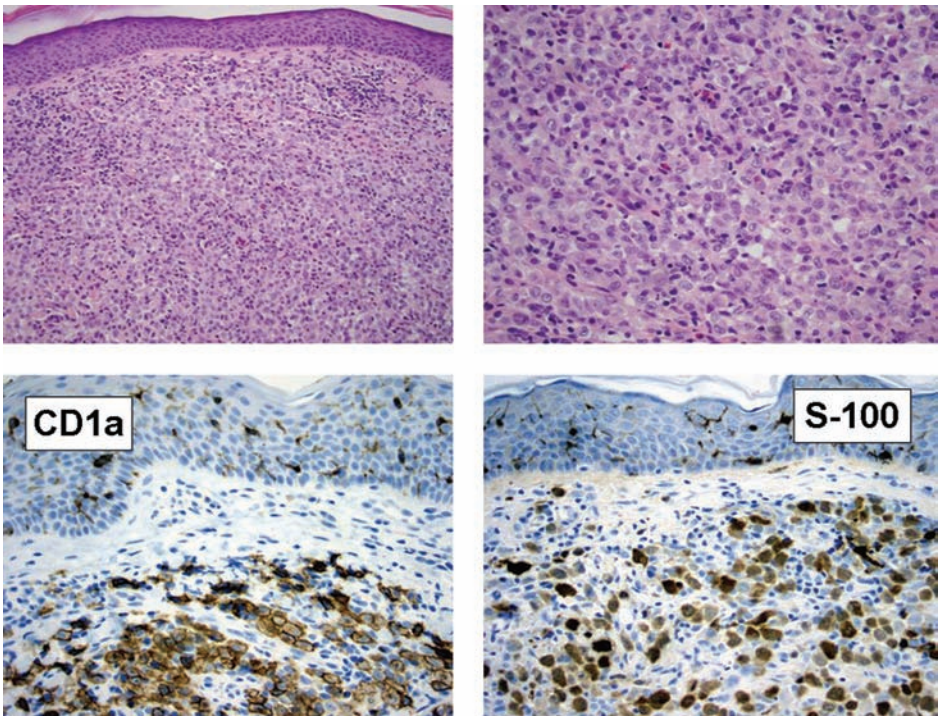

Figure 19 Langerhans cell histiocytosis. Intradermal proliferation of CD1a and S-100 positive epithelioid cells.

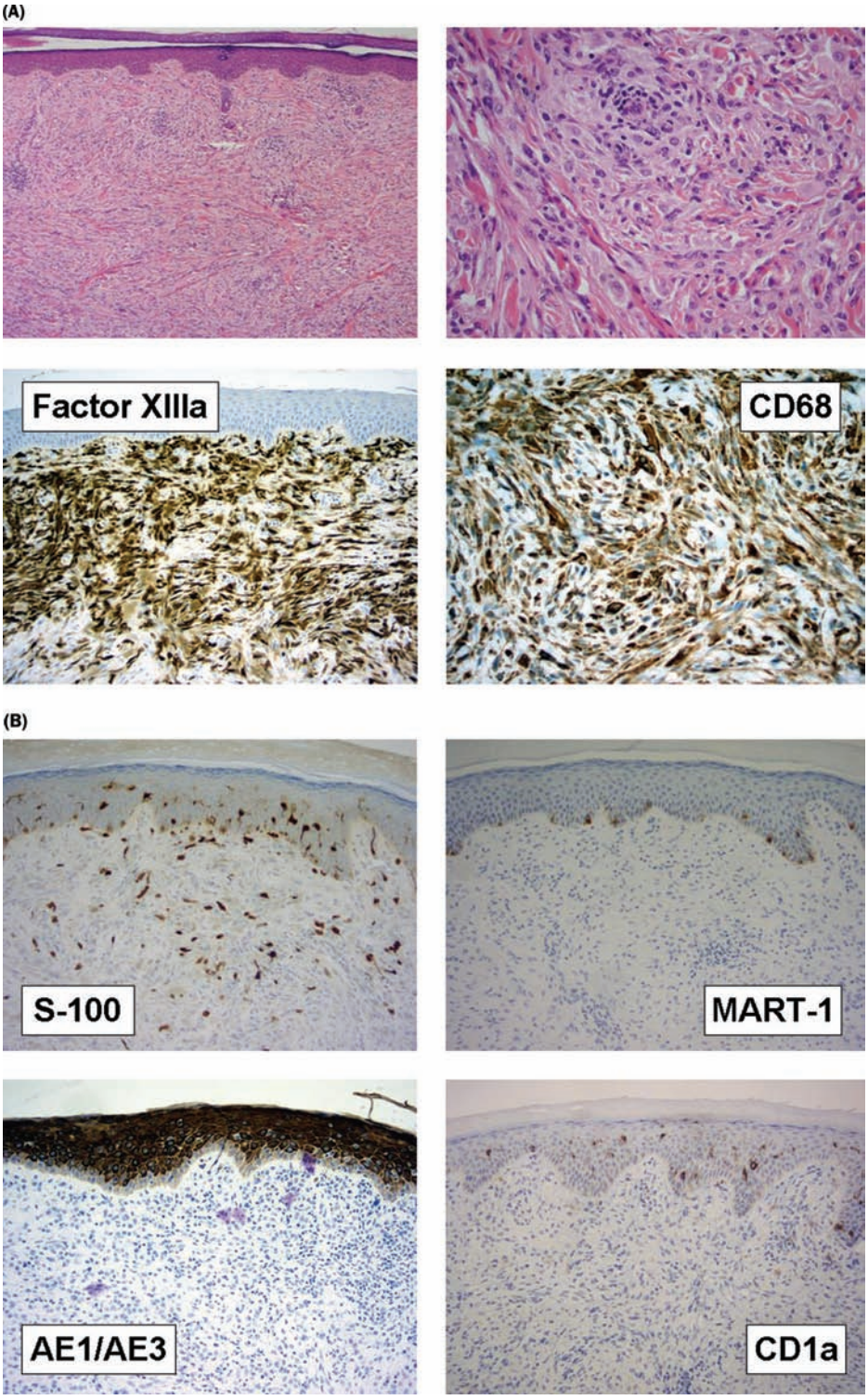

Figure 20 Epithelioid cell histiocytoma. Intradermal proliferation of epithelioid cells. Tumor cells are positive for Factor XIIIa and CD68 (**A**), and negative for S-100, MART-1, AE1/AE3, and CD1a (**B**).

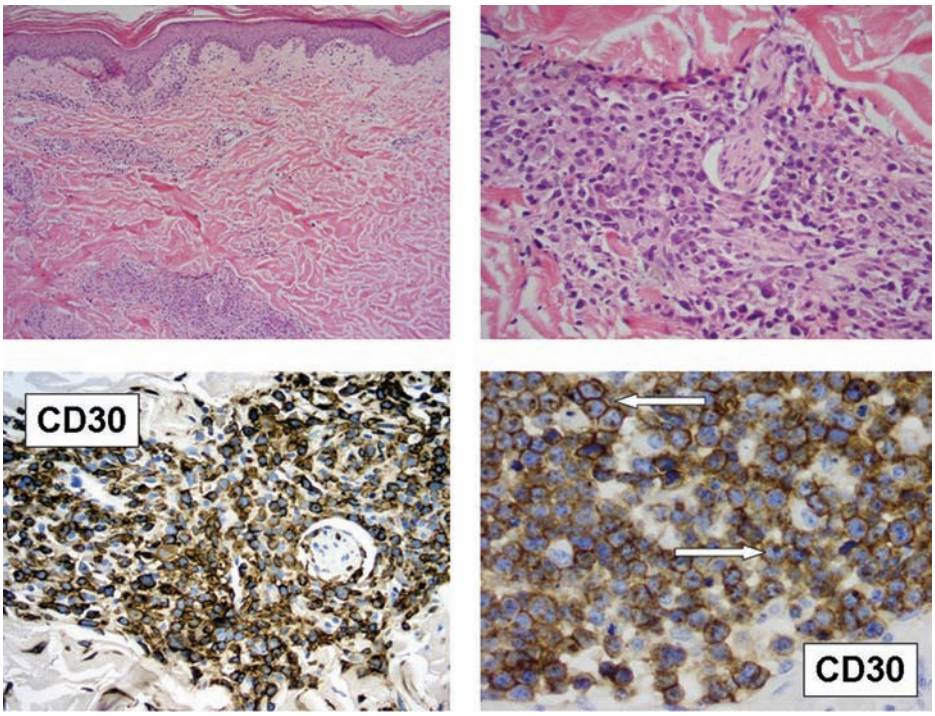

Figure 21 Lymphoma—large cell type. Intradermal proliferation of epithelioid cells. Tumor cells are positive for CD30 in a membraneous and perinuclear dot (*arrow*) pattern.

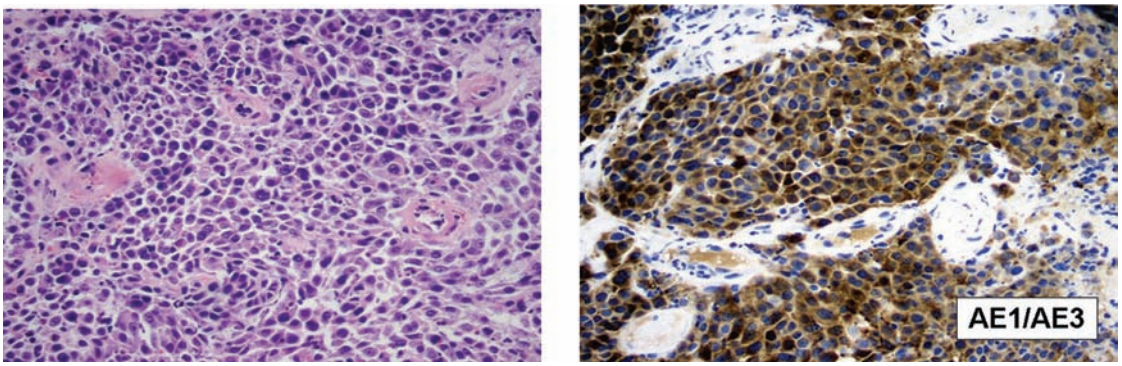

Figure 22 Squamous cell carcinoma (poorly differentiated). Proliferation of atypical epithelioid cells. Tumor cells are positive for AE1/AE3.

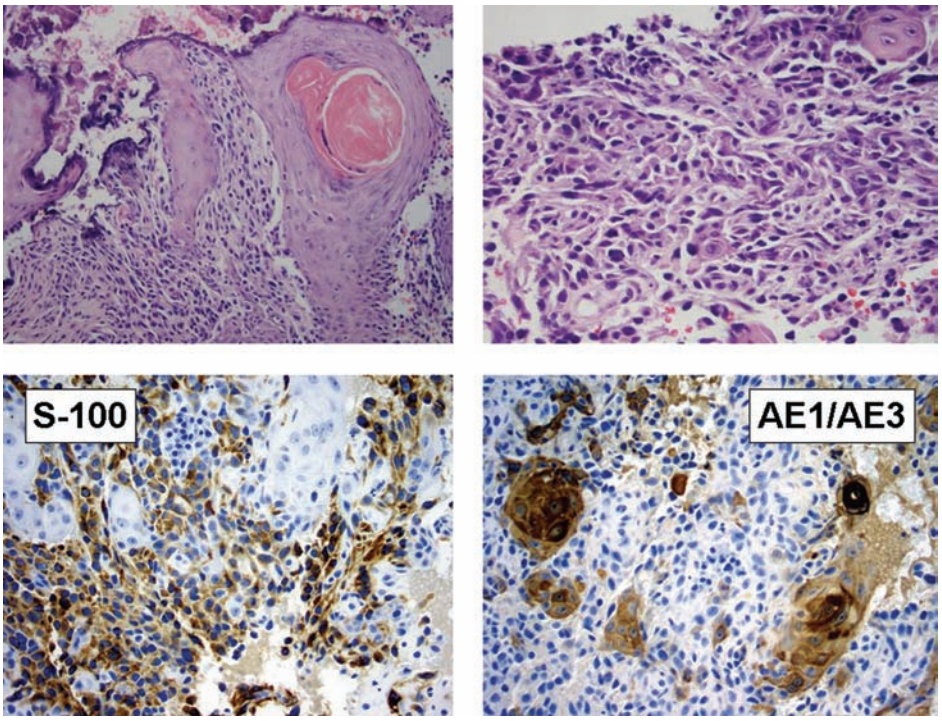

Figure 23 Malignant melanoma. Proliferation of atypical epithelioid cells. Tumor cells are positive for S-100. Adjacent epidermis with pseudo-carcinomatous hyperplasia is positive for AE1/AE3.

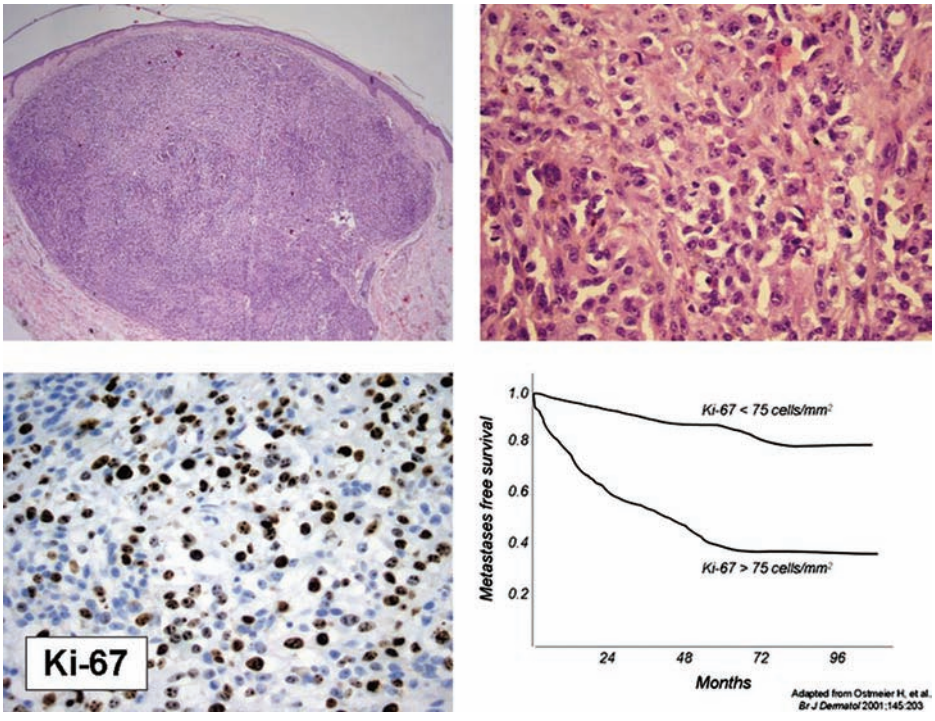

Figure 24 Tumor biology. Nodular malignant melanoma with Ki-67 immunohistochemical staining. Increased Ki-67 positivity (representing increased cellular proliferation) correlates with poorer prognosis.

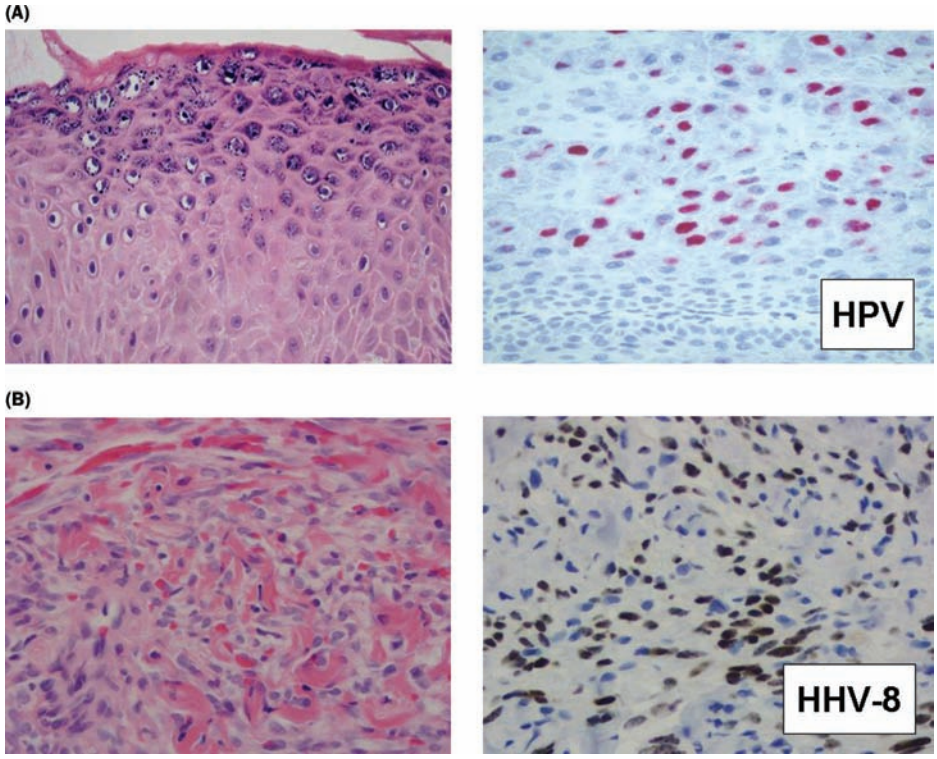

Figure 25 Infections. (**A**) Human papillomavirus infection in verruca vulgaris. (**B**) HHV-8 infection in Kaposi's sarcoma. *Abbreviations*: HHV, human herpesvirus; HPV, human papillomavirus.

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COLOR ATLAS OF DERMATOPATHOLOGY

DERMATOLOGY: CLINICAL & BASIC SCIENCE SERIES/32

Series Editor

Howard I. Maibach

about the book . . .

This outstanding dermatopathology atlas emphasizes the correlation of pathological findings with clinical presentations and presents a reader-friendly approach to the diagnosis and interpretation of skin biopsy results. With an abundance of color clinical and histologic photographs, and descriptions of numerous dermatological diseases and conditions, this source is a must-have for anyone preparing for dermatology or pathology board exams, or for those desiring a strong understanding of the clinical or pathological presentations of disease.

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about the editor . . .

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