The Bethesda System for Reporting Thyroid Cytopathology

Definitions, Criteria, and Explanatory Notes

Second Edition

Syed Z. Ali
Edmund S. Cibas
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Preface to the First Edition

This atlas is the offspring of the "The National Cancer Institute (NCI) Thyroid Fine Needle Aspiration (FNA) State of the Science Conference," hosted by the NCI and organized by Dr. Andrea Abati. Preparations for the conference began 18 months earlier with the designation of a steering committee and the establishment of a dedicated, permanent web site. The meeting took place on October 22 and 23, 2007, in Bethesda, Maryland, and was co-moderated by Susan J. Mandel and Edmund S. Cibas.

The discussions and conclusions regarding terminology and morphologic criteria from the meeting were summarized in publications by Baloch et al. [1, 2] and form the framework for this atlas. The atlas is organized by the general categories of "Nondiagnostic," "Benign," "Follicular Neoplasm/Suspicious for a Follicular Neoplasm," "Suspicious for Malignancy," and "Malignant," and it includes the definitions and morphologic criteria of these categories as set forth by Baloch et al. The majority of the conference participants also agreed on a category of "undetermined significance," which is incorporated in this atlas (Chap. 4).

It is critical that the cytopathologist communicate thyroid FNA interpretations to the referring physician in terms that are succinct, unambiguous, and helpful clinically. We recognize that the terminology used here is a flexible framework that can be modified by individual laboratories to meet the needs of their providers and the patients they serve. Historically, the terminology for thyroid FNA has varied markedly from one laboratory to another, creating confusion in some instances and hindering the sharing of data among multiple institutions. It is the hope of all the contributors to this atlas that it will be a valuable supplement to the terminology committee's extraordinary summary document.

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Preface to the Second Edition

The second edition of this atlas was inspired by new developments in the field of thyroid cytopathology since the publication of the first edition 8 years ago. These include revised guidelines for the management of patients with thyroid nodules [1], the introduction of molecular testing as an adjunct to cytopathologic examination, and the reclassification of the noninvasive follicular variant of papillary thyroid carcinoma as noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP)[2]. Much of the groundwork for this atlas was laid by a symposium entitled "The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC): Past, Present, and Future" at the 2016 International Congress of Cytology in Yokohama, Japan. Preparations for the symposium began 12 months earlier with the designation of a steering group and the appointment of an international panel composed of 16 cytopathologists and an endocrinologist, whose task was to review and summarize the published literature in English since the introduction of TBSRTC.

The symposium, moderated by Drs. Syed Ali and Philippe Vielh, took place on May 30, 2016, and the discussions and recommendations from the symposium have been summarized in a publication by Pusztaszeri et al. [3]. Based on the panel's recommendation, the six original general categories ("Nondiagnostic," "Benign," "Atypia of Undetermined Significance/Follicular Lesion of Undetermined Significance," "Follicular Neoplasm/Suspicious for a Follicular Neoplasm," "Suspicious for Malignancy," and "Malignant") have been retained in this second edition. The chapters devoted to these categories now have expanded and refined definitions, morphologic criteria, and explanatory notes.

It's gratifying to see that TBSRTC has been widely adopted in the USA and worldwide and endorsed by the American Thyroid Association [1]. It has gone far toward improving communication between cytopathologists and their clinical colleagues and has provided a uniform template for the sharing of data among investigators. It is our hope that it will continue to stimulate interest in the improvement of thyroid cytopathologic diagnosis and the betterment of patients with thyroid nodular disease.

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Overview of Diagnostic Terminology and Reporting

1

Zubair W. Baloch, David S. Cooper, Hossein Gharib, and Erik K. Alexander

With its inception, the Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) established a uniform, tiered reporting system for thyroid FNA specimens. Using TBSRTC, the cytopathologist can communicate thyroid FNA interpretations to the referring physician in terms that are succinct, unambiguous, and clinically useful [1, 2].

Since the widespread acceptance of TBSRTC in clinical practice, questions have arisen over the proper use of the diagnostic categories, the recommended management (e.g., repeat FNA vs. surgery), and the implied risks of malignancy. With regard to any revisions to the risks of malignancy of the categories, the following factors were taken into consideration with the second edition: patient demographics, nodule selection criteria, variation in cytopathologist experience and application of cytomorphologic diagnostic criteria, the overestimation of the risk of malignancy for some diagnostic categories if based only on cases that have undergone thyroid surgery [3], publication bias [3], and the newly described entity of noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) [4], formerly known as "encapsulated follicular variant of papillary thyroid carcinoma."

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Format of the Report

For clarity of communication, each thyroid FNA report should begin with a general diagnostic category. TBSRTC diagnostic categories are shown in Table 1.1. For three of the six categories, TBSRTC offers a choice of two different names. A laboratory should choose the one it prefers and use it exclusively for that category. Synonymous terms (e.g., AUS and FLUS) should not be used to denote two distinct interpretations.

Each category has an implied cancer risk, which ranges from 0 to 3% for the "benign" category to virtually 100% for the "malignant" category. As a function of these risk associations, each category is linked to evidence-based clinical management guidelines [5], as shown in Table 1.2, and discussed in more detail in the chapters that follow.

Table 1.1 The Bethesda System for Reporting Thyroid Cytopathology: diagnostic categories

I.	Nondiagnostic or Unsatisfactory[a]
	Cyst fluid only
	Virtually acellular specimen
	Other (obscuring blood, clotting artifact, drying artifact, etc.)
II.	Benign
	Consistent with a benign follicular nodule (includes adenomatoid nodule, colloid nodule, etc.)
	Consistent with chronic lymphocytic (Hashimoto) thyroiditis in the proper clinical context
	Consistent with granulomatous (subacute) thyroiditis
	Other
III.	Atypia of Undetermined Significance or Follicular Lesion of Undetermined Significance[a]
IV.	Follicular Neoplasm or Suspicious for a Follicular Neoplasm[a]
	Specify if oncocytic (Hürthle cell) type
V.	Suspicious for Malignancy
	Suspicious for papillary thyroid carcinoma
	Suspicious for medullary thyroid carcinoma
	Suspicious for metastatic carcinoma
	Suspicious for lymphoma
	Other
VI.	Malignant
	Papillary thyroid carcinoma
	Poorly differentiated carcinoma
	Medullary thyroid carcinoma
	Undifferentiated (anaplastic) carcinoma
	Squamous cell carcinoma
	Carcinoma with mixed features (specify)
	Metastatic malignancy
	Non-Hodgkin lymphoma
	Other

[a]The two terms for these categories are synonymous. A laboratory should use only one of these for reporting results.

Table 1.2 The Bethesda System for Reporting Thyroid Cytopathology: implied risk of malignancy and recommended clinical management

Diagnostic category	Risk of malignancy (%)	Usual management[a]
Nondiagnostic or Unsatisfactory	5–10[b]	Repeat FNA with ultrasound guidance
Benign	0–3[c]	Clinical and sonographic follow-up
Atypia of Undetermined Significance or Follicular Lesion of Undetermined Significance	~10–30[d]	Repeat FNA, molecular testing, or lobectomy
Follicular Neoplasm or Suspicious for a Follicular Neoplasm[e]	25–40[f]	Molecular testing, lobectomy
Suspicious for Malignancy	50–75	Near-total thyroidectomy or lobectomy[g,h]
Malignant	97–99	Near-total thyroidectomy or lobectomy[h]

[a]Actual management may depend on other factors (e.g., clinical, sonographic) besides the FNA interpretation.
[b]The risk of malignancy varies with the type/structure of the nodule, i.e., solid vs. complex vs. ≥50% cystic. Nondiagnostic aspirates from solid nodules are associated with a higher risk of malignancy as compared to those showing ≥50% cystic change and low-risk ultrasonographic features. See Chap. 2 for discussion [6, 7, 14]
[c]Estimate extrapolated from studies showing correlation between biopsied nodule and surgical pathology follow-up [8–11]
[d]Estimates extrapolated from histopathologic data from large case cohorts (including repeat atypical FNAs) and meta-analysis of the post 2007 literature [8, 12–15]
[e]Includes cases of follicular neoplasm with oncocytic features (aka Hürthle cell neoplasm)
[f]Estimates extrapolated from histopathologic data from large case cohorts and meta-analysis of the post 2007 literature (cited above and Ref. [16, 17])
[g]Some studies have recommended molecular analysis to assess the type of surgical procedure (lobectomy vs. total thyroidectomy)
[h]In the case of "suspicious for metastatic tumor" or a "malignant" interpretation indicating metastatic tumor rather than a primary thyroid malignancy, surgery may not be indicated

In the first edition of TBSRTC, the implied risk of malignancy for each diagnostic category was calculated and provided as a range based on a review of the literature at that time: 0–3% for benign, ~5–15% for atypia of undetermined significance (AUS) or follicular lesion of undetermined significance (FLUS), 15–30% for follicular neoplasm or suspicious for follicular neoplasm, 60–75% for suspicious for malignancy, and 97–99% for the malignant category [1]. In the second edition, these ranges have been revised, especially for the so-called "indeterminate" categories, representing estimates calculated primarily from studies of large case cohorts and meta-analyses of ultrasound-guided thyroid FNA published after 2007 [6–15]. It is important to note that the traditional method of estimating the risk of malignancy (ROM), which is based on histologic follow-up, i.e., dividing the number of patients with cancer by the total number of patients with surgical follow-up, overestimates the risk of malignancy, particularly for the nondiagnostic, benign, and AUS/FLUS categories, where there is selection bias given the relatively small proportion of nodules that undergo excision. On the other hand, when calculated using the total number of FNA specimens (with and without surgical follow-up) as the denominator, assuming that unresected nodules are benign, the ROM is most certainly

Table 1.3 Anticipated changes in the implied risk of malignancy of TBSRTC diagnostic categories and recommendations for comments due to the surgical pathology diagnosis of "noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP)"

Diagnostic category	Risk of malignancy with NIFTP (%)[a]	Optional note[b]
Nondiagnostic or Unsatisfactory	No significant change	None
Benign	No significant change	None
Atypia of Undetermined Significance or Follicular Lesion of Undetermined Significance	6–18	None
Follicular Neoplasm or Suspicious for a Follicular Neoplasm	10–40	The histopathologic follow-up of cases diagnosed as such includes follicular adenoma, follicular carcinoma, and follicular variant of papillary thyroid carcinoma, including its recently described indolent counterpart NIFTP.
Suspicious for Malignancy	45–60	The cytomorphologic features are suspicious for a follicular variant of papillary thyroid carcinoma and its recently described indolent counterpart NIFTP.
Malignant	94–96	A small proportion of cases (~3–4%) diagnosed as malignant – compatible with papillary thyroid carcinoma – may prove to be NIFTP on histopathologic examination.

[a]Change in the risk of malignancy in TBSRTC due to NIFTP is based on a limited number of retrospective studies [18–21]
[b]Ref. [22, 23]

underestimated. The actual ROM is expected to be in the midrange of the values obtained using these calculations and requires some extrapolation; the best current estimates are depicted in Table 1.2.

The reclassification of some thyroid neoplasms as NIFTP has implications for the ROM [16–20], and this is accounted for in Table 1.3. Comments as shown in Table 1.3 can be included in the report, especially if the cytopathologic features raise the possibility of NIFTP [21]. These features are discussed in more detail in the chapters that follow.

For some of the general diagnostic categories, subcategorization can be informative and is often appropriate; recommended terminology is shown in Table 1.1. Additional descriptive comments (beyond such subcategorization) are optional and left to the discretion of the cytopathologist. Notes and recommendations can be useful, especially due to the introduction of NIFTP terminology (Table 1.3). Some laboratories, for example, may wish to state the risk of malignancy associated with the general category, based on their own cytologic–histologic correlation or that found in the literature (Table 1.2). Sample reports, which we hope will be a useful guide, are provided in the remaining chapters.

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Nondiagnostic/Unsatisfactory

2

Barbara A. Crothers, Michael R. Henry, Pinar Firat, Mary C. Frates, and Esther Diana Rossi

Background

In order to provide useful diagnostic information for clinical management, a fine-needle aspiration (FNA) sample of a thyroid nodule should be representative of the underlying lesion. Real-time ultrasound guidance for thyroid FNA is recommended to confirm needle placement in the nodule. It is worth emphasizing that cellularity/adequacy is dependent not only on the technique of the aspirator but also on the inherent nature of the lesion (e.g., solid vs. cystic). High-quality specimens require proficient collection combined with excellent slide preparation, processing, and staining. In general, the adequacy of a thyroid FNA is defined by both the quantity and quality of the cellular and colloid components.

Historically, the terms "nondiagnostic" and "inadequate/unsatisfactory" have been used interchangeably by many but not all pathologists: some have interpreted the terms to mean different things [1, 2]. An unsatisfactory specimen is always

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nondiagnostic, but some technically satisfactory specimens may also be considered "nondiagnostic," that is, showing nonspecific features not conclusively representative of a particular entity. At the 2007 NCI Thyroid State of the Science conference, the terms "nondiagnostic (ND)" and "unsatisfactory (UNS)" were equated and recommended for the category that conveys an inadequate/insufficient sample [3]. In this application, these terms are synonymous, and the laboratory should choose the one it prefers and use it exclusively for this category. The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) is a flexible framework, however, and can be modified by the laboratory to suit the needs of its providers. Thus, if neither ND nor UNS appeals to providers, a more descriptive term like "insufficient for diagnosis" can be substituted. For the sake of simplicity, ND is used throughout this monograph to convey a sample that does not meet the adequacy criteria outlined below.

An assessment of specimen adequacy is an integral component of a thyroid FNA interpretation because it conveys the degree of certainty with which one can rely on the result. A good criterion of adequacy, when appropriately applied, ensures a low false-negative rate. Whereas the *quality* of a specimen is irrefutably critical to proper interpretation, controversy is introduced when rigid numerical criteria for cell *quantity* are imposed. TBSRTC recommends a minimum number of follicular cells (see "Definition" below), but this is admittedly based on convention: these criteria were developed at the Mayo Clinic and have been in wide use ever since [4].

Definition

A specimen is considered "nondiagnostic" or "unsatisfactory" if it fails to meet the following adequacy criteria.

Criteria for Adequacy

A thyroid FNA sample is considered adequate for evaluation if it contains a minimum of six groups of well-visualized (i.e., well stained, undistorted, and unobstructed) follicular cells, with at least ten cells per group, preferably on a single slide. Exceptions to this requirement apply to the following special circumstances:

1. *Solid nodules with cytologic atypia*. A sample that contains significant cytologic atypia is never considered ND. It is mandatory to report any significant atypia; a minimum number of follicular cells is not required.
2. *Solid nodules with inflammation*. Nodules in patients with lymphocytic (Hashimoto) thyroiditis, thyroid abscess, or granulomatous thyroiditis may contain only numerous inflammatory cells. Such cases are interpreted as benign and not as ND. A minimum number of follicular cells is not required.
3. *Colloid nodules*. Specimens that consist of abundant colloid are considered benign and satisfactory for evaluation. A minimum number of follicular cells is not required if easily identifiable colloid predominates.

Nondiagnostic/Unsatisfactory (Figs. 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, and 2.7)

The following scenarios describe cases considered nondiagnostic:

1. Fewer than six groups of well-preserved, well-stained follicular cell groups with ten cells each (see exceptions above)
2. Poorly prepared, poorly stained, or significantly obscured follicular cells
3. Cyst fluid, with or without histiocytes, and fewer than six groups of ten benign follicular cells (see "Explanatory Notes")

Explanatory Notes

Adequate samples are required to minimize false-negative reports of thyroid lesions [5, 6]. In this regard, the adequacy criteria proposed here have been successful, yielding false-negative rates under 3% (see Chap. 3). Given that 90–95% of ND nodules are benign (see section "Management" below), some have questioned whether TBSRTC criteria for adequacy are too stringent. Lowering the required number of follicular cells would reduce the number of ND interpretations and save many

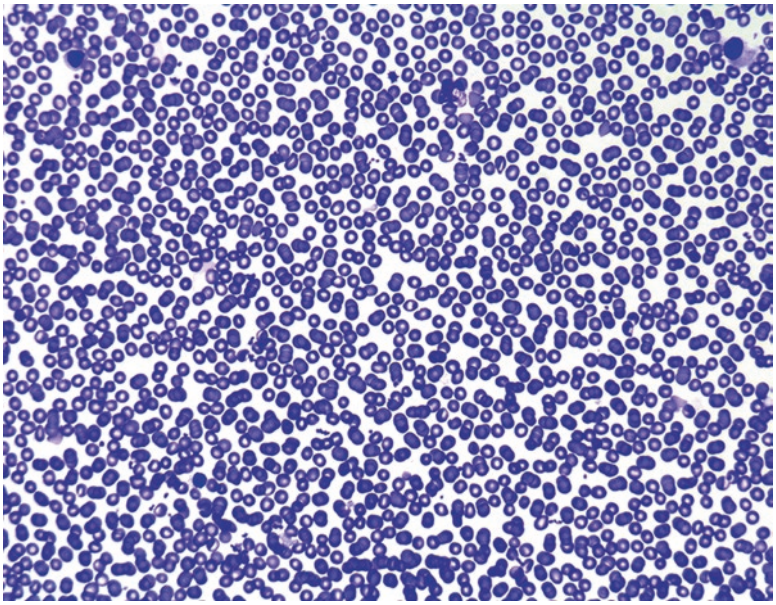

Fig. 2.1 Nondiagnostic. The smear shows abundant red cells, with rare lymphocytes and monocytes. The sample is devoid of thyroid parenchymal elements. Some thyroid nodules are very vascular and with repeated passes yield only blood. Employing a smaller gauge needle (26 or 27 gauge), avoiding negative pressure, and employing a shorter needle dwell time within the nodule may improve cellularity (smear, Diff-Quik stain).

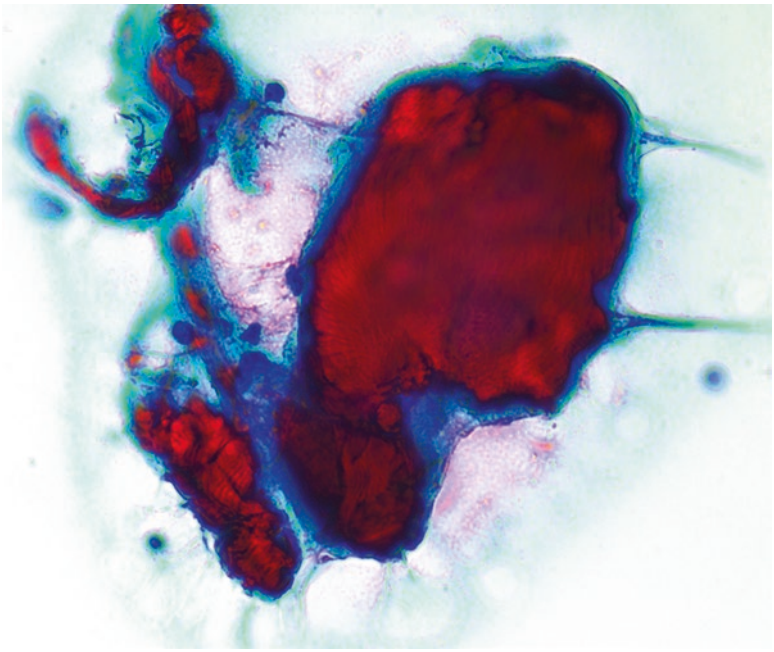

Fig. 2.2 Nondiagnostic. The smear shows a large fragment of skeletal muscle and no native thyroid tissue. This may occur when the needle traverses through the neck muscles. It is important not to confuse skeletal muscle with inspissated colloid (notice the cross striations in the muscle fragment, best seen at 7 o'clock) (smear, Papanicolaou stain).

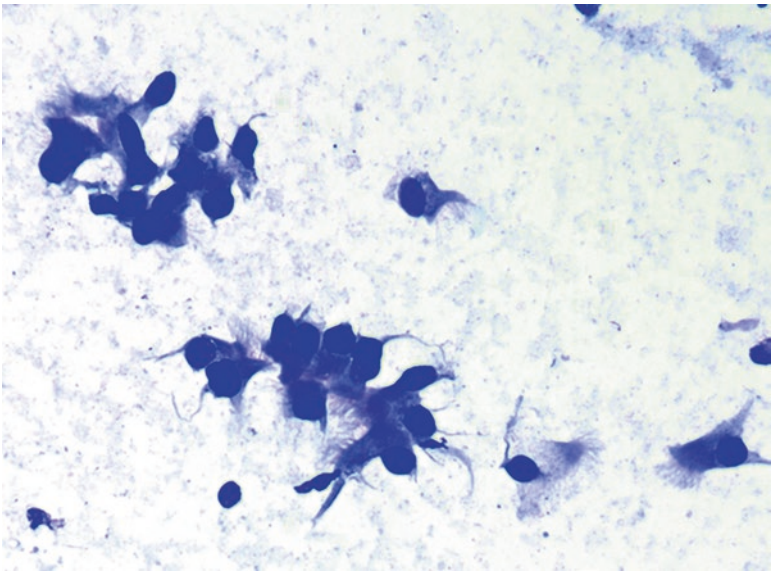

Fig. 2.3 Nondiagnostic. This FNA yielded ciliated respiratory epithelium from the trachea. Accidental puncture of the tracheal lumen is uncommon and typically happens in lesions of the thyroid isthmus. Such cases should be carefully evaluated for adequacy since they typically show only rare follicular epithelium (smear, Diff-Quik stain).

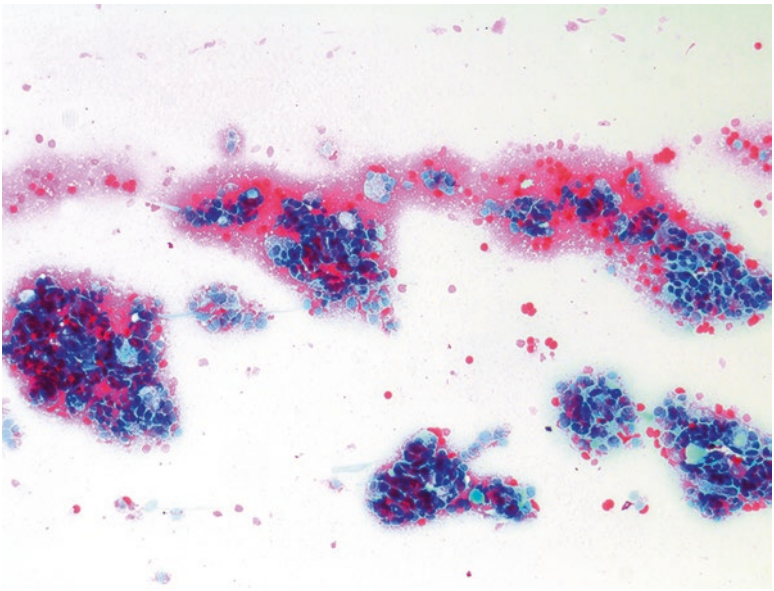

Fig. 2.4 Nondiagnostic. Extensive air-drying artifact in this alcohol-fixed smear limits cytologic interpretation. Such cases should be carefully evaluated for adequacy and are best managed by a repeat FNA with rapid wet fixation. Liquid-based cytology resolves such issues and may be considered if air-drying artifact is a repeated problem (smear, Papanicolaou stain).

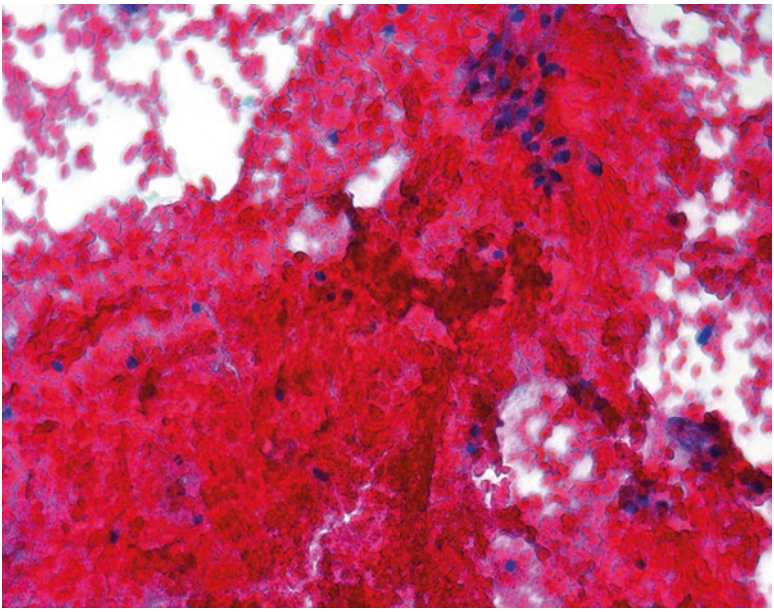

Fig. 2.5 Nondiagnostic. Extensive obscuring blood hinders the evaluation of the follicular cells (smear, Papanicolaou stain).

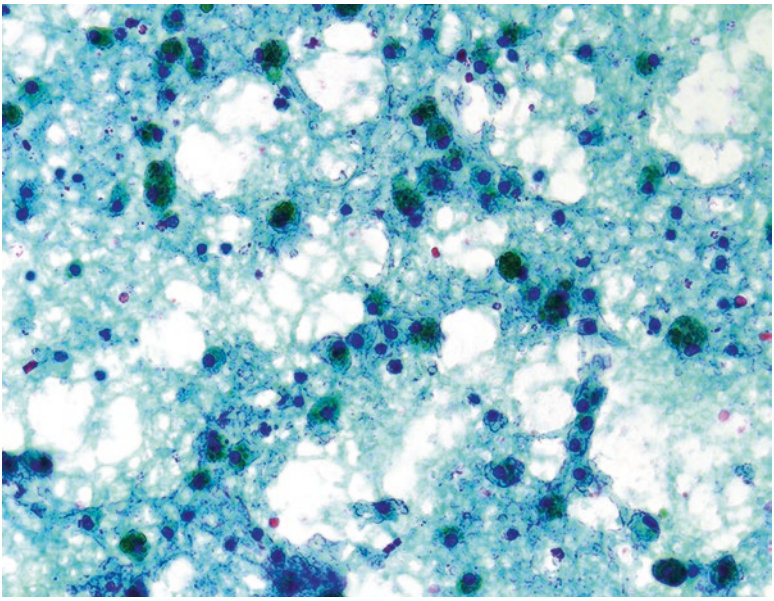

Fig. 2.6 Nondiagnostic (cyst fluid only). Abundant hemosiderin-laden macrophages and degenerated cyst fluid contents. Macrophages do not count toward specimen adequacy. Such cases, when devoid of significant background colloid, are interpreted as nondiagnostic (smear, Papanicolaou stain).

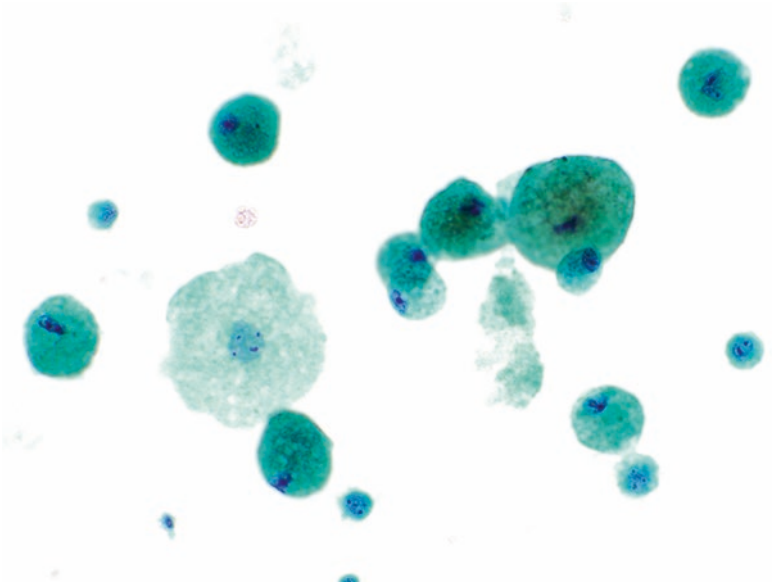

Fig. 2.7 Nondiagnostic (cyst fluid only). Macrophages are typically noncohesive, with abundant cytoplasm that often contains golden brown hemosiderin pigment with the Papanicolaou stain (SurePath preparation, Papanicolaou stain) (Case courtesy of Douglas R. Schneider, MD, Department of Pathology, Steward St. Elizabeth's Medical Center, Boston, MA, USA).

patients the need for a repeat FNA. Preliminary data suggest that requiring a smaller number of follicular cells would significantly reduce ND interpretations without significantly impacting the false-negative rate [7, 8]. There is yet no consensus on a lower number, however, and therefore the criteria have been retained, with the understanding that this is an evolving area that would benefit from more evidence.

Recommendations for adequacy generally apply only to the quantity of follicular cells and exclude consideration of macrophages, lymphocytes, and other nonmalignant cellular components [9, 10]. The ability to obtain follicular cells by FNA is dependent, in part, upon the nature of the lesion. The number of follicular cells necessary for a diagnosis is contingent upon the lesion aspirated because some lesions, such as benign cysts, do not yield many follicular cells.

Thyroid cancers are predominantly solid. Solid nodules and partially cystic nodules with cytologic atypia should always be considered adequate and reported as abnormal ("atypia/follicular lesion of undetermined significance," "suspicious for malignancy," etc., depending on the findings), with a comment describing any limiting factor(s) such as scant cellularity [11]. Follicular cells are not always present in aspirates of inflammatory lesions such as lymphocytic thyroiditis, thyroid abscesses, or granulomatous thyroiditis. Therefore, there is no minimum requirement for a follicular component when inflammation predominates. The presence of abundant colloid (as opposed to serum; Figs. 2.8 and 2.9) reliably identifies most benign processes despite scant follicular cells [12]. One group of follicular cells with features sufficient for the diagnosis of

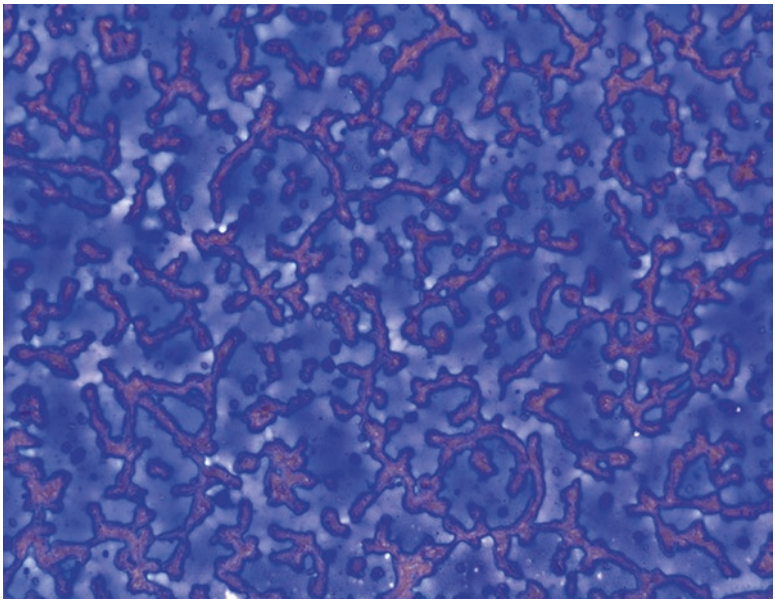

Fig. 2.8 Benign (satisfactory thyroid FNA). Abundant thin watery colloid coats the smear in this case of a benign follicular nodule ("colloid nodule"). Aspirates with large amounts of colloid are considered adequate for interpretation even when they contain less the six groups of follicular cells (smear Diff-Quik stain).

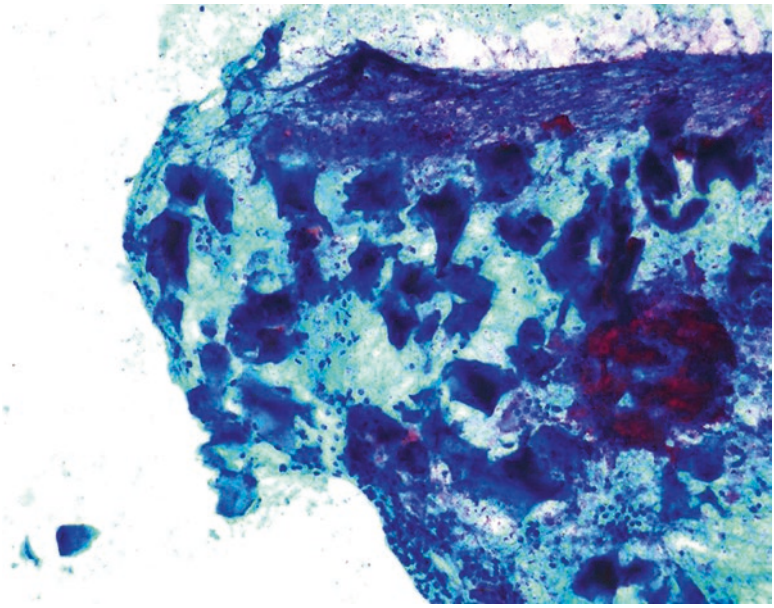

Fig. 2.9 Benign (satisfactory thyroid FNA). There is abundant dense colloid but only scant follicular cells (smear, Papanicolaou stain).

papillary thyroid carcinoma may constitute an adequate specimen in the proper clinical setting and should not be considered nondiagnostic despite scant cellularity [13, 14].

Cyst fluid may yield only macrophages, but the risk of malignancy is low for these lesions if they are simple and under 3 cm [9, 11, 15, 16]. The cytopathologist is not always privy to clinical or sonographic information, however, and in isolation, the possibility of a cystic papillary thyroid carcinoma cannot be excluded if a sample consists entirely of fluid and histiocytes. Younger patients with only cystic fluid have been shown to have a slightly higher risk of malignancy, primarily papillary carcinoma [16–18]. For this reason, these cases are reported as ND followed by the subcategory "cyst fluid only" (see "Sample Report 2"). In the proper clinical setting (e.g., ultrasound evidence of a simple, unilocular cyst), these specimens may be considered clinically adequate, even though they are reported as ND [9, 17, 19].

Occasionally, an adjacent anatomic site is aspirated, such as the trachea (Fig. 2.3) or sternocleidomastoid muscle (Fig. 2.2), yielding only nonthyroidal tissue. Such cases are ND.

Ultrasound gel must be wiped from the skin surface before needle insertion. If this is not done, the gel can significantly obscure or crowd out the cellular component, whether the sample is prepared by smearing or liquid-based methods (Fig. 2.10).

There does not appear to be any difference in specimen adequacy using follicular cells in liquid-based preparations (LBP) as opposed to smears, but an additional LBP slide may decrease the number of inadequate results [20]. Preliminary data suggest that FNAs from nodules with certain ultrasound features, such as unilocular cysts

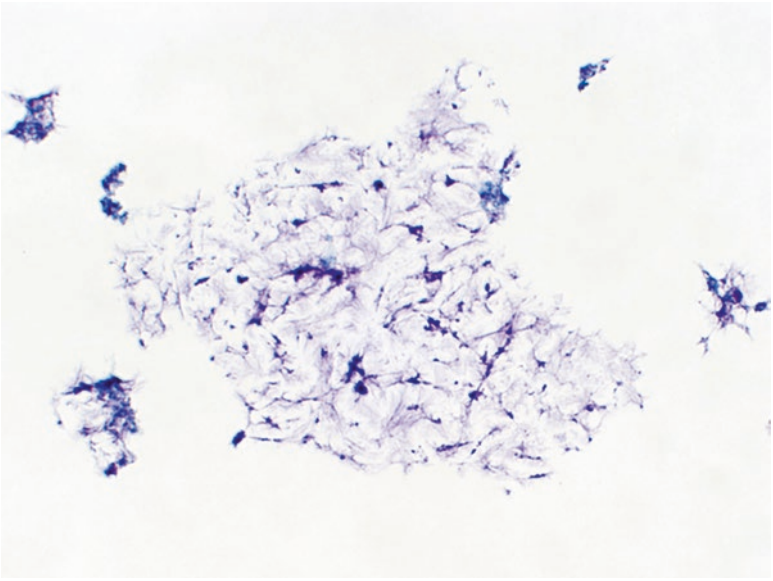

Fig. 2.10 Ultrasound gel. Ultrasound gel is recognized by its charateristic purple color with the Papanicolaou stain. It often has a granular texture and, with liquid-based preprations, a weblike structure. When abundant, it can contribute to a "nondiagnostic" interpretation (ThinPrep, Papanicolaou stain).

with or without small mural nodules, may be adequate with fewer total follicular cells provided they are not Hürthle cells or atypical [7].

The frequency of ND interpretations varies notably from laboratory to laboratory (range, 3–34%) [21, 22].

In TBSRTC, unless a sample is interpreted as ND, it is considered satisfactory for evaluation.

Management

The risk of malignancy for ND nodules is difficult to calculate precisely, because most ND nodules are not resected. Among surgically excised nodules initially reported as ND, the malignancy rate is 9–32% [23]. Surgically resected nodules, however, represent a selected subset of nodules that were either repeatedly ND or had worrisome clinical/sonographic features or both. Thus, surgically resected ND nodules overrepresent malignancies compared to the entire cohort of ND nodules. A reasonable extrapolation of the overall risk of malignancy for lesions in the ND category is 5–10% [24].

Nodules with an initial ND result should be re-aspirated unless the nodule is purely cystic [24–26]. The likelihood of a ND result increases with increasing cystic content in nodules, and high cystic content of nodules is an independent predictor of

a nondiagnostic cytology result [27]. Although it had been customary to wait several months before repeating an FNA to allow for resolution of biopsy-induced inflammation and potentially confounding atypia, there is little evidence to support such a restriction; intervals shorter than 3 months do not seem to increase the frequency of atypical results [28, 29]. Ultrasound guidance with immediate on-site adequacy evaluation is preferred for repeat aspirations after an initial ND specimen, especially for solid nodules [24]. In the absence of on-site evaluation for adequacy, obtaining a minimum of three separate samples of the nodule can reduce the rate of unsatisfactory specimens [22]. Performing a cell block from the residual LBP sample can convert some initially ND LBP FNAs into a satisfactory sample [30]. Repeating the FNA results in a diagnostic interpretation in up to 60–80% of cases, primarily in lesions with a smaller cystic component [24, 25, 31, 32]. Most nodules with a ND interpretation prove to be benign [13, 33]. After two successive ND/UNS specimens, close clinical and sonographic follow-up or surgery should be considered, depending upon the clinical findings. Because the risk of malignancy in cystic lesions is low, re-aspiration of most cystic nodules with an initial ND result should be performed only if the ultrasound findings are suspicious.

Sample Reports

Example 1 (Solid Nodule)

NONDIAGNOSTIC.

Specimen processed and examined, but nondiagnostic due to insufficient cellularity.

Note: A repeat aspiration should be considered if clinically indicated.

Example 2 (Cystic Lesion)

NONDIAGNOSTIC.

Cyst fluid only (see Note).

Specimen processed and examined, but nondiagnostic because it consists almost exclusively of histiocytes; interpretation is limited by insufficient follicular cells and/or colloid.

Note: Recommend correlation with cyst size and complexity on ultrasound to assist with further management of the lesion.

Example 3

UNSATISFACTORY.

Specimen processed and examined, but unsatisfactory due to poor fixation and preservation.

Note: A repeat aspiration should be considered if clinically indicated.

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Benign

3

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Thyroid fine needle aspiration (FNA) derives much of its clinical value from its ability to reliably identify benign thyroid nodules, thus sparing many patients with nodular thyroid disease unnecessary surgery. Because most thyroid nodules are benign, a benign result is the most common FNA interpretation (approximately 60–70% of all cases) [1, 2].

To report benign thyroid cytopathology results, the term "Benign" is preferred over other terms such as "Negative for malignancy" and "Non-neoplastic" [3, 4]. Benign cytopathology is associated with a very low risk of malignancy, and patients are usually followed conservatively with periodic clinical and radiologic examinations [2, 5, 6]. Benign results are further sub-classified as benign follicular nodule, thyroiditis, or other less common entities. Nodular goiter (NG) is the most commonly sampled lesion by FNA, and chronic lymphocytic or Hashimoto thyroiditis is the most commonly encountered form of thyroiditis.

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Benign Follicular Nodule

Background

Benign follicular nodule (BFN) is the most commonly encountered entity in thyroid cytopathology and encompasses a group of benign lesions with similar cytologic features that are classified histologically as nodular hyperplasia in nodular goiter (NG), hyperplastic (adenomatoid) nodules, colloid nodules, nodules in Graves' disease, and an uncommon subset of follicular adenomas composed predominantly of macrofollicular or normofollicular architecture. The distinction among these different histologic entities may not be possible by FNA, but this is of little importance because they are all benign, and can be managed in a similar, conservative manner. In surgical pathology, the noncommittal term BFN has been suggested for benign cellular nodules where distinction between follicular adenoma and hyperplastic nodule (HN) is not possible on histologic examination [7]. Cytologically, BFNs are characterized by variable amounts of colloid, benign-appearing follicular cells, oncocytic (Hürthle) cells, and macrophages.

Definition

The designation "benign follicular nodule" applies to a cytologic sample that is adequate for evaluation and consists of colloid and benign-appearing follicular cells in varying proportions. The general term BFN may be utilized in cytology reporting; subclassification as a more specific benign diagnosis such as colloid nodule, nodular goiter, hyperplastic/adenomatoid nodule, or Graves' disease may also be used, depending on the cytomorphologic findings and associated clinical presentation (see Sample Reports).

Criteria

Specimens are sparsely to moderately cellular.

Colloid is viscous, shiny, and light yellow or gold in color (resembling honey or varnish) on gross examination. It is dark blue-violet-magenta with Romanowsky-type stains and green or orange-pink with the Papanicolaou stain (Figs. 3.1a, b and 3.2a, b). It may be thin or thick in texture (Fig. 3.3a, b).

Thin, watery colloid often forms a "thin membrane/cellophane" coating or film with frequent folds that impart a "crazy pavement," "chicken wire," or mosaic appearance (see Fig. 3.1a, b). At times, it forms lacunae (Fig. 3.4b).

Thick (dense, "hard") colloid has a hyaline quality and often shows cracks (see Fig. 3.2a).

Follicular cells are arranged predominantly in monolayered sheets and are evenly spaced ("honeycomb-like") within the sheets (Figs. 3.3a, b and 3.4a).

Occasional follicular cells are arranged in intact, three-dimensional, variably-sized balls/spheres, and microtissue fragments (Figs. 3.5 and 3.6a).

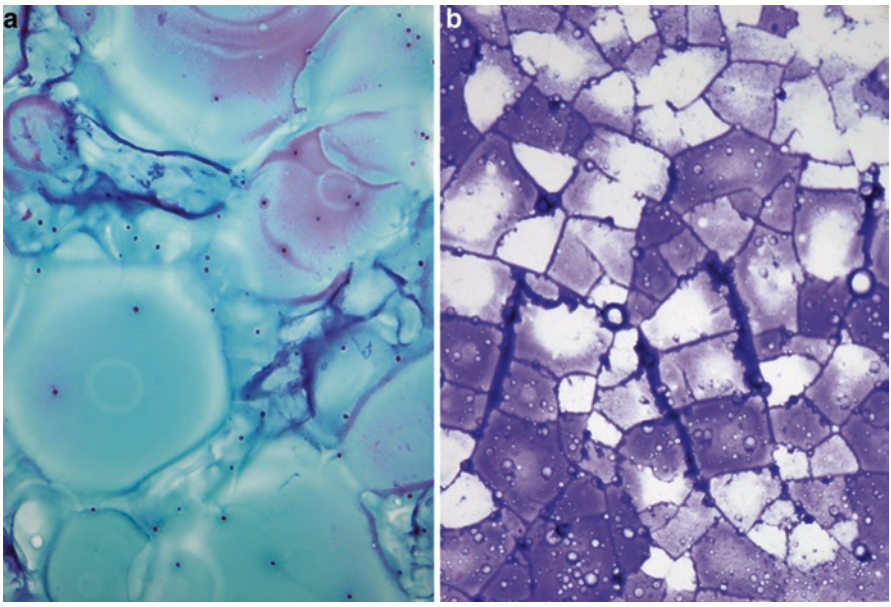

Fig. 3.1 Benign follicular nodule/colloid nodule: watery colloid. (**a**) Watery colloid is light green or pink with alcohol-fixed, Papanicolaou-stained preparations and has a "thin membrane" or "cellophane coating" appearance, often with coalescing "puddles" (smear, Papanicolaou stain). (**b**) Colloid stains blue-violet with air-dried, Romanowsky-stained preparations and often shows a chicken-wire appearance (smear, Diff-Quik stain).

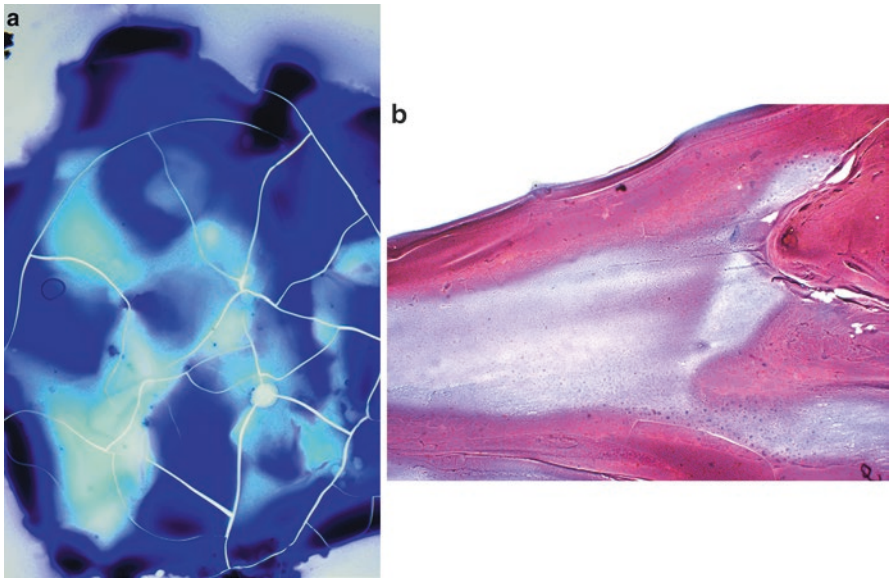

Fig. 3.2 Benign follicular nodule: thick colloid. (**a**) Colloid demonstrates a "stained glass cracking" appearance (smear, Diff-Quik stain). (**b**) Colloid is orange-pink or green-blue with alcohol-fixed Papanicolaou-stained preparations and can cover a major part of the glass slide surface (smear, Papanicolaou stain).

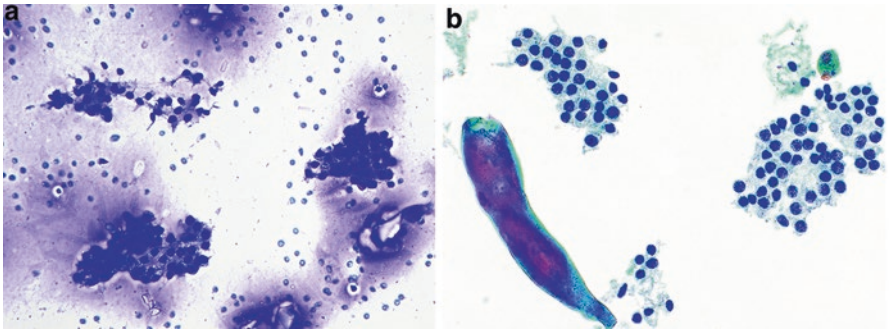

Fig. 3.3 Benign follicular nodule. Monolayered sheets of evenly spaced follicular cells have a honeycomb-like arrangement. (**a**) Watery colloid is present in the background (smear, Diff-Quik stain). (**b**) Thick colloid is present (ThinPrep, Papanicolaou stain).

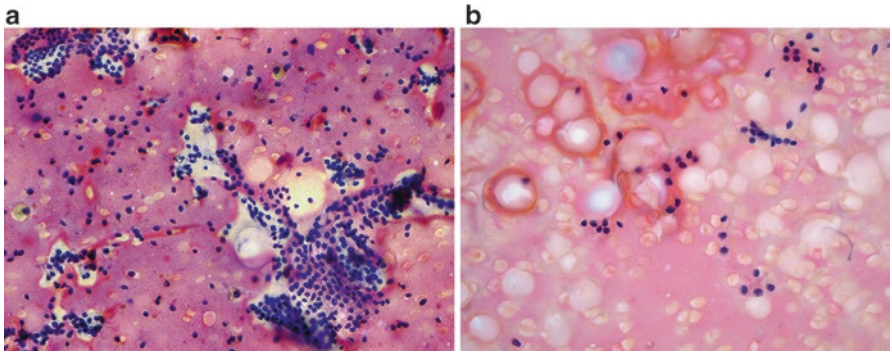

Fig. 3.4 Benign follicular nodule. (**a**) Monolayered sheets of follicular cells are the predominant finding. Stripped follicular cell nuclei are present in the background. When watery colloid is admixed with blood (note the pale-staining red blood cells), it can be difficult to recognize (smear, Papanicolaou stain). (**b**) Colloid is easier to recognize when it forms characteristic folds and lacunae (smear, Papanicolaou stain).

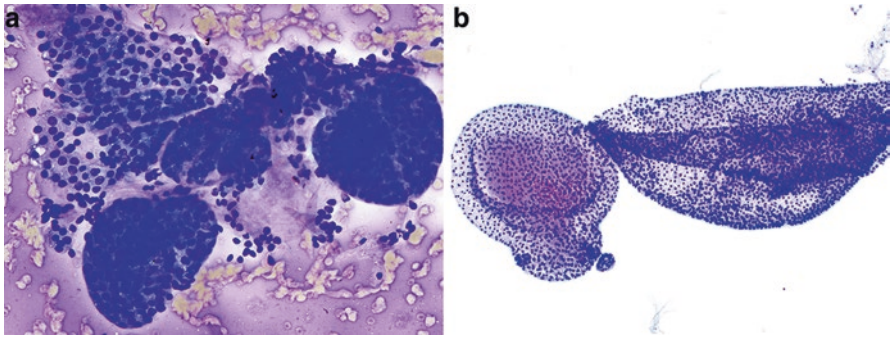

Fig. 3.5 Benign follicular nodule. Three-dimensional, variably sized balls/spheres are admixed with flat sheets. Within the spheres there is maintenance of polarity, including a relatively evenly spaced nuclear arrangement (**a** smear, Diff-Quik stain; **b** ThinPrep, Papanicolaou stain).

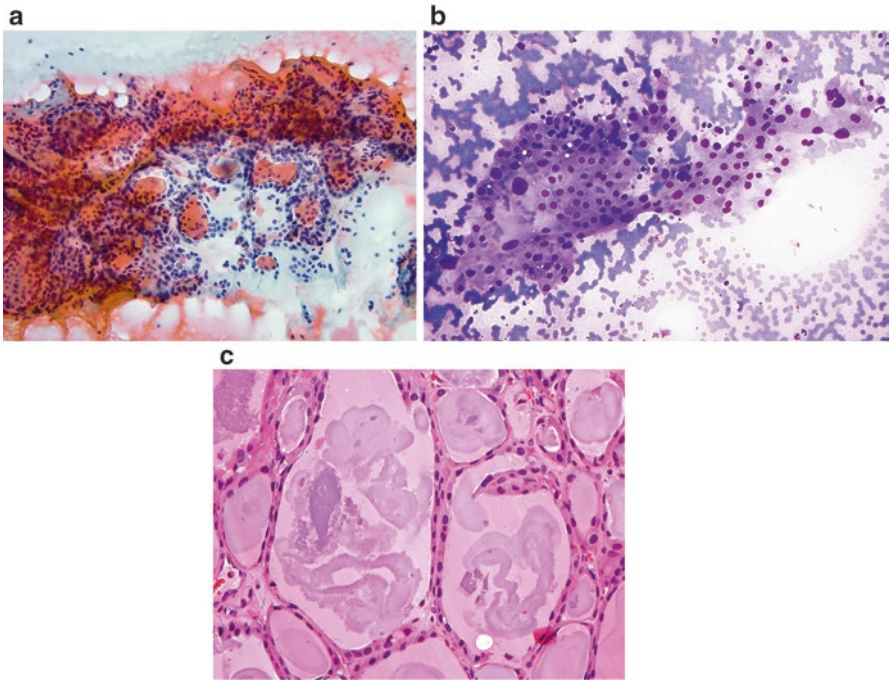

Fig. 3.6 Benign follicular nodule. (**a**) Microtissue fragments are admixed with flat sheets and colloid. There is follicle formation, but these are not microfollicles, because there is maintenance of polarity and the nuclei are evenly spaced (smear, Papanicolaou stain). (**b**) Hürthle cells (oncocytes) can be a prominent component of a benign follicular nodule (smear, Diff-Quik stain). (**c**) The corresponding histologic specimen shows predominantly macrofollicular architecture with compressed Hürthle cells (hematoxylin and eosin stain).

Hürthle cells (oncocytes) are sometimes present, in flat sheets and/or as isolated cells (Fig. 3.6b).

Microfollicles may be present but comprise a minority of the follicular cell population.

The follicular cells have scant or moderate amounts of delicate cytoplasm (Figs. 3.7a, b and 3.8a, b).

Green-black cytoplasmic granules may be seen, representing lipofuscin or hemosiderin pigment (see Fig. 3.7b).

Follicular cell nuclei are round to oval, approximately the size of a red blood cell (7–10 μ in diameter), and show a uniformly granular chromatin pattern (Figs. 3.7b, 3.8a, b).

Minimal nuclear overlapping and crowding can occur (Fig. 3.9a). Anisonucleosis is appreciated in some cases, but there is no significant nuclear pallor or nuclear membrane irregularity.

Small flat sheets of follicular cells without nuclear overlapping or atypia may be present and do not represent neoplastic microfollicles (Fig. 3.9b).

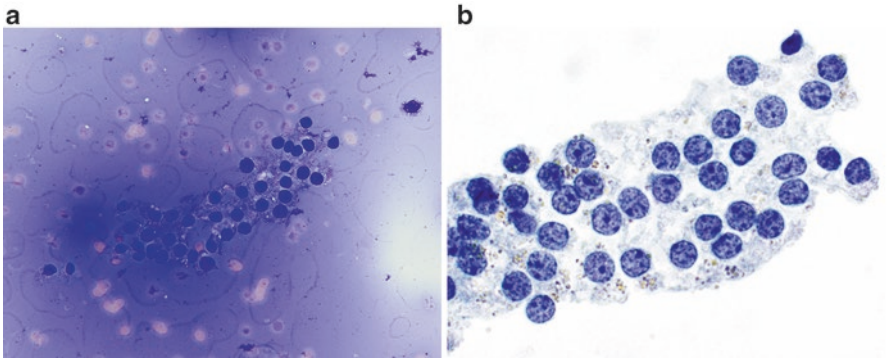

Fig. 3.7 Benign follicular nodule. (**a**) Benign follicular cells have delicate cytoplasm and ill-defined borders. The nuclei are uniformly spaced and approximately the size of red blood cells. Watery colloid is present in the background (smear, Diff-Quik stain). (**b**) Follicular cells may contain golden-brown cytoplasmic hemosiderin pigment (ThinPrep, Papanicolaou stain).

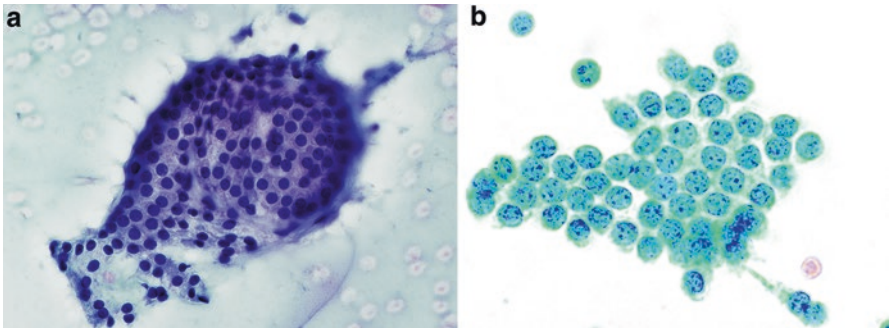

Fig. 3.8 Benign follicular nodule. Benign follicular cells have round to oval, monomorphic nuclei with finely granular chromatin and inconspicuous or absent nucleoli (**a** smear, Papanicolaou stain; **b** SurePath preparation, Papanicolaou stain). (Case **b** courtesy of Douglas R. Schneider, MD, Department of Pathology, Steward St. Elizabeth's Medical Center, Boston, MA, USA.)

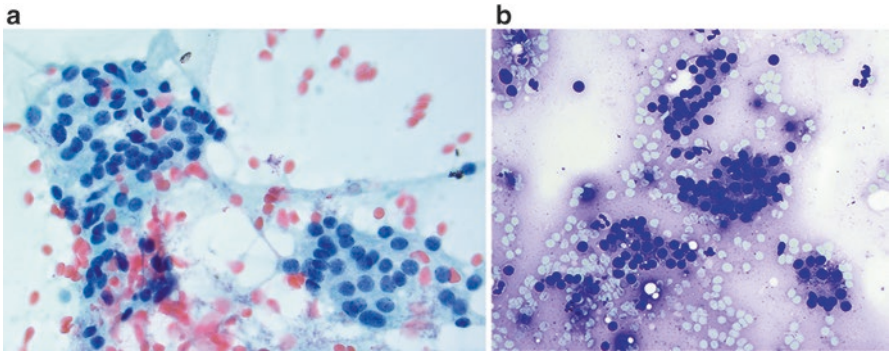

Fig. 3.9 Benign follicular nodule. (**a**) Nuclear overlapping and crowding may be observed in some clusters, but there is no significant nuclear enlargement or atypia (smear, Papanicolaou stain). (**b**) Small flat sheets without significant nuclear overlapping or atypia of follicular cells represent small fragments of macrofollicles, not microfollicles (smear, Diff-Quik stain).

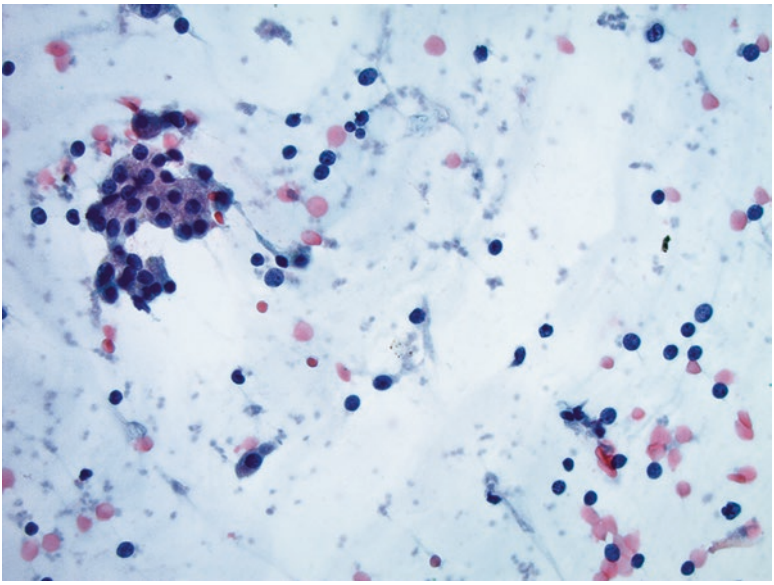

Fig. 3.10 Benign follicular nodule. Stripped ("naked") thyroid follicular cell nuclei may be seen in background; care must be taken not to mistake them for lymphocytes (smear, Papanicolaou stain).

Follicular cell nuclei may be stripped of cytoplasm and mistaken for lymphocytes (Fig. 3.10).

Papillary hyperplasia is occasionally seen (Fig. 3.11).

Follicular cells may appear shrunken, spindled, and degenerated when associated with abundant colloid (Fig. 3.12a, b).

Macrophages are commonly present and may contain hemosiderin pigment (Fig. 3.13).

Focal reparative changes are sometimes observed, especially in cystic lesions, including cyst lining cells with enlarged nuclei, finely granular chromatin, and a squamoid or spindle-shaped ("tissue-culture cell") appearance (Fig. 3.14a, b, c).

Explanatory Notes

The major differential diagnosis of a circumscribed follicular-patterned nodule in surgical resection specimens is hyperplastic/adenomatoid nodule (HN), follicular adenoma (FA), follicular carcinoma (FC), follicular variant of papillary thyroid carcinoma (FVPTC), and noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP). FVPTC and NIFTP are recognized primarily by their characteristic nuclear features. The great majority of FAs and FCs are solitary nodules and completely encapsulated, with a predominantly trabecular/solid or

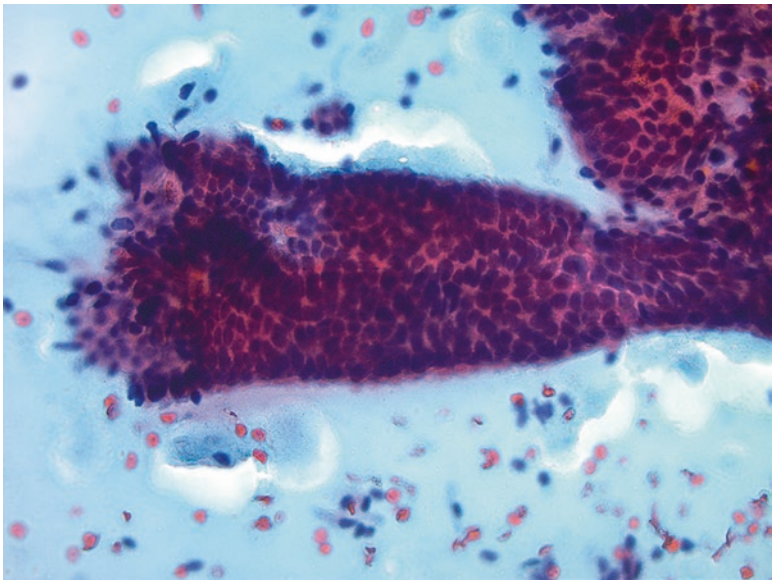

Fig. 3.11 Benign follicular nodule. Papillary hyperplasia may be seen in association with a hyperplastic nodule or follicular adenoma. The follicular cells usually remain arranged in flat sheets; true papillae are rarely apparent. Nuclear features of papillary thyroid carcinoma are absent (smear, Papanicolaou stain).

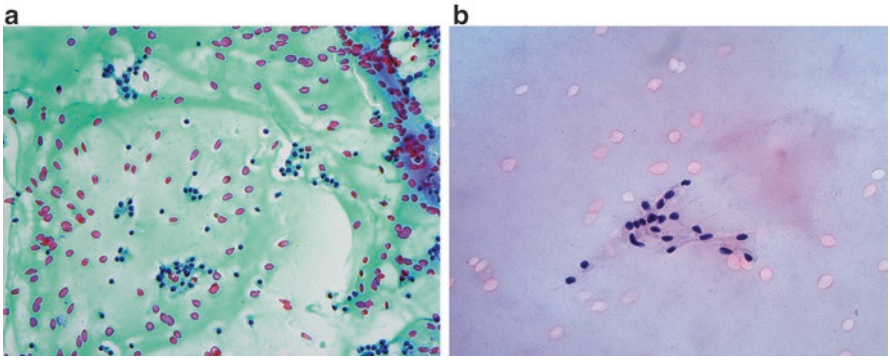

Fig. 3.12 Benign follicular nodule. Follicular cells suspended in abundant colloid tend to dissociate and may appear shrunken and spindled (**a**, **b**: smears, Papanicolaou stain).

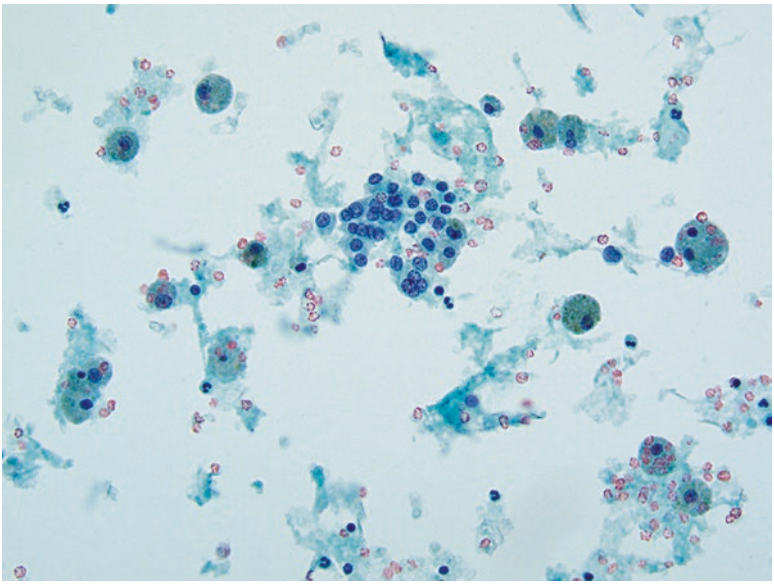

Fig. 3.13 Benign thyroid cyst. Prominent cystic degeneration often occurs in nodular goiter. Abundant macrophages and few benign thyroid follicular cells are present (smear, Papanicolaou stain).

microfollicular architecture, and, therefore, when aspirated they are most likely to be reported cytologically as FN/SFN or AUS/FLUS. Less frequently, a FA or FC may display a prominent macrofollicular or normofollicular pattern. Therefore, in surgical pathology specimens most nodules with a trabecular, solid, or microfollicular growth pattern are diagnosed as either FA or FC, depending on the absence or presence of invasion, respectively, whereas most nodules with a normofollicular or macrofollicular pattern are called HN [7]. The noncommittal term BFN has been suggested when the histologic distinction between HN and FA is not possible [7].

The term BFN is especially apt for cytology reporting because many of the histologic distinctions described above (solitary vs. multiple nodule, encapsulated vs. not) are not apparent on an aspiration sample. Thus BFN conveniently describes a morphologically diverse group of benign histologic lesions, ranging from the colloid nodule or nodular goiter with minimal cellularity and abundant colloid to the hyperplastic (adenomatoid) nodule with moderate cellularity and scant colloid [8–11]. The predominance of honeycomb-like sheets of benign follicular cells, admixed in some cases with Hürthle (oncocytic) cells (see Figs. 3.3–3.8), and variable amount of colloid is the hallmark of BFN.

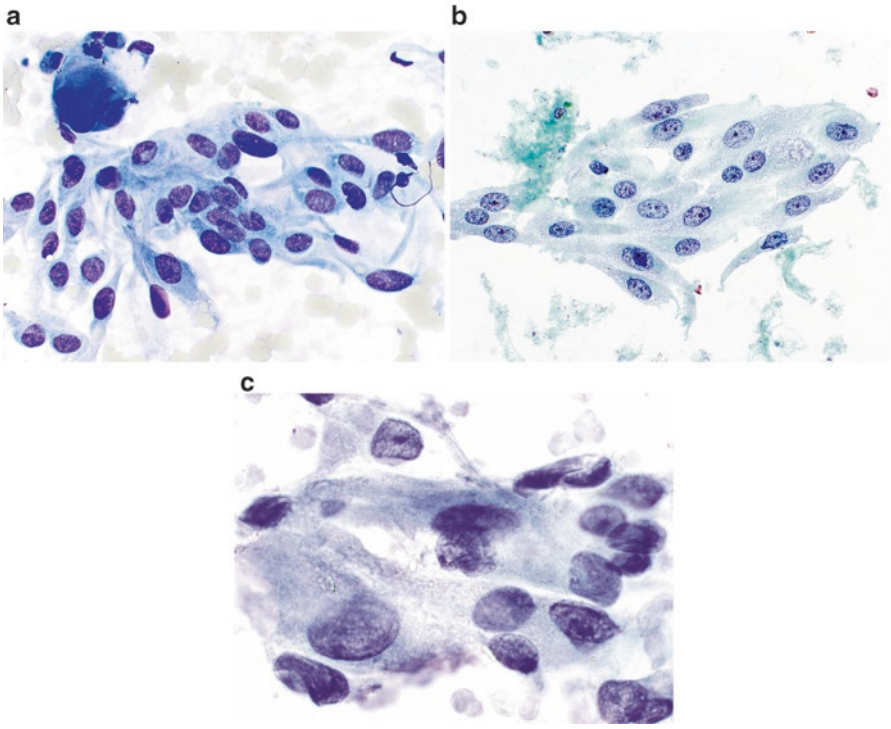

Fig. 3.14 Benign follicular nodule: cyst lining cells. (**a**, **b**) Reparative changes are commonly associated with cystic degeneration. Cyst lining cells are usually a small component of the benign aspirate and easily recognized because of their elongated shape and cohesive, flat and/or squamoid appearance, low nuclear/cytoplasmic ratio, and small prominent nucleoli. (**a** smear, Diff-Quik stain; **b** Papanicolaou stain). (**c**) Occasionally, these cells show elongated nuclei with nuclear grooves and powdery chromatin. When the changes are focal and mild, particularly if the background is overwhelmingly benign, they are easily recognized as reactive, but when more advanced and widespread they raise a concern for papillary thyroid carcinoma (smear, Papanicolaou stain).

Cytoplasmic lipofuscin and hemosiderin pigment granules (paravacuolar granules) are more commonly associated with benign nodules (Fig. 3.7b), but they can be found in malignant neoplasms and so have no diagnostic significance [12].

Watery colloid is most apparent with one of the Romanowsky-type stains like the commonly used Diff-Quik stain; it is less conspicuous but still visible with Papanicolaou-stained preparations (Figs. 3.1, 3.2, 3.3, and 3.4) and can be confused with serum in bloody specimens. Helpful clues to recognizing watery colloid on smears are the presence of cracking and folding in colloid, as well as its tendency to surround follicular cells and occasionally form lacunae (Fig. 3.4), whereas serum accumulates at the edges of the slide and around platelets, fibrin, and blood clots. Specimens consisting of abundant colloid only (e.g., colloid covering the majority of the surface of a smear), with rare or no follicular cells, are considered BFNs, reported as "Benign," and may be further described as "suggestive of..." or "consistent

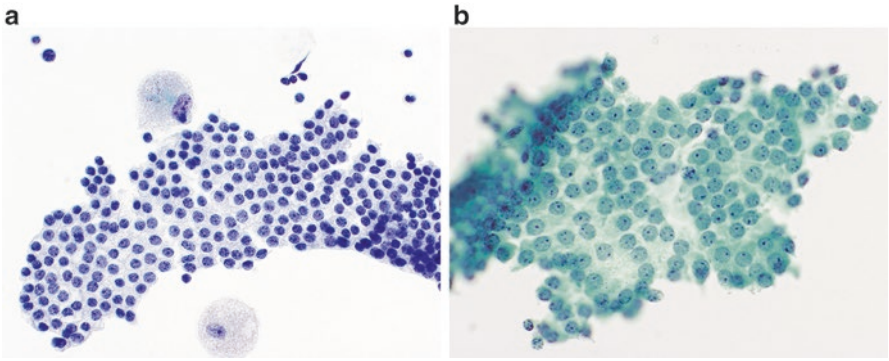

Fig. 3.15 Benign follicular nodule (liquid-based preparations). The follicular cells have pale cytoplasm and small, round, evenly spaced nuclei. (**a** ThinPrep, Papanicolaou stain; **b** SurePath, Papanicolaou stain). (Case **b** courtesy of Douglas R. Schneider, MD, Department of Pathology, Steward St. Elizabeth's Medical Center, Boston, MA, USA).

with colloid nodule" (Fig. 3.2b). Occasionally, the benign thyroid follicular cells are spindled and show evidence of dissociation when suspended in abundant colloid (Fig. 3.12a, b). If colloid is abundant, a diagnosis of BFN is appropriate, even if one cannot find six groups of well-preserved, well-visualized follicular cells, each with at least ten follicular cells.

The cytologic features and diagnostic accuracy of BFNs are generally similar between smears and liquid-based preparations, but there are a few differences [13, 14]. The amount of colloid is diminished in liquid-based preparations when compared with smears, but nuclear detail may be superior [15, 16]. Benign-appearing follicular cells are arranged in relatively smaller monolayer sheets, usually with less than 20–25 cells per sheet. The cells have pale cytoplasm and smaller and darker nuclei (Fig. 3.15a, b). Thick colloid appears as dense, dark blue-orange droplets; and watery colloid as thin, tissue paper-like sheets (Fig. 3.16a, b) [14]. Macrophages may have more abundant pale cytoplasm, enlarged, pale nuclei, and prominent nucleoli. Hürthle cells (oncocytes) may be arranged in a more dissociative pattern and appear shrunken compared to conventional smears, with irregularly shaped, variably sized nuclei and more prominence of the nucleoli (Fig. 3.26b).

Thyroid cysts with an inadequate number of follicular cells should be interpreted as "Nondiagnostic" or "Unsatisfactory," with a comment pertaining to the "cyst fluid only" nature of the aspirate (see Chap. 2) [17].

Thyroglossal duct cyst enters in the differential diagnosis of thyroid cystic lesions when an aspirate consists predominantly of proteinaceous material, inflammatory cells, and rare degenerated squamous or ciliated columnar cells (Fig. 3.17a, b). The diagnosis can be suggested in the appropriate clinical presentation (anterior midline neck cyst, usually above the thyroid isthmus and below the hyoid bone, or rarely just lateral to midline). Mature squamous cells and anucleated squames rarely predominate. If they do, the cyst may be indistinguishable from branchial cleft cyst [18].

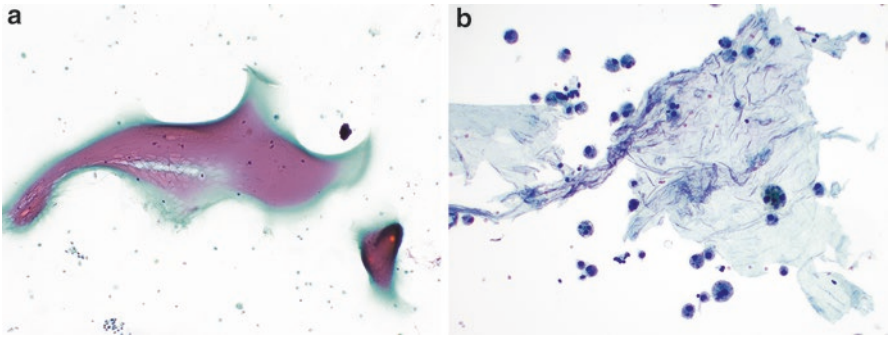

Fig. 3.16 Benign follicular nodule: colloid (liquid-based preparations). (**a**) Thick colloid on liquid-based preparations resembles its counterpart on smears (SurePath, Papanicolaou stain). (**b**) Watery colloid has a thin, "folded tissue-paper" appearance (ThinPrep, Papanicolaou stain). (Case **a** courtesy of Douglas R. Schneider, MD, Department of Pathology, Steward St. Elizabeth's Medical Center, Boston, MA, USA).

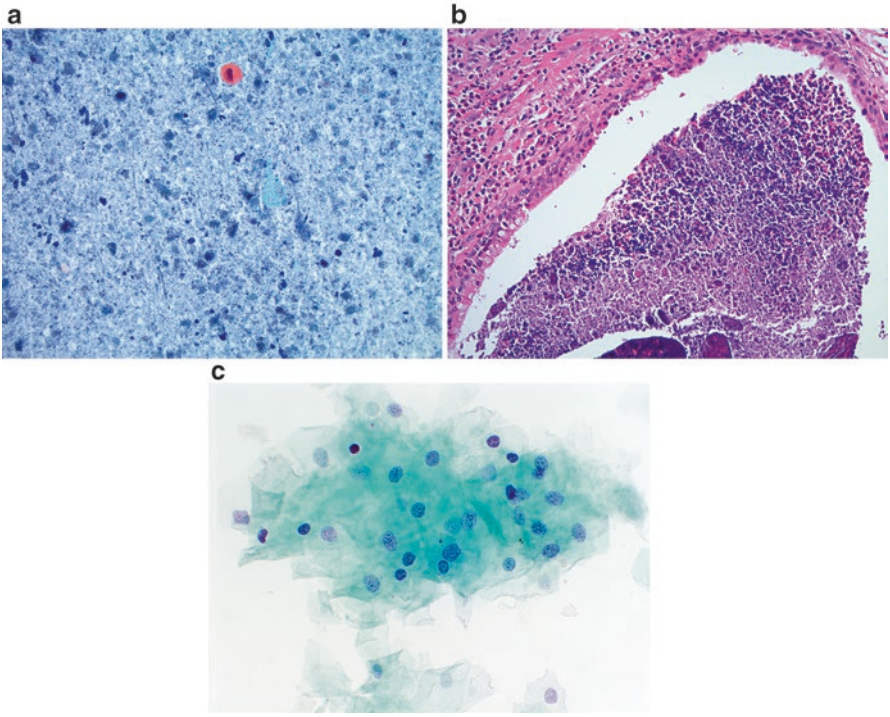

Fig. 3.17 Squamous cells in thyroid aspirates. (**a**) Thyroglossal duct cyst. Proteinaceous material, inflammatory cells, and a rare degenerated squamous cell are present (smear, Papanicolaou stain). (**b**) Thyroglossal duct cyst. The corresponding histopathologic specimen shows cyst contents (as observed in the fine needle aspirate) and a cyst wall lined by mixed squamous and cuboidal/columnar epithelium (hematoxylin and eosin stain). (**c**) Benign squamous cyst of thyroid. The cellular aspirate consists almost entirely of normal-appearing, mature nucleated squamous cells (smear, Papanicolaou stain).

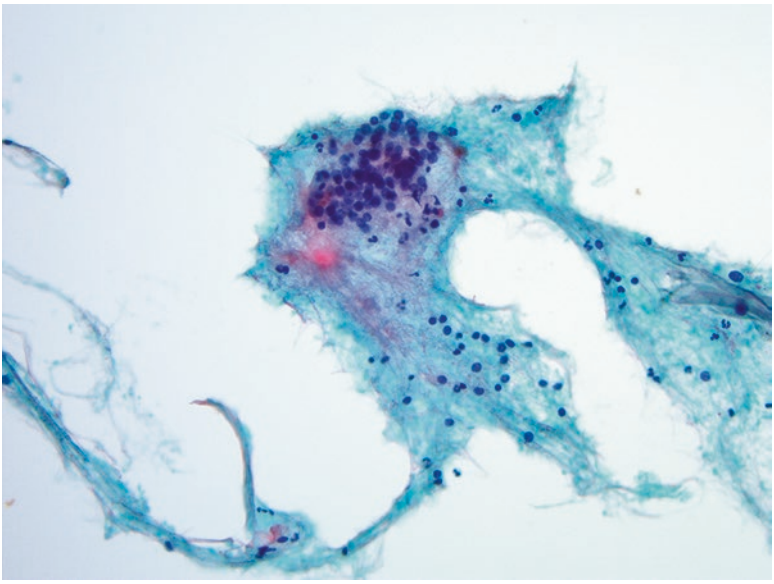

Fig. 3.18 Parathyroid cyst. This sparsely cellular specimen has rare groups of small round cells with dark overlapping nuclei and scant cytoplasm, suggestive of follicle formation (smear, Papanicolaou stain).

Occasional benign-appearing squamous cells may also result from squamous metaplasia associated with lesions such as lymphocytic thyroiditis and cystic papillary thyroid carcinoma.

A cellular sample comprised almost exclusively of mature, benign-appearing squamous cells has been associated with benign follow-up in the available but limited literature, and such cases may be reported as benign in the appropriate clinical setting (Fig. 3.17c) [19].

A not infrequently encountered cystic lesion is the parathyroid cyst, which may be clinically and cytologically mistaken for a thyroid cyst. Aspirated fluid from a parathyroid cyst, however, has a characteristic watery, clear gross appearance, is often acellular or hypocellular, and may show rare cohesive groups of small round cells with dark nuclei and scant cytoplasm, arranged in sheets or microfollicles (Fig. 3.18). The diagnosis of a parathyroid cyst can be established by immunohistochemistry (positive staining for parathormone and chromogranin, negative for thyroglobulin) and/or demonstration of elevated parathormone levels in the cyst fluid [20].

Moderately cellular BFNs may prompt consideration of a follicular neoplasm, but cellularity alone is not enough to merit the interpretation "Follicular neoplasm/Suspicious for a follicular neoplasm (FN/SFN)." Follicular cell crowding, overlapping, and microfollicle formation affecting a majority of the follicular cell population are the important features of the FN/SFN specimen [21]. Some BFNs do contain a minor component of microfollicles, but these tend to show no significant nuclear enlargement or nuclear overlapping and crowding. When microfollicles comprise a minority of the sample and are accompanied by a predominance of macrofollicle

fragments, the sample is interpreted as a BFN. Macrofollicle fragments range in size from small to large. A small fragment of benign-appearing follicular cells should not be misconstrued as a neoplastic microfollicle (Fig. 3.9b); an important defining feature of the neoplastic microfollicle is the significant crowding and overlapping of the follicular cells, sometimes accompanied by nuclear enlargement.

Papillary hyperplasia is defined histologically as a benign proliferation (either hyperplasia or adenoma) notable for the arrangement of follicular cells, usually in a single layer, around fibrovascular cores. Fortunately, papillary hyperplasia in the form of true papillae (defined as having fibrovascular cores) is rarely eoncountered in aspirates, but when it is it can be a diagnostic challenge [22]. More commonly, one sees large fragments of follicular cells associated with stromal tissue that only raises the question of a fibrovascular core. If there are no nuclear features of PTC, the case can be reported as benign (Fig. 3.11).

Hürthle (oncocytic) cells per se should not prompt the interpretation "Follicular neoplasm, Hürthle cell type/Suspicious for a follicular neoplasm, Hürthle cell type (FNHCT/SFNHCT)." A minor population of Hürthle (oncocytic) cells is a common finding in BFNs. Not uncommonly, Hürthle cells can be a prominent or even the predominant component of a BFN (Fig 3.6b), and in some cases there can be significant anisonucleosis and hyperchromasia of the Hürthle (oncocytic) cells. The interpretation FNHCT/SFNHCT should be reserved for cases that consist exclusively (or almost exclusively) of Hürthle cells [23] (see Chap. 6). An aspirate with a significant amount of colloid and a predominant but not exclusive Hürthle cell population is consistent with BFN in the appropriate clinical setting [23].

It is important to evaluate even colloid-rich aspirates for the presence of nuclear features of papillary thyroid carcinoma so as not to miss a macrofollicular variant of papillary carcinoma. This variant often presents with flat sheets without significant nuclear overlapping, resembling benign thyroid follicular cells on low magnification. Occasionally, an aspirate with the features of a BFN will contain a subpopulation of cells with reparative changes, and it is important not to confuse those changes with those of papillary carcinoma (Fig. 3.14a, b, c). When nuclear atypia (e.g., pallor, irregularity) goes beyond what is accepted for reactive/reparative changes, such cases are interpreted as "Suspicious for malignancy" or "Atypia of Undetermined Significance (AUS/FLUS)," depending on the extent and degree of the atypia (see Chaps. 4 and 7).

"Black thyroid" is a benign pigmentation of thyroid follicular cells in patients on chronic treatment with antiobiotics of the tetracycline family (e.g., minocycline) for conditions like acne. Follicular cells show abundant dark brown cytoplasmic pigment. It is darker than hemosiderin and likely represents a form of melanin (Fig. 3.19) [24, 25].

Amyloid goiter is a rare pathologic entity defined as a clinically apparent thyroid enlargement due to amyloid deposition. It is associated with both primary and secondary amyloidosis and results in a diffuse/bilateral involvement of the thyroid gland. Many patients present with symptoms of compression such as hoarseness, dysphagia, and dyspnea. FNA reveals abundant purple to pink/orange amorphous material morphologically similar to colloid but recognizable due to the presence of embedded fibroblasts (Fig. 3.20a, b) [26]. Focal amyloid deposits are also seen in medullary thyroid carcinoma and primary amyloidosis of the thyroid.

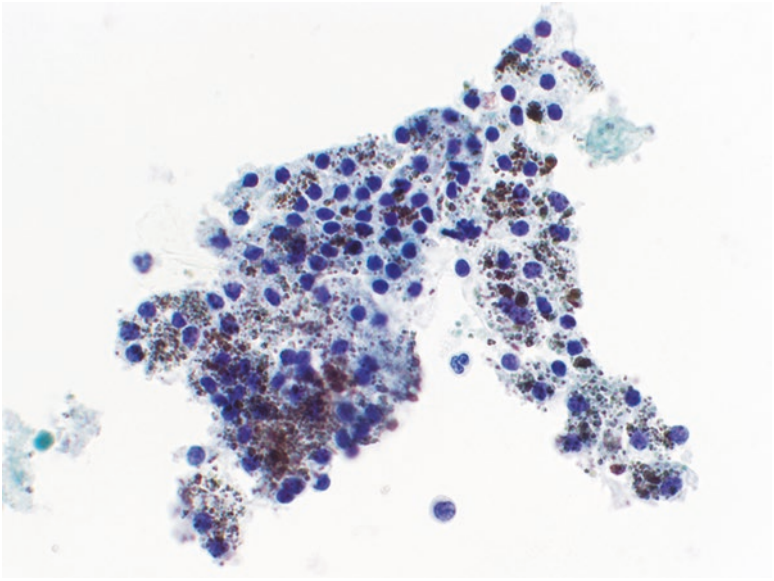

Fig. 3.19 Black thyroid. Follicular cells contain abundant dark brown pigment. Contrast with hemosiderin pigment in Fig. 3.7b (ThinPrep, Papanicolaou stain).

Graves' Disease

Graves' disease (GD) is an autoimmune diffuse hyperplastic thyroid disorder, commonly seen in middle-aged women and usually diagnosed clinically due to hyperthyroidism. Most patients have a diffuse rather than nodular enlargement of the thyroid gland and do not require FNA for diagnosis [27]. Occasionally, however, large and/or cold nodules develop that raise the suspicion of a co-existing malignancy and thus prompt FNA. The cytologic features of GD are non-specific, and clinical correlation is needed for a definitive diagnosis. Aspirates are often cellular and show similar features to non-Graves' BFNs, including abundant colloid and a variable number of follicular cells. Occasionally, lymphocytes and Hürthle cells (oncocytes) may be seen in the background.

Follicular cells are arranged in flat sheets and loosely cohesive groups, with abundant delicate, foamy cytoplasm [28] (Figs. 3.21 and 3.22). Nuclei are often enlarged, vesicular, and show prominent nucleoli. Few microfollicles may be observed. Distinctive "flame cells" may be prominent and are represented by marginal cytoplasmic vacuoles with red to pink frayed edges (best appreciated with Romanowsky-type stains) [27, 29] (Fig. 3.21). Flame cells, however, are not specific for GD and may be encountered in other non-neoplastic thyroid conditions, follicular neoplasms, and papillary carcinoma. Occasionally the follicular cells display focal chromatin clearing and rare intranuclear grooves (Fig. 3.23a). These changes are not diffuse, however, and other diagnostic nuclear features of papillary carcinoma are commonly

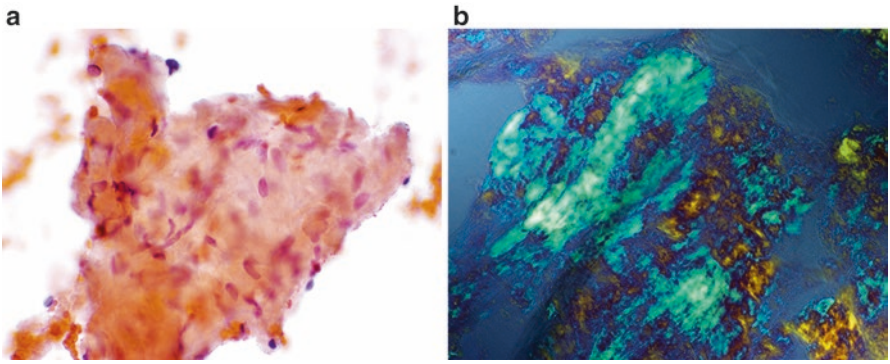

Fig. 3.20 Amyloid goiter. (**a**) Aspiration of abundant thick, glassy, amorphous material that stains pink/orange or purplish (depending on the stain used) is observed. Amyloid deposits are mostly parenchymal and hence often display embedded fibroblasts, a characteristic feature (smear, Papanicolaou stain). (**b**) A Congo red stain shows characteristic birefringence upon polarization, confirming the diagnosis (cell block section).

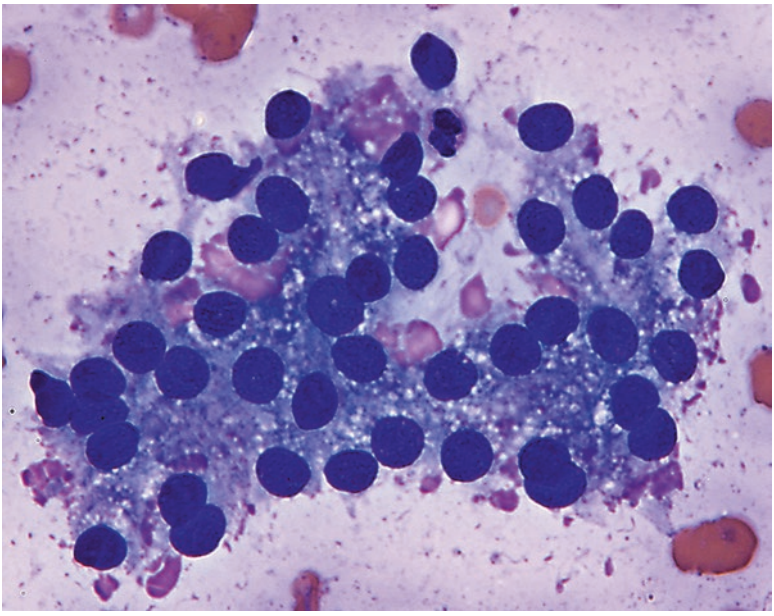

Fig. 3.21 Benign follicular nodule (patient with Graves' disease). Cells in monolayered sheets have abundant cytoplasm. Flame cells are distinctive for their marginal cytoplasmic vacuoles with red to pink frayed edges (smear, Diff-Quik stain).

absent. [30] Occasionally, treated GD shows prominent microfollicular architecture, significant nuclear overlapping and crowding, and considerable anisonucleosis. Care must be taken not to over-interpret these changes as malignant or neoplastic, and inquiry should be made regarding prior radioactive iodine therapy [31, 32] (Fig. 3.23b). Lymphocytes are usually not prominent in GD, but in some cases they may be present in significant numbers and mimic lymphocytic thyroidits [29, 31].

Lymphocytic Thyroiditis

Background

Lymphocytic thyroiditis (LT) encompasses a variety of conditions, including chronic lymphocytic (Hashimoto) thyroiditis, subacute lymphocytic thyroiditis (postpartum and silent thyroiditis), and focal lymphocytic (silent) thyroiditis [33]. Lymphocytic infiltrates may also be associated with Graves' disease, nodular goiter, and IgG4-related thyroiditis.

Chronic lymphocytic thyroiditis (CLT) or Hashimoto thyroiditis is the most common of these conditions and typically affects middle-aged women but is also seen in adolescents and children. Patients often develop diffuse thyroid enlargement but only become candidates for FNA when they develop nodularity or an increasing thyroid volume. It is usually associated with circulating antithyroglobulin and antithyroid peroxidase (antimicrosomal) antibodies. Histologically, CLT shows diffuse infiltration of the thyroid gland by lymphoplasmacytic infiltrates, lymphoid follicles, oncocytic metaplasia, and variable fibrosis and atrophy.

Other types of autoimmune thyroiditis show an identical histologic appearance in a focal or diffuse pattern. Subtyping of LT by cytology, e.g., as CLT, requires clinical and serologic correlation.

Definition

The designation "lymphocytic thyroiditis" applies to a cytologic sample composed of many polymorphic lymphoid cells associated with benign thyroid follicular cells and/or Hürthle (oncocytic) cells [34].

Criteria

Specimens are usually hypercellular, but advanced fibrosis or dilution with blood may decrease the apparent cellularity. An interpretation of lymphocytic thyroiditis does not require a minimum number of follicular or Hürthle (oncocytic) cells for adequacy [17].

Oncocytic cells (Hürthle cells), when present, are arranged in flat sheets or as isolated cells. They have abundant granular cytoplasm, large nuclei, and prominent nucleoli (Figs. 3.24a, b, 3.25, and 3.26a, b).

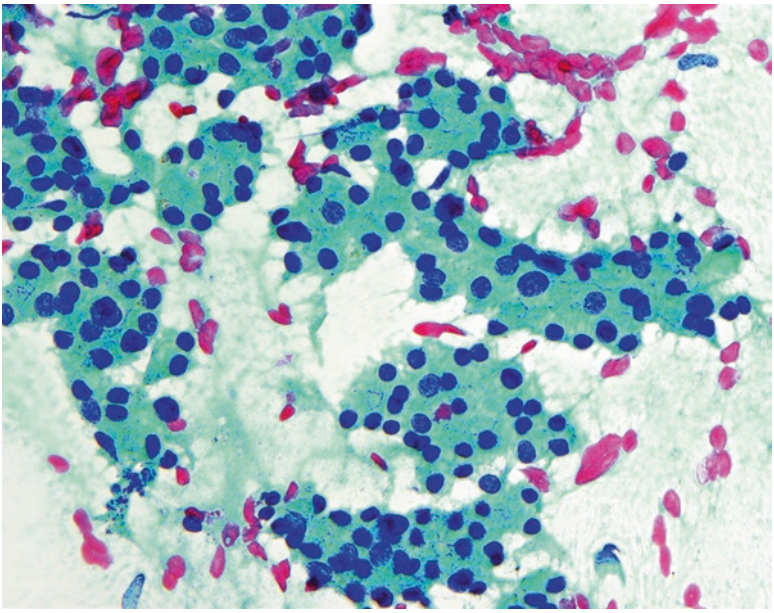

Fig. 3.22 Benign follicular nodule (patient with Graves' disease). The nuclei are often enlarged, vesicular, and show prominent nucleoli. Anisonucleosis is prominent. The cytoplasm has a granular, "oncocytoid" appearance (smear, Papanicolaou stain).

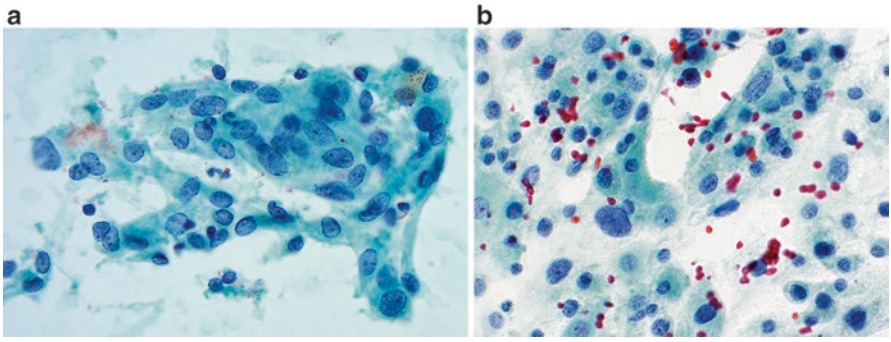

Fig. 3.23 Benign follicular nodule (patient with Graves' disease). (**a**) The follicular cells may display focal nuclear chromatin clearing and rare grooves. These changes are rarely diffuse, and other diagnostic nuclear features of papillary thyroid carcinoma are absent (smear, Papanicolaou stain). (**b**) There is marked anisonucleosis (smear, Papanicolaou stain).

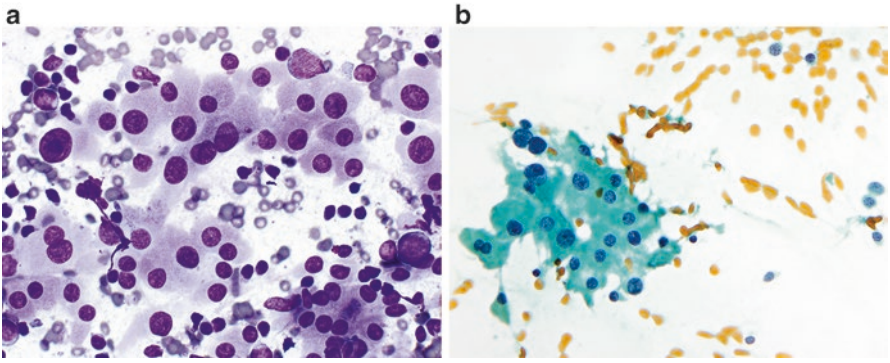

Fig. 3.24 Lymphocytic thyroiditis. (**a**) There is a mixed population of Hürthle cells (oncocytes) and polymorphic lymphocytes (smear, Diff-Quik stain). (**b**) Hürthle cells have abundant granular cytoplasm, large nuclei, and prominent nucleoli. There is mild anisonucleosis (smear, Papanicolaou stain).

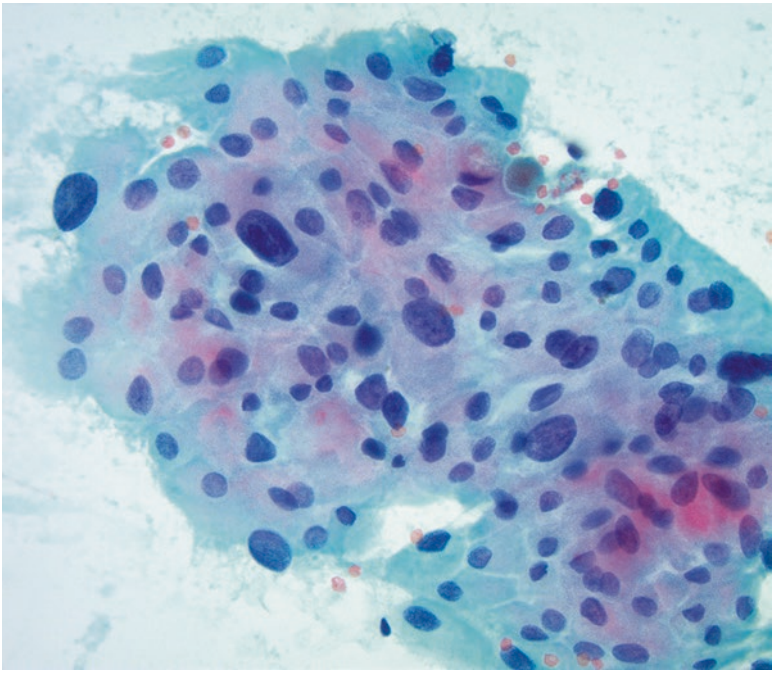

Fig. 3.25 Lymphocytic thyroiditis. Random nuclear atypia and prominent anisonucleosis of Hürthle cells (oncocytes) is not uncommonly associated with LT (smear, Papanicolaou stain).

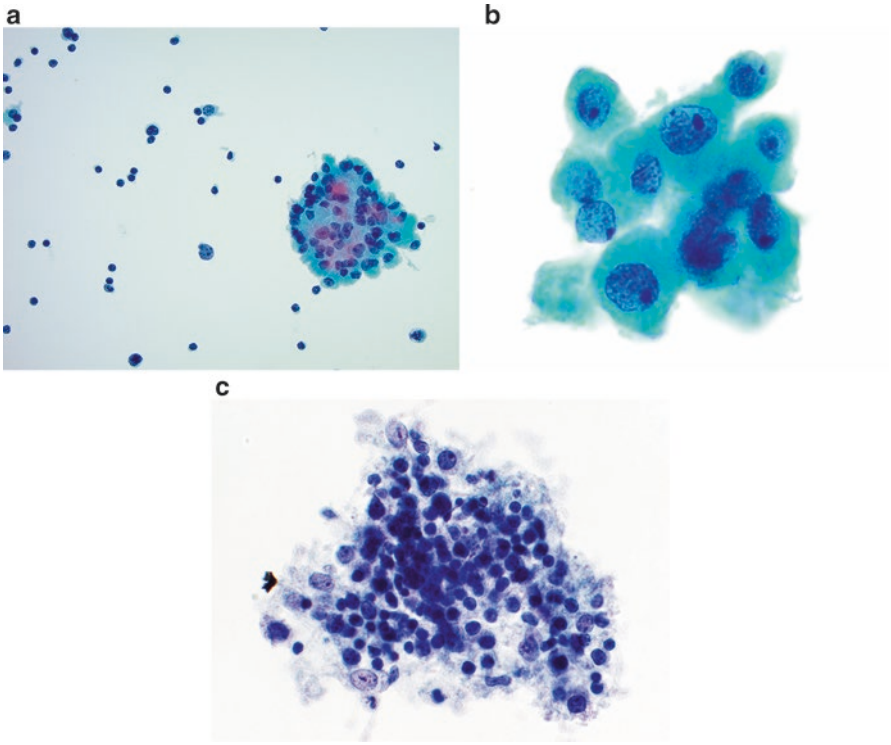

Fig. 3.26 Lymphocytic thyroiditis, liquid-based preparations. (**a**) Lymphocytes are dispersed as isolated cells and infiltrate clusters of Hürthle cells (ThinPrep, Papanicolaou stain). (**b**) Hürthle cells (oncocytes) have abundant granular cytoplasm and prominent nucleoli (SurePath, Papanicolaou stain). (**c**) Germinal center fragments are often present, comprised of a heterogeneous mix of polymorphic lymphocytes and larger dendritic cells (ThinPrep, Papanicolaou stain). (Case **b** courtesy of Douglas R. Schneider, MD, Department of Pathology, Steward St. Elizabeth's Medical Center, Boston, MA, USA).

Anisonucleosis of Hürthle cells (oncocytes) may be prominent. Sometimes mild nuclear atypia is encountered, including scattered nuclear clearing and grooves (Fig. 3.25).

The lymphoid population is polymorphic, including small mature lymphocytes, larger reactive lymphoid cells, and occasional plasma cells. The lymphoid cells may be in the background or infiltrating epithelial cell groups (see Fig. 3.26a). Intact lymphoid follicles and lymphohistiocytic aggregates may be seen (see Fig. 3.26c).

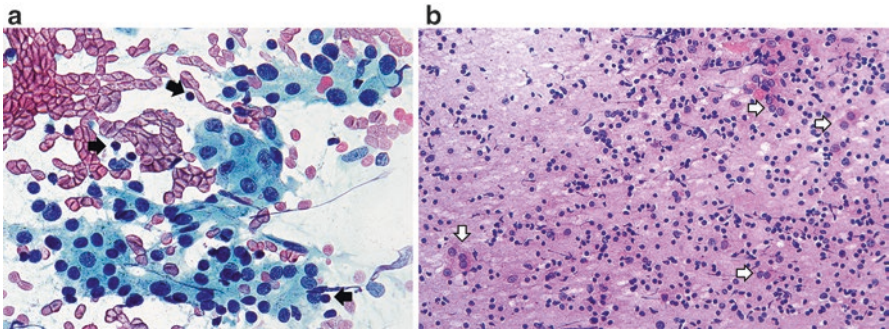

Fig. 3.27 Lymphocytic thyroiditis. (**a**) Hürthle cells may predominate in any given sample, raising the possibility of a Hürthle cell neoplasm. Rare lymphocytes are present in the background (*arrows*) (smear, Papanicolaou stain). (**b**) Lymphoid cells may predominate in an aspirate, raising the possibility of lymphoma. Rare Hürthle cells (oncocytes) are seen in the background (*arrows*) (smear, H&E stain).

Hürthle cells or lymphocytes may predominate in any given aspirate, raising the possibility of a Hürthle cell neoplasm or lymphoproliferative disorder, respectively (Fig. 3.27a, b).

Granulomatous (de Quervain) Thyroiditis

Granulomatous (de Quervain's) thyroiditis is a self-limited inflammatory condition of the thyroid that is usually diagnosed clinically and believed to be triggered by a viral infection. FNA is generally performed only if there is nodularity that raises the possibility of a co-existing malignancy. In the absence of granulomas, the cytologic findings are nonspecific. The biopsy procedure, however, may be quite painful for the patient, preventing adequate sampling.

Criteria

The cellularity is variable and depends on the stage of disease.

Granulomas (clusters of epithelioid histiocytes) are present (Fig. 3.28), along with many multinucleated giant cells.

The early stage demonstrates many neutrophils and eosinophils, similar to acute thyroiditis.

In later stages preparations are hypocellular. They show giant cells surrounding and engulfing colloid, epithelioid cells, lymphocytes, macrophages, and scant degenerated follicular cells [35].

In the involutional stage, giant cells and inflammatory cells may be absent; some specimens may be insufficient for evaluation.

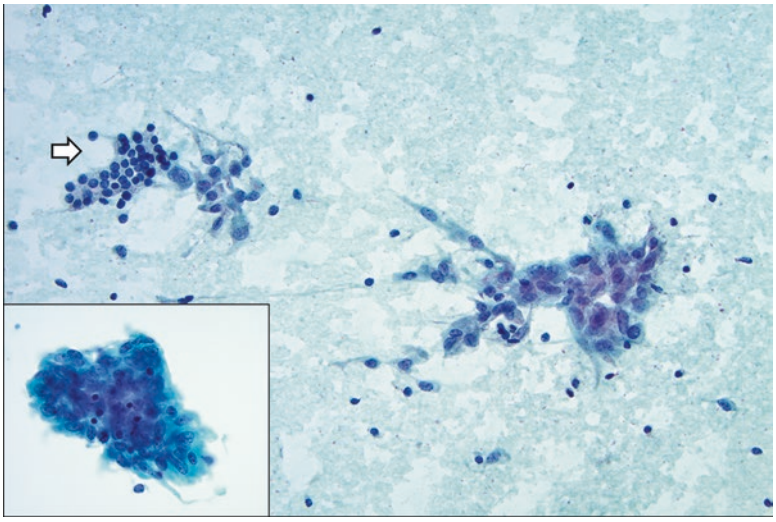

Fig. 3.28 Granulomatous thyroiditis. Epithelioid histiocytes, mixed inflammatory cells, and benign thyroid follicular cells (*arrow*) are present. Inset: Higher magnification of a granuloma (smears, Papanicolaou stain).

Acute Thyroiditis

Acute thyroiditis is a rare infectious condition of the thyroid, more commonly seen in immunocompromised patients.

Criteria

Numerous neutrophils are associated with necrosis, fibrin, macrophages, and blood (Fig. 3.29).

There are scant reactive follicular cells and limited to absent colloid.

Bacterial or fungal organisms are occasionally seen in the background, especially in immunocompromised patients. Cultures and special stains for organisms may be helpful in these situations.

Riedel Thyroiditis/Disease

This is the rarest form of thyroiditis and results in progressive fibrosis of the thyroid gland with extension into the soft tissues of the neck. Riedel thyroiditis (RT) is believed to be a manifestation of systemic IgG4 related disease in the thyroid, and one-third of patients develop fibrosing disorders in other organs [36]. A hard, fixed thyroid mass clinically simulates anaplastic thyroid carcinoma and lymphoma.

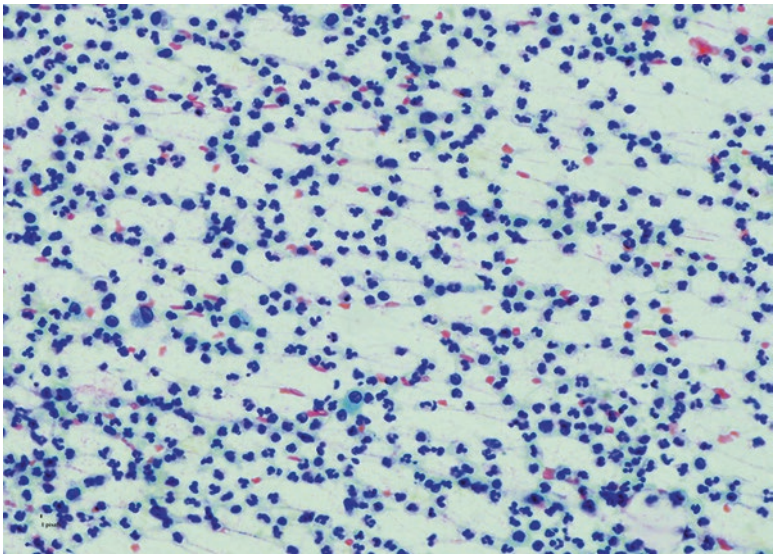

Fig. 3.29 Acute thyroiditis. There are numerous neutrophils and occasional macrophages (smear, Papanicolaou stain).

Criteria

The thyroid gland feels very firm on palpation.
The preparations are often acellular.
Collagen strands and bland spindle cells may be present (Fig. 3.30).
There are rare chronic inflammatory cells.
Colloid and follicular cells are usually absent.

Explanatory Notes

Chronic lymphocytic (Hashimoto) thyroiditis (CLT), granulomatous (de Quervain) thyroiditis, and subacute lymphocytic thyroiditis are the most common clinically significant types of thyroiditis. "Lymphocytic thyroiditis" (LT) is a general term applied to chronic inflammation of the thyroid, but most cases represent autoimmune thyroiditis. Autoimmune thyroiditis includes CLT and subacute lymphocytic thyroiditis.

CLT is the most frequently encountered autoimmune thyroiditis and globally the most common cause of hypothyroidism where iodine levels are sufficient [33]. Patients usually present with diffuse symmetric enlargement of the thyroid, but occasionally enlargement is localized and raises the suspicion of a neoplasm. CLT/Hashimoto thyroiditis had been characterized for many years as a well-defined clincopathologic entity but now is considered a heterogeneous disease. IgG4-related

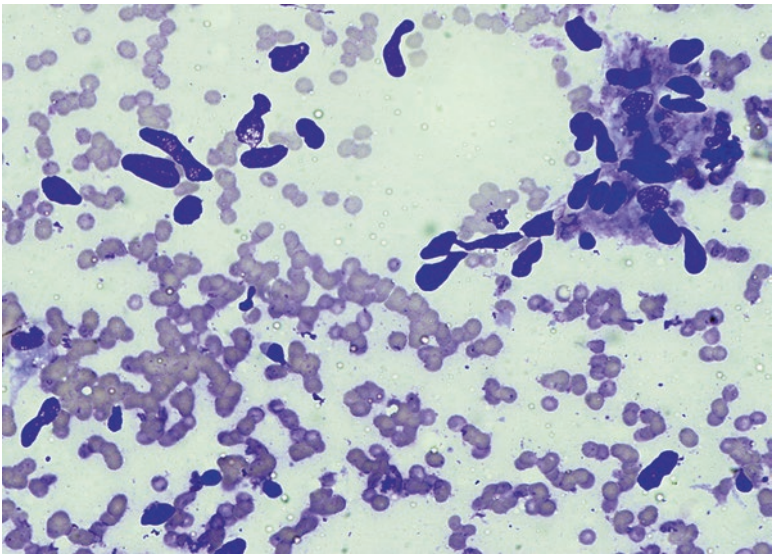

Fig. 3.30 Riedel thyroiditis/disease. This hypocellular smear contains scattered bland spindle cells and rare chronic inflammatory cells (smear, Diff-Quik stain).

thyroiditis is a new subtype of CLT characterized by inflammation rich in IgG4-positive plasma cells and marked fibrosis [37, 38]. A significant portion of cases of fibrosing Hashimoto thyroiditis and a minority of classic Hashimoto thyroiditis are now believed to belong to the spectrum of IgG4-related disease. Histologic features, however, remain the gold standard for establishing the diagnosis of IgG4-related disease, as cytology can not render a specific diagnosis, and elevated IgG4 plasma cells have been described in other inflammatory and malignant conditions. Unlike most other IgG4-related diseases, IgG4 related thyroiditis appears to be mostly confined to the thyroid, and lacks systemic manifestations.

Subacute lymphocytic thyroiditis is often refered to as painless thyroiditis, and patients can present with nodular enlargement. A similar process occurs in the postpartum period in up to 5% of women (postpartum thyroiditis) [33]. Most subacute lymphocytic thyroiditis patients have circulating antithyroid peroxidase antibodies or a family history of other autoimmune disorders. Cytology can not distinguish between the various subtypes of autoimmune thyroiditis.

In some patients with LT, the predominance of either the lymphoid or the oncocytic cell component may raise the possibility of lymphoma or a Hürthle cell neoplasm, respectively (Fig. 3.27a, b) [39, 40]. A monomorphic lymphoid population should raise the suspicion of lymphoma and prompt additional samples for flow cytometry to confirm the diagnosis (see Chap. 12). A polymorphic population of reactive lymphocytes raises the differential diagnosis of LT and intra- or peri-thyroid lymph node hyperplasia, but these can often be distinguished by their differing sonographic features. In pediatric patients, a population of small mature lymphocytes may represent intrathyroidal thymic tissue masquerading as a neoplasm, and

immunohistochemistry and/or flow cytometry can be applied to confirm the clinical diagnosis and potentially avoid unnecessary surgery [41]. The diagnosis of AUS/FLUS or "Suspicious for a Hürthle Cell Neoplasm" could be considered in cases with a sparse or absent lymphocytic infiltrate (see Chap. 6). Nodule size may be a consideration, as the rate of malignancy appears to be lower in Hürthle cell (oncocytic) nodules measuring less than 3.0 cm as compared to those equal or greater than 3.0 cm in size, regardless of associated chronic inflammation [42]. The follicular or Hürthle cells occasionally demonstrate focal reactive changes and mild atypia, including nuclear enlargement, grooves, and chromatin clearing [39]. Therefore, the diagnostic threshold for papillary carcinoma should be raised slightly if there is cytomorphologic evidence of LT. In some cases the features will be equivocal, in which case a diagnosis of AUS/FLUS or "Suspicious for malignancy" should be considered, depending on how well developed the nuclear changes are (see Fig. 7.8). At times, stripped follicular cell nuclei of a BFN may be misinterpreted as lymphocytes (see Fig. 3.10); care must be taken to identify the thin rim of cytoplasm surrounding true lymphocytes in order to avoid a false diagnosis of LT.

The diagnosis of LT on liquid-based preparations can be challenging, as the chronic inflammatory background may be decreased or absent [14, 15, 43]. Because the lymphoid cells tend to be evenly dispersed in the background with liquid-based preparations, they are easy to overlook at low magnification. Liquid-based preparations, which are designed to eliminate red blood cells, are relatively enriched for white blood cells, therefore, care must be taken not to over-interpret the normal lymphocytes of blood as indicative of LT. If the lymphoid cells are present in the normal proportion to neutrophils of peripheral blood, then the lymphoid cells are merely blood elements. In LT, there will be a marked increase in the proportion of lymphoid cells to other inflammatory cells, sometimes accompanied by germinal center fragments. With liquid-based preparations, oncocytic cells occasionally have irregular nuclei.

The cytologic findings are often nonspecific in acute, subacute, and Riedel thyroiditis (RT), and in some cases there may be an overlap with LT [34, 44]. In the presence of granulomas, other causes of granulomatous inflammation besides granulomatous thyroiditis (de Quervain) should be considered, including sarcoidosis and infection. Careful examination should be undertaken to exclude the possibility of an associated malignancy such as a sclerosing lymphoma or fibrosing anaplastic carcinoma.

Management

The risk of cancer for cytologically benign thyroid nodules is difficult to assess because only a minority of nodules with benign cytology (approximately 10%) undergo surgery [45]. A reliable false-negative rate can only be calculated if all patients undergo surgery (the "gold standard") regardless of their FNA result; this is neither practical nor feasible, however. Most published studies have confirmed that

a benign FNA diagnosis is associated with a very low false-negative rate, estimated to be in the range of 0–3% [46–52].

The 2015 American Thyroid Association (ATA) guidelines for the management of thyroid nodules strongly recommend that no further immediate diagnostic studies or treatment are required for benign cytology [6]. Given the very low risk of malignancy associated with benign thyroid cytology, the ATA recommends that follow-up should be determined by risk stratification based on ultrasound (US) pattern:

(A) *Nodules with high suspicion US pattern:* repeat US and US-guided FNA within 12 months;
(B) *Nodules with low to intermediate suspicion US pattern:* repeat US at 12–24 months. If there is evidence of growth or development of new suspicious sonographic features, the FNA could be repeated or observation continued with repeat US, with repeat FNA in case of continued growth;
(C) *Nodules with very low suspicion US pattern*: the utility of surveillance US is limited. If US is repeated, it should be done at >24 months.

If a nodule has undergone repeat US-guided FNA with a second benign cytology result, US surveillance for this nodule is no longer indicated [6].

It is apparent from recent published literature and the ATA management guidelines that repeat FNA and/or surgery is considered only for a selected subset of thyroid nodules with benign cytology, including those that are large, symptomatic, have worrisome clinical and/or sonographic characteristics, including significant US nodule growth (20% increase in at least two dimensions with a minimal increase of 2 mm or more than a 50% change in volume) or developing US abnormalities, such as irregular margins, microcalcifications, intra-nodular hypervascularity, and hypoechogenicity in solid areas [6].

Sample Reports

If an aspirate is interpreted as Benign, it is implied that the sample is adequate for evaluation. (An explicit statement of adequacy is optional.) Descriptive comments that follow are used to sub-classify the benign interpretation (see examples below). An educational note specifying the risk of malignancy for this interpretation, derived from the experience of the laboratory itself or from the literature, is optional.

Example 1

BENIGN.
Benign follicular nodule.

Example 2

BENIGN.

Benign-appearing follicular cells, colloid, and occasional oncocytic cells, consistent with a benign follicular nodule.

Example 3

BENIGN.

Benign follicular nodule, consistent with colloid nodule.

Example 4 (Clinical History of Nodular Goiter)

BENIGN.

Benign follicular nodule, consistent with nodular goiter.

Example 5

BENIGN.

Consistent with hyperplastic/adenomatoid nodule.

Example 6 (Clinical History Not Provided)

BENIGN.

Consistent with lymphocytic thyroiditis.

Example 7 (Clinical History Not Provided)

BENIGN.

Lymphocytes and benign follicular cells, consistent with lymphocytic thyroiditis.

Example 8 (Clinical History of Hashimoto Thyroiditis Provided)

BENIGN.

Consistent with chronic lymphocytic (Hashimoto) thyroiditis.

Example 9 (Not Known if the Patient Has Hashimoto Thyroiditis)

BENIGN.

Numerous polymorphic lymphoid cells and scattered Hürthle cells.

Note: The findings are suggestive of chronic lymphocytic (Hashimoto) thyroiditis in the proper clinical setting.

Example 10

BENIGN.

Proteinaceous material, macrophages, and rare benign-appearing but poorly preserved squamous cells.

Note: The findings are consistent with a benign developmental cyst such as a thyroglossal duct cyst. Clinical correlation advised.

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Atypia of Undetermined Significance/ Follicular Lesion of Undetermined Significance

4

Jeffrey F. Krane, Ritu Nayar, and Andrew A. Renshaw

Background

The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) defined and distinguished three different patterns of the so-called "indeterminate" aspirate, each with distinct cytologic features and risk associations for malignancy. Aspirates with cytologic features that are "suspicious for malignancy" (SUS) (see Chap. 7) have a higher risk of malignancy than those classified as "follicular neoplasm/suspicious for a follicular neoplasm" (FN/SFN) (or follicular neoplasm, Hürthle cell type/suspicious for a follicular neoplasm, Hürthle cell type; FNHCT/SFNHCT) (see Chaps. 5 and 6). The atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS) category is reserved for cases with a lesser degree of atypia, primarily cytologic and/or architectural in nature, insufficient to qualify for either of the suspicious categories. Such cases have a lower risk of malignancy, warranting separation from the other two indeterminate categories [1].

AUS/FLUS has been extensively studied since the advent of TBSRTC, but calculating the risk of malignancy (ROM) associated with this interpretation has been challenging. Because only a minority of AUS/FLUS cases undergo excision, estimating the ROM based on histologic follow-up alone overestimates the risk of malignancy due to selection bias: AUS/FLUS nodules are usually resected only if there are worrisome clinical or sonographic features, an abnormal repeat aspiration

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result, and/or an abnormal molecular testing result. AUS/FLUS nodules with a benign repeat aspiration and/or a benign molecular test result remain (appropriately) unresected. On the other hand, when calculated using the total number of AUS/FLUS specimens (regardless of surgical follow-up) as the denominator, assuming that unresected nodules are benign, the ROM is most certainly underestimated. The actual ROM is expected to be in between the values obtained using these two different calculations and requires some extrapolation. There is evidence that the ROM of AUS/FLUS has been further overestimated due to publication bias (unexpected/discrepant results are more likely to be published than expected findings) [2].

Despite these challenges, the overall low-risk nature of aspirates in this category has been borne out [3–5]; it is clearly lower than that of the SUS category but overlaps with the risks associated with the FN/SFN or FNHCT/SFNHCT categories. Follow-up studies since the introduction of TBSRTC and the AUS/FLUS category demonstrate notable variability in the use of this category [3–5]. The AUS/FLUS interpretation is associated with a ROM that is higher (~10–30%) than predicted when TBSRTC was introduced in 2008 (~5–15%). Furthermore, the risk differs according to the nature of the atypia prompting the AUS/FLUS interpretation [6–14]. AUS/FLUS aspirates with cytologic (nuclear) atypia have an approximately twofold higher ROM compared with AUS/FLUS cases with architectural atypia [11]. Hürthle cell-type AUS/FLUS has a lower ROM than other AUS/FLUS patterns [11]. The introduction of noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) terminology in 2016 [15] will likely alter these figures further, with early data suggesting that the ROM for AUS/FLUS may be reduced by as much as 45% [16, 17].

Definition

The diagnostic category “atypia of undetermined significance” (AUS)/“follicular lesion of undetermined significance” (FLUS) is reserved for specimens that contain cells (follicular, lymphoid, or other) with architectural and/or nuclear atypia that is not sufficient to be classified as suspicious for a follicular neoplasm, suspicious for malignancy, or malignant. On the other hand, the atypia is more marked than can be ascribed confidently to benign changes.

Although the term AUS is preferred, FLUS is an acceptable alternative for the great majority of cases in which the atypia is of follicular cell origin (i.e., not lymphoid or other). Laboratories should use only one term, either AUS or FLUS; the use of both terms in the same laboratory as a means of subclassification (e.g., AUS for cytologic atypia, FLUS for architectural atypia) is discouraged because this practice is confusing and antithetical to the concept that AUS and FLUS are synonymous.

It should be acknowledged that the reproducibility of AUS/FLUS is at best only fair [18]. In laboratories with very low AUS/FLUS rates [19–21], the rates of FN/SFN and FNHCT/SFNHCT are relatively elevated, suggesting that at least some

cases that might have been placed in the AUS/FLUS category are shifted into these categories. Similarly, an inverse relationship exists between the use of AUS/FLUS and the nondiagnostic/unsatisfactory category, indicating differing approaches to diagnostically limited material [20].

Criteria (Figs. 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 4.10, 4.11, 4.12, 4.13, 4.14, 4.15, and 4.16)

The heterogeneity of this category precludes describing all scenarios for which an AUS/FLUS interpretation is appropriate. The most common situations, however, are outlined here. These scenarios are organized to facilitate subclassification of AUS/FLUS aspirates, if desired. Subclassification is encouraged primarily to enhance communication with other pathologists and clinicians and to facilitate further refinement of the category as new information becomes available and new entities (like NIFTP) are defined. Descriptive language may occasionally influence management; for example, a repeat aspirate is more likely to be of benefit when the initial aspirate is scant or poorly preserved, whereas molecular testing may be preferred for follow-up of a cellular, well-preserved aspirate with diffuse mild atypia.

Different terms may be considered for AUS/FLUS subqualifiers. One approach is to subclassify according to the most likely diagnosis (e.g., "rule out papillary carcinoma," "rule out follicular neoplasm"). Although this approach has the merit of directness, there is potential for confusion with the SUS, FN/SFN, or FNHCT/SFNHCT categories, with attendant overtreatment. Alternatively, cases can be subqualified with descriptive language that is less provocative to clinicians and patients (e.g., "cytologic atypia" rather than "rule out papillary carcinoma"). Such descriptive language is preferred due to its less provoking nature and is therefore used exclusively throughout the following discussion.

1. Cytologic atypia
   (a) *Focal cytologic atypia* (Fig. 4.1)
   Most of the aspirate appears benign, but rare cells have nuclear enlargement, pale chromatin, and irregular nuclear contours (especially common in patients with lymphocytic (Hashimoto) thyroiditis). Nuclear pseudoinclusions are typically absent. Rare pseudoinclusions by themselves may prompt an AUS/FLUS diagnosis, but if they are accompanied by other compelling features of papillary carcinoma, the case should be considered suspicious for malignancy. Alternatively, a sample may be paucicellular and contain cells as described above.
   (b) *Extensive but mild cytologic atypia* (Fig. 4.2)
   Many if not most cells have mildly enlarged nuclei with slightly pale chromatin and only limited nuclear contour irregularity. Nuclear pseudoinclusions are typically absent.
   (c) *Atypical cyst-lining cells* (Fig. 4.3)
   The cytomorphology of cyst-lining cells has been well described [22], and the majority of them can be recognized as such and diagnosed as benign.

In rare cases, however, there is more atypia than usual, and it is appropriate to diagnose these as AUS/FLUS. Cyst-lining cells may appear atypical due to the presence of nuclear grooves, prominent nucleoli, elongated nuclei and cytoplasm, and/or rare intranuclear pseudoinclusions in an otherwise predominantly benign-appearing sample.

(d) *"Histiocytoid" cells* (Fig. 4.4)
These cells are characteristic of cystic papillary carcinoma [23, 24], which can be difficult to diagnose due to sampling and interpretation issues [25]. Aspirates containing histiocytoid cells often have numerous histiocytes but few benign follicular cells. The histiocytoid cells are larger than histiocytes, typically isolated but sometimes in microfollicular arrangements or clusters. Compared with histiocytes, they often have rounder nuclei, a higher nuclear-to-cytoplasmic ratio, and "harder" (glassier) cytoplasm, without the hemosiderin or microvacuolization of histiocytes, though larger, discrete vacuoles are present. Epithelial (keratins) and histiocytic (CD68, PU.1) immunostains are potentially useful but often of limited value due to scant cellularity, unless a cell block has been made from the fluid.

2. Architectural atypia
   (a) A scantly cellular specimen with rare clusters of follicular cells, almost entirely in microfollicles or crowded three-dimensional groups and with scant colloid (Fig. 4.5). Although this pattern is low risk, AUS/FLUS is warranted due to concern regarding limited sampling of a lesion that would merit an FN/SFN diagnosis if the specimen were more cellular.
   (b) Focally prominent microfollicles with minimal nuclear atypia (Fig. 4.6).
   A more prominent than usual population of microfollicles may occur (and may be disproportionately apparent on a minority of smears) in a moderately or markedly cellular sample, but the overall proportion of microfollicles is not sufficient for a diagnosis of FN/SFN. This usually arises with direct smears and consists of a single slide or an area of the slide that looks different than the rest of the aspirate. This pattern should not be confused with an overall mixed, but predominantly macrofollicular, aspirate, which should be called benign.
3. Cytologic and architectural atypia (Fig. 4.7)
   The patterns described above are not mutually exclusive. The presence of both mild cytologic and architectural atypia may be more common with NIFTP, but this has not been firmly established.
4. Hürthle cell aspirates
   (a) A sparsely cellular aspirate comprised exclusively (or almost exclusively) of Hürthle cells with minimal colloid (Fig. 4.8). Although this pattern is very low risk, AUS/FLUS is warranted due to concern for limited sampling of a lesion that would merit an FNHCT/SFNHCT diagnosis if the specimen were highly cellular.
   (b) A moderately or markedly cellular sample composed exclusively (or almost exclusively) of Hürthle cells, yet the clinical setting suggests a benign

Hürthle cell nodule, such as in lymphocytic (Hashimoto) thyroiditis or a multinodular goiter (MNG) (Figs. 4.9 and 4.10).

- If the Hürthle cells are all in cohesive flat sheets without nuclear atypia and there is abundant colloid, a benign diagnosis is generally warranted in the absence of high-risk clinical or radiologic findings (see Chap. 6 for further discussion).
- There may be clinical evidence of lymphocytic (Hashimoto) thyroiditis, but lymphocytes are absent. Alternatively, a clinical diagnosis of Hashimoto thyroiditis has not been established, yet the presence of some lymphocytes (insufficient for a definitive diagnosis) raises concern for Hashimoto thyroiditis. A repeat aspirate or additional clinical evaluation may resolve the diagnostic uncertainty.
- When multiple nodules in the same patient show features that would otherwise prompt a diagnosis of FNHCT/SFNHCT, AUS/FLUS may be preferred on the presumption that MNG with multiple hyperplastic Hürthle cell nodules is more probable than concurrent Hürthle cell neoplasms.

5. Atypia, not otherwise specified (NOS)
   (a) A minor population of follicular cells shows nuclear enlargement, often accompanied by prominent nucleoli (Fig. 4.11).

   This pattern of nuclear atypia does not raise concern for papillary carcinoma and is, therefore, best classified as NOS. Specimens from patients with a history of radioactive iodine, carbimazole, or other pharmaceutical agents can usually be diagnosed as benign, assuming that the appropriate clinical history is available, but AUS/FLUS may be appropriate when the findings are particularly pronounced or there is uncertainty regarding the clinical history.

   (b) Psammomatous calcifications in the absence of nuclear features of papillary carcinoma (Fig. 4.12).

   Psammoma bodies raise concern for papillary carcinoma and should prompt careful scrutiny of follicular cells to identify the nuclear features of papillary carcinoma. "Lamellar bodies" of inspissated colloid may be indistinguishable from true psammomatous calcifications. In liquid-based preparations, small globules of thick colloid may display radial cracking, simulating psammoma bodies. The overall predictive value of psammoma bodies for papillary carcinoma is estimated to be about 50% [26], and, in the absence of a concerning population of follicular cells, this finding is best classified as AUS/FLUS.

   (c) Rare instances of atypia warranting an AUS/FLUS designation not explicitly described elsewhere in this chapter.

6. Atypical lymphoid cells, rule out lymphoma (Fig. 4.13)
   There is an atypical lymphoid infiltrate (for which a repeat aspirate for flow cytometry is desirable), but the degree of atypia is insufficient for the general category "suspicious for malignancy."

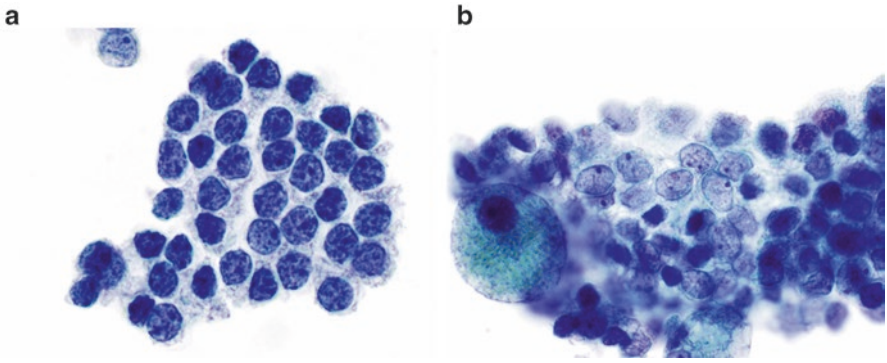

Fig. 4.1 Atypia of undetermined significance with cytologic atypia. (**a**) Most of the follicular cells are arranged in benign-appearing macrofollicle fragments. (**b**) Rare cells have pale nuclei and mildly irregular nuclear membranes. When such cells are very few in number, an atypical interpretation is more appropriate than "suspicious for malignancy" (ThinPrep, Papanicolaou stain).

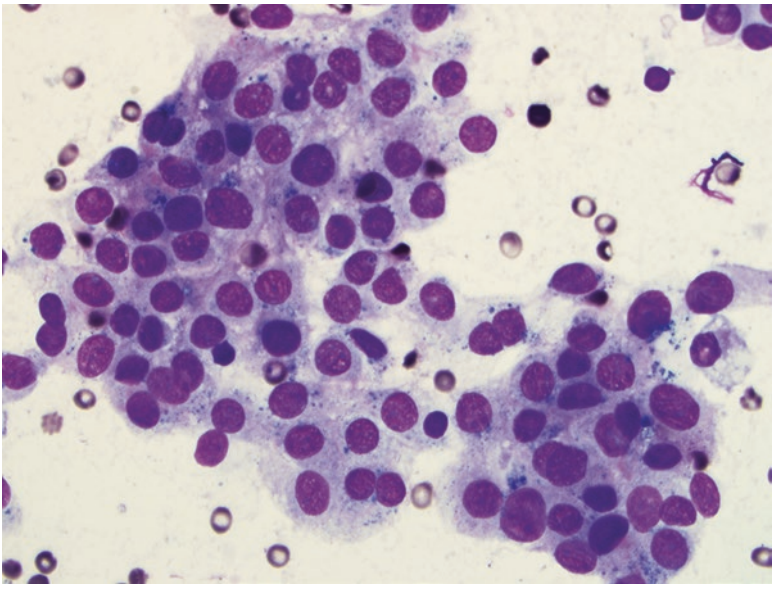

Fig. 4.2 Atypia of undetermined significance with cytologic atypia. Follicular cells show mild enlargement of most nuclei and contain hemosiderin pigment. Follow-up was papillary carcinoma. Hemosiderin does not preclude the possibility of papillary carcinoma (smear, Diff-Quik stain) (From Ali et al. [51]. All Rights Reserved).

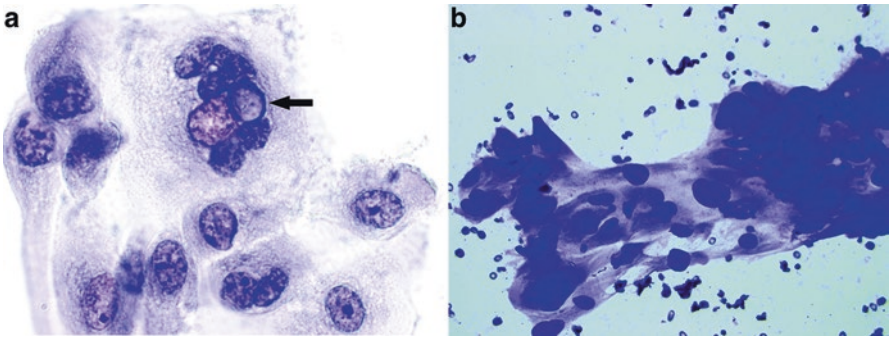

Fig. 4.3 Atypia of undetermined significance with cytologic atypia. (**a**) In this sparsely cellular specimen, some cells have abundant cytoplasm, enlarged nuclei, and prominent nucleoli. One nucleus has an apparent intranuclear pseudoinclusion (*arrow*). Such changes may represent atypical but benign cyst-lining cells, but a papillary carcinoma cannot be entirely excluded (ThinPrep, Papanicolaou stain). (**b**) Reparative-like changes of cyst-lining cells can mimic some cytologic features of papillary carcinoma (smear, Romanowsky stain).

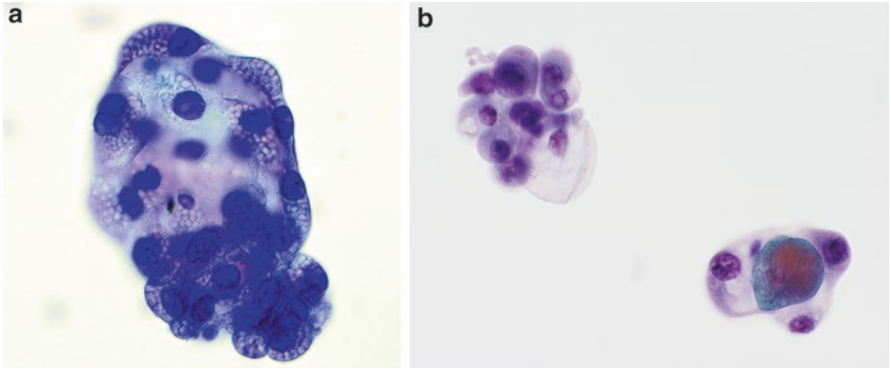

Fig. 4.4 Atypia of undetermined significance with cytologic atypia. (**a**) Cystic papillary carcinoma cells often show degenerative vacuoles; these cells have been termed "histiocytoid." A useful feature for recognizing them and distinguishing them from histiocytes is the sharply defined edges of the vacuoles, as opposed to the "fluffy" vacuoles of histiocytes (smear, Papanicolaou stain). (**b**) In this example, a loose cluster and a microfollicular group exhibit both "hard" cytoplasm and large cytoplasmic vacuoles (ThinPrep, Papanicolaou stain) (A: From Ali et al. [51]. All Rights Reserved).

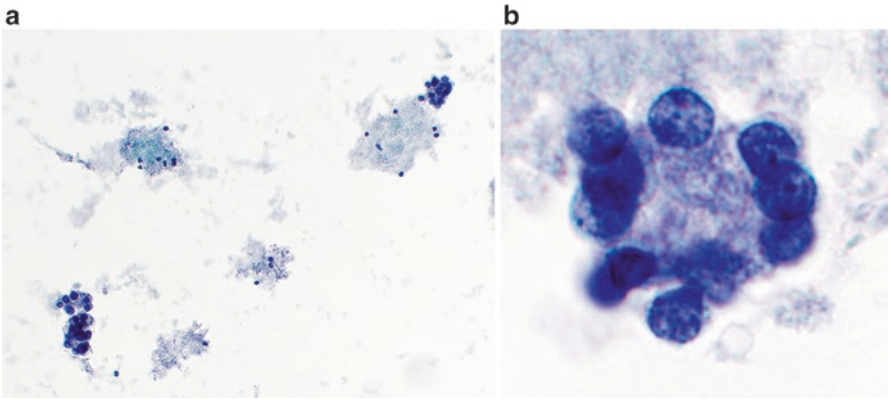

Fig. 4.5 Atypia of undetermined significance with architectural atypia. (**a**) Scanning magnification reveals a sparsely cellular specimen with a predominance of microfollicles. (**b**) High magnification of a microfollicle (ThinPrep, Papanicolaou stain).

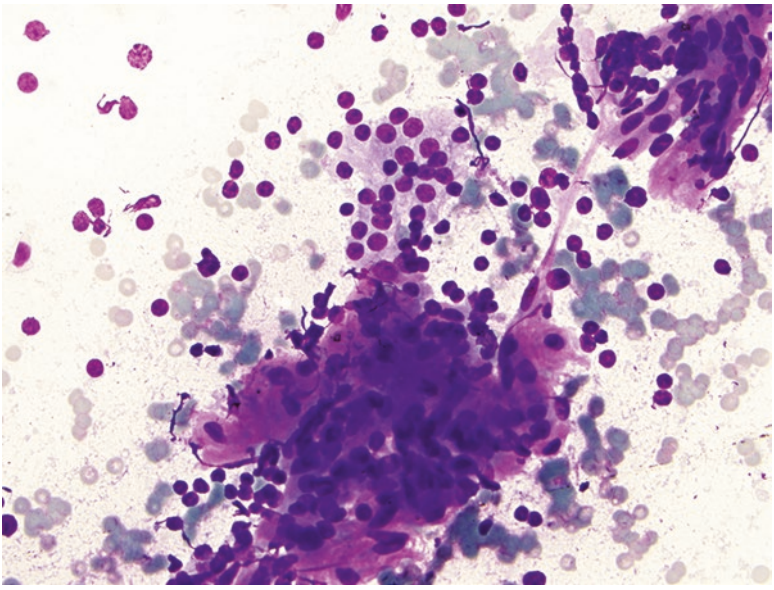

Fig. 4.6 Atypia of undetermined significance with architectural atypia. The smear shows cells arranged in a trabecular configuration with associated endothelial cells/blood vessels. Naked nuclei are prominent in the background, and colloid is absent. This proved to be a parathyroid adenoma on resection (smear, Diff-Quik stain) (From Ali et al. [51]. All Rights Reserved).

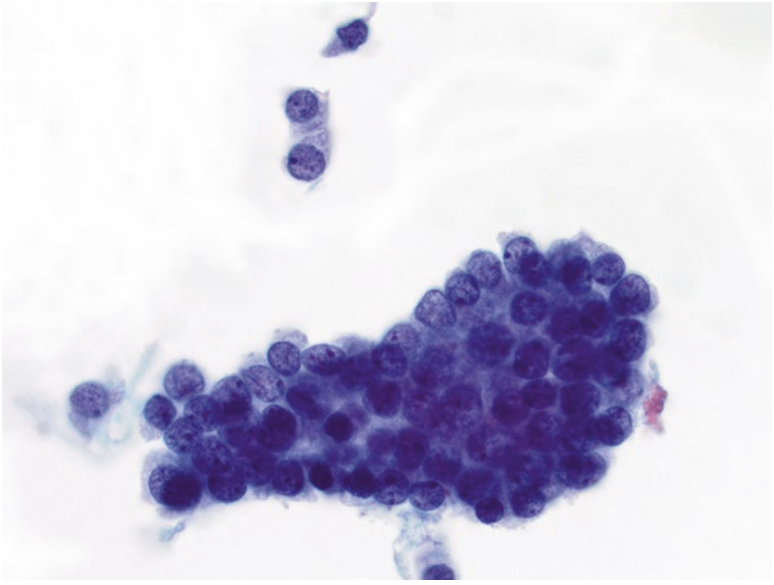

Fig. 4.7 Atypia of undetermined significance with architectural and cytologic atypia. Architectural atypia is manifested by a crowded three-dimensional configuration of follicular cells. Cytologic atypia is also evident, with nuclear enlargement, slight chromatin pallor, and a rare nuclear groove. The excised nodule was diagnosed as NIFTP (ThinPrep, Papanicolaou stain).

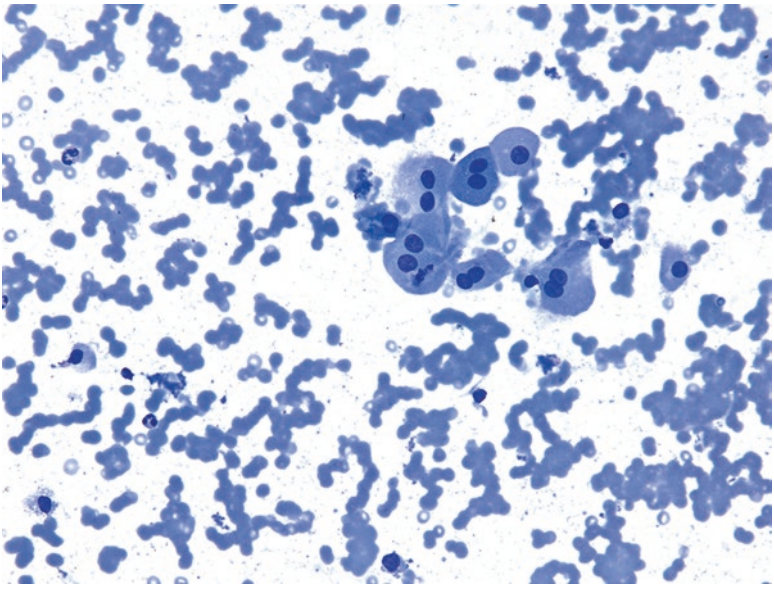

Fig. 4.8 Atypia of undetermined significance, Hürthle cell type. The aspirate is sparsely cellular with abundant blood. The few cells present are almost exclusively Hürthle cells (smear, Diff-Quik stain).

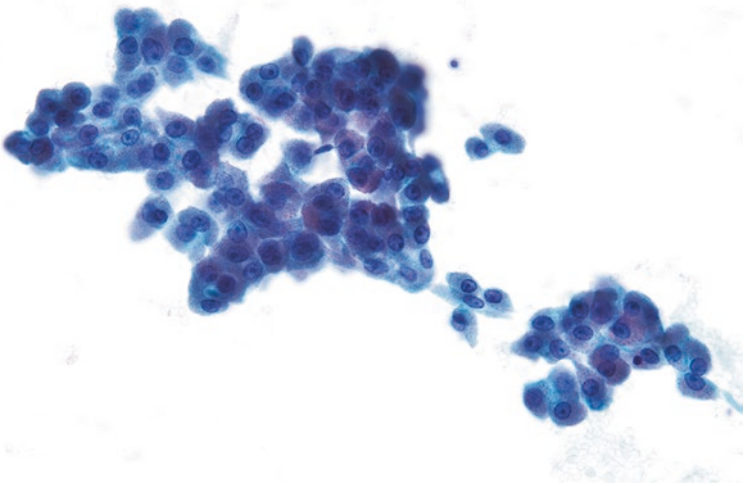

Fig. 4.9 Atypia of undetermined significance, Hürthle cell type (patient with multinodular goiter). This patient had two nodules, both showing almost exclusively oncocytic follicular cells (smear, Papanicolaou stain).

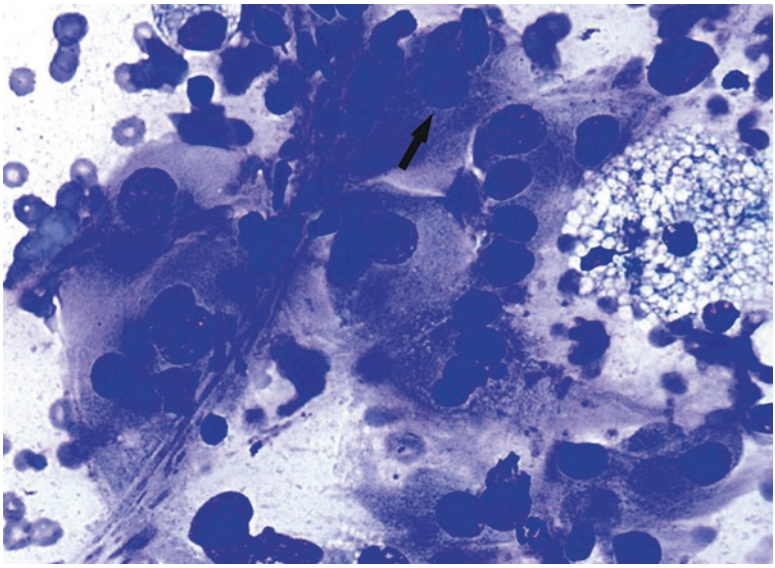

Fig. 4.10 Atypia of undetermined significance, Hürthle cell type (patient with history of Hashimoto thyroiditis). These Hürthle cells show nuclear enlargement and a rare nuclear pseudoinclusion (*arrow*) (smear, Diff-Quik stain).

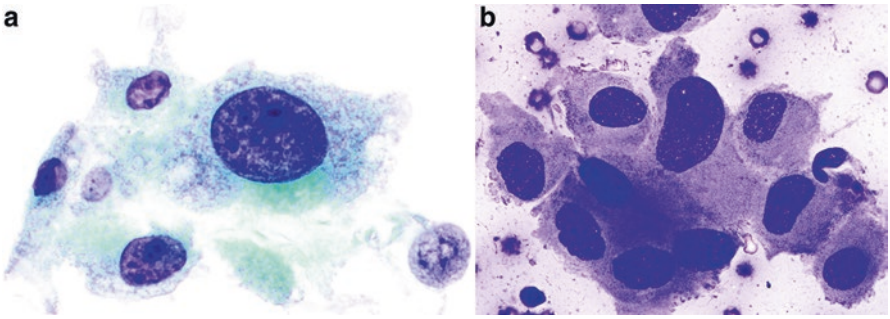

Fig. 4.11 Atypia of undetermined significance, not otherwise specified. The nuclear atypia in these specimens does not raise concern for papillary carcinoma. (**a**) These follicular cells, in a patient with Graves' disease treated with methimazole (Tapazole®), show marked nuclear enlargement and anisonucleosis (ThinPrep, Papanicolaou stain). (**b**) These atypical follicular cells were obtained from a patient with a history of ionizing radiation to the neck (smear, Romanowsky stain).

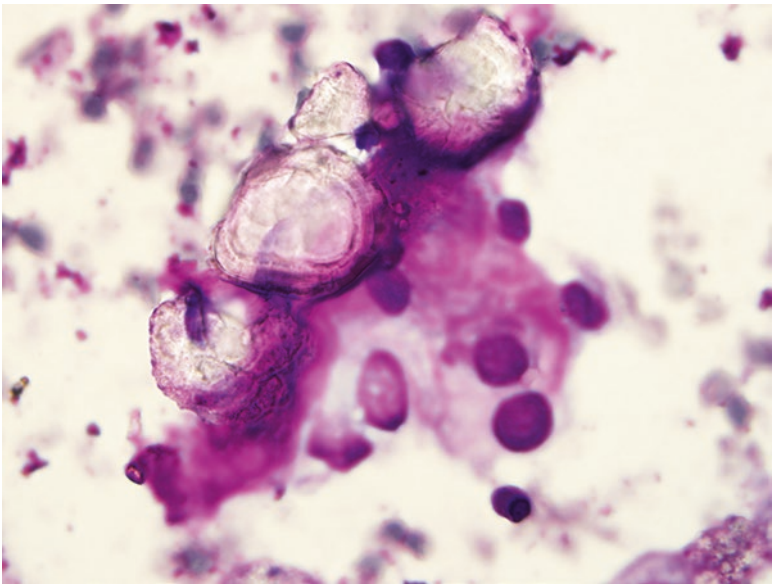

Fig. 4.12 Atypia of undetermined significance, not otherwise specified. Psammoma bodies are a characteristic feature of papillary carcinoma. They form at the tip of a papilla due to circumferential avascular necrosis, resulting in the concentric lamellations of the classic psammoma body. Psammoma bodies are non-birefringent and composed of calcium phosphate (smear, Diff-Quik stain) (From Ali et al. [51]. All Rights Reserved).

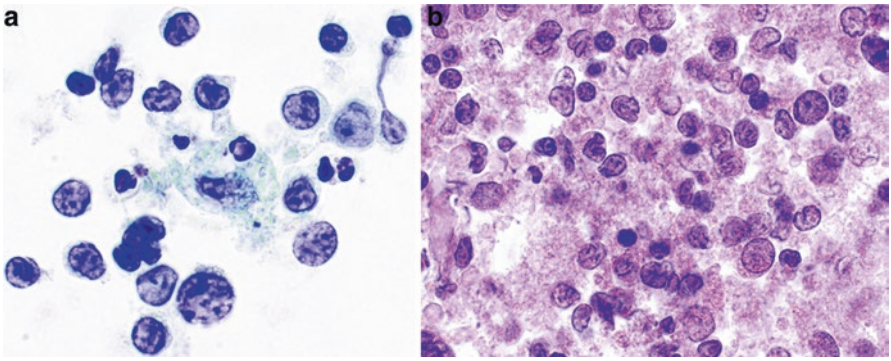

Fig. 4.13 Atypia of undetermined significance with atypical lymphoid cells. (**a**) The sample is composed of a heterogeneous infiltrate of lymphoid cells, including occasional atypical forms. There is a tingible body macrophage in the center of the field. Clonality studies were not available in this case (ThinPrep, Papanicolaou stain). (**b**) The cell block shows similar features (hematoxylin and eosin stain).

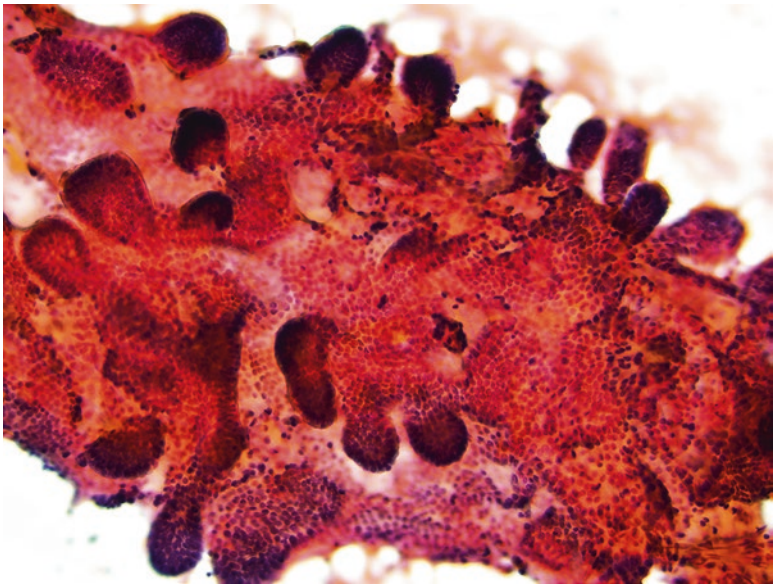

Fig. 4.14 Benign (papillary hyperplasia). Papillary projections are seen in papillary carcinoma, but Graves' disease and other hyperplastic thyroid nodules can show benign papillary proliferations. It is critical to carefully examine the cells, especially their nuclear features; a diagnosis of papillary carcinoma should not be rendered on architecture alone. In this case, the patient went to surgery and was found to have papillary hyperplasia in an involuting hyperplastic nodule (smear, Papanicolaou stain) (From Ali et al. [51]. All Rights Reserved).

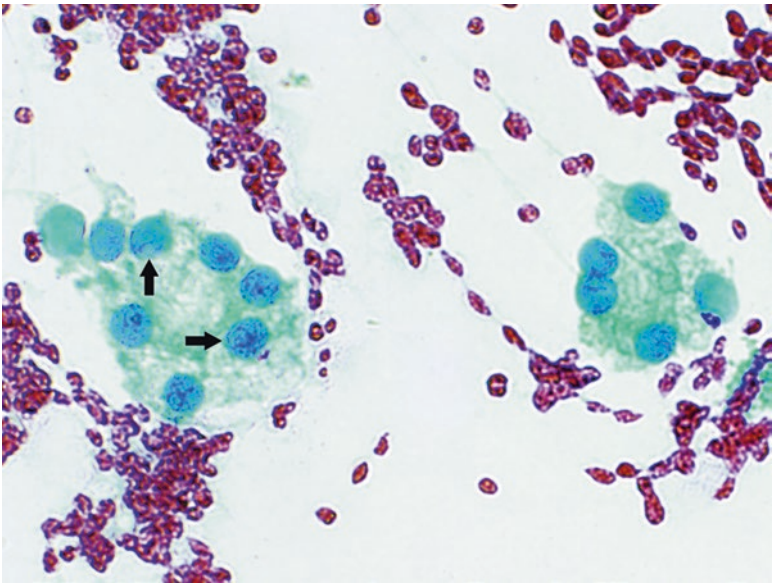

Fig. 4.15 Air-drying artifact. Inadvertent air-drying of alcohol-fixed smears leads to suboptimal nuclear detail (e.g., artifactual pallor, enlargement), including poorly defined, possible nuclear pseudoinclusions (*arrows*). Except in rare instances, such changes can be recognized as artifactual and not diagnosed as atypia of undetermined significance (smear, Papanicolaou stain).

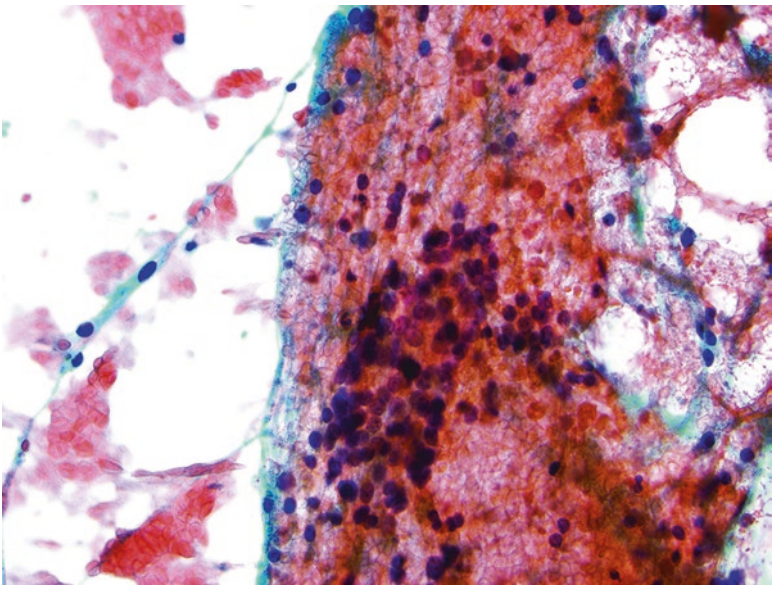

Fig. 4.16 Blood and clotting artifact. Extensive blood and clotting can distort the arrangement of follicular cells and make them look artifactually crowded. These findings should be discounted when assessing the architectural arrangement of the follicular cells. Without demonstrable atypia or sufficient benign follicular cells, such cases warrant a nondiagnostic/unsatisfactory interpretation (smear, Papanicolaou stain).

Explanatory Notes

AUS/FLUS usage varies widely; this interpretation has been reported to account for as little as 1% to as much as 22% of thyroid FNAs [3]. Many of the studies of AUS/FLUS were retrospective, however, with pre-TBSRTC terminology retrofitted to TBSRTC categories. Despite efforts to define this category and provide specific criteria, AUS/FLUS has, at best, only fair reproducibility [18]. A provisional goal of limiting AUS/FLUS interpretations to approximately 7% of all thyroid FNA interpretations was proposed in the previous edition of TBSRTC atlas [1]. In practice, many laboratories struggle to achieve this figure; an upper limit of 10% may be more realistic. Additionally, it has also been proposed that the AUS:malignant ratio may be a useful laboratory quality measure that should not exceed 3.0 [27].

By themselves, compromising factors like sparse cellularity, air-drying artifact, obscuring blood, and excessive clotting artifact do not warrant an AUS/FLUS diagnosis; such specimens should be called nondiagnostic (or unsatisfactory) if adequacy criteria are not satisfied and there is no atypia. Nevertheless, a diagnosis can be made on many compromised specimens: cases with prominent air-drying artifact, obscuring blood, and/or clotting artifact can still be diagnosed as benign if there are sufficient well-preserved, well-visualized follicular cells, and they can be diagnosed as abnormal (e.g., AUS/FLUS) if there is discernible atypia.

AUS/FLUS is an interpretation of last resort and should be used judiciously. For example, the mere presence of some Hürthle cells or cyst-lining cells, with their customary mild nuclear alterations (e.g., nuclear grooves, finely granular or pale chromatin), does not warrant an AUS/FLUS designation if there is ample evidence of benign follicular cells and abundant colloid. Isolated follicular cells with minimal alterations (isolated nuclear enlargement, pale chromatin, or nuclear grooves) or occasional microfollicles also do not merit the AUS/FLUS category. Mixed, but predominantly macrofollicular, architectural patterns are best classified as benign. Papillae in the absence of any nuclear features of papillary carcinoma (Fig. 4.14) are indicative of papillary hyperplasia and should be interpreted as benign [28].

AUS/FLUS specimens may be compromised by sparse cellularity that precludes a more definitive classification. A common example is the sparsely cellular aspirate with a predominance of crowded follicular cells in microfollicular or trabecular arrangements (“architectural atypia”) (Fig. 4.5). In a moderately-to-markedly cellular specimen, most samples with a predominance of follicular cells in crowded microfollicular or trabecular groups merit the interpretation FN/SFN (see Chap. 5). In general, cytologists are appropriately reluctant to make that interpretation on a sparsely cellular sample because the lesion may not have been properly sampled. A similar example is the sparsely cellular aspirate that is comprised exclusively of Hürthle cells (Fig. 4.8). In a moderately or markedly cellular specimen, a sample that consists entirely of Hürthle cells usually merits the interpretation FNHCT/SFNHCT (see Chap. 6). Most cytologists, again, are appropriately reluctant to make that interpretation in a sparsely cellular aspirate because of sampling concerns.

Specimen preparation artifacts may potentially raise concern for AUS/FLUS. Inadvertent air-drying of alcohol-fixed smears may result in follicular cells with enlarged nuclei that have pale but slightly smudgy chromatin and irregular nuclear outlines (Fig. 4.15). Alternatively, excessive blood clotting can impair the presentation of follicular cells, often giving the false impression of architectural crowding due to the entrapment of cells in the clot or the false impression of nuclear grooves due to fibrin strands (Fig. 4.16). These artifacts by themselves are not associated with an increased risk of malignancy. If the artifacts described above are focal, clearly recognizable, and associated with benign material elsewhere, such cases should be diagnosed as benign. Alternatively, when the artifacts are so pervasive as to preclude fulfilling standard adequacy criteria for well-preserved follicular cells, such aspirates should be deemed nondiagnostic/unsatisfactory for evaluation. Only rare cases where there is uncertainty – are the cytologic changes artifactual in origin or truly atypical? – should result in an AUS/FLUS diagnosis. The possibility of a compromised sample with artifactual changes should be acknowledged when reporting these specimens.

The possibility of a parathyroid lesion [29–32] should be considered when crowded three-dimensional clusters or trabecular arrangements are present. About 25–30% of these lesions can be recognized based on the presence of salt and pepper chromatin with or without abundant granular cytoplasm and accompanying crowded architecture. Immunohistochemistry and ancillary studies (parathyroid hormone assays, molecular studies) can confirm the diagnosis when it is considered by the pathologist, radiologist, or clinician, but without clinicopathologic correlation, many such nodules are not recognized as parathyroid in origin, especially when intrathyroidal. Both the Afirma gene expression classifier and the ThyroSeq test, used for molecular testing of AUS/FLUS aspirates, recognize the expression profile of parathyroid cells [33–35].

A moderately or markedly cellular aspirate from a solitary nodule that is composed virtually exclusively of Hürthle cells is reported as FNHCT/SFNHCT (see Chap. 6). In some clinical settings, namely, lymphocytic (Hashimoto) thyroiditis and MNG, this pattern is believed to be more highly predictive of a hyperplastic Hürthle cell nodule (and less predictive of a Hürthle cell neoplasm) than usual [36]. It is thus acceptable to diagnose an exclusively Hürthle cell specimen in a patient with Hashimoto thyroiditis or MNG as AUS/FLUS. If interpreted as AUS/FLUS, an explanatory note that raises the possibility of a Hürthle cell hyperplasia can be very helpful (see Sample Reports 4 and 5). The great majority of malignancies that develop in patients with known Hashimoto thyroiditis are papillary carcinomas; Hürthle cell carcinoma in the setting of Hashimoto thyroiditis is rare. As a result, cases with obvious Hashimoto thyroiditis and an atypical collection of Hürthle cells should typically be diagnosed as benign. The note that accompanies an AUS/FLUS interpretation in these settings is meant to more accurately reflect the underlying risk of malignancy, which, although not precisely characterized, is likely lower than that of FNHCT/SFNHCT in general. The goal is to provide the clinician with the opportunity to avoid an unnecessary lobectomy in some of these patients. In this setting, the clinical decision to follow a patient rather than perform a lobectomy will

often be based on clinical and sonographic correlation; it is not clear whether a repeat aspiration is likely to add any helpful information.

The distinction between AUS/FLUS and suspicious for malignancy is problematic in aspirates with focal features of papillary carcinoma. AUS/FLUS with cytologic atypia is associated with papillary carcinoma in 28–56% of cases [6, 10]. As described, this pattern has rare cells (typically less than 20 in number [37]) with enlarged, often overlapping, nuclei, pale chromatin, irregular nuclear outlines, and nuclear grooves. When accompanied by well-defined, intranuclear pseudoinclusions and/or psammomatous calcifications, these findings are even more highly associated with papillary carcinoma [38]. A second pattern highly associated with the follicular variant of papillary carcinoma (and potentially with NIFTP) is diffuse but subtle nuclear enlargement, focal nuclear irregularity, and only occasional intranuclear grooves, often with a microfollicular architecture [39]. Such aspirates are usually better classified as suspicious for malignancy (see Chap. 7) when nuclear alterations are prominent; "suspicious for a follicular neoplasm" is more appropriate when microfollicular architecture is more pronounced (see Chap. 5). The AUS/FLUS designation should be reserved for cases with few cells that have distinct but mild nuclear atypia (Fig. 4.1) and cases with more extensive but very mild nuclear atypia (Fig. 4.2). It must be acknowledged that precisely defining this distinction is difficult; pathologist experience influences the recognition and correct classification of these cases. Expert consultation may be warranted, especially in challenging cases. Additionally, with the advent of NIFTP, a subset of the above cases will no longer be classified as carcinoma at resection [16, 17].

Cyst-lining cells are reactive follicular and/or mesenchymal cells associated with cystic degeneration of thyroid nodules. As such, they have very characteristic features and can be diagnosed as benign in most cases (see Fig. 3.14) [22]. They are typically elongated, with pale chromatin, occasional intranuclear grooves, and relatively large nucleoli, and are virtually always associated with hemosiderin-laden macrophages. The spindle-shaped morphology of the cell and nucleus, reminiscent of reparative epithelium in cervical, bronchial, and gastrointestinal cytologic specimens, is helpful in distinguishing these cells from papillary carcinoma. In some cases, however, the cells are more closely packed, less elongated, and, as a result, more difficult to distinguish definitively from papillary carcinoma (Fig. 4.3b) [22]. In these uncommon instances, a diagnosis of AUS/FLUS is appropriate.

Isolated nuclear enlargement, typically with prominent nucleoli, is common in benign thyroid nodules and by itself does not indicate malignancy. In patients treated with radioactive iodine, carbimazole, or other pharmaceutical agents, nuclear enlargement can be especially prominent [40–42]. When the changes are mild and characteristic in a specimen accompanied by a clinical history of such treatment, a benign interpretation should be rendered. In some patients, however, the changes can be extreme and raise the possibility of papillary carcinoma or other malignancy (Fig. 4.11) [41, 42]. In such cases, an AUS/FLUS interpretation is warranted.

Most AUS/FLUS cases are based on follicular cell atypia, but in rare cases, the AUS designation may be appropriate for non-follicular and even non-epithelial

atypia. An example of non-epithelial atypia that may warrant the AUS category is an atypical or monomorphous lymphoid infiltrate, especially in the setting of long-standing Hashimoto thyroiditis and/or a large or rapidly growing nodule. In some cases, the findings are not sufficiently concerning to warrant a suspicious or malignant diagnosis. Aspirates that have a prominent, somewhat polymorphous, lymphoid component may raise concern for an extranodal marginal zone B-cell lymphoma (Fig. 4.13). If clonality studies are not available, an AUS diagnosis, with a recommendation for a repeat aspirate for flow cytometry, is appropriate.

Management

The 2015 American Thyroid Association guidelines recommend conservative management in most instances for an initial AUS/FLUS interpretation, with either repeat FNA or molecular testing [43]. A repeat FNA usually results in a more definitive cytologic interpretation; only about 10–30% of initially AUS/FLUS nodules are reported again as AUS/FLUS when the FNA is repeated [44–46]. Mutational testing for AUS/FLUS exhibits low sensitivity for the *BRAF* V600E mutation alone, reflecting the observation that malignancies identified from the AUS/FLUS category are low risk relative to the malignant and suspicious for malignancy categories [35, 47]. Expanded mutation panels exhibit higher sensitivity, although specificity is diminished by the increased prevalence of *RAS* mutations. In a blinded, multi-institutional study of the Afirma gene expression classifier (GEC), a negative result with AUS/FLUS aspirates reduced the ROM from 24% to 5%, a result that justifies observation over surgery for patients with a negative GEC test [48]. Approximately one-half of AUS/FLUS cases have a negative GEC result. A negative GEC result is more likely in AUS/FLUS with isolated architectural atypia than AUS/FLUS with cytologic atypia or cytologic plus architectural atypia [49]. The Hürthle cell pattern of AUS/FLUS has a lower rate of GEC benign results despite its very low risk of malignancy [50]. The decision regarding surgery (typically lobectomy) vs. continued observation is based on a synthesis of cytologic, molecular, clinical, and radiologic findings as well as clinical risk factors and patient preference. The ROM of an AUS/FLUS nodule selected for surgical excision varies greatly and is dependent on the subtype of AUS/FLUS, with a mean ROM of 47% for AUS/FLUS with cytologic atypia and only 5% for AUS/FLUS due to Hürthle cell atypia [6–11]. The introduction of NIFTP will diminish the overall ROM for AUS/FLUS, although it should be emphasized that surgical excision is indicated for NIFTP [16, 17].

Sample Reports

If an aspirate is interpreted as AUS/FLUS, it is implied that the sample is adequate for evaluation. (An explicit statement of adequacy is optional.) Narrative comments are strongly recommended to further describe the findings. A differential diagnosis

and a recommendation may also be helpful for cases that fall into the AUS/FLUS category. Subclassification of AUS/FLUS according to the most common patterns described above, and particularly the higher risk group of cases with cytologic atypia, is encouraged. Generic descriptors (e.g., "focal cytologic atypia," "architectural atypia") are preferred over phrases associated with malignancy (e.g., "rule out papillary carcinoma," "pseudoinclusions"), which may prompt surgery rather than the intended more conservative management.

Example 1
ATYPIA OF UNDETERMINED SIGNIFICANCE.
Sparsely cellular aspirate comprised of follicular cells with architectural atypia. Colloid is absent.

Note: Molecular testing or a repeat aspirate may be helpful if clinically indicated.

Example 2
FOLLICULAR LESION OF UNDETERMINED SIGNIFICANCE.
Follicular cells with mild cytologic atypia.

Note: Molecular testing or a repeat aspirate may be helpful if clinically indicated.

Example 3
ATYPIA OF UNDETERMINED SIGNIFICANCE.
Follicular cells, predominantly benign appearing, with focal cytologic atypia.

Note: Molecular testing or a repeat aspirate may be helpful if clinically indicated.

Example 4 (FNA of a Patient with Multiple Hurthle Cell Nodules)
ATYPIA OF UNDETERMINED SIGNIFICANCE.
The specimen is moderately cellular and consists almost exclusively of Hürthle cells. Colloid is scant, and there is no apparent increase in lymphoid cells.

Note: In a patient with multiple Hurthle cell nodules, the findings likely represent Hürthle cell hyperplasia in the setting of multinodular goiter, but a Hürthle cell neoplasm cannot be entirely excluded. Clinical correlation is advised.

Example 5 (FNA of a Nodule in a Patient with a History of Hashimoto Thyroiditis)
ATYPIA OF UNDETERMINED SIGNIFICANCE.
The sample consists exclusively of Hürthle cells.

Note: In a patient with Hashimoto thyroiditis, the findings likely represent Hürthle cell hyperplasia, but a Hürthle cell neoplasm cannot be entirely excluded. Clinical-radiologic correlation is advised.

Example 6 (FNA of a Nodule in a Patient Treated with ^{131}I)
ATYPIA OF UNDETERMINED SIGNIFICANCE.
Marked cytologic atypia of follicular cells.

Note: In a patient treated with radioiodine, the findings likely represent reactive, treatment-related changes, but a neoplasm cannot be entirely excluded. Clinical correlation is advised.

Example 7
ATYPIA OF UNDETERMINED SIGNIFICANCE.
Numerous relatively monomorphic lymphoid cells.

Note: The findings are atypical and raise the possibility of a lymphoproliferative lesion, but immunophenotyping studies could not be performed because of insufficient material. An additional aspiration, with apportioning of fresh needle-rinse fluid for flow cytometry, might be helpful if clinically indicated.

Example 8
ATYPIA OF UNDETERMINED SIGNIFICANCE.
Psammomatous calcifications are present in a background of benign-appearing follicular cells and colloid.

Note: Psammomatous calcifications in isolation are associated with both benign and malignant conditions, including papillary thyroid carcinoma. Correlation with clinical and radiologic findings is recommended.

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Follicular Neoplasm/Suspicious for a Follicular Neoplasm

5

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Background

Prior to the introduction of the Bethesda System for Reporting Thyroid Cytopathology, there was great variability in the way thyroid aspirates that are suspicious for a follicular neoplasm were reported, as demonstrated by a review of the literature compiled for the National Cancer Institute (NCI)-sponsored Thyroid Fine-Needle Aspiration State of the Science Conference in 2007 [1]. The terminology used ranged from broad terms like "follicular lesion," "follicular proliferation," and "indeterminate" to the more specific terms like "rule out/suggestive of/suspicious for follicular neoplasm" or "follicular neoplasm" [2–10]. Much of this variability resulted from the fact that the so-called follicular lesions, comprised of nodular goiter (nodular hyperplasia), follicular adenoma, follicular variant of papillary carcinoma, follicular carcinoma, and the recently described noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP), have overlapping cytomorphologic features and cannot be accurately distinguished by FNA alone. Nevertheless, certain cytologic features are very useful in raising the

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possibility of a neoplasm, most importantly the possibility of a carcinoma. In this regard, FNA can be considered a screening test, selecting for surgery those nodules with a greater probability of malignancy. The final diagnosis depends upon lobectomy because capsular and/or vascular invasion is the sine qua non of follicular carcinoma. In 2016 an international panel convened to review the 2007 terminology and criteria and proposed changes based on current knowledge [11]. The panel preferred having just one term for this category but recognized that, for practical purposes, the terms "follicular neoplasm" and "suspicious for a follicular neoplasm" are equally acceptable. A laboratory should choose the one it prefers and use it exclusively for that category. These synonymous terms should not be used separately to denote two distinct and different interpretations. "Suspicious for a follicular neoplasm (SFN)" is preferred over "follicular neoplasm (FN)" by some laboratories because a significant proportion (up to 35%) of cases that fulfill the criteria described herein prove not to be neoplasms but rather hyperplastic proliferations in nodular goiter [3–5, 12, 13]. The term SFN acknowledges this limitation, provides a rational framework for cytologic-histologic correlation, and preserves the credibility of cytopathologists with their clinical colleagues and the patients they serve. The goal of this category is to identify all potential follicular carcinomas and refer them for appropriate follow up, most often a diagnostic lobectomy [14]. It is not the goal of FNA to identify all follicular neoplasms, because adenomas are clinically innocuous, and there is little if any evidence to suggest progression from adenoma to carcinoma in the thyroid. Nevertheless, the terms FN and SFN are preferred over "suspicious for follicular carcinoma" for several reasons. Both FN and SFN have an established tradition in many laboratories; the terms recognize the impossibility of distinguishing adenoma from carcinoma by FNA; and both terms recognize that the majority of cases interpreted as FN/SFN turn out to be follicular adenomas simply because follicular adenomas outnumber follicular carcinomas in the population.

It is important to point out that cytologic-histologic correlation for the follicular-patterned thyroid nodules is hindered somewhat by the imperfect reproducibility among histopathologists in the diagnosis of nodular hyperplasia, follicular adenoma, follicular carcinoma, the follicular variant of papillary carcinoma, and the recently recognized noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) [15–17].

Definition

The general diagnostic category "follicular neoplasm" or "suspicious for a follicular neoplasm" refers to a cellular aspirate comprised of follicular cells, most of which are arranged in an altered architectural pattern characterized by significant cell crowding and/or microfollicle formation. The sample should be at least moderately cellular; sparsely cellular aspirates are excluded from this category and could be interpreted as *atypia of undetermined significance* or *follicular lesion of undetermined significance* (see Chap. 4). Cases that demonstrate suspicious or definitive nuclear features for papillary carcinoma are excluded from this category and should be classified as *suspicious*

for malignancy or *malignant*, respectively. Follicular-patterned aspirates with mild nuclear changes, such as increased nuclear size, nuclear contour irregularity, and/or chromatin clearing, can be classified as FN/SFN so long as true papillae and intranuclear pseudoinclusions are absent; a note that some nuclear features raise the possibility of an invasive follicular variant of papillary carcinoma or the more indolent noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) can be included [18, 19].

Criteria

Cytologic preparations are moderately or markedly cellular (Fig. 5.1a, b).
There is a significant alteration in follicular cell architecture, characterized by cell crowding, microfollicles, and dispersed isolated cells (Fig. 5.2a, b).
Follicular cells are normal-sized or enlarged and relatively uniform, with scant or moderate amounts of cytoplasm.
Nuclei are usually round and slightly hyperchromatic, with inconspicuous nucleoli (Fig. 5.2a, b).
Some nuclear atypia may be seen, either enlarged, variably sized nuclei, and prominent nucleoli (Fig. 5.3a, b) or enlarged nuclei with nuclear contour irregularity and mild and/or focal chromatin clearing.
Colloid is scant or absent.

Explanatory Notes

The hallmark of the FN/SFN specimen is the presence of a significant architectural alteration in the majority of the follicular cells. The altered architecture takes the form of crowded and overlapping follicular cells (Fig. 5.4a, b), some or most of which are arranged as microfollicles. To improve reproducibility, it has been

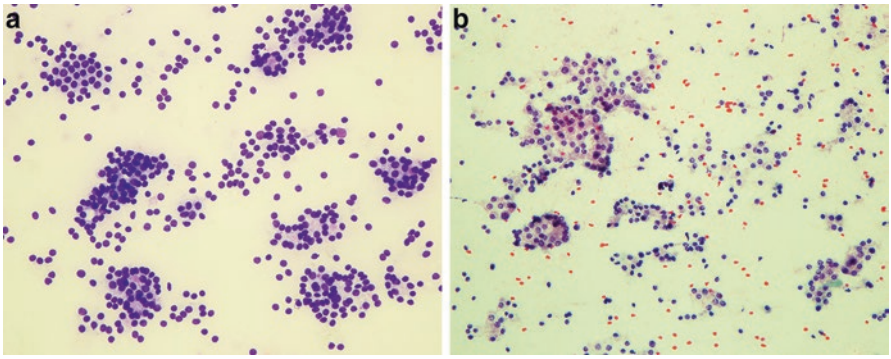

Fig. 5.1 Follicular neoplasm/suspicious for a follicular neoplasm. (**a**, **b**) Low magnification shows a highly cellular aspirate composed of uniform follicular cells arranged in crowded clusters and microfollicles (**a** smear, Diff-Quik stain; **b** smear, Papanicolaou stain).

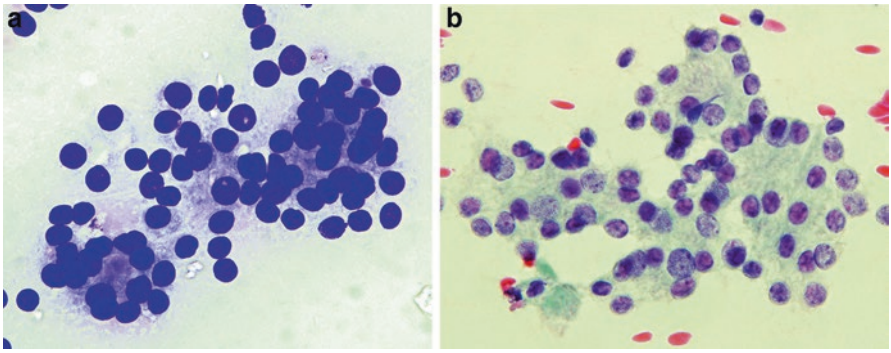

Fig. 5.2 Follicular neoplasm/suspicious for a follicular neoplasm. (**a**) The crowded follicular cells have round nuclei of similar size and faint cytoplasm (smear, Diff-Quik stain). (**b**) Follicular cells are arranged as microfollicles and have round nuclei, evenly dispersed, granular chromatin, and small nucleoli (smear, Papanicolaou stain).

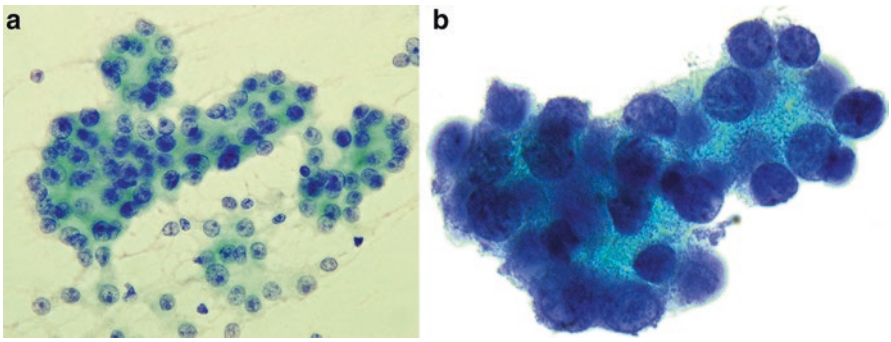

Fig. 5.3 Follicular neoplasm/suspicious for a follicular neoplasm. (**a**, **b**) Follicular cells in crowded, microfollicular arrangements show slight size variation, chromatin that is more "open" (less granular), and enlarged nucleoli (**a** smear, Papanicolaou stain; **b** ThinPrep, Papanicolaou stain).

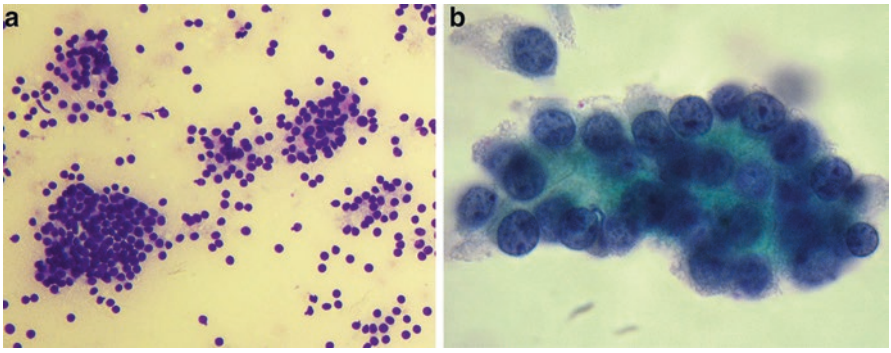

Fig. 5.4 Follicular neoplasm/suspicious for a follicular neoplasm. (**a**, **b**) Microfollicles demonstrate nuclear overlap. Some are loosely cohesive clusters, and there are dispersed, isolated cells (**a** smear, Diff-Quik stain; **b** ThinPrep, Papanicolaou stain).

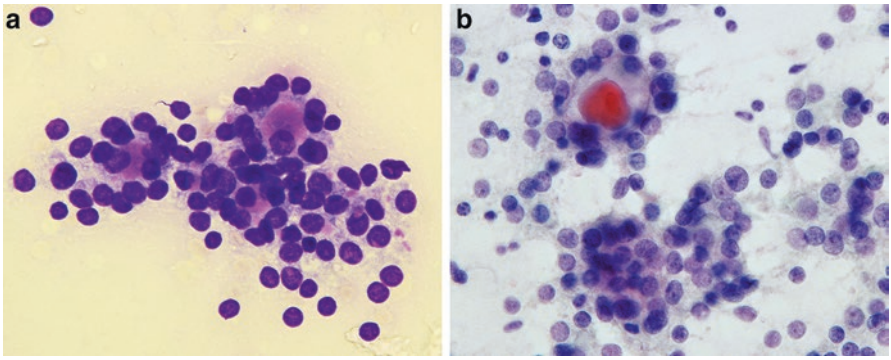

Fig. 5.5 Follicular neoplasm/suspicious for a follicular neoplasm. (**a**, **b**) Microfollicles may contain small amounts of colloid (**a** smear, Diff-Quik stain; **b** smear, Papanicolaou stain).

proposed that the "microfollicle" designation must be limited to crowded, flat groups of less than 15 follicular cells arranged in a circle that is at least two-thirds complete [15], but this recommendation has not been tested in a prospective study. A small amount of inspissated colloid may be present within the microfollicle (Fig. 5.5a, b). Microfollicles tend to be relatively uniform in size ("equisized"). In some cases, crowded follicular cells form ribbons of overlapping cells ("trabeculae") that are more prominent than the microfollicles (Fig. 5.6).

It is important to recognize that rare macrofollicle fragments as well as some background colloid may be present in FN/SFN specimens. A small fragment of follicular cells is not necessarily a microfollicle: an important defining feature of the microfollicle is the crowding and overlapping of the follicular cells.

Cystic change is not common unless the neoplasm is large, at which point it may undergo central degenerative change with associated findings (foamy and hemosiderin-laden macrophages).

Although most FN/SFNs are highly cellular specimens, cellularity by itself is not sufficient to merit this designation [20]. If the majority of follicular cells are arranged in macrofollicle fragments (variably sized fragments without overlap or crowding), the sample can be considered benign. Similarly, nuclear atypia by itself is not diagnostic of malignancy or even neoplasia, as hyperplastic nodules and follicular adenomas can demonstrate nuclear enlargement and hyperchromasia [21–23].

An occasional dilemma is the sparsely cellular sample composed predominantly of microfollicles. Most cytologists are reluctant to make an FN/SFN interpretation on a sparsely cellular sample because of the discrepancy between the cellularity and the cell pattern. It is reasonable to interpret such cases as *atypia of undetermined significance* (or *follicular lesion of undetermined significance*) (see Chap. 4). In such cases, a repeat aspiration and/or molecular testing is a reasonable approach and is likely to resolve the discrepancy.

In some instances, both architectural features concerning for a follicular neoplasm and nuclear features concerning for papillary carcinoma are present.

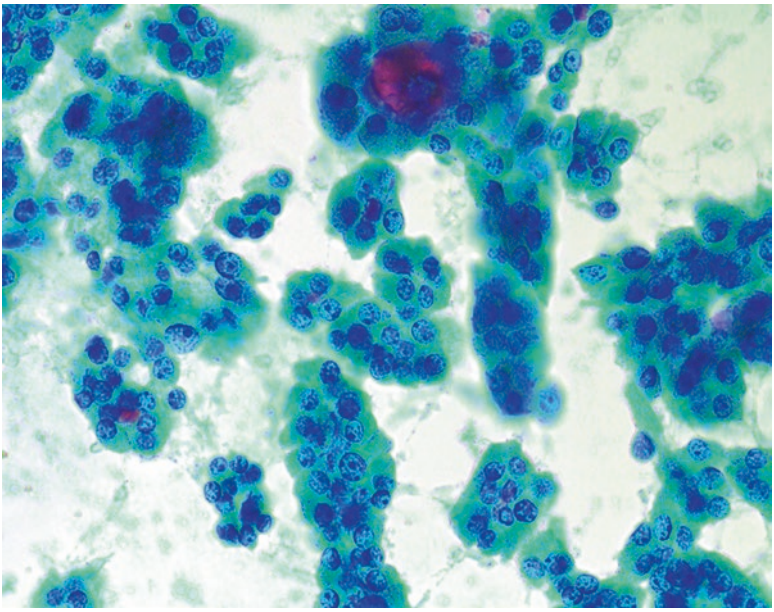

Fig. 5.6 Follicular neoplasm/suspicious for a follicular neoplasm. In some cases, trabeculae of crowded follicular cells are more conspicuous than microfollicles (smear, Papanicolaou stain).

If the follicular cells show definitive nuclear features of papillary thyroid carcinoma, including frequent intranuclear pseudoinclusions, and if there are at least focal elements associated with classical papillary carcinoma (psammoma bodies and/or true papillae), the specimen should not be interpreted as FN/SFN but rather as "*malignant*, papillary thyroid carcinoma" [18, 24, 25]. If nuclear features of papillary carcinoma are not definitive or architectural features of classical papillary carcinoma are absent, such aspirates raise concern for invasive follicular variant of papillary carcinoma or NIFTP. Whether such aspirates are better classified as FN/SFN or "*suspicious for malignancy*, suspicious for papillary thyroid carcinoma" will be dictated by the quality and quantity of the cytologic changes. In either instance, an explanatory note regarding concern for NIFTP/invasive follicular variant of papillary carcinoma is warranted [17]. (See section "Sample reports," Example 4.) For lesions deemed borderline between FN/SFN and *suspicious for malignancy*, it may be more prudent to opt for the FN/SFN designation because the FN/SFN diagnosis is more likely to prompt a limited surgical approach (lobectomy).

Fine needle aspirations of parathyroid adenomas are composed of cells that resemble crowded and overlapping follicular cells (Fig. 5.7). Even when the FNA is performed with ultrasound guidance, it may not be clear to the aspirator that the lesion arises from a parathyroid gland rather than the thyroid, particularly for

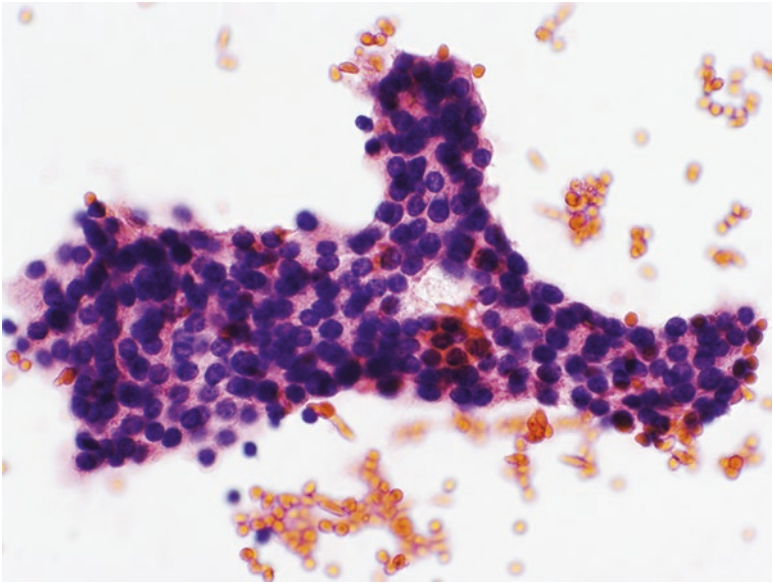

Fig. 5.7 Follicular neoplasm/suspicious for a follicular neoplasm. These crowded, uniform cells are arranged in thick trabeculae mimicking neoplastic follicular cells. Lobectomy revealed an unsuspected parathyroid adenoma (smear, hematoxylin, and eosin stain).

parathyroid glands located within the thyroid parenchyma or thyroid capsule. When submitted as a "thyroid FNA" specimen, parathyroid adenomas are often misinterpreted as FN/SFN. If there is a clinical suspicion that the lesion may be parathyroid, or if there are cellular features suggesting that possibility (e.g., crowded trabeculae in an aspirate lacking colloid), then the possibility of a parathyroid lesion might be suggested in the report [26]. (See section "Sample reports," Example 5.) The gene expression classifier Afirma (Veracyte, Inc.), which can be used as an adjunct to cytology for FN/SFN cases, includes a cassette that recognizes the gene expression profile of parathyroid neoplasms [27, 28].

There are robust data on the predictive value of the FN/SFN interpretation because most patients with this FNA result undergo surgery [3, 4, 9, 12]. The likelihood that the nodule is neoplastic is 65–85%. The rate of malignancy is significantly lower, at 25–40% (see Table 1.2, Chap. 1). Moreover, not all the malignancies prove to be follicular carcinomas: many if not most of the malignancies (27–68%) are interpreted histologically as papillary thyroid carcinoma [3, 4, 9, 12]. There are a number of explanations for this discrepancy. Some tumors, particularly the follicular variant of papillary carcinoma and NIFTP, may have cellular features of papillary carcinoma that are not fully developed throughout the entire nodule and thus may not be appreciated in the FNA sample. In other cases, however, the discrepancy may be due to the imperfect reproducibility of the histologic diagnoses of follicular carcinoma and follicular variant of papillary carcinoma [15].

Management

According to the 2015 American Thyroid Association management guidelines, diagnostic surgical excision (lobectomy) is the long-established standard of care for this diagnosis [14]. After consideration of clinical and sonographic features, however, molecular testing may be used to supplement malignancy risk assessment data in lieu of proceeding directly with surgery [14, 29, 30].

Sample Reports

If an aspirate is interpreted as FN/SFN, it is implied that the sample is adequate for evaluation. (An explicit statement of adequacy is optional.) The general category FN/SFN is a self-sufficient interpretation; narrative comments that follow are optional. An educational note specifying the risk of malignancy for this interpretation, derived from the laboratory itself or from the literature, is optional.

Example 1
SUSPICIOUS FOR A FOLLICULAR NEOPLASM.

Example 2
FOLLICULAR NEOPLASM.

Example 3
SUSPICIOUS FOR A FOLLICULAR NEOPLASM.
Cellular aspirate of follicular cells with a predominantly microfollicular architecture, scattered isolated cells, and scant colloid.

Example 4
SUSPICIOUS FOR FOLLICULAR NEOPLASM (*SEE NOTE*).

Note: Although the architectural features suggest a follicular neoplasm, some nuclear features raise the possibility of an invasive follicular variant of papillary carcinoma or its recently described indolent counterpart, NIFTP; definitive distinction among these entities is not possible on cytologic material.

Example 5
SUSPICIOUS FOR A FOLLICULAR NEOPLASM.
Cellular aspirate composed predominantly of crowded uniform cells without colloid. The features suggest a follicular neoplasm, but the possibility of a parathyroid lesion cannot be excluded. Correlation with clinical, serologic, radiologic, and molecular test findings (if any) should be considered.

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6 Follicular Neoplasm, Hürthle Cell (Oncocytic) Type/Suspicious for a Follicular Neoplasm, Hürthle Cell (Oncocytic) Type

William C. Faquin, Claire W. Michael, Andrew A. Renshaw, and Philippe Vielh

Background

Ewing coined the term "Hürthle cell" in 1928 based upon the description of a cell by Hürthle in 1894. The term has become entrenched in the thyroid lexicon, even though Hürthle's original description is now believed to represent a parafollicular or C-cell of the thyroid gland [1]. In 1898, Askanazy was the first to describe the follicular-derived Hürthle cell as we know it today [2]. The Hürthle cell or oncocyte (also called Askanazy cell and oxyphilic cell) is defined morphologically as a thyroid follicular cell with an abundance of finely granular cytoplasm that reflects an excessive number of mitochondria. (For the sake of brevity, the term "Hürthle cell" will be used henceforth for Hürthle (oncocytic) cells and lesions.) In Hürthle cell tumors, this striking cellular alteration appears to be a consequence of alterations of mitochondrial and nuclear DNA that codes for proteins involved in oxidative phosphorylation, e.g., GRIM-19 [3–5]. Most Hürthle cells have an enlarged, round to oval nucleus, and they often have a prominent nucleolus.

Hürthle cells are commonly seen in reactive/hyperplastic conditions like lymphocytic (Hashimoto) thyroiditis (LT) and multinodular goiter (MNG), where they are considered metaplastic, nonneoplastic cells, but they can also be neoplastic

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(Hürthle cell adenoma and Hürthle cell carcinoma). The World Health Organization (WHO) considers Hürthle cell adenoma and Hürthle cell carcinoma as variants of follicular adenoma and carcinoma; the current WHO term for these is follicular adenoma or carcinoma, Hürthle cell (oncocytic) type [6]. In the Bethesda System for Reporting Thyroid Cytopathology (TBSRTC), FNA specimens that are suspicious for a Hürthle cell (oncocytic) neoplasm are distinguished from those suspicious for a non-Hürthle cell follicular neoplasm for two reasons: (1) there is a striking morphologic difference between these two cytologic patterns, which raises different diagnostic considerations, and (2) there are data to suggest that follicular and Hürthle cell carcinomas may be genetically different neoplasms [3–5, 7]. For example, the PAX8-PPARγ rearrangement is seen in 26–53% of follicular carcinomas but rarely in Hürthle cell carcinomas [8, 9].

In TBSRTC, the terms "follicular neoplasm, Hürthle cell type" and "suspicious for a follicular neoplasm, Hürthle cell type" are equally acceptable for this category (see Sample Reports at the end of this chapter). "Suspicious for a follicular neoplasm, Hürthle cell type (SFNHCT)" is preferred over "follicular neoplasm, Hürthle cell type (FNHCT)" by some laboratories because a significant proportion of cases (16–25%) prove not to be neoplasms but rather hyperplastic proliferations of oncocytes in nodular goiter or LT [10, 11].

Hürthle cell carcinomas are uncommon, representing only 15–20% of all follicular carcinomas [12]. As with (non-oncocytic) follicular adenoma and carcinoma, the distinction between Hürthle cell adenoma and Hürthle cell carcinoma is based upon histologic evidence of transcapsular and/or vascular invasion. For this reason, thyroid FNA is used as a screening test for the detection of a probable oncocytic neoplasm that requires surgical excision (lobectomy) for precise histologic classification [13]. Although FNA is highly sensitive for detecting oncocytic carcinomas, its specificity is low: most nodules diagnosed by FNA as FNHCT/SFNHCT are benign; the risk of malignancy is 10–40% [10, 11, 14–16]. Currently, no ancillary techniques reliably distinguish between a Hürthle cell adenoma and Hürthle cell carcinoma.

Definition

The interpretation "follicular neoplasm, Hürthle cell type" or "suspicious for a follicular neoplasm, Hürthle cell type" refers to a cellular aspirate that consists exclusively (or almost exclusively) of Hürthle cells. Hürthle cells with nuclear features of papillary carcinoma are excluded from this category, although in some cases the distinction may be difficult (see Explanatory Notes).

Criteria

Specimens are moderately to markedly cellular.
The sample consists exclusively (or almost exclusively) of **Hürthle cells**:

- Abundant finely granular cytoplasm (blue or gray pink with Romanowsky stains, green with Papanicolaou, pink with hematoxylin and eosin)

- Enlarged, central or eccentrically located, round nucleus
- Prominent nucleolus
- Small cells with high nuclear/cytoplasmic (N/C) ratio (small-cell dysplasia)
- Large cells with at least two times variability in nuclear size (large-cell dysplasia)

The Hürthle cells are dispersed predominantly as isolated cells but sometimes arranged in crowded, syncytial-like arrangements.
Binucleation is fairly common.
There is usually little or no colloid.
There are virtually no lymphocytes (excluding blood elements) or plasma cells.
Transgressing vessels are present in some cases as well as intracytoplasmic "colloid" inclusions (lumens) [17].

Explanatory Notes

The FNHCT/SFNHCT aspirate is at least moderately cellular (Fig. 6.1) and, excluding blood elements, is composed exclusively of Hürthle cells (Fig. 6.2) [7, 18–21]. Sparsely cellular samples do not qualify for this interpretation. A small number of benign follicular cells may be present, but this is uncommon, usually representing sampling of the adjacent thyroid tissue. Similarly, lymphocytes are usually absent or rare. In most cases, the Hürthle cells are dispersed predominantly as isolated cells (Fig. 6.3) or as irregular three-dimensional groups (Fig. 6.2) [20, 21]. An important

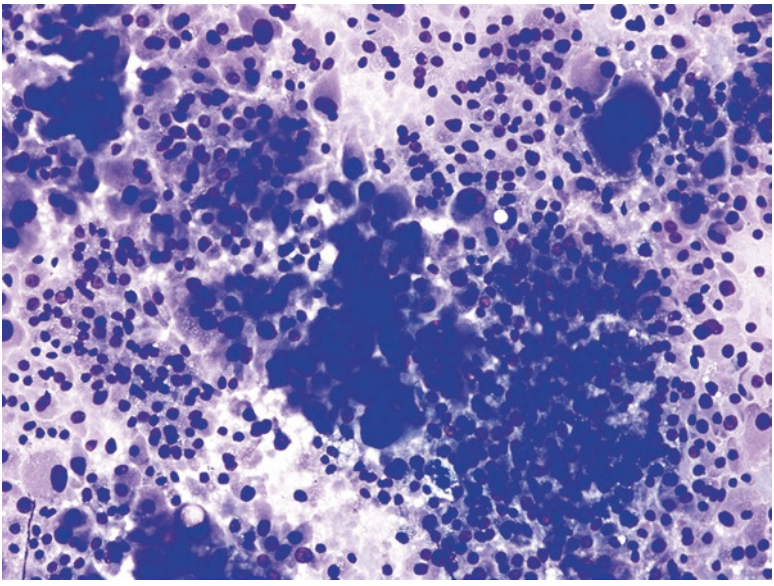

Fig. 6.1 Follicular neoplasm, Hürthle cell (oncocytic) type/suspicious for a follicular neoplasm, Hürthle cell (oncocytic) type. The aspirate is very cellular and consists of oncocytes (Hürthle cells) of variable size arranged as isolated cells and in crowded groups; colloid is absent. Large-cell dysplasia is present (smear, Diff-Quik stain).

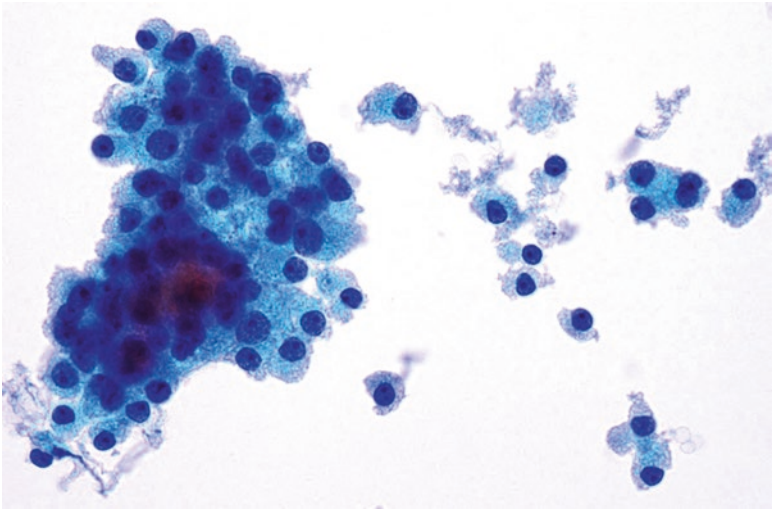

Fig. 6.2 Follicular neoplasm, Hürthle cell (oncocytic) type/suspicious for a follicular neoplasm, Hürthle cell (oncocytic) type. The aspirate consists of a pure population of Hürthle cells in crowded groups and as isolated cells. The background lacks colloid and lymphocytes (ThinPrep, Papanicolaou stain).

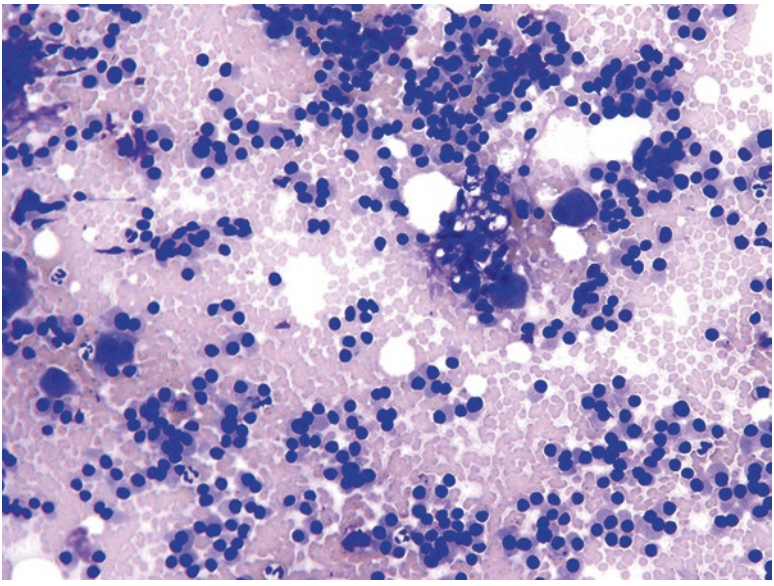

Fig. 6.3 Follicular neoplasm, Hürthle cell (oncocytic) type/suspicious for a follicular neoplasm, Hürthle cell (oncocytic) type. The aspirate is cellular and consists exclusively of Hürthle cells in an isolated-cell pattern simulating medullary thyroid carcinoma (smear, Diff-Quik stain).

criterion is the presence of Hürthle cell "atypia," of which there are two types. The atypia (henceforth referred to as dysplasia) can be in the form of very large cells with abundant granular cytoplasm that demonstrate at least twofold variability in nuclear size ("large-cell dysplasia") (Figs. 6.4 and 6.5) or relatively small Hürthle cells notable for less abundant granular cytoplasm and a higher nuclear/cytoplasmic ratio than usual Hürthle cells ("small-cell dysplasia") (Figs. 6.6 and 6.7) [22, 23]. Admixtures of small and large Hürthle cells are seen in some cases (Figs. 6.8 and 6.9). Importantly, dysplasia (particularly large-cell dysplasia) by itself is an unreliable feature for the diagnosis – in fact, very marked hyperchromasia, anisonucleosis, and nuclear membrane irregularity of Hürthle cells can be seen in MNG and LT [7]. Cellular cases lacking dysplasia are suggestive of a benign nodule. Colloid is usually scant or absent, although a rare subset of Hürthle cell carcinomas with colloid has been described [23, 24]. Transgressing vessels are present in some cases and strongly support the diagnosis of a neoplasm over a nonneoplastic/metaplastic proliferation (Figs. 6.10 and 6.11) [17].

When an aspirate has all (or most) of the aforementioned features, the diagnosis of FNHCT/SFNHCT is straightforward. Problems arise with regard to (1) the minimum necessary criteria for the diagnosis, (2) the best way to handle oncocytic proliferations in a patient with MNG or LT, and (3) the distinction from follicular carcinoma, papillary carcinoma, medullary carcinoma, and parathyroid tumors.

1. *Minimum necessary criteria*

With regard to the *minimum criteria* for diagnosing FNHCT/SFNHCT, there are four general problematic scenarios:

The Sparsely Cellular Specimen Composed Entirely of Oncocytes A sparsely cellular aspirate certainly does not preclude a Hürthle cell carcinoma [22]. Most cytopathologists, however, are reluctant to make the diagnosis of FNHCT/SFNHCT on a scant aspirate; these aspirates are most appropriately diagnosed as "atypia of undetermined significance (AUS)" or "follicular lesion of undetermined significance (FLUS)" (see Chap. 4). A reaspiration may resolve the diagnostic difficulty.

The Moderately or Markedly Cellular Specimen Composed Exclusively of Hürthle Cells (or "Hürthle-oid" Cells) Without Atypia (Dysplasia) The moderately or markedly cellular aspirate composed entirely of Hürthle cells but lacking small-cell or large-cell dysplasia is more controversial. If a pure population of non-atypical Hürthle cells is accompanied by abundant colloid (particularly non-watery colloid), it is acceptable to interpret the sample as benign. If colloid is scant or absent, there are two different approaches to the cellular aspirate composed entirely of Hürthle cells without dysplasia. Some cytopathologists diagnose such cases as FNHCT/SFNHCT. Two groups of investigators have shown, however, that aspirates lacking small-cell and large-cell dysplasia are almost never malignant [20, 22, 23]. As a result, some cytopathologists diagnose pure Hürthle cell cases without dysplasia as benign, accompanied by an optional note: "Although the predominance of oncocytes raises the

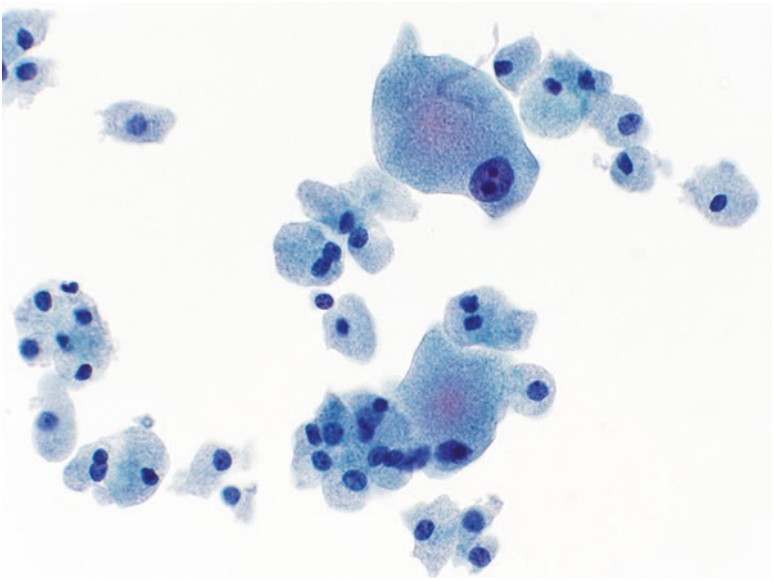

Fig. 6.4 Follicular neoplasm, Hürthle cell (oncocytic) type/suspicious for a follicular neoplasm, Hürthle cell (oncocytic) type. The aspirate consists of numerous dispersed Hürthle cells. The nuclei are highly variable in size, demonstrating large-cell dysplasia (ThinPrep, Papanicolaou stain).

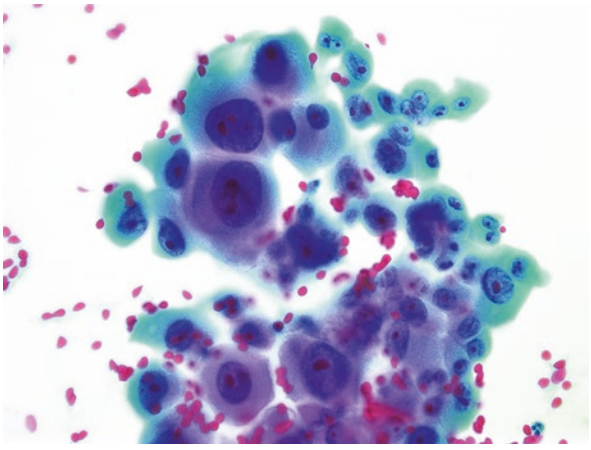

Fig.6.5 Follicular neoplasm, Hürthle cell (oncocytic) type/suspicious for a follicular neoplasm, Hürthle cell (oncocytic) type. This cellular aspirate consists of loosely cohesive, large Hürthle cells with marked anisonucleosis (large-cell dysplasia) and macronucleoli (smear, Papanicolaou stain).

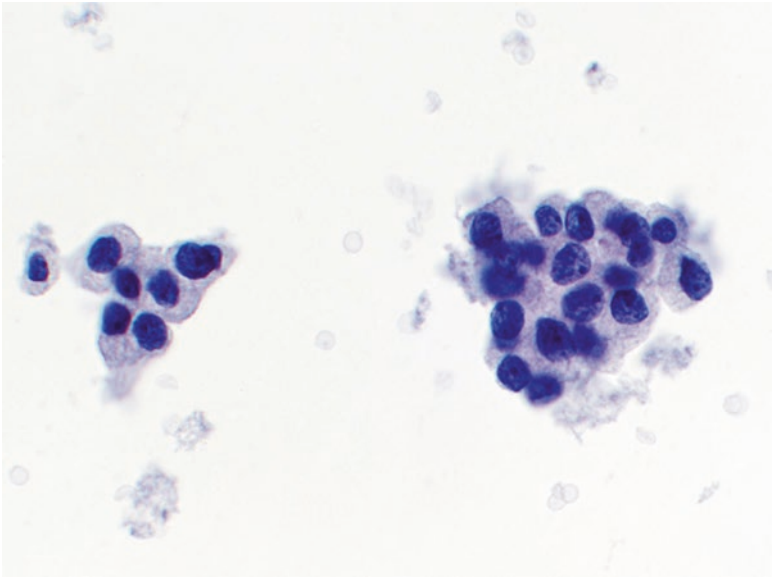

Fig. 6.6 Follicular neoplasm, Hürthle cell (oncocytic) type/suspicious for a follicular neoplasm, Hürthle cell (oncocytic) type. The aspirate consists of numerous variably sized groups of crowded Hürthle cells. Although demonstrably oncocytic, they have less cytoplasm than "usual" Hürthle cells, demonstrating small-cell dysplasia (ThinPrep, Papanicolaou stain).

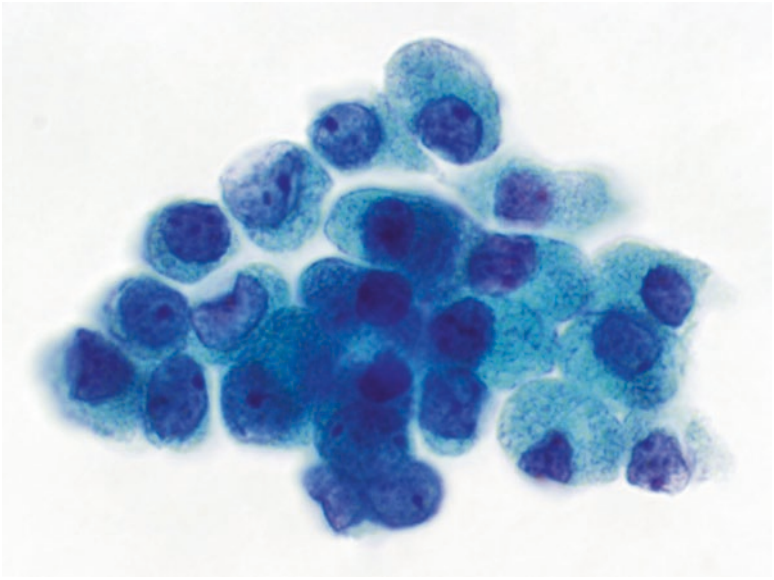

Fig. 6.7 Follicular neoplasm, Hürthle cell (oncocytic) type/suspicious for a follicular neoplasm, Hürthle cell (oncocytic) type. The aspirate is comprised almost exclusively of small Hürthle cells ("small-cell dysplasia") (ThinPrep, Papanicolaou stain).

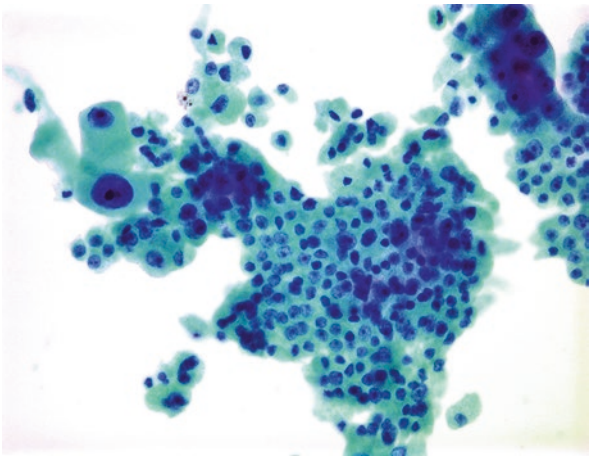

Fig. 6.8 Follicular neoplasm, Hürthle cell (oncocytic) type/suspicious for a follicular neoplasm, Hürthle cell (oncocytic) type. This cellular aspirate consists exclusively of Hürthle cells arranged in syncytial-like sheets and as isolated cells. The cells exhibit marked variation in cell and nuclear size (mixed small- and large-cell dysplasia) (ThinPrep, Papanicolaou stain).

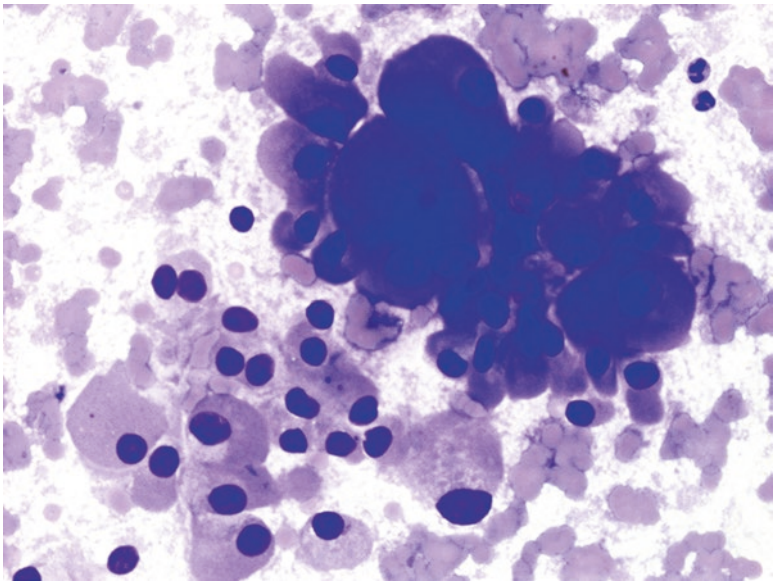

Fig. 6.9 Follicular neoplasm, Hürthle cell (oncocytic) type/suspicious for a follicular neoplasm, Hürthle cell (oncocytic) type. The aspirate consists of loosely cohesive oncocytes. The cells are highly variable in size and amount of cytoplasm, transitioning from gigantic cells with abundant cytoplasm and macronucleoli to smaller, uniform Hürthle cells with a high nuclear/cytoplasmic ratio. Both large-cell and small-cell dysplasia are present (smear, Diff-Quik stain).

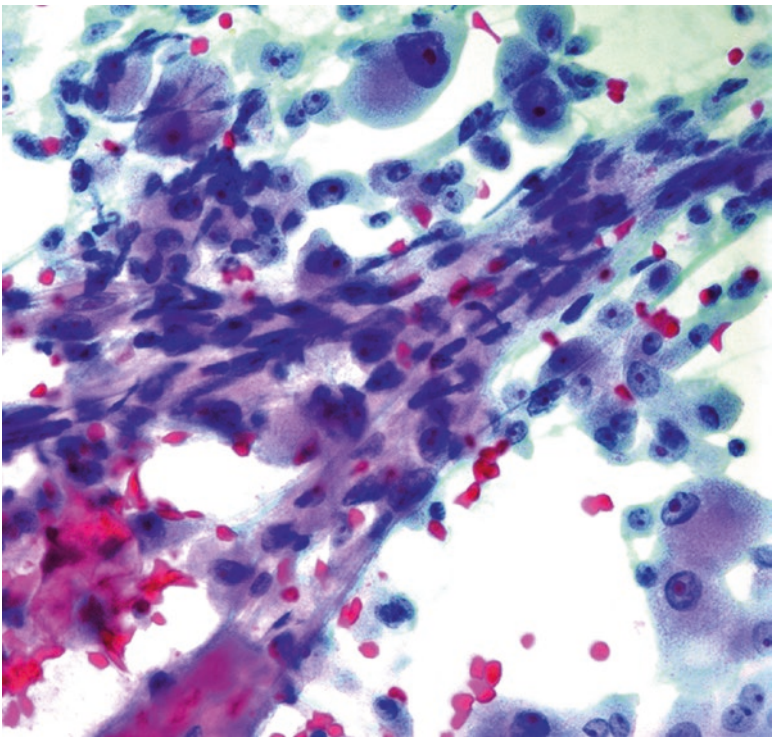

Fig. 6.10 Follicular neoplasm, Hürthle cell (oncocytic) type/suspicious for a follicular neoplasm, Hürthle cell (oncocytic) type. This cellular aspirate consists of noncohesive Hürthle cells with both large- and small-cell dysplasia. Colloid is absent, and transgressing vessels are present (smear, Papanicolaou stain).

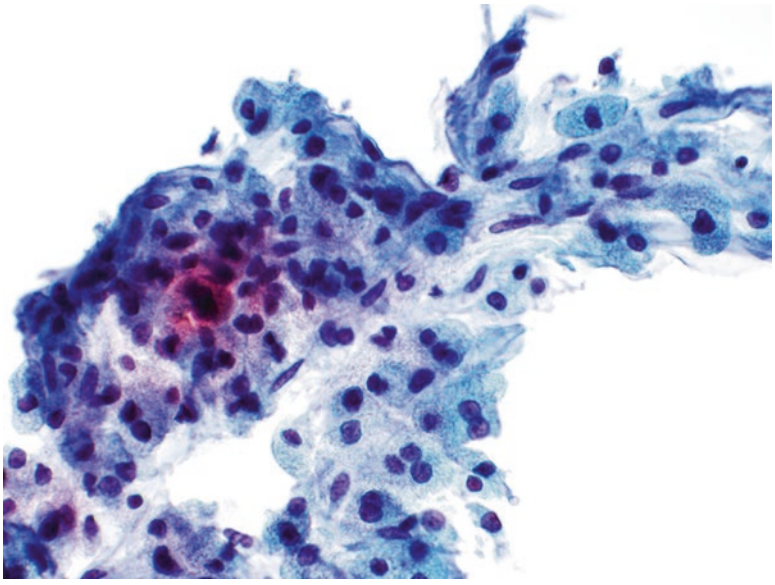

Fig. 6.11 Follicular neoplasm, Hürthle cell (oncocytic) type/suspicious for a follicular neoplasm, Hürthle cell (oncocytic) type. Transgressing vessels associated with Hürthle cell neoplasms can be seen with liquid-based preparations (ThinPrep, Papanicolaou stain).

possibility of a Hürthle cell neoplasm, the absence of dysplasia suggests that it is benign." Typically, such patients are followed clinically with periodic physical and sonographic examinations. Similarly, it is not uncommon to encounter a relatively bland aspirate composed of cells with minimal dysplasia but "Hürthle-oid" features with more granular cytoplasm than is seen in typical follicular cells but not as much as is seen in usual Hürthle cells. Most of these cases can also be diagnosed as benign with a similar (optional) note ("the findings raise the possibility of a Hürthle cell neoplasm, but the lack of dysplasia suggests it is benign").

The Clearly Abnormal Specimen with Partial or Minimal Hürthle Cell Differentiation There are clearly abnormal cases (markedly cellular specimens with crowding and overlapping of cells, etc.) where Hürthle cell differentiation is focal rather than diffuse or not as well developed as in most Hürthle cell neoplasms. In such cases, the diagnostic choices are "follicular neoplasm/suspicious for a follicular neoplasm" versus FNHCT/SFNHCT. When Hürthle cell differentiation is clear-cut but only focal, it is advisable to follow the guidelines of the WHO, which consider only those follicular neoplasms that are comprised of >75% Hürthle cells to be a Hürthle cell neoplasm [6]. Thus, a suspicious FNA in which <75% of the abnormal cells are well-developed Hürthle cells should be diagnosed as "follicular neoplasm/suspicious for a follicular neoplasm" rather than FNHCT/SFNHCT. When Hürthle cell differentiation is not clear-cut (more granular cytoplasm than normal follicular cells, but not as much as usual Hürthle cells), it is often impossible to make a definitive distinction between follicular and Hürthle cell differentiation. Because the usual management is the same for both entities, a practical solution is to diagnose these aspirates as "follicular neoplasm/suspicious for a follicular neoplasm," with the comment "Some Hürthle cell differentiation is present, and therefore a Hürthle cell neoplasm cannot be ruled out."

The Clearly Abnormal Specimen with Colloid Some clearly abnormal samples (at least moderately cellular, exclusively Hürthle cell population with dysplasia) demonstrate colloid [18, 23, 24]. This is almost always "watery colloid," however. Despite the watery colloid, such cases should be diagnosed as FNHCT/SFNHCT. Finding hard colloid in this setting would be exceptional; such cases should likely be diagnosed as AUS/FLUS.

2. *Hürthle cell proliferations in patients with multinodular goiter and lymphocytic thyroiditis*

The classic FNHCT/SFNHCT pattern can be mimicked by a variety of other conditions, particularly MNG with focal Hürthle cell change and LT with Hürthle cell hyperplasia. Prominent Hürthle cell metaplasia often accompanies MNG. Typically one sees a mixture of elements: flat, cohesive sheets of Hürthle cell admixed with normal follicular cells and a moderate to abundant amount of colloid (Fig. 6.12). Aspirates with these features are easily recognized as benign and should not be interpreted as FNHCT/SFNHCT. Thus, whereas most aspirates of Hürthle

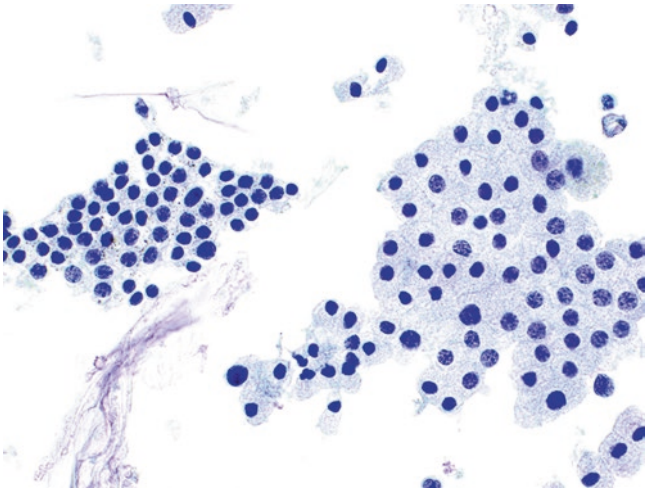

Fig. 6.12 Benign (multinodular hyperplasia with a prominent oncocytic component). There are benign follicular cells (*left*) and Hürthle cells (*right*) in cohesive flat sheets, with a moderate amount of watery ("tissue-paper") colloid. Such cases should not be called "follicular neoplasm, Hürthle cell (oncocytic) type/suspicious for a follicular neoplasm, Hürthle cell (oncocytic) type" (ThinPrep, Papanicolaou stain).

cell neoplasms consist of a pure population of Hürthle cells, a mixture of Hürthle cells and non-oncocytic follicular cells is more indicative of a hyperplastic nodule. Exceptions to this rule occur and represent a limitation in the precise classification of these lesions by FNA. It is possible, for example, to aspirate normal follicular cells from adjacent thyroid tissue when aspirating a Hürthle cell neoplasm, particularly if the FNA is done without ultrasound guidance. Thus, a minor component of normal follicular cells does not exclude a Hürthle cell neoplasm. Conversely, some nodules in patients with MNG are composed exclusively of Hürthle cells (with or without significant nuclear dysplasia); such benign hyperplastic nodules masquerade as a Hürthle cell neoplasm. Clinical-cytologic correlation is a reasonable approach in such cases and can be performed by either the cytopathologist or the clinician. For example, in a patient known to have multiple nodules, it is acceptable to diagnose an exclusively Hürthle cell specimen as either FNHCT/SFNHCT or as AUS/FLUS. If interpreted as AUS/FLUS, an explanatory note that raises the possibility of Hürthle cell hyperplasia can be helpful (see Chap. 4, Sample Report Example 4). The goal is to provide the clinician with the opportunity to avoid an unnecessary lobectomy in some of these patients. Note that in this setting, the usual management of a patient with an AUS/FLUS result – a repeat aspiration – is unlikely to add any helpful information.

In most nodules from patients with LT, lymphocytes predominate over Hürthle cells, and the benign aspirate is easily distinguished from a Hürthle cell neoplasm on this basis. In some patients with LT, however, Hürthle cell proliferation can

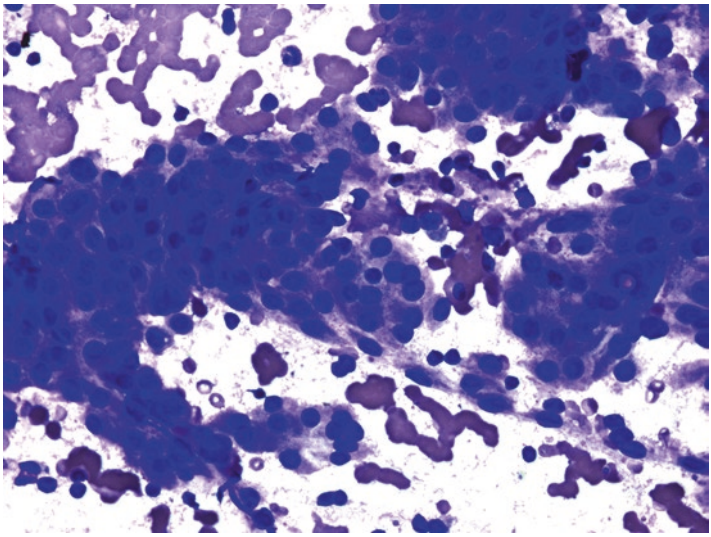

Fig. 6.13 Atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS). This oncocytic nodule in a patient with lymphocytic (Hashimoto) thyroiditis exhibits a predominance of Hürthle cells in crowded groups with very few lymphocytes. In a patient with a known clinical diagnosis of lymphocytic (Hashimoto) thyroiditis, such cases can be interpreted as AUS/FLUS (smear, Diff-Quik stain).

produce nodules that exceed 1 cm in diameter and are composed of Hürthle cells with little or no lymphoid infiltrate (Fig. 6.13) [25]. When the lymphoid component is absent or inconspicuous, it can be difficult to exclude a Hürthle cell neoplasm. There may be a clue to the correct interpretation: in LT nodules, the Hürthle cells are "atypical" in a stereotypical way (they form small cohesive clusters of three to ten cells containing large nuclei and smudgy, sometimes glassy chromatin). This nuclear atypia can mimic that found in papillary carcinoma, but it is not typical of Hürthle cell neoplasia.

Knowing that a patient has LT may impact the interpretation. In a patient known to have LT, it is acceptable to diagnose an exclusively (or virtually exclusively) Hürthle cell specimen as either FNHCT/SFNHCT or AUS/FLUS. Data suggest that the criteria for FNHCT/SFNHCT have a lower predictive value for malignancy when a patient has LT [26]. If interpreted as AUS/FLUS, a note explaining that a benign Hürthle cell hyperplasia is favored can be very helpful (see Chap. 4, see Sample Report Example 5). As in patients with MNG, the note that accompanies the AUS/FLUS interpretation in a patient with LT is meant to more accurately reflect the underlying risk of malignancy, which, although not well characterized, is considered to be lower than for FNHCT/SFNHCT in general. The goal is to provide the

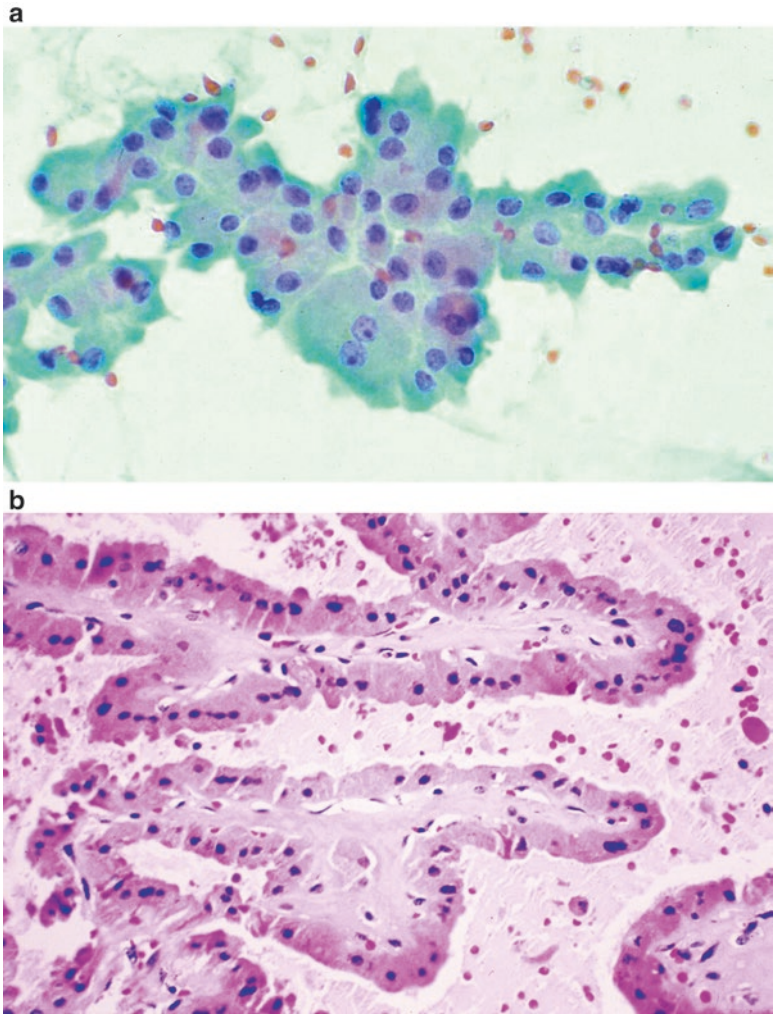

Fig. 6.14 Follicular neoplasm, Hürthle cell (oncocytic) type/suspicious for a follicular neoplasm, Hürthle cell (oncocytic) type. (**a**) This cellular aspirate was comprised exclusively of Hürthle cells, without overt nuclear features of papillary thyroid carcinoma (smear, Papanicolaou stain). (**b**) Histologic examination revealed a Hürthle cell carcinoma with papillary architecture. A subset of Hürthle cell neoplasms exhibits papillary architecture, with occasional cells that have an oval, pale, and grooved nucleus but lacking intranuclear pseudoinclusions. In such cases it can be difficult to distinguish a Hürthle cell neoplasm from an oncocytic papillary thyroid carcinoma, not just cytologically but also histologically (hematoxylin and eosin stain).

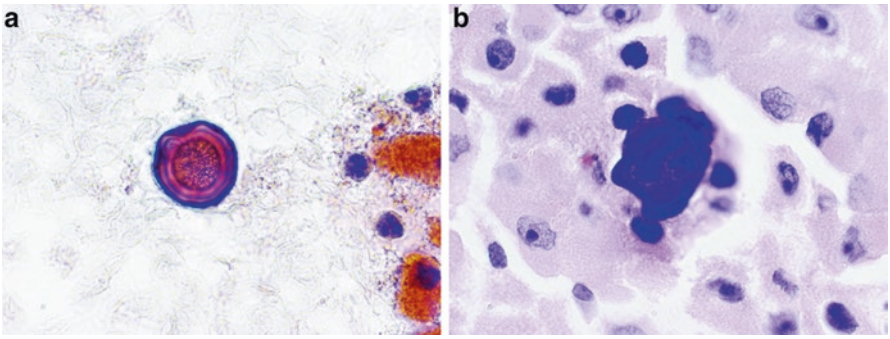

Fig. 6.15 Follicular neoplasm, Hürthle cell (oncocytic) type/suspicious for a follicular neoplasm, Hürthle cell (oncocytic) type. (**a)** A minority of Hürthle cell neoplasms contain concentrically laminated concretions that are indistinguishable from psammoma bodies (smear, Papanicolaou stain). The correct diagnosis depends on the accompanying cellular features. (**b)** The histologic specimen revealed a Hürthle cell (oncocytic) adenoma with similar concretions (hematoxylin and eosin stain).

clinician with the opportunity to avoid an unnecessary lobectomy in some of these patients. Note that in this setting, the usual management for an AUS/FLUS diagnosis – a repeat aspiration – is unlikely to provide any helpful information. The AUS/FLUS interpretation in this setting does not ask for a repeat aspiration, but rather encourages clinical-cytologic correlation to more accurately predict the risk of malignancy.

3. *Distinction from other tumors*

The differential diagnosis of FNHCT/SFNHCT includes other neoplasms. Hürthle cell neoplasms can exhibit some of the architectural and nuclear features of papillary carcinoma, including micropapillary groups (Fig. 6.14), fibrovascular cores, pale chromatin, grooves, and intranuclear pseudoinclusions, as well as occasional psammoma body-like concretions [6] (Fig. 6.15). Conversely, the cells of many classic papillary carcinomas often show focal oncocytic differentiation. This is particularly extensive in the Hürthle cell (oncocytic) variant of papillary carcinoma (see Chap. 8). The abundance of granular cytoplasm in these neoplasms mimics that of a Hürthle cell neoplasm. Attention to nuclear details usually permits a distinction, but in some cases, it may not be possible to determine with certainty whether an aspirate is best classified as a papillary carcinoma or FNHCT/SFNHCT. Such aspirates can be diagnosed either as FNHCT/SFNHCT or "suspicious for malignancy," accompanied by an explanatory note that includes the differential diagnosis of papillary carcinoma and a Hürthle cell neoplasm. Many of these borderline lesions can be accurately diagnosed at the time of frozen section based on architectural features; thus patients with this diagnosis are candidates for lobectomy with frozen section and possible completion thyroidectomy at a single surgical procedure.

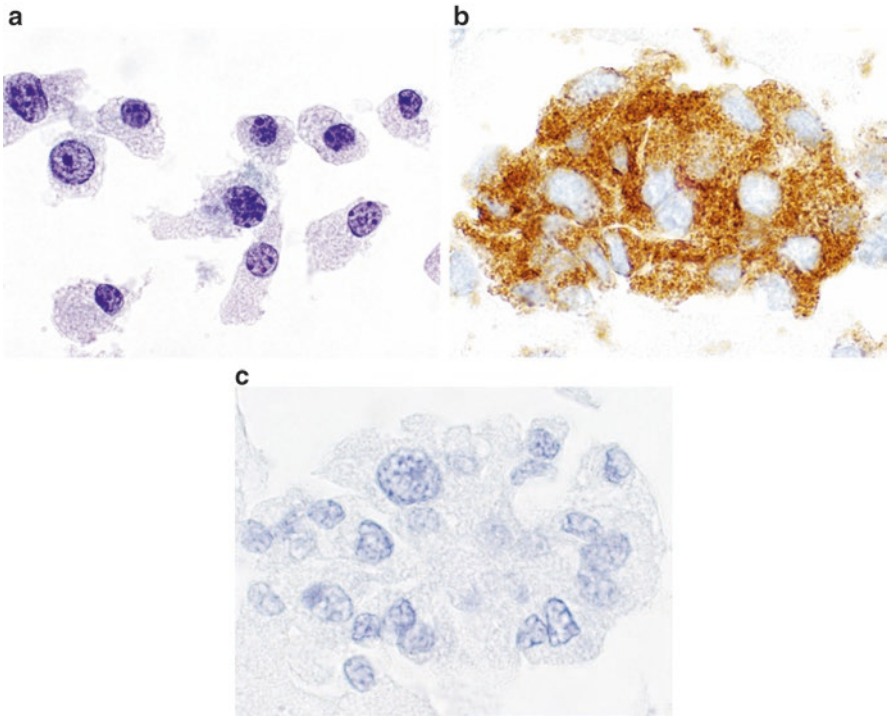

Fig. 6.16 Follicular neoplasm, Hürthle cell (oncocytic) type/suspicious for a follicular neoplasm, Hürthle cell (oncocytic) type. (**a**) Some Hürthle cell neoplasms can be difficult to distinguish from a medullary carcinoma by cytomorphology alone. This case demonstrates a population of cells with abundant cytoplasm and occasional eccentrically placed nuclei (ThinPrep, Papanicolaou stain). (**b**) Immunohistochemical studies on a cell block preparation are positive for thyroglobulin. (**c**) The suspicious cells are negative for calcitonin.

Some of the characteristic features of Hürthle cell neoplasms overlap with those of a medullary thyroid carcinoma (Fig. 6.16). Many medullary carcinomas are comprised of isolated cells with abundant granular cytoplasm. The prominent nucleolus of most Hürthle cell neoplasms is absent from most medullary carcinoma cells. With Romanowsky stains, the cytoplasmic granules of Hürthle cells are blue, whereas those of medullary carcinoma are usually red. Intranuclear pseudoinclusions may be seen in medullary carcinoma and are typically absent or extremely rare in Hürthle cell neoplasms. Immunohistochemistry is especially useful in the distinction between Hürthle cells and medullary carcinoma: Hürthle cell neoplasms are positive for thyroglobulin and negative for calcitonin, whereas medullary carcinomas are negative for thyroglobulin but positive for calcitonin and chromogranin. When using immunostains, a panel of immunohistochemical stains, including some that are expected to be positive (e.g., thyroglobulin) and others expected to be negative (e.g., calcitonin), is preferable to solitary antibody staining, because aberrant results can occur with any given antibody. Because the surgical approach to patients

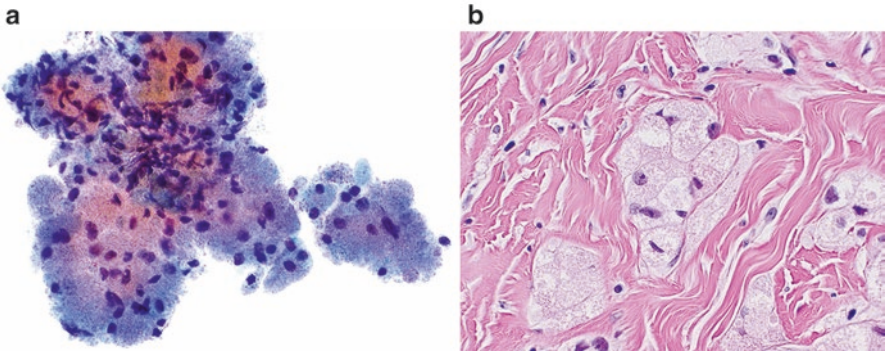

Fig. 6.17 Granular cell tumor of the thyroid. (**a**) Because they have abundant granular cytoplasm, these neoplasms mimic Hürthle cell (oncocytic) tumors to perfection. (ThinPrep, Papanicolaou stain). (**b**) Histologic sections revealed nests of neoplastic cells infiltrating collagenized stroma (hematoxylin and eosin stain).

with medullary carcinoma often differs from that for a Hürthle cell neoplasm, cytologists should have a low threshold for confirmatory ancillary studies anytime they consider a diagnosis of medullary carcinoma.

Granular cell tumors presenting as a thyroid mass are very rare but a very good cytomorphologic mimic of a Hürthle cell neoplasm [27, 28] (Fig. 6.17). If suspected, the diagnosis can be confirmed by immunohistochemistry: granular cell tumors are strongly immunoreactive for S-100 protein and negative for keratins.

Parathyroid adenomas (and the rare parathyroid carcinomas) usually mimic a follicular neoplasm, but some have abundant granular cytoplasm and mimic instead a Hürthle cell neoplasm (Fig. 6.18). Sometimes the radiologist will consider a parathyroid tumor based on imaging characteristics, and occasionally there will be serologic testing results to raise this possibility. In many cases, however, a parathyroid tumor will not be suspected clinically, and the possibility of a parathyroid tumor will need to be raised based on morphologic evaluation of the FNA specimen. Unfortunately, only 20–30% of these parathyroid lesions are recognized on fine needle aspiration [29–31]. In contrast to Hürthle cell neoplasms, the cells of a parathyroid adenoma with abundant granular cytoplasm are monomorphous, with round nuclei and "salt and pepper" chromatin. Parathyroid tumors are immunoreactive for chromogranin, synaptophysin, and parathyroid hormone (PTH) and are negative for thyroglobulin and TTF-1. Hürthle cell neoplasms have more finely textured chromatin, more anisonucleosis, and more highly irregular nuclei; they are immunoreactive for TTF-1 and thyroglobulin. The Afirma Gene Expression Classifier (Veracyte, Inc., South San Francisco, CA) (see Management, below) includes a "cassette" that recognizes the expression profile of parathyroid proliferations and is useful in distinguishing these from Hürthle cell neoplasms [32, 33]. If cyst fluid is obtained and submitted for chemical analysis, a high PTH level is diagnostically helpful [30]. A conclusive distinction will not always be possible, especially if immunohistochemistry is not available or is inconclusive. In such cases, the possibility of a parathyroid tumor can be raised in the note that accompanies the interpretation.

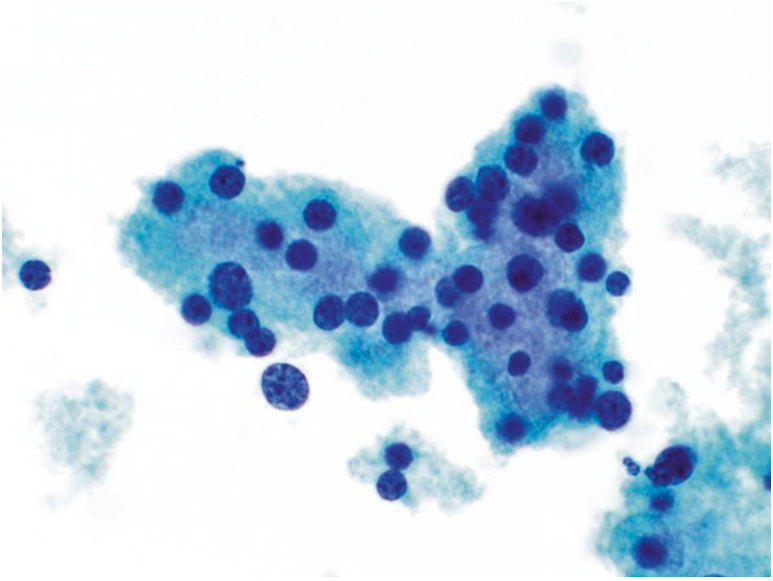

Fig. 6.18 Parathyroid carcinoma. Some parathyroid neoplasms have abundant oncocytic cytoplasm (ThinPrep, Papanicolaou stain).

Management

Diagnostic surgical excision is the long-established standard of care for the management of nodules interpreted as FNHCT/SFNHCT. As with all thyroid nodules, informed patient preference and clinical and sonographic features should be considered in the management decision. According to the 2015 American Thyroid Association guidelines, molecular testing may be used to supplement the malignancy risk assessment in lieu of proceeding directly with surgery [34].

Mutational analysis is generally unhelpful in identifying Hürthle cell carcinomas and distinguishing them from adenomas: *RET/PTC* rearrangements and *RAS* mutations can be seen in both adenomas and carcinomas, and *PAX8/PPARγ* rearrangements are very rare in Hürthle cell carcinomas [5, 8, 9]. The Afirma Gene Expression Classifier (GEC) (Veracyte, Inc., South San Francisco, CA), optimized for negative predictive value, can be a useful adjunct to cytology by sparing some patients an unnecessary lobectomy [35]. The GEC classifies an aspirate as "benign" or "suspicious" based on an expression profile of more than 100 genes. Up to one-third of patients with an FNHCT/SFNHCT cytology have a benign GEC, and most of these patients are spared an unnecessary lobectomy [36]. On the other hand, a suspicious GEC in this setting provides little additional benefit beyond the cytologic interpretation.

Sample Reports

If an aspirate is interpreted as FNHCT/SFNHCT, it is implied that the sample is adequate for evaluation. (An explicit statement of adequacy is optional.) The interpretation FNOT/SFNOT is self-sufficient; narrative comments that follow are optional.

Example 1
Suspicious for a follicular neoplasm, Hürthle cell (oncocytic) type.

Example 2
Follicular neoplasm, Hürthle cell (oncocytic) type.

Example 3
Suspicious for a Hürthle cell (oncocytic) neoplasm.
Cellular aspirate consisting predominantly of oncocytes in syncytial-like sheets and crowded clusters.

Example 4
Hürthle cell (oncocytic) neoplasm.
Cellular aspirate consisting of abundant isolated oncocytes in the absence of colloid.

Example 5
Suspicious for a Hürthle cell (oncocytic) neoplasm.
Cellular aspirate of follicular cells with oncocytic features, including occasional nuclear grooves and focal papillary architecture. The findings raise the possibility of an oncocytic neoplasm with papillary features, but a papillary thyroid carcinoma cannot be excluded.

Example 6
Suspicious for a Hürthle cell (oncocytic) neoplasm.
Cellular aspirate composed of cells with abundant granular cytoplasm. The findings raise the possibility of an oncocytic neoplasm, but a parathyroid tumor cannot be excluded. Correlation with clinical findings, imaging findings, and serologic testing results might be helpful.

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Suspicious for Malignancy

7

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Background

Most primary thyroid malignancies have distinctive cytologic features and are easily recognized on fine needle aspiration (FNA). The exceptions are follicular and Hürthle cell carcinomas (addressed in Chaps. 5 and 6). Although the cytologic features of papillary thyroid carcinoma (PTC), medullary thyroid carcinoma (MTC), and lymphoma are well-established (see Chaps. 8, 9, and 12), in any given specimen, they may be quantitatively and/or qualitatively insufficient for a definitive diagnosis. The reasons for diagnostic uncertainty in such cases

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include suboptimal sampling or cellular preservation, an unusual variant of PTC or MTC, or overlapping cytomorphologic (particularly nuclear) features with other thyroid lesions. The reactive, involutional, and metaplastic changes of benign follicular cells in some cases of lymphocytic (Hashimoto) thyroiditis can be difficult to distinguish from those of PTC, and the lymphoid cells of thyroiditis can be difficult to distinguish from those of a lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma). A diagnostic category that conveys a strong suspicion for malignancy, therefore, is a necessity for thyroid FNA, and in the Bethesda system, it is termed "suspicious for malignancy (SFM)." SFM is a heterogeneous category because it includes a variety of different malignancies. Most SFM cases are suspicious for PTC, although in many published series, the type of suspected malignancy is not specified. SFM diagnoses account for approximately 3% (range 1.0–6.3%) of all thyroid FNAs [1–4]. As with any indeterminate diagnosis, this category should be used judiciously so that patients are managed as appropriately as possible.

The ultimate goal of separating a "suspicious" from a "malignant" category is to preserve the very high positive predictive value (PPV) of the malignant category without compromising the overall sensitivity of FNA. An SFM interpretation indicates to the clinical-surgical team the less than definitive nature of the diagnosis and allows for more conservative management options (e.g., surgical lobectomy) if indicated. A distinction between a malignant and suspicious diagnosis (and between suspicious and atypical) is admittedly subjective. A malignant diagnosis should be reserved for those cases that show sufficient cellularity and most, if not all, of the diagnostic features of the entity in question. An SFM interpretation is appropriately rendered when some of the diagnostic features are either absent or equivocal [5].

SFM is used for thyroid FNAs that are more likely than not malignant. The PPV of the SFM category is approximately 70% (range 53–100%) [1, 2, 6–15]. These numbers overestimate the malignancy risk because they don't account for the reclassification of the "non-invasive follicular variant of papillary thyroid carcinoma" as "noninvasive follicular thyroid neoplasm with papillary-like nuclear features" (NIFTP), given the indolent behavior of this thyroid tumor [16]. The malignancy risk of the SFM category falls to approximately 50% (range 45–60%) when NIFTPs are not counted as malignant [17, 18]. NIFTP is, nevertheless, a "surgical disease" (i.e., surgery is necessary for these nodules), and the higher risk estimate (70%, above) is arguably still appropriate for SFM if risk estimates are defined for *surgical disease*.

Definition

The diagnostic category "suspicious for malignancy" (SFM) is used when some cytomorphologic features (most often those of PTC) raise a strong suspicion of malignancy but the findings are not sufficient for a conclusive diagnosis. Specimens

that are suspicious for a follicular or Hürthle cell neoplasm are excluded from this category (see Chaps. 5 and 6). For the category SFM, the morphologic changes are of such a degree that a malignancy is considered more likely than not.

Criteria

Suspicious for Papillary Thyroid Carcinoma

Pattern A (*Patchy Nuclear Changes Pattern*, Figs. 7.1 and 7.2)

The sample is moderately or highly cellular.

Unremarkable follicular cells (arranged predominantly in macrofollicle fragments) are admixed with cells that have nuclear enlargement, nuclear pallor, nuclear grooves, nuclear membrane irregularity, and/or nuclear molding.

Intranuclear pseudoinclusions (INCIs) are very few or absent, and psammoma bodies and papillary architecture are absent.

Pattern B (*Incomplete Nuclear Changes Pattern*, Fig. 7.3)

The sample is sparsely, moderately, or highly cellular.

There is generalized mild-to-moderate nuclear enlargement with mild nuclear pallor.

Nuclear grooves are evident, but nuclear membrane irregularity and nuclear molding are minimal or absent.

Intranuclear pseudoinclusions (INCIs) are very few or absent, and psammoma bodies or papillary architecture is absent.

Pattern C (*Sparsely Cellular Specimen Pattern*)

Many of the features of PTC (see Chap. 8) are present, but the sample is very sparsely cellular.

Pattern D (*Cystic Degeneration Pattern*, Fig. 7.4)

There is evidence of cystic degeneration based on the presence of hemosiderin-laden macrophages.

Scattered groups and sheets of follicular cells have enlarged, pale nuclei and some have nuclear grooves, but INCIs are very few or absent, and psammoma bodies or papillary architecture is absent.

There are occasional large, atypical, “histiocytoid” cells with enlarged nuclei and abundant vacuolated cytoplasm.

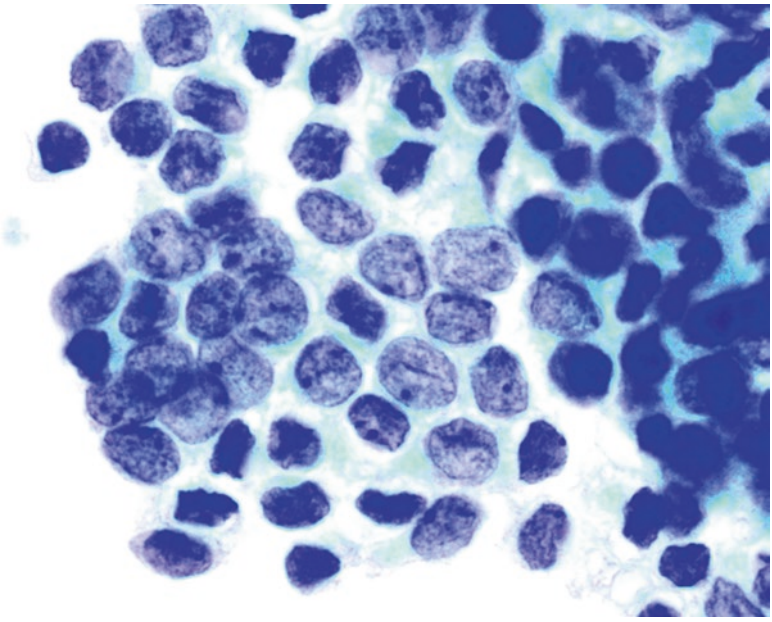

Fig. 7.1 Suspicious for papillary thyroid carcinoma. This sheet of follicular cells displays some features of papillary carcinoma, including nuclear enlargement, powdery chromatin, nuclear membrane irregularity, nuclear grooves and molding, and small nucleoli. These changes were patchy, however, and other follicular cell sheets looked benign (ThinPrep, Papanicolaou stain).

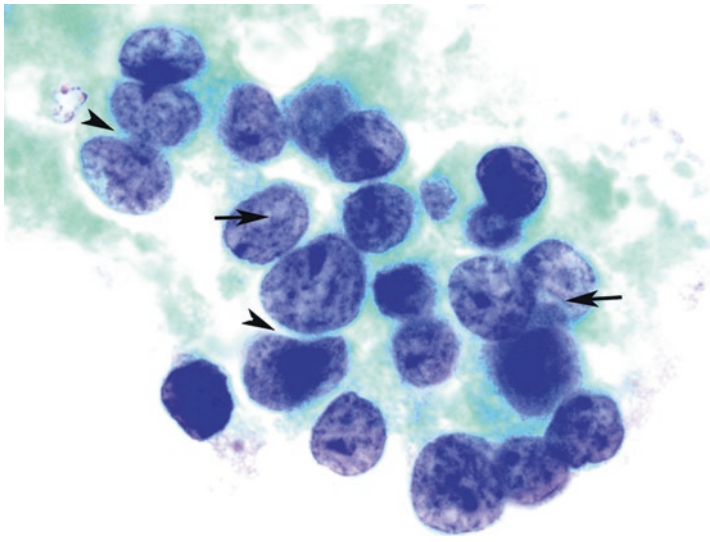

Fig. 7.2 Suspicious for papillary thyroid carcinoma. This loose sheet of follicular cells demonstrates enlarged nuclei, powdery chromatin, nucleoli, and nuclear grooves. There are some questionable (i.e., small, poorly defined) intranuclear pseudoinclusions (*arrows*) and slight nuclear molding (*arrow heads*). These changes were patchy, however, and other follicular cells looked entirely benign (ThinPrep, Papanicolaou stain).

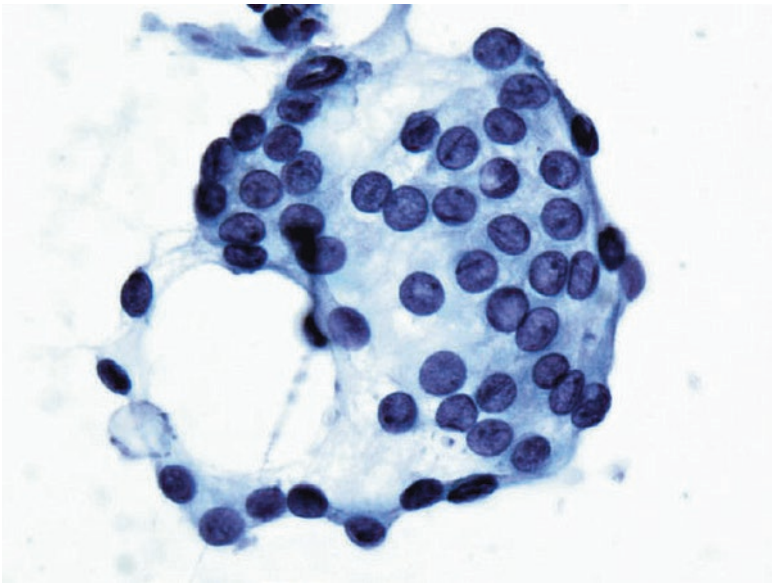

Fig. 7.3 Suspicious for papillary thyroid carcinoma. In this specimen, there were generalized but mild nuclear changes. A loose sheet of follicular cells shows slightly enlarged nuclei, variable chromatin pallor, small but prominent nucleoli, nuclear grooves, and minimal molding (ThinPrep, Papanicolaou stain).

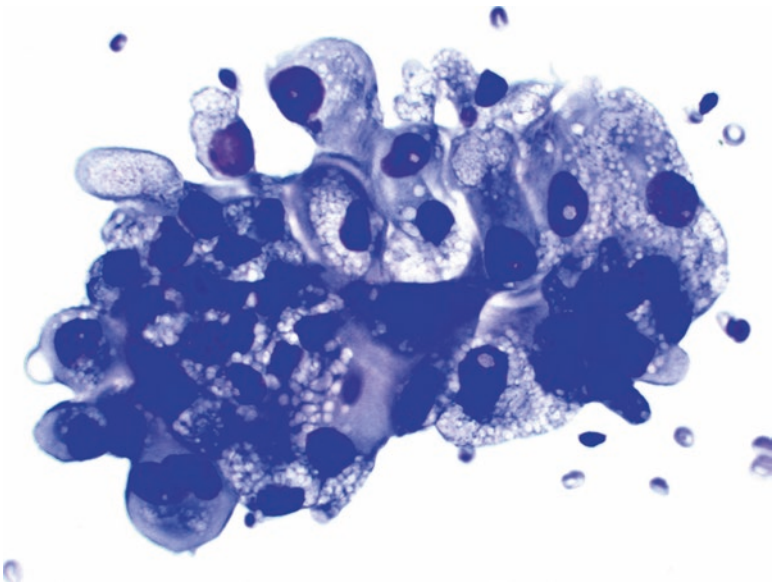

Fig. 7.4 Suspicious for papillary thyroid carcinoma. There is a loose sheet of histiocytoid cells with vacuolated cytoplasm, occasional small nucleoli, and small intranuclear pseudoinclusions (smear, Diff-Quik stain).

Suspicious for Medullary Thyroid Carcinoma (Figs. 7.5 and 7.6)

The sample is sparsely or moderately cellular.

There is a monomorphic population of noncohesive small- or medium-sized cells with a high nuclear/cytoplasmic (N/C) ratio (? lymphoid lesion,? medullary carcinoma).

Nuclei are eccentrically located, with smudged chromatin due to suboptimal preservation; there are no discernible cytoplasmic granules.

There may be small fragments of amorphous material – colloid versus amyloid.

There is inadequate material for ancillary immunohistochemical studies to confirm a diagnosis of medullary carcinoma.

Suspicious for Lymphoma (Fig. 7.7)

The cellular sample is composed of numerous monomorphic small- to intermediate-sized lymphoid cells.

There is inadequate material for ancillary flow cytometery or immunohistochemical studies to confirm a diagnosis of lymphoma.

The sample is sparsely cellular and contains atypical lymphoid cells.

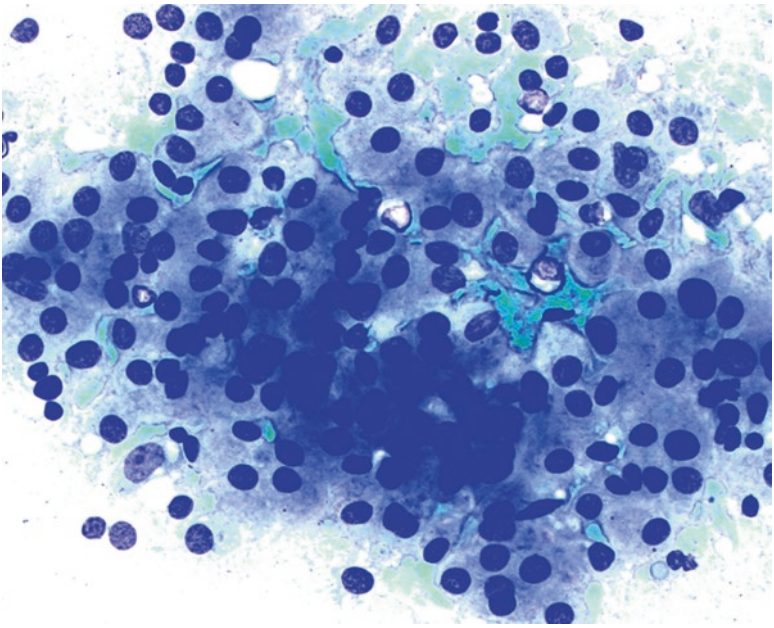

Fig. 7.5 Suspicious for medullary thyroid carcinoma. There is a loose group of cells with relatively uniform nuclei; occasional larger nuclei with prominent nucleoli are present. The ill-defined cell borders make it difficult to discern the nature of the cytoplasm, the nuclear/cytoplasmic ratio, and the plasmacytoid contours of these cells. The stripped nuclei resemble small lymphocytes (smear, Diff-Quik stain).

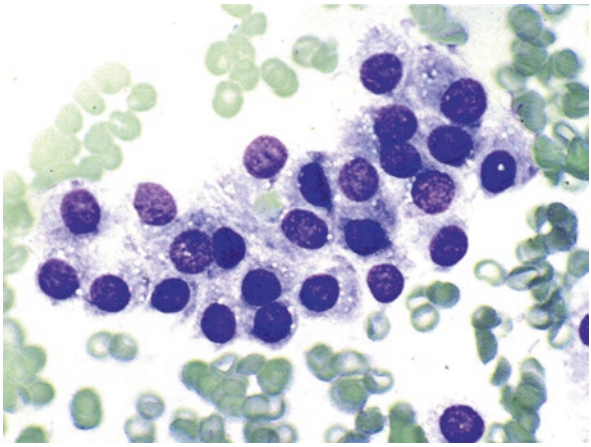

Fig. 7.6 Suspicious for medullary thyroid carcinoma. This loose sheet of relatively uniform cells has granular and vacuolated cytoplasm and ill-defined cell borders. The cells appear slightly degenerated, making it difficult to discern their features with certainty (smear, Diff-Quik stain).

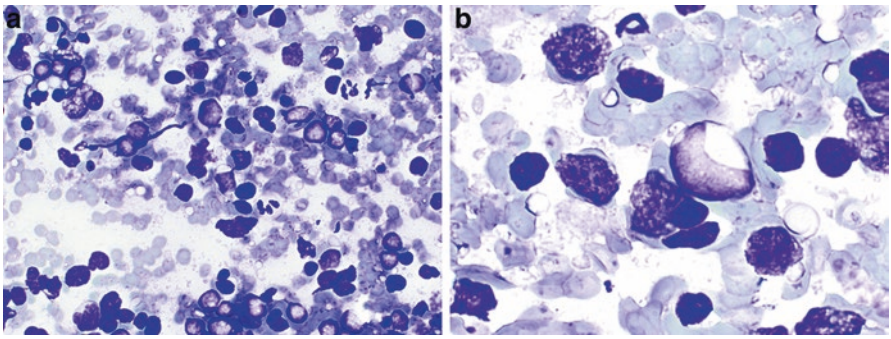

Fig. 7.7 Suspicious for lymphoma. (**a**) This hemodilute sample is comprised exclusively of lymphoid cells, many of which appear poorly preserved. (**b**) At higher magnification, rare large atypical lymphoid cells are present, but most of the cells are disrupted and appear as bare nuclei. In the absence of immunophenotyping studies that demonstrate clonality, the findings are suspicious but not conclusive for malignant lymphoma (smear, Diff-Quik stain).

Suspicious for Malignancy, Not Otherwise Specified

(See Explanatory Notes)

Explanatory Notes

Suspicious for Papillary Thyroid Carcinoma

The criteria for the most common general patterns of "SFM, suspicious for PTC," are outlined above. Because diagnostic histopathologic features of PTC can be patchy within a tumor nodule, FNAs of these nodules can also be heterogeneous. Unfortunately, this pattern is mimicked by a number of benign conditions like lymphocytic thyroiditis, cystic degenerative changes, and radioiodine and carbimazole treatment [5]. The nuclear changes of follicular cells in lymphocytic thyroiditis include focal enlargement, grooves, prominence of nucleoli, and chromatin clearing (Fig. 7.8); an abundance of lymphocytes and plasma cells does not exclude the possibility of a coexisting PTC [19].

Cyst lining cells associated with cystic degeneration have very characteristic features and can be diagnosed as benign in most cases [20]. These cells are typically elongated, with pale chromatin, and occasional nuclear grooves, and relatively large

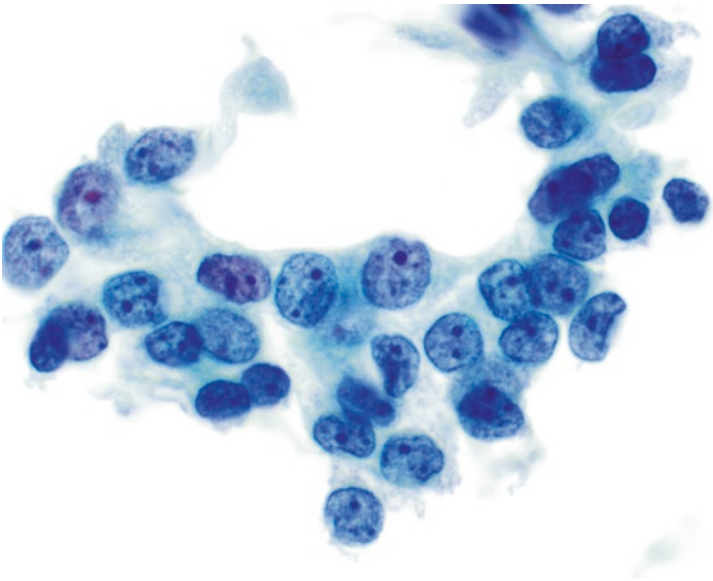

Fig. 7.8 Suspicious for papillary thyroid carcinoma (patient with Hashimoto thyroiditis). This sheet of unevenly distributed follicular cells shows nuclear enlargement, pale chromatin, nuclear irregularity, and prominent nucleoli (ThinPrep, Papanicolaou stain).

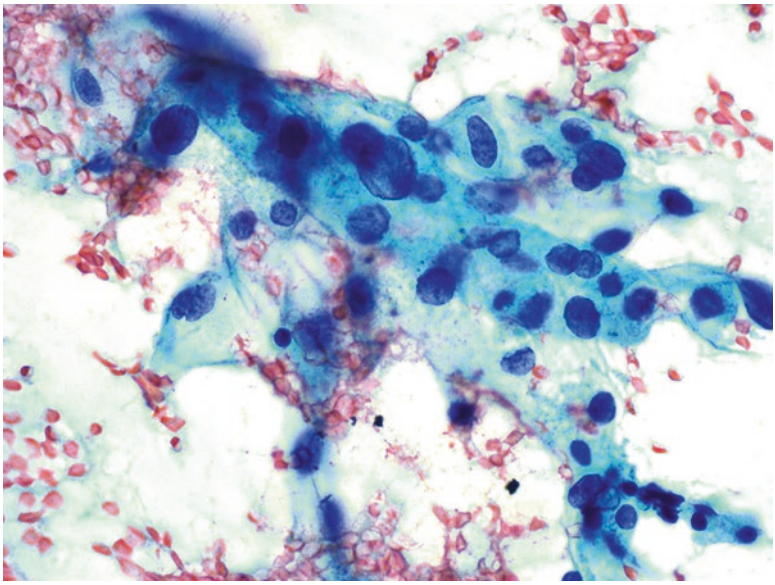

Fig. 7.9 Suspicious for papillary thyroid carcinoma. Follicular cells adjacent to areas of infarction, hemorrhage, and cyst formation ("cyst lining cells") can have nuclear changes similar to those of papillary thyroid carcinoma. When nuclear enlargement, pallor, and grooves are widespread throughout the specimen, the diagnosis "suspicious for malignancy" may be unavoidable (smear, Papanicolaou stain).

nucleoli, and are virtually always associated with hemosiderin-laden macrophages and benign-appearing macrofollicle fragments. The spindle-shaped morphology of the cell and nucleus, reminiscent of reparative epithelium in cervical Pap specimens, is helpful in distinguishing these cells from PTC. In some cases, however, the distinction from PTC is more challenging. A diagnosis of AUS is appropriate for some cases (see Chap. 4), but in their most marked form, they can be highly worrisome, and an SFM interpretation may be warranted (Fig. 7.9).

In patients treated with radioactive iodine, carbimazole, or other pharmaceutical agents, nuclear atypia can be especially prominent [21–23]. In some patients, the nuclear changes can be extreme and raise the possibility of PTC or other malignancy. As with cyst lining cells in their most extreme form, such cases warrant an SFM interpretation (Fig. 7.10).

Instead of being patchy, the nuclear changes are sometimes generalized but mild and incomplete. Again, such relatively subtle generalized changes are seen in some PTCs, particularly the follicular variant, but can be mimicked by benign lesions like a follicular adenoma. For this reason, when generalized but mild, the findings are best interpreted as SFM, suspicious for PTC.

As discussed in detail in Chap. 8, a number of histologic variants of PTC are distinguished by some variation from the defining features of a classic PTC [24–31]. These include the common follicular variant (Fig. 7.11), as well as less

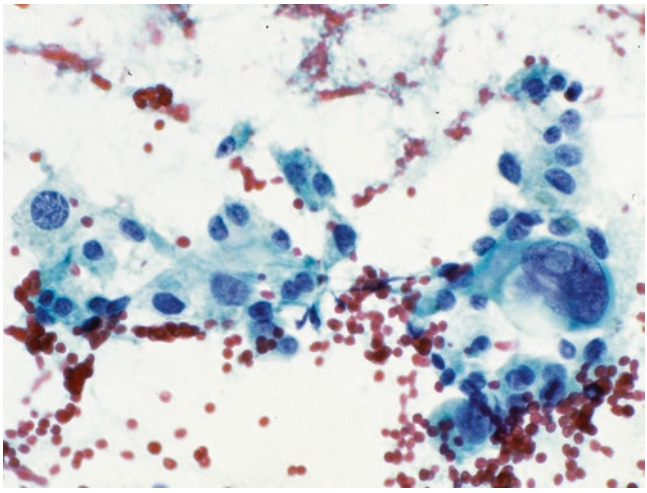

Fig. 7.10 Suspicious for papillary thyroid carcinoma (patient treated with radioiodine for nodular goiter). These follicular cells demonstrate marked anisonucleosis, pale chromatin, and a prominent intranuclear cytoplasmic pseudoinclusion. Although the findings may represent treatment effect, the possibility of papillary thyroid carcinoma cannot be excluded when the atypia is as marked as in this case (smear, Papanicolaou stain).

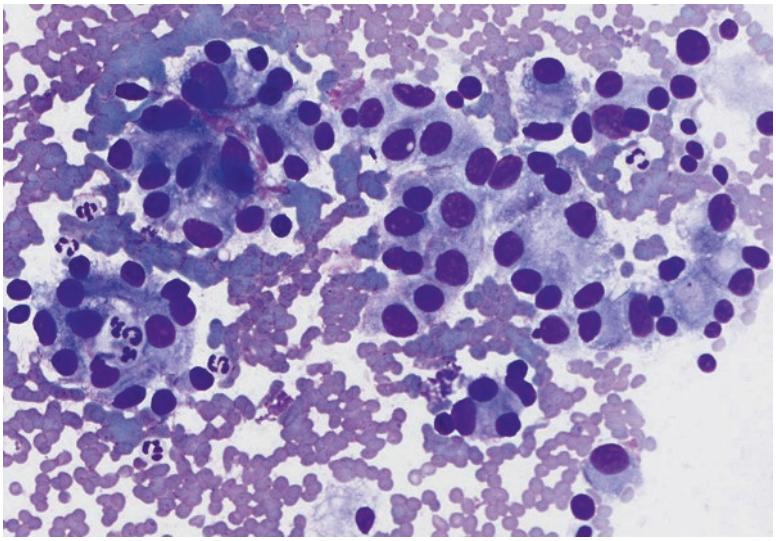

Fig. 7.11 Suspicious for papillary thyroid carcinoma. These representative microfollicular groups display nuclear enlargement, variable chromatin pallor, and rare nuclear grooves. Surgical resection of the nodule revealed a NIFTP (smear, Diff-Quik stain).

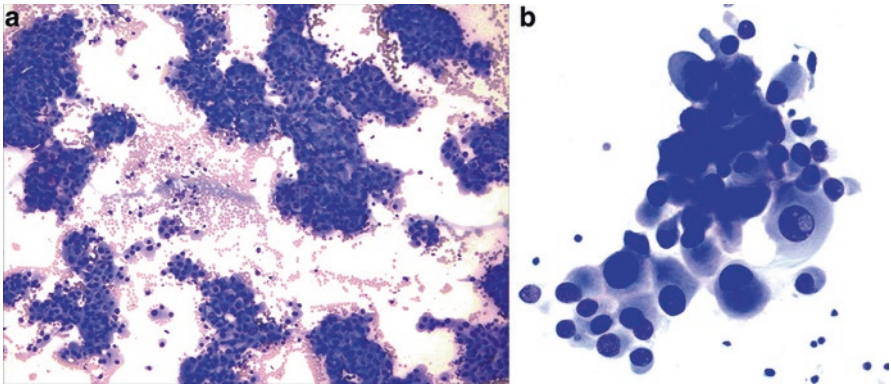

Fig. 7.12 Suspicious for papillary thyroid carcinoma, oncocytic variant. (**a**) This low-magnification image reveals a hypercellular specimen with many groups of follicular cells with abundant cytoplasm (smear, Diff-Quik stain). (**b**) High magnification confirms the presence of abundant cytoplasm and reveals an intranuclear cytoplasmic pseudoinclusion. Although the findings are suspicious for papillary carcinoma, a Hürthle cell neoplasm cannot be entirely excluded (smear, Diff-Quik stain).

frequently encountered variants like the oncocytic (Fig. 7.12a, b) and columnar variants, as well as PTCs with cystic degeneration, to name just a few. These morphologic differences are reflected in FNA specimens and can in some instances cause uncertainty in diagnosis. They may result in a sense of incompleteness or patchiness of expression of typical PTC features, leading to an interpretation of SFM rather than malignant.

The follicular variant of PTC (FVPTC) poses a challenge for FNA. This tumor, with follicular architecture but nuclear changes of PTC, has variable clinical behavior, ranging from the indolence of NIFTP to the aggressiveness of the invasive follicular variant of PTC. Just as for the distinction between follicular adenoma and follicular carcinoma, histopathologic evaluation is necessary to identify the features of malignancy (i.e., invasion) that cannot be appreciated by FNA. Most FVPTCs and NIFTPs are diagnosed cytologically as either SFM, suspicious for a follicular neoplasm (SFN), or atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS); relatively few are interpreted as malignant [9, 18, 32]. The cytomorphologic features of NIFTP and FVPTC overlap across the diagnostic categories: predominantly microfollicular architecture and attenuated nuclear features of PTC (fine chromatin, pale nuclei, and nuclear grooves) are encountered in both the SFM and AUS/FLUS categories [32–34]. It remains to be seen whether any collection of cytologic features is sufficiently reliable to allow prospective identification of NIFTP and its distinction from an invasive FVPTC by FNA alone. For the subset of FNAs diagnosed as SFM that have microfollicular architecture with some nuclear features of PTC but lack intranuclear pseudoinclusions, papillae, or psammoma bodies, an educational note can be helpful (see Sample Reports, Example 2 below) [35].

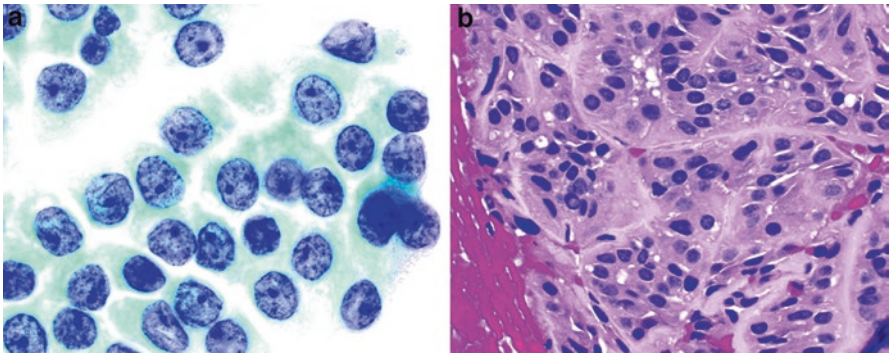

Fig. 7.13 Suspicious for papillary thyroid carcinoma. (**a**) A loose sheet of follicular cells shows nuclear enlargement; pale, powdery chromatin; nuclear grooves; and prominent nucleoli (ThinPrep, Papanicolaou stain). (**b**) A cell block preparation from the FNA reveals the nested pattern of the atypical cells, along with their pale chromatin and obvious intranuclear cytoplasmic pseudoinclusions. The subsequent thyroidectomy revealed a hyalinizing trabecular tumor (cell block, H&E stain).

Hyalinizing trabecular tumor (HTT) shares many morphologic features with PTC, including nuclear grooves and abundant nuclear pseudoinclusions (Fig. 7.13a, b). Although it may be related to PTC, it is generally distinguished from PTC histologically based on its circumscription, trabecular growth pattern, and intratrabecular hyaline material [36]. These distinguishing features are difficult to appreciate by FNA, and many HTTs are interpreted as malignant or SFM. Cytoplasmic staining for MIB-1 (as opposed to the nuclear staining pattern used in other contexts to establish a proliferative index) is a distinctive feature of HTT and can be helpful as an adjunct to cytomorphology [37].

Cystic PTCs, like other PTC variants, have unusual features that differ from those of the classic PTC, sometimes obscured by blood and macrophages. Some contain large cells with abundant dense or vacuolated cytoplasm and pleomorphic nuclei ("histiocytoid cells") (Fig. 7.4). Such PTCs can be difficult to diagnose with certainty as malignant [30, 31].

Suspicious for Medullary Thyroid Carcinoma

A specimen may be less than definitive for the diagnosis of MTC due to technical issues like cellularity and preservation (Fig. 7.6) or unusual cytomorphologic presentations [38]. In such cases, a definitive diagnosis of MTC can be made if sufficient material is available for immunocytochemical stains (see Chap. 9) or if the cytologic findings are interpreted in the proper clinical context (such as a markedly elevated serum calcitonin level).

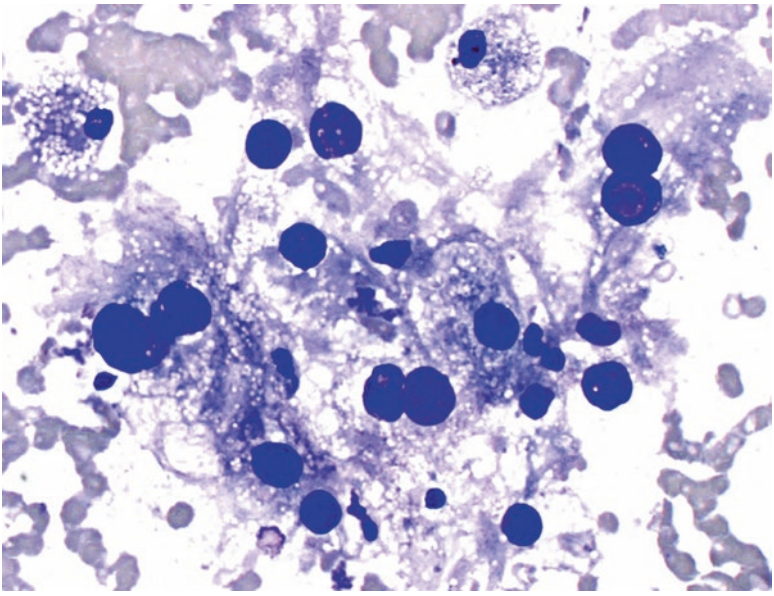

Fig. 7.14 Suspicious for malignancy, cannot classify further. Scattered cells have abundant finely vacuolated cytoplasm, and one cell displays a large intranuclear cytoplasmic pseudoinclusion. The subsequent thyroidectomy showed metastatic renal cell carcinoma (smear, Diff-Quik stain).

Suspicious for Lymphoma

The inability to render a definitive diagnosis of diffuse large B-cell lymphoma is usually the result of technical limitations (e.g., suboptimal sampling and preservation, Fig. 7.7) [39], whereas a definitive diagnosis of a low-grade lymphoma (e.g., a MALT or low-grade follicular lymphoma) is intrinsically more challenging in the absence of ancillary studies [40–42]. MALT lymphoma of the thyroid can be difficult to distinguish from lymphocytic thyroiditis without immunophenotyping by flow cytometry or immunocytochemistry, and a suspicious diagnosis may be prudent [43]. When a monomorphic population of small-to-intermediate-sized cells predominates in a thyroid FNA, the suspicion of a low- or intermediate-grade lymphoma should be raised.

Suspicious for Malignancy, Not Otherwise Specified

Other primary thyroid malignancies like undifferentiated (anaplastic) carcinoma and poorly differentiated carcinoma are encountered in the thyroid, as are metastases (Fig. 7.14). Although a diagnosis of malignancy is easily rendered in many cases, a specific diagnosis requires correlation with clinical and immunocytochemical findings. Suboptimal cellularity or preservation can lead to uncertainty and result in an SFM interpretation.

Management

In general, clinical-surgical recommendations relating to a "SFM, suspicious for PTC" FNA result, have been framed by the relatively high rate of malignancy in this category, which would typically elicit consideration for offering a procedure intended for malignancy, most commonly a total thyroidectomy, which is well-tolerated in expert hands [44–46]. Important non-cytologic clinical data available through careful preoperative clinical and radiographic risk stratification should be introduced into the conversation as it relates to the recommendation for surgery and its extent. These factors improve the estimation of the prevalence of malignancy and include key historical features such as family history or history of irradiation, physical exam characteristics such as fixation of the mass to the adjacent cervical viscera, laryngeal exam including the finding of vocal cord paralysis ipsilateral to the mass [47], and the ultrasonographic appearance of the index nodule. Ultrasonographic preoperative stratification of nodules is increasingly important, as emphasized in the most recent American Thyroid Association (ATA) guidelines for thyroid nodule workup, and is additive to cytologic evaluation in the estimation of malignancy in a given nodule [14].

New ATA initiatives to reduce the extent of surgery for many low-risk thyroid cancers (4 cm or smaller, without extrathyroidal extension and lacking regional nodal metastasis) and decrease routine use of postoperative radioactive iodine treatment increasingly raise the possibility for lobectomy as initial surgical management [14]. Also, the recognition of the indolence of NIFTP further supports a less aggressive initial surgical procedure in some patients [16]. The reclassification of some nodules as NIFTP alters the rate of malignancy for SFM, with the emerging literature suggesting an overall decrease in the 15–20% range [17, 18]. The exact clinical and surgical impact of this is yet to be determined but clearly will help push the pendulum toward consideration of a more conservative initial surgical procedure in many circumstances. Many other factors relate to the decision of unilateral versus bilateral surgery, including the patient's acceptance of a more aggressive initial surgical procedure and thyroid hormone suppression, their willingness to have a potential second procedure, and the potential for surgery to affect the patient's use of voice in their profession. Frozen section has limited utility for SFM nodules [46, 48].

Role for Ancillary Studies

Historically, there has been limited utility for ancillary molecular studies for an "SFM, suspicious for PTC" FNA diagnosis, given the relatively high risk of malignancy necessitating surgery. According to the most recent ATA guideline recommendations, after consideration of clinical and sonographic features, molecular testing may be considered in nodules with SFM, suspicious for papillary carcinoma cytology if such data would be expected to alter surgical decision making [14]. The

recent recommendation by the ATA regarding the Afirma gene expression classifier states that the test is "not reflexively performed nor routinely recommended for the SFM cytologic category, but may be requested if clinically indicated." [15] Although NIFTP nodules tend to lack BRAF V600E mutations and instead often harbor either RAS or PAX8/PPARγ mutations, it remains to be seen whether molecular testing will help to prospectively identify NIFTP nodules given the proper clinical and cytologic context [49–51].

Aside from suspicious FNA diagnoses where papillary thyroid carcinoma is the concern, ancillary studies can be very helpful for patients with the diagnosis "suspicious for MTC" or "suspicious for lymphoma." An elevated serum calcitonin level and/or immunoreactivity for calcitonin, synaptophysin, and chromogranin can lead to a conclusively malignant interpretation of medullary thyroid carcinoma. A repeat FNA to obtain cells for flow cytometry can better characterize any lymphocyte population, thus helping provide a definite diagnosis for patients with an initial "suspicious for lymphoma" interpretation. In these instances, the case may be moved from the suspicious to the malignant category once the results of the ancillary tests become available. The need for ancillary testing may be anticipated if rapid onsite evaluation (ROSE) is performed, allowing additional samples to be collected without the need to recall patients for repeat testing.

Sample Reports

If an aspirate is interpreted as SFM, it is implied that the sample is adequate for evaluation. (An explicit statement of adequacy is optional.) Narrative comments that follow are used to specify which malignancy/ies the findings are suspicious for. A microscopic description is optional.

Example 1
SUSPICIOUS FOR MALIGNANCY.
Suspicious for papillary thyroid carcinoma.

Example 2
SUSPICIOUS FOR MALIGNANCY.
Suspicious for papillary thyroid carcinoma; see Note.

Note: The overall cytomorphologic features are suggestive of a follicular variant of papillary carcinoma or its recently described indolent counterpart, noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP). Definitive distinction between these entities is not possible on cytologic material.

Example 3
SUSPICIOUS FOR MALIGNANCY.
Suspicious for medullary thyroid carcinoma.

Note: Correlation with serum calcitonin level or re-aspiration for immunohistochemical studies might be helpful for definitive diagnosis if clinically indicated.

Example 4
SUSPICIOUS FOR MALIGNANCY.
Suspicious for lymphoma.

Note: Re-aspiration for flow cytometry might be helpful to better characterize the lymphocyte population if clinically indicated.

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Papillary Thyroid Carcinoma, Variants, and Related Tumors

8

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Background

Papillary thyroid carcinoma (PTC) is the most common malignant neoplasm of the thyroid gland, accounting for approximately 85% of all cancers at this site. It occurs in all age groups, including children, with a peak incidence in the third to fourth decades, and an M/F ratio of 1:4. The incidence of thyroid carcinomas has nearly tripled in the last three decades, with PTC accounting for most of the surge [1–3]. The mortality rate remained stable during this time, however, suggesting that the more indolent forms of PTC are increasingly diagnosed. Although traditionally considered the most common type of PTC, conventional (classic) PTC has diminished in relative frequency compared to PTC variants, especially in view of the increasing awareness and recognition of the follicular variant of PTC (FVPTC) [3].

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Given the revision in nomenclature that reclassified the noninvasive FVPTC as "noninvasive follicular thyroid neoplasm with papillary-like nuclear features" (NIFTP) [4], this trend in the increase of PTC and FVPTC diagnosis may be reversed in the future. Risk factors for PTC include external radiation to the neck during childhood, exposure to ionizing radiation, and genetic susceptibility [1]. PTC usually presents as a thyroid nodule, often discovered incidentally on routine examination, but a minority of patients present with metastatic disease in neck lymph nodes. PTC spreads via lymphatics to the regional lymph nodes and, less frequently, to the lungs. It generally carries a good prognosis; death secondary to PTC is rare [1].

A malignant thyroid FNA diagnosis accounts for approximately 5% (range, 2–16%) of all thyroid FNAs [2, 5], the majority of them PTCs. When a definite diagnosis of PTC is made by FNA, 94–96% prove to be PTC on histologic follow-up, taking into consideration the reclassification of some PTCs as NIFTP [2, 5]. Conventional PTCs are characterized histologically by numerous papillae lined by cuboidal to low columnar neoplastic follicular cells with distinctive nuclear features. A significant proportion of PTCs exhibit variant architectural and/or cytologic features from those of conventional PTC. Furthermore, some PTC variants have different genetics and biological behavior than conventional (classic) PTC. An awareness of the cytomorphologic spectrum of PTC variants helps prevent misdiagnosis, but it is not necessary to specify the subtype of PTC on an FNA specimen. In the following sections, conventional (classic) PTC and its variants are described separately to highlight some of the morphologic heterogeneity in this family of tumors.

Given the reclassification of some follicular variants of PTC as "neoplasms" rather than overt malignancies, it is desirable to eliminate from the malignant category tumors likely to harbor a NIFTP. To accomplish this goal, a suspected PTC with an exclusively follicular architecture, especially one that lacks intranuclear cytoplasmic pseudoinclusions and psammoma bodies (e.g., many follicular variants of PTC), is best interpreted as "suspicious for malignancy" rather than malignant. This approach leaves other subtypes of PTC in the malignant category but minimizes the contribution of FVPTC and NIFTP. It is unlikely that NIFTPs can be completely eliminated from the malignant category, however, and some pathologists may prefer to include an educational note to reinforce this limitation (see "Sample Reports" below).

Conventional (Classic) Papillary Thyroid Carcinoma

Definition

Conventional (classic) PTC is a malignant epithelial tumor derived from the thyroid follicular epithelium that displays papillary architecture and characteristic nuclear alterations.

Criteria

Cells arranged in papillae and/or monolayers
Cellular swirls ("onion-skin" or "cartwheel" patterns) (some cases)
Enlarged and crowded nuclei, often molded
Oval or irregularly shaped nuclei
Longitudinal nuclear grooves
Intranuclear cytoplasmic pseudoinclusions (INCIs)
Pale nuclei with powdery chromatin
Thick nuclear membranes
Marginally placed micronucleoli, solitary or multiple
Psammoma bodies
Multinucleated giant cells
Variable amount of colloid; may be stringy, ropy, or "bubblegum"-like
"Hobnail" cells
Oncocytic (Hürthle cell) metaplasia
Squamoid metaplasia
"Histiocytoid" cells
There are some minor differences between smears and liquid-based preparations (LBP) with regard to the diagnosis of conventional (classic) PTC [6–8]. Awareness of the cytomorphological features observed with the use of the LBP method is helpful.

Cytological Features More Frequent in LBP Compared to Smears

Convoluted nuclei
Eosinophilic nucleoli
Perinucleolar halo
Trabecular and hobnail patterns
Tall cells
Collagenous stroma
Naked capillaries
Intercellular spaces

Cytological Features Less Frequent in LBP Compared to Smears

Pale nuclei
Papillary pattern and tissue fragments

Explanatory Notes

Although several nuclear alterations are characteristic, none of them is diagnostic of PTC in isolation or low frequency. Only when relatively widespread and in combination are they diagnostic of PTC, whether one is examining smears or LBP [6, 7]. The minimum criteria and number of neoplastic cells necessary for an unequivocal diagnosis are uncertain and probably not definable, either cytologically or histopathologically. In other words, the minimum quantitative threshold (e.g., the number of cells needed with nuclear grooves and/or INCIs) for a diagnosis of PTC in cytological or histologic specimens remains undefined. If, in the judgment of the cytologist, a case has some features of PTC but falls short of an unequivocal diagnosis, it is interpreted as "Suspicious for PTC" or "Atypia (or Follicular Lesion) of Undetermined Significance (AUS/FLUS)" (see Chaps. 7 and 4, respectively), depending on the quality and quantity of the changes and the reviewer's degree of suspicion for PTC.

The cells of a conventional (classic) PTC are typically arranged in syncytial-like flat sheets ("monolayers") with crowded and overlapping nuclei (Figs. 8.1, 8.2, and 8.3). The latter feature often leads to conspicuous nuclear molding (Fig. 8.3). Nuclear crowding, overlapping, and molding are important diagnostic features that help distinguish the cells of PTC from benign follicular cells. The monolayered sheet is characteristic of conventional (classic) PTC and mimics the flat sheet of a macrofollicular fragment typical of benign follicular nodules, such

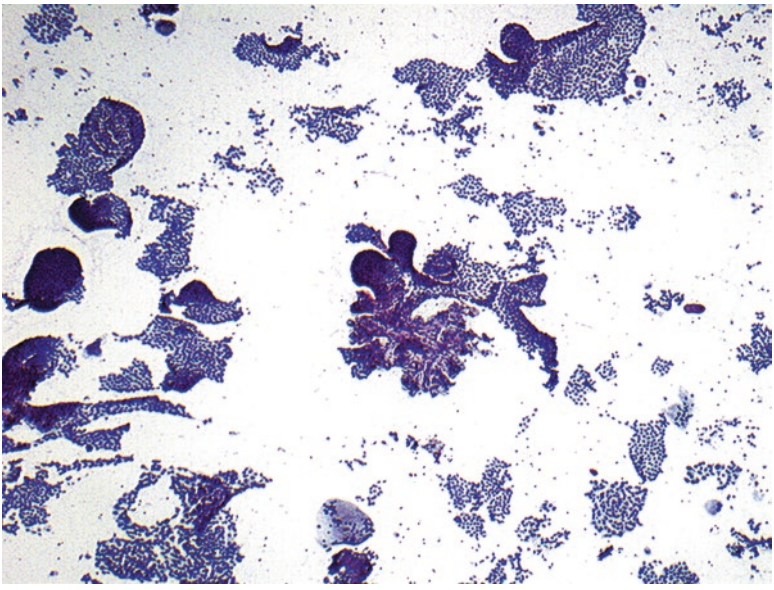

Fig. 8.1 Papillary thyroid carcinoma. Preparations are often highly cellular and composed of numerous monolayer sheets and occasional papillary-like fragments (smear, Papanicolaou stain).

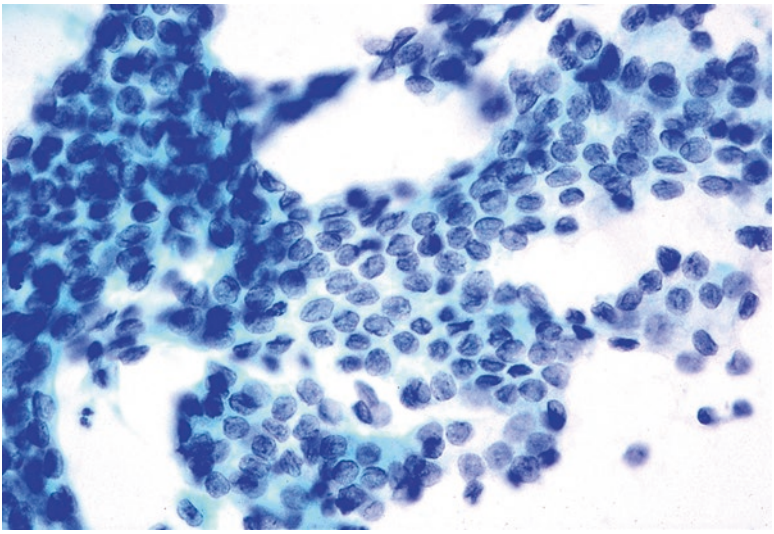

Fig. 8.2 Papillary thyroid carcinoma. Monolayer sheets with a syncytial-like appearance are characteristic of papillary thyroid carcinoma. These flat sheets resemble those of benign follicular nodules; attention to the nuclear features is essential for this distinction (smear, Papanicolaou stain).

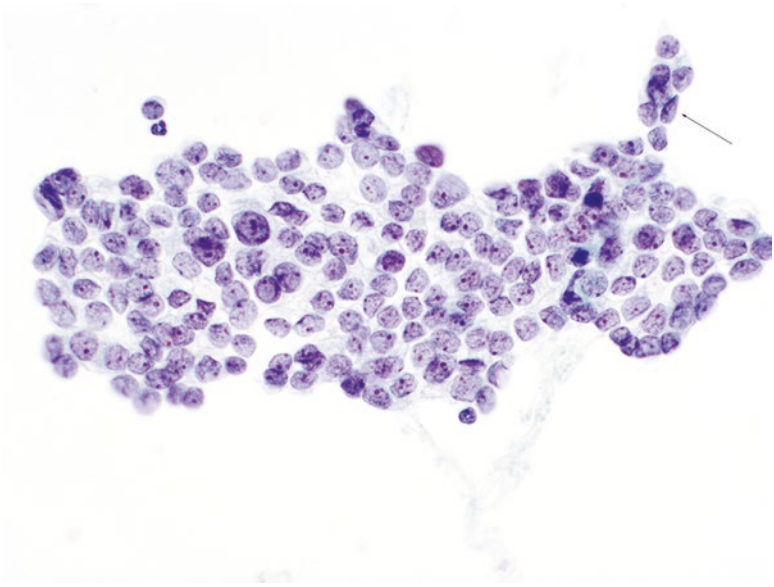

Fig. 8.3 Papillary thyroid carcinoma. This monolayer sheet is comprised of cells with irregular nuclei that show focal molding (*arrow*) (ThinPrep, Papanicolaou stain).

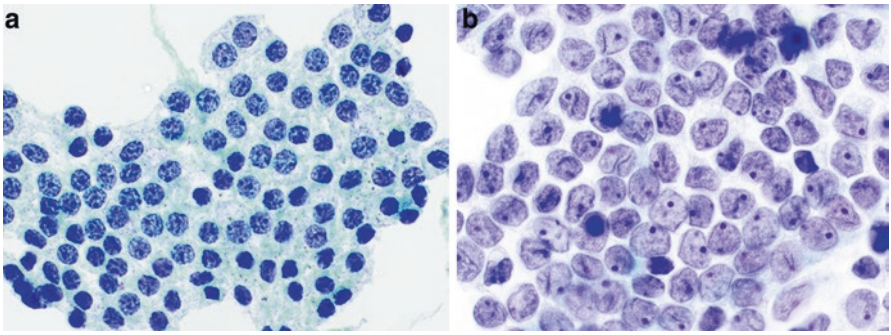

Fig. 8.4 Comparison of benign follicular cells with the cells of papillary thyroid carcinoma. (**a**) Benign follicular cells (nodular goiter). (**b**) Compared with those of the benign follicular cells, the nuclei of papillary carcinoma are larger, paler, more crowded, and more irregular in contour (**a**, **b**, ThinPrep, Papanicolaou stain).

as those commonly seen in nodular hyperplasia (Fig. 8.4). The distinction requires particular attention to the arrangement of the cells in the sheets (evenly spaced vs. crowded) and their nuclear features to avoid a false-negative diagnosis. The architectural pattern varies depending on the type of PTC (see below), but FNAs from a conventional PTC often display true papillary fragments (i.e., with a fibrovascular core) (Figs. 8.5 and 8.6), papillary-like fragments (rounded shape with smooth edges but lacking a fibrovascular core) (Fig. 8.7), and cellular swirls. Cellular swirls (Fig. 8.8) are flat, concentrically organized aggregates of about 50–200 tumor cells with a perpendicular arrangement of the most peripherally located ovoid cells relative to the radius of the swirl (sometimes also called an "onion-skin" pattern) [9]. Cellular swirls are a distinctive feature of the conventional (classic) PTC, seen in about 17% of cases (smears and LBP) and have not been reported in benign thyroid nodules [7, 9]. Although individually dispersed neoplastic cells are seen in PTC, a pattern of predominantly isolated cells is highly unusual (in contrast to medullary carcinoma).

The cells of PTC vary in size (medium to large) and shape (cuboidal, columnar, polygonal, sometimes spindle-shaped and even "histiocytoid"). Cell borders are usually well-demarcated. The amount and texture of cytoplasm also vary greatly. In some cases, the cells have scant cytoplasm, but abundant oncocytic (granular) cytoplasm is common, although usually a focal finding. When extensive, it signals an oncocytic variant of PTC. A hobnail pattern was recently suggested as a useful diagnostic criterion, especially on LBP [6, 7], and has been reported in several variants of PTC (hobnail, diffuse sclerosing, cystic). "Hobnail pattern" is the term employed to describe cells characterized by a high nuclear/cytoplasmic ratio and apical/eccentric placement of the nuclei that produces a surface bulge like hobnails [7, 10, 11]. The hobnail pattern is usually associated with a loss of cellular polarity and cohesiveness and, when extensive, may be associated with aggressive behavior

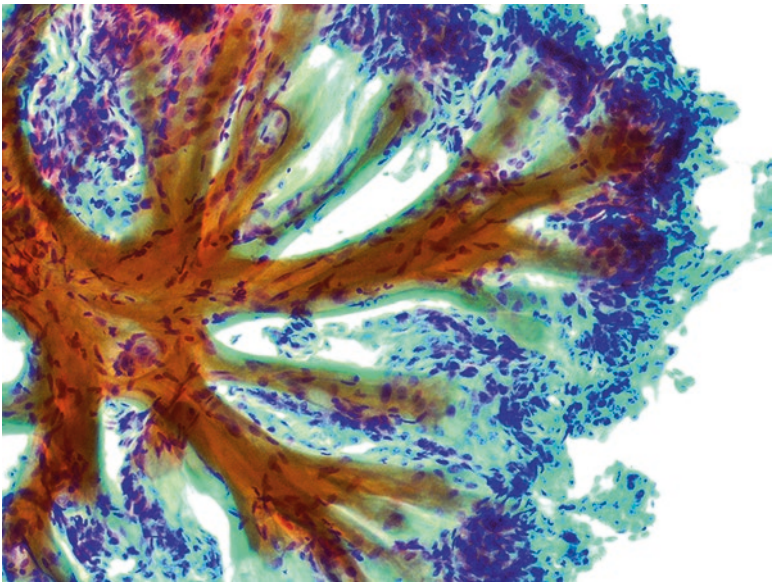

Fig. 8.5 Papillary thyroid carcinoma. True papillary tissue fragments, comprised of fibrovascular cores lined by neoplastic cells, are seen in the conventional type of papillary thyroid carcinoma (smear, Papanicolaou stain).

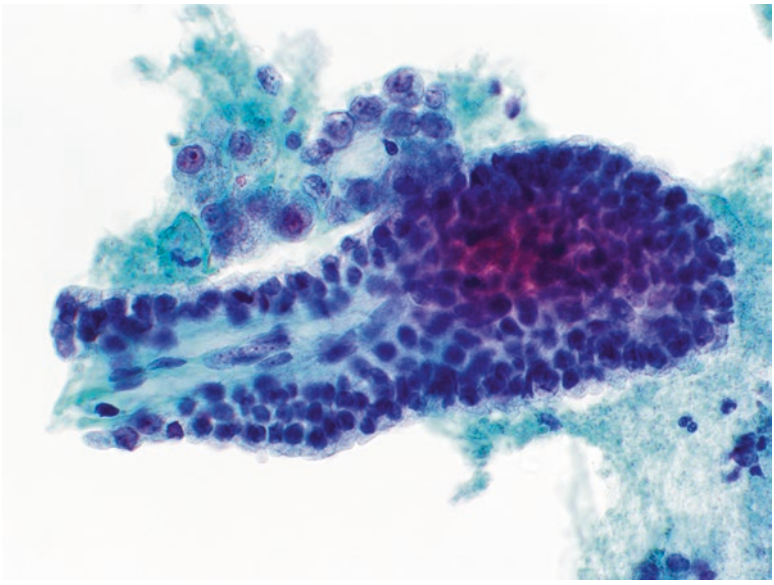

Fig. 8.6 Papillary thyroid carcinoma. The neoplastic cells surround a fibrovascular core (ThinPrep, Papanicoalou stain).

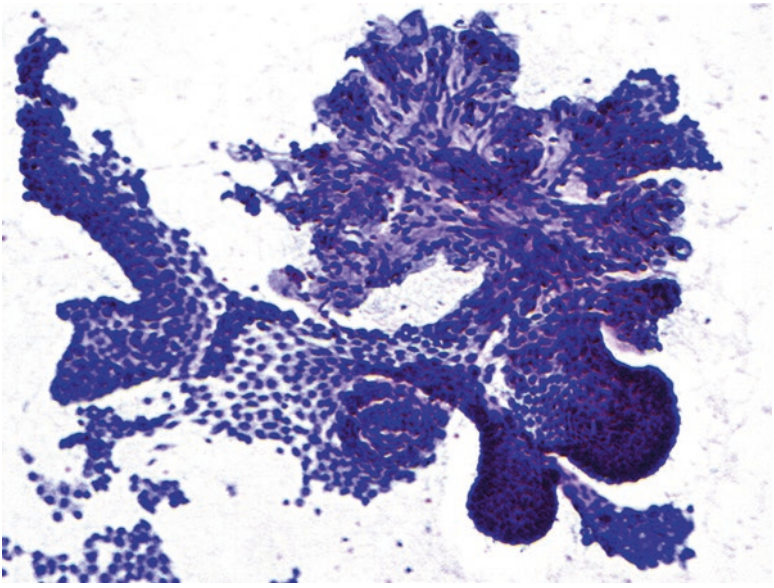

Fig. 8.7 Papillary thyroid carcinoma. There is a mixture of flat sheets and rounded, papillary-like fragments without fibrovascular cores (ThinPrep, Papanicoalou stain).

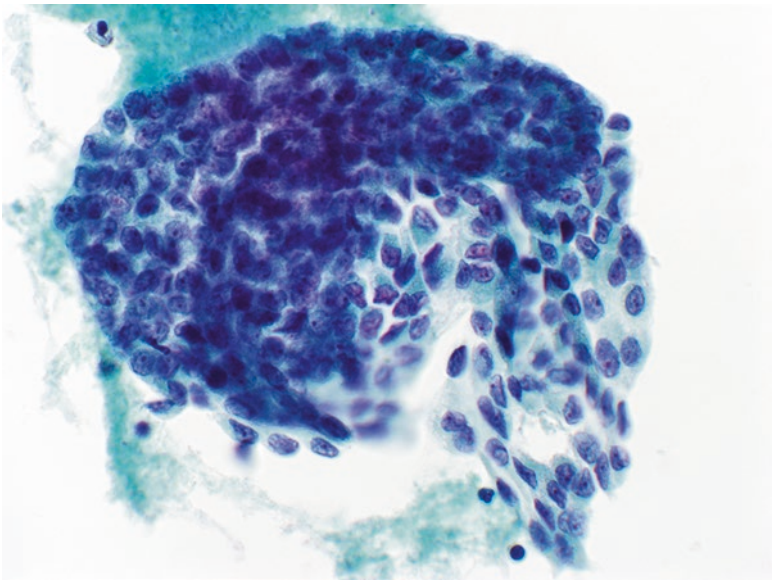

Fig. 8.8 Papillary thyroid carcinoma. Cellular swirls are highly characteristic of the conventional (classic) papillary thyroid carcinoma. They are a concentric aggregate of tumor cells in which many of the peripheral cells have ovoid (rather than round) nuclei and are oriented perpendicular to the radius of the swirl (ThinPrep, Papanicolaou stain).

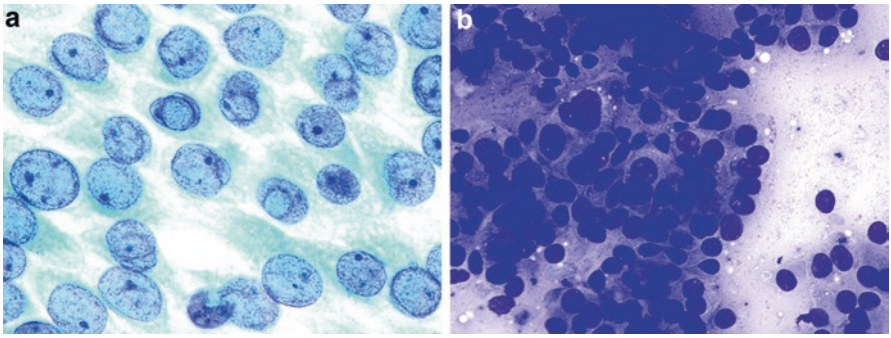

Fig. 8.9 Papillary thyroid carcinoma. (**a**) Intranuclear cytoplasmic pseudoinclusions (INCIs) and micronucleoli are shown. Note that the two INCIs share the same aqua color and granular texture as the surrounding cytoplasm (smear, Papanicolaou stain). (**b**) A large INCI occupying most of the nucleus is seen in the center. The remaining nuclei show variation in size and shape (smear, Diff-Quik stain).

(see "Hobnail Variant" below) [10, 11]. Changes resembling squamous metaplasia (moderate-to-abundant dense cytoplasm and cells that fit together like pavement stones) are also seen, usually only as a focal finding in conventional (classic) PTC. Hyperkeratinized squamous cells (orangeophilic cytoplasm on Papanicolaou stain) and keratin pearls, however, are rare. Histiocytoid cells are characterized by extensive cytoplasmic vacuolation (like that of benign histiocytes) and typically arise in a PTC that has undergone cystic changes (see Fig. 7.4).

The defining features of PTC are seen in the nuclei. They can be round or oval but are often highly irregular in contour; the nuclear contour irregularity is often one of the first clues to the diagnosis (Fig. 8.4b). Convoluted nuclei, where more than half of the nuclear membrane is wrinkled, are very specific for PTC on LBP (97.3%) [6]. The chromatin of a conventional PTC nucleus is usually pale, finely textured, and evenly distributed (powdery), unlike the dark and coarsely textured benign follicular cell nucleus (Fig. 8.4b). This chromatin characteristic is more easily appreciated with alcohol-fixed Papanicolaou-stained smears than air-dried Diff-Quik preparations or LBP, and it may be absent in some variants of PTC (e.g., columnar cell). This pallor parallels the optically clear appearance of PTC nuclei in formalin-fixed tissue ("Orphan Annie eyes"), which is attributed to a fixation artifact that renders the nucleus practically empty in appearance.

Intranuclear cytoplasmic pseudoinclusions (INCIs) are seen in 50–100% of aspirates of PTC, depending on the subtype of PTC (Figs. 8.9 and 8.10). For example, INCIs are most frequent and florid in the tall cell variant, whereas they are often rare or absent in the follicular variant. INCIs are not specific for PTC; they can be seen in aspirates of medullary thyroid carcinoma, poorly differentiated thyroid carcinoma, anaplastic thyroid carcinoma, hyalinizing trabecular tumor, NIFTP, and very rarely, benign thyroid nodules (e.g., nodular goiter, follicular adenoma) and lymphocytic thyroiditis. INCIs should therefore always be interpreted in light of the

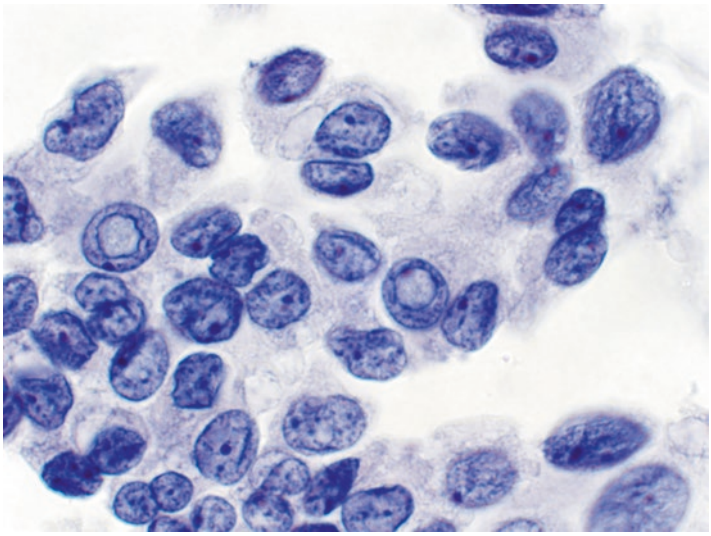

Fig. 8.10 Papillary thyroid carcinoma. Two intranuclear cytoplasmic pseudoinclusions (INCIs) are seen. (ThinPrep, Papanicoalou stain).

other architectural and nuclear features in a given FNA. Ultrastructurally, INCIs are membrane-bound spheroidal masses of cytoplasm that protrude into the nuclei. Thus, a true INCI displays the same color/texture of adjacent cytoplasm and is sharply bordered by a rim of condensed chromatin, like a "wire loop." These features help distinguish INCIs from common mimics: degenerative and artifactual vacuoles, fixation artifacts, and superimposed red blood cells.

Nuclear grooves are another hallmark of PTC [12]. Akin to INCIs, they are best seen with alcohol-fixed, Papanicolaou-stained preparations (Fig. 8.11) and are less conspicuous with air-dried Romanowsky-stained smears (e.g., Diff-Quik). Nuclear grooves and INCIs are manifestations of nuclear membrane redundancy; a nuclear groove, for example, results from a nucleus folded onto itself [13]. Although a sensitive feature for the cytologic diagnosis of PTC, nuclear grooves are not specific and can be seen in a variety of other thyroid neoplasms such as oncocytic neoplasms and nonneoplastic conditions like lymphocytic thyroiditis. Quantification studies have shown that PTC tends to have more nuclear grooves than other lesions, but they have not shown that a specific number of grooves establishes a definite diagnosis. For this reason, they should not be relied upon in isolation to make a diagnosis of PTC. In addition, nuclear grooves are useful only when identified within follicular epithelial cells; care must be taken not to misinterpret histiocytes or Langerhans cells, which are characterized by elongated, oval nuclei with nuclear grooves, for the cells of PTC.

The nuclei of PTC typically display one to three micronucleoli, often positioned underneath the nuclear membrane ("marginal"). On LBP, they are commonly eosinophilic (89%) and associated with a perinucleolar halo ("bare nucleoli") (63%) [6]. The latter has been reported to be very specific for PTC (96%) [6].

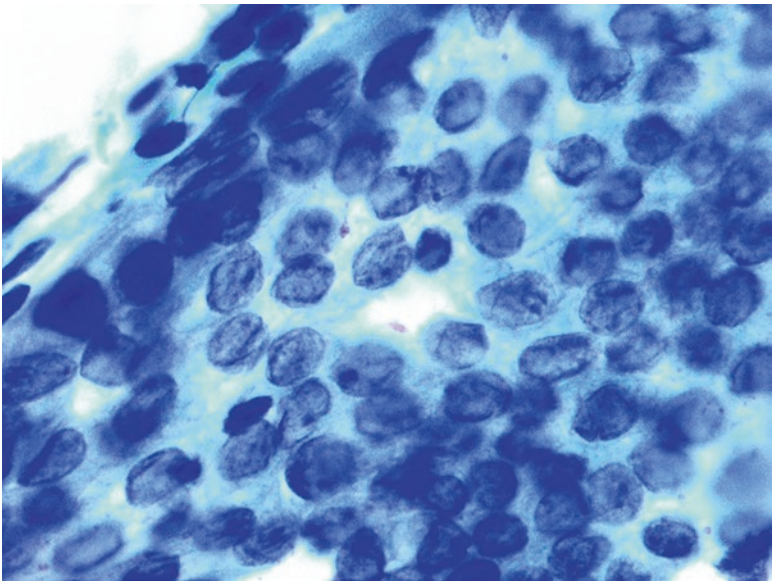

Fig. 8.11 Papillary thyroid carcinoma. Close inspection at high magnification shows frequent nuclear grooves, finely textured (powdery) chromatin, and micronucleoli (smear, Papanicolaou stain).

Multinucleated giant cells of histiocytic lineage are commonly seen in aspirates of PTC, even when cystic degeneration is not present (Fig. 8.12). Although common, they are not specific for PTC, and similar cells are seen in other conditions, both benign and malignant. The cells can be very large, and their nuclei can vary in number from few to numerous. They are part of the host response to the malignancy, along with other type of immune cells (e.g., Langerhans cells, lymphocytes, and mast cells).

Psammoma bodies (PBs) are seen less frequently in FNA samples of PTC (4–20% of cases) than in histologic specimens (40–60%). They can be solitary or multiple and isolated or attached to cells (Fig. 8.13). PBs alone (i.e., not associated with altered cells) are nonspecific and can be seen in medullary thyroid carcinoma, lymphocytic thyroiditis, Graves' disease, and even nodular goiter. Calcifications resembling PBs occur in oncocytic neoplasms and represent calcification of colloid. The positive predictive value (PPV) for PTC of PBs in isolation is 50%; when seen in association with the cytologic features of PTC, the PPV is 100% [14].

The background usually contains relatively scant colloid, but some variants (see below) can have abundant colloid. Colloid may be watery or dense and stringy with ropy strands ("bubblegum" colloid). The background is usually clean; necrotic debris is extremely uncommon. Hemosiderin-laden macrophages, representing hemorrhage and cystic changes, are common in PTC and can be prominent. Variable numbers of lymphocytes can be seen due to an underlying lymphocytic thyroiditis. When lymphocytes predominate, a Warthin-like or diffuse sclerosing variant (DSV)

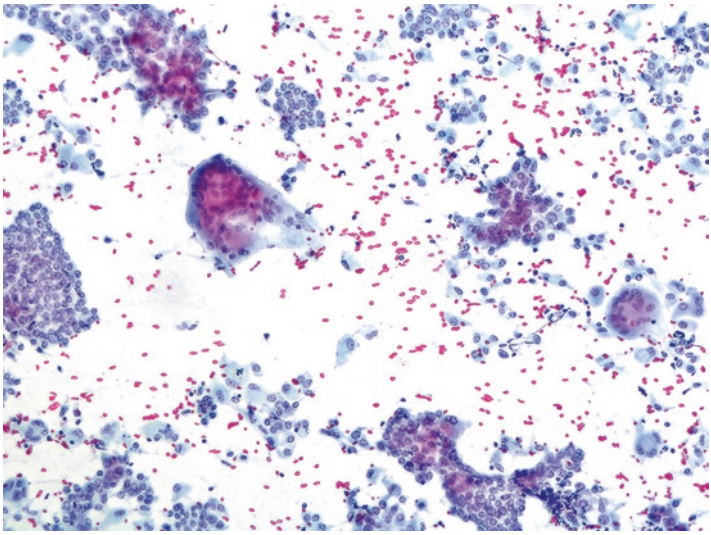

Fig. 8.12 Papillary thyroid carcinoma. Multinucleated giant cells accompany monolayered sheets of tumor cells. Although multinucleated giant cells are often seen in PTCs, they are a nonspecific finding (smear, Papanicolaou stain).

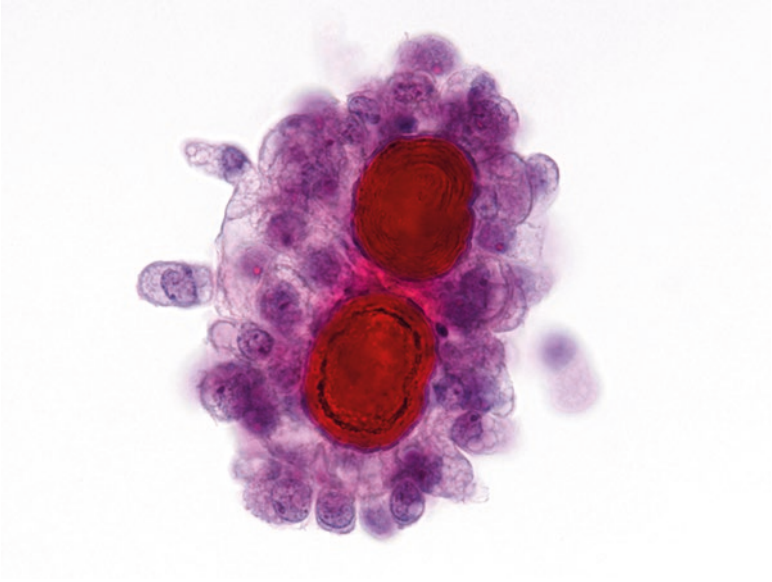

Fig. 8.13 Papillary thyroid carcinoma. Psammoma bodies are concentric rings and are lined here by atypical cells with oval, pale nuclei. Note that the tumor cells surrounding psammoma bodies show hobnail features (ThinPrep, Papanicolaou stain).

of PTC should be considered (see below). Caution should be exercised when nuclear abnormalities are seen in follicular cell clusters with intimately admixed lymphocytes, as these nuclear changes may be reactive and not malignant.

Given an adequate sample, it is relatively straightforward to diagnose conventional (classic) PTC by FNA. Although false-negative and false-positive diagnoses occasionally occur, they can be minimized by adopting a conservative approach to a sparsely cellular or otherwise suboptimal specimen. This recommendation applies as well to cases with focal or limited nuclear changes.

Variants of Papillary Thyroid Carcinoma

A substantial proportion of PTCs exhibit variant architectural and/or cytologic features from those of conventional (classic) PTC. Variants of PTC, by definition, have at least some of the essential nuclear features of PTC but a different architectural pattern, unusual cytoplasmic features, or different background characteristics, such as the quantity and texture of the colloid, the type of stroma, and the presence or absence of a prominent lymphoplasmacytic infiltrate. More than ten variants of PTC have been documented [1, 2]. Some are associated with more aggressive and others with more indolent behavior than conventional PTC [1, 2]. The variants with less favorable outcomes are the tall cell, columnar cell, and hobnail variants [2]. The solid variant and the diffuse sclerosing variant may be associated with a less favorable outcome, but the data remain conflicting [2]. In contrast, the noninvasive FVPTC is indolent, with virtually no metastatic or recurrence potential, and for this reason has been reclassified as NIFTP (see "Follicular Variant and NIFTP" below) [4].

Recognition of PTC variants at the time of FNA is generally unnecessary [2]. Precise subtyping is rarely possible or reliable, because the predominant pattern may not have been sampled (many PTCs show more than one growth pattern and/or cell type). Furthermore, because some of these variants are very rare, familiarity with their morphologic features may be impractical, and the PPV of any set of specific features (described mostly in retrospective studies) is hard to predict. Nonetheless, the architectural and cytologic features that distinguish these lesions from conventional PTC histologically are often observed cytologically, and awareness of the phenotypic characteristics of the various subtypes can diminish the risk of misdiagnosis.

Follicular Variant and NIFTP

Definition

The follicular variant of PTC (FVPTC) is completely or almost completely composed of small- to medium-sized follicles lined by cells with variable nuclear features of PTC.

Noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) is an encapsulated or well-demarcated neoplasm with follicular-patterned

morphology and variable nuclear features of PTC, without capsular or vascular invasion. This term was introduced to recognize the indolent behavior of thyroid neoplasms previously classified as noninvasive FVPTC.

Background

It has long been recognized that some PTCs are composed primarily if not exclusively of follicles rather than papillae. FVPTC is now the most common variant of PTC and represents nearly 30% of PTCs in some series [3, 15–20]. FVPTC consists of several distinct subtypes. The vast majority of these tumors are composed of microfollicles; however, some FVPTCs are composed of normal-sized follicles. Tumors composed predominantly of macrofollicles are a different and distinct subset of PTC (see "Macrofollicular Variant" below) [1].

There are two distinct groups within FVPTC that differ morphologically, genetically, and clinically:

1. *FVPTC with an infiltrative growth pattern* is associated with frequent lymph node metastases, a risk of recurrence, and *BRAF*^{V600E} mutations, similar to conventional PTC ("BRAF-like PTCs") [2, 21]. *Diffuse FVPTC* is a rare and aggressive variant of infiltrative FVPTC that typically occurs in young females, extensively involving one lobe or both lobes in a multinodular fashion, with frequent distant metastases in the lungs and/or bones with or without concurrent regional lymph node metastases.
2. The *encapsulated FVPTC* is characterized by a follicular growth pattern with no papillae formation and total tumor encapsulation, and the diagnosis rests on finding characteristic nuclear features of PTC. Historically, encapsulated FVPTC has been a controversial entity with poor diagnostic (cytologic and histologic) reproducibility. Most encapsulated FVPTCs show no invasive growth, whereas in about one-third of cases, tumor capsular and/or vascular invasion is found [2]. At the present time, 50–75% of all FVPTC belong to this subtype [2]. These tumors, which frequently harbor *RAS* mutations, are biologically, genetically, and clinically closer to the follicular adenoma/carcinoma group than the PTC group ("RAS-like PTCs") [21]. Encapsulated FVPTC with invasion tend to spread in a fashion similar to follicular thyroid carcinoma, with distant lung and bone metastases and infrequent lymph node metastases. In the absence of capsular or vascular invasion, encapsulated FVPTCs have a very low risk of recurrence or extrathyroidal spread, even in patients treated by lobectomy alone, provided that the tumor is completely excised [2, 4]. Therefore, a carefully defined subset of encapsulated FVPTC has been reclassified as NIFTP, using strict histologic inclusion and exclusion criteria [4].

NIFTP is a very low risk tumor that likely represents a preinvasive stage of invasive encapsulated FVPTC [4]. The paradigm shift in terminology has important clinical consequences and affects the cytologic diagnosis of thyroid nodules [15, 16, 22–24]. NIFTP comprises approximately 20–25% of all tumors previously classified as thyroid malignancies [15, 16, 22–24]. Accordingly, adoption of this

terminology lowers the frequency of a histopathologic diagnosis of thyroid cancer. It also causes an overall decrease in the risk of malignancy (ROM) associated with thyroid FNA diagnoses, especially in the indeterminate diagnostic categories but also in the malignant category, because NIFTP comprises a subset, albeit small (3–4%), of thyroid FNAs currently classified as malignant [15, 16, 22–24].

Criteria

Samples are usually hypercellular, with syncytial-like fragments containing microfollicles ("rosettes"). Dispersed microfollicular clusters, isolated neoplastic follicles, and some sheets with branched irregular contours may also be present.

Some colloid may be present, typically dense-staining, thick, and sometimes within neoplastic follicles.

In contrast to conventional PTC, the nuclear changes are often subtle. The following features are usually absent or inconspicuous: papillary and papillary-like fragments, multinucleated giant cells, INCIs, psammoma bodies, and marked cystic change.

Explanatory Notes

The degree to which the characteristic nuclear features of PTC are displayed in FVPTC and NIFTP varies from case to case, with a wide quantitative and qualitative spectrum (Figs. 8.14 and 8.15). Some FVPTCs, usually those that are infiltrative, have prominent classic nuclear features of PTC, but with others, especially the

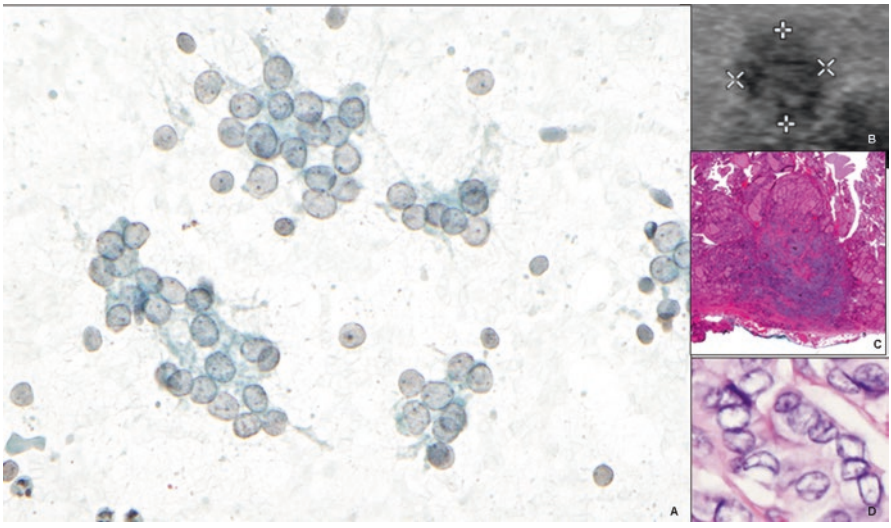

Fig. 8.14 Papillary thyroid carcinoma, follicular variant. (**a**) The aspirates show microfollicles with crowded, enlarged clear oval nuclei (smear, Papanicolaou stain). (**b**) Ultrasound shows solid nodule with blurred margins (**c**) correlating with infiltrative margin in histology. (**d**) Histologically, the tumor is composed of microfollicles with "Orphan Annie eye" "clear nuclei (hematoxylin and eosin stain).

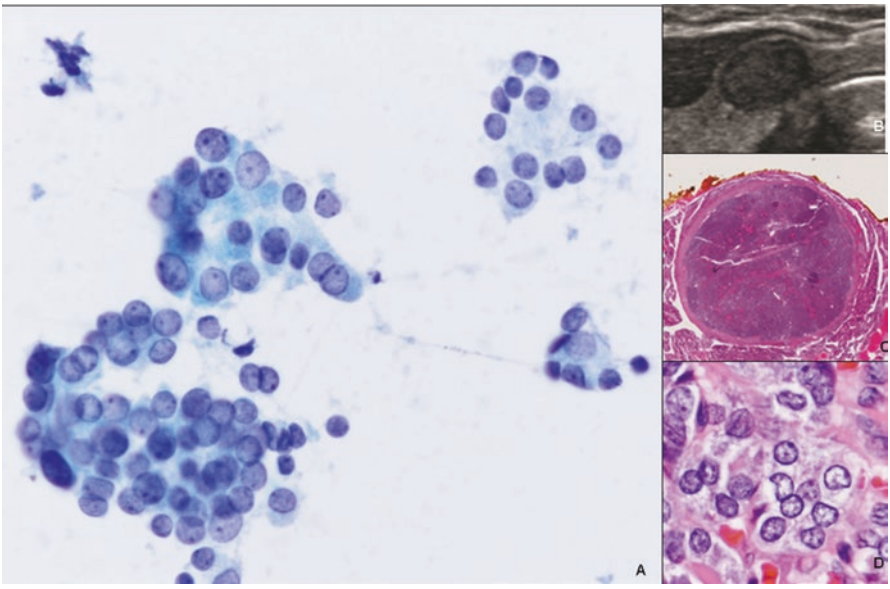

Fig. 8.15 Noninvasive follicular thyroid neoplasm with papillary-like nuclear features (formerly called encapsulated follicular variant of papillary thyroid carcinoma). (**a**) The aspirate shows microfollicles with crowded, enlarged, clear, oval nuclei along with microfollicles with small dark nuclei (smear, Papanicolaou stain). (**b**) Ultrasound shows well-circumscribed solid nodule with a rim, correlating with encapsulation (**c**). (**d**) Histologically, the tumor is composed of microfollicles with "Orphan Annie eye" clear nuclei (hematoxylin and eosin stain).

encapsulated FVPTC (including NIFTP), the features are only partially and focally displayed. For this reason, a distinction among the various "follicular-patterned" lesions of the thyroid (e.g., nodular goiter, follicular adenoma, NIFTP, FVPTC) is sometimes troublesome [17]. FVPTC is, in fact, one of the most problematic variants of PTC to diagnose, both cytologically and histologically. Because of the significant overlap in the cytologic features between FVPTC and NIFTP, a definite distinction between these entities is not possible by FNA.

FNA specimens from FVPTCs can be separated in two different groups. In the first (30–40% of cases), the FVPTC is easily recognizable as malignant due to widespread nuclear features of PTC but difficult to distinguish from a conventional PTC. In the second group, which represents the majority of FVPTC and NIFTP cases, the tumor cells show only mild nuclear enlargement and elongation, chromatin clearing, and thick nuclear membranes, and INCIs and nuclear grooves are rare or absent. These cytologic samples typically fall into one of the indeterminate categories: suspicious for PTC (25–35%), FN/SFN (25–30%), or AUS/FLUS (10–20%) [15, 16, 22–24]. Particular attention must be paid to the presence of ovoid, pear-shaped, and cerebriform (or raisin-shaped) nuclei. NIFTPs are often associated with more subtle nuclear features than infiltrative FVPTC and classical PTC [22–24]. To avoid overtreatment, it is highly desirable to exclude potential NIFTP cases from the

malignant category and limit this category to conventional and other variants of PTC. Preliminary data suggest that a definitive ("malignant") diagnosis of PTC should be reserved for cases that have, in addition to other characteristic features, at least one of the following: papillary architecture, psammoma bodies, and INCIs [22–24]. Nevertheless, given the histologic criteria for NIFTP [4], it is unlikely that NIFTPs can be completely eliminated from the malignant category. Thus, some pathologists may prefer to include an educational note to reinforce this limitation (see Chap. 1, Table 1.3, as well as "Sample Reports" below).

Molecular and ultrasonographic features can be helpful to suggest noninvasive FVPTC or NIFTP at the time of FNA diagnosis. Because *RAS* mutations are the most commonly identified genetic abnormality in noninvasive FVPTC and NIFTP, these neoplasms show a very high association with other follicular-patterned neoplasms [4, 21]. *PAX8/PPARγ* translocations, *THADA* fusions, and $BRAF^{K601E}$ mutations are also found on occasion [21]. In contrast, $BRAF^{V600E}$ mutations and *RET* fusions, common in conventional PTC, are absent in NIFTP [4, 21]. Sequencing with large multigene panels may one day assist in the detection of NIFTP. On ultrasound, most NIFTPs are benign-appearing, round-to-oval, circumscribed nodules with a hypoechoic rim [17]. The definite diagnosis of a FVPTC or NIFTP, however, can only be made after complete histological analysis of the tumor and its capsule.

Macrofollicular Variant

Definition

The macrofollicular variant is a PTC in which over 50% of the follicles are arranged as macrofollicles (follicles measuring more than 200 μm in diameter).

Criteria

The sample consists of monolayered (two-dimensional) sheets of neoplastic epithelium and/or variably sized follicles.

Convincing nuclear changes of PTC must be present for a definite interpretation of malignancy.

In contrast to conventional PTC, the diagnostic nuclear features are often more subtle (as with FVPTC).

Papillary structures and psammoma bodies are not seen.

Abundant thin colloid or fragments of thick colloid may be present.

Explanatory Notes

The macrofollicular variant of PTC (MFVPTC) is one of the rarest histologic variants of PTC [1]. It is characterized by a low incidence of lymph node metastasis, but when metastases occur, the macrofollicular architecture is usually maintained. The differential diagnosis of MFVPTC includes the benign follicular nodule seen with nodular goiter and the follicular adenoma of macrofollicular type. MFVPTC is easily underappreciated at low magnification due to the abundance of thin colloid, the

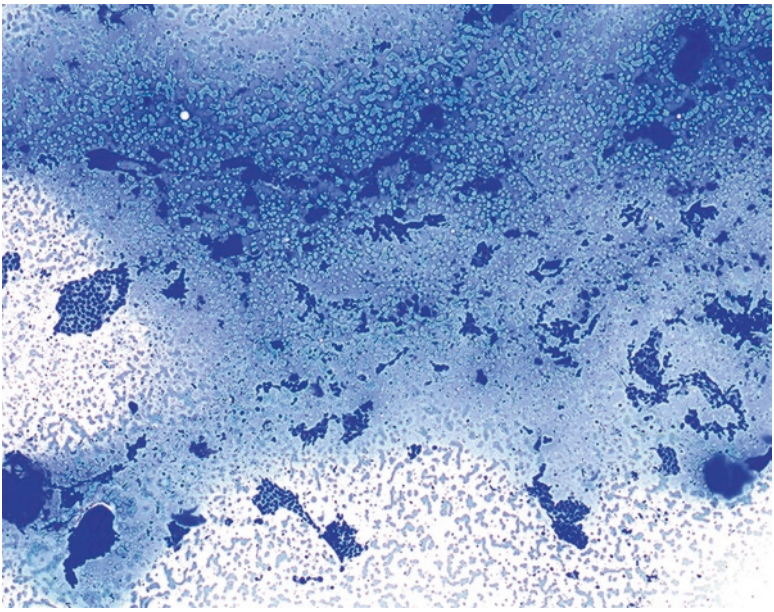

Fig. 8.16 Papillary thyroid carcinoma, macrofollicular variant. The neoplastic cells resemble those of a benign thyroid nodule at scanning magnification. In such cases, there can be abundant thin colloid and relatively few sheets of cells. The difference lies in the nuclear features, which are better appreciated at high magnification (smear, Diff-Quik stain).

low cellularity, and the subtle and focal nuclear atypia. Thus, careful attention to nuclear features is necessary for all benign-appearing thyroid aspirates. Cytologically, the neoplastic cells usually have round/ovoid nuclei, either small or conspicuous, eccentrically located nucleoli, chromatin clearing, nuclear overlapping, and nuclear grooves (Figs. 8.16 and 8.17) [25, 26]. Only 45% of cases show INCIs, which range from rare to few [25]. Moderate-to-abundant thin and focally thick colloid and macrophages are often present. In contrast, psammoma bodies and papillary structures have not been reported. If follicular cells with round/ovoid nuclei, small-to-prominent, eccentrically located nucleoli, nuclear overlapping, and chromatin clearing are present in a background of abundant colloid, it is prudent to consider the possibility of MFVPTC and render a diagnosis of at least AUS/FLUS (instead of a benign colloid nodule) [25].

Cystic Variant

Definition

The cystic variant is a PTC that is predominantly cystic, comprised of thin, watery fluid, abundant histiocytes, and hypervacuolated tumor cells.

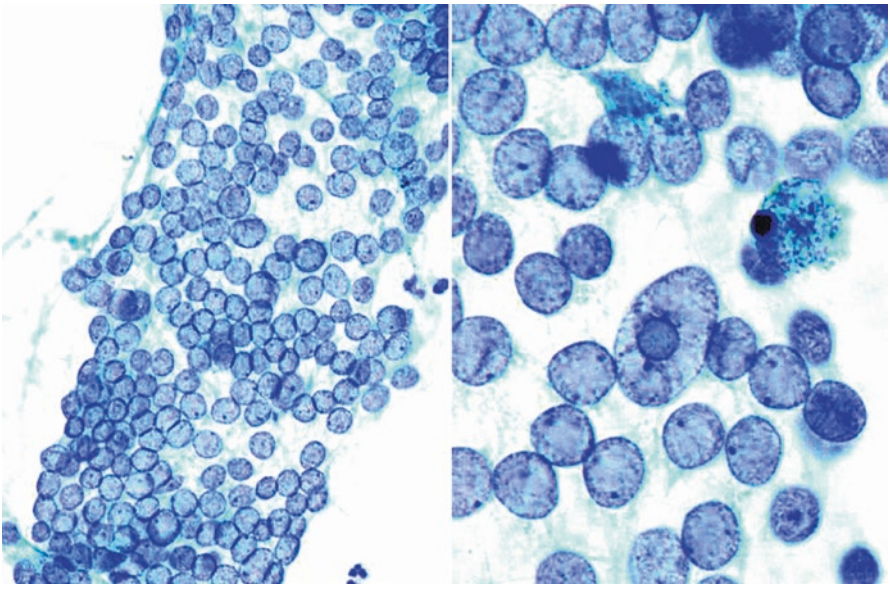

Fig. 8.17 Papillary thyroid carcinoma, macrofollicular variant. *Left*, There is a large sheet of tumor cells with crowded, "Orphan Annie eye" nuclei; *Right*, An intranuclear pseudoinclusion is present in the large oval nucleus. Note also the peripheral micronucleoli (smear, Papanicolaou stain).

Criteria

The neoplastic cells are typically arranged in small groups with irregular borders; sheets, papillae, or follicles may also be present.

Tumor cells look "histiocytoid" (hypervacuolated).

Macrophages, often containing hemosiderin, are present.

There is a variable amount of thin or watery colloid.

Convincing nuclear changes of PTC must be present for a definite diagnosis of malignancy.

In contrast to conventional PTC, fine, powdery chromatin is usually less prominent.

Explanatory Notes

PTC is the most common malignant neoplasm of the thyroid to undergo cystic change. The amount of cystic change varies from case to case; approximately 10% of PTCs are almost entirely cystic [27, 28]. FNAs of cystic PTC show varying proportions of macrophages, colloid, and vacuolated "histiocytoid" neoplastic cells (see Fig. 7.4) [27, 28]. A few small papillae comprised of viable tumor cells are sometimes present. The neoplastic cells have more abundant, granular, or vacuolated cytoplasm than those of conventional PTC. The tumor cells frequently appear more rigid and polygonal than normal follicular cells and display enlarged, oval- to irregularly

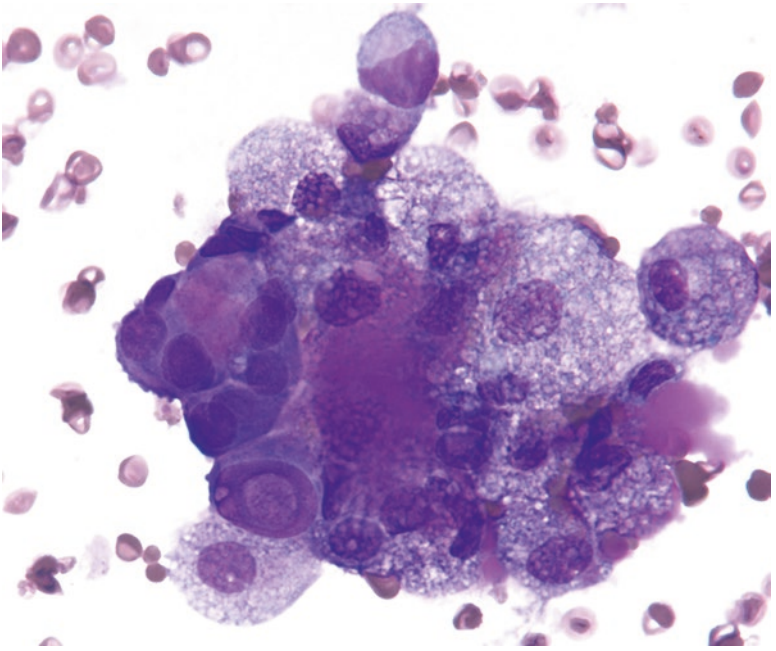

Fig. 8.18 Papillary thyroid carcinoma, cystic variant. There is prominent cystic change with numerous hemosiderin-laden macrophages. A small cluster of neoplastic cells has smooth, dense cytoplasm, and one cell has a large intranuclear cytoplasmic pseudoinclusion (smear, Diff-Quik stain).

shaped nuclei with prominent nuclear grooves and occasional INCIs (Fig. 8.18). Some of the characteristic nuclear features of PTC, however, like pale, "powdery" chromatin, are often less apparent or even conspicuously absent (Fig. 8.19).

It should be noted that similar atypical cells are sometimes seen in entirely benign follicular nodules with cystic change. These reactive cells may appear "histiocytoid" or they may be arranged in streaming sheets ("cyst lining cells"). Cyst lining cells have enlarged nuclei, nucleoli, nuclear pallor, and occasional nuclear grooves. Their benign nature is betrayed by their elongated shape and the lack of nuclear crowding. In some cases, however, the nuclear changes of cyst lining cells can be extreme, and they occasionally show INCIs. Such cases are therefore properly diagnosed as "suspicious for papillary carcinoma" or AUS/FLUS (see Chaps. 7 and 4, respectively).

Whereas some aspirates of cystic PTC are composed of abundant neoplastic cells and are readily interpreted as PTC, others have no neoplastic cells at all and are best interpreted as "nondiagnostic; cyst fluid only." Indeed, cystic PTC has long been recognized as a possible cause of false-negative thyroid FNAs. This concern is less common with the precise sampling of the subcentimeter solid mural nodule within the cyst under high-resolution ultrasound guidance.

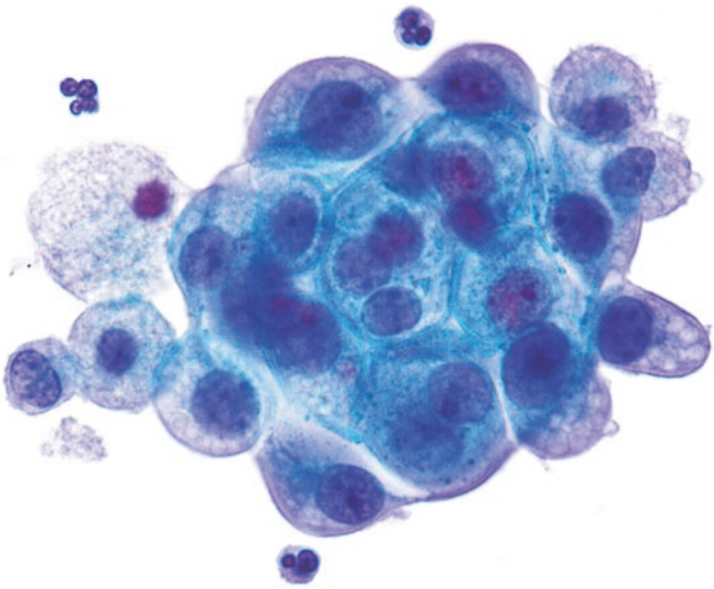

Fig. 8.19 Papillary thyroid carcinoma, cystic variant. Most of the cells in this image are neoplastic. They have abundant granular cytoplasm, hence the descriptor "histiocytoid." Classic nuclear features of papillary thyroid carcinoma are absent, but there is conspicuous nuclear enlargement (ThinPrep, Papanicolaou stain).

Oncocytic Variant

Definition

The oncocytic variant is a thyroid tumor with nuclear changes characteristic of PTC but composed predominantly of oncocytic cells with variable architecture (follicular, papillary, solid).

Criteria

The sample is composed predominantly of oncocytic cells (polygonal cells with abundant granular cytoplasm), arranged in papillae, sheets, microfollicles, or as isolated cells.

Convincing diagnostic nuclear changes of PTC must be present for a definite diagnosis of PTC.

Lymphocytes are absent or few in number.

Explanatory Notes

Focal oncocytic change is seen in many PTCs, including the conventional (classic) PTC. Only when the changes are widespread does the tumor merit distinction as an oncocytic variant of PTC (Figs. 8.20 and 8.21) [29, 30]. Aspirates of the oncocytic variant of PTC resemble those from other follicular cell-derived

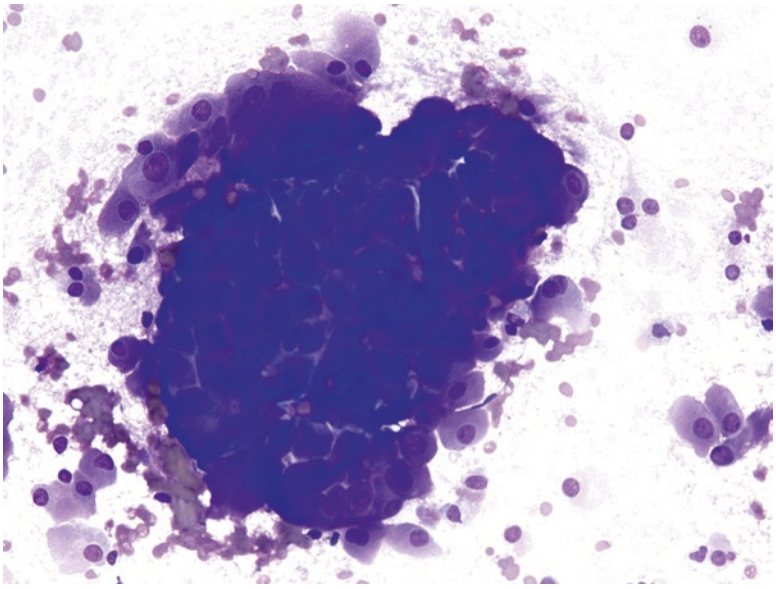

Fig. 8.20 Papillary thyroid carcinoma, oncocytic variant. The entire neoplasm is composed of oncocytic (Hürthle-like) cells that have abundant granular cytoplasm. The nuclear features of papillary carcinoma are not readily apparent in this image; such cases are good mimics of Hürthle cell neoplasms (smear, Diff-Quik stain).

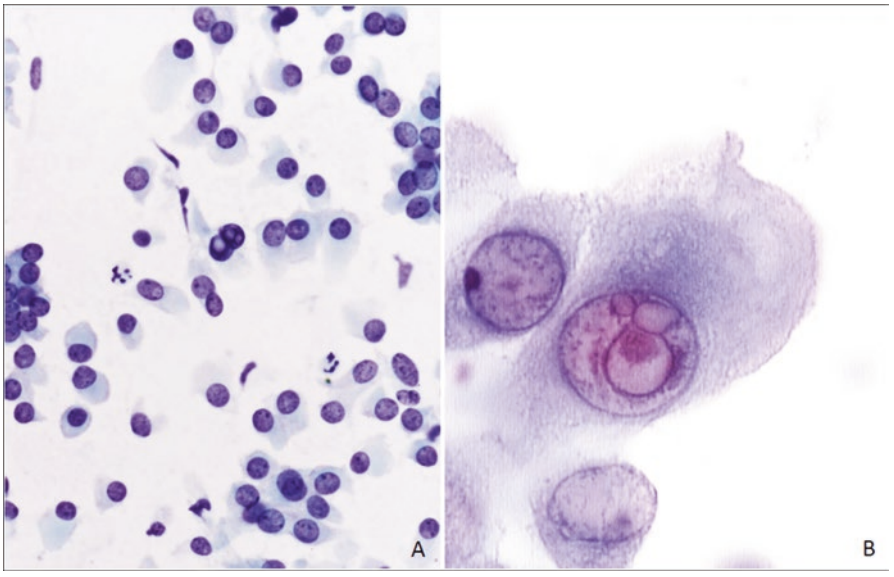

Fig. 8.21 Papillary thyroid carcinoma, oncocytic variant. (**a**) Loosely cohesive polygonal to plasmacytoid oncocytic (Hürthle-like) cells have atypical, clear nuclei with eccentric micronucleoli and rare intranuclear pseudoinclusions without nuclear grooves; such cases are good mimics of medullary thyroid carcinoma. (**b**) Multiple small and large intranuclear pseudoinclusions are seen in a large oncocytic cell with abundant granular cytoplasm (smears, Papanicolaou stain).

oncocytic proliferations, the oncocytic variant of medullary thyroid carcinoma, and other oncocytic neoplasms (e.g., metastatic renal cell carcinoma). The characteristic nuclear features of PTC, therefore, must be searched for whenever an aspirate is composed predominantly of oncocytes (Hürthle cells). Non-PTC oncocytic lesions generally have rounder nuclei and more prominent nucleoli than the oncocytic variant of PTC. In addition, non-PTC follicular cell-derived oncocytic proliferations may have nuclear grooves and slight nuclear pallor, but INCIs are very rarely seen. When the full nuclear features of PTC are evident, PTC can be readily diagnosed on FNA. When the nuclear features of PTC are not widespread, the case is best classified as suspicious for a follicular neoplasm/follicular neoplasm, Hürthle cell (oncocytic) type, or as suspicious for PTC, oncocytic type. Lymphocytes are typically absent in FNAs of the oncocytic variant of PTC; if present in large numbers, a Warthin-like variant of PTC should be considered.

Warthin-Like Variant

Definition

The Warthin-like variant of PTC is a circumscribed thyroid tumor with papillary architecture and lymphoid follicles that resembles a Warthin tumor of the parotid gland. It is often associated with Hashimoto thyroiditis [1, 31]. The neoplastic cells have abundant granular cytoplasm and the nuclear features of PTC.

Criteria

The neoplastic cells are oncocytic and arranged in papillae and as dispersed cells.

A lymphoplasmacytic background is present. The lymphocytes and plasma cells permeate the fibrovascular stalk and are intimately associated with the tumor cells.

Convincing nuclear changes of PTC must be present for a definite diagnosis of malignancy.

Explanatory Notes

Because of the mixture of oncocytes and lymphocytes, FNAs from the Warthin-like variant of PTC resemble those from Hashimoto thyroiditis (Fig. 8.22) [31]. The oncocytic cells of Hashimoto thyroiditis, however, typically have a round nucleus with a prominent single nucleolus; the nuclei of PTC (including the Warthin-like variant), by contrast, are more irregular in contour, and nucleoli are less prominent. The oncocytic cells in Hashimoto thyroiditis may show nuclear clearing and grooves, but papillary fragments and INCIs are usually not seen.

Tall Cell Variant

Definition

The tall cell variant (TCV) is an aggressive form of PTC composed predominantly of elongated (“tall”) tumor cells (their height is at least three times their width) with abundant dense granular cytoplasm and the typical nuclear changes of PTC.

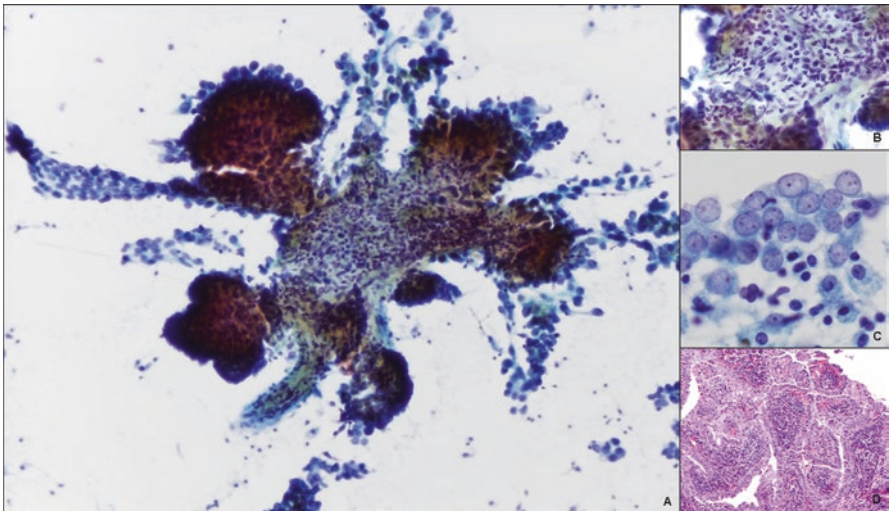

Fig. 8.22 Papillary thyroid carcinoma, Warthin-like variant. (**a**) The aspirate shows papillary fragments in a lymphocytic background (smear, Papanicolaou stain). (**b**) The fibrovascular cores are engorged with lymphocytes (smear, Papanicolaou stain). (**c**) The epithelial cells are also intimately associated with lymphocytes. The nuclei are enlarged, oval, and clear (smear, Papanicolaou stain). (**d**) Histologically, the tumor resembles a Warthin tumor of the salivary gland, with tumor epithelium surrounding lymphoid aggregates. Typical nuclear features of papillary carcinoma can be seen at high power (not shown) (hematoxylin and eosin stain).

Criteria

The neoplastic cells are most commonly polygonal with centrally located nuclei but can be elongated and cylindrical with an eccentrically placed nucleus ("tail-like cells" or "tadpole cells"). They have granular cytoplasm with prominent cytoplasmic borders.

Some lymphocytes may be present.

Convincing nuclear changes of PTC must be present for a definite diagnosis of malignancy.

In contrast to conventional PTC:

- The nuclei tend to be larger and more elongated.
- The nuclear chromatin is sometimes less powdery and more granular.
- The nucleoli can be prominent and centrally placed.
- Mitotic figures may be present.
- Psammoma bodies are fewer in number.
- INCIs tend to be more frequent and more often multiple within one nucleus, imparting a "soap-bubble" appearance to the nucleus.

Explanatory Notes

The TCV tends to occur in elderly patients and is more common in men than other PTCs [1, 2]. It frequently presents as a large and bulky tumor, often with extrathyroidal extension and vascular invasion [2]. It is more aggressive than the conventional PTC and has a higher incidence of local recurrence, central neck involvement, and distant metastasis [1, 2]. If 10% or more of a PTC has tall cell features, the tumor is associated with an adverse clinical outcome. Therefore, the identification of a minor tall cell component is important for histologic classification. Up to 90% of TCVs harbor the *BRAF*^{V600E} mutation. *TERT* promoter mutations, which are associated with a worse outcome in PTCs, are also significantly more prevalent in TCV (31%) compared to conventional (classic) PTC (<10%).

The TCV is easily recognized as a PTC due to the prominence of the nuclear features of PTC, especially nuclear grooves and INCIs, which are frequent and easily identified (Figs. 8.23, 8.24, and 8.25) [32, 33]. Tall cell features may be easier to assess on LBPs than on conventional smears (Fig. 8.25) [6, 8], but, as with all PTCs, it is not essential to specify the variant by FNA.

Columnar Cell Variant

Definition

The columnar cell variant (CCV) is characterized by columnar cells with hyperchromatic, oval, and pseudostratified nuclei and supranuclear or subnuclear cytoplasmic vacuoles, reminiscent of a colonic adenoma or secretory-type endometrium. The cells are typically arranged in papillae, but trabeculae and follicles can also be seen.

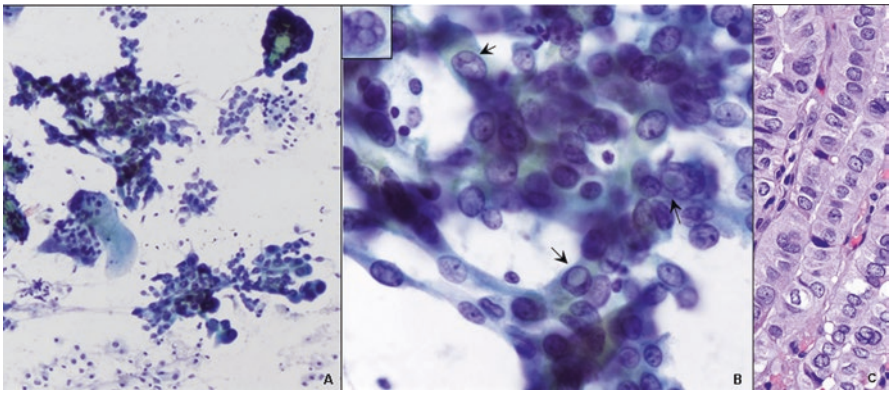

Fig. 8.23 Papillary thyroid carcinoma, tall cell variant. (**a**) The smear shows elongated cells in loosely cohesive arrangements (smear, Papanicolaou stain). (**b**) The cytoplasm is elongated, with frequent nuclear pseudoinclusions and rare soap-bubble nuclei (*inset*) (smear, Papanicolaou stain). (**c**) Histologically, this variant is comprised of tall rectangular tumor cells with eosinophilic cytoplasm arranged in parallel rows (hematoxylin and eosin stain).

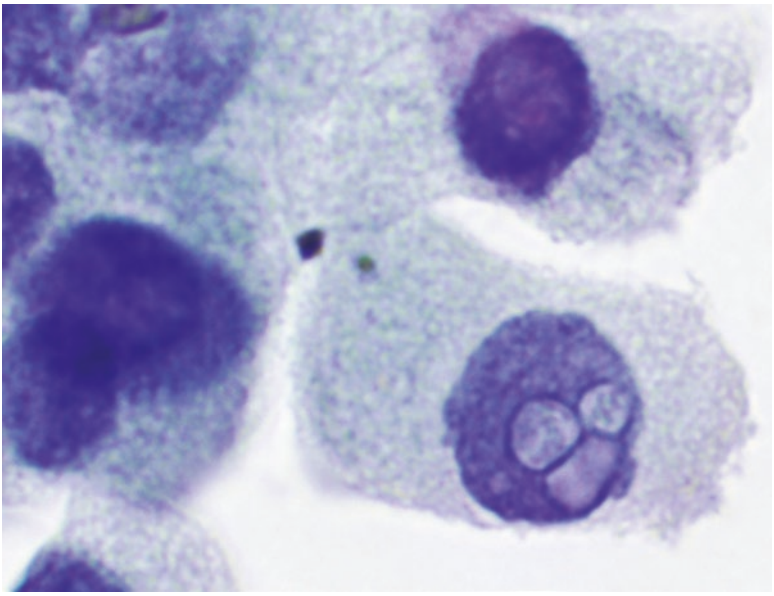

Fig. 8.24 Papillary thyroid carcinoma, tall cell variant. "Soap-bubble-like" intranuclear pseudoinclusions are often seen in the tall cell variant of papillary thyroid carcinoma (ThinPrep, Papanicolaou stain).

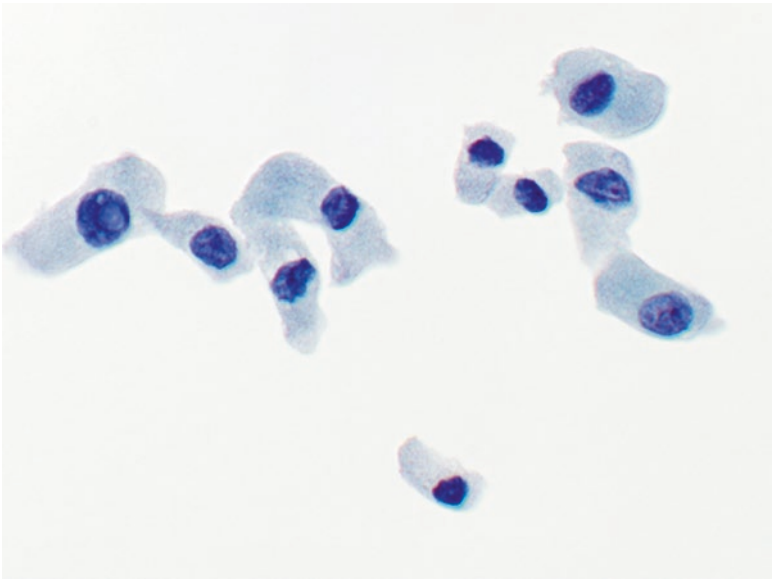

Fig. 8.25 Papillary thyroid carcinoma, tall cell variant. The "tallness" of these cells is readily appreciated. When this morphology is seen throughout the sample, one can raise the possibility of a tall cell variant in the FNA report (ThinPrep, Papanicolaou stain).

Criteria

Smears are cellular and generally lack colloid.
The neoplastic cells are arranged as papillae, clusters, and flat sheets, sometimes with small tubular structures.
The nuclei are elongated and pseudostratified.
Focal cytoplasmic vacuolization may be present.
Convincing nuclear changes of PTC must be present for a definitive diagnosis of malignancy.
In contrast to conventional PTC:

- The nuclear features of PTC (grooves, INCIs) are much less prominent.
- The nuclear chromatin tends to be hyperchromatic rather than pale and powdery.
- Colloid and cystic changes (macrophages) are typically not seen.

Explanatory Notes

The CCV is one of the least common variants of PTC and occurs primarily in males. It is an aggressive tumor associated with a higher risk of distant metastases and tumor-related mortality, especially in cases with extrathyroidal extension [1, 2]. The *BRAF*^{V600E} mutation is found in one-third of cases [2].

Because the nuclei of the columnar cell variant are darker than those of the typical PTC, and because the other typical nuclear features of PTC are less pronounced (Fig. 8.26), the neoplastic cells of the CCV may be mistaken for benign respiratory epithelial cells (seen when the trachea is penetrated), but cilia are not identified.

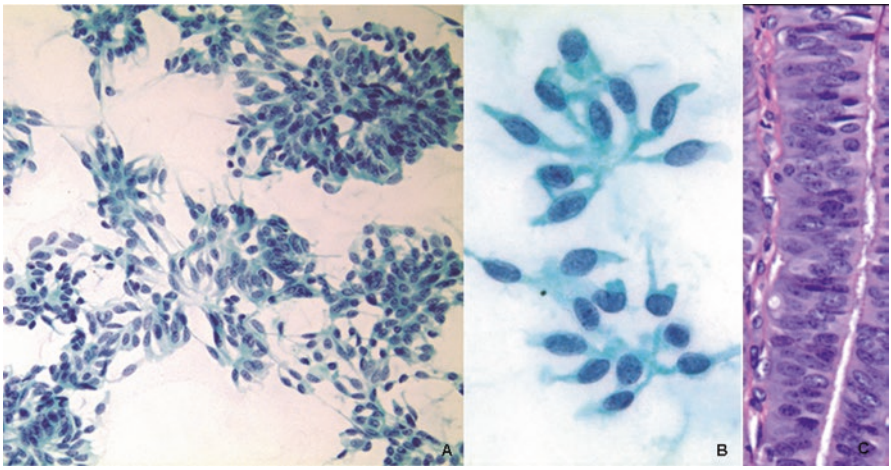

Fig. 8.26 Papillary thyroid carcinoma, columnar cell variant. (**a**) The aspirate shows loosely cohesive spindle-shaped cells (smear, Papanicolaou stain). (**b**) The cytoplasm is bipolar and wispy, and cigar-shaped nuclei have few characteristic features of papillary thyroid carcinoma (smear, Papanicolaou stain). (**c**) Histologic examination shows rows of pseudostratified columnar cells with elongated hyperchromatic nuclei and scanty cytoplasm (hematoxylin and eosin stain) (Courtesy of Dr. Tamar Giorgadze, MD, PhD of Medical College of Wisconsin).

The dark and stratified nuclei of CCV can also mimic a metastasis from a colorectal or endometrial primary [34], but the necrotic background commonly present in metastatic disease from these primaries is unusual in CCV. Clinico-radiological correlation, in addition to a limited immunocytochemical panel that includes thyroglobulin and TTF1, can be very helpful. Importantly, PAX8 is expressed in both CCV and gynecological carcinomas, and CDX2 is expressed in up to 50% of CCV, limiting the diagnostic value of these two markers.

Solid Variant

Definition

The solid variant of PTC (SVPTC) is defined histologically by the presence of solid areas that lack papillae, follicles, and colloid storage and occupy at least 50% of the lesion. The neoplastic cells have typical nuclear features of PTC.

Criteria

Smears are variably cellular and generally lack colloid.

The neoplastic cells may appear as cohesive, syncytial-type three-dimensional tissue fragments, microfollicles/trabeculae, or noncohesive, single cells.

The nuclei usually show the typical nuclear features of PTC, but they may be less elongated (rounder) and darker than those of conventional PTC.

True papillary formations with fibrovascular cores are scant or absent.

Explanatory Notes

SVPTC is a rare variant (approximately 3% of PTCs) that is still poorly characterized. Its prevalence is high among survivors of the Chernobyl nuclear incident (up to 30%), where it is associated with *RET/PTC3* rearrangements (radiation-induced). This variant is also more common in children without radiation exposure. There are conflicting reports about its behavior [2, 35]. Because of the lack of criteria with high specificity and sensitivity, the preoperative diagnosis of SVPTC is hardly ever made or suggested on cytology (Fig. 8.27). Most cases of SVPTC are diagnosed as malignant or suspicious for malignancy (PTC or FVPTC) [35]. The microfollicular pattern of SVPTC is difficult to distinguish from other follicular-patterned lesions, including FVPTC and follicular neoplasms, and the typical nuclear features of PTC may be patchy in a subset of cases. In contrast, cohesive, syncytial, three-dimensional tissue fragments appear to be unique to SVPTC and likely correlate with the nested pattern of the tumor cells observed histologically [35]. This pattern differs from the monolayered sheets typical of conventional (classic) PTC. A nonspecific single-cell pattern can also be seen in SVPTC and may correlate with infiltrative tumor growth and more aggressive behavior [35]. This pattern can mimic medullary thyroid carcinoma, but the two tumors can be distinguished by their nuclear features. There is also significant morphological overlap between SVPTC and poorly differentiated thyroid carcinoma (PDTC). PDTC may have occasional nuclear grooves and INCIs but the cells usually have more granular chromatin and scant cytoplasm, with a high nuclear/cytoplasmic ratio. The presence of mitoses and necrosis is helpful to suggest PDTC,

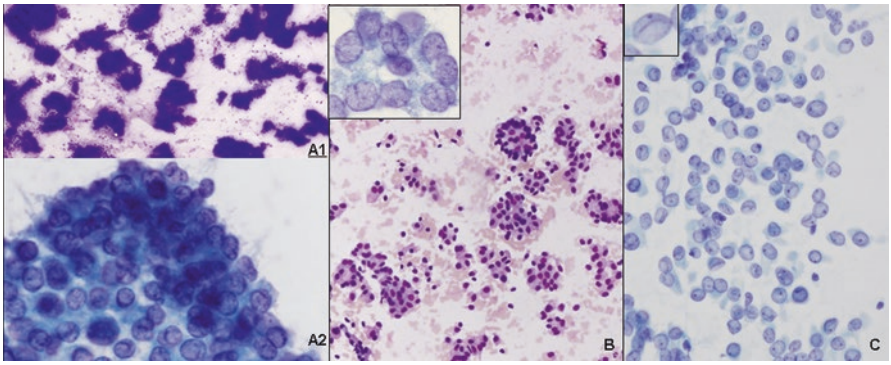

Fig. 8.27 Papillary thyroid carcinoma, solid variant. This variant may demonstrate three different cytologic patterns: (**a**) a cohesive, syncytial tissue-fragment pattern, (**b**) a microfollicular/trabecular pattern, and (**c**) a noncohesive, single-cell pattern. All three patterns have characteristic nuclear features of papillary carcinoma: convoluted clear nuclei in a2, nuclear clearing and convolution in the *inset* of **b**, and nuclear clearing and grooves in **c** (a1, **b**: smears, Diff-Quik stain; a2, **c** and *insets*: smears, Papanicolaou stain).

but these features are not always present (see Chap. 10). Clinico-radiological correlation can also be very helpful. Although SVPTC in children can have significant necrosis, they behave like a PTC and do not have the aggressiveness of a PDTC.

Diffuse Sclerosing Variant

Definition

The diffuse sclerosing variant (DSV) is characterized by diffuse involvement of one or both thyroid lobes, extensive lymphovascular invasion, numerous psammoma bodies, squamous metaplasia, marked lymphocytic infiltration, and prominent fibrosis.

Criteria

The smears are moderately to highly cellular with scant or absent colloid.

The neoplastic cells are arranged in three-dimensional ball-like clusters and cohesive clusters intermingled with inflammatory cells, but conventional monolayered syncytial and papillary clusters may also be present.

The neoplastic cells are round, polygonal, or columnar, with dense cytoplasm and distinct cytoplasmic borders. Hobnail cells protruding from cell clusters are often present.

In contrast to conventional PTC:

- There is less chromatin pallor.
- There are fewer INCIs and nuclear grooves (<50% of cases).
- Large septate or unilocular cytoplasmic vacuoles are common.
- Squamous metaplastic changes are common.
- Numerous lymphocytes and psammoma bodies are present in the background.

Explanatory Notes

This relatively uncommon variant occurs in young patients, especially women, and typically presents as a goiter without a dominant mass, reflecting a diffuse involvement of the gland that mimics Hashimoto thyroiditis and/or lymphoma. Sonograms reveal a characteristic "snowstorm appearance" due to numerous and widespread microcalcifications. There is a higher incidence of lymph node and lung metastases at presentation, and the prognosis may be less favorable than for conventional PTC, although the data remain controversial [1, 2]. On FNA, the highly cellular aspirate is notable for numerous monomorphic small lymphocytes (Fig. 8.28) and can be misleading for lymphocytic thyroiditis or malignant lymphoma. It's worth remembering that in lymphocytic thyroiditis, atypical follicular cells are commonly encountered, and nuclear grooves and INCIs are sometimes present [36]. Furthermore, there is a lower incidence of characteristic nuclear features of PTC in DSV. Three-dimensional clusters of tumor cells with hobnail features and cytoplasmic vacuoles, abundant psammoma bodies, and squamoid differentiation (Fig. 8.29) all suggest the possibility of a DSV.

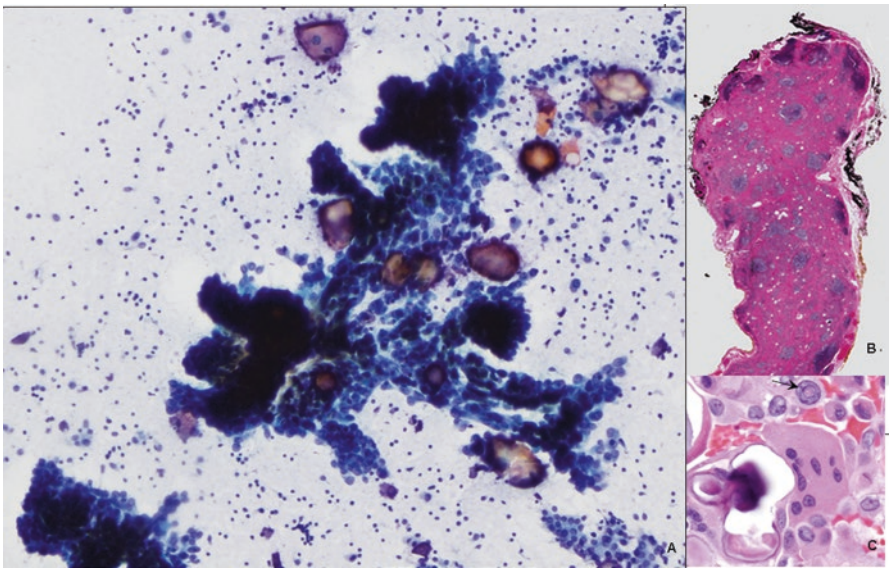

Fig. 8.28 Papillary thyroid carcinoma, diffuse sclerosing variant. (**a**) The aspirate shows papillary fragments associated with psammoma bodies in a lymphocytic background. The nuclear chromatin is darker than in the conventional papillary thyroid carcinoma. (**b**) On histologic examination, the thyroid gland shows numerous lymphoid follicles and many small "holes." (**c**) The holes are from popped out psammoma bodies.

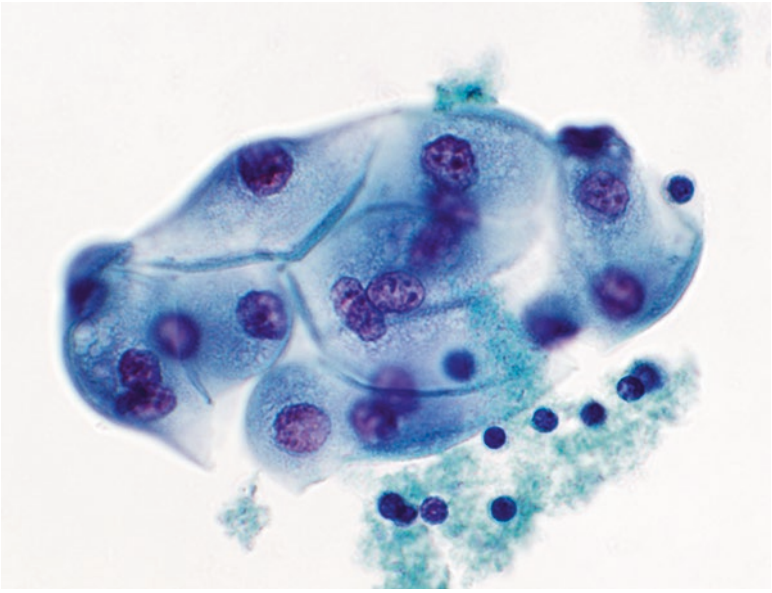

Fig. 8.29 Papillary thyroid carcinoma, diffuse sclerosing variant. The neoplastic cells in this image are "squamoid": they have a flat, polygonal shape with sharply demarcated cell membranes, and they fit together like jigsaw pieces (but there is no overt keratinization.) This squamoid appearance is sometimes encountered as a focal finding in conventional (classic) papillary carcinomas, but in the diffuse sclerosing variant, this feature is often widespread. Note that these cells lack the usual nuclear features of papillary carcinoma (ThinPrep, Papanicolaou stain).

Cribriform-Morular Variant

Definition

The cribriform-morular variant of PTC (CMV-PTC) is characterized by cribriform and solid architecture lacking colloid. The cells are tall and columnar or spindle-shaped, and squamoid morules are present. The tumor cell nuclei are often hyperchromatic and pseudostratified, although typical nuclear features of PTC are also found. Some nuclei within the morules contain a peculiar nuclear clearing caused by biotin accumulation.

Criteria

The smears are hypercellular.
Colloid is absent.
The tall, columnar neoplastic cells have a papillary-like arrangement.
Round to oval slit-like empty spaces formed by spindle to ovoid cells within cell clusters are present (cribriform pattern).
Cell clusters with eddy formation (morules) are present.
Spindle-shaped tumor cells are present in the background.
Pale-staining nuclei with thickened nuclear membranes (peculiar nuclear clearing) is present focally.
Nuclear grooves are present, but INCIs are less common than in the conventional PTC (58% of cases).
Foamy or hemosiderin-laden histiocytes are often present in the background.
Hyaline material can be seen within cell clusters or in the background.
Psammoma bodies and multinucleated giant cells are absent.
The neoplastic cells show nuclear and cytoplasmic positivity for β-catenin (in the FAP-associated CMV-PTCs only).

Explanatory Notes

CMV-PTC is an uncommon variant of PTC with a very frequent association with familial adenomatous polyposis (FAP) or Gardner syndrome and often precedes by several years the development of polyposis coli [2, 37, 38]. A sporadic form occurs in patients who do not carry a germline mutation of *APC* gene. Generally, FAP-associated CMV-PTC occurs in younger patients and is multifocal, whereas sporadic CMV-PTC presents as a solitary thyroid nodule. CMV-PTC is generally an indolent tumor, especially in its sporadic form. There is significant overlap between the architectural and nuclear features of CMV-PTC and other variants of PTC (conventional, tall cell, columnar cell) (Fig. 8.30). Nevertheless, CMV-PTC demonstrates several peculiar cytologic findings, which, when combined with an aberrant positive β-catenin nuclear immunostain (seen in the FAP-associated CMV-PTC cases only), can allow a preoperative diagnosis of CMV-PTC, ruling out more aggressive variants like the tall cell variant [37, 38].

Hobnail Variant

Definition

The hobnail variant of PTC is characterized by the loss of cellular polarity/cohesiveness, with apically placed nuclei and bulging of the apical cell surface (hobnail features) in more than 30% of neoplastic cells.

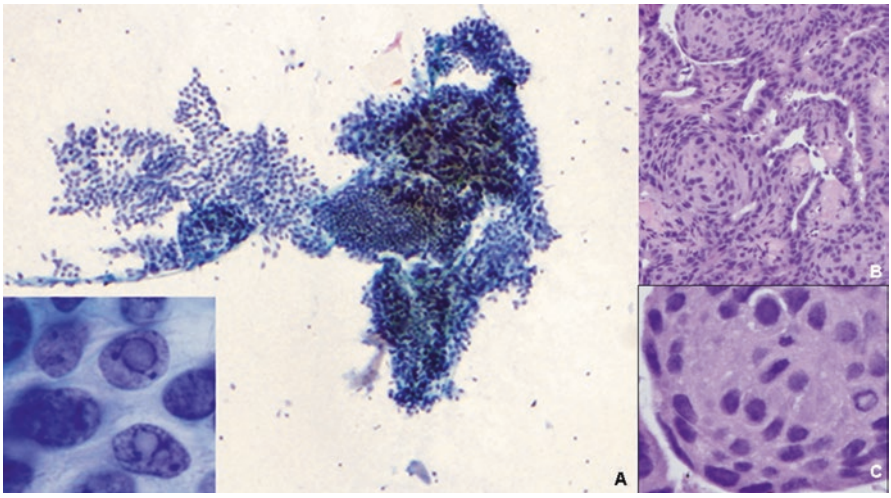

Fig. 8.30 Papillary thyroid carcinoma, cribriform-morular variant. (**a**) The aspirate shows large fragments of cohesive epithelium with a complicated arrangement (smear, Papanicolaou stain). The nuclear chromatin is dark, but nuclear pseudoinclusions are present (*inset*). (**b**) Histologically, the tumor is characterized by cribriform morula formation ((hematoxylin and eosin stain). (**c**) Higher magnification shows the characteristic morules (hematoxylin and eosin stain).

Criteria

The neoplastic cells show loss of polarity and cohesiveness.

Single cells with eccentric nuclei and tapering cytoplasm ("comet-like" or "tear drop-like" cells) are present.

Neoplastic cells with an apically or eccentrically placed nucleus (hobnail features) can be seen in papillary or micropapillary clusters.

Multiple soap-bubble-like INCIs and typical nuclear features of PTC are present.

Cell blocks may reveal papillary or micropapillary fragments lined by hobnail cells.

Explanatory Notes

The hobnail variant is a recently described rare variant associated with frequent distant metastases (typically to the lungs) and an increased risk of tumor-related death in small series (Fig. 8.31) [2, 10, 11]. The *BRAF*^{V600E} mutation is found in 70–80% of cases [10]. These tumors may require more aggressive treatment than conventional PTCs. There is significant morphological overlap with other aggressive variants of PTC such as the tall cell, columnar cell, and diffuse sclerosing variants. Hobnail morphology can be identified in LBPs and may occur also in the context of oncocytic, cystic, and clear cell changes. The hobnail variant also needs to be differentiated from metastases to the thyroid gland that have hobnail and/or micropapillary growth patterns (e.g., breast, lung, ovary). Additional studies with

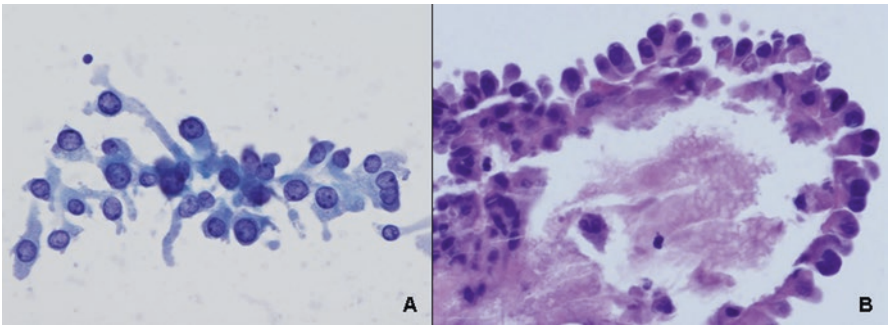

Fig. 8.31 Papillary thyroid carcinoma, hobnail variant. (**a**) The tumor cells in this variant are characterized by an eccentric location of the nucleus in elongated cytoplasm (hobnail-like) (smear, Papanicolaou stain). (**b**) The histologic counterpart shows similar features (hematoxylin and eosin).

large patient cohorts are needed to further clarify the biological behavior of this variant and the relevance of hobnail morphology in the context of cystic and/or encapsulated tumors and other variant growth patterns.

Related Tumors

Hyalinizing Trabecular Tumor/Hyalinizing Trabecular Adenoma

Definition

The hyalinizing trabecular tumor (HTT) or hyalinizing trabecular adenoma is a rare tumor of follicular cell origin characterized by trabecular growth, marked intratrabecular hyalinization, and the nuclear changes of PTC.

Criteria

Cohesive neoplastic cells are radially oriented around amyloid-like hyaline stromal material.
Cells can be round- or spindle-shaped.
INCIs and nuclear grooves are numerous.
Occasional psammoma bodies may be present.
Cytoplasmic paranuclear yellow bodies may be present.
Papillary and sheetlike fragments are absent.

Explanatory Notes

HTT is a controversial entity. Despite significant morphologic and genetic similarities with PTC, it may be better regarded as a variant of follicular adenoma rather than PTC [39, 40]. Patients with HTT follow a benign clinical course in the vast majority of cases (>99%) [40]. A total thyroidectomy and/or radioiodine treatment are usually not warranted for HTT. Because the morphologic features of HTT overlap significantly with those of PTC [39, 40], HTT is very difficult to recognize as

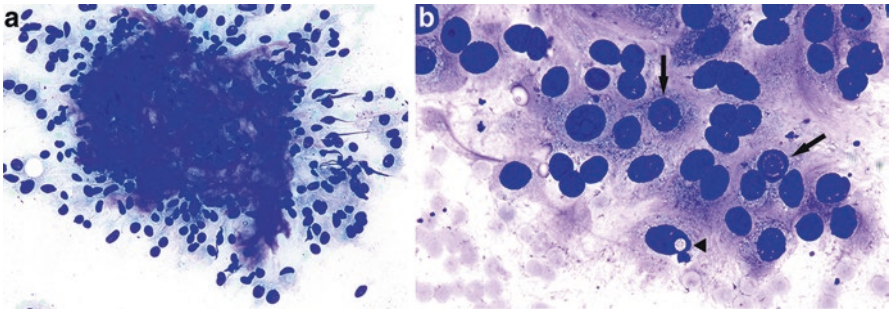

Fig. 8.32 Hyalinizing trabecular tumor/adenoma. (**a**) A core of metachromatic hyaline material insinuates among cells with oval nuclei, anisonucleosis, and abundant cytoplasm (smear, Diff-Quik stain). (**b**) Oval neoplastic nuclei have occasional intranuclear cytoplasmic pseudoinclusions (INCIs, *arrows*). Note the clear hole in one of the adjacent nuclei (*arrowhead*), a mimic of INCIs, but recognizable as an artifact because the hole is white rather than the color and texture of cytoplasm (smear, Papanicolaou stain).

such in an FNA specimen (Fig. 8.32). Most HTTs are interpreted as PTC or "suspicious for PTC." The demonstration of aberrant cytoplasmic expression of MIB-1 by immunohistochemistry supports the diagnosis of HTT. In contrast to PTC, *BRAF*^{V600E} mutations have not been found in HTT, but HTT harbors a *RET/PTC* rearrangement in a significant subset of cases (up to 62%), rekindling a possible relationship to PTC. The ultrasound findings of HTT usually show a well-defined iso- or hypoechoic solid nodule that more closely resembles a follicular neoplasm or FVPTC than a classic PTC.

Management

Surgical consultation is recommended for patients with an FNA interpretation that is conclusive for PTC; subtyping the PTC cytologically is not necessary and generally doesn't affect management [2]. The decision to perform surgery and the extent of surgery (lobectomy vs. total thyroidectomy) depend on the patient's age and overall health status and the size and sonographic characteristics of the tumor [2]. A cytologic diagnostic of PTC almost always leads to thyroid surgery. Active surveillance is an alternative to immediate surgery in a subset of patients, including those with very low risk tumors (e.g., papillary microcarcinomas without clinically evident metastases or local invasion and no convincing cytologic or molecular evidence of aggressive disease) [2]. For patients with thyroid cancer between 1 and 4 cm in diameter without extrathyroidal extension and without clinical evidence of lymph node metastases (cN0), the initial surgical procedure can be either a near-total/total thyroidectomy or a lobectomy [2]. Thyroid lobectomy alone may be a sufficient initial treatment for low risk PTCs, but the treatment team may choose total thyroidectomy to enable radioiodine therapy or to enhance follow-up based upon disease features and/or patient preferences [2]. If surgery is chosen for

patients with microcarcinomas (<1 cm) without extrathyroidal extension and cN0, the initial surgical procedure should be a thyroid lobectomy unless there are clear indications to remove the contralateral lobe [2]. Thyroid lobectomy alone is a sufficient treatment for small, unifocal, intrathyroidal carcinomas in the absence of prior head and neck irradiation, familial thyroid carcinoma, or clinically detectable cervical nodal metastases [2].

Sample Reports

The general category "MALIGNANT" is used whenever the cytomorphologic features are conclusive for malignancy. If an aspirate is interpreted as malignant, it is implied that the sample is adequate for evaluation. An explicit statement of adequacy is optional. Descriptive comments that follow are used to subclassify the malignancy and summarize the results of special studies, if any. If the findings are suspicious but not conclusive for malignancy, the general category "SUSPICIOUS FOR MALIGNANCY" should be used (see Chap. 7).

Example 1
MALIGNANT.
Papillary thyroid carcinoma.

Example 2
MALIGNANT.
Papillary thyroid carcinoma. See note.

Note: With the recent reclassification of a subset of indolent thyroid malignancies as "noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP)," the positive predictive value of the malignant category for thyroid FNA is expected to drop from 99 to about 94–96%. Thus, a small proportion of cases interpreted as malignant by FNA may prove to be NIFTP upon histologic examination.

Example 3
MALIGNANT.
Papillary thyroid carcinoma, favor tall cell variant.

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Medullary Thyroid Carcinoma

9

Michiya Nishino, Marc P. Pusztaszeri, and Martha B. Pitman

Background

According to the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database, medullary thyroid carcinoma (MTC) comprises approximately 1–2% of thyroid carcinomas; this value is lower than previous estimates because of the relative increase in the incidence of papillary thyroid carcinoma (PTC) over the past several decades [1]. Looking ahead, the recent reclassification of the noninvasive follicular variant of PTC as "noninvasive follicular thyroid neoplasm with papillary-like nuclear features" (i.e., not a malignancy) will undoubtedly increase the proportion of thyroid malignancies comprised of MTC in the future [2].

MTC occurs in sporadic and heritable forms. Sporadic MTC (70–80% of cases) typically presents as a solitary thyroid nodule in adults. In contrast, patients with hereditary MTC usually develop multifocal bilateral thyroid tumors, and the age of presentation varies with the syndrome. Hereditary syndromes include multiple endocrine neoplasia (MEN) type 2A, familial medullary thyroid carcinoma (FMTC), and MEN type 2B. Table 9.1 summarizes the clinical and pathologic features of the sporadic and hereditary forms of MTC.

MEN2 syndromes and FMTC show an autosomal dominant mode of inheritance and are associated with pathogenic germline mutations of the *RET* gene, encoded on chromosome 10, that result in constitutive activation of the RET receptor tyrosine kinase.

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Table 9.1 Clinical and pathologic features of hereditary and sporadic medullary thyroid carcinoma

	MEN2A	FMTC	MEN2B	Sporadic MTC
Proportion	~20% of MTC (~80% of hereditary cases)	~4% of MTC (~15% of hereditary cases)	~1% of MTC (~5% of hereditary cases)	70–80% of MTC
		May be considered a variant/ spectrum of MEN2A		
Age at presentation	Early adulthood (third to fourth decades)	Adulthood (fifth to sixth decades)	Infancy/childhood	Adulthood (fifth to sixth decades)
Genetics	Germline *RET* mutation (most commonly exon 10 and exon 11)	Germline *RET* mutation (most commonly exon 10 and exon 11)	Germline *RET* mutation (95% with exon 16 codon M918T mutations; <5% with exon 15 codon A883F mutation)	Somatic *RET* mutations (most commonly codon M918T) in 25–45%
				1–7% of presumed sporadic MTC have germline *RET* mutations
				Somatic *RAS* mutations identified in *RET* wild-type cases
Inheritance	Autosomal dominant	Autosomal dominant	Autosomal dominant	N/A
Associated diseases	Pheochromocytoma (50%); hyperparathyroidism (20–35%); variants with cutaneous lichen amyloidosis, Hirschsprung disease	Absence of pheochromocytoma, hyperparathyroidism, or other endocrinopathies	Aggressive MTC with early spread to lymph nodes; pheochromocytoma (50%); mucosal ganglioneuromas; Marfanoid habitus; everted eyelids; thick lips	N/A
Number of thyroid nodules	Usually multicentric/ bilateral	Usually multicentric/bilateral	Usually multicentric/bilateral	Usually a solitary nodule
C-cell hyperplasia	Present	Present	Present	Usually absent

MEN2A multiple endocrine neoplasia type 2A, *FMTC* familial medullary thyroid cancer, *MEN2B* multiple endocrine neoplasia type 2B, *MTC* medullary thyroid carcinoma

Mutations in the extracellular domain of *RET* (e.g., codons 609, 611, 618, 620, and 634) result in kinase activation via ligand-independent receptor dimerization, and mutations in the catalytic domain of *RET* (e.g., codon 918) result in kinase activation independent of ligand or receptor dimerization. There is a strong correlation between specific pathogenic mutations and phenotype, vis-à-vis MEN2 subtype, aggressiveness of MTC, and association with other manifestations such as Hirschsprung disease and cutaneous lichen amyloidosis [1, 3]. Somatic *RET* mutations have been identified in up to 50% of sporadic MTC [4, 5]. Among larger series, between 1 and 7% of patients with presumed sporadic MTCs are found to have hereditary disease, underscoring the importance of germline *RET* mutation testing in all patients diagnosed with MTC [1, 6, 7].

Most cases of MTC demonstrate characteristic cytomorphology, a distinctive immunophenotype, and variable stromal amyloid deposition (Table 9.2). Nevertheless, MTC can show a wide variety of cell shapes, cytoplasmic features, and growth patterns, leading to the description of a large number of MTC variants: papillary (or pseudopapillary), follicular, giant cell, spindle cell, small cell and neuroblastoma-like, paraganglioma-like, oncocytic, clear cell, angiosarcoma-like, squamous cell, melanin producing, and amphicrine (mucin producing) [8]. Recognizing and reporting any specific variant of MTC is not important for clinical management. This morphologic heterogeneity, however, leads to significant diagnostic challenges in the morphologic evaluation of this neoplasm (Table 9.3) [9].

Definition

MTC is a malignant neuroendocrine neoplasm derived from the parafollicular cells (C cells) of the thyroid gland.

Criteria

Aspirates show moderate to marked cellularity.

Numerous isolated cells alternate with syncytium-like clusters in variable proportions.

Cells are plasmacytoid, polygonal, round, and/or spindle-shaped. Long cell processes are seen in some cases.

The neoplastic cells usually show only mild to moderate pleomorphism.

Rare bizarre giant cells may be seen; they can be numerous in the giant-cell variant.

Nuclei are round, oval, or elongated and often eccentrically placed, with finely or coarsely granular ("salt and pepper") chromatin.

Binucleation is common. Multinucleation is less often observed.

Nucleoli are usually inconspicuous but can be prominent in some cells.

Nuclear pseudoinclusions are occasionally noted. Nuclear grooves are rare or absent.

Cytoplasm is granular and variable in quantity. Small red-purple granules are seen with Romanowsky stains in some cases. Rare cases show cytoplasmic melanin pigment.

Table 9.2 Cytologic differential diagnosis of medullary thyroid carcinoma

Tumor	Cytoarchitecture and background	Cytoplasm	Nucleus	ICC/stains	
				Positive	Negative
Medullary thyroid carcinoma	Isolated, dispersed cells and/or syncytium-like clusters; amyloid	Plasmacytoid, epithelioid, giant, spindle-shaped. Red-purple granules with Romanowsky-type stains	Round, ovoid, or elongated, with granular chromatin. INCI and binucleation (some cases)	CT, CEA, NE markers, TTF1, PAX8 (variable), Congo red (amyloid)	TG
Follicular neoplasm	Microfollicles/crowded groups	Scant to moderate	Round, hyperchromatic, variable nuclear enlargement	TTF1, TG, PAX8	CT, CEA, NE markers
Hürthle-cell neoplasm	Isolated, dispersed cells and syncytium-like clusters	Abundant, finely granular (blue-gray with Romanowsky-type stains)	Round and enlarged, with moderate irregularity and prominent nucleolus	TTF1, TG, PAX8	CT, CEA, NE markers
Papillary thyroid carcinoma	Papillae, sheets, microfollicles	Variable, depending on subtype	Enlarged and ovoid with irregular contours, grooves, INCI, and chromatin pallor	TTF1, TG, PAX8	CT, CEA, NE markers
Hyalinizing trabecular tumor	Cohesive clusters associated with hyaline matrix	Epithelioid to spindled	Enlarged, with irregular contours, grooves, INCI, and chromatin pallor	TTF1, TG, Ki67 (membranous)	CT, CEA, NE markers
Poorly differentiated thyroid carcinoma	Crowded groups, isolated, dispersed cells	Scant, occasionally plasmacytoid	Round, with variable enlargement and binucleation; apoptosis; mitosis	TTF1, PAX8, TG (variable)	CT, CEA
Anaplastic thyroid carcinoma	Isolated, dispersed cells and crowded groups. Variable necroinflammatory debris	Epithelioid, spindled, variable sizes	Enlarged, with variable pleomorphism, nucleolar prominence, multinucleation; necrosis/apoptosis; mitotic activity	PAX8 (variable)	TTF1, TG, CT, CEA, NE markers

Tumor	Cytoarchitecture and background	Cytoplasm	Nucleus	ICC/stains	
				Positive	Negative
Melanoma	Isolated, dispersed cells	Epithelioid, spindled, variable sizes. Variable melanin pigmentation	Enlarged, with prominent nucleoli	S100-protein, HMB45, Melan-A, SOX10	CK, CT, CEA, NE markers
Parathyroid	Sheets, cords, acini	Moderate amount, often granular	Round, with granular chromatin	NE markers, PTH, GATA3	CT, CEA, TTF1, TG
Plasmacytoma	Isolated, dispersed cells; amyloid	Moderate amount with eccentric nuclei ("plasmacytoid")	Round, with granular chromatin	CD138, kappa or lambda Ig light chain restriction, Congo red (amyloid)	CT, TTF1, NE markers
Paraganglioma	Isolated, dispersed cells and loose clusters	Moderate to abundant amount of delicate cytoplasm	Round, with granular chromatin, anisonucleosis	NE markers, S100-protein (sustentacular cells)	CK, CT

CEA carcinoembryonic antigen, *CK* cytokeratin, *CT* calcitonin, *ICC* immunocytochemistry, *Ig* immunoglobulin *INCI* intranuclear cytoplasmic pseudoinclusions, *NE* neuroendocrine, *PTH* parathyroid hormone, *TG* thyroglobulin

Table 9.3 Variants of medullary thyroid carcinoma and associated differential diagnostic considerations

MTC variant	Differential diagnosis
Amphicrine (mucin and calcitonin-producing cells)	Secretory carcinoma, metastatic adenocarcinoma
Clear cell	Renal cell carcinoma, follicular neoplasm with clear cells
Follicular/tubular	Follicular neoplasm
Giant cell	Undifferentiated (anaplastic) thyroid carcinoma (UTC)
Melanin-producing/pigmented	Melanoma
Mixed follicular and medullary	Follicular neoplasm
Oncocytic (oxyphilic)	Oncocytic variants of follicular neoplasm and PTC
Papillary/pseudopapillary	Papillary thyroid carcinoma (PTC)
Paraganglioma-like	Paraganglioma, hyalinizing trabecular tumor
Small cell/neuroblastoma-like	Small-cell carcinoma of the lung, lymphoma
Spindle cell	Sarcoma, UTC
Squamous	Squamous-cell carcinoma, UTC, PTC with squamous differentiation/metaplasia

MTC medullary thyroid carcinoma (Adapted from [9]. With permission from Wolters Kluwer Health, Inc.)

Amyloid is often present and appears as dense, amorphous material that resembles thick colloid.

With liquid-based preparations, fine cytoplasmic vacuolization can be prominent.

Cells are typically strongly immunoreactive for calcitonin, CEA, neuroendocrine markers (chromogranin, synaptophysin), and TTF1. Immunoreactivity for PAX8 is variable. Cells are negative for thyroglobulin (aberrant results occasionally occur).

Explanatory Notes

Cytologic preparations from MTC are usually moderately or highly cellular and composed of a mixture of noncohesive cells (Fig. 9.1) and crowded, syncytium-like aggregates (Fig. 9.2) [8–12]. Occasionally, rosette-forming, follicular, and pseudopapillary architecture can be seen. Most aspirates show a mixture of cell morphologies, including polygonal, round, and plasmacytoid shapes (all with round to ovoid nuclei) (Fig. 9.3), as well as spindled cells with elongated nuclei (Fig. 9.4). Tumor cells have a variable amount of cytoplasm, sometimes replete with red-purple granules after Romanowsky-type staining of air-dried smears (Fig. 9.5). A minority of cases demonstrate cytoplasmic vacuoles, melanin-like pigment (Fig. 9.6), and intracytoplasmic lumina (Fig. 9.7) [8]. With liquid-based preparations, fine cytoplasmic vacuolization can be prominent (see Fig. 9.6). Typically, most of the tumor cells demonstrate only mild to moderate nuclear pleomorphism, with occasional cells showing markedly enlarged or bizarre-appearing nuclei [8, 10]. Binucleation is common [8, 10]. Intranuclear pseudoinclusions (indistinguishable from those seen

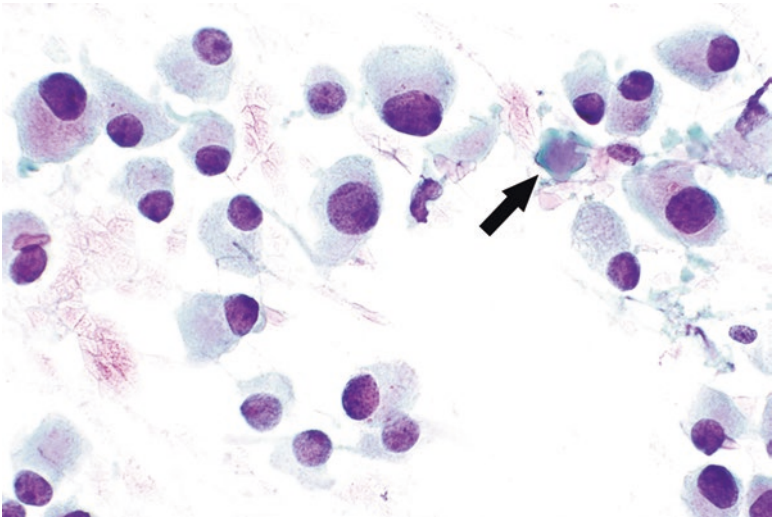

Fig. 9.1 Medullary thyroid carcinoma. Predominantly dispersed plasmacytoid or polygonal cells have granular ("salt and pepper") chromatin and small or indistinct nucleoli. A small fragment of amyloid is present (*arrow*) (smear, Papanicolaou stain).

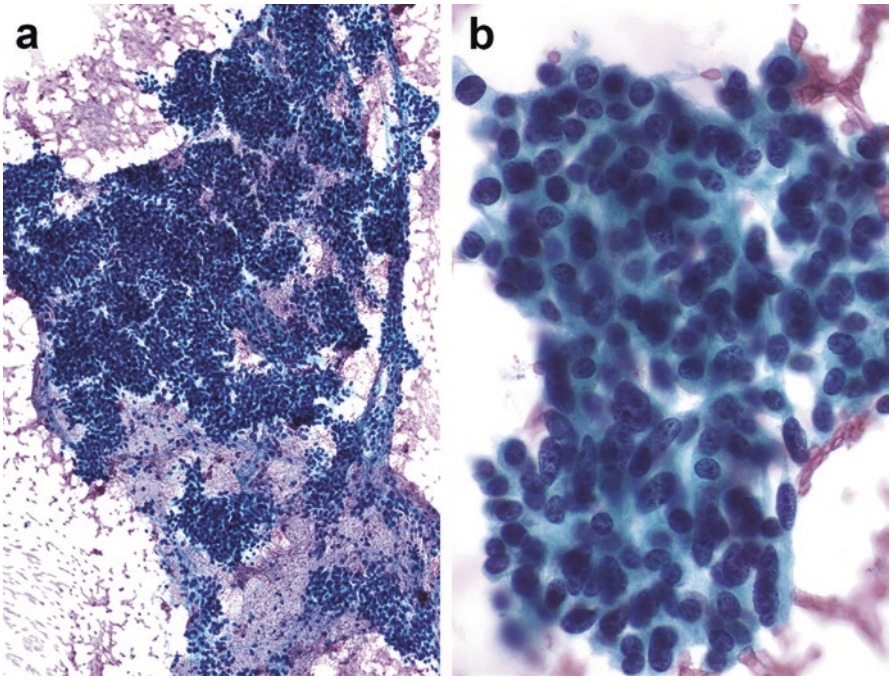

Fig. 9.2 Medullary thyroid carcinoma. (**a**) In some cases a cohesive, syncytium-like pattern of crowded cells predominates, with few isolated cells. (**b**) In this example, tumor cells exhibit less abundant cytoplasm, round to ovoid nuclei, and coarse chromatin. Medullary thyroid carcinomas with this pattern mimic a follicular neoplasm, poorly differentiated thyroid carcinoma, and parathyroid neoplasms (smear, Papanicolaou stain).

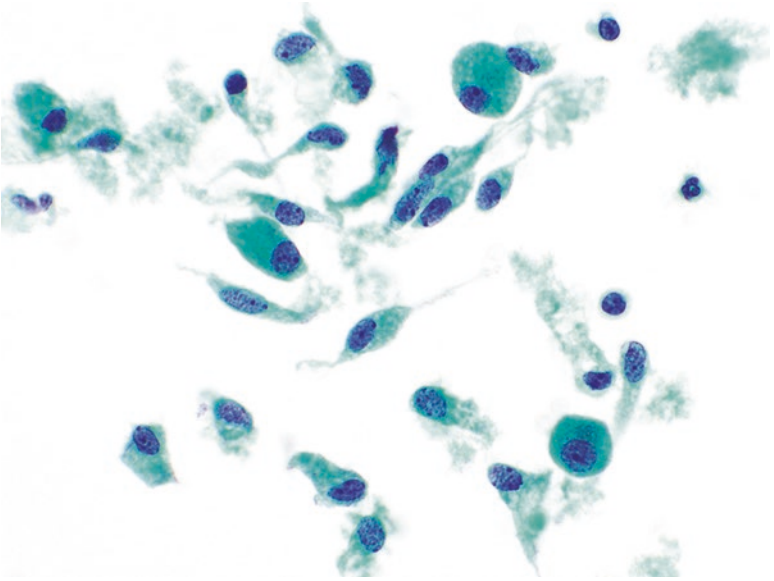

Fig. 9.3 Medullary thyroid carcinoma. A variety of shapes (round, polygonal, plasmacytoid, and spindled) are noted in this noncohesive population of tumor cells (ThinPrep, Papanicolaou stain).

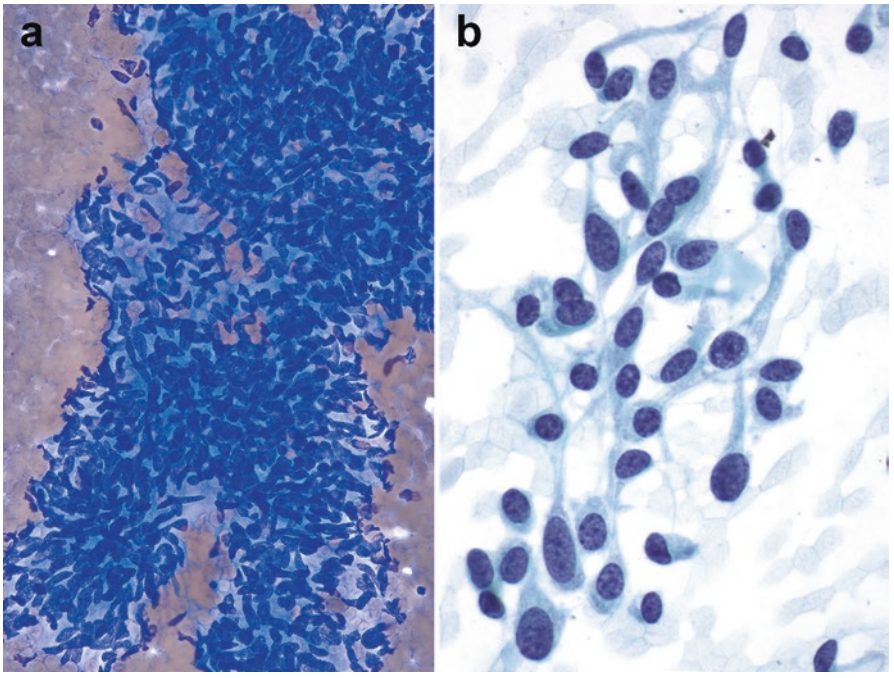

Fig. 9.4 Medullary thyroid carcinoma. (**a**) The spindle-cell variant can have a syncytium-like arrangement (smear, Diff-Quik stain). (**b**) The spindle-cell variant has prominent interdigitating cytoplasmic processes with oval nuclei. Smooth nuclear membranes, granular chromatin, and inconspicuous nucleoli are maintained (smear, Papanicolaou stain).

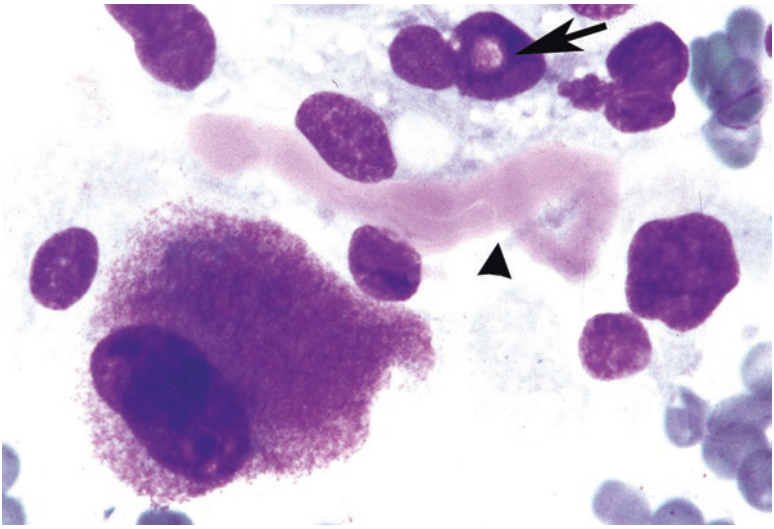

Fig. 9.5 Medullary thyroid carcinoma. A large tumor cell with abundant cytoplasm demonstrates red cytoplasmic granules with a Romanowsky-type stain. Note also the presence of amyloid (*arrowhead*) and a tumor cell with an intranuclear pseudoinclusion (*arrow*) (smear, Diff-Quik stain).

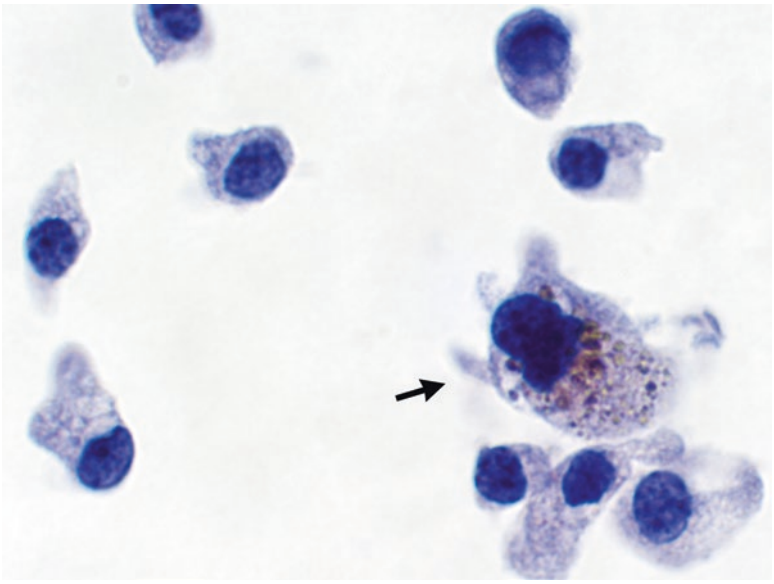

Fig. 9.6 Medullary thyroid carcinoma. Pigmentation and/or melanocytic differentiation can be seen in medullary thyroid carcinoma (*arrow*), which raises the possibility of a metastatic melanoma. Even without pigmentation, melanoma is a mimic of medullary thyroid carcinoma because both often demonstrate an isolated-cell pattern, epithelioid or spindled morphology, and binucleation. Immunocytochemistry on the cell block in this case confirmed the diagnosis of medullary thyroid carcinoma (ThinPrep, Papanicolaou stain).

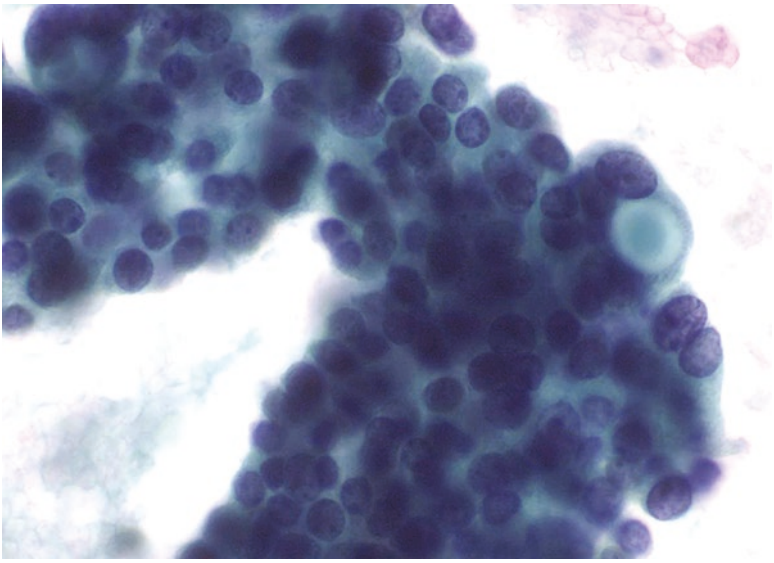

Fig. 9.7 Medullary thyroid carcinoma. Cytoplasmic vacuoles or lumina are occasionally seen in medullary thyroid carcinoma (smear, Papanicolaou stain).

in papillary thyroid carcinoma) are seen in a limited number of cells in ~20–50% of cases (Fig. 9.8) [8, 10, 13]. Nuclear grooves are rare [13]. Rare cases show scant cytoplasm and nuclear molding, resembling small-cell carcinoma (Fig. 9.9). Amyloid is identified in approximately one-third to one-half of MTC aspirates (Figs. 9.10 and 9.11) [8, 10, 14]. It is virtually indistinguishable from colloid without the cellular context and is not diagnostic of MTC by itself, since amyloid may be present in papillary thyroid carcinoma (rarely) and amyloid goiter [15, 16]. Colloid is present in about 30% of MTC aspirates and is more frequent in medullary thyroid microcarcinoma, likely due to incidental colloid sampling from surrounding thyroid follicles [10, 17]. Calcifications (including psammoma bodies) have been reported in approximately 3% of MTC [8, 10].

Diagnosing MTC by FNA can be challenging given its diverse appearances and cytologic overlap with other tumors. Although the sensitivity of FNA for a definitive and specific diagnosis of MTC has been reported to be as high as 89% in a single-institution study, a meta-analysis revealed a substantially lower sensitivity of 56% (range 12–88%), thus highlighting the challenge that MTC poses to the cytologist [10, 18]. Immunocytochemistry (ICC) is extremely helpful for distinguishing MTC from its cytologic mimics (Table 9.2). Most MTCs are immunoreactive for "C-cell markers" (calcitonin, CEA), neuroendocrine markers (synaptophysin, chromogranin) [19–25], and TTF1 [19, 21, 26–28] and are negative for thyroglobulin (Fig. 9.12) [22, 29]. Staining for PAX8 varies considerably among studies (0–75%), with positive cases generally showing only focal immunoreactivity [27, 30–32]. Therefore, TTF1 and PAX8 are not helpful for distinguishing MTC from follicular

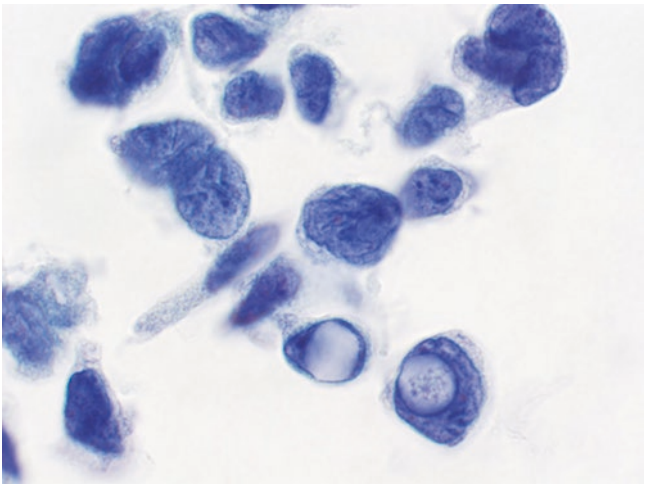

Fig. 9.8 Medullary thyroid carcinoma. Intranuclear cytoplasmic pseudoinclusions can be seen, mimicking papillary thyroid carcinoma (ThinPrep, Papanicolaou stain).

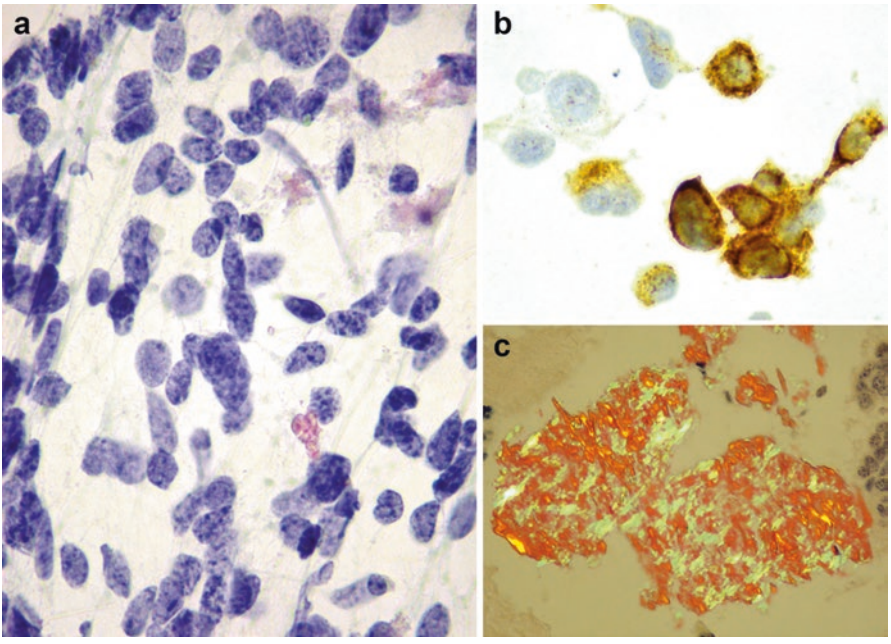

Fig. 9.9 Medullary thyroid carcinoma, small-cell variant. (**a**) Rare cases of medullary thyroid carcinoma exhibit scant cytoplasm and nuclear molding, resembling small cell carcinoma of the lung and other sites (smear, Papanicolaou stain). (**b**) Immunoreactivity for calcitonin and (**c**) Congo red staining for amyloid on cell block preparations support the diagnosis of medullary thyroid carcinoma. Nevertheless, because their immunprofiles can overlap and both tumors can contain amyloid, the distinction requires correlation with clinical findings.

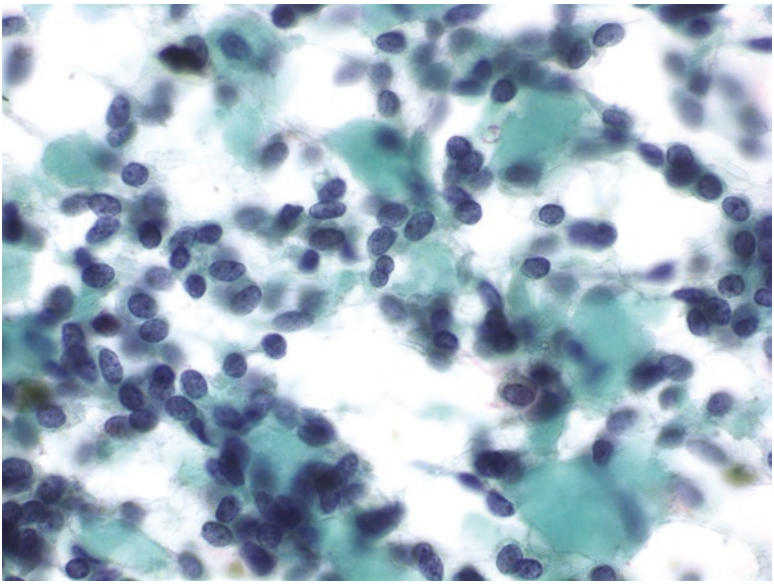

Fig. 9.10 Medullary thyroid carcinoma. In this smear, amyloid is abundant and readily appreciated as a light-green, waxy, amorphous deposit (Papanicolaou stain).

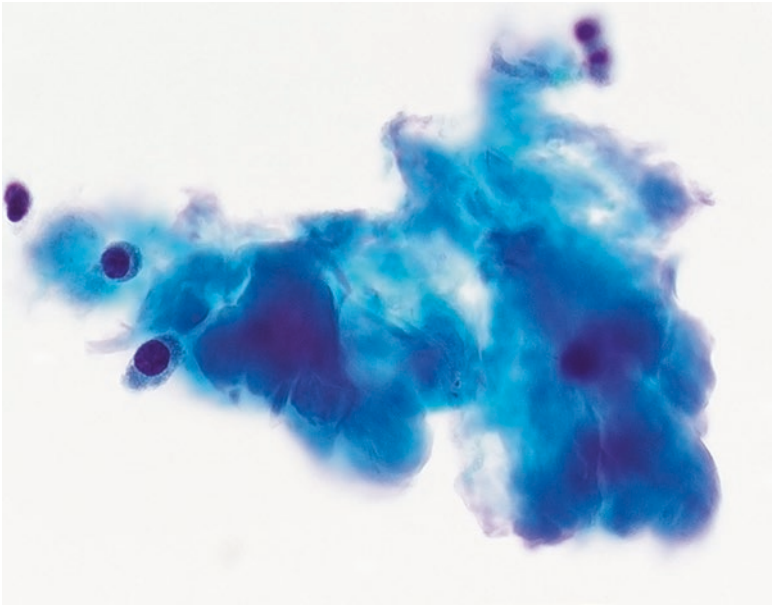

Fig. 9.11 Medullary thyroid carcinoma. Amyloid has the same dense, amorphous, and waxy appearance on liquid-based preparations as it does on smears (ThinPrep, Papanicolaou stain).

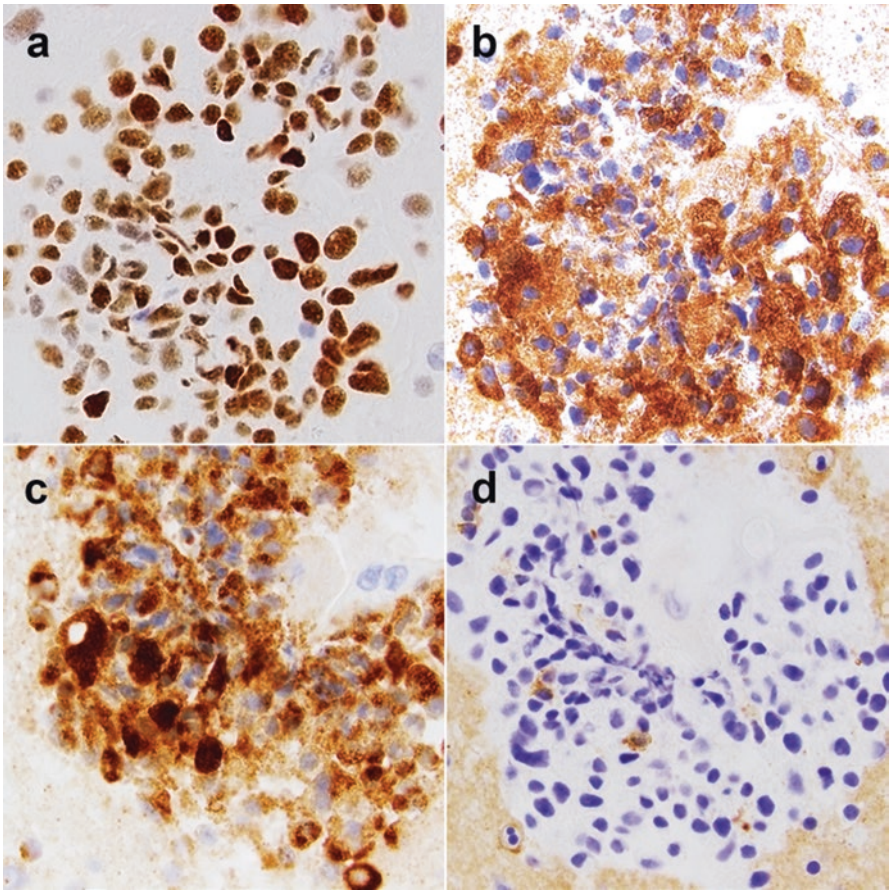

Fig. 9.12 Medullary thyroid carcinoma. The tumor cells (on cell block preparations) are immunoreactive for (**a**) TTF1 (nuclear), (**b**) calcitonin (cytoplasmic), and (**c**) chromogranin (cytoplasmic). (**d**) Tumor cells are negative for thyroglobulin.

cell-derived thyroid neoplasms. A Congo red stain can confirm the presence of amyloid, which supports the diagnosis of MTC in the context of characteristic malignant cells. The measurement of calcitonin levels in needle rinsings (washout fluid) from FNAs of thyroid nodules, thyroidectomy beds, and/or lymph nodes, can be helpful. This is particularly true in patients with elevated serum calcitonin levels and/or when FNA findings are inconclusive for MTC, e.g., when confirmation by ICC is not possible given limited material or equivocal staining results [1, 33]. Overall, this test is reliable, inexpensive, and associated with fast turnaround time. In order to avoid repetition of the FNA for this purpose, calcitonin measurement in FNA washout fluid should be anticipated in all clinically suspected cases of MTC and for all patients with MEN2. The Afirma Gene Expression Classifier (Veracyte, Inc., South San Francisco, CA), in common use for nodules interpreted as atypia of

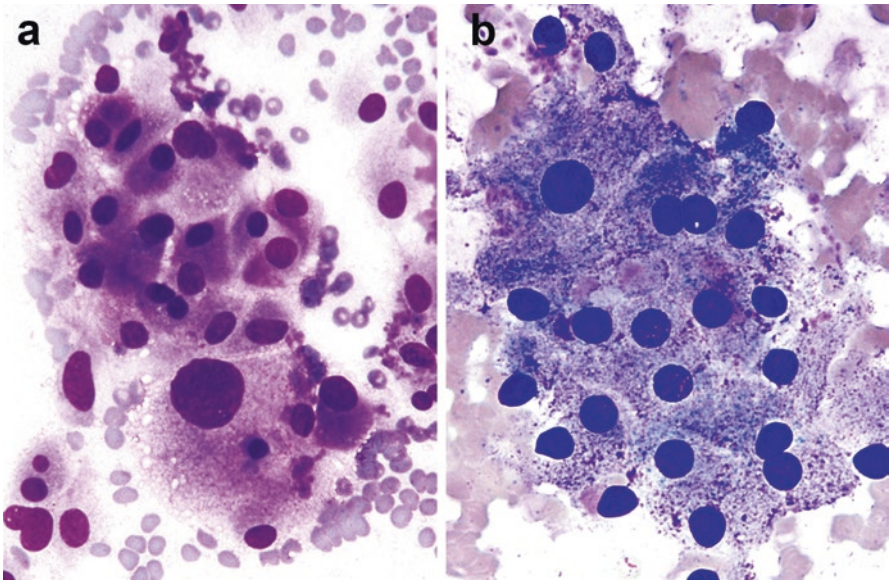

Fig. 9.13 Medullary thyroid carcinoma (*left*) versus Hürthle-cell neoplasm (*right*). (**a**) With Romanowsky-type stains, the cells of some (but not all) medullary thyroid carcinomas are noteworthy for abundant red cytoplasmic granules (smear, Diff-Quik). (**b**) In contrast, Hürthle cells have blue-gray cytoplasmic granules with Romanowsky-type stains (smear, Diff-Quik).

undetermined significance (AUS)/follicular lesion of undetermined significance (FLUS) or follicular neoplasm (FN)/suspicious for follicular neoplasm (SFN), includes an MTC classifier that is effective in identifying the MTCs hidden in the substantial population of nodules with indeterminate cytology [34, 35].

The differential diagnosis of MTC includes the full spectrum of follicular cell-derived thyroid tumors (Table 9.2). Aspirates of Hürthle-cell (oncocytic) neoplasms often yield noncohesive cells with abundant granular cytoplasm, resembling some MTCs (Fig. 9.13). Papillary thyroid carcinoma (PTC) and hyalinizing trabecular tumor (HTT) can also mimic MTC by virtue of their intranuclear pseudoinclusions [36]. In particular, certain variants of PTC (tall cell, oncocytic) can have elongated or abundant cytoplasm, similar to that of some MTC cells [37]. Poorly differentiated thyroid carcinoma (PDTC) can resemble MTC; both have similar cytoarchitecture (crowded insular/nested groups and/or noncohesive cells), variable binucleation and chromatin granularity, and occasional plasmacytoid shape (Fig. 9.14) [38]. Like MTC, cells of undifferentiated (anaplastic) thyroid carcinomas (UTC) can have a multitude of appearances, including epithelioid, plasmacytoid, spindled, and giant-cell forms (Fig. 9.15) [39]. Increased mitotic activity, apoptosis, and necrosis should raise concern for PDTC or UTC rather than MTC. For each of the above possibilities, a panel of immunostains (calcitonin, CEA, synaptophysin, chromogranin) helps distinguish MTC from follicular cell-derived thyroid neoplasms.

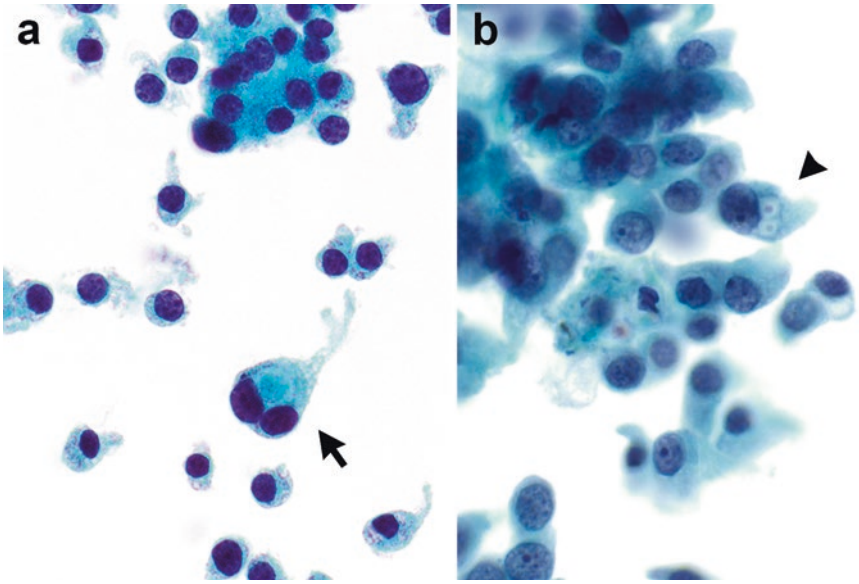

Fig. 9.14 Medullary thyroid carcinoma (*left*) versus poorly differentiated thyroid carcinoma (*right*). (**a**) Medullary thyroid carcinomas often demonstrate an isolated-cell pattern, plasmacytoid cytomorphology, and they occasionally have cytoplasmic lumina (ThinPrep, Papanicolaou stain). (**b**) Poorly differentiated thyroid carcinomas have similar features, and intracytoplasmic lumina are sometimes seen (ThinPrep, Papanicolaou stain).

Additional mimics of MTC include other neuroendocrine lesions in the head and neck, such as paraganglioma and parathyroid adenoma, both of which resemble MTC morphologically, and all are immunoreactive for synaptophysin and chromogranin. Additional immunostains help discriminate MTC (CEA+, calcitonin+, cytokeratin [CK]+) from paraganglioma (CEA-, calcitonin-, CK-, S100-protein+ sustentacular cells) and parathyroid neoplasms/hyperplasia (CEA-, calcitonin-, PTH+, GATA3+) [40, 41]. Metastatic neuroendocrine tumors to the thyroid gland or cervical lymph nodes mimic MTC and can be associated with elevated serum calcitonin levels [42]. In particular, moderately differentiated neuroendocrine carcinomas (atypical carcinoid) of the larynx are frequently positive for calcitonin and/or CEA. In contrast to MTC, however, most laryngeal atypical carcinoids are negative for TTF1 [19]. Correlation with clinical and radiographic findings plays a critical role in distinguishing MTCs from extra-thyroidal neuroendocrine tumors. Of other tumors metastatic to the thyroid, melanoma is a noteworthy mimic of MTC: the variable cell shape, frequent binucleation, nuclear pseudoinclusions, and dispersed cell pattern of many melanomas are features shared by many MTCs. In a patient with a history of melanoma, MTCs can be recognized by their immunoreactivity for cytokeratins and C-cell markers, the lack of staining for melanocytic markers (HMB45, S100-protein, Melan-A, SOX10), and the absence of macronucleoli. MTCs with a prominent spindle-cell pattern resemble mesenchymal lesions; immunoreactivity for CK, calcitonin, and neuroendocrine markers can be used to confirm

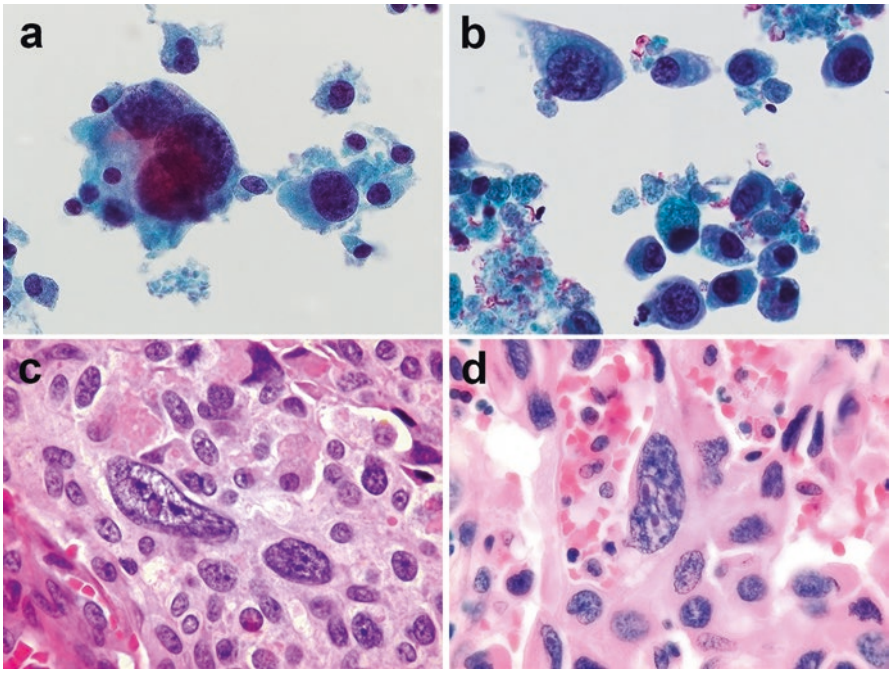

Fig. 9.15 Medullary thyroid carcinoma (*left*) versus undifferentiated/anaplastic thyroid carcinoma (*right*). (**a**) The giant-cell variant of medullary thyroid carcinoma exhibits markedly enlarged, epithelioid tumor cells with pleomorphic nuclei, often admixed with more conventional-appearing tumor cells (ThinPrep, Papanicolaou stain). Multinucleation may be seen, as in this example. (**b**) Note the resemblance to undifferentiated (anaplastic) thyroid carcinoma, which can also exhibit an epithelioid cytomorphology and nuclear pleomorphism (ThinPrep, Papanicolaou stain). This rapidly growing primary thyroid tumor was positive for PAX8 and negative for TTF1, calcitonin, synaptophysin, and chromogranin. Histologic images of medullary thyroid carcinoma (**c**) and undifferentiated thyroid carcinoma (**d**) demonstrate similar nuclear and cytoplasmic features (hematoxylin and eosin stain).

the diagnosis of MTC in this setting [43]. Finally, plasma cell neoplasms resemble MTC because a dispersed cell pattern, "plasmacytoid" morphology, and amyloid deposition are shared by both tumors. Plasmacytomas of the thyroid are exceptionally rare but have been described [44]. Expression of CD138 and immunoglobulin light chain restriction favor a plasma cell neoplasm, whereas expression of C-cell and neuroendocrine markers supports a diagnosis of MTC.

Management

Following a cytologic diagnosis of MTC, preoperative studies should include a neck ultrasound and measurement of serum calcitonin and CEA. Systemic imaging studies may be indicated for patients with clinical or laboratory evidence of metastatic disease. Genetic testing for germline *RET* mutations should also be performed, and

patients with hereditary MTC should be evaluated for pheochromocytoma and hyperparathyroidism prior to thyroid surgery [1]. For patients with pheochromocytoma, alpha/beta-adrenergic blockade and resection of the adrenal tumor should precede thyroidectomy for MTC. Surgical treatment of MTC is usually total thyroidectomy and central lymph node dissection, with consideration of lateral cervical lymph node dissection depending on imaging studies and serum calcitonin levels. For patients with advanced, progressive MTC, tyrosine kinase inhibitors such as vandetanib (targeting RET, EGFR, VEGFR) and cabozantinib (targeting RET, c-MET, VEGFR) can be used as single-agent first-line systemic chemotherapy [1].

Sample Reports

The general category "MALIGNANT" is used whenever the cytomorphologic features are conclusive for malignancy. If an aspirate is interpreted as MALIGNANT, it is implied that the sample is adequate for evaluation (an explicit statement of adequacy is optional). Descriptive comments that follow are used to subclassify the malignancy as an MTC and summarize the results of special studies, if any. If the findings are suspicious but not conclusive for malignancy, the general category "SUSPICIOUS FOR MALIGNANCY" should be used (see Chap. 7).

Example 1
MALIGNANT.
Medullary thyroid carcinoma.

Note: A Congo red stain is positive for amyloid. Immunocytochemistry performed on cell block/cytocentrifuge/liquid-based preparations (choose one) shows that the malignant cells are immunoreactive for calcitonin, CEA, chromogranin, and TTF1 and negative for thyroglobulin.

Example 2
MALIGNANT.
Consistent with medullary thyroid carcinoma.

Note: Cytomorphologic features are characteristic of medullary thyroid carcinoma, but tissue is insufficient for confirmatory immunocytochemical studies. Serum chemistry for calcitonin and CEA and/or repeat FNA for calcitonin measurement in the washout fluid warrant clinical consideration.

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Poorly Differentiated Thyroid Carcinoma

10

Massimo Bongiovanni, Guido Fadda, and William C. Faquin

Background

Poorly differentiated thyroid carcinoma (PDTC) was first proposed as a distinct subtype of thyroid malignancy by Carcangiu et al. [1]. These authors reinterpreted the original observation made in 1907 by Langhans, who described a locally aggressive tumor with a peculiar architecture: tumor cells arranged in large, round to oval formations, the so-called insulae [2]. Currently, there are two recognized subtypes of PDTC – insular and non-insular [3].

In 2006, formal criteria (known as the Turin criteria) were established for the histologic diagnosis of PDTC [4]. To qualify histologically as PDTC, tumors must have a solid, trabecular, and/or insular pattern of growth; conventional nuclear features of papillary thyroid carcinoma should not be present throughout the tumor; and at least one of the following features must be present: mitotic activity ≥3/10 high-power fields (HPFs), tumor necrosis, and convoluted nuclei. Some PDTCs have prominent oncocytic (Hürthle cell) features [5, 6].

PDTC is a rare malignancy, accounting for 0.3–6.7% of all thyroid cancers [3]. The age at presentation is between 18 and 63 years with a slight female predilection. It has an aggressive clinical behavior intermediate between that of the well-differentiated thyroid carcinomas (papillary carcinoma, follicular carcinoma, and

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Hürthle cell carcinoma) and undifferentiated (anaplastic) thyroid carcinoma. PDTCs often present at an advanced stage, have a propensity for local recurrence, and tend to metastasize to regional lymph nodes, lung, and bones. The mean 5-year survival of patients with PDTC is approximately 50% [3, 4]. Well-differentiated thyroid carcinomas with a focal (10% or greater) PDTC component follow a more aggressive clinical course than standard well-differentiated carcinomas of the thyroid [7].

Definition

PDTC is a thyroid carcinoma of follicular cell origin characterized by an insular, solid, or trabecular growth pattern. In its pure form, PDTC lacks conventional nuclear features of papillary thyroid carcinoma and is distinguished from the latter by the presence of poorly differentiated features: mitoses, necrosis, or small convoluted nuclei. The most classic form of PDTC is the insular type, defined by its "cellular nests" or insular cell groups outlined by a thin fibrovascular border. In a subset of cases, PDTCs can also be associated with a better differentiated component showing typical microscopic features of papillary or follicular carcinoma variably admixed with poorly differentiated cells. The presence of oncocytic (Hürthle cell) features does not exclude a diagnosis of PDTC.

Criteria

Cellular preparations display an insular, solid, or trabecular cytoarchitecture (Figs. 10.1, 10.2, 10.3, and 10.4).

There is a uniform population of malignant follicular cells with scant cytoplasm (sometimes plasmacytoid) (Fig. 10.5) or with oncocytic features (Fig. 10.6).

The cells have a high nuclear/cytoplasmic (N/C) ratio with variable nuclear atypia (Figs. 10.7 and 10.8).

Colloid is scant.

Apoptosis and mitotic activity are present (Fig. 10.9).

Necrosis is often present (Fig. 10.10).

In liquid-based cytology, PDTC exhibits the same cytomorphology, characterized by a population of cells with a high N/C ratio and focal nuclear atypia (Figs. 10.2 and 10.5).

Explanatory Notes

Cytologically, PDTCs are difficult to recognize as such because they are rare; their cytomorphologic features overlap with those of follicular neoplasms; and their characteristic FNA features do not have great specificity. Based upon a limited number of published case reports and small series, aspirates of PDTC are often cellular with scant colloid [8–19]. The cells of PDTC have a monomorphic appearance at

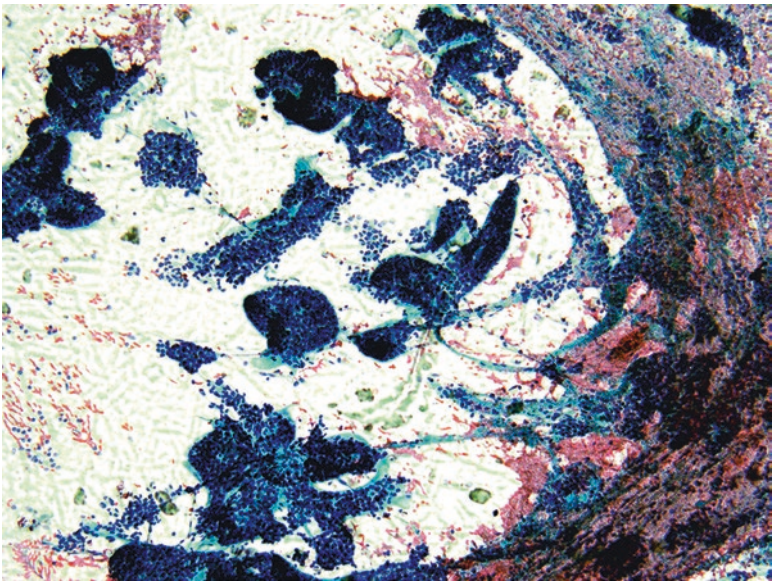

Fig. 10.1 Poorly differentiated thyroid carcinoma. A low magnification view reveals small follicular cells arranged in crowded insulae (smear, Papanicolaou stain).

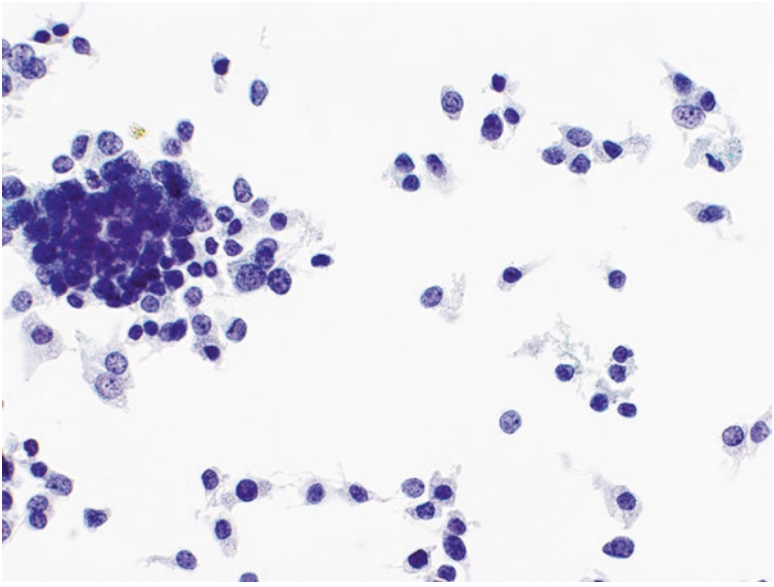

Fig. 10.2 Poorly differentiated thyroid carcinoma. The monomorphic cells are arranged in crowded three-dimensional groups and scattered as isolated cells (ThinPrep, Papanicolaou stain).

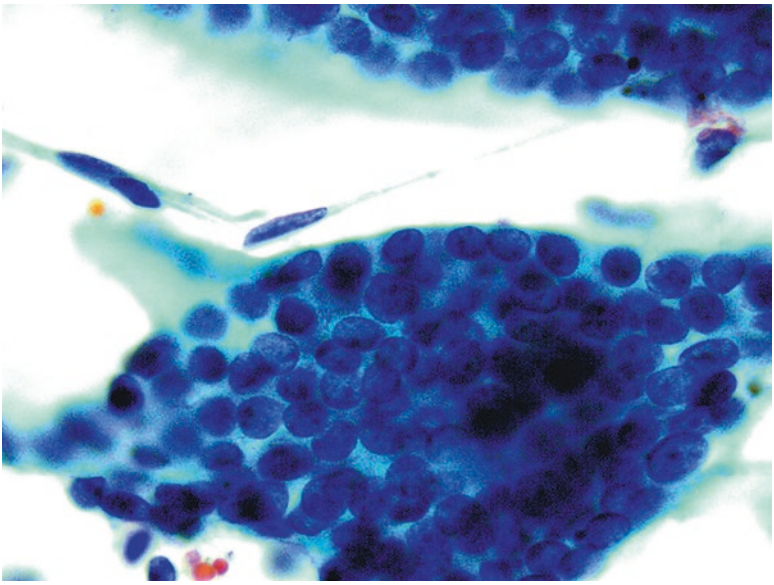

Fig. 10.3 Poorly differentiated thyroid carcinoma. Endothelium wrapping around cell groups can often be found highlighting the insular arrangements (smear, Papanicolaou stain).

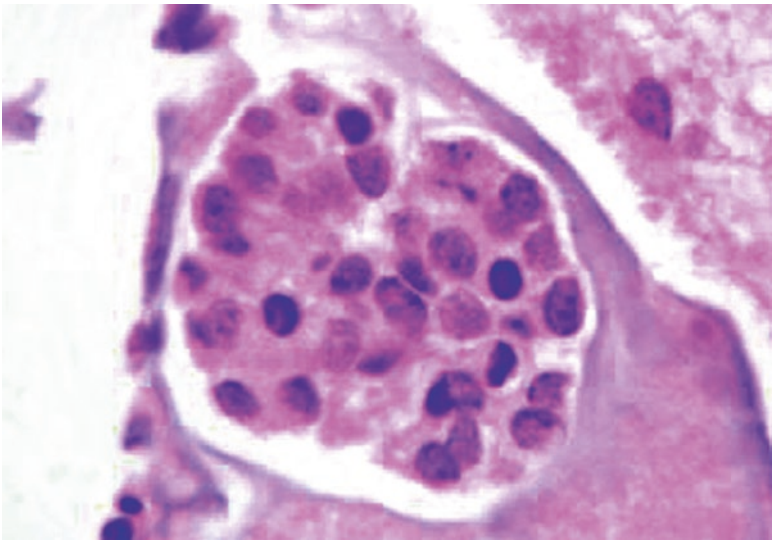

Fig. 10.4 Poorly differentiated thyroid carcinoma. This cell block demonstrates the arrangement of cells in insular groups (cell block, H&E stain).

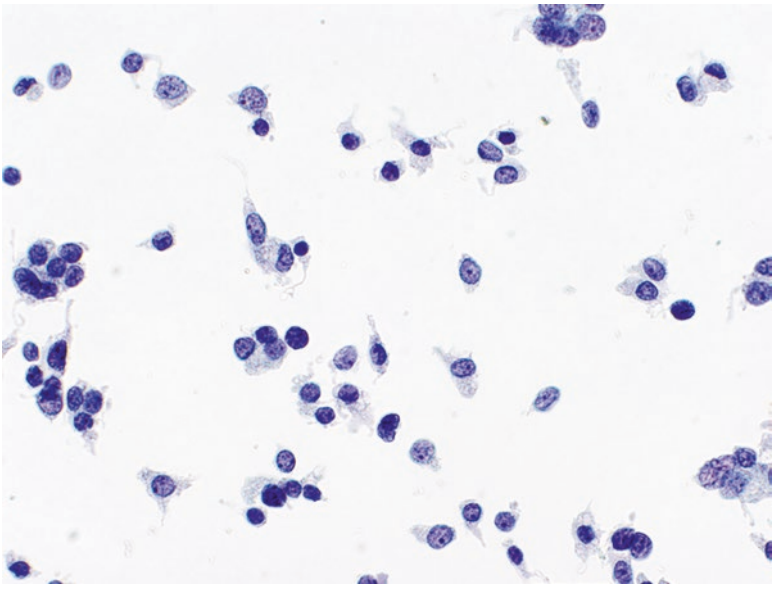

Fig. 10.5 Poorly differentiated thyroid carcinoma. In some cases, the malignant cells are arranged predominantly as isolated cells. They can have a plasmacytoid cytomorphology, as seen here (ThinPrep, Papanicolaou stain).

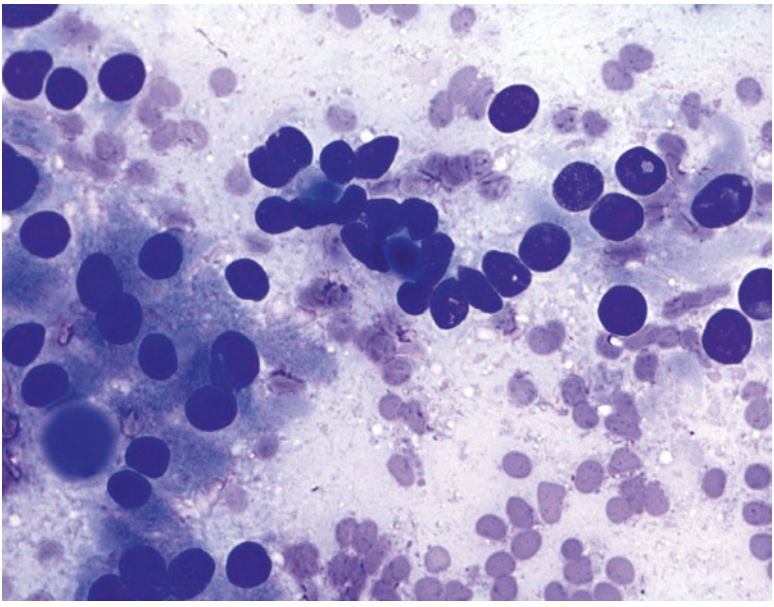

Fig. 10.6 Poorly differentiated thyroid carcinoma. In some cases, the cells have oncocytic cytoplasm. Some bare nuclei are also present (smear, Diff-Quik stain).

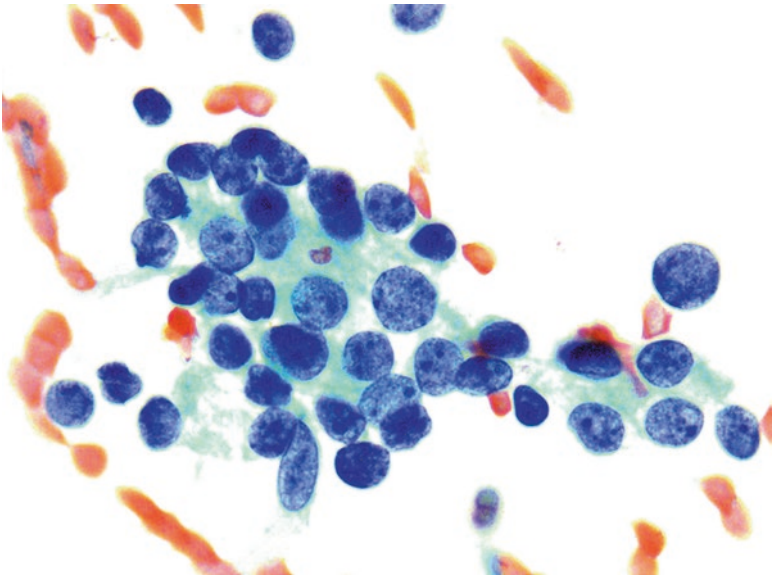

Fig. 10.7 Poorly differentiated thyroid carcinoma. Some tumors demonstrate only mild nuclear atypia, with small nucleoli and delicate chromatin (smear, Papanicolaou stain).

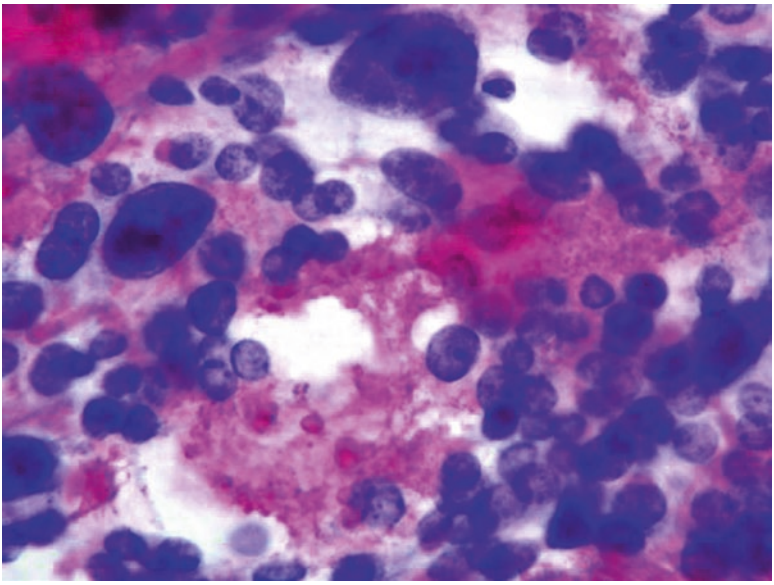

Fig. 10.8 Poorly differentiated thyroid carcinoma. Some aspirates exhibit marked nuclear atypia. In this example, there is impressive anisokaryosis (smear, Papanicolaou stain).

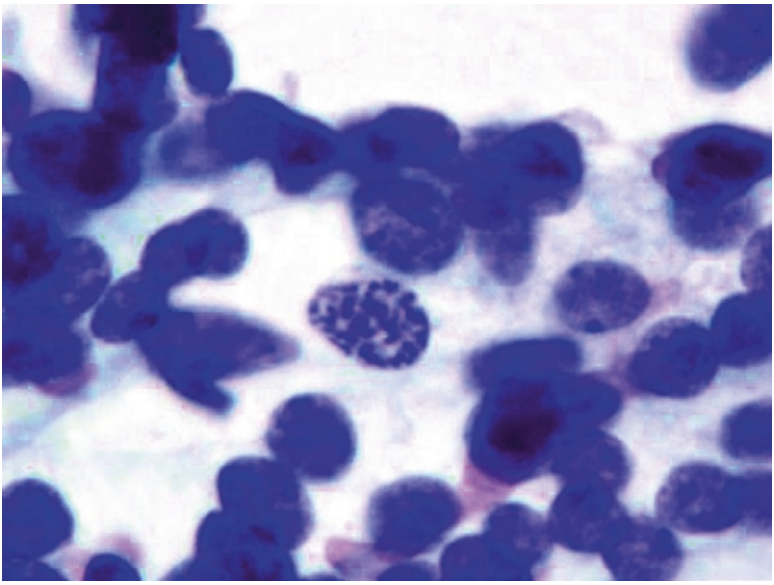

Fig. 10.9 Poorly differentiated thyroid carcinoma. Aspirates of poorly differentiated carcinomas often contain mitotically active cells (smear, Papanicolaou stain).

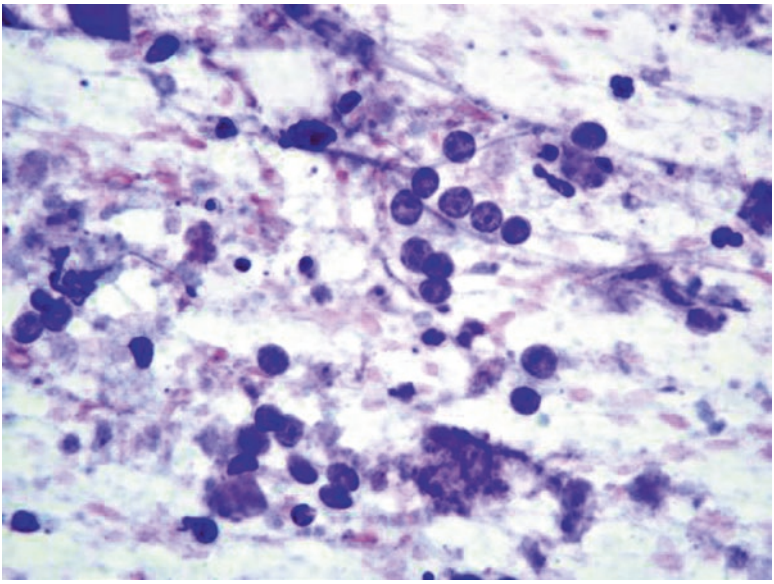

Fig. 10.10 Poorly differentiated thyroid carcinoma. Necrotic debris (cytoplasmic and nuclear fragments) is seen in some poorly differentiated carcinomas (smear, Papanicolaou stain).

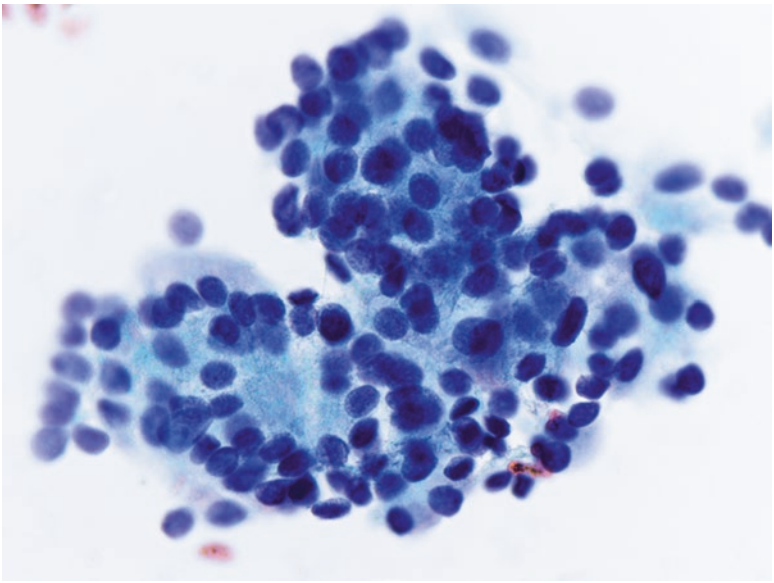

Fig. 10.11 Poorly differentiated thyroid carcinoma. The presence of microfollicles does not preclude the possibility of a poorly differentiated thyroid carcinoma (smear, Papanicolaou stain).

low magnification owing to their high N/C ratio and round nuclei, but at higher magnification variable degrees of atypia can be found along with abrupt nucleomegaly. Numerous isolated cells alternate with large solid fragments of mitotically active and apoptotic cells. The proportion of isolated cells versus fragments varies from case to case. Necrosis is often seen. The tumor cells are positive for keratins, thyroglobulin, thyroid transcription factor (TTF)-1, and PAX8 [20].

The insular form of PDTC is identified histologically by its characteristic arrangement of cells in insulae with peripheral endothelial wrapping and peripheral alignment of nuclei. A similar pattern can be recognized in a subset of PDTC aspirates. Depending upon whether a well-differentiated component is also present, aspirates of PDTC can exhibit microfollicles (Fig. 10.11), nuclear grooves, and pseudoinclusions (Fig. 10.12). In the majority of cases, PDTCs are diagnosed cytologically as "suspicious for a follicular neoplasm." In two large series of PDTCs sampled by FNA, around 35% of cases were prospectively recognized as "poorly differentiated carcinoma" by FNA [17, 19]. The other cases were diagnosed mostly as "suspicious for a follicular neoplasm" or as "carcinoma," either papillary carcinoma, follicular variant of papillary carcinoma, or not otherwise specified. Using logistic regression analysis, the features most predictive of PDTC were its characteristic cytoarchitecture (neither macrofollicular nor microfollicular), severe crowding, high N/C ratio, and isolated cells [19].

According to the authors of the WHO volume on *Pathology and Genetics of Tumours of Endocrine Organs*, "a definitive diagnosis of poorly differentiated carcinoma can be made only at the histological level" [3]. The combination of

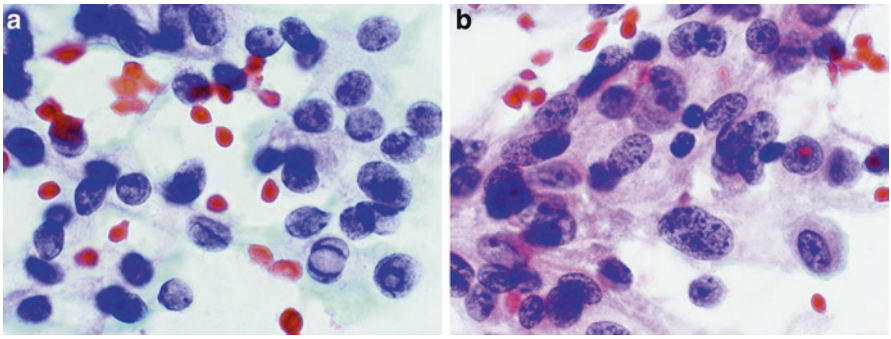

Fig. 10.12 Poorly differentiated thyroid carcinoma. (**a**) In some cases, tumors show features of papillary carcinoma, including nuclear grooves and pseudoinclusions. (**b**) There can be significant nuclear pleomorphism (**a**, **b**, smears, Papanicolaou stain).

cytomorphologic features described above, however, is suggestive of PDTC in FNA specimens. Clinical and ultrasonographic correlation is also helpful: PDTCs are usually large tumors with extrathyroidal extension.

Certain other primary thyroid tumors and metastatic malignancy should be considered in the differential diagnosis. A subset of PDTCs exhibits a predominantly isolated-cell pattern in FNA samples (Fig. 10.13). When this occurs, together with a "salt- and pepper-like" chromatin pattern, the possibility of medullary thyroid carcinoma should be excluded by immunocytochemistry. In contrast to medullary thyroid carcinoma, most PDTCs are strongly immunoreactive for thyroglobulin (Fig. 10.14) and negative for calcitonin and CEA. In addition, PDTCs are rarely immunoreactive for the neuroendocrine markers synaptophysin and chromogranin. TTF-1 is not useful for this distinction because both PDTC and medullary thyroid carcinoma are positive. Based purely on cytomorphology, a PDTC resembles a metastasis from an extrathyroidal primary tumor: both yield cellular specimens with nuclear atypia and necrosis and colloid is scant in both. The positive immunoreactivity of PDTCs for thyroglobulin, TTF-1 and PAX 8 [20] helps to exclude a metastasis. Undifferentiated (anaplastic) thyroid carcinomas are also characterized by unusual cytomorphologic patterns (see Chap. 11) together with necrosis and increased mitotic activity, but PDTCs lack the marked nuclear pleomorphism, high-grade atypia, and sarcomatoid features of undifferentiated carcinomas. The subset of PDTCs with a predominantly isolated-cell pattern and plasmacytoid cytomorphology can suggest a lymphoproliferative disorder, but PDTCs are negative for CD45 and markers of B cells (e.g., CD19, CD20) and plasma cells (e.g., CD138). Recent studies have shown that immunohistochemical expression of p53 is often observed in PDTC [21].

Management

Because of their poor clinical prognosis, PDTCs are usually managed more aggressively than well-differentiated thyroid carcinomas, with consideration of postoperative ^{131}I therapy [22]. For stage T3 PDTCs without distant metastases, as

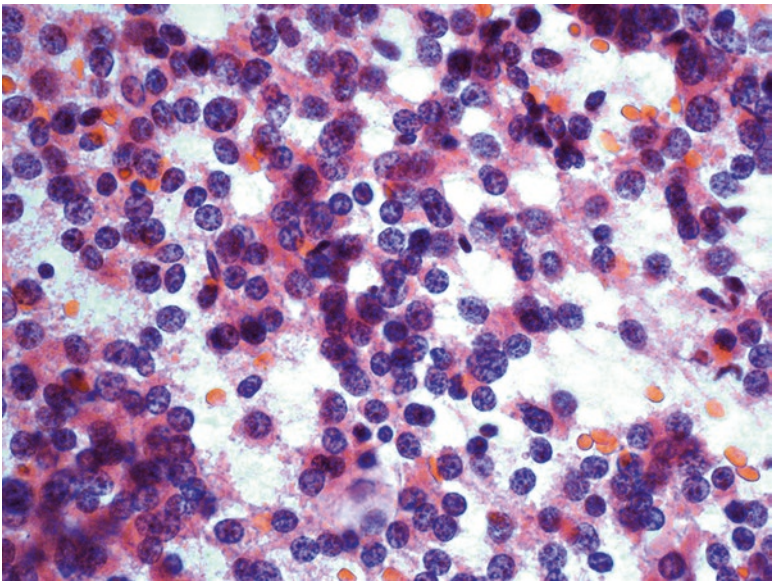

Fig. 10.13 Poorly differentiated thyroid carcinoma. Because some aspirates are comprised predominantly of isolated cells with granular chromatin, they mimic both medullary thyroid carcinoma and metastatic neoplasms (smear, Papanicolaou stain).

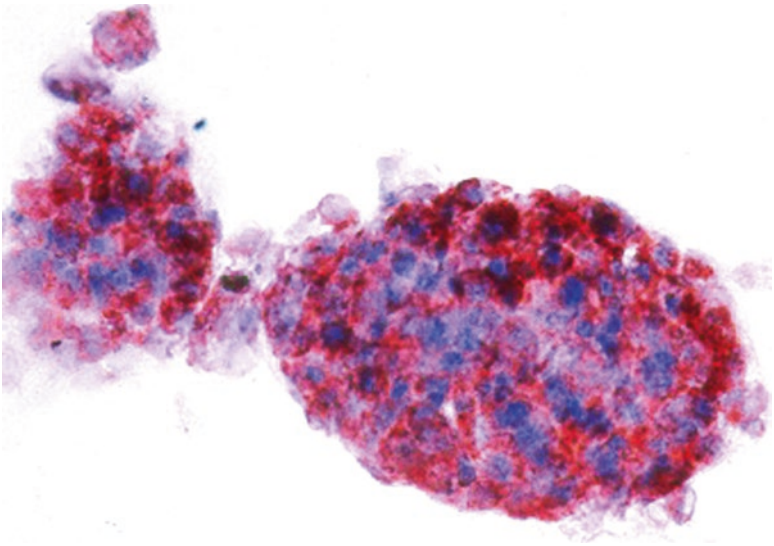

Fig. 10.14 Poorly differentiated thyroid carcinoma. Poorly differentiated thyroid carcinomas are positive for thyroglobulin, which helps to distinguish them from medullary thyroid carcinoma and metastatic tumors (ThinPrep, thyroglobulin immunoperoxidase reaction).

well as all T4 tumors and cases with regional lymph node involvement, patients benefit from external beam radiotherapy in addition to surgery.

Sample Reports

The general category "MALIGNANT" is used whenever the cytomorphologic features are conclusive for malignancy. If an aspirate is interpreted as MALIGNANT, it is implied that the sample is adequate for evaluation. (An explicit statement of adequacy is optional.) Descriptive comments that follow are used to subclassify the malignancy and summarize the results of special studies, if any. If the findings are suspicious but not conclusive for malignancy, the general category "SUSPICIOUS FOR MALIGNANCY" should be used (see Chap. 7). Many PDTCs overlap morphologically with follicular neoplasms and are therefore inevitably interpreted as "SUSPICIOUS FOR A FOLLICULAR NEOPLASM" (or "FOLLICULAR NEOPLASM").

Example 1
MALIGNANT.
Highly cellular aspirate with atypical follicular cells, necrosis, and scant colloid, most consistent with poorly differentiated thyroid carcinoma.

Example 2
MALIGNANT.
Papillary thyroid carcinoma with poorly differentiated features, suggestive of poorly differentiated thyroid carcinoma.

Example 3
SUSPICIOUS FOR A FOLLICULAR NEOPLASM.
Atypical follicular cells with a prominent isolated-cell component, focal necrosis, and mitotic activity.

Note: Immunostains on cell block sections show that the lesional cells are immunoreactive for thyroglobulin and TTF-1 and negative for calcitonin. The findings suggest the possibility of a poorly differentiated thyroid carcinoma.

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Undifferentiated (Anaplastic) Carcinoma and Squamous Cell Carcinoma of the Thyroid

11

Gregg A. Staerkel, Justin A. Bishop, Vinod B. Shidham, and Matthew A. Zarka

Background

Undifferentiated (anaplastic) thyroid carcinoma (UTC), also called "giant- and spindle-cell carcinoma," is an extremely aggressive thyroid malignancy. Accounting for less than 5% of thyroid cancers [1–3], it carries the poorest prognosis of all, significantly worse than well-differentiated and poorly differentiated thyroid carcinomas [4]. Most patients succumb to their disease within 6 months to 1 year of the initial diagnosis, typically as a result of tumor involvement of vital structures within the neck [2, 5]. Characteristic clinical features are associated with UTCs. These tumors are rarely seen in individuals below the age of 50 (<10% of cases) [3, 5, 6]. There is a female predominance (2–4:1) [3–7]. Patients present with a hard, nodular thyroid gland, and most have a rapidly growing mass. Neck enlargement is due to marked tumor growth, with or without reactive fibrosis, which infiltrates into surrounding extrathyroidal soft tissues, e.g., muscle, trachea, esophagus, and adjacent skin, cartilage, and bone [5]. Half of the patients with UTC report significant neck

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compression that can result in dyspnea, dysphagia, hoarseness, and/or pain [2, 5]. One-quarter to one-half of patients present with lymphadenopathy and/or distant metastases, most commonly to the lungs [2, 4, 6]. A history of long-standing goiter [2, 4, 6] and thyroid function tests indicating euthyroidism (despite extensive thyroid gland destruction) [2, 6] are common.

Definition

UTC is a high-grade, pleomorphic, epithelial-derived malignancy with epithelioid and/or spindle-cell features.

Criteria

Aspirates show variable cellularity but are usually moderately to markedly cellular.
Neoplastic cells are arranged as isolated cells and/or in variably sized groups.
Cells are epithelioid (round to polygonal) and/or spindle-shaped and range in size from small- to giant-sized. "Plasmacytoid" and "rhabdoid" cell shapes are seen.
Nuclei show enlargement, irregularity, extreme pleomorphism, clumping of chromatin with parachromatin clearing, prominent irregular nucleoli, intranuclear pseudoinclusions, eccentric nuclear placement, and multinucleation.
Necrosis, extensive inflammation (predominantly neutrophils, "abscess-like"), and/or fibrous connective tissue may be present.
Neutrophilic infiltration of tumor cell cytoplasm can be seen.
Mitotic figures are often numerous and abnormal.
Osteoclast-like giant cells (nonneoplastic) are conspicuous in some cases.
Tumors have the following immunocytochemical and molecular profile:

- Pan-keratins, PAX 8, and vimentin are often positive but can be focal.
- TTF-1 and thyroglobulin are usually negative.
- TP53, CTNNB1 (β-catenin), RAS (i.e., HRAS, KRAS, and NRAS), and BRAF V600E mutations are seen in up to 80%, 70%, 50%, and 30% of cases, respectively.

Explanatory Notes

Cellularity is variable. Some aspirates are sparsely cellular, due in part to the marked fibrosis and hyalinization seen in some tumors [7–9]. When fibrosis predominates, the resulting low cellularity can hamper interpretation (Fig 11.1). In other cases, widespread tumor necrosis yields a sparsely cellular sample with few viable malignant cells [7] (Fig. 11.2). Due to rapid infiltrative tumor growth, aspirations can result in the acquisition of tumor cells admixed with extrathyroidal tissue such as skeletal muscle (Fig. 11.3).

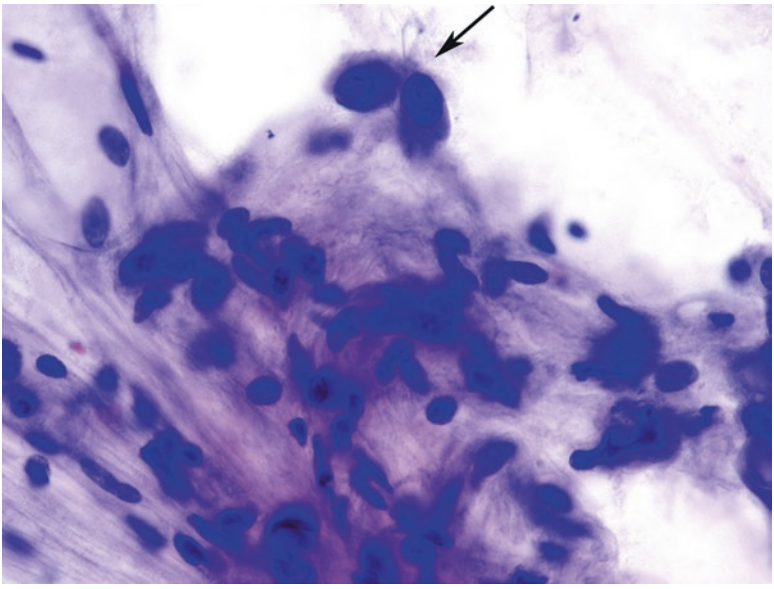

Fig. 11.1 Undifferentiated (anaplastic) thyroid carcinoma. Aspiration of tumors with abundant fibrosis can yield low cellularity. If cells lack marked nuclear atypia (*arrow*), rendering a definitive diagnosis can be difficult. Clinical correlation is important (smear, Papanicolaou stain).

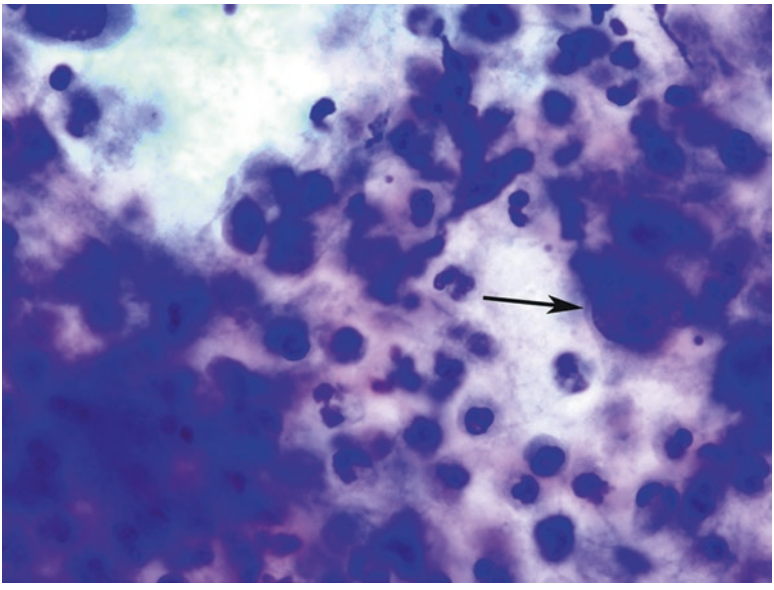

Fig. 11.2 Undifferentiated (anaplastic) thyroid carcinoma. Widespread tumor necrosis and associated inflammation can hinder diagnosis because well-preserved malignant cells are few and far between (*arrow*) (smear, Papanicolaou stain).

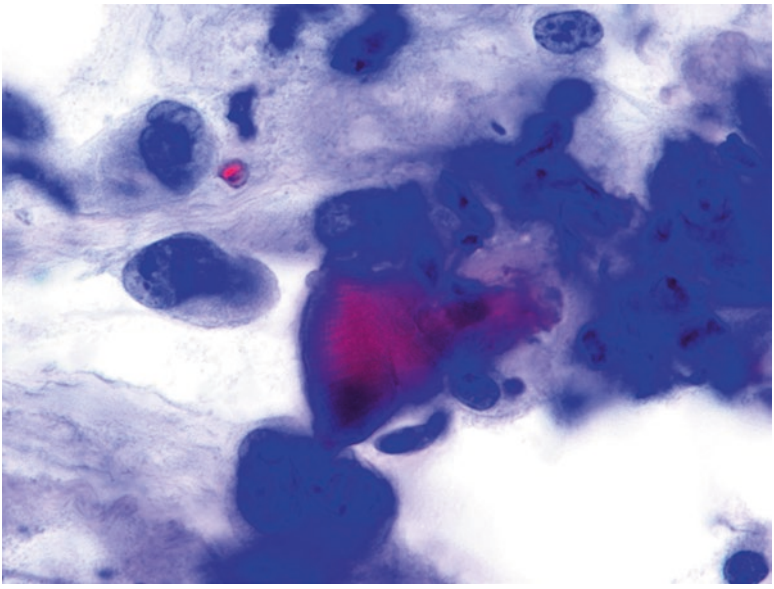

Fig. 11.3 Undifferentiated (anaplastic) thyroid carcinoma. Rapid tumor growth and invasion of extrathyroidal tissues is common. Aspiration samples can contain skeletal muscle fragments (*center*) as well as anaplastic tumor cells (smear, Papanicolaou stain).

Isolated cells and small- to medium-sized cell groups can be found in most cases (Figs. 11.4, 11.5, 11.6, and 11.7). In spindle-cell predominant UTCs, larger tumor tissue fragments can reveal a storiform-like pattern [6] (Fig. 11.8). Follicles, papillae, and trabecular/nested cell groups are not features of UTC.

Small to gigantic malignant cells may be epithelioid (round to polygonal) or spindle-shaped [7, 10, 11] (Figs. 11.4, 11.5, 11.6, and 11.7). A given tumor often displays a mixture of cell shapes and sizes (Figs. 11.4 and 11.9). Nuclear pleomorphism can be striking, with giant, bizarre, hyperchromatic forms [7, 10, 11] (Figs. 11.10 and 11.11). Nuclei may be variably positioned within the cells, but can be uniformly eccentric, resulting in a plasmacytoid morphology [7] (Fig. 11.12). Intranuclear cytoplasmic pseudoinclusions (Fig. 11.13), prominent nucleoli (Fig. 11.14), coarse chromatin (Fig. 11.6), and parachromatin clearing (Fig. 11.14) may be identified [7, 10, 11]. Neutrophilic infiltration of tumor cells (Fig. 11.15), osteoclast-like giant cells (Fig. 11.16), necrosis, fibrotic tissue fragments, and mitotic figures (Fig. 11.5) may be present in variable proportions [7–11].

Some UTCs have a focus of coexisting well-differentiated and/or poorly differentiated thyroid carcinoma, most often papillary thyroid carcinoma [5, 6, 9–11], but sometimes follicular carcinoma [5, 6, 12], Hürthle cell carcinoma [5, 6], insular carcinoma [4, 10] and other types of poorly differentiated carcinomas, or medullary thyroid carcinoma. Consequently, on occasion several components are observed in an aspirate. Hence, thorough sampling and attention to the possibility of multiple components are imperative so that the identification of the most significant

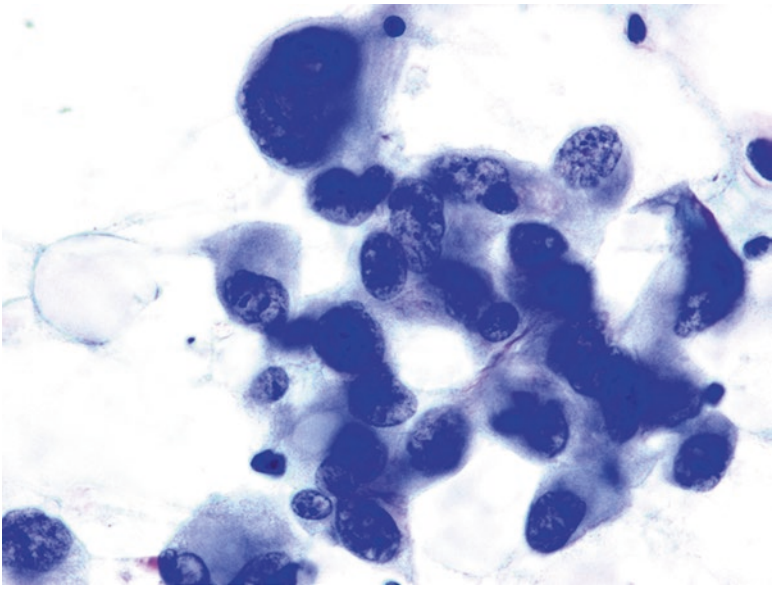

Fig. 11.4 Undifferentiated (anaplastic) thyroid carcinoma. Cells are epithelioid (polygonal) in appearance. Variation in cell and nuclear size is evident. Parachromatin clearing and nuclear contour irregularity are prominent (smear, Papanicolaou stain).

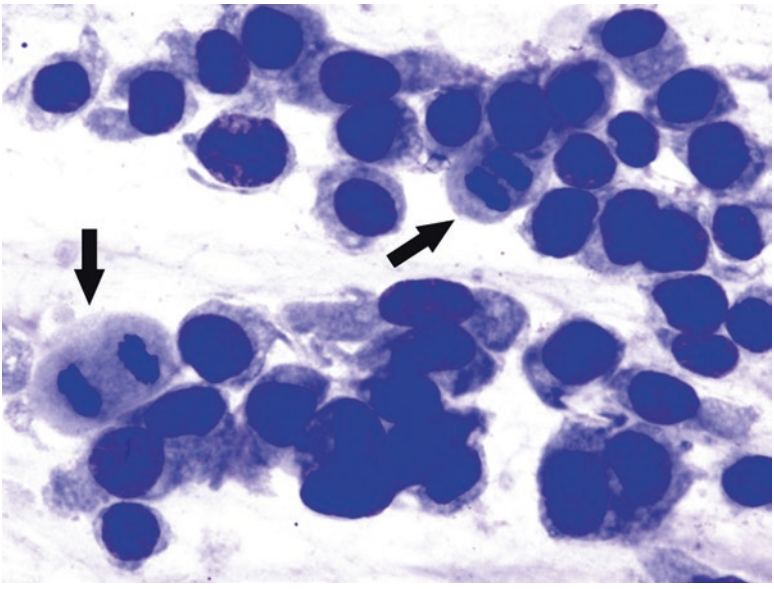

Fig. 11.5 Undifferentiated (anaplastic) thyroid carcinoma. The neoplastic cells are mostly round, with scant to moderate cytoplasm. There is less pleomorphism of nuclear size and shape than in most cases of UTC, but mitotic figures (*arrows*) are easily found (smear, Diff-Quik stain).

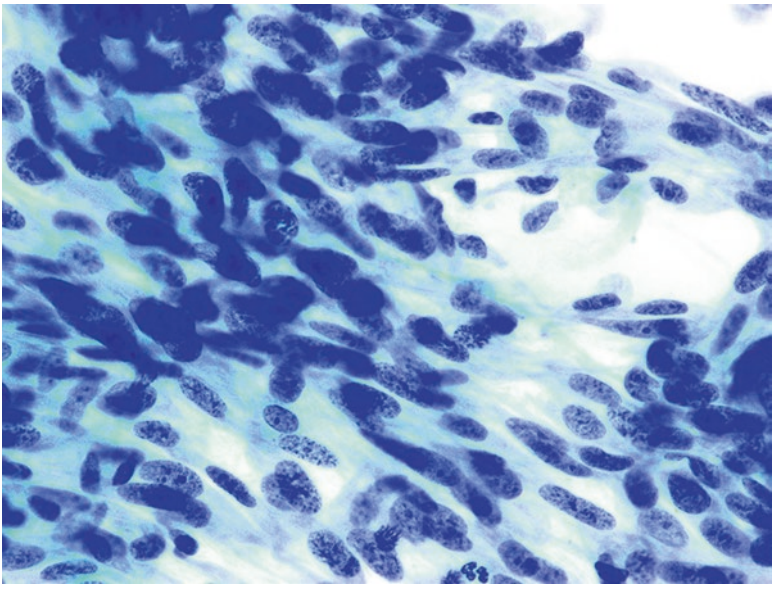

Fig. 11.6 Undifferentiated (anaplastic) thyroid carcinoma. All neoplastic cells are strikingly spindle-shaped, resembling the cells of a sarcoma. Although chromatin is coarse, parachromatin clearing, prominent nucleoli, and nuclear irregularity are not apparent (smear, Papanicolaou stain).

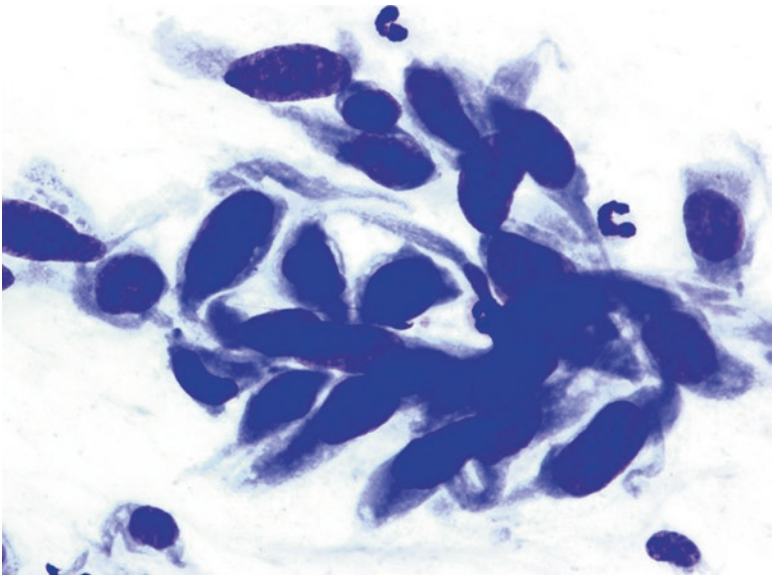

Fig. 11.7 Undifferentiated (anaplastic) thyroid carcinoma. Tumor cells are notably spindle-shaped, with long, tapering cytoplasmic processes (smear, Diff-Quik stain).

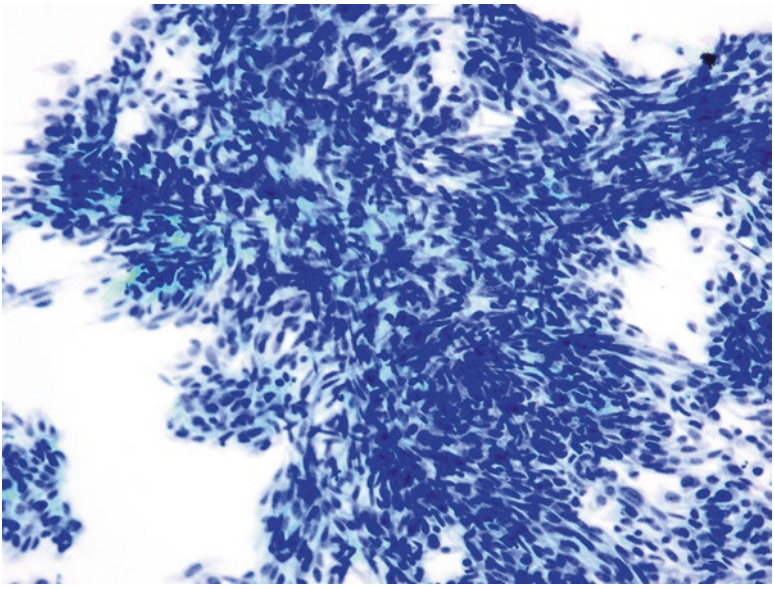

Fig. 11.8 Undifferentiated (anaplastic) thyroid carcinoma. Tumors with a predominantly spindle-cell morphology can appear as microbiopsy fragments. A storiform pattern can be appreciated (smear, Papanicolaou stain).

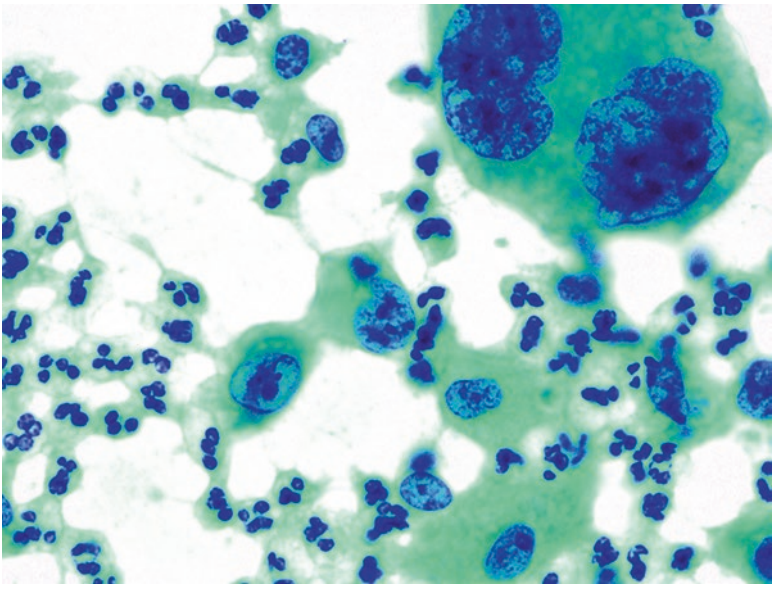

Fig. 11.9 Undifferentiated (anaplastic) thyroid carcinoma. These tumors can be associated with abundant inflammatory cells, typically neutrophils. A multinucleated tumor giant cell with bizarre nuclear features and smaller, isolated, less anaplastic malignant cells are readily identifiable (smear, Papanicolaou stain).

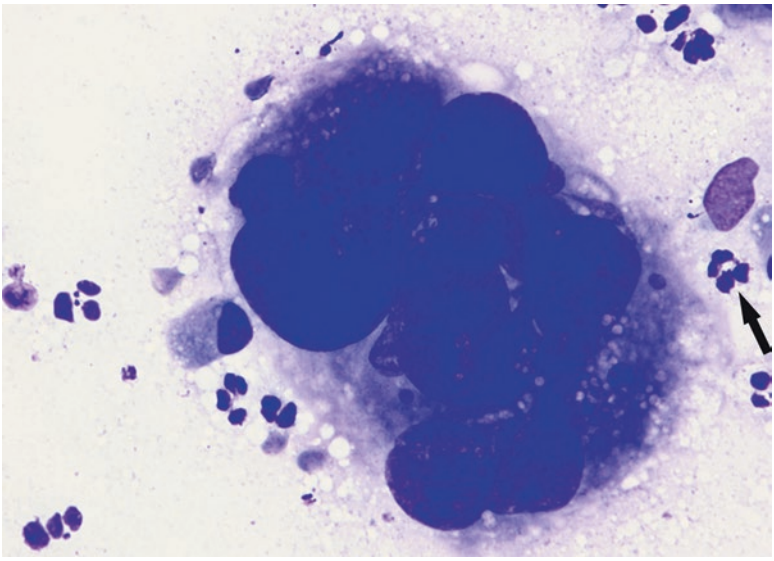

Fig. 11.10 Undifferentiated (anaplastic) thyroid carcinoma. Bizarre multinucleated tumor giant cells are found in some aspirations. The size of this tumor giant cell can be fully appreciated when compared to the adjacent neutrophils (*arrow*) (smear, Diff-Quik stain).

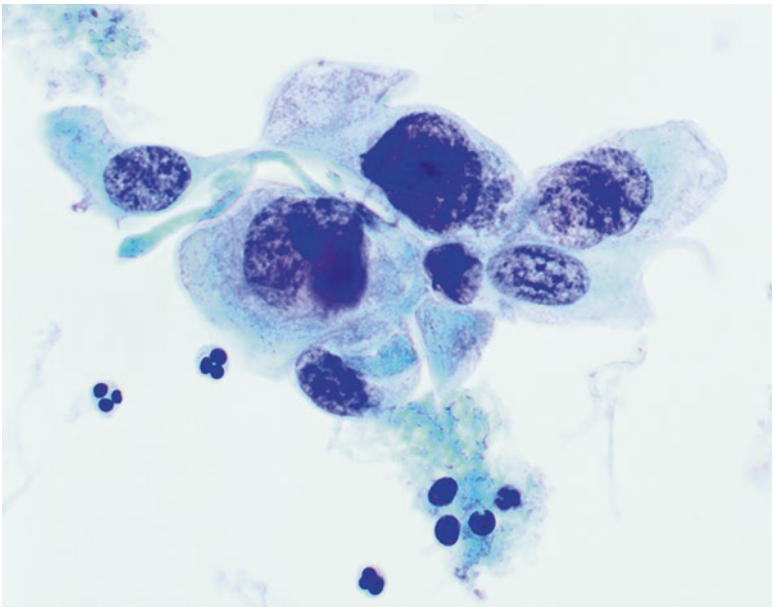

Fig. 11.11 Undifferentiated (anaplastic) thyroid carcinoma. Variably pleomorphic tumor giant cells with coarse chromatin are seen in a loosely cohesive cell group (ThinPrep, Papanicolaou stain).

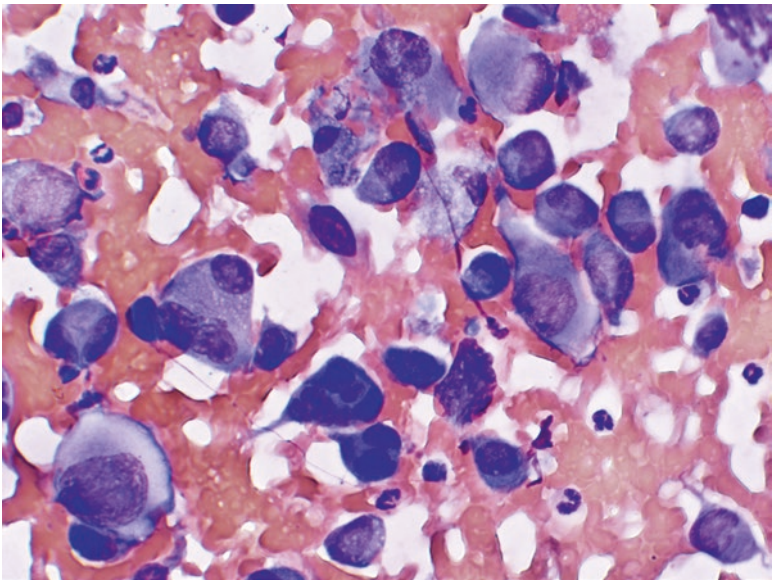

Fig. 11.12 Undifferentiated (anaplastic) thyroid carcinoma. In some cases, the epithelioid tumor cells have a conspicuously plasmacytoid appearance (smear, Diff-Quik stain).

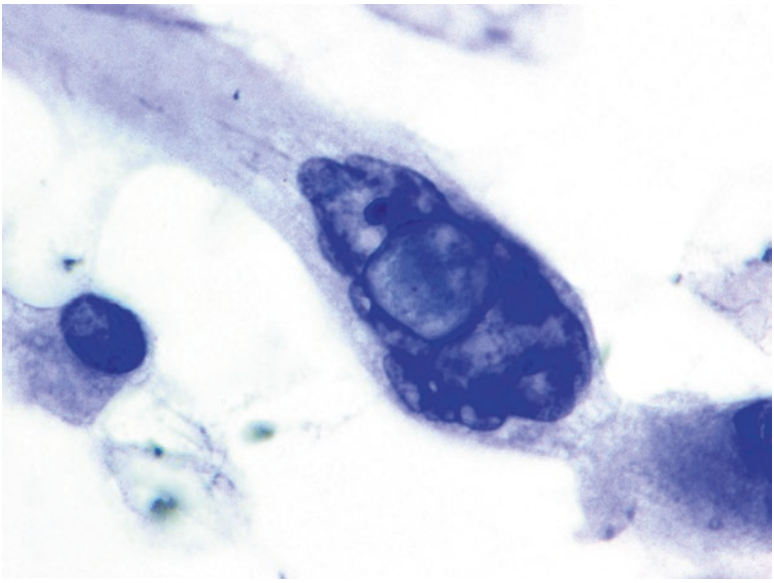

Fig. 11.13 Undifferentiated (anaplastic) thyroid carcinoma. A giant spindle-shaped tumor cell has a massive intranuclear cytoplasmic pseudoinclusion. Other nuclear features include enlargement, contour irregularity, and a prominent nucleolus (smear, Papanicolaou stain).

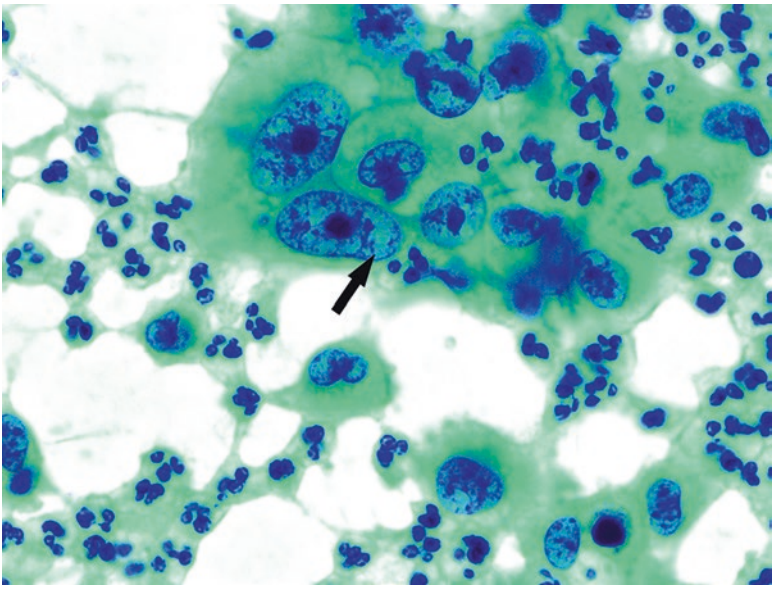

Fig. 11.14 Undifferentiated (anaplastic) thyroid carcinoma. Epithelioid tumor cells display size variation, mononucleated and binucleated forms, macronucleoli, and clumped chromatin with parachromatin clearing (*arrow*). Acute inflammatory cells are present in the background (smear, Papanicolaou stain).

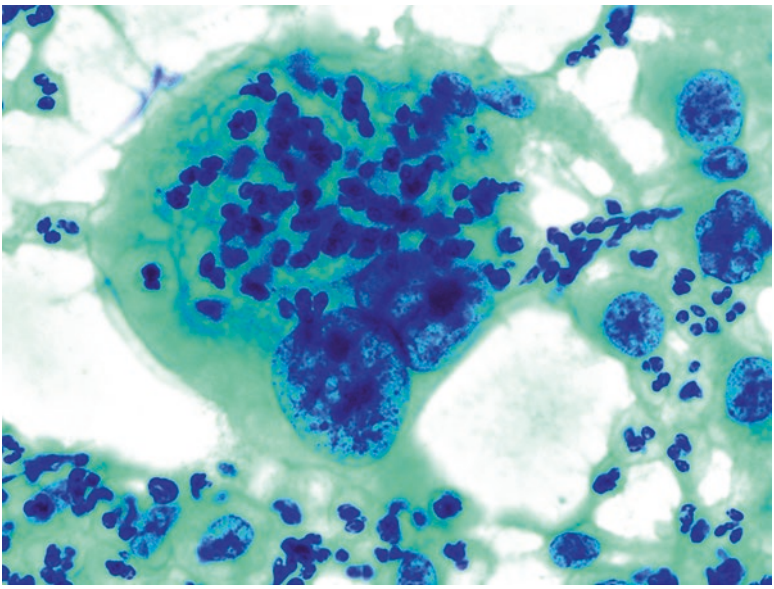

Fig. 11.15 Undifferentiated (anaplastic) thyroid carcinoma. There is conspicuous infiltration of a multinucleated tumor giant cell by neutrophils (smear, Papanicolaou stain).

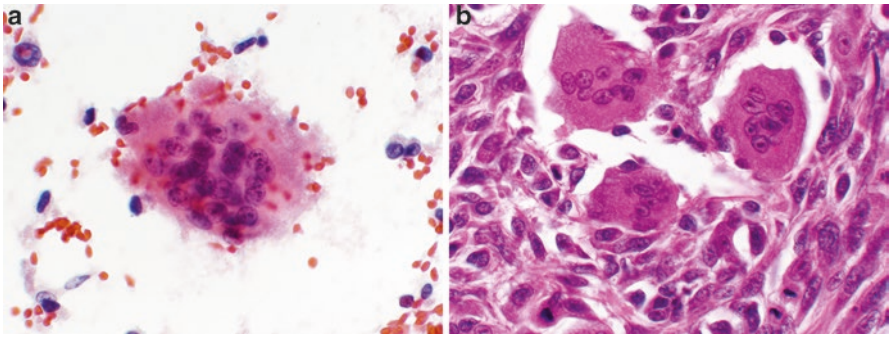

Fig. 11.16 Undifferentiated (anaplastic) thyroid carcinoma. (**a**) Some UTCs contain numerous nonneoplastic, osteoclast-like giant cells (smear, Papanicolaou stain). (**b**) The osteoclast-like giant cells are scattered among the malignant cells (thyroidectomy, hematoxylin and eosin stain).

(i.e., least differentiated) cellular pattern is made. The frequent coexistence of a nidus of well-differentiated thyroid cancers within a UTC suggests that UTC represents dedifferentiation of a well-differentiated thyroid cancer through a multistep process of carcinogenesis [2, 12]. This is supported by the occasional observation of UTC in metastatic foci from patients whose primary thyroid carcinomas were well differentiated [5, 12].

The most reliable immunostains yielding a positive result in UTCs are as follows: pan-keratins, with rates of expression ranging from 50% to 100% of cases [6, 13]; PAX8 (the most specific immunostain indicative of UTC's thyroid gland origin), seen in 76–79% of cases [14–16] (Fig. 11.17); and vimentin, present in 50–100% of cases, especially in the spindle-cell tumor component [6, 14]. Because thyroglobulin and TTF-1 are usually negative [6, 13] and PAX8 is negative in a quarter of cases, challenges occur with sparsely cellular samples or aspirates of spindle-cell tumors that are negative for keratins. In these cases, an erroneous diagnosis of sarcoma might be entertained, but primary sarcomas of the thyroid are rare. Therefore, determining that the tumor is centered in the thyroid gland based on imaging findings can help resolve this concern. Other entities in the differential diagnosis of UTC include insular thyroid carcinoma, medullary thyroid carcinoma, lymphoma, and a metastasis. Compared to UTC, insular carcinoma has a lesser degree of nuclear atypia (lacking prominent nucleoli), a strikingly monotonous appearance with a trabecular/nested architecture, and lacks spindle-shaped cells and osteoclast-like giant cells. Medullary thyroid carcinoma, overall, is usually less pleomorphic than UTC, has finely stippled chromatin, and usually contains amyloid. Osteoclast-like giant cells and necrosis are absent in medullary carcinoma. If doubt remains after morphologic assessment, immmunochemistry can be helpful, inasmuch as medullary carcinomas are reactive for calcitonin and chromogranin, and UTCs are negative. The most difficult mimic to exclude is often a metastasis (e.g., melanoma, sarcomatoid renal cell carcinoma, squamous cell or large cell

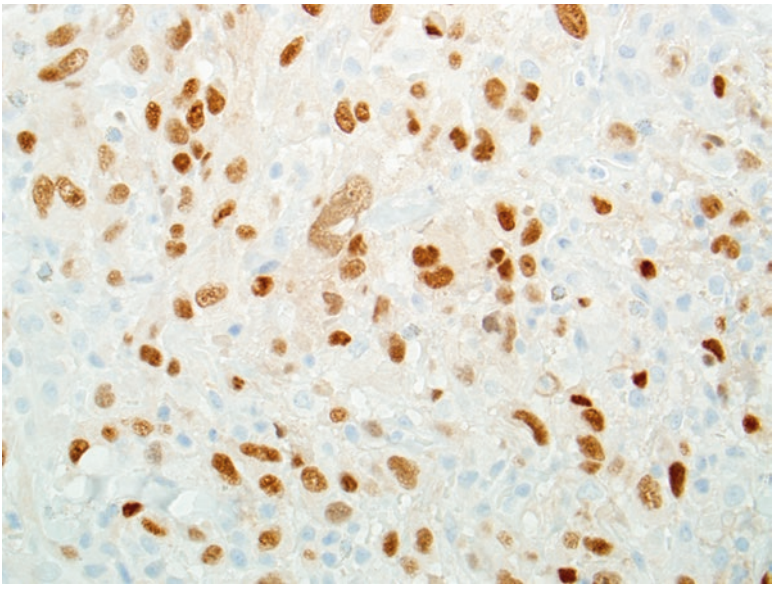

Fig. 11.17 Undifferentiated (anaplastic) thyroid carcinoma. PAX8, one of the most useful immunomarkers in this setting, displays crisp nuclear positivity (cell block, PAX8 immunostain).

carcinoma of the lung). Ruling out a thyroid metastasis requires knowledge of the patient's prior cancer history, clinical correlation (e.g., the size and the anatomic distribution of other extrathyroidal tumor masses), and selective immunostaining.

In paucicellular aspirates due to necrosis and/or fibrosis, an underappreciation of rare malignant cells can lead to a misdiagnosis of a reactive process (e.g., Riedel thyroiditis) [8].

Molecular alterations that are seen with some frequency include the early thyroid carcinogenesis mutations of RAS and BRAF (up to 50% and 30% of cases, respectively) and the late carcinogenesis mutations of TP53 and CTNNB1 (β-catenin) which lead to progressive loss in thyroid differentiation (up to 80% and 70% of cases, respectively) [14, 17].

Management

The overall survival of patients with UTC has not changed significantly in over 20 years. One-fifth of patients require tracheostomy due to airway obstruction during the course of their disease [18].

Complete surgical resection, with or without preoperative hyperfractionated radiotherapy and/or chemotherapy to enhance resectability through tumor shrinkage, is the optimal treatment strategy [1, 18]. Suppression with radioactive iodine is

largely ineffective for the treatment of UTC [1, 5, 18]. In cases where potential cure cannot be achieved, reducing the tumor burden through surgery facilitates the efficacy of postoperative radiation and/or chemotherapy [18]. In patients fit enough to tolerate these regimens, length of survival is improved [6, 18]. Not surprisingly, younger patients (<45 years old) and individuals with smaller tumors without extensive extrathyroidal extension or metastases have the best outcome [3, 5, 6]. The advent of novel therapies such as molecular targeted treatments holds promise; to date, they are largely directed at the BRAF mutation [19]. Other mutation targets are found in much lower frequencies than BRAF, which in turn suggests a more limited potential role for other targeted therapies. One patient with such a mutation in the mTOR pathway showed a dramatic 18 month response to the mTOR inhibitor Everolimus until resistance developed [20].

Squamous Cell Carcinoma of the Thyroid

Squamous cell carcinoma (SQC) of the thyroid accounts for less than 1% of thyroid cancers. Like UTC, it occurs in the elderly and has a similar (dismal) prognosis.

Definition

Squamous cell carcinoma of the thyroid is a malignant tumor that shows exclusively squamous differentiation.

Criteria

Cytologic samples are composed almost exclusively of large, pleomorphic keratinized cells.
Necrosis may be present.

Explanatory Notes and Management

Most squamous cell carcinomas of the thyroid are poorly differentiated. The differential diagnosis includes UTC and metastatic SQC. Primary squamous cell carcinomas of the thyroid are morphologically and immunochemically indistinguishable from squamous cell carcinomas of other organs (Fig. 11.18). For this reason, correlation with clinical and imaging findings is essential for excluding a metastasis. The behavior of squamous cell carcinomas of the thyroid is similar to that of UTC, as is the clinical management. In fact, given that squamous cell carcinoma sometimes coexists with UTC and is frequently PAX8 positive, it may simply represent a form of UTC.

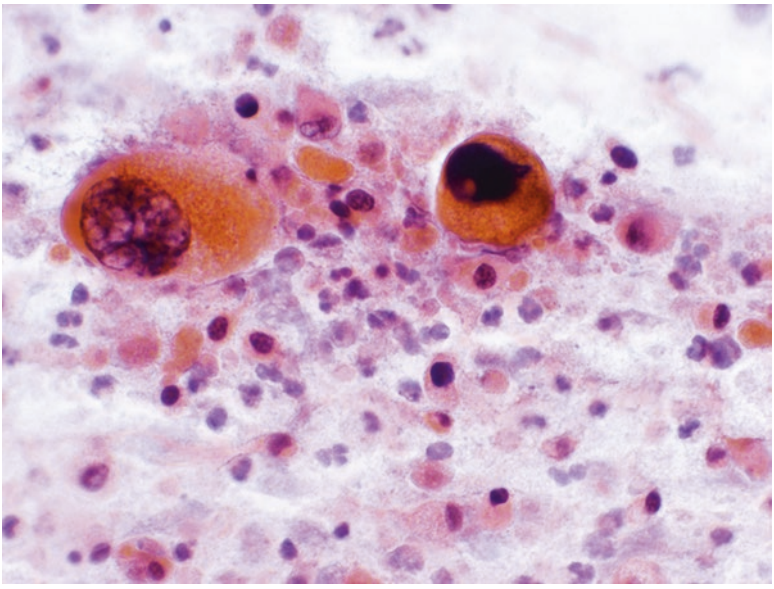

Fig. 11.18 Squamous cell carcinoma of the thyroid. The sample is composed of large pleomorphic cells with conspicuous dense orangeophilia of the cytoplasm. There is abundant necrosis, and nuclei show degenerative changes (i.e., dark, smudged, and/or marginated chromatin) (smear, Papanicolaou stain).

Sample Reports

The general category "MALIGNANT" is used whenever the cytomorphologic features are conclusive for malignancy. If an aspirate is interpreted as malignant, it is implied that the sample is adequate for evaluation. An explicit statement of adequacy is optional. Descriptive comments that follow are used to subclassify the malignancy and summarize the results of special studies, if any. If the findings are suspicious but not conclusive for malignancy, the general category "SUSPICIOUS FOR MALIGNANCY" should be used (see Chap. 7).

Example 1
MALIGNANT.
Undifferentiated (anaplastic) thyroid carcinoma.

Note: Immunocytochemistry shows that the malignant cells are focally immunoreactive for pan-cytokeratins AE1/3 and PAX8 and negative for thyroglobulin and TTF-1.

Example 2
MALIGNANT.
High-grade carcinoma, consistent with undifferentiated (anaplastic) thyroid carcinoma.

Note: Immunocytochemistry shows that the malignant cells are focally immunoreactive for cytokeratins AE1/3, PAX8, and vimentin and negative for thyroglobulin, TTF-1, HMB-45, and S-100 protein. The prior clinical history of malignant melanoma is noted.

Example 3
MALIGNANT.
Consistent with squamous cell carcinoma of the thyroid.

Note: The distinction between a primary squamous cell carcinoma of the thyroid and a metastasis to the thyroid from a primary elsewhere is not possible by cytomorphology or immunochemistry. Correlation with clinical and imaging findings is advised.

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Metastatic Tumors, Lymphomas, and Rare Tumors of the Thyroid

12

Lester J. Layfield and Kennichi Kakudo

Background

Metastases from distant organs and direct extension from tumors in adjacent organs are uncommon but important to recognize in fine needle aspiration (FNA) samples of thyroid nodules. In rare cases, a metastasis to the thyroid can even be the initial presentation of a distant malignancy. Tumors of nearby structures that can involve the thyroid include those of the pharynx, larynx, esophagus, mediastinum, and regional lymph nodes [1]. The most common tumors that present clinically as metastases to the thyroid are cancers of the lung, breast, skin (especially melanoma), colon, and kidney [2–6]. The frequency varies in surgical vs. autopsy series (2.7–4.0%). Metastases, including micrometastases, are found in up to 10% of cancer autopsies [2]. Metastatic carcinomas characteristically present in one of three patterns: (1) multiple small discrete nodules less than 2 mm in diameter, (2) solitary large nodules, and (3) diffuse involvement. When small nodules are present, FNA samples reveal neoplastic cells admixed with indigenous follicular epithelial cells. With routine and special stains, distinction from a primary neoplasm of the thyroid is often achievable, but, to assist with this, clinicians are expected to provide the history of any malignancy on the requisition form [7].

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Malignant lymphomas occur as primary malignancies of the thyroid, but they can also involve the thyroid gland secondarily as a manifestation of systemic disease [8]. Most primary thyroid lymphomas are of B-cell lineage [8]. Lymphomas represent approximately 5% of thyroid neoplasms, usually associated with Hashimoto thyroiditis [8]. As primary tumors of the thyroid, plasma cell neoplasms, Hodgkin lymphoma, and Langerhans cell histiocytosis are rare but do occur.

Metastatic Renal Cell Carcinoma

Criteria

Samples show moderate to high cellularity.
Cells are dispersed individually and in small clusters, fragmented papillae, or sheets.
Cells have abundant pale, finely granular, clear, or vacuolated cytoplasm.
Nuclei are round to oval, often with large nucleoli.
Samples are frequently bloody.

Explanatory Notes

A majority of the metastatic renal cell carcinomas (RCCs) to the thyroid are of the clear cell type and present as either solitary or multiple nodules [9, 10], occurring as many as 20 years after the resection of the primary neoplasm [10].

Metastatic RCC displays moderately to highly cellular, often bloody, preparations [11]. Cells appear singly and in cohesive clusters, fragmented papillae, and sheets (Fig. 12.1). The individual cells have abundant pale, finely vacuolated cytoplasm with Romanowsky-stained preparations and abundant clear or finely granular cytoplasm with the Papanicolaou stain (Fig. 12.2). The nuclear/cytoplasmic ratio is low. The nuclei are round or oval and vary in size and shape. The nuclear chromatin is finely granular. The prominence of the nucleoli is directly proportional to the grade of the RCC. Intranuclear cytoplasmic pseudoinclusions are found in a minority of metastatic RCCs. With air-dried, Romanowsky-stained smears, strands of pink, hyaline, or fibrillary stroma with attached fusiform cells are characteristic of high-grade RCCs.

The distinction between clear cell RCC and follicular and Hürthle cell neoplasms can be difficult, particularly if the RCC is occult or if the history of RCC is not provided [12]. Immunostaining for thyroid markers (e.g., thyroglobulin, thyroid transcription factor-1 (TTF-1), and calcitonin) and RCC markers (e.g., RCC antigen, CD10) can aid in the differential diagnosis.

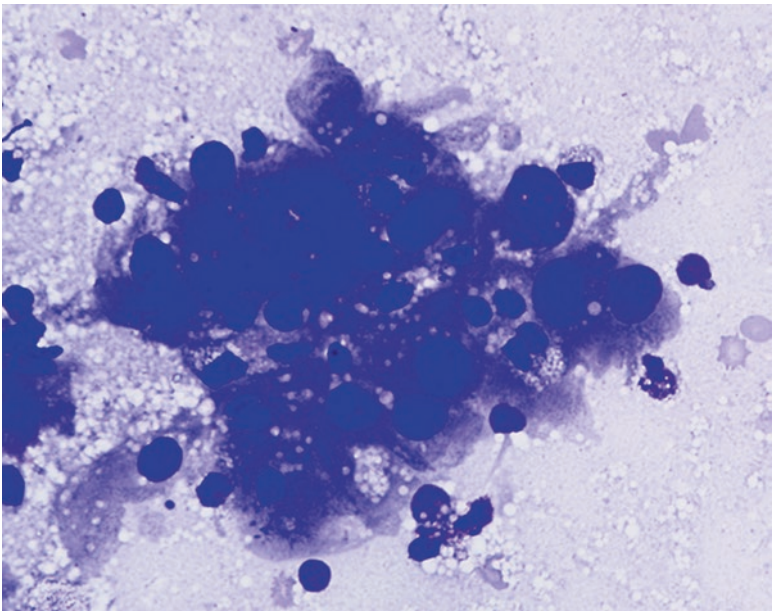

Fig. 12.1 Metastatic renal cell carcinoma, clear cell type. The malignant cells have finely vacuolated cytoplasm (smear, Diff-Quik stain).

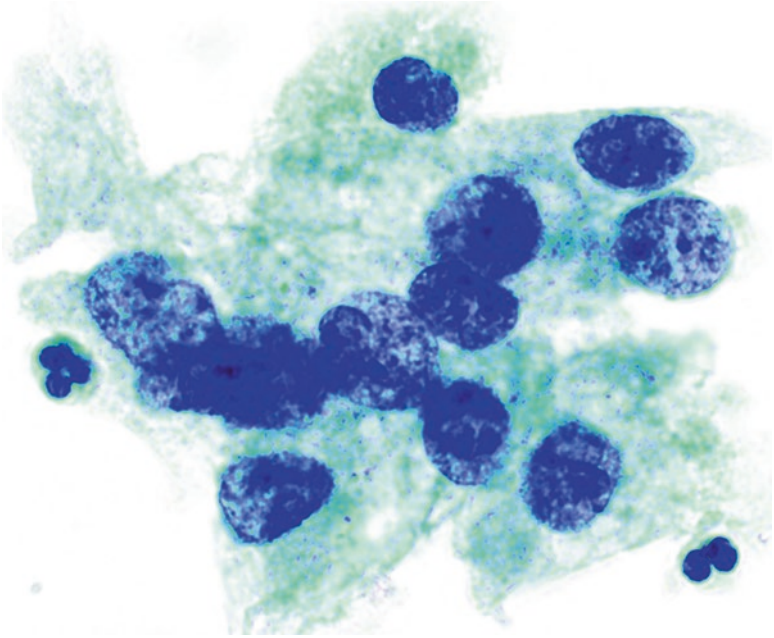

Fig. 12.2 Metastatic renal carcinoma, clear cell type. Cells in a small cluster have abundant finely granular cytoplasm. Note the adjacent neutrophils for size comparison (ThinPrep, Papanicolaou stain).

Metastatic Malignant Melanoma

Criteria

Aspirates are moderately or markedly cellular.
Most cells are noncohesive.
Cells are variable in size and shape and include plasmacytoid, spindle-shaped, and anaplastic forms.
Nuclei are large and often eccentrically placed.
Intranuclear cytoplasmic pseudoinclusions can be present.
Intracytoplasmic pigment is not common but can be seen as fine granules in neoplastic cells or coarse granules in histiocytes.
Cells are usually immunoreactive for S-100 protein, melanA, SOX-10, and HMB45.

Explanatory Notes

Aspirates from metastatic melanoma are characterized by many dispersed cells, with marked variability in size; oval, plasmacytoid, fusiform, and anaplastic forms are typical (Fig. 12.3) [13]. Eccentrically positioned nuclei are usually round or ovoid and vary in size and number. The cells typically have well-defined cytoplasm. Intranuclear cytoplasmic pseudoinclusions are seen. Intracytoplasmic pigment is

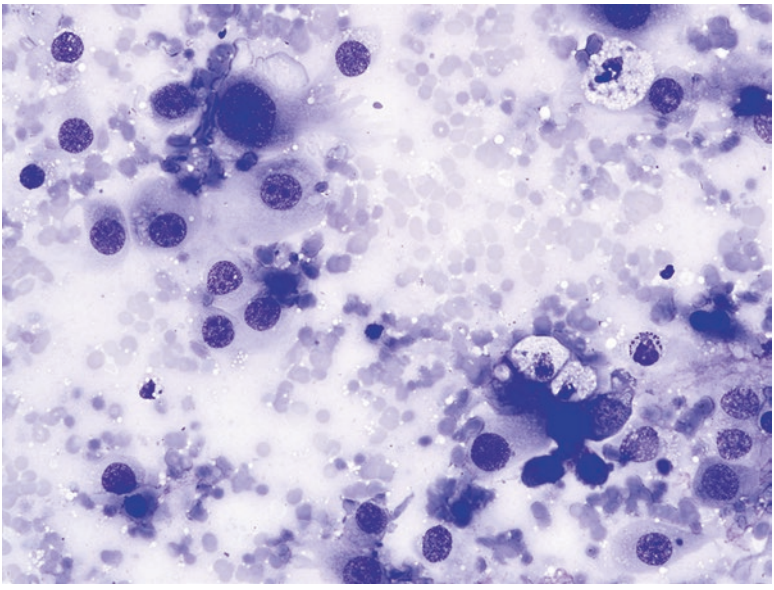

Fig. 12.3 Metastatic melanoma. The malignant cells are isolated and loosely aggregated. They are large, oval, and plasmacytoid cells with abundant granular cytoplasm, hyperchromatic nuclei, and prominent nucleoli. Foamy histiocytes are present (smear, Diff-Quik stain).

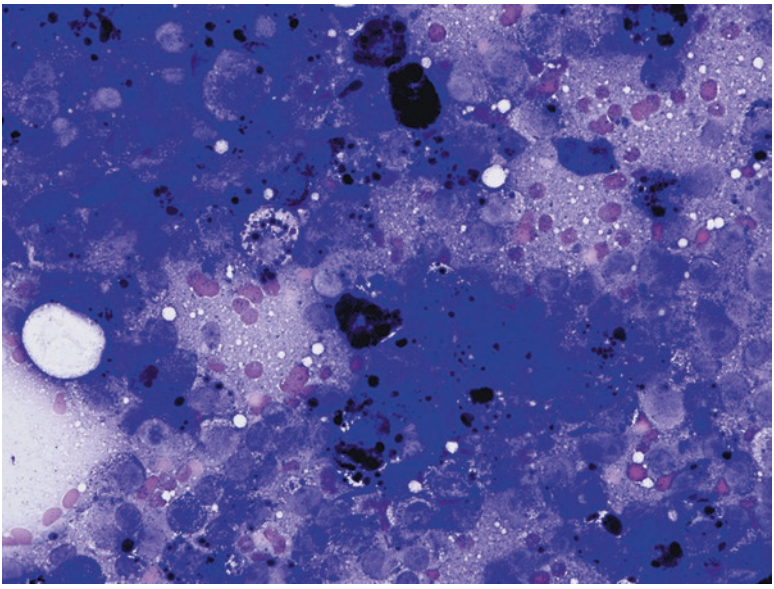

Fig. 12.4 Metastatic melanoma. Most of the pigment is engulfed by macrophages ("melanophages") (smear, Diff-Quik stain).

not common but may be seen as fine granules in the cytoplasm or dark staining in perinuclear areas. More often, melanin is found as coarse granules in histiocytes (Fig. 12.4) [13]. Primary thyroid carcinomas with melanin pigment have been reported and are a histologic variant of medullary carcinoma of the thyroid (see Fig. 9.6). Immunocytochemistry can be helpful in this distinction: positivity for calcitonin favors a medullary thyroid carcinoma.

The distinction between melanoma and an undifferentiated (anaplastic) thyroid carcinoma can be difficult. Aspirates from melanoma are generally more cellular than those of undifferentiated carcinoma, with more intact isolated cells. Immunostains can be helpful: melanoma cells are positive for S-100 protein, HMB45, SOX-10, and melanA; these markers are negative in undifferentiated carcinoma.

Metastatic Breast Carcinomas

Criteria

Samples are of moderate to high cellularity with a uniform population of oval or polygonal cells.
Cells lie singly and in small clusters; the isolated cells retain their cytoplasm.
Cells are often immunoreactive for estrogen and progesterone receptors, GATA-3, and mammaglobin and are negative for TTF-1, PAX-8, and thyroglobulin.

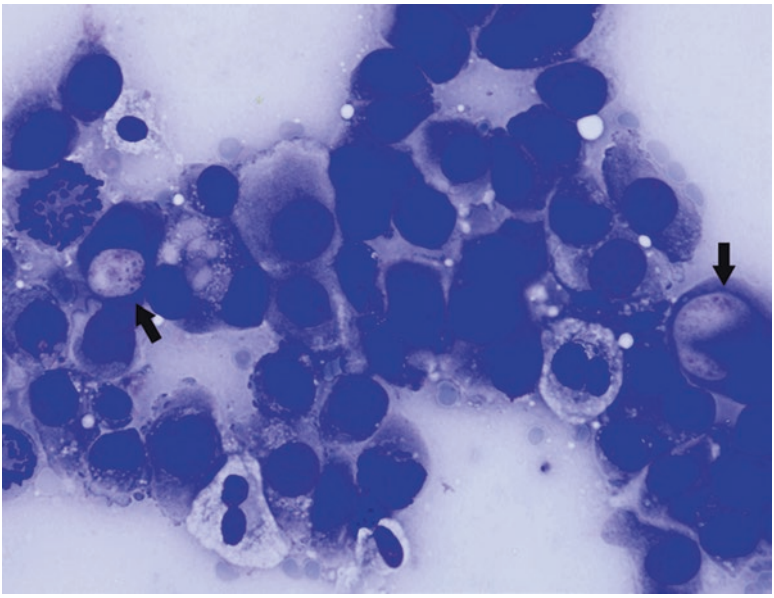

Fig. 12.5 Metastatic ductal carcinoma of the breast. Medium-sized cells have large eccentric nuclei and purple intracytoplasmic vacuolar granules (magenta bodies, *arrows*) that represent mucin vacuoles (smear, Diff-Quik stain).

Explanatory Notes

Adenocarcinoma of the breast is one of the most common tumors to metastasize to the thyroid [14], and the most common type is infiltrating ductal carcinoma. Smears are of moderate to high cellularity, with a uniform population of polygonal or oval cells. The cells appear singly and in clusters. The single cells retain their cytoplasm. The clusters are often angular.

With air-dried smears, purple cytoplasmic inclusions (magenta bodies) may be seen in metastatic breast cancer of both ductal and lobular types (Fig. 12.5). Many metastatic adenocarcinomas of the breast have cells similar to neoplastic follicular cells. The cells of infiltrating ductal adenocarcinoma are larger than those of follicular neoplasms but smaller than those of Hürthle cell neoplasms. The presence of microfollicles favors a thyroid neoplasm over a metastatic mammary carcinoma.

Immunohistochemical stains for thyroid (e.g., thyroglobulin, TTF-1, calcitonin and PAX-8) and for breast antigens (e.g., estrogen and progesterone receptors, mammaglobin, and GATA-3) can be helpful for the separation of metastatic mammary carcinoma from benign and malignant neoplastic follicular/parafollicular cells.

Metastatic Pulmonary Carcinomas

Criteria

Non-small Cell Carcinomas

Isolated, dispersed cells and cell clusters.
Large cells with variable amounts of cytoplasm, sometimes abundant.
Nucleoli can be prominent.

Small Cell Carcinomas

Isolated, dispersed cells and cell clusters.
Small cells with scant cytoplasm.
Oval-to-elongated nuclei, nuclear molding.
Finely granular chromatin.
Inconspicuous nucleoli.
Mitoses, necrosis.

Explanatory Notes

Metastatic small cell carcinoma (SmCC) of the lung may resemble insular thyroid carcinoma but has more fragile nuclei and cytoplasm and thus greater smearing artifact than primary thyroid neoplasms. Both metastatic pulmonary SmCC and insular carcinoma are immunoreactive for neuron-specific enolase (NSE), chromogranin, and synaptophysin, whereas only insular carcinomas are thyroglobulin-positive.

Adenocarcinomas of pulmonary origin are composed of medium-sized to large cells in sheets or clusters/balls (Figs. 12.6 and 12.7). The cells may be columnar, with round to oval, eccentrically positioned nuclei and prominent nucleoli. Both primary thyroid tumors and non-small cell bronchogenic carcinomas may be TTF-1-positive, precluding this antigen as a distinguishing marker. Bronchogenic adenocarcinomas are characteristically of higher nuclear grade than follicular neoplasms of the thyroid gland. Metastatic adenocarcinomas of pulmonary origin are more likely to contain intracytoplasmic mucin.

Squamous cell carcinomas typically demonstrate marked irregularities of nuclear shape and size. Keratinization, best seen with the Papanicolaou stain, is found in both well- and moderately differentiated metastatic squamous cell carcinomas. Immunohistochemistry for p40 can be helpful in identifying poorly differentiated squamous cell carcinomas. The distinction between a primary squamous carcinoma of the thyroid (see Chap. 11) and a metastasis from a squamous cell carcinoma of the lung, however, is not possible based on cytomorphology or immunoprofile. Clinical history and imaging findings are indispensable for separating these two neoplasms.

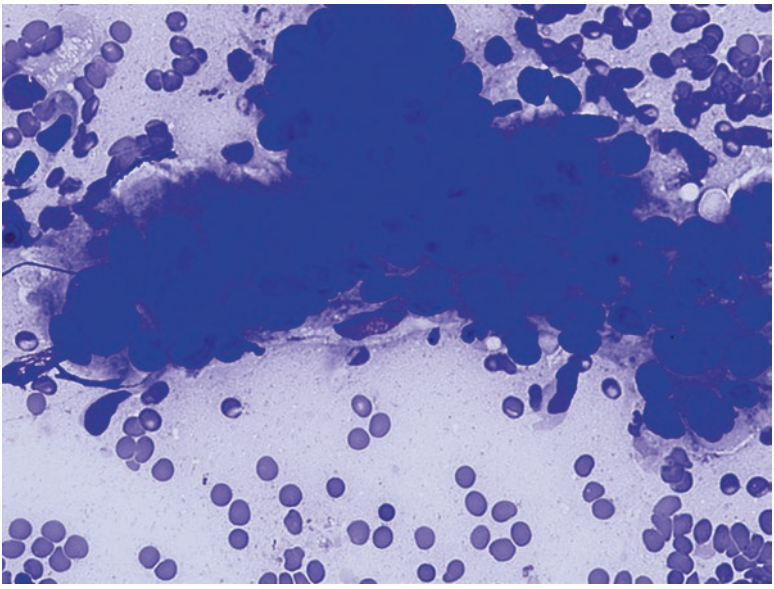

Fig. 12.6 Metastatic non-small cell lung carcinoma. Irregular cell clusters and spherical groups are composed of polygonal and columnar cells (smear, Diff-Quik stain).

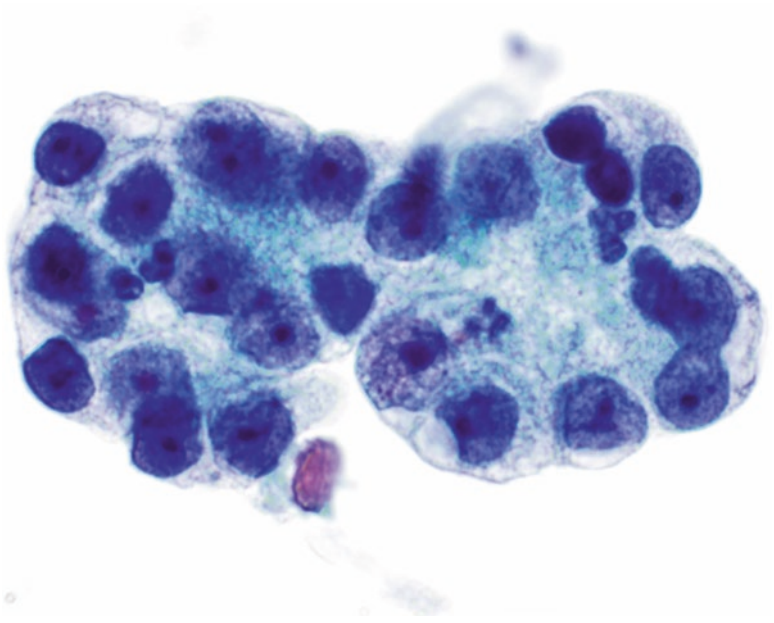

Fig. 12.7 Metastatic non-small cell lung carcinoma. Medium-sized cells have large nuclei, prominent nucleoli, and ample finely granular cytoplasm. The cells are arranged in spherical clusters (ThinPrep, Papanicolaou stain).

Other Metastatic Malignancies

Examples of less common metastatic neoplasms to the thyroid gland are shown in Figs. 12.8, 12.9, and 12.10. Diagnosis by FNA is contingent upon the clinical history, often with the support of immunohistochemistry.

Lymphoma Involving the Thyroid Gland

Criteria

Samples derived from lymphomas are often markedly cellular and composed of noncohesive round to slightly oval cells.
The background contains numerous lymphoglandular bodies, best seen with a Romanowsky-type stain on air-dried preparations.
Cells of marginal zone lymphoma are about twice the size of a small mature lymphocyte.
Nuclei have vesicular ("open") chromatin (with Papanicolaou-stained preparations) and small nucleoli.
Diffuse large B-cell lymphomas contain cells with moderate to abundant basophilic cytoplasm on air-dried preparations stained with a Romanowsky-type stain.
Nuclei have coarse chromatin with one or more prominent nucleoli.

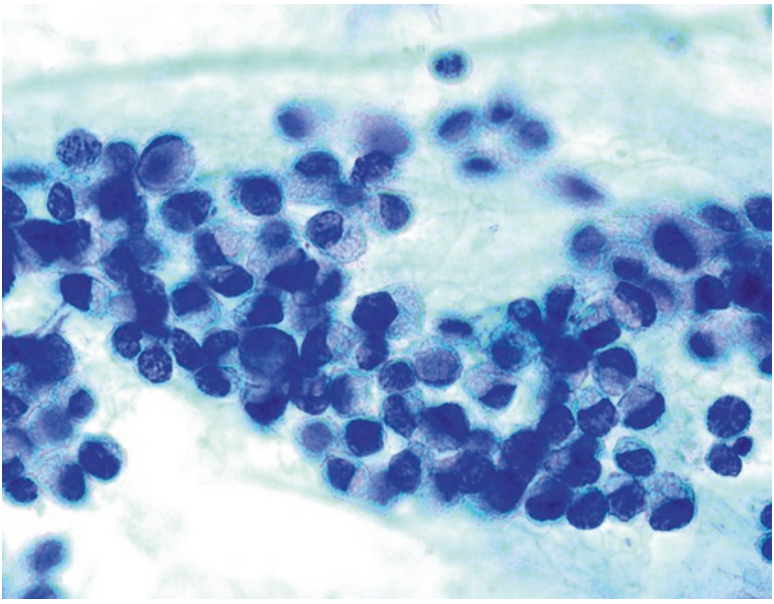

Fig. 12.8 Metastatic gastric signet-ring cell carcinoma. Uniform dispersed cells have a high N/C ratio and intracytoplasmic mucinous vacuoles (smear, Diff-Quik stain) (Courtesy of Dr. QK Li, the Johns Hopkins Hospital, Baltimore, MD).

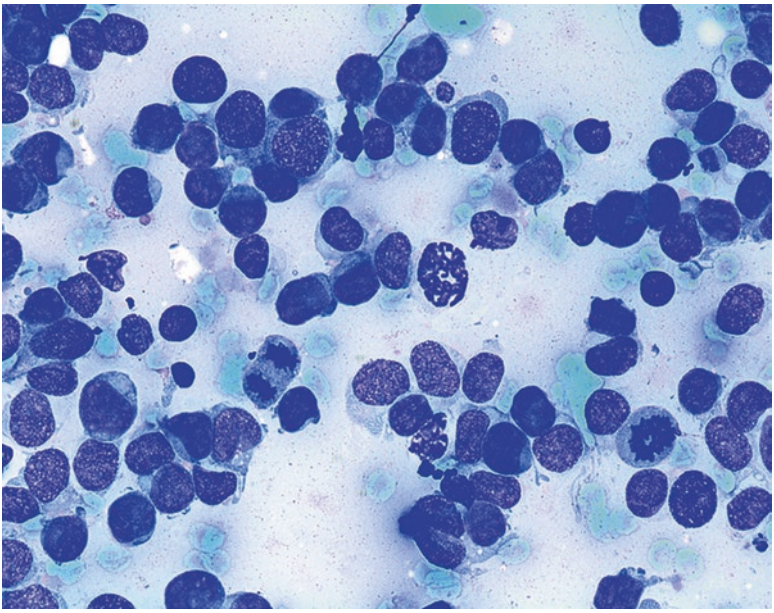

Fig. 12.9 Metastatic Merkel cell carcinoma. Dispersed small round blue cells have a high nuclear/cytoplasmic ratio and frequent mitotic figures (smear Diff-Quik stain).

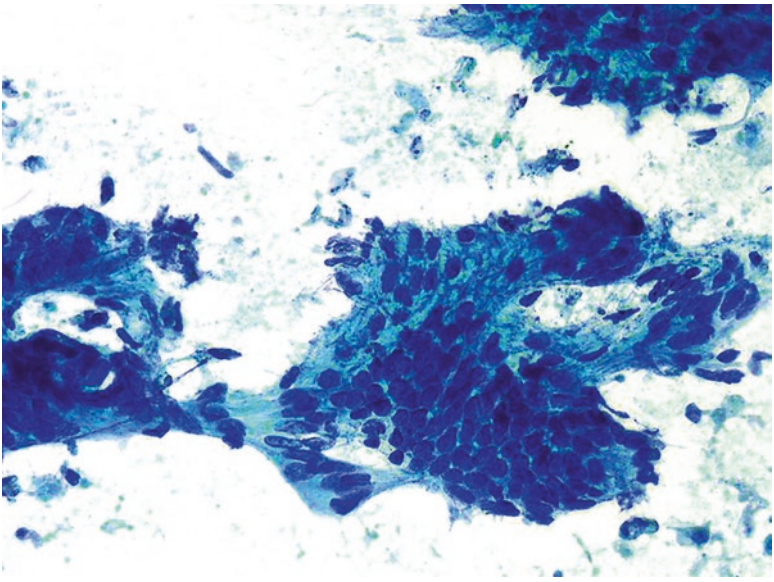

Fig. 12.10 Metastatic colonic adenocarcinoma. Columnar cells with nuclear stratification are associated with granular necrotic debris in the background (smear, Papanicolaou stain).

Explanatory Notes

The majority of primary lymphomas of the thyroid gland are non-Hodgkin lymphomas (NHLs) of B-cell phenotype (98%) [15], and two-thirds are preceded by Hashimoto thyroiditis. Most NHLs of the thyroid gland are either diffuse large B-cell lymphomas or extranodal marginal zone B-cell lymphomas of mucosa-associated lymphoid tissue (MALT). Distinction of thyroid lymphoma from Hashimoto thyroiditis may be difficult [16]. There are at least three different patterns of lymphoma on FNA [17]. One is characterized by a mixture of small and large lymphocytes. This pattern can be seen in Hashimoto thyroiditis as well, but the absence of oncocytes (Hürthle cells), follicular epithelial cells, and plasma cells favors lymphoma. The second pattern is a monotonous population of large lymphocytes and is morphologically diagnostic of lymphoma. The third pattern is characterized by a monomorphous population of small lymphocytes, which may represent lymphoma or an inactive thyroiditis. Immunophenotyping studies are essential for the diagnosis of lymphoma in morphologically equivocal cases. A clonal relationship between Hashimoto thyroiditis and thyroid lymphoma may exist [18], and clonal B-cell populations by flow cytometry have been reported in patients with Hashimoto thyroiditis [19, 20]. Caution is advised, therefore, in interpreting flow cytometric results.

Secondary involvement of the thyroid gland by lymphoma is more frequent than primary disease. Approximately 20% of patients with disseminated lymphoma demonstrate thyroid involvement.

Extranodal Marginal Zone B-Cell Lymphoma (MALT Lymphoma)

FNA preparations from MALT lymphomas are markedly cellular and composed of lymphocytes in isolation and in clusters [21, 22]. Numerous lymphoglandular bodies are present. The cells are small- to intermediate-sized, about twice as large as a small mature lymphocyte [21]. Most cells have a moderate amount of cytoplasm (Fig. 12.11). Small nucleoli are present. A small number of larger cells with eccentrically placed nuclei, coarse chromatin, and prominent nucleoli are present. These cells are admixed with lesser numbers of centrocytic cells, monocytoid B cells, and plasma cells. In some cases, plasmacytoid cells dominate [23]. Often, a small number of thyroid follicular and oncocytic cells are admixed with the lymphocytes [21].

Diffuse Large B-Cell Lymphoma

Aspirates of diffuse large B-cell lymphoma are highly cellular, with many lymphoglandular bodies in the background. The cells are monomorphic, noncohesive large lymphocytes (Fig. 12.12) [21]. With air-dried smears and a Romanowsky-type

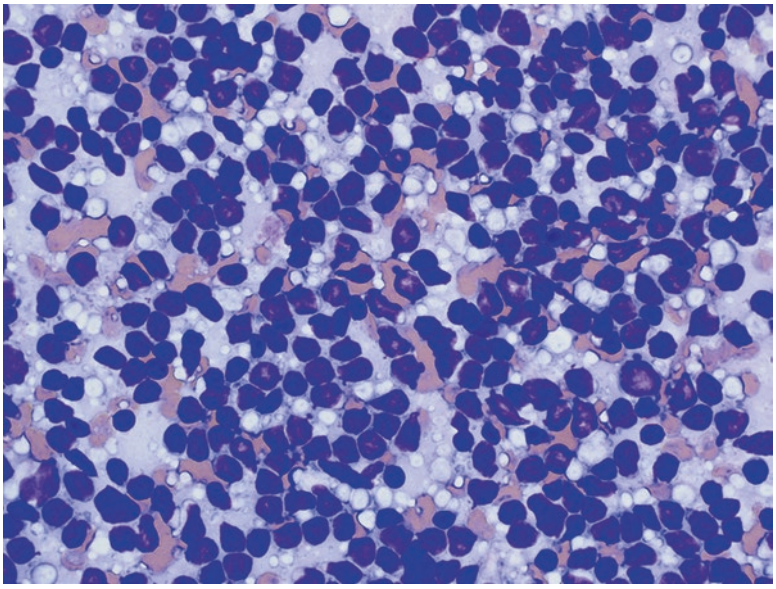

Fig. 12.11 Primary MALT-type lymphoma of the thyroid. There is an abundance of uniform intermediate-sized cells with small nucleoli and granular chromatin (smear, Diff-Quik stain).

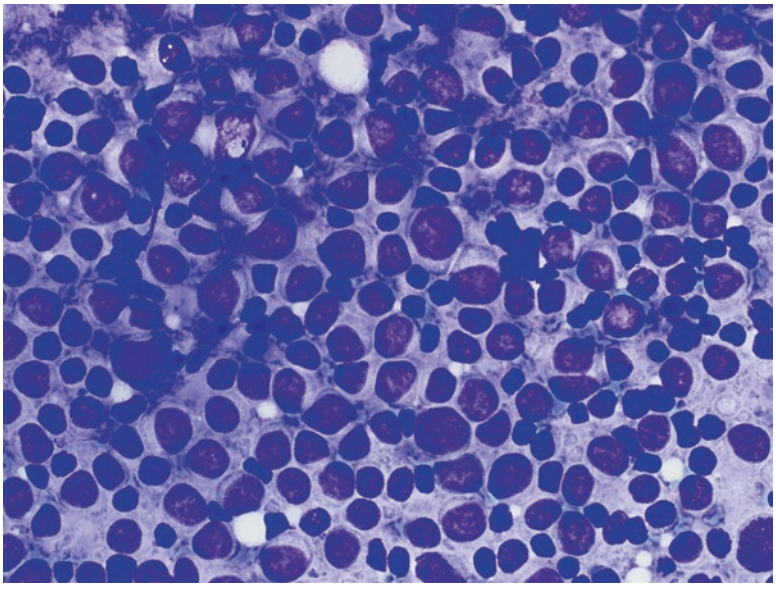

Fig. 12.12 Diffuse large B-cell lymphoma of the thyroid. The smear is cellular and composed mostly of large lymphoid cells whose nuclei are three to five times larger than those of the smaller lymphocytes (smear, Diff-Quik stain).

stain, the cells have moderate to abundant basophilic cytoplasm. The nuclei possess coarse chromatin with one or more prominent nucleoli [21]. Nuclei striped of cytoplasm are numerous, and necrotic debris may be present. Flow cytometry may reveal light chain restriction of the CD45- and CD20-positive neoplastic cells [24]. Follicular epithelial cells are usually absent. Separation of these lymphomas from Hashimoto thyroiditis is straightforward [24].

Hodgkin Lymphoma

Hodgkin lymphoma of the thyroid is rare and can mimic a primary thyroid epithelial tumor or thyroiditis clinically and cytologically [25] (Fig. 12.13). The cellularity of FNAs varies from case to case. In some cases, Reed-Sternberg (RS) cells are present in a mixed background of small lymphocytes, plasma cells, eosinophils, histiocytes, fibroblasts, and capillaries, but the RS cells may not be recognized as such because primary Hodgkin lymphoma of the thyroid is such a rare disease. Instead, the RS cells are considered atypical but of uncertain significance. In some cases, their large size raises the possibility of an anaplastic (undifferentiated) carcinoma, but clinical and imaging features can help distinguish these two very

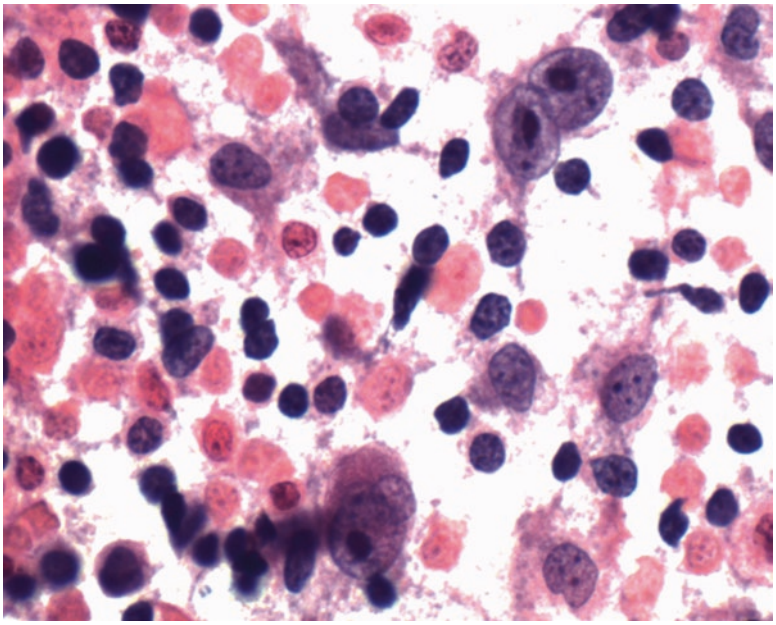

Fig. 12.13 Hodgkin lymphoma of the thyroid. The cells range widely in size and include scattered very large binucleated and multinucleated cells with features of Reed-Sternberg cells (smear, hematoxylin, and eosin stain).

different neoplasms. In other cases, RS cells may be inconspicuous or absent, and such cases are often misinterpreted as thyroiditis; repeated FNAs are sometimes required for definitive diagnosis. Most cases prove to be of nodular sclerosis type; the marked fibrosis associated with this subtype may result in a paucicellular aspirate. Thus, FNA has relatively low accuracy for the diagnosis of thyroid Hodgkin lymphoma. Examination of incisional biopsy material is usually necessary to confirm the diagnosis, but when adequate material is obtained, FNA may be valuable in raising the possibility of Hodgkin lymphoma, thereby helping to guide subsequent clinical intervention.

Rare Neoplasms of the Thyroid Gland

Paraganglioma

Definition

Paraganglioma of the thyroid is an intrathyroidal neuroendocrine tumor of paraganglionic origin.

Criteria

Moderately cellular smears.
Background rich in red blood cells.
Cells arranged in clusters, occasionally as microfollicles.
Lesser numbers of single cells and "naked" nuclei.
Intact cells have granular cytoplasm, often with wispy, poorly defined edges.
Cytoplasm may appear vacuolated.
Nuclei have stippled chromatin and may contain pseudoinclusions.
Some cells have metachromatic cytoplasmic granules.

Explanatory Notes

Primary paragangliomas of the thyroid are very rare [26]. Bonafide examples likely arise from small paraganglia located beneath the thyroid capsule [27]. These neoplasms must be distinguished from paragangliomas extending into the thyroid gland from other sites as well as mimics like hyalinizing trabecular tumor of the thyroid and medullary thyroid carcinoma. Figures 12.14 and 12.15 demonstrate the characteristic cytomorphology of a primary paraganglioma.

Langerhans Cell Histiocytosis

Definition

Langerhans cell histiocytosis is a proliferation of dendritic Langerhans cells with varying numbers of eosinophils.

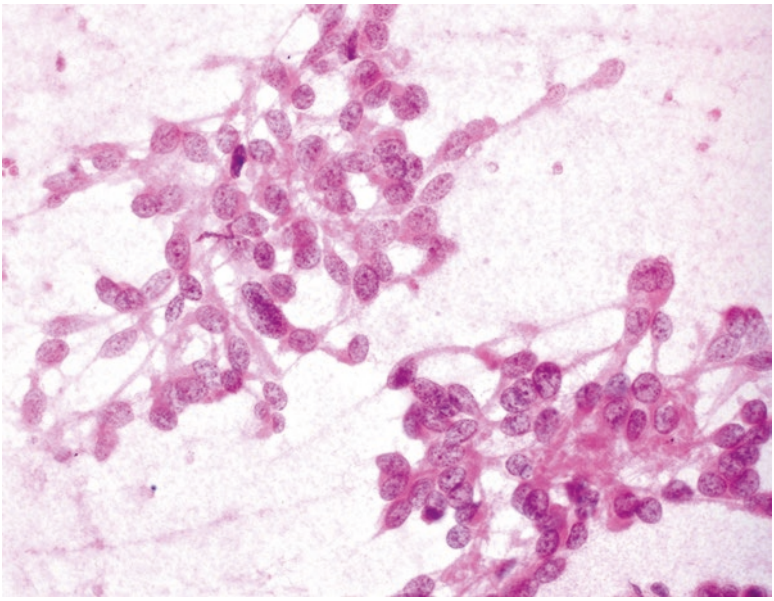

Fig. 12.14 Paraganglioma of the thyroid. FNA of an intrathyroidal paraganglioma is characterized by groups of bland spindle cells with scant wispy cytoplasm (smear, hematoxylin, and eosin stain).

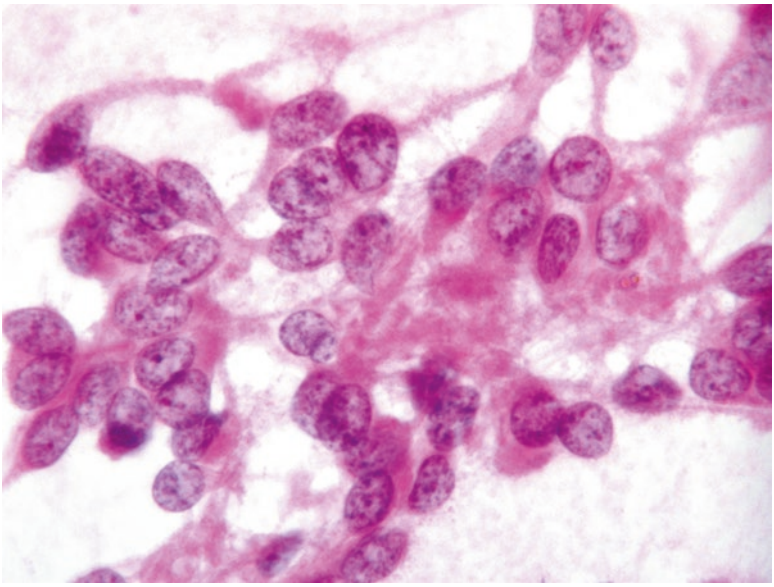

Fig. 12.15 Paragangliomas of the thyroid. Higher magnification of Fig. 14. Some aspirates from Paraganglioma of the thyroid contain microfollicle-like structures composed of cells with pale wispy cytoplasm (smear, hematoxylin, and eosin stain).

Criteria

Moderate to marked cellularity.
Discrete, mostly isolated large mononucleated or multinucleated Langerhans cells with prominent nuclear membrane irregularity (deep nuclear clefting/grooves) and abundant pale vacuolated cytoplasm.
Eosinophils.
Scant or absent follicular cells and colloid.

Explanatory Notes

Primary Langerhans cell histiocytosis (LCH) of the thyroid is rare; when encountered, its unusual features can cause diagnostic difficulties. The key to the diagnosis is recognizing the distinctive features of the neoplastic Langerhans cells, in particular, the strangely misshapen nuclei associated with abundant foamy cytoplasm [28]. Although there is a superficial resemblance to ordinary macrophages, the marked irregularity of LCH nuclei is not seen in benign macrophages (Fig. 12.16). If eosinophils are conspicuous, they are an additional clue. These tumors have been mistaken for papillary thyroid carcinoma, medullary thyroid

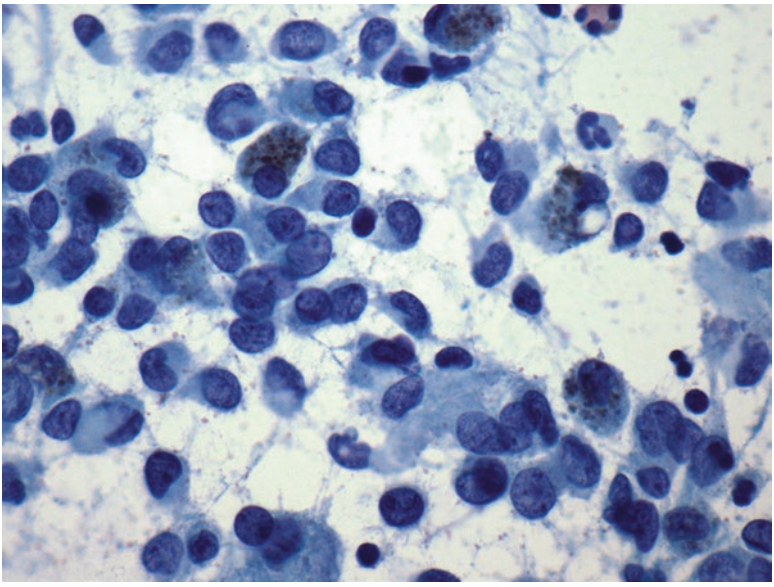

Fig. 12.16 Langerhans cell histiocytosis of the thyroid. The neoplastic cells have variably shaped nuclei, including some that are deeply folded, which mimic the nuclear groove characteristic of papillary carcinoma. Hemosiderin-laden macrophages are also present. Eosinophils were prominent elsewhere on the smear (smear, Papanicolaou stain).

carcinoma, poorly differentiated thyroid carcinoma, and a follicular neoplasm [28]. The diagnosis can be confirmed with immunohistochemistry: Langerhans cells are immunoreactive for CD1a and Langerin.

Mucoepidermoid Carcinoma

Definition

Mucoepidermoid carcinoma is a malignant epithelial neoplasm with epidermoid and mucinous differentiation.

Criteria

Variable proportions of squamous cells (nonkeratinized and keratinized) and mucous cells.
Keratin pearls.
Extracellular mucin.
Eosinophils (some cases).

Explanatory Notes

Mucoepidermoid carcinoma (MEC) is most commonly a tumor of the salivary glands, but it also occurs at other sites. Primary MEC of the thyroid is rare, comprising about 0.5% of all thyroid malignancies. An association with a papillary thyroid carcinoma is seen in about half of cases [29]. Cytologic diagnosis is challenging and depends on identifying a mixture of so-called "intermediate-type" squamous cells (nonkeratinized, cuboidal cells), keratinized cells, and mucous cells. The differential diagnosis includes papillary thyroid carcinoma and squamous cell carcinoma of the thyroid. MECs of the thyroid are usually immunoreactive for thyroglobulin and TTF-1.

Sclerosing mucoepidermoid carcinoma with eosinophilia (SMECE) is a related tumor with distinctive clinical and pathologic features. Although histologically and cytologically similar to MEC (Figs. 12.17 and 12.18), it is usually seen in patients with Hashimoto thyroiditis. Like MEC of the thyroid, SMECE is positive for TTF-1, but (unlike MEC) it is negative for thyroglobulin.

Mammary Analog Secretory Carcinoma

Definition

Mammary analog secretory carcinoma is a malignant epithelial tumor that histologically and cytologically markedly resembles secretory carcinoma of the breast.

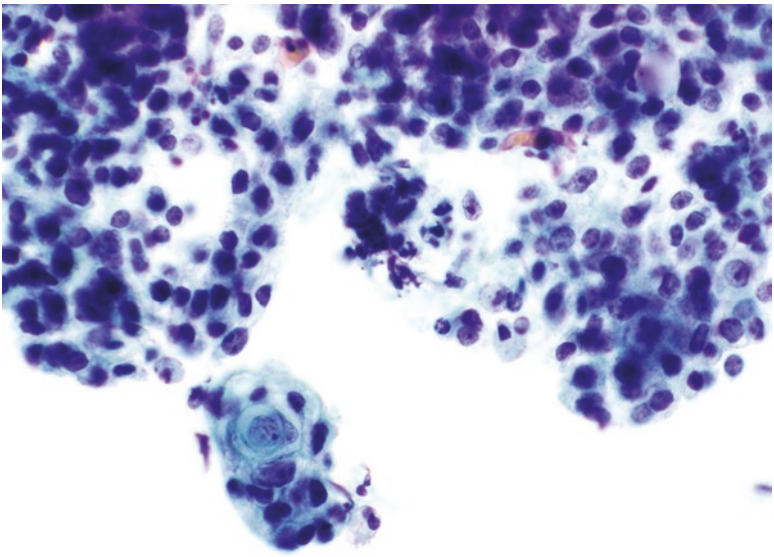

Fig. 12.17 Sclerosing mucoepidermoid carcinoma with eosinophilia. This neoplasm is comprised mainly of "intermediate cells": nonkeratinizing immature, cuboidal squamous cells. A small squamous pearl is also present (ThinPrep, Papanicolaou stain).

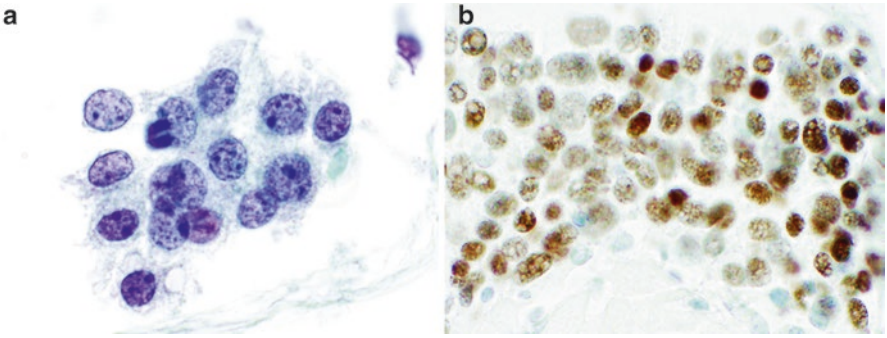

Fig. 12.18 **a** Sclerosing mucoepidermoid carcinoma with eosinophilia. The intermediate cells have round nuclei, granular chromatin, and prominent nucleoli. Cytoplasm is thin and granular (ThinPrep, Papanicolaou stain). **b** *Inset*: The tumor cells are immunoreactive for TTF-1.

Criteria

Highly cellular specimen.
Cells arranged in sheets, branching pseudopapillae.
Round nuclei, prominent nucleoli, and grooves.
Granular and/or vacuolated cytoplasm.
Occasional solitary large cytoplasmic vacuole.

Explanatory Notes

Mammary analog secretory carcinoma (MASC) was first described as a tumor of the salivary glands in 2010. In 2016, Dogan et al. described three cases arising in the thyroid gland [30]. Cytologic preparations are highly cellular, and the cells are mostly cohesive, arranged in sheets and branching clusters lacking fibrovascular cores (Figs. 12.19 and 12.20). The nuclei are round and nucleoli prominent; cytoplasm is vacuolated and/or granular. Occasional cells have a large solitary cytoplasmic vacuole. The cells are positive for mammaglobin, GCDFP-15, S-100 protein, p63, weakly positive for PAX-8, and negative for TTF-1 and thyroglobulin. Like its salivary gland and breast counterparts, MASC of the thyroid harbors the *ETV6–NTRK3* fusion.

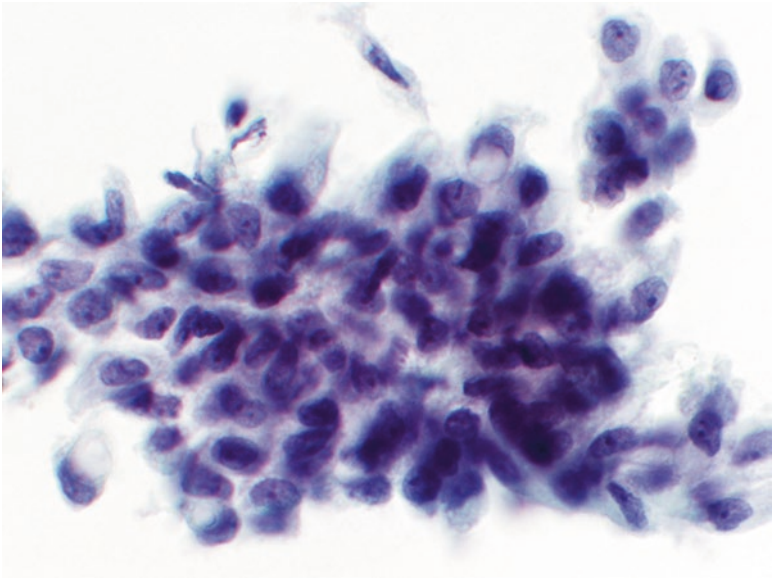

Fig. 12.19 Mammary analog secretory carcinoma of the thyroid. The cells are arranged in groups, as seen here, and as isolated cells. Note that some cells have prominent large, solitary cytoplasmic vacuoles (ThinPrep, Papanicolaou stain).

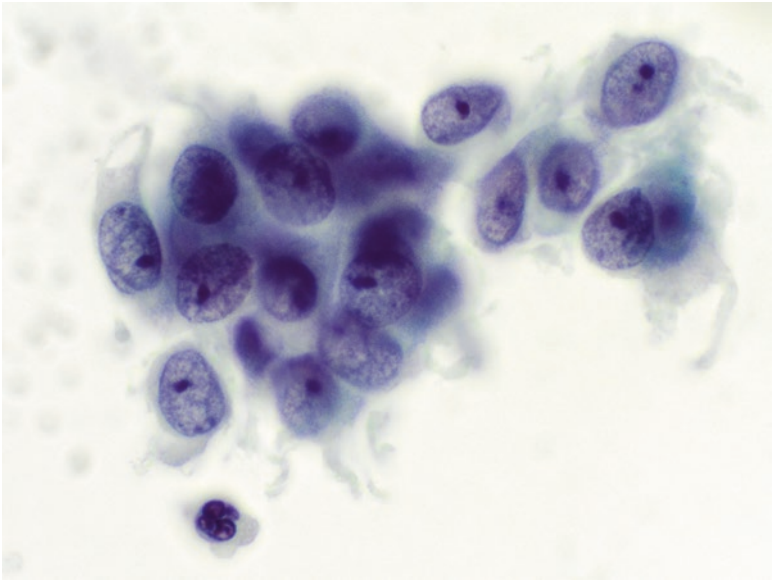

Fig. 12.20 Mammary analog secretory carcinoma of the thyroid. The cells have prominent nucleoli (ThinPrep, Papanicolaou stain).

Ectopic Thymoma

Definition

A primary thymoma of the thyroid (ectopic thymoma) is a thymic epithelial tumor occurring in the thyroid.

Criteria [31–33]

The cytologic features depend on the type of thymoma present.

Type A Thymoma (Fig. 12.21)
Individual and tightly cohesive groups of spindle cells.
Bland oval to spindle-shaped nuclei.
Fine granular chromatin.
Indistinct to absent nucleoli.
Spindle cells often have scant or absent cytoplasm ("naked" nuclei).
Small mature lymphocytes in background.

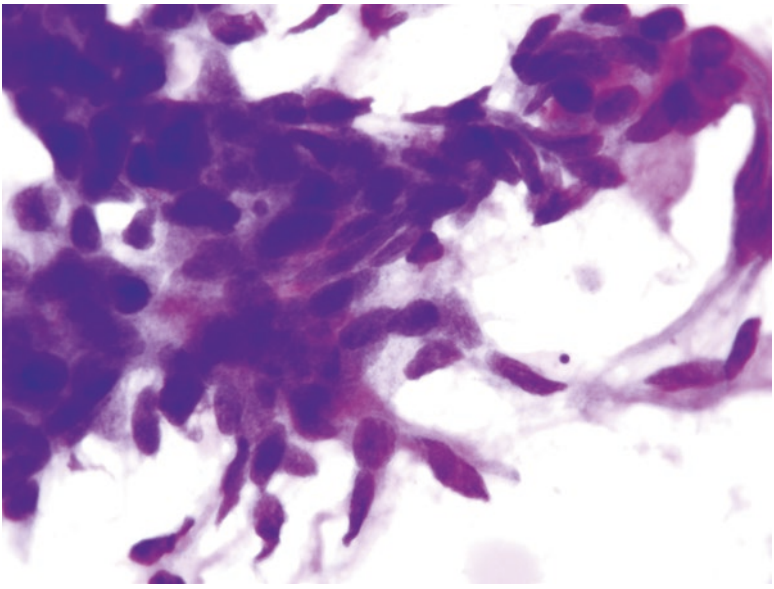

Fig. 12.21 Thymoma of the thyroid. Type A thymomas characteristically display variable proportions of lymphocytes and groups of spindle cells, often with scant cytoplasm and spindle-shaped nuclei with finely granular chromatin (smear, Diff-Quik stain).

Type B Thymoma (Fig. 12.22)

Variably cellular smears with a mixture of mature lymphocytes and clusters of polygonal epithelial cells.

Epithelial component characterized by bland round nuclei with fine granular chromatin.

Small or absent nucleoli.

Moderate to abundant amounts of cytoplasm in epithelial cells.

Explanatory Notes

Thymomas most commonly occur in the anterior mediastinum but may rarely involve the lower pole of the thyroid gland. Residual normal thymic tissue may accompany the thymoma within the thyroid.

Type B thymomas may resemble papillary thyroid carcinomas, whereas type A thymomas can resemble a lymphoma, a mesenchymal neoplasm, or a carcinoid tumor [32]. Intrathyroid epithelial thymoma/carcinoma showing thymus-like differentiation (ITET/CASTLE) occurs in the thyroid [34]. This neoplasm is the malignant counterpart of thyroid thymoma and is a low-grade malignancy. The cytologic features of ITET/CASTLE have been described [32]. It should be separated whenever possible from squamous cell carcinoma, metastatic and primary, as these latter two neoplasms are high-grade malignancies.

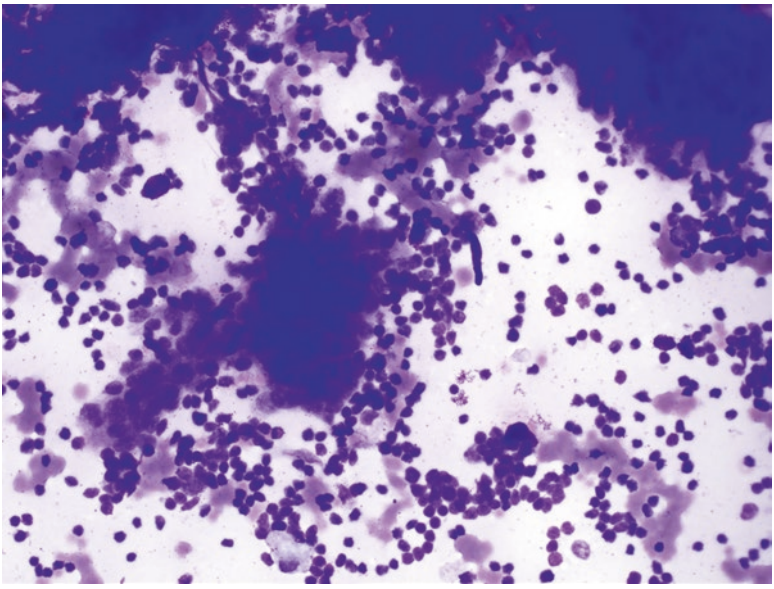

Fig. 12.22 Thymoma of the thyroid. Type B thymomas are characterized by prominent numbers of uniform small lymphocytes and groups of polygonal epithelial cells (smear, Diff-Quik stain).

Spindle Epithelial Tumor with Thymus-Like Differentiation (SETTLE)

Definition

Spindle epithelial tumor with thymus-like differentiation (SETTLE), also called spindle cell tumor with thymus-like differentiation, is a rare malignant tumor of the thyroid characterized histologically by lobulated architecture and a biphasic cellular composition, with spindle-shaped epithelial cells that merge into glandular structures [35]. It probably develops from the branchial pouch or a thymic remnant. Most reported cases have occurred in young male patients [33, 35].

Criteria [35, 36]

Highly or moderately cellular smears.
Dissociated uniform spindle cells with oval, bland nuclei.
Some groups and aggregates of spindle cells.
Occasional groups of epithelial cells.
Rare or absent mitotic figures.
Spindle cells are immunoreactive for cytokeratin and vimentin and nonreactive for thyroglobulin and calcitonin.

Explanatory Notes

SETTLE is difficult to specifically diagnose cytologically. It must be separated from medullary carcinoma of the thyroid and a variety of spindle cell neoplasms including primary synovial sarcoma of the thyroid and type A thymomas.

Other Rare Primary Neoplasms of the Thyroid Gland

A number of benign mesenchymal neoplasms occur in the thyroid gland, including lipomas, hemangiomas, schwannomas, and leiomyomas. Rarely, sarcomas arise in the thyroid, most frequently angiosarcomas, synovial sarcomas, osteosarcomas, and chondrosarcomas [37–41]. The cytomorphology of these primary thyroid sarcomas is identical to that of their more common counterparts in soft tissue.

Rarely, epithelial malignancies including mucoepidermoid carcinomas may arise primarily within the thyroid and have an appearance identical to those arising within the salivary glands [29].

Management

Metastases to the Thyroid

Surgery is generally not indicated if the FNA is conclusive for a metastasis to the thyroid, and it may not be indicated if the results are suspicious for metastatic disease. Referral to an oncologist is appropriate.

Malignant Lymphomas and Hodgkin Lymphoma

Hodgkin lymphoma of the thyroid often requires surgical excision and chemotherapy, with or without radiation therapy [25]. For non-Hodgkin lymphoma of the thyroid, combined modality therapy (two or more of surgery, radiation therapy, and chemotherapy) is the usual approach.

Rare Primary Tumors of the Thyroid

Surgical excision (lobectomy or near-total thyroidectomy) is generally indicated.

Sample Reports

The general category “malignant” is used whenever the clinical and microscopic features are conclusive. The type of metastatic, lymphoid, or rare thyroid malignancy should be stated whenever possible. If features are suspicious but not

conclusive for malignancy, the category "suspicious for malignancy" is used. Some aspirates, particularly those that raise the possibility of a lymphoma of MALT-type but lacking corroborative immunophenotyping data, are more appropriately categorized as "atypia of undetermined significance (AUS)" (See Chap. 4, Sample Report Example 9). If an aspirate is interpreted as malignant, suspicious, or AUS, it is implied that the sample is adequate for evaluation (an explicit statement of adequacy is optional).

Example 1
MALIGNANT
Diffuse large B-cell lymphoma.

Note: Flow cytometry shows a CD45- and CD20-positive monoclonal B-cell population.

Example 2
SUSPICIOUS FOR MALIGNANCY
Suspicious for metastatic adenocarcinoma of the breast

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