Chapter 5
The Bethesda System for Reporting Thyroid Cytopathology (BSRTC)

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Thyroid Fine Needle Aspiration: The Bethesda System for Reporting Thyroid Cytopathology (BSRTC)

Fine needle aspiration (FNA) has been reported as "the most accurate and cost-effective method for evaluating thyroid nodules" by the 2015 American Thyroid Association (ATA) Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer [1]. FNA is a safe and simple procedure and can be performed by palpation in an outpatient office or under image guidance (see Chap. 4). While ultrasound guidance (USG) is not a requirement for FNA of palpable thyroid nodules, more and more thyroid FNAs have been performed by USG. There is also accumulating evidence that USG improves diagnostic accuracy and reduces nondiagnostic rates [2–4]. Ultrasound has also been suggested to be complementary in managing thyroid nodules that were found to be suspicious for malignancy by cytology, with lower risk of malignancy observed for those thyroid nodules showing benign ultrasonographic findings [5–7].

Sensitivity and specificity of thyroid FNA have been measured in the last few decades, and it has been proven as a highly sensitive tool for evaluation of thyroid nodules [8–15]. It has also been established that the sensitivity and specificity of thyroid FNA is greatest for both benign and malignant diagnoses, while in the indeterminate categories, the surgical correlates lack accuracy. To further complicate this issue, there is no shortage of terminology among cytopathologists for reporting this group of FNAs.

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In clinical practice, for diagnoses other than benign and malignant, terminology such as "atypical," "indeterminate," "suspicious," "cannot rule out," and similar wording is prone to cause significant confusion, not only for the clinicians, but also among the expert cytopathologists reviewing the same specimen. Obviously, this is not a mere academic reason to seek a unifying terminology but is an important clinical, patient care concern. Thyroid FNA diagnoses must be communicated with the clinical team appropriately to assure the best clinical management decisions. Both the surgeon and the patient must be aware of the significance of the FNA diagnosis to ensure evidence-based decision-making.

To standardize the terminology for thyroid FNA reporting and to provide better communication among physicians, the National Cancer Institute (NCI) hosted the multidisciplinary "Thyroid Fine Needle Aspiration State of the Science" conference in Bethesda, Maryland, on October 22–23, 2007, with 154 registrants including pathologists, surgeons, endocrinologists, and radiologists. The meeting was organized by Andrea Abati, M.D.

The outcome of this conference was detailed in an atlas in 2010 [16]. According to the Bethesda system, a six-tiered reporting system is suggested that included three atypical/indeterminate categories as outlined below.

1. Nondiagnostic or unsatisfactory
2. Benign
3. Atypia of undetermined significance or follicular lesion of undetermined significance (AUS/FLUS)
4. Follicular neoplasm/suspicious for follicular neoplasm (including oncocytic lesions)
5. Suspicious for malignancy
6. Malignant

In the years following the publication of this reporting system, multiple studies confirmed the utility of the Bethesda terminology [17–21]. Few institutional modifications and suggestions were also reported [22–28]. However, currently, this system seems to be the most widely accepted terminology for reporting thyroid cytology in the literature. It is important, however, to note that institutional variations depending on patient populations and interobserver variability among cytopathologists are well established [29–32]. Therefore, it is highly recommended that each practice collect their own data with case distributions and malignancy risks. We will look into the categories in detail and point out possible areas of weakness, particularly in the "indeterminate" categories, with clinical implications and malignancy risks for each category.

Components of Thyroid Fine Needle Aspiration

Follicular Cells The main cellular components of thyroid FNA are the follicular cells (see Fig. 5.1), the primary functional cells of thyroid parenchyma, responsible for production of thyroid hormones. Cells are arranged in three-dimensional groups

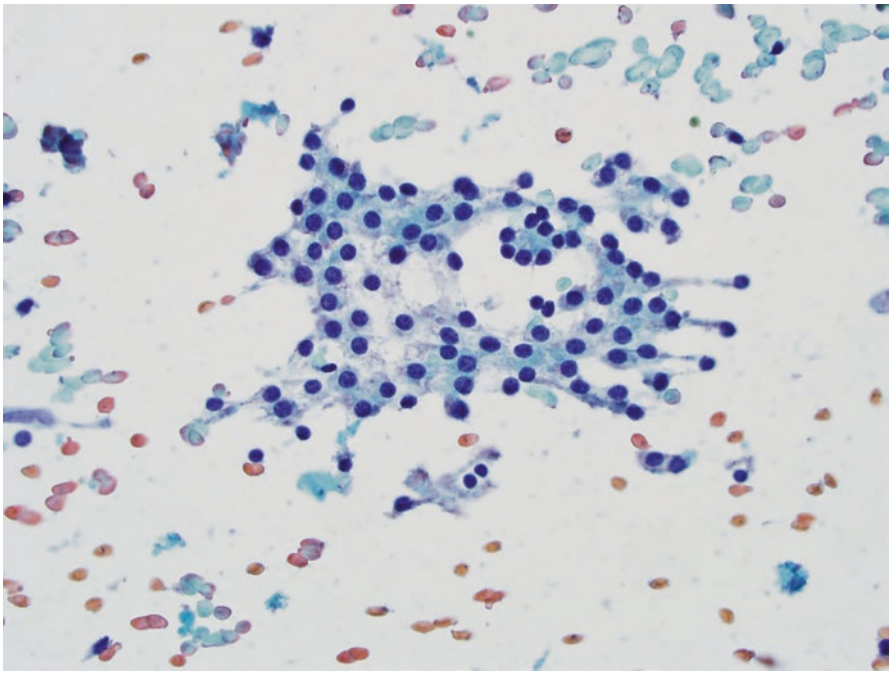

Fig. 5.1 Follicular cells. Bland follicular cells with round-to-oval nuclei, smooth nuclear contours; cytoplasm is fine and friable

of variable sizes with colloid in the central lumen storing thyroglobulin. On FNA specimens, cells may be seen individually or forming intact follicles on smeared slides. C-cells, responsible for calcitonin production, are not identified in thyroid FNAs unless they form a neoplastic mass.

Oncocytic (Hürthle) Cells These are large, epithelial cells with abundant, granular cytoplasm, engorged with mitochondria (see Fig. 5.2). Although the term oncocyte (meaning "swollen cell") may be more appropriate, Hürthle cell terminology has been entrenched in medical practice and is used commonly. While similar morphologic changes can also be seen in thyroid C-cells, the term Hürthle cell implies a follicular cell origin.

Colloid Colloid is the storage form of thyroglobulin that is packed inside follicles in the thyroid. It is a homogeneous, viscous material with characteristic smearing pattern on FNA slides. Pathologists who perform thyroid FNAs can easily identify colloid grossly by the smearing characteristics and shiny, smooth, and homogeneous, honey-like features on glass slides before fixation.

Inflammatory Cells Both acute and chronic inflammatory cells can be seen in thyroid FNAs and may be secondary to infectious and autoimmune inflammatory processes and neoplasias of the hematolymphoid system.

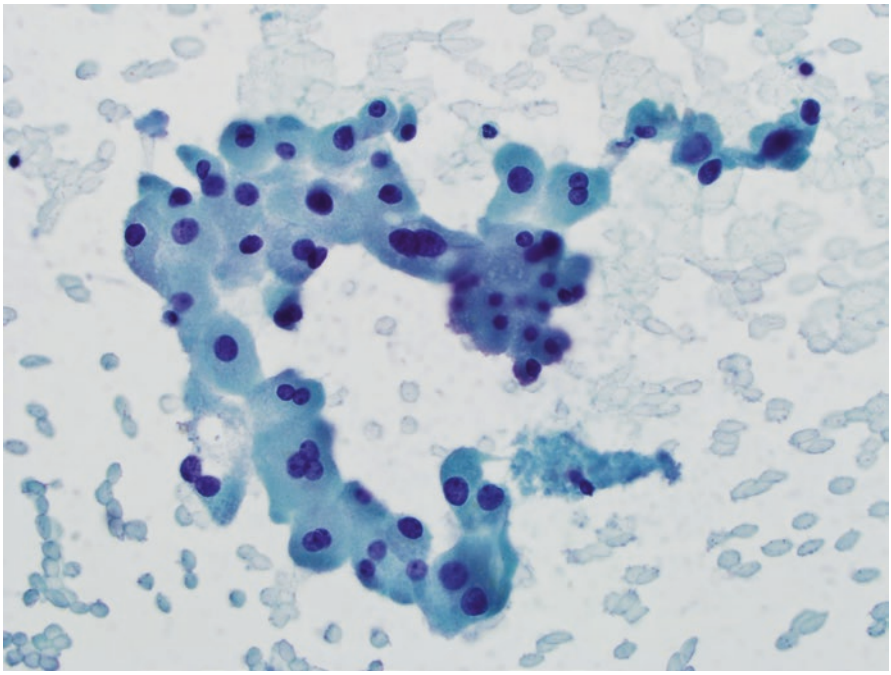

Fig. 5.2 Hürthle cells. Group of cells with abundant, granular cytoplasm and single or multiple, round-to-oval, smooth nuclei. There may be prominent nucleoli

Macrophages Macrophages serve as scavenger cells in tissue. In the thyroid, they may be seen in association with thyroid cysts, where they are characterized by their vacuolated ("foamy") cytoplasm with or without pigment (mostly hemosiderin) (see Fig. 5.3).

Stromal and Vascular Components Depending on the underlying pathologic processes, vascular, stromal, neural, or skeletal muscle fragments may be present in thyroid FNA specimens.

Diagnostic Categories

Nondiagnostic or Unsatisfactory

The main reason for specifying adequacy of thyroid FNA specimens is to avoid false-negative diagnoses. To reduce the risk of false negatives, the cytopathologist should be able to identify the tissue appropriately. This, however, involves multiple parameters including the operator, slide preparation, proper fixation and staining, and also the inherent characteristics of the nodule itself, such as solid vs. cystic components, hemorrhage into the lesion, degenerative or necrotic changes

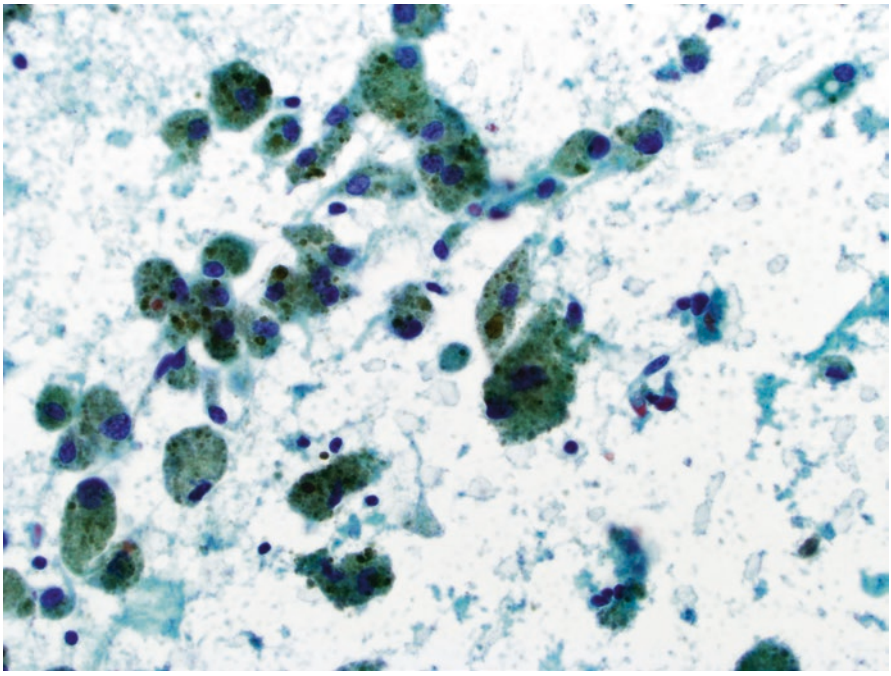

Fig. 5.3 Cyst contents with abundant pigment-laden histiocytes

and amount of sclerosis, calcification, or ossification involving the nodule. Therefore, there is no single criterion for the adequacy of thyroid FNAs. It should also be noted that the adequacy discussion applies to specimens that would otherwise be reported as benign; in other words, if a specimen is considered for any diagnosis other than benign, it should not be reported as nondiagnostic or unsatisfactory, but instead findings should be communicated in an appropriate manner in the pathology report. In this context, the value of detailed verbal or written communication cannot be overemphasized. While in certain practices, a terminology of nondiagnostic implies the features and findings are not "diagnostic for a specific entity," and the term unsatisfactory is used when there is insufficient material for proper evaluation; the two forms a single diagnostic category in the Bethesda system.

One of the earlier reports on quantitative criteria for adequacy was from Dr. Goellner at Mayo Clinic giving actual numbers of follicular cells necessary for adequacy [33]. While "adequacy" reflects much more than the number of follicular cells on glass slides, this proposal by Goellner has remained useful for reporting thyroid cytology for decades and was also included in the Bethesda terminology. For this purpose, six groups of well-visualized cells, each with ten follicular cells, should be considered an "adequate" specimen for evaluation of thyroid nodules in the appropriate setting. This means that the cytologic specimen should be sufficient to identify the "lesion," with clinical and preferably radiologic correlates.

The exceptions to the quantitative requirements for adequacy are those that would identify the lesion in the thyroid as anything other than benign or otherwise guide the clinical or surgical management of the patient. Examples include colloid nodules or inflammatory processes where the follicular cell component may not be well represented or not present at all in the aspirate smears.

Cyst contents without sufficient follicular epithelial cells are considered nondiagnostic. The main concern for these cases is a cystic papillary thyroid carcinoma. In such instances, the aspirates are reported as nondiagnostic with a statement that the FNA shows "cyst contents only." Still, such smears have a very low risk of malignancy particularly for nodules smaller than 4 cm in size and those that shrink after the FNA procedure [34].

Similarly, obscuring blood, preservation and/or fixation artifacts, and staining problems can render the specimen nondiagnostic even if the cellularity is quantitatively "sufficient."

While there are wide variations in the literature for the nondiagnostic category, overall it averages around 10 % [14, 15, 35–40]. In a meta-analysis including a large series in the post-Bethesda era, Bongiovanni reported an average nondiagnostic rate of 13 %, ranging from 1.8 to 23.6 %, in over 25 thousand FNAs [20].

The risk of malignancy for nondiagnostic specimens is difficult to assess in small series without sufficient follow-up, because the majority of these cases do not lead to surgical intervention. The studies that report a malignancy risk for this group with surgical follow-up overestimate the malignancy risk because of selection bias, i.e., the patients with surgical follow-up usually have additional indications for excision, such as increasing size, clinical symptoms, or abnormal or suspicious findings on imaging that skew the risk stratification for these patients. Overall, the malignancy risk with nondiagnostic specimens is actually very low. While it ranges from 0.6 to 39 % in different series, depending on how the data is collected, the malignancy risk is especially low for nodules without suspicious radiologic findings and smaller lesions [15, 35–37, 39, 41, 42]. In a study including 393 cases with an original nondiagnostic FNA but with adequate cytologic, surgical, or ultrasound follow-up, only 2.3 % were associated with malignancy [41]. In this series, the risk increased significantly with each 1 cm increase in any dimension of the nodule [41].

The overall inadequacy rate may decrease with ultrasound guidance [2, 3]. On-site evaluation of thyroid FNAs, with or without USG, may also prove helpful in further reducing the nondiagnostic rate of thyroid FNAs [38, 43, 44]. However, it should be emphasized that more important than any USG or aspiration technique is the experience and competency of the operator performing the procedure and also the cytologist evaluating the specimen [45]. The Bethesda system recommendation for nondiagnostic aspirates is a repeat FNA but "no sooner than 3 months later," preferably with ultrasound guidance and rapid, on-site adequacy evaluation. While ultrasound guidance is likely to reduce the nondiagnostic rate, similar to on-site evaluation, there is no convincing data in the literature that requires a specific time interval for a repeat aspirate. Actually, recent studies that looked into this recommendation did not find any basis for a 3-month period in their series [46, 47]. Furthermore, no contraindication is proven for immediate repeat aspirate, either. On

the other hand, it seems reasonable to allow the tissue repair to prevent overinterpretation of reparative/reactive changes as an atypical or neoplastic process particularly by an inexperienced cytopathologist. However, additional factors, including patient compliance, clinical and ultrasonographic findings, and operator experience should all be considered in deciding the most appropriate follow-up. This is particularly evidenced by studies that showed clinical and radiologic follow-up was as acceptable as a repeat aspirate for initially nondiagnostic thyroid FNAs, particularly in the absence of suspicious radiologic findings [41, 48, 49].

Benign

While FNA diagnosis of thyroid nodules can be utilized for confirmation of malignancy or determination of the extent of surgery, the primary purpose of a thyroid FNA is to document that the nodule is benign and no surgical excision is necessary. As the overwhelming majority of thyroid nodules are benign, in most practices, at least 60 % of thyroid FNAs are reported as such [9, 11, 14, 15, 33]. Therefore, thyroid FNA has been an extremely useful tool in prevention of many unnecessary thyroidectomies. When a benign diagnosis is rendered on cytology, the nodule can safely be followed clinically and radiologically, and no further immediate diagnostic studies are indicated [50].

The benign diagnosis includes multiple entities, including benign follicular nodule, colloid nodule, and inflammatory conditions.

Benign follicular nodule is the most common diagnosis for thyroid FNAs. As the name implies, this group consists of follicular-patterned lesions, which encompasses a large and diverse group of lesions including the broad term of "follicular hyperplastic nodules" and also some "follicular adenomas." Follicular hyperplastic nodules include multinodular or uninodular goiters, dominant hyperplastic nodules, nodules in the background of Graves' disease, and colloid nodules (see below). Generally, differentiation of these entities on cytology has little or no clinical significance, as their clinical management will be the same, or in the case of Graves' disease, the diagnosis is usually established on clinical grounds.

The main cytologic characteristic of a benign follicular nodule is presence of colloid and a mixture of bland follicular cells, commonly including Hürthle cells. Therefore, proper identification of colloid on cytologic material is very important. It is common for colloid to "wash off" with fixation. Therefore, it is best seen on stained air-dried smears as dark blue-magenta-colored material. Colloid may be thick, dark, and cracked, or it may be "watery" as clouds of bluish tinge on smears (see Fig. 5.4). To an untrained eye, it may be difficult to differentiate colloid from serum.

When specimens show abundant colloid, even in the absence of follicular cells, those cases are reported as "benign" or "colloid nodule" as the malignancy risk for such lesions is considered to be extremely low [51]. However, in practice, this is a relatively rare occurrence. These can be considered as one end of the spectrum of "macrofollicular lesions." The term colloid nodule should be reserved for those lesions that are clearly dominated by definite colloid on smears. Additionally, the

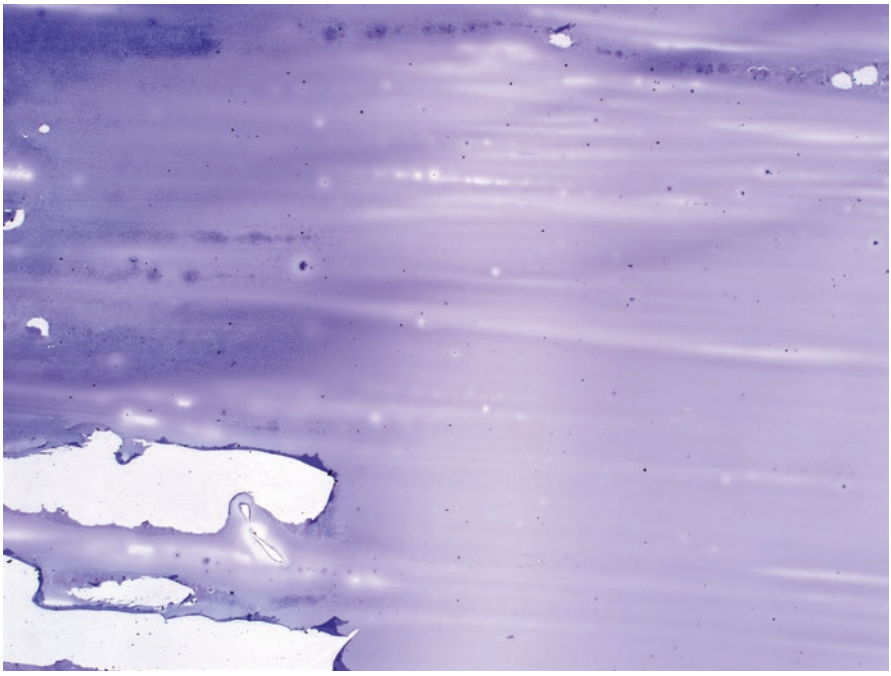

Fig. 5.4 Colloid. Homogeneous, viscous, gel-like material that forms smooth smears on glass slides. It may crack or fold on the edges

cytologic findings should be supported by the imaging characteristics of the nodule sampled. A specimen with abundant colloid should not be reported as benign or adequate if the ultrasonographic features are consistent with a solid lesion.

In addition to colloid, follicular epithelial cells are commonly seen in smears from benign follicular nodules (see Fig. 5.5). They may be seen as sheets or follicles of various sizes. It is important to note that a minor component of microfollicles can be seen in benign follicular nodules, and presence of microfollicles in such a background should not be interpreted as atypical or follicular neoplasm. Follicles show a range of sizes and three-dimensional intact follicles can be seen. As the size of the follicles decrease, it is more likely to see colloid in the center of the follicles. Depending on the aspiration technique and the size of the needle, occasional thick tissue fragments may be seen; however, in a fine needle aspiration specimen, three-dimensional groups of follicles (instead of occasional individual follicles) should not be seen. Cellularity may be low to moderate and occasionally marked; however, there is a mixture of follicular architecture, ranging from small to large macrofollicles, flat sheets, and occasional microfollicles.

It is at this point pertinent to mention what constitutes a microfollicle. So far, the best definition of a microfollicle is by Renshaw as “less than 15 cells, arranged in a circle that is at least two-thirds complete, and flat.” Microfollicles can also be seen as small, compact, three-dimensional “spheres” with colloid in the center.

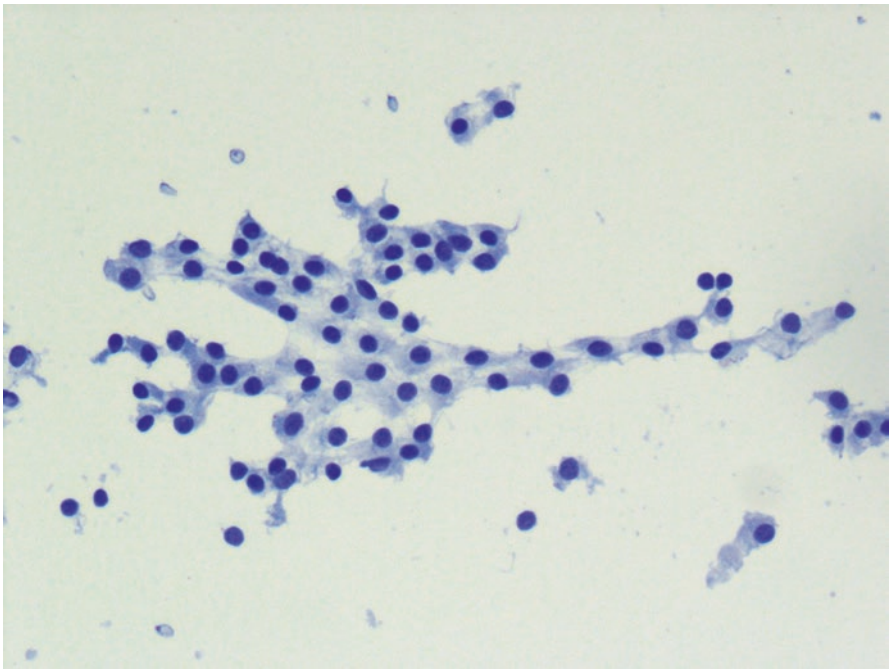

Fig. 5.5 Benign follicular nodule. Bland follicular epithelial cells without nuclear atypia

Follicular epithelial cells are bland, with moderate to abundant cytoplasm. Cytoplasm may be smooth or granular depending on the amount of cytoplasmic organelles and the metabolic activity of the cells. During the aspiration and smearing of the specimen, the cytoplasm may be ripped off, and scattered naked nuclei may be present in the background. Nuclei of normal follicular cells have a very slight variation in size, shape, and chromatin pattern. They are round to oval, monotonous cells with smooth, homogeneous chromatin. The nuclear membrane is usually very smooth and regular, without indentations, grooves, or intranuclear inclusions. Occasionally, one or two small, inconspicuous nucleoli may be seen but without angulations.

Hürthle cells or oncocytes are commonly seen as a part of benign follicular nodules. While Hürthle cell terminology for oncocytic lesions of the thyroid is a misnomer as Hürthle cells are actually the C-cells of dogs [52], it has been well established in the literature and clinical practice to use the name Hürthle for oncocytic cells in this location. Hürthle cells have abundant cytoplasm filled with mitochondria, which gives a homogeneously granular appearance to these cells. Nuclei are round to oval, moderately enlarged, and usually with a single prominent nucleolus. Hürthle cells may also show marked nuclear enlargement, membrane irregularities, and hyperchromasia, which should not be interpreted as atypia or malignancy. It should be noted that there may be "early Hürthle cells" with features intermediate between bland follicular epithelial cells and Hürthle cells.

Background is usually dominated by colloid and may be bloody. Bloody background is a sign of high vascularity and more commonly seen with neoplastic nodules; however, needle size, aspiration technique, and medications such as blood thinning agents may be related to markedly bloody aspirates.

The benign follicular nodule category should not be considered a diagnosis of exclusion. A nodule should not be diagnosed as benign if features are not diagnostic for any specific lesion. The cytopathologist should identify the features of a benign follicular nodule for appropriate diagnosis.

Thyroiditis

Hashimoto Thyroiditis Lymphocytic thyroiditis and Hashimoto thyroiditis seem to be different phases of an autoimmune disease characterized by autoantibodies against thyroid-related antigens. Immune-mediated injury with both cellular and antibody-mediated mechanisms leads to tissue damage, regeneration, and eventually exhaustion of the tissue leading to the morphologic changes.

Four characteristic histo-morphological features of Hashimoto thyroiditis are:

1. Lymphocytic infiltration with germinal centers
2. Hürthle cell metaplasia
3. Follicular atrophy (microfollicles)
4. Fibrous bands of scarring (fibrous variant)

However, Hashimoto thyroiditis is not a single pathologic entity, and there is a wide variation of morphologic features differing in severity and predominant morphologic feature on histology (see Fig. 5.6). Similarly, features of Hashimoto thyroiditis on cytology show marked variations. The major cytologic features of Hashimoto thyroiditis (see Fig. 5.7) are:

1. Presence of a mixed population of lymphoid cells including small, mature lymphocytes, reactive lymphocytes, and occasional plasma cells. Germinal centers may be identified on cytologic smears.
2. Sheets and scattered Hürthle cells with granular cytoplasm, enlarged nuclei, and prominent nucleoli usually predominate the follicular epithelial component on cytology.
3. Presence of microfollicles is not a sign of follicular neoplasia and should not be over-interpreted in these cases.
4. Stromal fragments with capillaries are also seen associated with Hashimoto thyroiditis.

Commonly, the lymphocytic cells seem to intermingle with the epithelial clusters; however, the only finding of Hashimoto thyroiditis may be a slight but definite chronic inflammatory infiltrate in the background of a cellular thyroid aspirate with a mixed Hürthle cell population.

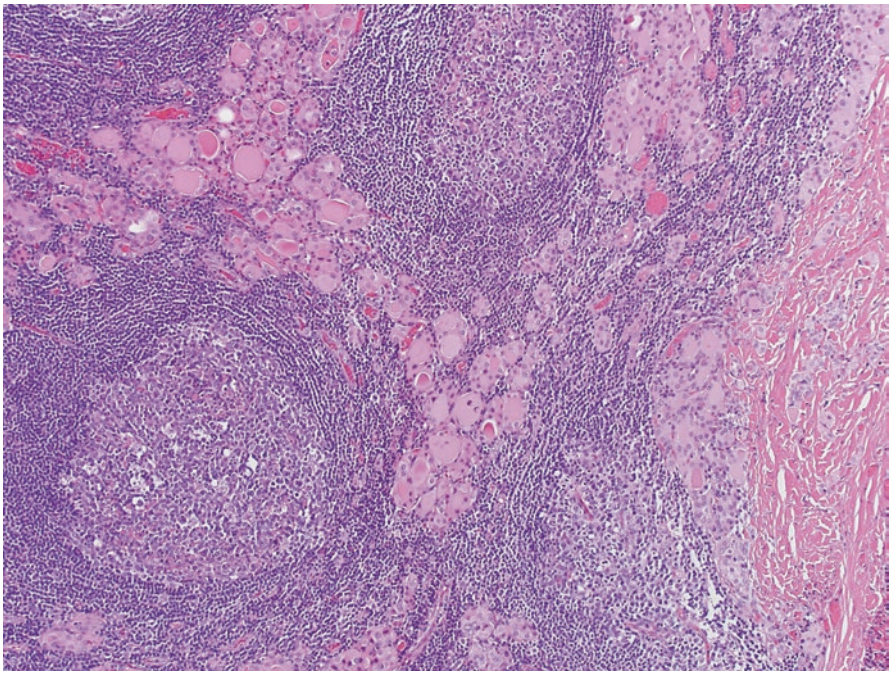

Fig. 5.6 Hashimoto thyroiditis. Histologic section shows thyroid parenchyma infiltrated by abundant lymphoid cells with germinal centers. Follicular epithelial component shows atrophy and prominent Hürthle cell changes

No minimum cytologic requirements are established for diagnosis of Hashimoto thyroiditis on cytology. Some require identification of all four components, including capillaries in smears, while others may report presence of a lymphoid infiltrate as evidence of lymphocytic (Hashimoto) thyroiditis.

Granulomatous Thyroiditis This is an idiopathic disease, usually seen in middle-aged women with painful thyroiditis, often with fever. It is usually bilateral; however, it may be asymmetrical and rarely aspirated. Diagnosis of granulomatous thyroiditis may be possible on aspiration cytology; however, the cellularity varies depending on the activity of the inflammation. The findings are those of a granulomatous inflammation with foreign body type, multinucleated giant cells, the most characteristic finding of this disease (see Fig. 5.8); however, it should be emphasized that multinucleated giant cells can commonly be seen in a variety of thyroid aspirates with and without malignancy, and mere presence of multinucleated cells should not be interpreted as granulomatous thyroiditis. Epithelioid histiocytes and well-formed granulomas may be seen on cytology, some surrounding colloid. Follicular epithelial cells may be abundant in the background, including Hürthle cells. Colloid may be minimal.

Acute Thyroiditis Acute thyroiditis has a typical clinical presentation and usually is not subjected to FNA, unless a drainage and microbiology culture are planned.

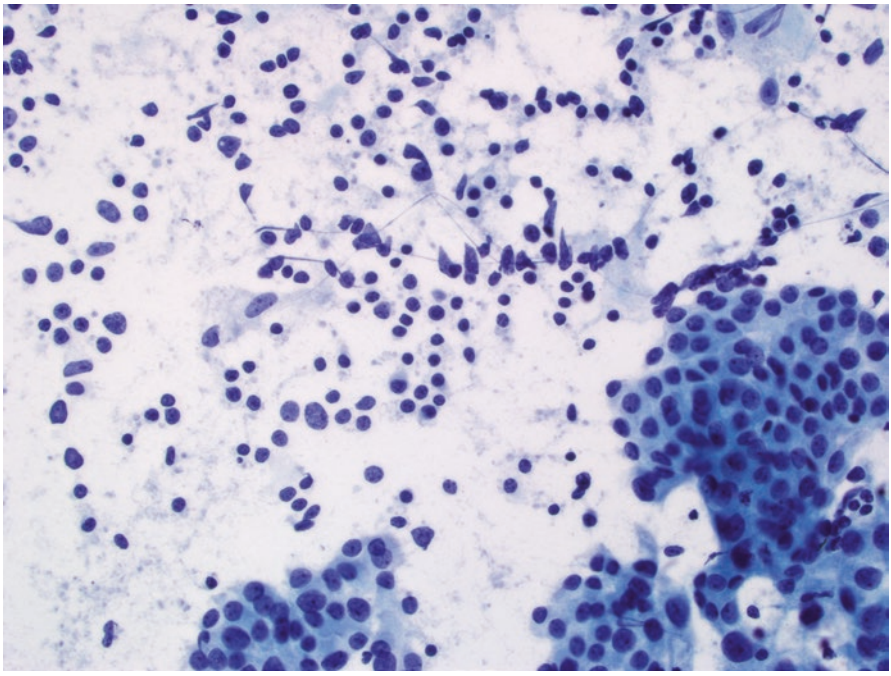

Fig. 5.7 Hashimoto thyroiditis. Most characteristic features of Hashimoto thyroiditis are cellular smears with variable amount of lymphocytic infiltrate and Hürthle cells

FNA material shows abundant acute inflammation and background debris (see Fig. 5.9). Follicular epithelial cells may be a minor component in the background if identified at all. Epithelial cells usually show reactive atypia, which should not be interpreted as neoplastic.

Graves' Disease Graves' disease is an autoimmune thyroiditis, more commonly seen in middle-aged women as diffuse hyperplasia of the thyroid. The patients are usually diagnosed clinically with hyperthyroidism. The disease usually involves the thyroid in a diffuse fashion and is not aspirated. Occasionally, asymmetrical involvement and nodules may be seen on imaging or palpation that may be followed with FNA.

The cytologic features of Graves' disease are not specific and clinical correlation is very helpful. Overall, findings are similar to other benign follicular nodules; however the cellularity may be marked and raise concern for follicular neoplasia. Smears are cellular with mixed follicular cells showing micro- and macrofollicles, a very helpful feature in differentiating these lesions from follicular neoplasms, particularly for those cases where the background colloid is minimal. Occasional papillary hyperplastic groups may be seen, but clinical history and absence of nuclear atypia should steer the cytologist from over-interpreting these as papillary carcinoma.

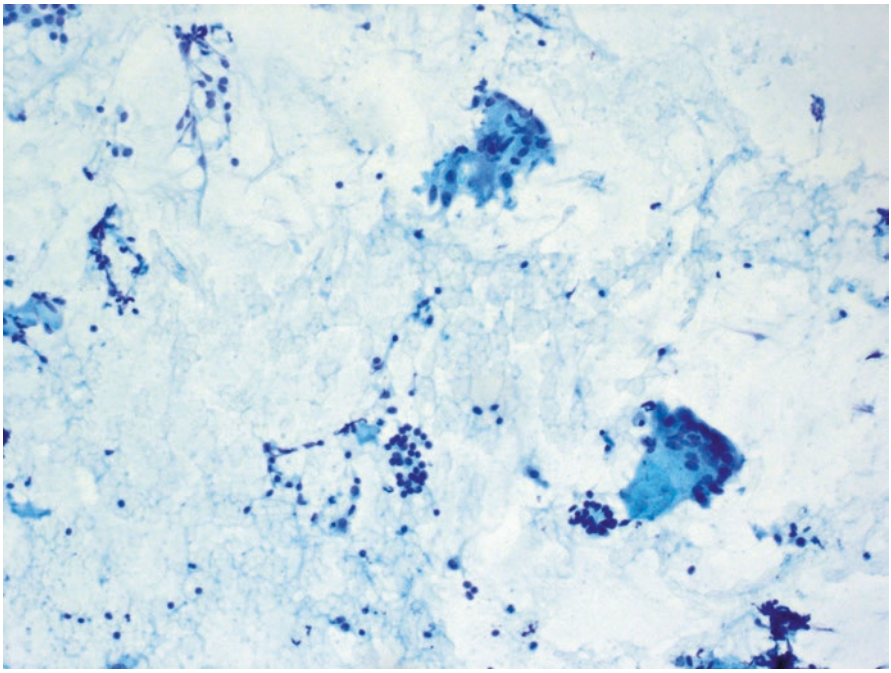

Fig. 5.8 Subacute thyroiditis. Bland follicular cells, lymphocytes, and multinucleated giant cells are seen

A mixed lymphoid background with or without Hürthle cells may be present; however, it is usually much less pronounced than Hashimoto thyroiditis.

Riedel Thyroiditis This is a very rare form of thyroiditis characterized by marked fibrosis extending outside the thyroid parenchyma, raising concern for malignancy. Cytologically, specimens are usually not cellular and may show mixed chronic inflammation with relative lack of follicular cells and colloid. In this clinical setting, the most important finding is the absence of a cytologically diagnostic malignancy, such as anaplastic carcinoma or sarcoma.

Atypia of Undetermined Significance or Follicular Lesion of Undetermined Significance (AUS/FLUS)

This is the most controversial category in the Bethesda system; however, it serves a specific purpose in reporting and management of thyroid nodules with certain morphologic features. It should be noted that this category does not pertain to a single type of lesion or pathologic correlate but should rather be considered to be any type of lesion identified on cytology with a malignancy risk higher than benign but lower

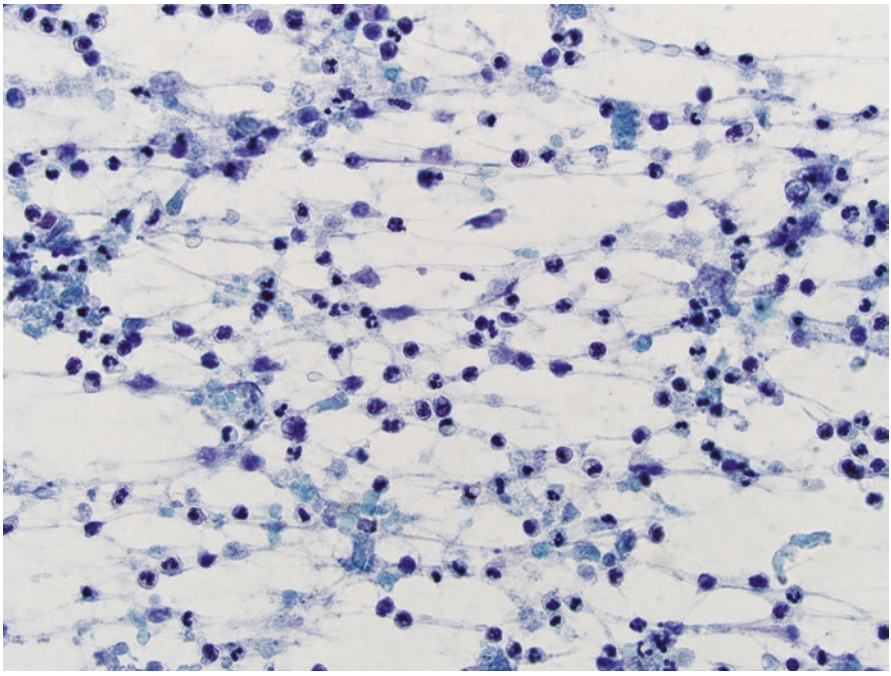

Fig. 5.9 Acute thyroiditis. Acute inflammatory infiltrate. Follicular cells may not be identified in smears

than follicular neoplasia/suspicious for follicular neoplasia or suspicious for malignancy, i.e., in the range of 5–15 % [16]. This is the range that is considered by some to be not high enough for immediate surgical intervention but too high for routine follow-up. The definition of AUS/FLUS is broad and covers multiple scenarios. The most common scenarios described in the Bethesda system involve those lesions where there is a small but definitive concern for a follicular neoplasm, Hürthle cell neoplasm, or malignancy (papillary thyroid carcinoma); however, atypia involving lymphoid or other cells types including medullary carcinoma can also be in this category. The lesion may not be well represented on the aspirate slides due to various reasons such as low cellularity, obscuring hemorrhage, and preservation/staining artifacts, or the clinical background may only partially explain the atypia seen in the specimen, such as Hashimoto thyroiditis, history of radiation exposure, or drugs such as carbimazole.

In the Bethesda system, specific situations are listed with a final "not otherwise categorized." To prevent overutilization of this category as a "wastebasket" diagnosis, a recommendation was made to limit this category in the range of 7 % of all thyroid FNAs. As expected, the reproducibility of this category is far from perfect [32] and the terminology is used differently in many practices [23, 53]. Additionally, the recommended malignancy risks for this group showed marked variability in the literature, usually exceeding the expected range of 5–15 % [27, 54–61].

Since BSRTC became more widely accepted and used, the risk stratification of the atypical category showed significant variations not only among institutions but also how it is reported. While the Bethesda system does not recommend subdividing the AUS/FLUS category, many suggested that the atypical category should be reported in subgroups with descriptive qualifiers as they represent different risks of malignancy. Considering the recent reported findings in the current literature, this category can, at least theoretically, be divided into the following subgroups [27, 54–62]:

1. AUS with nuclear atypia, concerning for papillary thyroid carcinoma (PTC); however, findings are not sufficient for a diagnosis of "suspicious for malignancy" or "malignancy." These mostly include atypia in a limited number of cells. There is a significant body of literature showing that this group has the highest risk of malignancy, ranging from 28 to 56 %.

   These cases show focal nuclear enlargement and nuclear membrane irregularities including grooves and homogenous pale chromatin in an otherwise benign FNA (see Fig. 5.10). It should be noted that, in many series, it may be appropriate to place these cases into the "suspicious for malignancy" category instead of AUS. It is of great importance for the cytopathologist to interpret

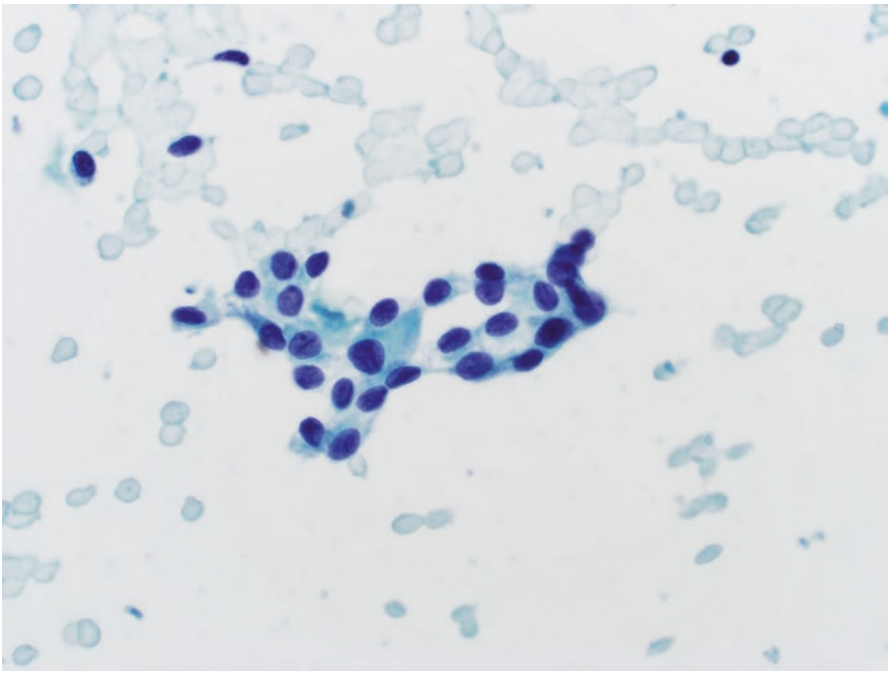

Fig. 5.10 Atypical of undetermined significance. Small, cohesive epithelial cells with finely granular chromatin and nuclear grooves. Nuclei are somewhat more elongated than round. No Hürthle cell morphology is evident. In isolation, this epithelial group raises concern; however, it is not sufficient for the cytologic diagnosis of suspicious for PTC or malignancy

cytologic atypia and features of PTC appropriately. Only those cases that the nuclear features cannot be explained by reactive changes in the background of Hashimoto thyroiditis, history of radiation, medications, identifiable cyst-lining cells, etc., should be reported as atypical. Similarly, if there is a pattern of atypical features or a separately identifiable population of cells with atypical features raising concern for PTC, those should be reported as "suspicious for malignancy." In many institutions, any intranuclear cytoplasmic invaginations (INCI) seen in follicular epithelial cells on a well-fixed, appropriately stained slide are reported as at least suspicious for malignancy, not AUS. For these reasons, the reader should become familiar with the diagnostic features of PTC described in the sections below.

AUS with prominent microfollicles in a sparsely cellular specimen or in the background of a mixed pattern where findings are not supportive of a diagnosis of follicular neoplasm (see Fig. 5.11). Overall, the risk of malignancy in this category is relatively low, on average 5–25 %, depending on how the data is obtained. In our experience, the risk is closer to the lower end of the spectrum.

2. *AUS with predominance of Hürthle cells* in a sparsely cellular specimen or in the background of Hashimoto thyroiditis or multinodular goiter. This category seems to be more heterogeneous and complex; however, it seems to have a very low risk of malignancy, less than 10 % in most series.

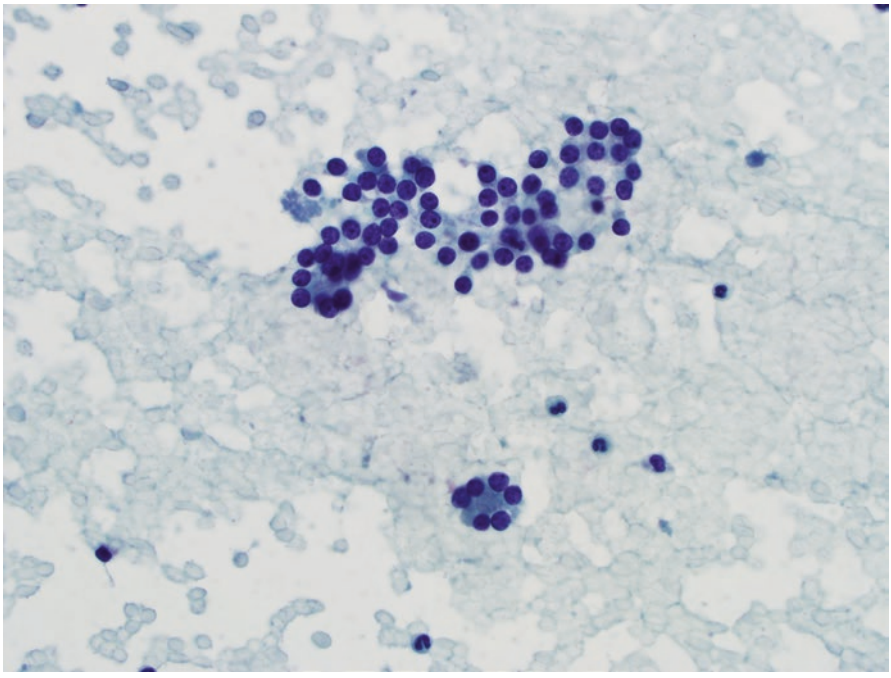

Fig. 5.11 Microfollicles. Bland follicular cells forming flat or three-dimensional groups with 15 cells or less

Some authors further characterize Hürthle cells as those with dysplasia and those without dysplasia; however the reproducibility of this practice is not well established, mostly because Hürthle cells associated with benign proliferations commonly show nuclear enlargement, chromatin clumping, hyperchromasia, nuclear membrane irregularities, and degenerative changes with or without high nuclear-to-cytoplasmic (N/C) ratios. However, if there is a monotonous population of Hürthle cells, particularly without background benign features or Hashimoto thyroiditis, it is still appropriate to report these cases AUS/FLUS.

3. *AUS*, *not otherwise specified* (*NOS*), involving other cellular components, including lymphoid cells in Hashimoto thyroiditis or atypia that cannot be characterized due to specimen processing and staining problems. History of radiation exposure including radioactive iodine and other drugs may also show nuclear atypia, which may be diagnosed as AUS/FLUS. Cytologic changes seen in cyst-lining cells can also be in this group. Obviously, this is a mixed group with overall risk of malignancy averaging 8–36 %.

   It is important to clearly communicate the cytologic findings in the pathology report. If the clinical team is not aware of the significance of the findings and relative risks that are associated with individual diagnoses, it is best to include a comment about clinical significance in reporting individual cases. This is best accomplished by obtaining institutional data as there is significant variation in risk of malignancy in different practice settings [55, 63].

   In most practices, the next step after a diagnosis of AUS/FLUS is repeat aspiration. Similar to the discussion for nondiagnostic aspirates, an appropriate interval of 3 months has been suggested, but there is no evidence to support this interval. In over half of AUS/FLUS cases, a repeat FNA will be diagnostic, most often with a benign diagnosis [37, 64–66], thus significantly reducing unnecessary thyroid surgery.

   It should also be noted that the malignancy risk associated with only surgically excised cases show an erroneously elevated malignancy risk for this category, as those cases may have additional clinical or imaging findings suspicious for malignancy.

Follicular Neoplasm/Suspicious for Follicular Neoplasm (Including Oncocytic Lesions)

Follicular-patterned lesions form the largest and most heterogeneous group in the thyroid ranging from benign, non-neoplastic follicular hyperplasias to follicle-forming infiltrating carcinomas. These lesions share common morphologic features on cytology, and FNA is not a reliable tool for differentiating these lesions on cytologic grounds. Diagnosis of malignancy relies on histologic evidence of an infiltrative lesion, which cannot be assessed on aspiration specimens. Therefore, a follicular neoplasia (FN) diagnosis on cytology covers the main differential of cellular hyperplastic nodules, follicular adenomas, follicular carcinomas, and follicular variant of

papillary thyroid carcinoma (FVPTC). A recently updated terminology for some of the lesions that used to be included in the category of encapsulated follicular variant of papillary carcinoma, i.e., "noninvasive follicular thyroid neoplasm with papillary-like nuclear features" (NIFTP), should also be included in this differential (see discussion below) [67]. In a recent study, 56% of these benign lesions that were surgically removed had a preoperative cytologic diagnosis of follicular neoplasm [68]. In addition, some rare tumors, such as medullary carcinomas, poorly differentiated thyroid carcinomas, parathyroid proliferations, and some metastatic carcinomas, may also be reported as FN [69].

In the Bethesda system, the FN category is considered to carry a malignancy risk of 15–30%. Considering the heterogeneous nature of this category, it is possible to divide this group into subgroups with separate morphologic characteristics and corresponding malignancy risks.

1. *Bland hypercellular follicular lesions*: Benign follicular hyperplasia is the most common histologic lesion in the thyroid, and FNA can easily classify these lesions as benign with high sensitivity and specificity. However, those lesions with marked cellularity, overcrowding, and abundant microfollicles with scant background colloid enter the spectrum of FN (see Fig. 5.12). Even in histologic sections, definitive diagnosis depends on complete evaluation of the entire capsule of the lesion, which is not possible on cytology. Therefore, the spectrum

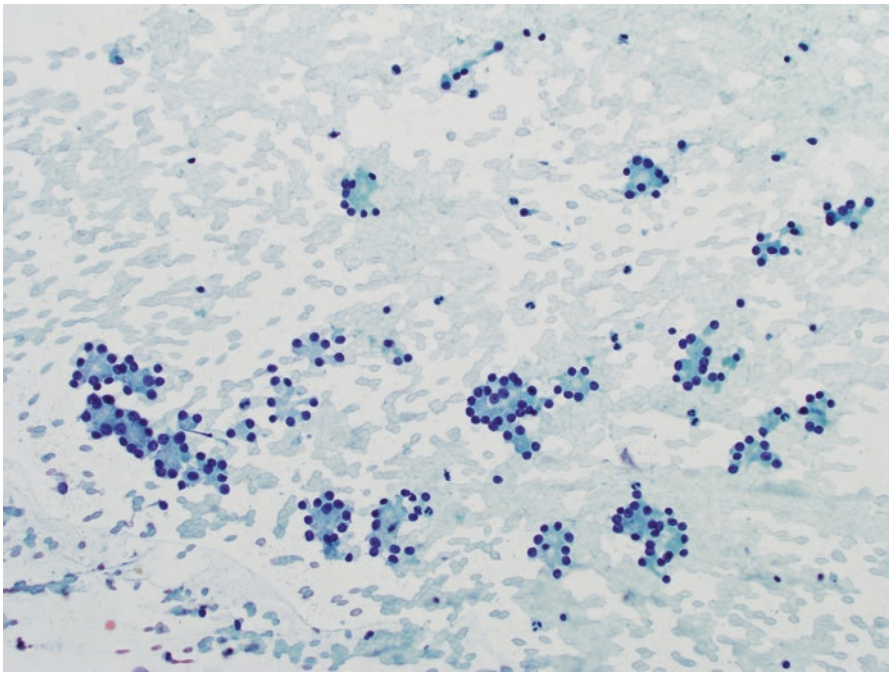

Fig. 5.12 Bland hypercellular follicular lesions. Bland follicular epithelial cells with abundant microfollicles in the background of scant to absent colloid. No nuclear atypia is present

of lesions in this group includes cellular hyperplastic nodules on one end and invasive follicular carcinomas on the other. Increased nuclear-to-cytoplasmic (N/C) ratios, marked cellularity, dyscohesion, and three-dimensional clusters have been suggested as possible signs of "malignancy" in this group; however, these have not been proven to be reproducible in larger studies [70, 71].

The border between the Bethesda system categories of AUS/FLUS and FN is not well defined; however, increased cellularity with microfollicles and "uniformity" of both cells and architecture are reliable signs of neoplasia. Characteristically, there are more cells than colloid in FN.

Overall risk of malignancy in this group of FN shows a wide range in different clinical practices, depending on the terminology used, but seems to be in the range of 25–30% [14, 15, 42, 65, 72–75].

2. *Microfollicular lesions with nuclear atypia*: Cases that show nuclear features of PTC should not be diagnosed as FN, and those with concern for the possibility of PTC should be reported as suspicious for malignancy. However, it has been well documented that characteristic nuclear features of PTC may not be obvious, particularly in follicular variant of PTC (FVPTC) [76–81]. Therefore, these lesions are commonly diagnosed with other follicular-patterned lesions in the FN category.

   For FNAs with a prominent follicular pattern and only rare nuclear membrane irregularities, the most appropriate diagnosis may still be FN; however, we believe that if the pathologist considers PTC in the differential diagnosis of an otherwise classic FN pattern, it should be noted in the cytology report. This has been supported by the fact that the majority of malignancies associated with FN diagnoses are PTC, particularly FVPTC [14, 15, 65, 72, 74, 75, 82]. It is important to note that cases where the pathologist renders an FN diagnosis with a possibility of PTC have a significantly higher risk of malignancy on excision [78, 83], usually intermediate between the FN and suspicious categories, commonly greater than 50%. Any atypical nuclear features, particularly nuclear enlargement, grooves, and syncytial clusters, are highly significant and, due to their associated increased risk of malignancy, should be reported (see Fig. 5.13).
3. *Hürthle cell neoplasias*: Hürthle cells are morphologically distinct follicular cells with abundant, granular cytoplasm with enlarged, round-to-oval nuclei and prominent nucleoli. Cytoplasmic granularity is the result of abundant mitochondria, which also show irregular morphologic features [84].

   Hürthle cells are modified follicular cells, and, morphologically, similar features may be seen in different tumors in the thyroid and also in other organs (oncocytic neoplasms of the salivary gland, kidney, esophagus, etc.). Therefore, it is unlikely that these are a specific or separate type of cells but instead an end point in cellular differentiation. Abundant granular cytoplasm with large, round-to-oval nuclei and conspicuous nucleoli can also be seen in some cases of papillary thyroid carcinoma (PTC) and medullary thyroid carcinoma (MTC); however, those should not be diagnosed as Hürthle cell neoplasia but PTC and MTC, respectively. As with any other PTC, the diagnosis of Hürthle cell variant is made on the nuclear features. While some nuclear enlargement and nuclear membrane

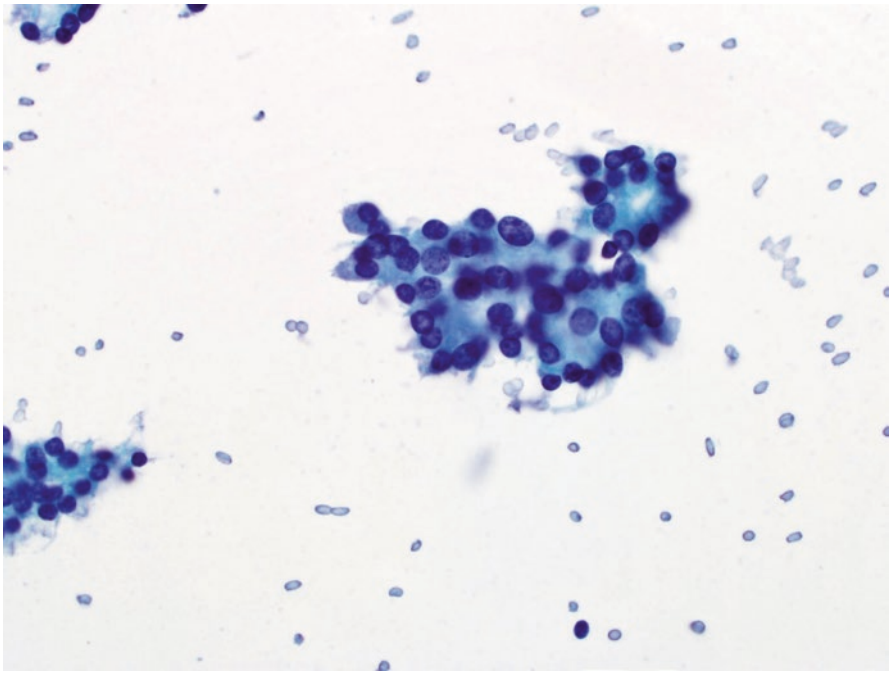

Fig. 5.13 Microfollicular lesions with nuclear atypia. Cohesive clusters forming microfollicles; however, anisonucleosis and areas of chromatin clumping and clearing are evident

irregularities may be seen in Hürthle cell lesions, finely granular chromatin and intranuclear pseudoinclusions are not features of Hürthle cells and should raise concern for PTC. Although not truly a Hürthle cell lesion, occasional MTCs with abundant granular cytoplasm may have overlapping morphologic features. Typical neurosecretory granules of MTC stain red in Romanowsky stains, in contrast to the blue staining granularity of Hürthle cells [16, 85].

Follicular neoplasm, Hürthle cell type (FNHCT), is the terminology suggested by the Bethesda system where the risk of malignancy for this diagnosis was reported to be the same as other follicular neoplasias, i.e., 15–30 %. The diagnostic features of the FNHCT are the same as FN of non-Hürthle cell type. Specimens show abundant cellularity with a dominant monotonous population of Hürthle-type cells with little or no colloid in the background (see Fig. 5.14). Most Hürthle cell lesions show little or no cohesive characteristics, and large three-dimensional clusters are only rarely seen in Hürthle cell tumors. When present, they are highly suggestive of FNHCT. It should also be noted that Hürthle cells are common components of benign follicular nodules and Hashimoto thyroiditis. Therefore, the mere presence of an abundant Hürthle cell component is not an atypical finding in the background of such benign lesions. Hürthle cells should be considered atypical or neoplastic when the cytologic specimen is dominated by a monotonous Hürthle cell component. Some cytologic features have also been suggested

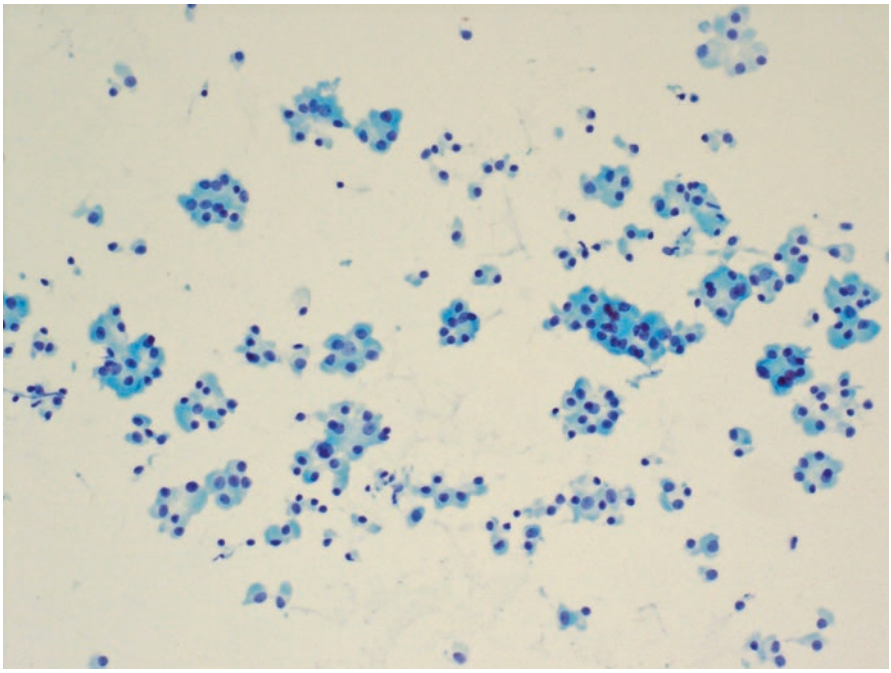

Fig. 5.14 Hürthle cell neoplasm. Monotonous population of abundant Hürthle cells with no colloid in the background. Surgical excision of this lesion showed a Hürthle cell carcinoma with angioinvasion

to identify malignancy in oncocytic lesions, such as small cell or large cell dysplasia, dyscohesion, scant colloid, and syncytia formation; however, these features are more significant for the diagnosis of Hürthle cell tumors than diagnosis of Hürthle cell carcinoma on cytologic grounds [86].

BSRTC places these lesions in the same risk category with other FNs. We believe Hürthle cell neoplasia is an uncommon diagnosis and should be reserved for those with an abundant, monotonous population of Hürthle cells with dyscohesion, minimal to absent of colloid, and lack of features of chronic thyroiditis. When these criteria are applied, the risk of malignancy is probably close to the non-Hürthle cell FN. However, depending on how strictly the criteria are applied, the risk of malignancy may be significantly lower, due to the fact that Hürthle cells are very commonly seen in nonneoplastic thyroid nodules.

4. *Follicular neoplasias*, *not otherwise specified*:

As with other classification schemes, not all cases can be categorized into certain groups, and there will be cases with morphologic features not specific enough for any further classification. In our experience, some medullary carcinomas, parathyroid lesions, poorly differentiated carcinomas, and some metastatic lesions may show features of FN. Chronic thyroiditis should be briefly mentioned in this section as aspirates may show features resembling FN. If clinical

history of thyroiditis is present or any of the morphologic features of thyroiditis are identified, including chronic inflammation (other than those present in peripheral blood), admixed Hürthle cells, and transgressing vessels, a cytologic diagnosis of FN should be made with extreme caution, if ever, as the overwhelming majority of such cases are benign [87].

Suspicious for Malignancy

This is not a specific category with defined morphologic features but instead an intermediate group of lesions where a diagnosis of malignancy is suspected but cannot be definitively established. In the Bethesda system, certain scenarios are listed as patterns that fall into this category [16]:

1. Patchy malignant nuclear changes in a benign background
2. Incomplete nuclear changes of malignancy
3. Features of malignancy in a sample with very low cellularity
4. Nuclear atypia in a cystic background

Although these descriptions may give the cytologist an idea about the morphologic features that are commonly associated with this diagnosis, we do not believe that it is possible to group and categorize all cases that are suspicious for malignancy. Additionally, there is no convincing evidence that categorizing different suspicious patterns has any clinical significance or specific malignancy risks. Instead, it should be considered as when the diagnosis of malignancy, mostly PTC, cannot be established with certainty (see Fig. 5.15). It should be noted that this is an intermediate category without set morphologic borders, similar to the atypical group, and the definition and practical applications will be quite subjective and operator dependent. It is recommended that individual practices collect their own data to document the risk of malignancy associated with this diagnosis in their practice.

This category comprises about 1.3–9 % of all thyroid FNAs and, as expected, shows variations in different patient populations and cytology practices [14, 15, 37, 42]. It is important to note that, particularly in the older literature, the suspicious and follicular neoplasia categories may have been reported together [9, 33, 88].

The malignancy risk for this category is also variable and operator/population dependent. In the Bethesda system, the malignancy risk for this category is suggested to be in the range of 60–75 %, which seems to be in line with the majority of reported series. In Bongiovanni's meta-analysis of multiple series with a combined case number of over 25,000, the average malignancy risk was 75 % [20]. More recently, however, the Endocrine Pathology Society has introduced the term "noninvasive follicular thyroid neoplasm with papillary-like nuclear features" (NIFTP) for a subset of thyroid tumors that were previously called malignant [67]. In a small series published by Maletta [68], 27 % of cases of NIFTP were preoperatively interpreted as suspicious for malignancy. As this is a new terminology that classifies cases that were previously called malignant as benign, the long-term impact of this change on malignancy risk is yet to be determined in larger series.

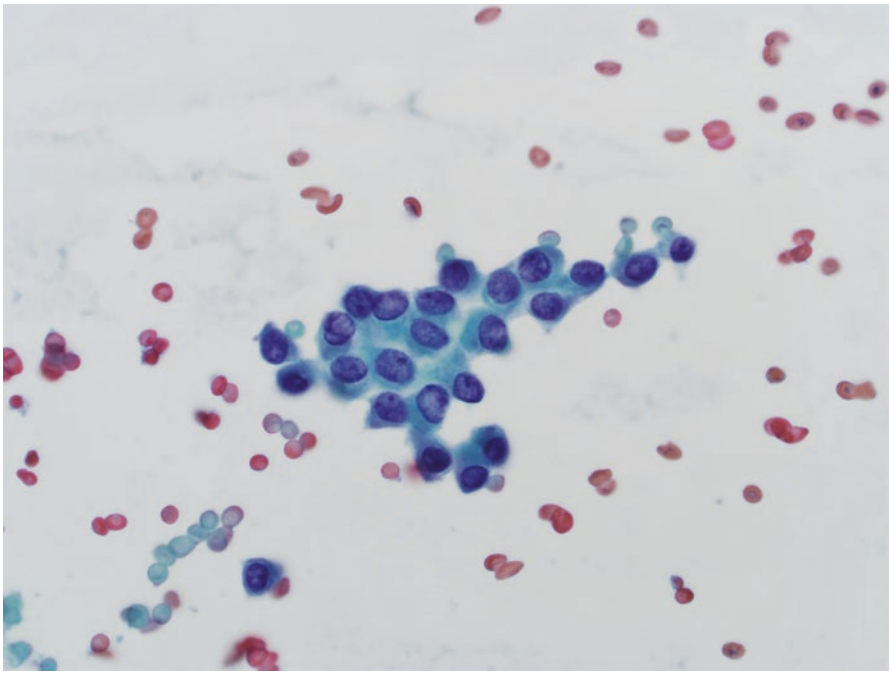

Fig. 5.15 Suspicious for papillary thyroid carcinoma. Small cohesive epithelial group with nuclear membrane irregularities that, in isolation, may not be sufficient for diagnosis of papillary thyroid carcinoma. Surgical excision of this lesion showed papillary carcinoma

The majority of malignancies in the suspicious category are PTC, as expected. Therefore, most centers follow-up with a lobectomy for these cases, usually with intraoperative frozen section evaluation. We believe that these cases should be the primary indication for frozen section evaluation of thyroid nodules. However, it has been also suggested that a total thyroidectomy would be a more cost-effective approach for these patients [89]. The 2015 ATA guidelines strongly recommend surgical management similar to that of malignant cytology depending on clinical and imaging features and patient preference.

For the majority of cases, the suspicion is for PTC; however, depending on the morphologic features, other tumors such as medullary carcinoma, lymphoma, or metastatic lesions can be reported in this group. Literature on these non-PTC cases is limited and likely to show a malignancy risk close to or above the risk for "suspicious for PTC."

Malignant

In approximately 4–8 % of thyroid FNAs, a definitive diagnosis of malignancy can be rendered [14]. These are cases where the diagnostic morphologic, immunophenotypic, or molecular features for a specific thyroid malignancy are adequately

present. Additional information that is provided in the pathology report should include descriptive language that specifies the type of malignancy and results of ancillary studies that contributed to the diagnosis.

Papillary Thyroid Carcinoma (PTC) Papillary thyroid carcinoma is the most common malignancy in this category, estimated to comprise 80 % of thyroid malignancies, with a generally good prognosis [90]. The classic cytologic features of PTC are often easily identified on FNA, making it a safe, effective, minimally invasive, and inexpensive method to diagnose malignancy [16]. Aspirates of classic papillary thyroid carcinoma are typically hypercellular, with the cells typically arranged in monolayered sheets, swirls, or papillary structures. These papillary clusters often exhibit branching with nuclear palisading. However, it is the characteristic nuclear features that, when adequately present, give the cytologist the most assurance to render a diagnosis of PTC. These include nuclear enlargement and often elongation with pale, powdery nuclear chromatin, enhanced nuclear membranes, and micronucleoli. Nuclear membrane irregularities manifest as linear nuclear grooves (more sensitive) and intranuclear cytoplasmic inclusions (more specific). Thick ("bubble gum") colloid, psammoma bodies, and multinucleated giant cells are helpful features when present, but they are not necessary to render this diagnosis (see Fig. 5.16).

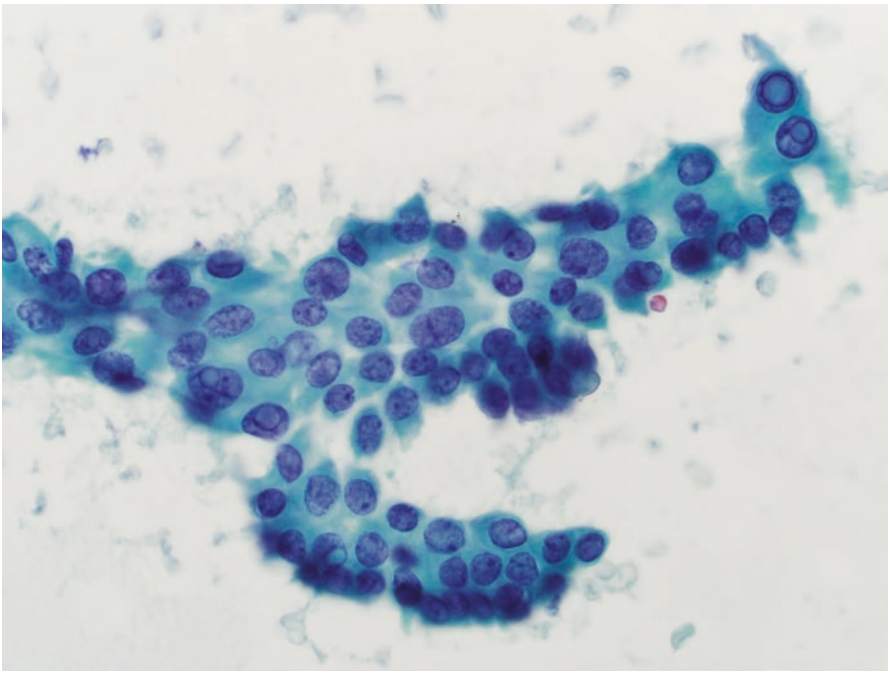

Fig. 5.16 Papillary thyroid carcinoma: Cohesive cluster of epithelial cells with anisocytosis, nuclear membrane irregularities including prominent intranuclear pseudoinclusions, more specific feature of this diagnosis

Although a few immunochemical markers have been suggested as helpful in establishing a diagnosis of PTC, most cases can be confidently diagnosed based on the cytomorphologic features alone. However, many cytologic variants of PTC have been described, including but not limited to follicular (predominantly microfollicles) [91], macrofollicular (>50 % macrofollicular architecture) [92], cystic (hypervacuolated tumor cells and macrophages) [93], oncocytic (granular cytoplasm) [94], Warthin-like (oncocytic tumor cells in a lymphoplasmacytic background) [95], tall cell (an aggressive PTC with elongated tumor cells that are three times higher than wide) [96], and columnar cell (also aggressive with stratified, elongated nuclei) [97] variants. The classic cytologic features of PTC may be more subtle in these variants, which may hinder a definitive diagnosis and relegate the case to the previously mentioned indeterminate categories [98].

A subgroup of encapsulated follicular variant of PTC has been identified to behave in a benign fashion. This subgroup is characterized by the absence of capsular or vascular invasion (i.e., noninvasive), lack of psammoma bodies, mitotic activity less than 3 per 10 high-power fields, no tumor necrosis, and none of the cytomorphologic characteristics of other PTC variants (such as tall cell, solid, etc.). A new terminology, namely, "noninvasive follicular thyroid neoplasm with papillary-like nuclear features" (NIFTP) has been proposed for these tumors by the Endocrine Pathology Society to avoid the term "carcinoma" [67]. However, it should be kept in mind that these lesions may show diagnostic features of PTC on preoperative cytologic evaluation. In a series of 96 histologically proven NIFTP cases, 2 had been called malignant on cytology [68].

Medullary Thyroid Carcinoma (MTC) Medullary thyroid carcinoma is an aggressive differentiated cancer arising from parafollicular C-cells, accounting for approximately 5 % of all thyroid malignancies [99]. Most cases are sporadic, which typically present as a solitary thyroid nodule in adulthood, while the less common hereditary forms associated with multiple endocrine neoplasia 2 (MEN2) are usually identified as multifocal disease at an earlier age [90]. On FNA cytology, MTC is characterized by cellular smears composed of plasmacytoid, spindled, and/or epithelioid/Hürthloid cells [16]. The cells are typically dyscohesive and show variation in nuclear size and shape, with frequent binucleation and multinucleation. Given the neuroendocrine nature of parafollicular C-cells that give rise to MTC, nuclear chromatin has a granular ("salt-and-pepper") appearance, and nucleoli are inconspicuous (see Fig. 5.17). Cytoplasmic secretory granules may also be seen. The presence of intranuclear cytoplasmic inclusions and extracellular amyloid (which often appears like thick "bubble gum" colloid) may cause confusion with PTC. In contrast to colloid, amyloid does not exhibit typical cracking artifact, and if Congo red stain is performed on the cytologic preparation, it should exhibit characteristic apple-green refringence on polarizing microscopy.

Rare cytologic variants of MTC have been described, including the small cell, giant cell, clear cell, squamoid, melanotic, and mucinous variants [100]. Architecturally, besides the dispersed cell pattern, other rare presentations include rosette forming, follicular, papillary, and trabecular patterns. These different variants

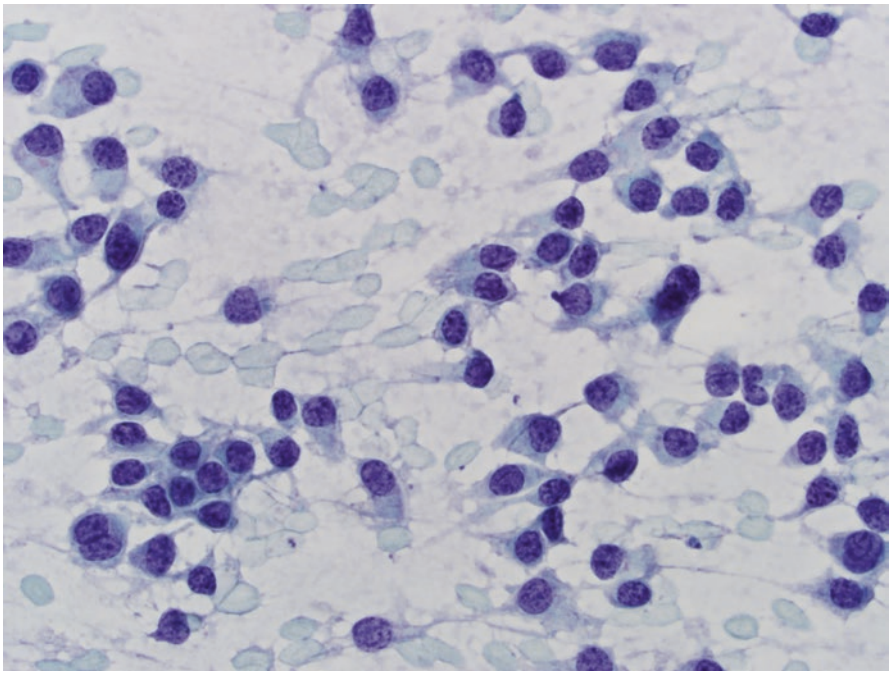

Fig. 5.17 Medullary thyroid carcinoma: Cellular specimen with scattered dyscohesive cells, some with binucleation. Characteristic "salt-and-pepper" granularity of the chromatin is a feature of neuroendocrine differentiation

may pose a challenge in the diagnosis of MTC. Fortunately, immunochemistry for calcitonin can help establish a diagnosis of MTC in its classic and variant forms, with sensitivity ranging from about 75 % in sporadic cases to 100 % in hereditary cases. Calcitonin immunostain is also relatively specific for MTC, although nonspecific staining may be seen in oncocytic neoplasms. Immunostains for carcinoembryonic antigen (CEA) and chromogranin A may also provide additional confirmatory evidence for a diagnosis of MTC. The sensitivity of CEA stain is comparable to calcitonin, but it is less specific, as it is elevated in a variety of benign and malignant conditions [101]. Since MTC is not a follicular cell-derived malignancy, negative thyroglobulin stain can serve as a pertinent negative in the FNA workup of suspected MTC. If cytologic material is not sufficient for confirmatory immunostains, measurement of serum calcitonin and CEA may be recommended [102].

Poorly Differentiated Thyroid Carcinoma (PDTC) Poorly differentiated thyroid carcinoma is a moderately aggressive thyroid malignancy that shows only limited cytologic features of follicular differentiation. In original descriptions of this tumor, the cells were noted to form large round to oval groups or "insulae" [103]. However, both insular and non-insular (trabecular and solid) histologic patterns of PDTC are currently recognized [90], with FNA smears showing variable proportions of cells

in cohesive groups or presenting as single dyscohesive cells [16]. Cytologically, these tumors are characterized by a high cell/colloid ratio. PDTC nuclei are small with only mild to at most moderate atypia, but the abundance of mitotic figures and necrosis are clues to the more aggressive nature of this tumor. PDTC may present as a focal finding in an otherwise well-differentiated (papillary, follicular, or Hürthle cell) carcinoma, or its cytologic features may overlap with other tumors (especially follicular neoplasms and medullary thyroid carcinoma), which may lead to its misclassification [104].

Undifferentiated (Anaplastic) Thyroid Carcinoma (UTC) Undifferentiated (anaplastic) thyroid carcinoma is the most aggressive of thyroid malignancies with the poorest survival compared to well-differentiated and poorly differentiated thyroid carcinomas [90]. They mostly occur in the elderly. By definition, these tumors show no specific thyroid differentiation. Well-prepared FNA smears are highly cellular (unless there is marked fibrosis), with giant cells, spindle cells, and squamoid cells exhibiting marked pleomorphism including single or multiple bizarre nuclei [16]. There is coarse chromatin clumping with one or more prominent nucleoli. Mitotic figures (including atypical forms) and necrosis are often prominent; excessive necrosis may diminish the number of diagnostic cells. Osteoclast-like giant cells may be present. Due to invasion of adjacent structures, extrathyroidal elements such as skeletal muscle may be seen in the FNA sample. Since by definition UTC shows no specific thyroid differentiation, TTF-1 and thyroglobulin immunochemistry are usually negative [105]. The most reliable immunostain for UTC is pankeratin but even that stain is negative in up to half of cases. This misleading staining pattern may raise the possibility of sarcoma, but it should be noted that primary sarcomas of the thyroid are extremely rare.

Squamous Cell Carcinoma (SQC) Squamous cell carcinoma of the thyroid is a rare but also highly aggressive thyroid malignancy. Cytologically, it is exclusively composed of large pleomorphic epithelial cells with keratinization, usually associated with necrosis [90]. Cytologically and immunophenotypically, SQC of the thyroid is identical to SQC of other sites, thus correlation with clinical and imaging findings is necessary to rule out metastasis. SQC may be confused with UTC exhibiting abundant squamoid cells, but this distinction is not clinically significant as the management for both malignancies is similar [106].

Primary Lymphoma Primary lymphoma is a relatively uncommon thyroid malignancy, comprising approximately 5 % of thyroid tumors and extranodal lymphomas [90]. Preexisting Hashimoto thyroiditis is a risk factor for developing primary thyroid lymphoma, the vast majority of which are of B-cell type and are thought to arise from mucosa-associated lymphoid tissue (MALT) [107]. Hodgkin lymphoma and plasma cell neoplasms of the thyroid are rare, often representing direct extension from a nearby lymph node or thymic mass and MALT-type lymphoma with prominent plasmacytic differentiation, respectively. The FNA cytomorphology will depend on the specific type of lymphoma [16]. Large cell lymphoma typically presents as a dense, dyscohesive population of large atypical

lymphocytes, similar to large cell lymphoma of other sites. Cytoplasmic fragments (lymphoglandular bodies) are commonly seen. Extranodal marginal zone B-cell lymphoma, on the other hand, is characterized by a mixed lymphoplasmacytic population, which may be difficult to distinguish from thyroiditis [108]. Therefore, if appropriate cytologic material is available, ancillary studies such as flow cytometry, immunochemistry, or molecular testing are usually necessary to arrive at a definitive diagnosis [109].

Secondary Tumors Secondary tumors of the thyroid may be the result of hematolymphoid spread of distant malignancies [110] or direct extension from adjacent organs such as the pharynx, larynx, trachea, esophagus, cervical lymph nodes, cervical soft tissue, and mediastinum [111]. Although in clinical series metastases to the thyroid are less common and usually present as solitary masses, in autopsy series up to 25 % of patients with disseminated malignancy are found to have thyroid involvement, typically in the form of multiple variably sized nodules. The most common primary malignancies include kidney, breast, lung, uterus, stomach, colorectal, melanoma, and leukemia/lymphoma [112, 113]. Rare cases of metastatic nasopharyngeal carcinoma [114], choriocarcinoma [115], and sarcoma [116] have also been reported in the thyroid. FNA diagnosis of secondary thyroid malignancy is often aided by immunochemistry and clinical history of a known extrathyroidal tumor, although occasionally the thyroid tumor may be the first manifestation of disease [117].

The positive predictive value of malignancy in a thyroid FNA is over 97 % [42]. Surgical management of a malignant diagnosis is generally thyroidectomy, except for certain diagnoses including metastasis, lymphoma, and undifferentiated carcinoma, which should be determined based on the individual features of the case.

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