Benign

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Tarik M. Elsheikh, Béatrix Cochand-Priollet,
Soon Won Hong, and Mary K. Sidawy

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.

T.M. Elsheikh (✉)
Department of Pathology, Cleveland Clinic,
9500 Euclid Ave. L-25, Cleveland, OH 44195, USA
e-mail: elsheit@ccf.org; elsheikht@gmail.com

B. Cochand-Priollet
Department of Pathology, Cochin Hospital-University Paris 5, Paris, France

S.W. Hong
Department of Pathology, GangNam Severance Hospital/Yonsei University,
College of Medicine, Seoul, Republic of Korea

M.K. Sidawy
Department of Pathology, MedStar Georgetown University Hospital, Washington, DC, USA

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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).

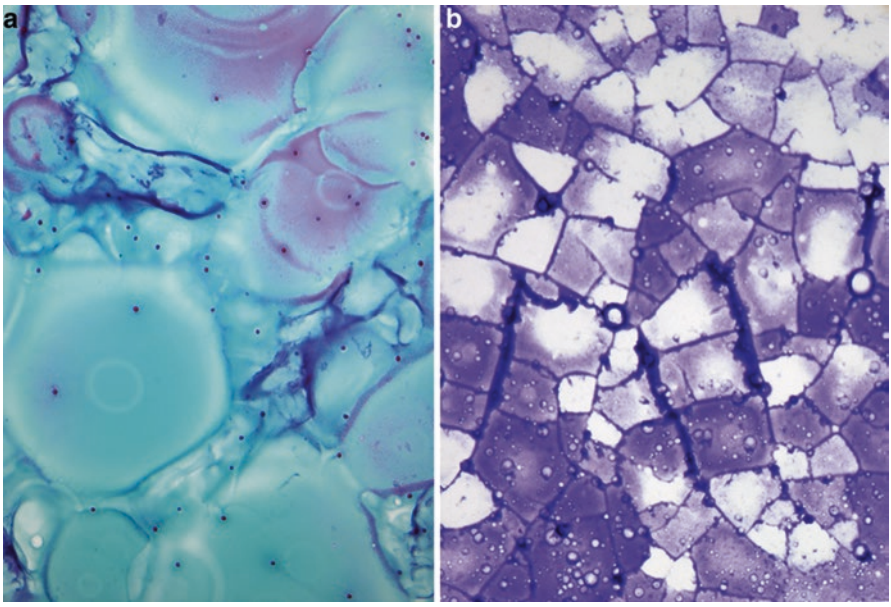

Fig. 3.1 Benign follicular nodule/colloid nodule: watery colloid. (**a**) Watery colloid is light green or pink with alcohol-fixed, Papanicolaou-stained preparations and has a "thin membrane" or "cellophane coating" appearance, often with coalescing "puddles" (smear, Papanicolaou stain). (**b**) Colloid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

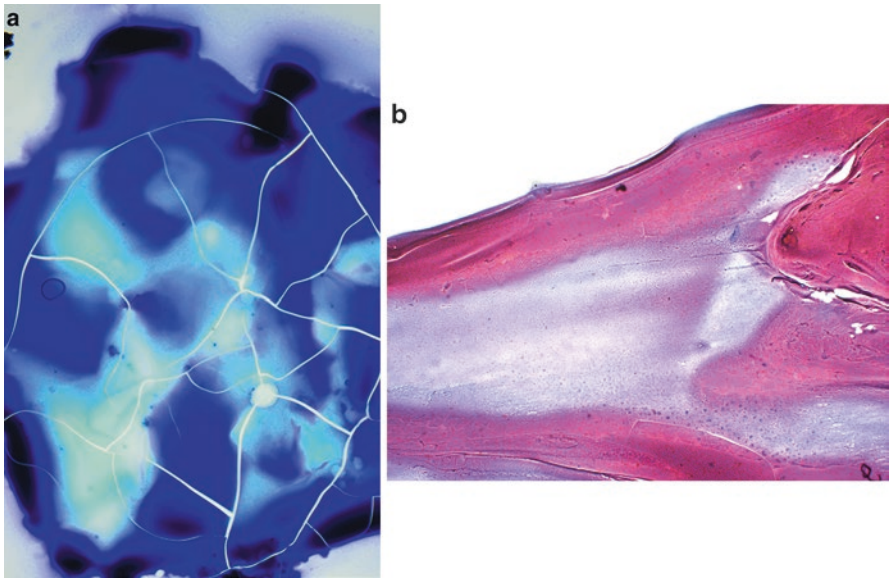

Fig. 3.2 Benign follicular nodule: thick colloid. (**a**) Colloid demonstrates a "stained glass cracking" appearance (smear, Diff-Quik stain). (**b**) Colloid is orange-pink or green-blue with alcohol-fixed Papanicolaou-stained preparations and can cover a major part of the glass slide surface (smear,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

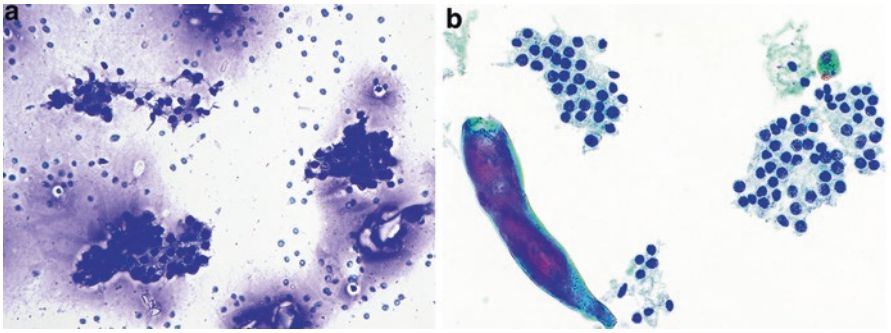

Fig. 3.3 Benign follicular nodule. Monolayered sheets of evenly spaced follicular cells have a honeycomb-like arrangement. (**a**) Watery colloid is present in the background (smear, Diff-Quik stain). (**b**) Thick colloid is present (ThinPrep, Papanicolaou stain).

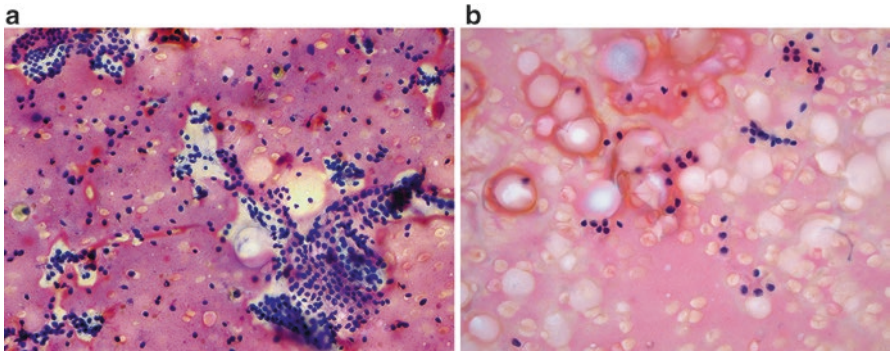

Fig. 3.4 Benign follicular nodule. (**a**) Monolayered sheets of follicular cells are the predominant finding. Stripped follicular cell nuclei are present in the background. When watery colloid is admixed with blood (note the pale-staining red blood cells), it can be difficult to recognize (smear, Papanicolaou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

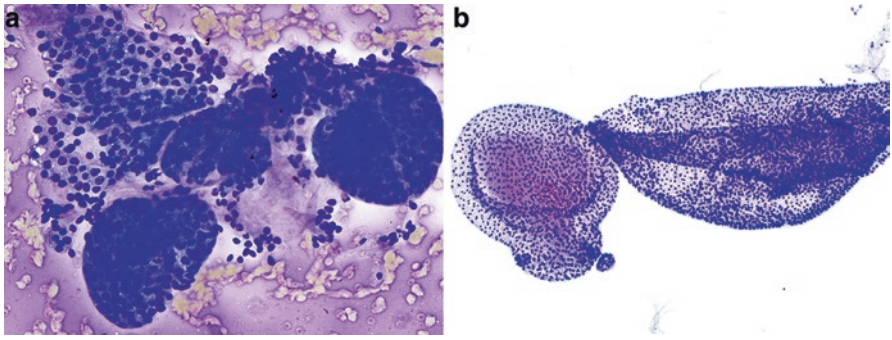

Fig. 3.5 Benign follicular nodule. Three-dimensional, variably sized balls/spheres are admixed with flat sheets. Within the spheres there is maintenance of polarity, including a relatively evenly spaced nuclear arrangement (**a** smear, Diff-Quik stain; **b** ThinPrep, Papanicolaou stain).

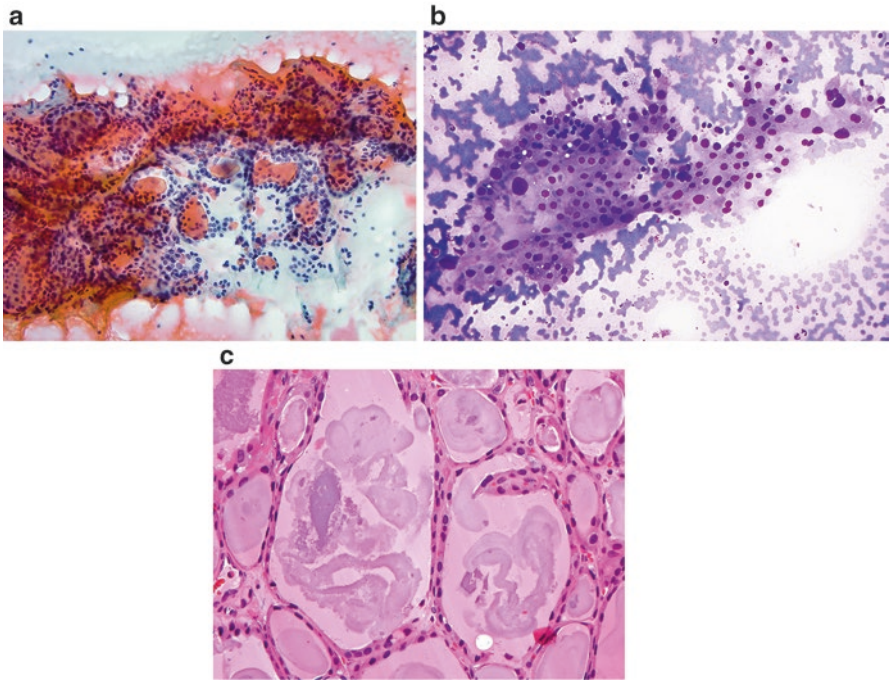

Fig. 3.6 Benign follicular nodule. (**a**) Microtissue fragments are admixed with flat sheets and colloid. There is follicle formation, but these are not microfollicles, because there is maintenance of polarity and the nuclei are evenly spaced (smear, Papanicolaou stain). (**b**) Hürthle cells (oncocytes) 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).

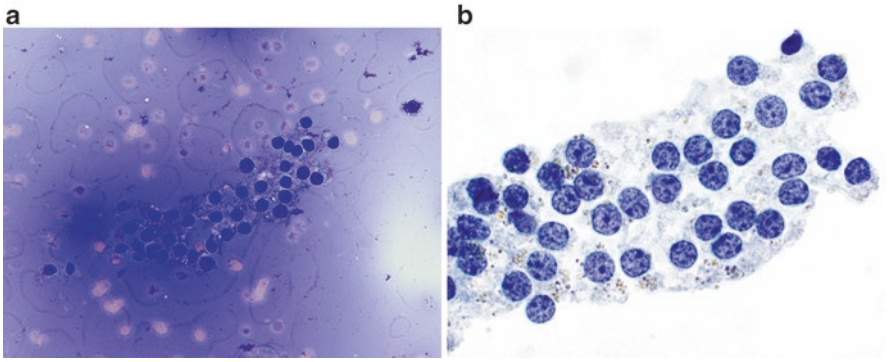

Fig. 3.7 Benign follicular nodule. (**a**) Benign follicular cells have delicate cytoplasm and ill-defined borders. The nuclei are uniformly spaced and approximately the size of red blood cells. Watery colloid is present in the background (smear, Diff-Quik stain). (**b**) Follicular cells may contain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

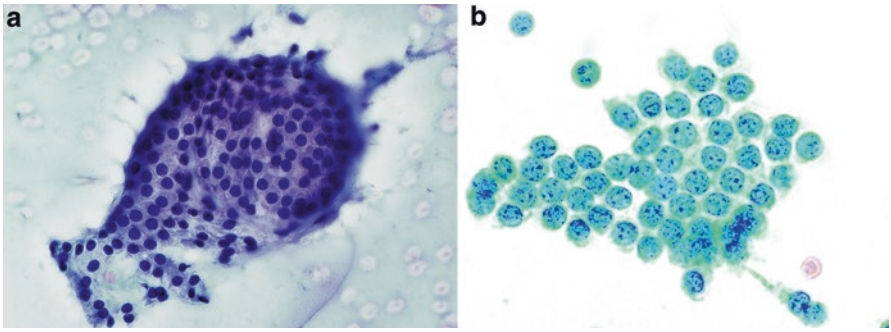

Fig. 3.8 Benign follicular nodule. Benign follicular cells have round to oval, monomorphic nuclei with finely granular chromatin and inconspicuous or absent nucleoli (**a** smear, Papanicolaou stain; **b** SurePath preparation, Papanicolaou stain). (Case **b** courtesy of Douglas R. Schneider, MD, Department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

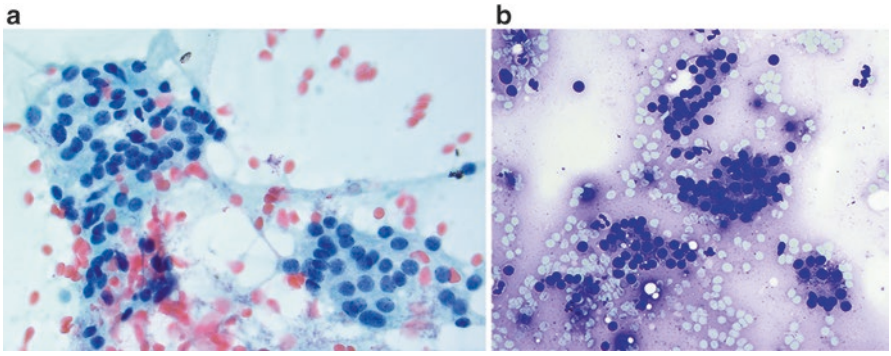

Fig. 3.9 Benign follicular nodule. (**a**) Nuclear overlapping and crowding may be observed in some clusters, but there is no significant nuclear enlargement or atypia (smear, Papanicolaou stain). (**b**) Small flat sheets without significant nuclear overlapping or atypia of follicular cells represent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

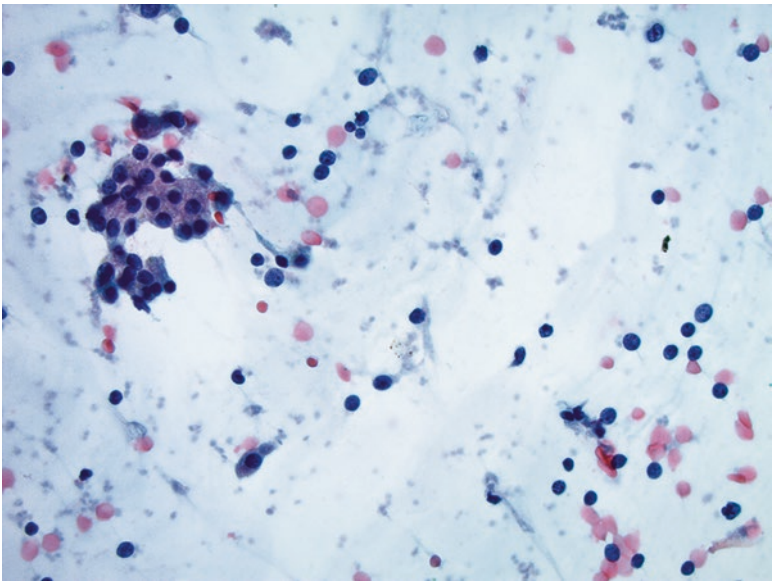

Fig. 3.10 Benign follicular nodule. Stripped ("naked") thyroid follicular cell nuclei may be seen in background; care must be taken not to mistake them for lymphocytes (smear, Papanicolaou stain).

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

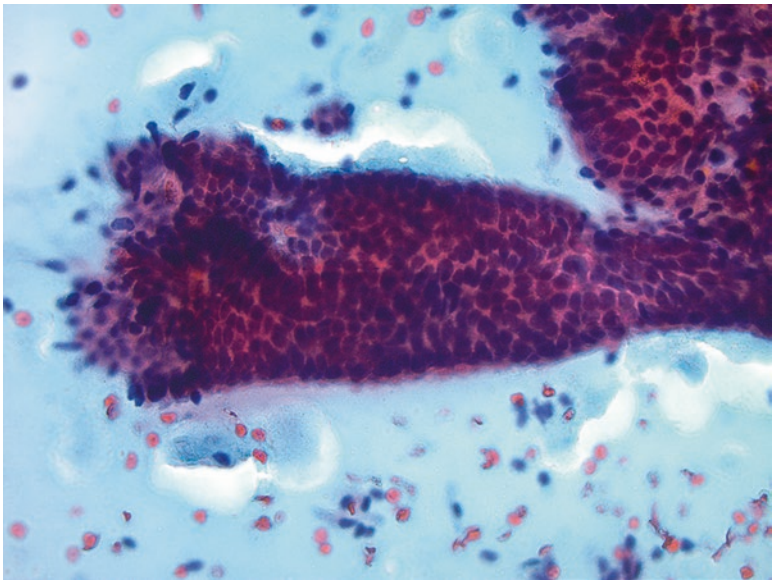

Fig. 3.11 Benign follicular nodule. Papillary hyperplasia may be seen in association with a hyperplastic nodule or follicular adenoma. The follicular cells usually remain arranged in flat sheets; true papillae are rarely apparent. Nuclear features of papillary thyroid carcinoma are absent (smear, Papanicolaou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

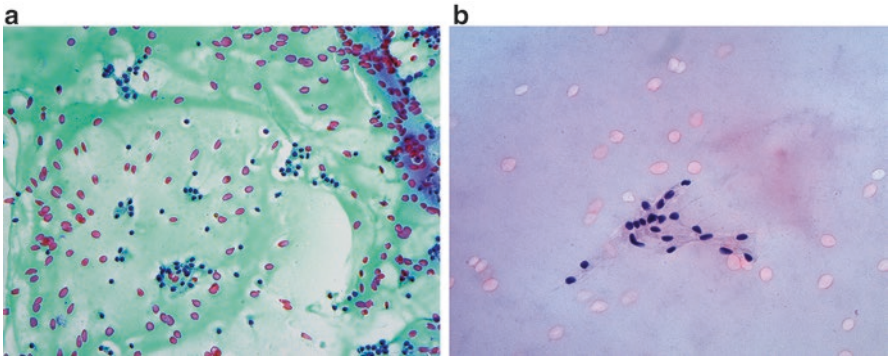

Fig. 3.12 Benign follicular nodule. Follicular cells suspended in abundant colloid tend to dissociate and may appear shrunken and spindled (**a**, **b**: smears, Papanicolaou stain).

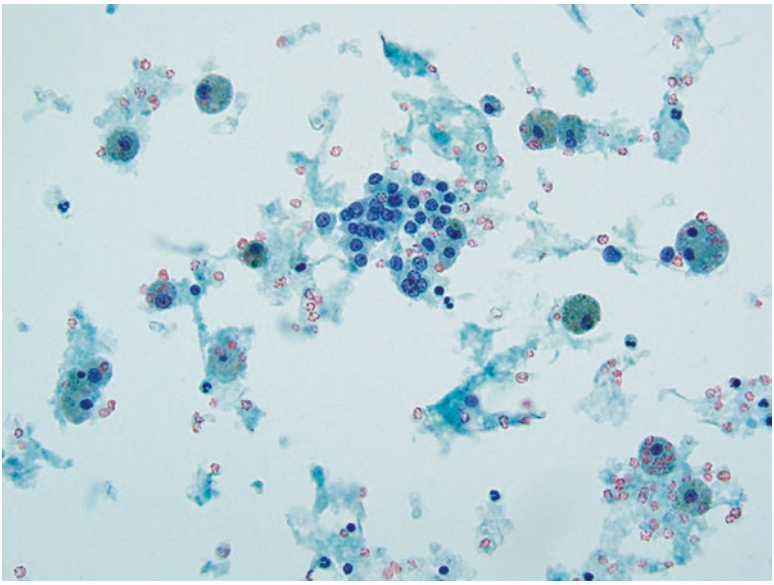

Fig. 3.13 Benign thyroid cyst. Prominent cystic degeneration often occurs in nodular goiter. Abundant macrophages and few benign thyroid follicular cells are present (smear, Papanicolaou stain).

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.

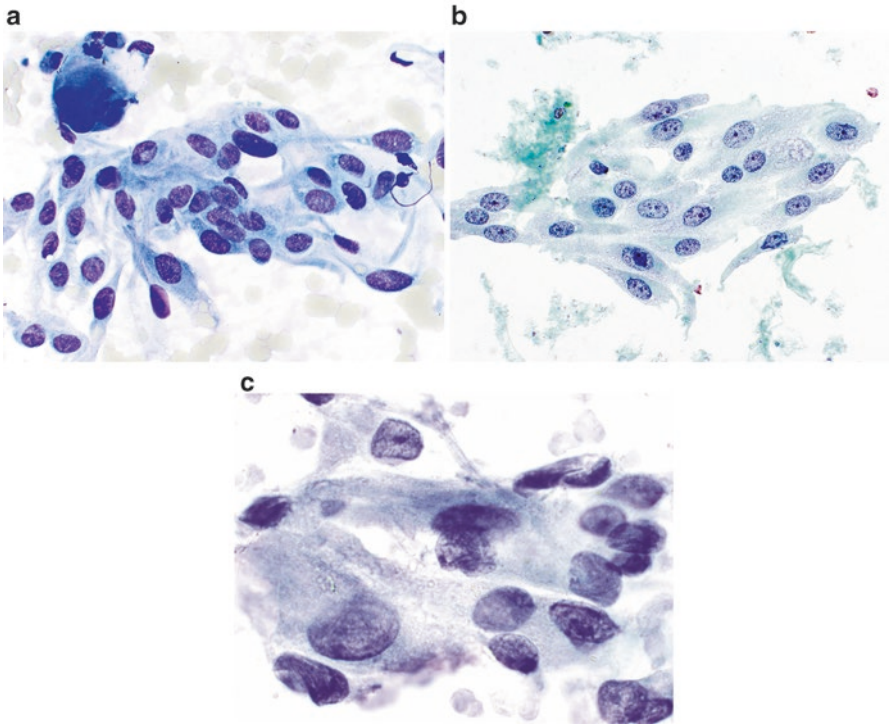

Fig. 3.14 Benign follicular nodule: cyst lining cells. (**a**, **b**) Reparative changes are commonly associated with cystic degeneration. Cyst lining cells are usually a small component of the benign aspirate and easily recognized because of their elongated shape and cohesive, flat and/or squamoid appearance, 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

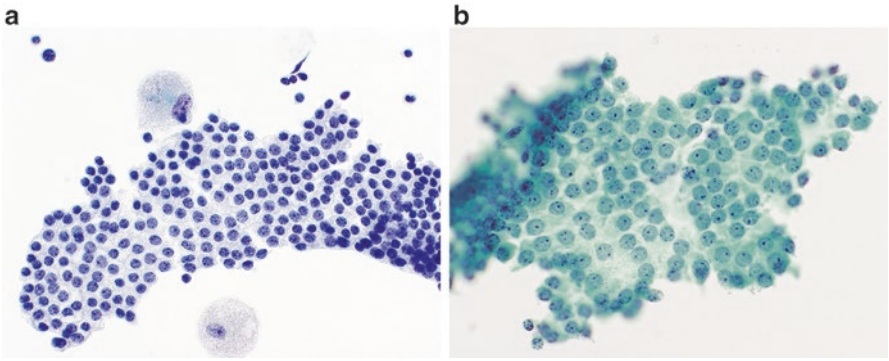

Fig. 3.15 Benign follicular nodule (liquid-based preparations). The follicular cells have pale cytoplasm and small, round, evenly spaced nuclei. (**a** ThinPrep, Papanicolaou stain; **b** SurePath, Papanicolaou stain). (Case **b** courtesy of Douglas R. Schneider, MD, Department of Pathology, Steward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

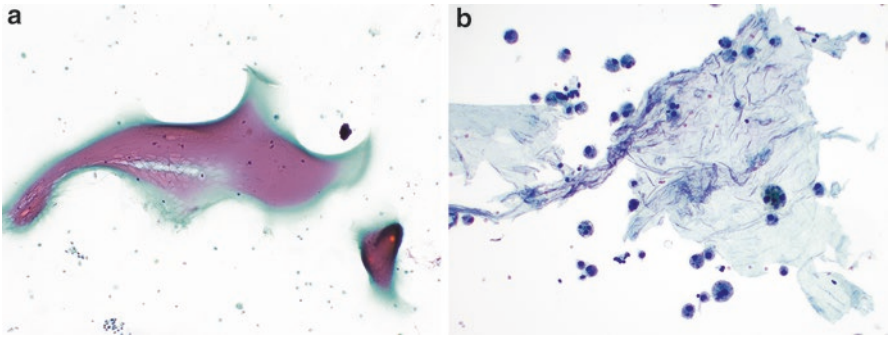

Fig. 3.16 Benign follicular nodule: colloid (liquid-based preparations). (**a**) Thick colloid on liquid-based preparations resembles its counterpart on smears (SurePath, Papanicolaou stain). (**b**) Watery colloid has a thin, "folded tissue-paper" appearance (ThinPrep, Papanicolaou stain). (Case **a**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

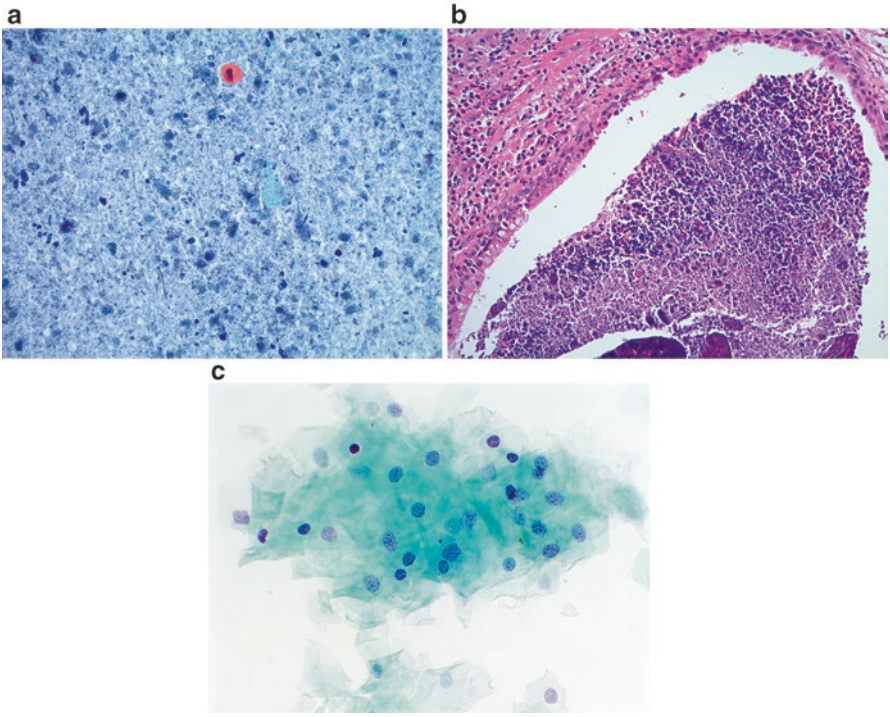

Fig. 3.17 Squamous cells in thyroid aspirates. (**a**) Thyroglossal duct cyst. Proteinaceous material, inflammatory cells, and a rare degenerated squamous cell are present (smear, Papanicolaou stain). (**b**) Thyroglossal duct cyst. The corresponding histopathologic specimen shows cyst contents (as observed 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).

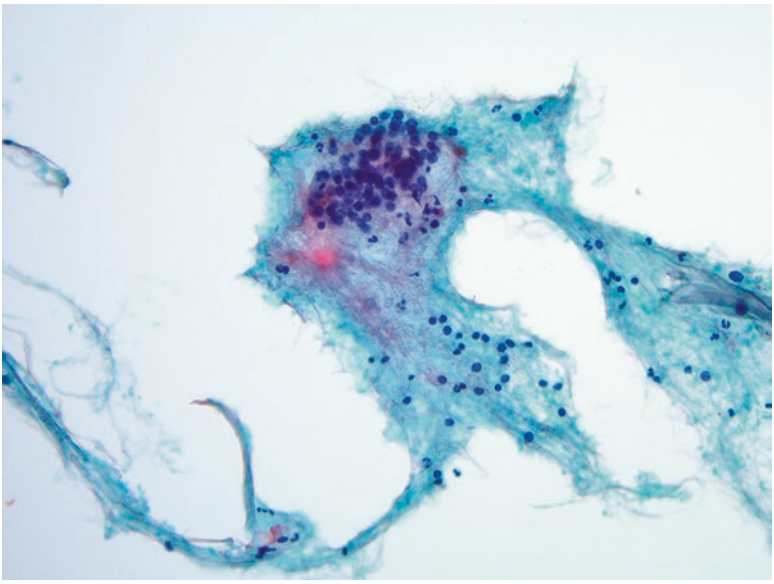

Fig. 3.18 Parathyroid cyst. This sparsely cellular specimen has rare groups of small round cells with dark overlapping nuclei and scant cytoplasm, suggestive of follicle formation (smear, Papanicolaou stain).

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.

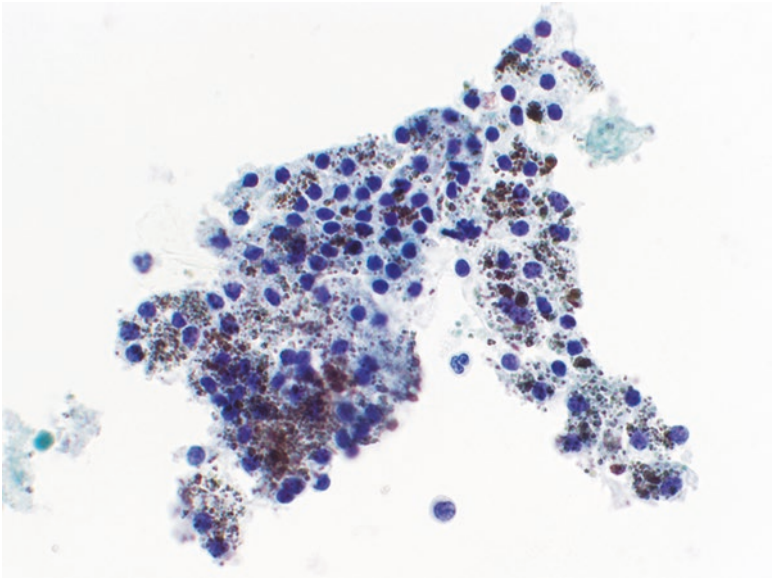

Fig. 3.19 Black thyroid. Follicular cells contain abundant dark brown pigment. Contrast with hemosiderin pigment in Fig. 3.7b (ThinPrep, Papanicolaou stain).

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

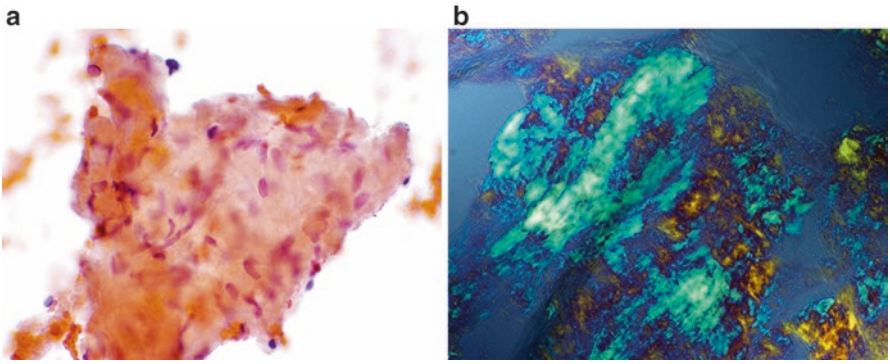

Fig. 3.20 Amyloid goiter. (**a**) Aspiration of abundant thick, glassy, amorphous material that stains pink/orange or purplish (depending on the stain used) is observed. Amyloid deposits are mostly parenchymal and hence often display embedded fibroblasts, a characteristic feature (smear, Papanicolaou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

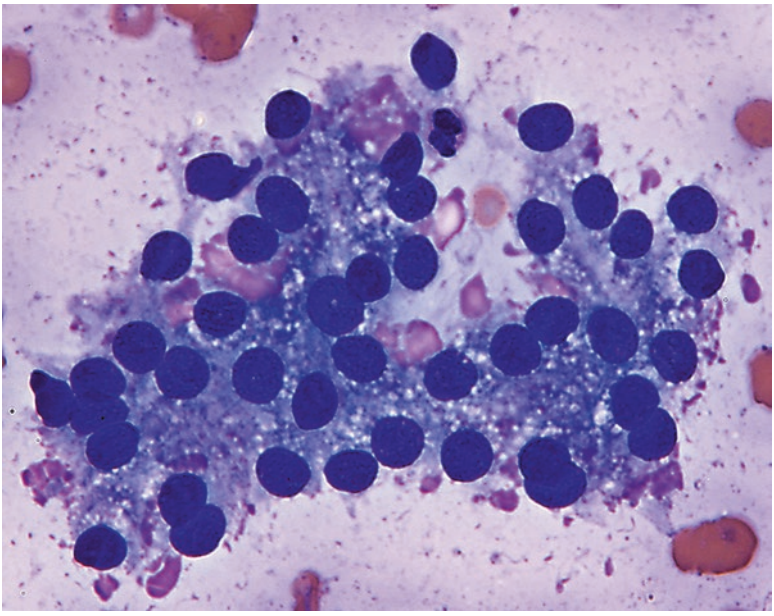

Fig. 3.21 Benign follicular nodule (patient with Graves' disease). Cells in monolayered sheets have abundant cytoplasm. Flame cells are distinctive for their marginal cytoplasmic vacuoles with red to pink frayed edges (smear, Diff-Quik stain).

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).

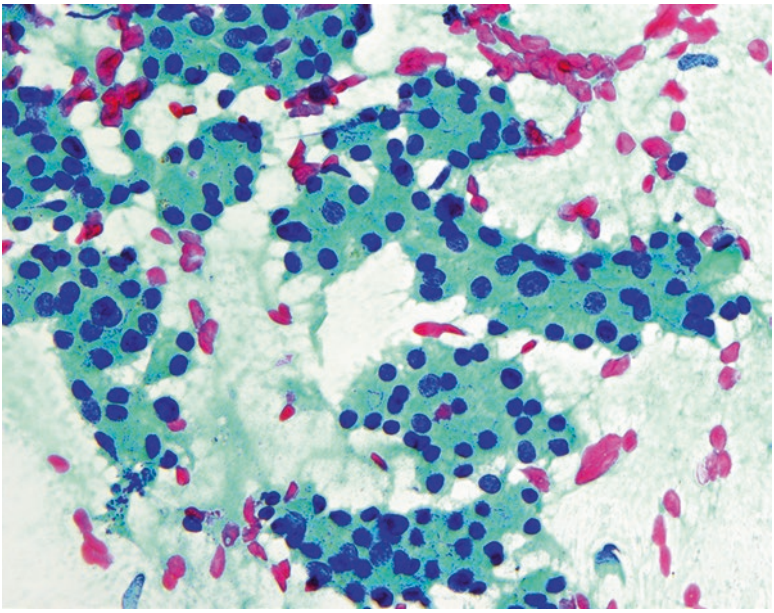

Fig. 3.22 Benign follicular nodule (patient with Graves' disease). The nuclei are often enlarged, vesicular, and show prominent nucleoli. Anisonucleosis is prominent. The cytoplasm has a granular, "oncocytoid" appearance (smear, Papanicolaou stain).

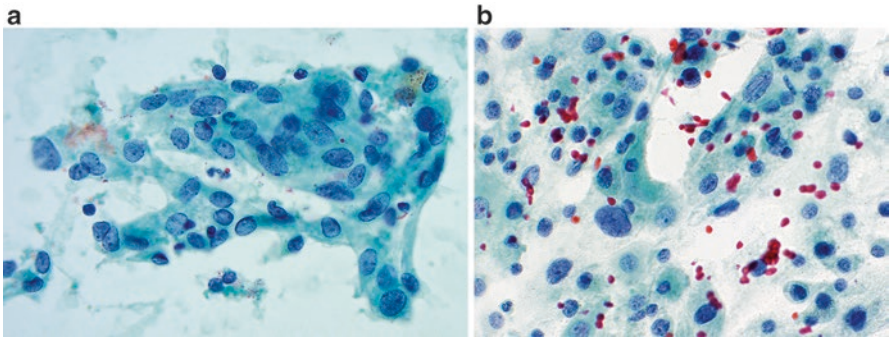

Fig. 3.23 Benign follicular nodule (patient with Graves' disease). (**a**) The follicular cells may display focal nuclear chromatin clearing and rare grooves. These changes are rarely diffuse, and other diagnostic nuclear features of papillary thyroid carcinoma are absent (smear, Papanicolaou stain).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

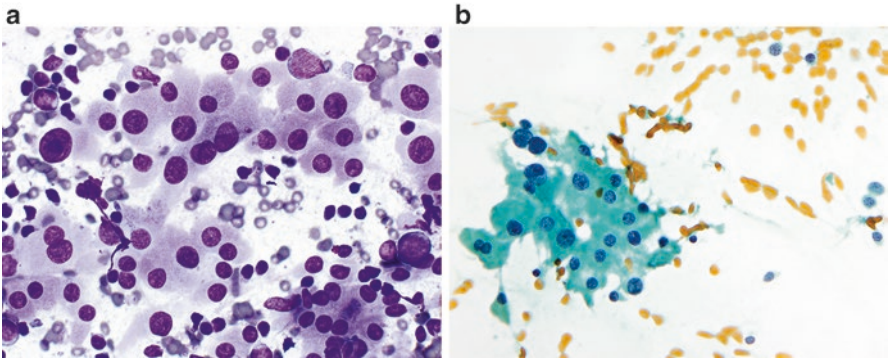

Fig. 3.24 Lymphocytic thyroiditis. (**a**) There is a mixed population of Hürthle cells (oncocytes) and polymorphic lymphocytes (smear, Diff-Quik stain). (**b**) Hürthle cells have abundant granular cytoplasm, large nuclei, and prominent nucleoli. There is mild anisonucleosis (smear, Papanicolaou stain).

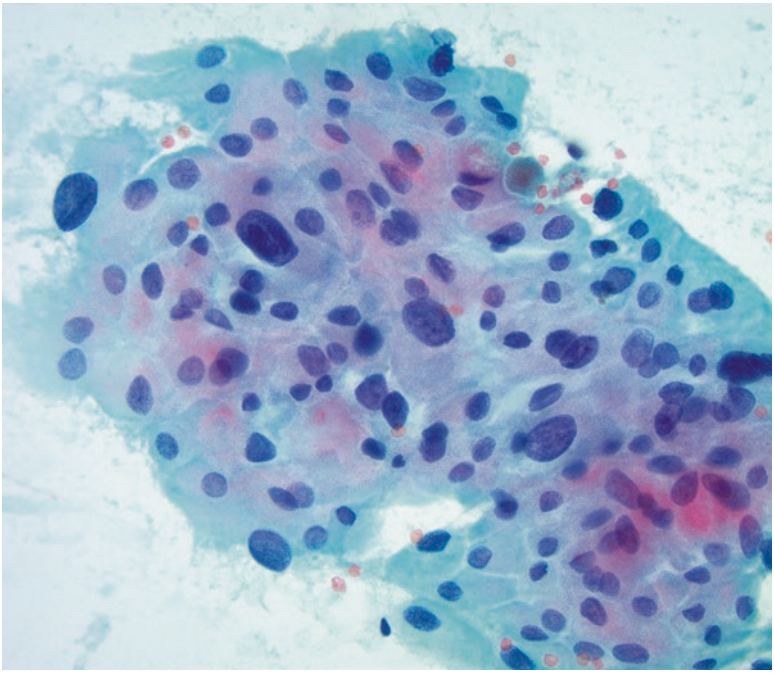

Fig. 3.25 Lymphocytic thyroiditis. Random nuclear atypia and prominent anisonucleosis of Hürthle cells (oncocytes) is not uncommonly associated with LT (smear, Papanicolaou stain).

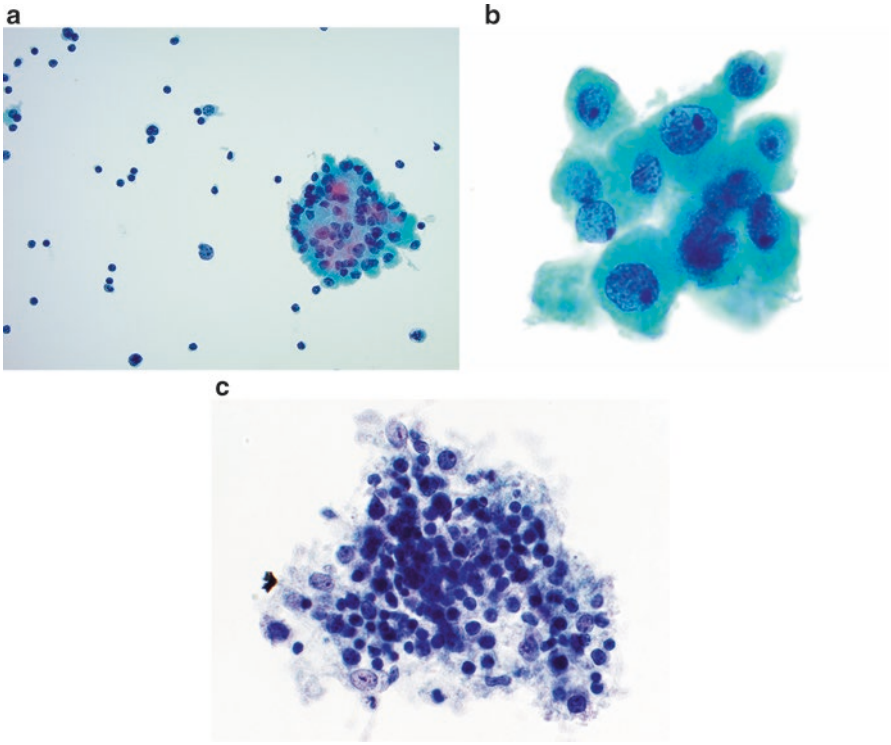

Fig. 3.26 Lymphocytic thyroiditis, liquid-based preparations. (**a**) Lymphocytes are dispersed as isolated cells and infiltrate clusters of Hürthle cells (ThinPrep, Papanicolaou stain). (**b**) Hürthle cells (oncocytes) have abundant granular cytoplasm and prominent nucleoli (SurePath, Papanicolaou 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).

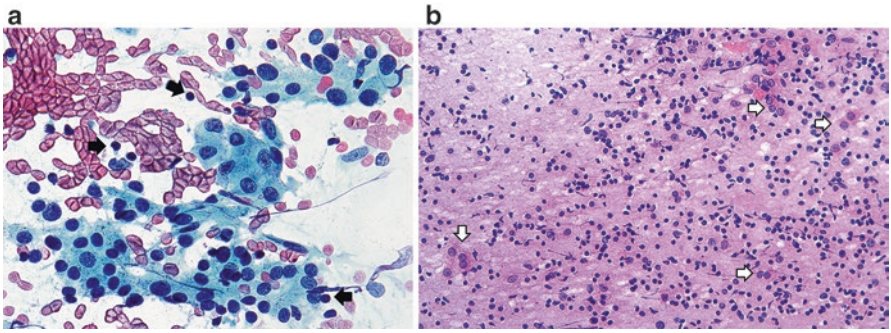

Fig. 3.27 Lymphocytic thyroiditis. (**a**) Hürthle cells may predominate in any given sample, raising the possibility of a Hürthle cell neoplasm. Rare lymphocytes are present in the background (*arrows*) (smear, Papanicolaou stain). (**b**) Lymphoid cells may predominate in an aspirate, raising the possibility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

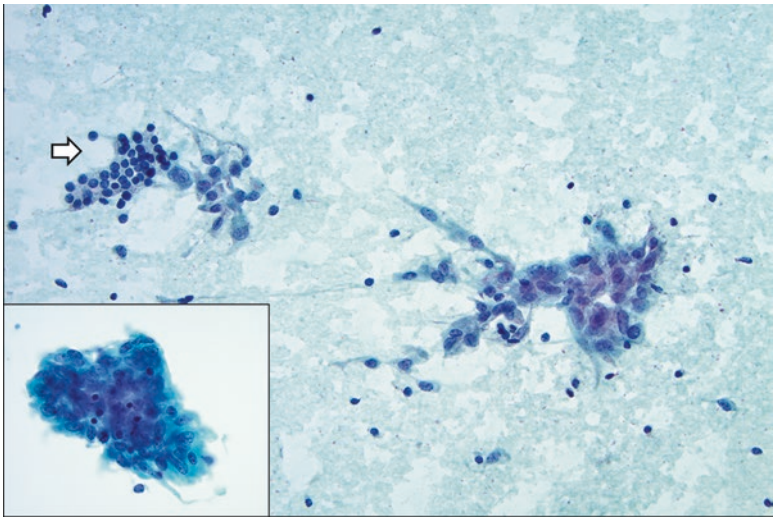

Fig. 3.28 Granulomatous thyroiditis. Epithelioid histiocytes, mixed inflammatory cells, and benign thyroid follicular cells (*arrow*) are present. Inset: Higher magnification of a granuloma (smears, Papanicolaou stain).

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.

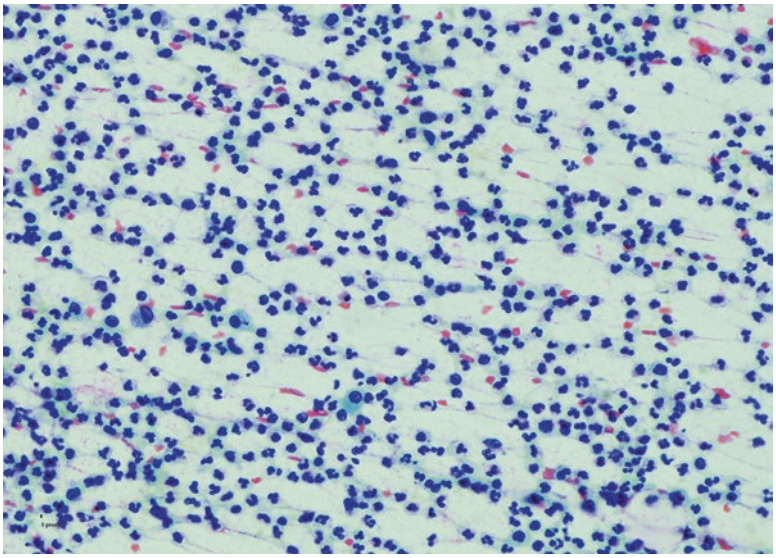

Fig. 3.29 Acute thyroiditis. There are numerous neutrophils and occasional macrophages (smear, Papanicolaou stain).

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

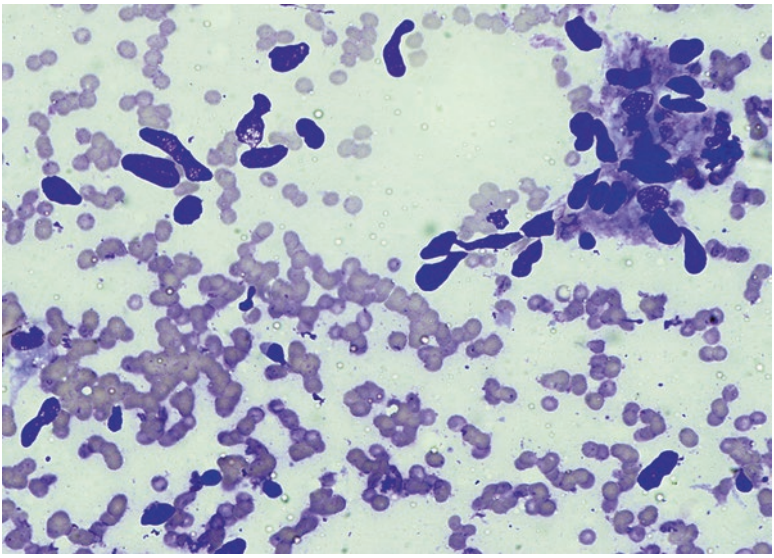

Fig. 3.30 Riedel thyroiditis/disease. This hypocellular smear contains scattered bland spindle cells and rare chronic inflammatory cells (smear, Diff-Quik stain).

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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