Fine Needle Aspiration of Benign Thyroid Nodules

4

Rana S. Hoda and Elizabeth Austin

Introduction to Benign Thyroid Lesions

- The prevalence of thyroid nodules in the general population ranges from 2% to 6%, but only 10–20% of these nodules are malignant. The clinical challenge is to identify those nodules requiring surgical management.
- In this clinical setting, fine needle aspiration (FNA) represents an invaluable diagnostic tool for characterizing thyroid nodules. FNA aids in identifying nodules that require surgery and decreases the overall incidence of thyroidectomy in patients with benign disease. It has found worldwide application because of its simplicity, safety, cost-effectiveness, and accuracy, with a reported sensitivity of 80–98% and specificity of 58–100%.
- Benign cytology is the most common diagnostic result of FNA, with a reported negative predictive value (NPV) greater than 95%.
- The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) predicts that the risk of malignancy (ROM) of a solitary thyroid nodule with a benign cytology on FNA is 0–3%. However, a meta-analysis of 14 studies encompassing over 43,000 patients reported a significantly higher ROM of 3–5%, when resection was used as the gold standard [35].
- The overall false-negative (FN) rate depends on four important parameters: sampling error, poor specimen quality, scant specimen, and cytologic interpretation.
  - Sampling errors can result from multiple factors, including the nature of the nodules, multiple suspicious nodules, the use of palpation-guided FNA (PGFNA) vs. ultrasound-guided FNA (USGFNA), the FNA technique, and the skill of the operator.
  - Poor specimen quality, usually encountered with conventional smears (CS), includes poor cellular preservation due to multiple smear-related artifacts such as air-drying artifact, overlapping and thick cellular areas, and abundant blood and ultrasound gel. All these elements partially or completely obscure cell details. In such cases, identifying benign or neoplastic cells can be a challenge.
  - Scant specimen can be due to the nature of the lesion, inadequate sampling, or the discarding of diagnostic sample with the needle and syringe after CS have been made.
  - Cytologic interpretation errors occur most commonly in nodules with focal features of papillary thyroid carcinoma (PTC) or microPTC.
- The cytologic criteria for FNA of thyroid lesions were devised on conventional smears, which have been the preparation of choice, especially in settings where rapid onsite specimen evaluation (ROSE) is available.

Liquid-Based Preparations (LBP) in Benign Thyroid FNA

- Despite the initial controversy regarding the efficacy of the use of LBP alone, good results have been achieved in recent years [9, 14, 18, 36, 41]. Studies have shown that ThinPrep® (TP) has diagnostic equivalence to CS, but one should acknowledge the cytologic differences between the two preparations with regard to the amount and character of colloid, architectural features, background elements, and nuclear and cytoplasmic details.
- Details of the LBP collection and processing techniques and cellular morphology have previously been published [25].
- For a reliable diagnosis on LBP, features of thyroid FNA as seen on CS need to be slightly modified.
- Accurate recognition of benign lesions on LBP requires familiarity with the alterations in the amount and character of colloid, architecture, and cytomorphology (Tables 4.1 and 4.2).

R. S. Hoda (✉) · E. Austin
CBLPath, Rye Brook, NY, USA
e-mail: rhoda@cblpath.com

© Springer Nature Switzerland AG 2020

R. S. Hoda et al. (eds.), *Atlas of Thyroid Cytopathology on Liquid-Based Preparations*,
https://doi.org/10.1007/978-3-030-25066-9_4

Table 4.1 Features of benign lesions in LBP and conventional smears

Cytological features	SurePath (SP)	ThinPrep (TP)	Conventional smears (CS)
Cellularity	Increased, allows assessment of overall specimen cellularity but not individual passes	Increased, allows assessment of overall specimen cellularity but not individual passes	Variable, allows assessment of cellularity for each pass with ROSE
Macrofollicles	3-D, cells in orderly honeycomb	Flat monolayer, may be smaller; cells in orderly honeycomb	Large to medium-sized, cells in orderly honeycomb
Clusters	More clustered, with cellular overlap	Tighter, crowded with cellular overlap	Loose aggregates of cells, may be crowded
3-D Configuration	Present, more 3-D, difficult to interpret, requires continuous focusing at higher magnification	May be seen, easy to interpret, loss of cellular preservation may be seen in the large aggregates	May be seen, easy to interpret
Single Cells and Cell Shrinkage	Increased, cell shrinkage apparent	Increased, cell shrinkage apparent	Not increased; no cell shrinkage
Cytoplasm	Fewer details, fragile, fragmented, lipofuscin pigment visible	May be disrupted, with naked nuclei, lipofuscin pigment visible	May be disrupted with naked nuclei, lipofuscin pigment visible
Nuclei	Fewer details, shrunken, round, regular with dense chromatin; PTC nuclear features retained	Shrunken, round, regular with dense chromatin, PTC nuclear features retained with few INPI	Maintained size and all diagnostic features
Amount of Colloid	Reduced and different	Reduced and different	Abundant watery colloid
Thin Colloid	Wrinkled tissue paper, napkin fold, granular	Wrinkled tissue paper, napkin fold, granular	Diffuse thin layer or coalescing "broken glass" pieces
Thick Colloid	Dense, in chunks, round to oval aggregates or dense droplets	Fragmented chunks, round to oval aggregates or dense droplets	Diffuse dried and cracked "desert sand" or diffuse thick bands
Number of Macrophages	Present, hemosiderin pigment retained	Increased, hemosiderin pigment retained	Present, hemosiderin pigment retained
Stroma	Reduced	Reduced and fragmented	Retained as large fragments
Lymphocytes in LT	Increased, evenly dispersed; fewer lymphohistiocytic aggregates	Increased, evenly dispersed; fewer lymphohistiocytic aggregates	Increased, dispersed, and lymphohistiocytic aggregates
Obscuring Elements (blood, US gel)	Reduced, clean background, less/no obscuring elements	Reduced, clean background, less/no obscuring elements	Present; background usually bloody, with obscured cells
Artifacts	Reduced; 3-D clusters, cells in different planes of focus and cellular overlap present	None/reduced; cells in one plane, no cellular overlap, cells in the periphery appear distorted	Several due to technique, including air-drying, thick cellular areas, overlapping cell clusters
Additional Slides	Processed from residual specimen	Processed from residual specimen	Cannot be prepared
Sensitivity and Accuracy	Currently recommended use with CS	91.0% sensitivity; 89.4% accuracy; similar to CS; can be used as a sole preparation	Similar to LBP, can be used with LBP

3-D three-dimensional, *FN* false negative, *INPI* intranuclear pseudoinclusions, *LBP* liquid-based preparations, *LT* lymphocytic thyroiditis, *PTC* papillary thyroid carcinoma, *ROSE* rapid onsite specimen evaluation, *US* ultrasound

Table 4.2 Morphologic criteria for benign thyroid lesions on LBP and CS

Histological Diagnosis	SurePath (SP)	ThinPrep (TP)	Conventional Smears (CS)
MNG/BFN	Small sheets, clusters, and macrofollicles of small, monomorphic follicular cells with clear or granular cytoplasm, wrinkled tissue paper–like thin colloid, or small clumps or globules of dense colloid, histiocytes	Small sheets, clusters, and macrofollicles of small, monomorphic follicular cells with clear or granular cytoplasm, wrinkled tissue paper–like thin colloid, or small clumps or globules of dense colloid, histiocytes	Abundant, diffuse thin or thick colloid; large sheets and macrofollicles of small follicular cells, histiocytes
Colloid Nodule	Small clumps of dense colloid (colloid globules)	Small clumps of dense colloid (colloid globules)	Abundant and clumped
Lymphocytic (Hashimoto's) Thyroiditis	Mixture of small clusters of follicular cells and/or Hürthle cells, lymphocytes; small clumps of colloid. Multinucleated histiocytes may or may not be present.	Mixture of small clusters of follicular cells and/or Hürthle cells, lymphocytes; small clumps of colloid. Multinucleated histiocytes may or may not be present (diagnosed less frequently on TP slides than on CS).	Inflammatory cells (mostly mature lymphocytes, few plasma cells), epithelioid histiocytes; lymphohistiocytic aggregates, small clusters of follicular cells, sometimes with Hürthle cell metaplasia; scant colloid. Multinucleated histiocytes are diagnosed more frequently on CS than on TP.

MNG/BFN multinodular goiter/benign follicular nodule

- In addition, although TP and SurePath™ (SP) are both LBP, one must also be aware of the subtle differences between the two methods (Table 4.3).
- A study by the College of American Pathologists, as part of their Interlaboratory Comparison Program in Non-Gynecologic Cytology [19], concluded that LBPs performed better than CS for cases with a benign reference diagnosis. Cytopathologists also seemed to have the highest concordance for this diagnosis.
- The benign entities discussed in this chapter are those most commonly encountered in thyroid FNA practice. For less common benign entities, readers are referred to specialty textbooks.

Multinodular Goiter/Benign Follicular Nodule (MNG/BFN)

- Goiter is thyroid enlargement. A simple goiter can become multinodular through repeated episodes of hyperplasia and involution (degeneration) of follicular epithelium with colloid accumulation within dilated follicles. Grossly, the thyroid gland shows asymmetric diffuse or nodular enlargement. The nodules are irregular and variable in size. Histology reveals multiple irregularly dilated and variably sized microfollicles and macrofollicles, lined by flattened to hyperplastic epithelium, with or without degenerative cystic and hemorrhagic change (Fig. 4.1a, b).

Table 4.3 Morphological criteria for benign thyroid lesions on SP and TP

Technical and Cytological Features	SurePath (SP)	ThinPrep (TP)
Technique	Method employs density gradient separation and centrifugation, a cell enrichment process producing cells devoid of blood and other obscuring materials. The cells of interest are separated as a result of the simple sedimentation of cells on the slide surface without any applied pressure, and the SP method produces a more 3-D configuration for both single cells and clusters than CS and TP.	Membrane filtration method; the cells of interest are separated when the liquid collection medium is drawn through a filter using negative pressure pulse.
Cells	Tends to retain large tissue fragments, cellular elongation	More cellular dyscohesion and fragmentation
Lymphocytes	Number of lymphocytes is slightly increased; infiltrate follicular cells, lymphocytes are evenly dispersed, with fewer lymphohistiocytic aggregates than CS	Number of lymphocytes increased but less than in SP; infiltrate follicular cells, lymphocytes are evenly dispersed, with fewer lymphohistiocytic aggregates than CS
Peripheral Blood Contamination	Lymphocytes from the lysed blood may give a false assessment of lymphocytic thyroiditis	Lymphocytes from the lysed blood may give a false assessment of lymphocytic thyroiditis
Diagnosis	Easier method for diagnosis of lymphocytic thyroiditis than the TP method	Less easy than SP and CS
Experience for Interpretation	Required to avoid diagnostic pitfalls	Required to avoid diagnostic pitfalls

CS conventional smears

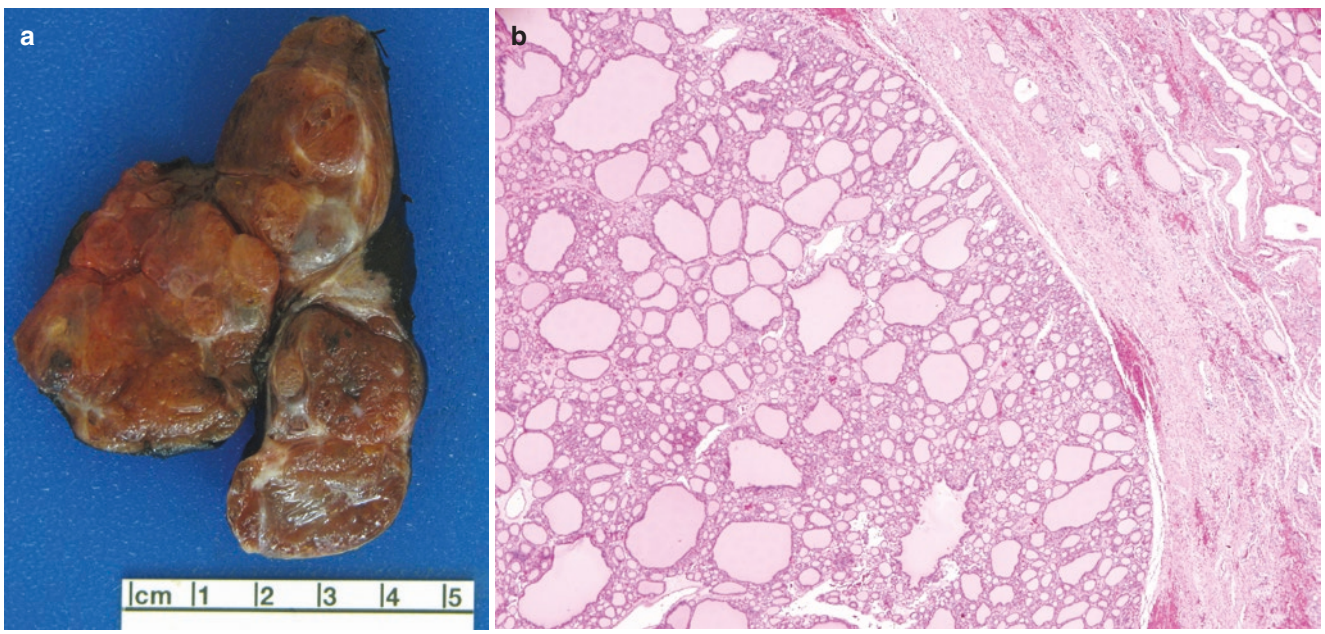

Fig. 4.1 Multinodular goiter (MNG). (**a**) MNG of the thyroid gland with asymmetric nodular enlargement. The nodules are irregular, brown, and variable in size. (**b**) Histology of MNG with multiple irregularly dilated follicles of variable sizes, including both microfollicles and macrofollicles (H&E stain)

- MNG/BNF reflects morphologic changes of the different stages of the disease, which include early follicular hyperplasia, cycles of involution/regeneration, and nodule formation. Hürthle cell metaplasia, hemorrhage, cystic degeneration, and calcification may occur in all stages.

Cytology of MNG/BFN on LBP

- Typical features of MNG/BFN are easily identified on the two LBP, TP and SP, with subtle differences from and similarities to the features seen on CS (*see* Table 4.2).
- The main overall differences between LBP and CS are that architecture is more disrupted in LBP: sheets, macrofollicles and microfollicles appear smaller and tighter and follicular cells may reveal more cell shrinkage, with smaller nuclear size, lower nuclear-cytoplasmic (N:C) ratio, more disruption of the cytoplasm, an increase in the number of naked nuclei, and a prominence of nucleoli. Thick and thin colloid appears more clumped than on CS (Fig. 4.2a–i).
- In TP, uniform follicular cells form small, flat, orderly sheets with cells arranged in a "honeycomb" configuration, with macrofollicles (spheres or balls), cell clusters, a few microfollicles, and singly dispersed cells with colloid, histiocytes, and other degenerative changes in the background (*see* Fig. 4.2a–d).
- In SP, follicular cells also appear as both flat, orderly sheets in a "honeycomb" arrangement and as macrofol-

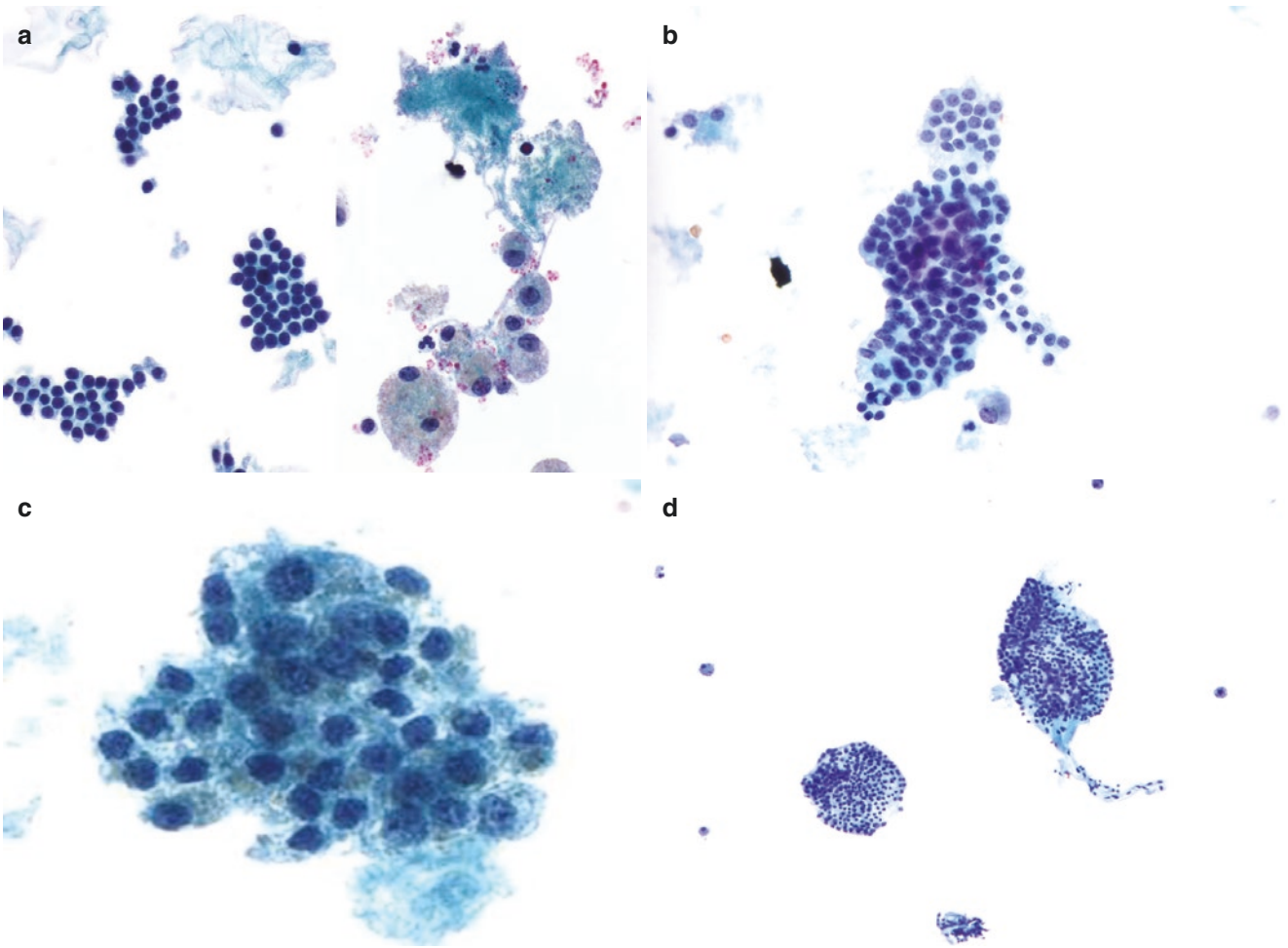

Fig. 4.2 Cytology of MNG. (**a**–**d**) Typical field of view in MNG showing benign follicular cells, hemosiderin pigment-laden macrophages, and colloid in the two liquid-based preparations (LBP), ThinPrep® (TP, **a**–**d**) and SurePath™ (SP, **e**–**g**), and in conventional smears (CS, **h** and **i**). Note subtle differences between the two LBP. (**a**–**c**) In TP, follicular cells form small, flat sheets with "honeycomb" arrangement of benign-appearing, uniform follicular cells with coarsely textured chromatin. Note the granular clumps of thin colloid and green-black granules of lipofuscin pigment (**c**). (**d**) Macrofollicles (spheres or balls) with oval and round configuration of benign-appearing follicular cells. (**a**–**d**, Pap stain, TP). (**e**–**g**) SP shows large, flat, and orderly sheets of follicular cells. Cell sheets are usually bigger and less fragmented than with TP, but the various sheets of follicular cells and background elements appear at various planes of focus. A macrofollicle (**g**) appears evenly spaced with round, uniform nuclei and low nuclear-cytoplasmic (N:C) ratio. All intracytoplasmic pigments are retained (**e**–**g**, Pap stain, SP). (**h**, **i**) In CS of MNG, note similarity in the macrofollicular architecture with that in **d**. Thin colloid has a faint, diffuse, cracked appearance. (**h**, Diff-Quik (DQ) stain, CS; **i**, Pap stain, CS)

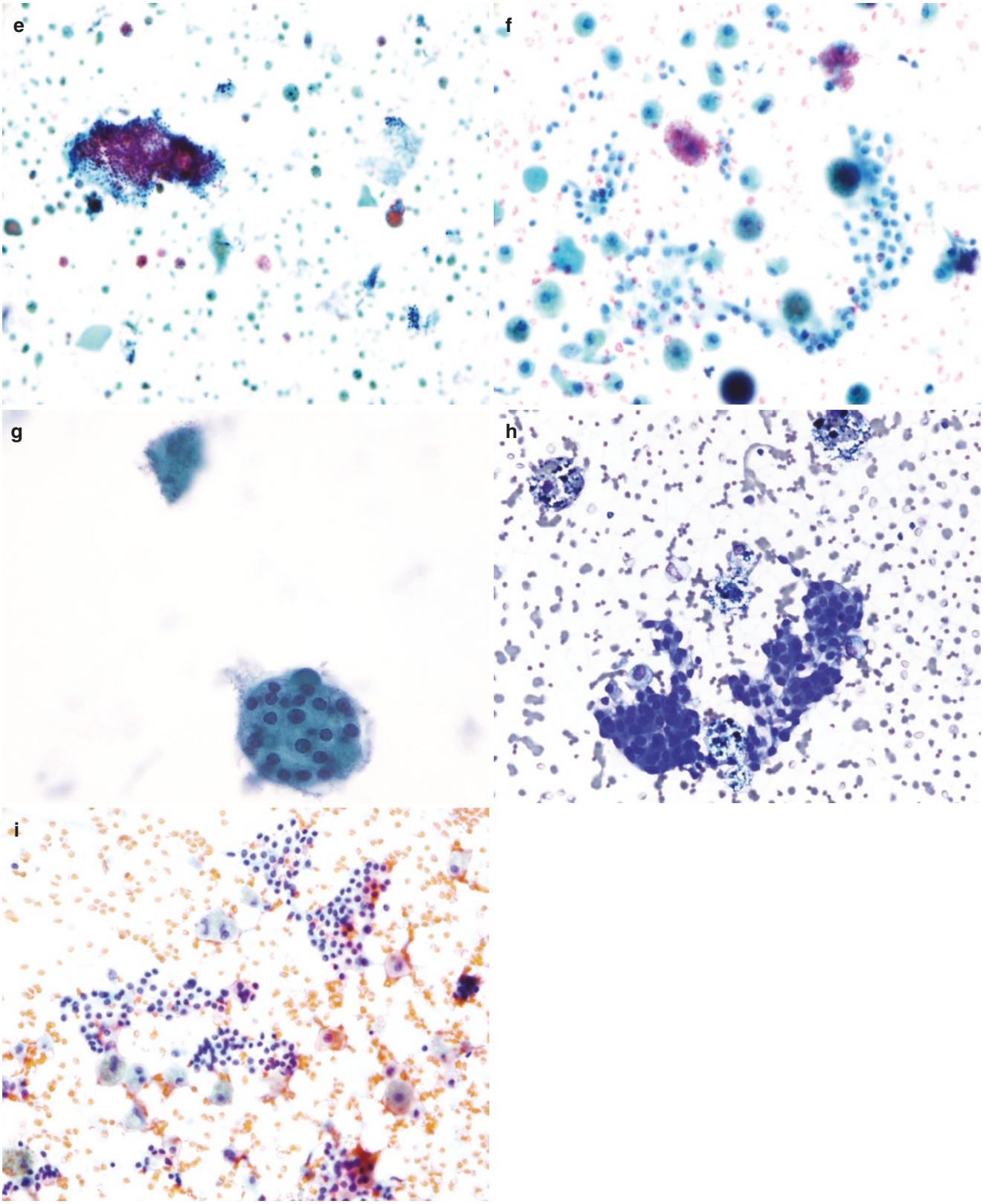

Fig. 4.2 (continued)

licles, cell clusters, a few microfollicles, and singly dispersed cells. Cell sheets are usually bigger and less fragmented than on TP. The follicular cells appear smaller and at various planes of focus, revealing a more three-dimensional (3-D) appearance of cell clusters, which may be difficult to interpret and require constant focusing at higher magnifications. Background elements of colloid, histiocytes, and other degenerative changes are retained and may also appear in different planes of focus (*see* Fig. 4.2e–g).

- On CS, follicular cells form small and large flat and folded sheets and large and medium-sized macrofollicles. Cytology correlates well with histology and LBP, with subtle differences (*see* Fig. 4.2h, i).
- On LBP, macrofollicles may appear smaller, but they remain intact and maintain similar features to CS. Unlike CS, where blood may obscure cell detail, the cells are clearly visible as benign on LBP (Figs. 4.3a–e and 4.4a, b).
- Colloid is readily identified on LBP (*see* Figs. 4.2a, b, e and 4.3a).
- Thin and thick colloid has a unique appearance:
  - Thin, watery colloid appears diffuse or as aggregates of granular deposits, napkin-folds, and sheets of wrinkled tissue paper (Fig. 4.5a–d). Watery colloid appears more clumped in TP than in SP, where it may be more diffuse in distribution. On CS, this type of colloid forms a diffuse, thin layer or appears as coalescing "broken glass" pieces (Fig. 4.5e, f).
  - In LBP, thick colloid appears as markedly fragmented chunks, round to oval aggregates, or dense droplets (globules), which show a dual staining pattern with a blue-staining periphery and central eosinophilia on Pap stain (Figs. 4.6a, b). On CS, this type of colloid appears as diffuse, dried and cracked desert sand, as diffuse thick bands, or as bigger globules (Figs. 4.6c, d).
- Cytoplasmic pigments are retained, including hemosiderin (*see* Figs. 4.2a, e and 4.5a, d) and green-black granules of lipofuscin pigment (Fig. 4.2c).
- Hürthle cell metaplasia is commonly observed in MNG/BFN, appearing similar to CS with subtle differences. The cells are polarized, with round nuclei, granular cytoplasm, and a low N:C ratio. In LBP, nuclei may appear smaller, and cytoplasm can either retain the granular quality or have a soft, lacy appearance with distinct boundaries (Fig. 4.7a–d).

Salient Points for LBP in MNG/BFN

- In LBP, collection of specimens in an alcohol-based preservative solution eliminates air-drying artifacts.
- Immediate cell fixation in LBP allows for better visualization of cytomorphology of follicular cell clusters.
- In LBP, the background is clean, as the collection medium also disintegrates red blood cells and mucus that may interfere with cytologic interpretation.
- Cells in each LBP slide are representative of all the material that is collected in the vial.
- Preparation of two LBP -based slides will improve specimen adequacy.
- In LBP, alterations in background, architecture, and cytomorphology can be understood to be a result of the fixation, homogenizing, and filtration process. These steps explain the cell shrinkage, appearance of colloid, fragmentation of cell sheets and macrofollicles, and follicular cell morphology.
- In the TP method, the cells of interest are separated when the liquid collection medium is drawn through a filter using negative pressure pulse. Thus, the cells appear in a true monolayer, but colloid, lymphocytes, and large tissue fragments are reduced, and the tissue fragments are more fragmented than on CS.
- In the SP method, the cells of interest are separated as a result of simple sedimentation and are transferred onto the slide surface without any applied pressure, so both single cells and clusters have a more 3-D configuration than on CS or TP.
- Various types of metaplasia, including Hürthle cell and squamous metaplasia, are often seen in MNG/BFN. These are seen as flat sheets, 3-D clusters, or single cells.
- The approach to diagnosis of MNG/BNF involves assessment of two elements, the amount of colloid and the number of follicular cells. Generally, the more colloid, the more likely the lesion is benign, and the more cells, the more likely the lesion is neoplastic. In TP, the amount of thin colloid may be diminished and is therefore difficult to quantify, requiring a closer evaluation of architectural and cytological features.
- However, a large study by the College of American Pathologists [19] found that LBP perform better than CS for MNG/BFN. The key diagnostic features of MNG/BFN, including watery colloid and follicular cells in macrofollicles and as large tissue fragments, are easily identified and better preserved in LBP than in CS.
- Features favoring MNG/BFN include variation in cytologic features between follicular cell groups in nuclear size, chromatin compaction, and amount of cytoplasm; focal marked nuclear pleomorphism as part of benign endocrine atypia; and the presence of macrophages (after cystic PTC is excluded).
- Follicular cells at the peripheral edge of the TP slide commonly appear distorted, blurred, and poorly-stained, an artifact associated with the TP technique.
- Ultrasound gel may mimic colloid. It appears as blue-purple, lace-like material, which may be closely associated with follicular cells (*see* Fig. 3.4). Lack of thyroglobulin staining confirms ultrasound gel.

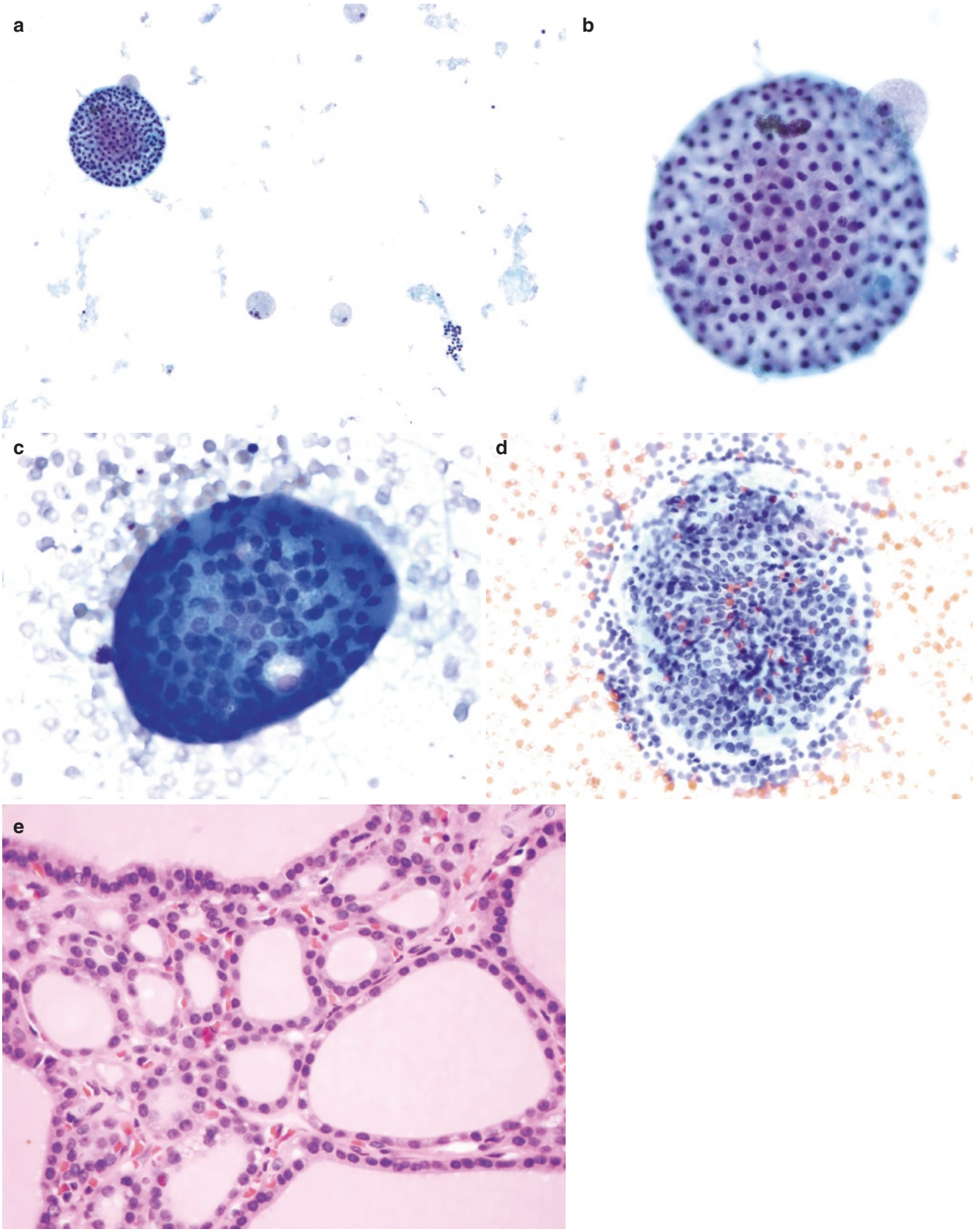

Fig. 4.3 Macrofollicles. (**a**, **b**) Macrofollicle in TP with oval and round configuration of benign follicular cells. Although this is a 3-D structure it retains a monolayer appearance of evenly spaced follicular cells in the same plane of focus, and all cells are visible in one plane. Note the thin colloid (Pap stain, TP). (**c**, **d**) Macrofollicle in CS with similar appearance (**c**, DQ stain, CS; **d**, Pap stain, CS). (**e**) Histology of MNG with microfollicles and macrofollicles, lined by flattened to hyperplastic epithelium (H&E stain)

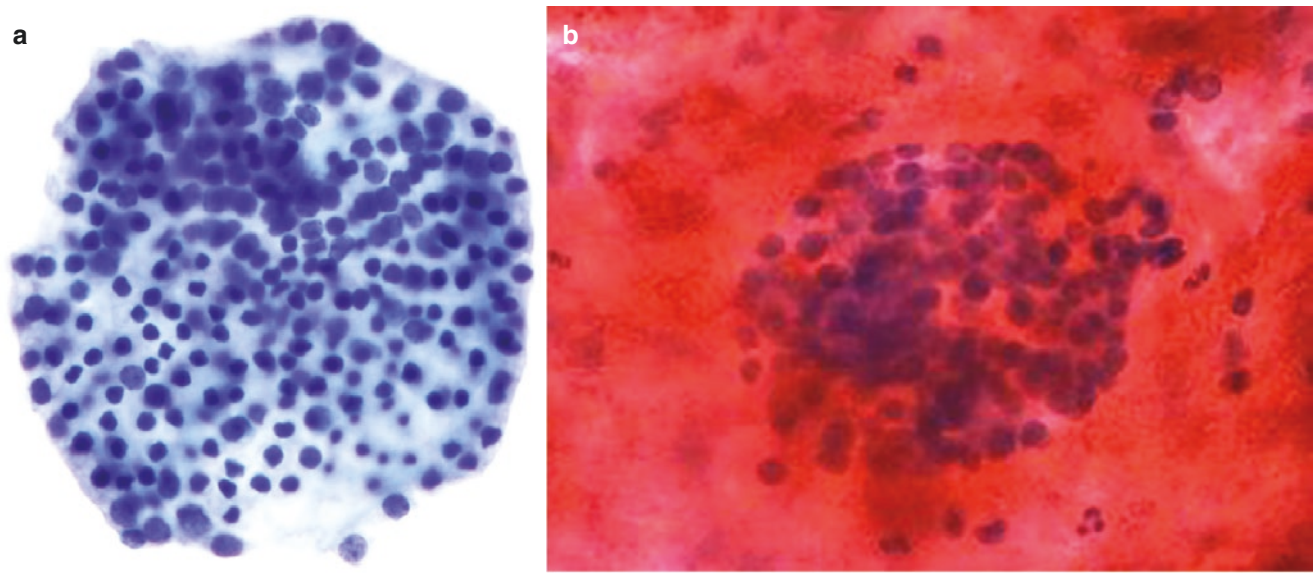

Fig. 4.4 Macrofollicles in LBP and CS. The appearance of MNG/BFN in TP (**a**) and SP is similar to the features seen in CS (**b**), with subtle differences. Note the similarities between the macrofollicular appearance in CS and that seen in Figs. 4.2d, g and 4.3a, b, except that abundant blood partially obscures cell detail in CS. (**a**, Pap stain, TP; **b**, Pap stain, CS)

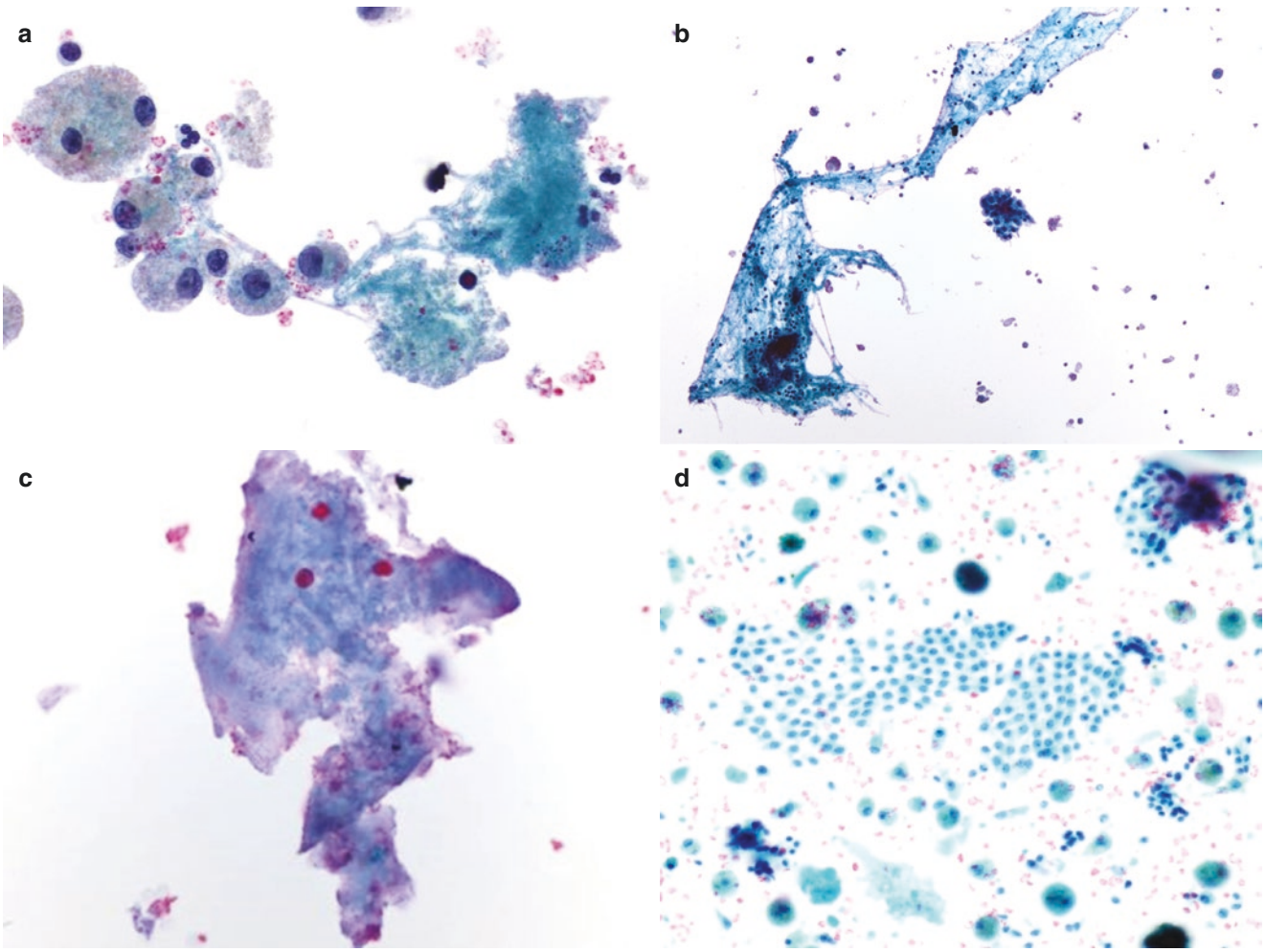

Fig. 4.5 Thin colloid in LBP and CS. Colloid is readily identified on LBP with a unique appearance of thin and thick colloid. (**a**–**d**) Thin, watery colloid appears as diffuse or aggregates of granular deposits, napkin-folds, and sheets of wrinkled tissue paper. Note the retained cytoplasmic hemosiderin pigment (**a**–**c**, Pap stain, TP; **d**, Pap stain, SP.) (**e**, **f**) On CS, this type of colloid forms a diffuse, thin layer or coalescing "broken glass" pieces. (**e**, DQ stain, CS; **f**, Pap stain, CS)

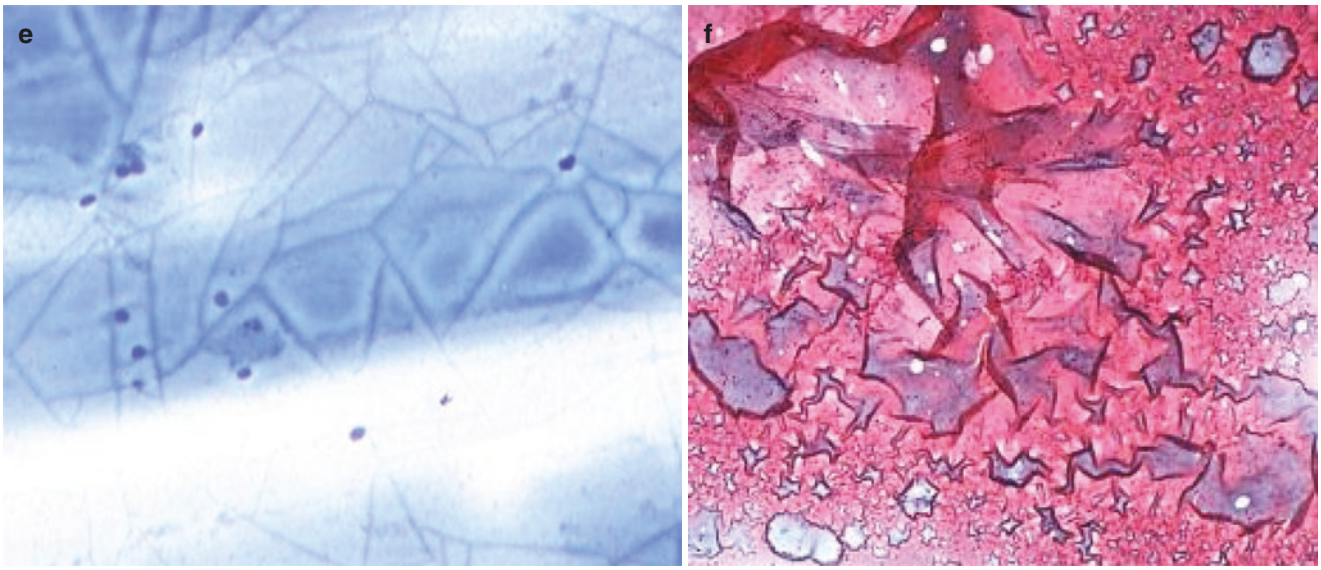

Fig. 4.5 (continued)

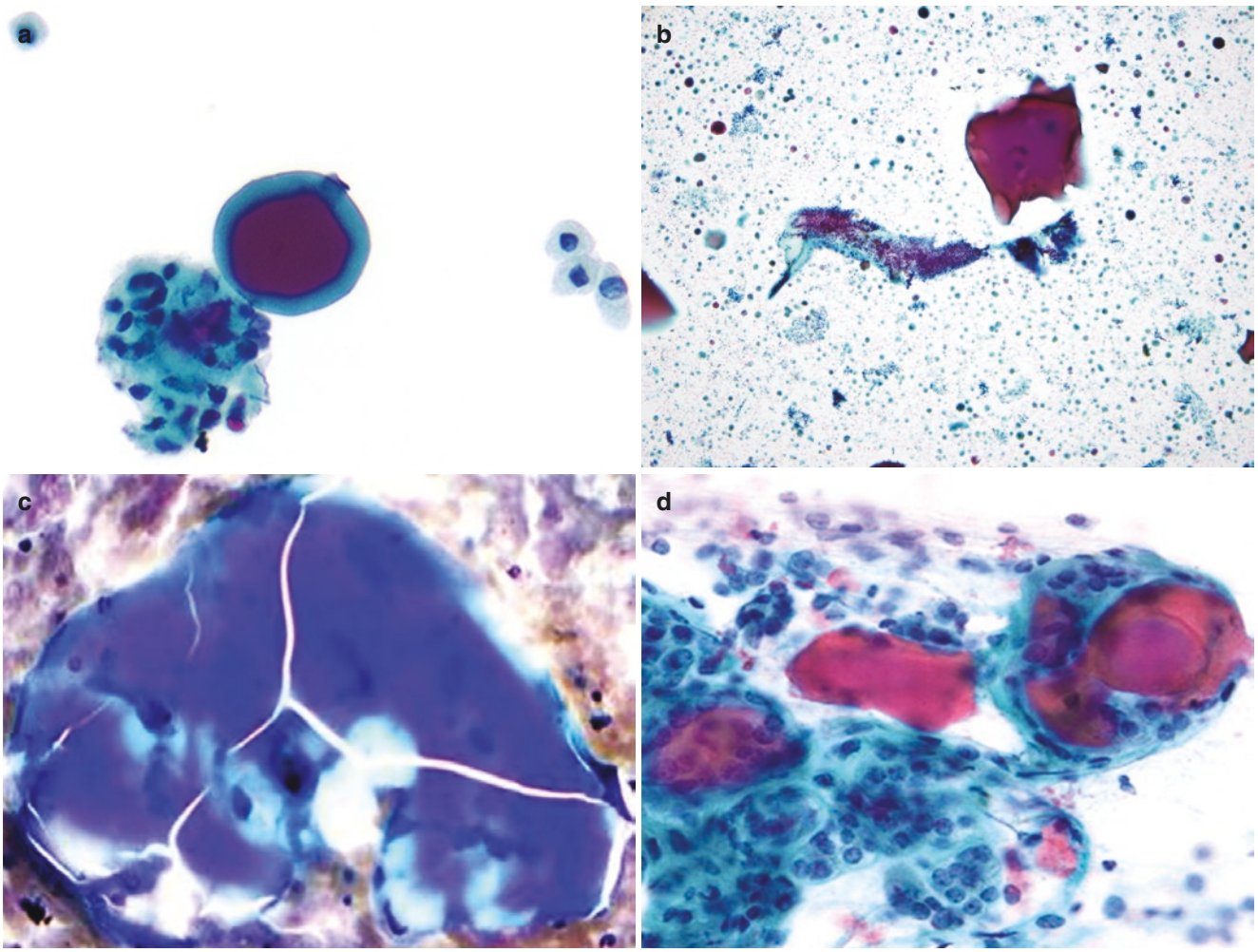

Fig. 4.6 Thick colloid in LBP and CS. (**a**, **b**) On LBP. thick colloid has a unique appearance, appearing as markedly fragmented chunks, round to oval aggregates, or dense droplets (globules), which show a dual staining pattern with a blue-staining periphery and central eosinophilia on Pap stain (**a**, Pap stain, TP; **b**, Pap stain, SP.) (**c**) On CS, this type of colloid appears as diffuse dried and cracked desert sand (DQ stain, CS). (**d**) On CS, thick colloid can appear in bigger, eosinophilic globules (Pap stain, CS)

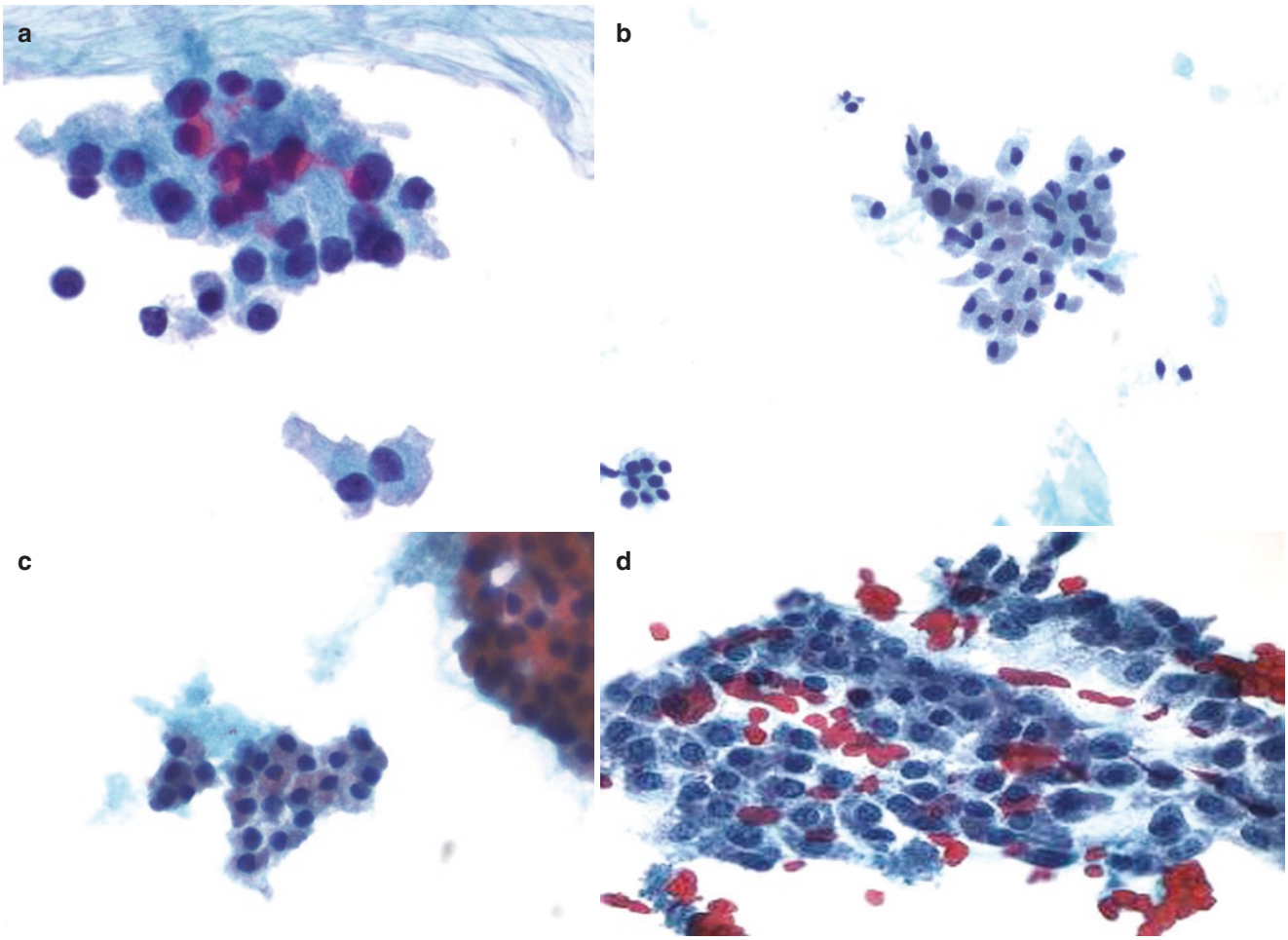

Fig. 4.7 Hürthle cell metaplasia in LBP and CS. (**a**–**c**) Hürthle cell metaplasia is commonly observed in MNG/BFN. In LBP, it appears similar to CS, with subtle differences. In LBP, the cells are polarized with round nuclei, granular cytoplasm, and low N:C ratio. The nuclei may appear smaller, and cytoplasm can either retain the granular quality or have a soft, lacy appearance with distinct boundaries (**a**, **b**, Pap stain, TP; **c**, Pap stain, SP). (**d**) The only difference in CS for Hürthle cell metaplasia is the larger sheet of cells (Pap stain, CS)

- Studies have demonstrated a higher incidence of thyroid cancer in patients with MNG than in the general population.
- Cytopathologists have maximum concordance for interpretation of the benign category.
- The false-negative (FN) rate of a benign diagnosis is 0–3% if noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) and microPTC are excluded.
- The main causes for FN diagnoses include errors of sampling and cytologic interpretation. Sampling errors occur with inadequate biopsy of the nodule harboring malignancy. Interpretation error may occur with poor specimen quality, such as multiple CS with air-drying artifact, thick cellular areas, and/or obscuring background blood.
- Poor specimen quality can occur when the material is not representative, scant, or poorly preserved so that neoplastic cells cannot be identified. Poor specimen quality is also implicated in false-positive (FP) diagnoses, when the cytopathologist attempts to force a diagnosis in cases with marginal material.
- FN diagnoses may also occur when focal features of classic PTC are misinterpreted as Hürthle cells or cyst-lining cells. The morphology of the latter may overlap with PTC.
- To reduce FN diagnoses, cases in which a clearly defined macrofollicular component is not identified should not be classified as benign. Whether these cases are best classified as atypical or nondiagnostic is less clear [35].
- The advent of USGFNA has decreased rates of nondiagnostic cytology and FN rates.
- False-positive diagnosis of nodular hyperplasia in LBP may occur when a hyperplastic nodule shows increased cellularity, papillary-like formation, and microfollicles. True papillae are absent and microfollicles are usually a small component.
- When the FNA yields a benign result, the NPV is >95%; when the FNA yields a malignant result, the positive predictive value (PPV) is >99%.

- The American Thyroid Association (ATA) recommends a conservative follow-up strategy for a benign cytologic diagnosis [22]

Main Differences Between LBP and CS in MNG/BFN

- As suggested by Tables 4.1 and 4.2, the morphology of MNG/BFN in LBP differs from CS in two aspects:
  - The cells in each slide are a monolayered or 3-D representative sample of the entire material collected in the vial. The residual preservative solution contains a variable amount of leftover sample.
  - The automated process causes some changes in background, architecture, and cellular morphology, the most important being the appearance of colloid, as shown on Figs. 4.5 and 4.6.
- Reduction or loss of the watery colloid makes quantitation difficult in LBP; it is more straightforward in CS. In TP, the amount of thin colloid may be diminished and therefore is difficult to quantify, requiring a closer evaluation of the architectural and cytological features.
- Cells are smaller, with pronounced shrinkage, and clusters of follicular cells are more crowded and tighter.
- Nuclear and cytoplasmic details are superior, particularly in TP, even with smaller cell size.
- Macrophages have more abundant pale cytoplasm, enlarged pale nuclei, and prominent nucleoli.
- Hürthle cells may be shrunken and more dissociated.

Partially Cystic Thyroid Nodules (PCTNs) in MNG/BFN

- Prominent cystic degeneration often occurs in MNG/BFN, comprising numerous macrophages and an adequate number of follicular cells (Fig. 4.8a).
- True epithelial cysts in the thyroid are rare.
- Thyroid cysts with an inadequate number of follicular cells should be interpreted as Nondiagnostic or Unsatisfactory (ND/Unsat), as the frequency of malignancy ranges from 5.2% to 17.6% in cystic thyroid nodules, similar to the rate for solid thyroid nodules. Some sonographic features associated with malignancy in a PCTN include microcalcifications, irregular borders, and intranodular vascularity. In the absence of worrisome US features, 2015 ATA guidelines recommend conservative management [22].
- Reparative changes of cyst-lining cells is commonly seen as a focal finding with cystic degeneration.
- Cyst-lining cells are elongated, polygonal, and cohesive, with dense or soft spindled cytoplasm, elongate to oval nuclei with grooves, powdery chromatin, and small to prominent nucleoli. The N:C ratio is low (Fig. 4.8b, c).
- Differential diagnosis of reparative changes in cyst-lining cells include cystic papillary thyroid carcinoma (PTC). Cells in cystic PTC lack spindle-cell morphology, and they show nuclear crowding and papillary microarchitecture (Fig. 4.8d).
- Immunocytochemistry for CK-19, galectin-3, HBME-1 and anti-CITED1 can be useful in distinguishing cystic PTC from benign cysts.

Thyroglossal Duct Cyst

- Thyroglossal duct cyst (TDC) is a common congenital anomaly of the thyroid gland, usually found centrally.
- Normally, the thyroglossal duct obliterates and disappears by the tenth week of gestation, but a thyroglossal remnant can remain in the form of a cyst, tract, or duct, or as ectopic thyroid within a cyst or duct.
- TDC usually presents as a painless cystic mass in the neck.
- It is treated by total thyroidectomy and surgical excision of the TDC.
- Cytologically, CS show columnar or round epithelial cells dispersed as sheets, small strips, or singly in a diffuse to granular proteinaceous background with histiocytes. Nuclei are round to oval with even chromatin. Cilia seen at the terminal end stain magenta in Diff-Quik (DQ) stain and eosinophilic Pap stain (Fig. 4.9a).
- In LBP, TDC proteinaceous material forms granular clumps and shows dispersed histiocytes and small clusters of ciliated, columnar epithelial cells. Nuclear morphology is well preserved, and the cilia stain light pink (Figs. 4.9b, c).
- The differential diagnosis of TDC includes branchial cleft cyst, lipoma, metastatic thyroid carcinoma, dermoid cyst, sebaceous cyst, and an enlarged lymph node.
- PTC can arise in a TDC, but this occurs in only 1% of all cases of TDC.

Squamous Metaplasia (SM) in Thyroid Nodules on LBP

- Squamous metaplasia (SM) is rare in thyroid nodules, but it is seen in non-neoplastic and neoplastic lesions including thyroid cysts, nodular hyperplasia, Hashimoto's thyroiditis, and PTC.
- In CS, SM shows two-dimensional sheets with a pulled-out appearance. Cells are enlarged and elongated to spindled. Nuclei are crowded, with pale to dark chromatin and

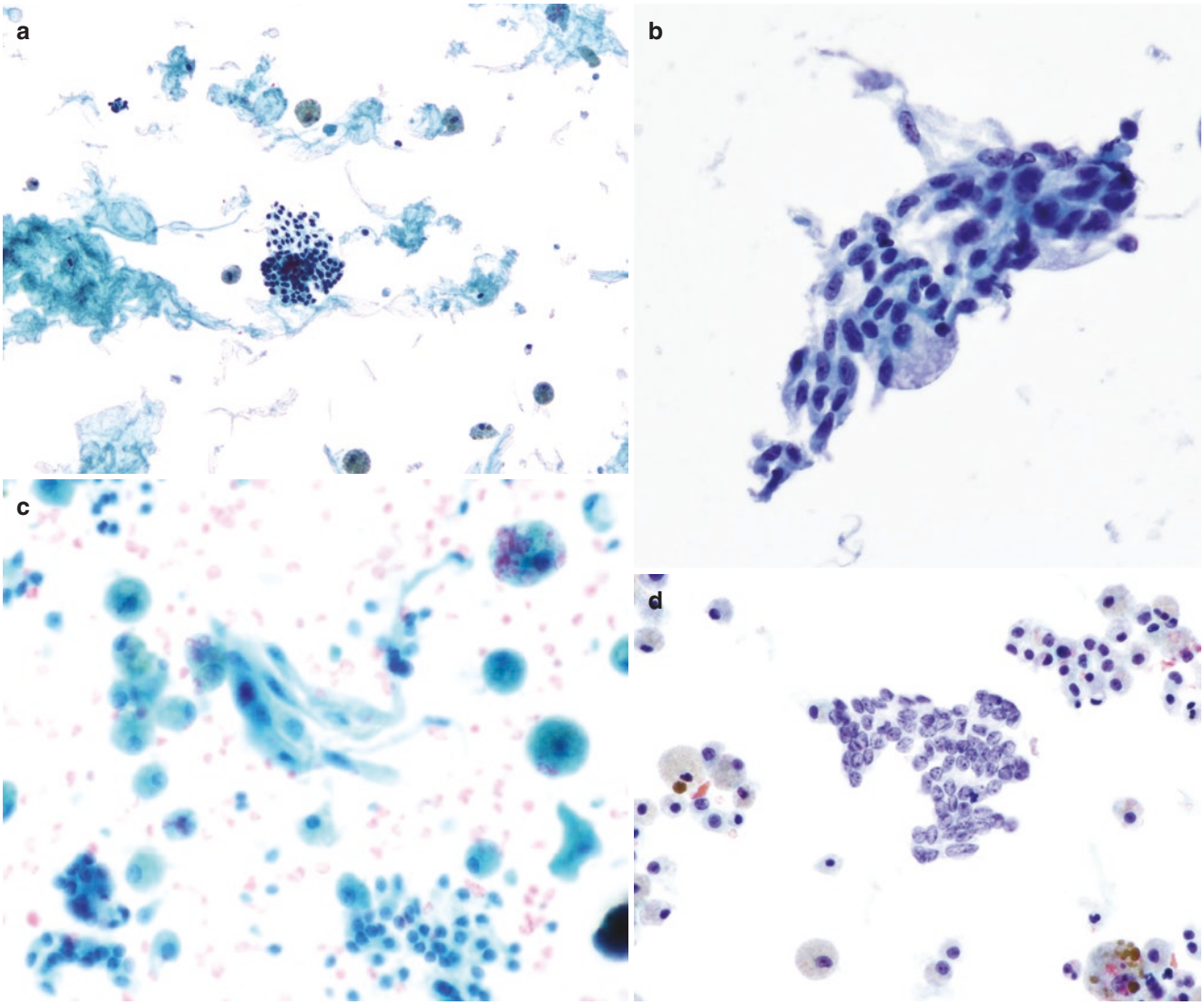

Fig. 4.8 Cystic degeneration in LBP and CS. Cystic degeneration often occurs in MNG/BFN, comprising numerous macrophages and an adequate number of follicular cells. (**a**) Cystic degeneration in a TP shows a flat sheet of uniform follicular cells in a background of abundant thin colloid and scattered hemosiderin-laden macrophages. (**b**) Reparative changes of cyst-lining cells (CLC) is commonly seen as a focal finding with cystic degeneration. CLC are elongated, polygonal, spindled, and cohesive, with slightly dense spindled cytoplasm, elongated to oval nuclei with grooves, powdery chromatin, and small to prominent nucleoli. The N:C ratio is low (**a**, **b**, Pap stain, TP). (**c**) In SP, cystic degeneration shows all features seen in TP, including sheets of uniform follicular cells and CLC in a background of abundant thin colloid and scattered hemosiderin-laden macrophages (Pap stain, SP). (**d**) Cystic papillary thyroid carcinoma (PTC) is in the differential diagnosis of CLC. Cells in cystic PTC show all nuclear features of the neoplasm, including irregularity, overlap, powdery chromatin, grooves, and pseudoinclusions. The cells lack the spindle-cell morphology of CLC. Immunocytochemistry for CK-19, galectin-3, HBME-1, and anti-CITED1 can be useful in distinguishing cystic PTC from benign CLC (Pap stain, TP)

intranuclear grooves; rarely, pseudoinclusions can be seen. Cytoplasm is dense and squamoid with distinct borders (Fig. 4.10a, b).

- In LBP, SM shows similar cells. The cells appear more cohesive and cell sheets appear tighter (Fig. 4.10c). A histologic diagnosis may show nodular hyperplasia with extensive SM (Fig. 4.10d).
- SM should be in the differential diagnosis of thyroid nodules with potentially benign cystic changes.
- Extensive SM with reactive atypia is a diagnostic dilemma in FNA. It may mimic malignancy, including PTC and squamous cell carcinoma, and lead to false-positive results.
- Surgical resection may be an appropriate approach to confirm its benign nature.

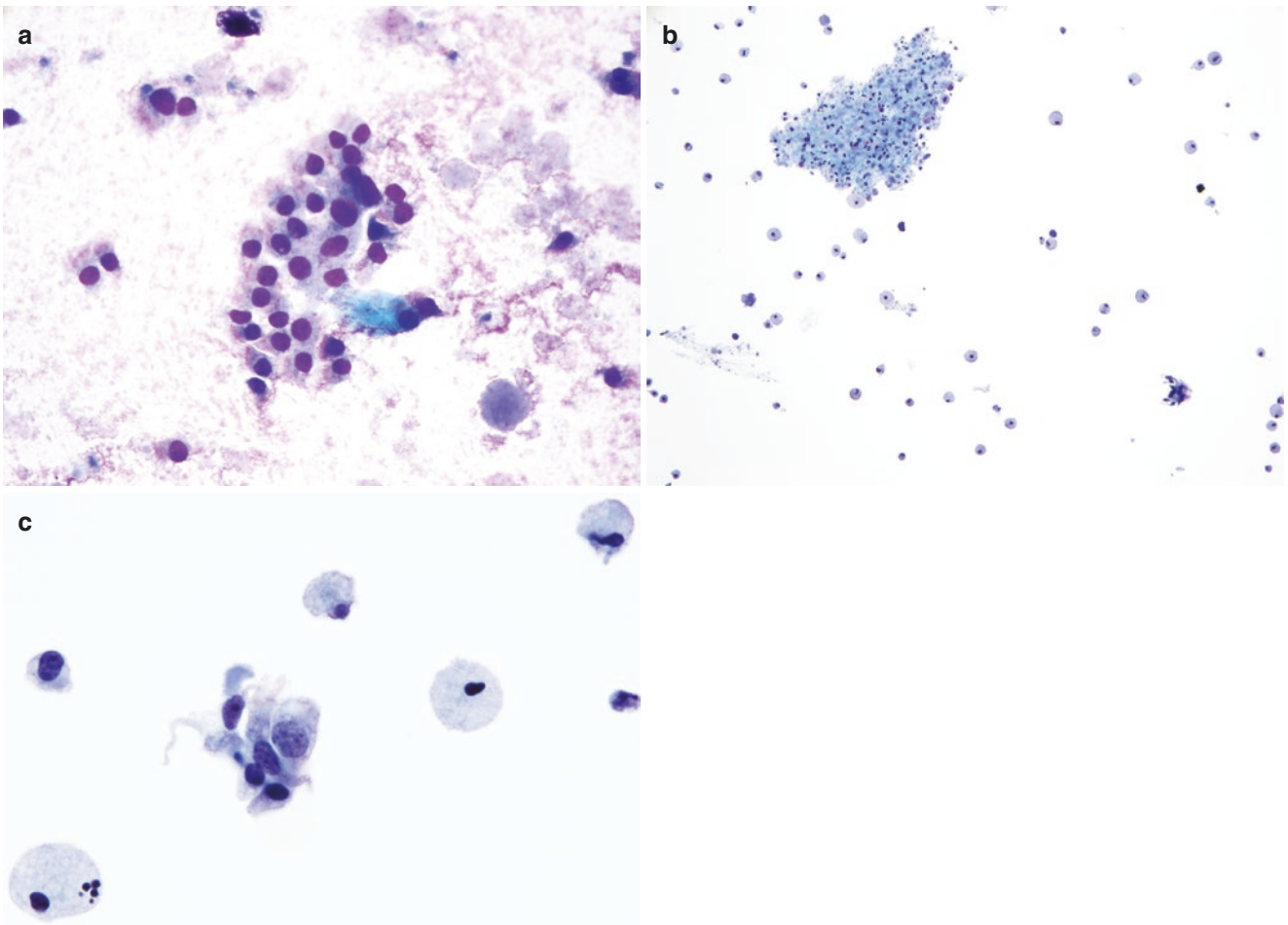

Fig. 4.9 Thyroglossal duct cyst (TDC). (**a**), CS shows small sheets and small strips of columnar to round epithelial cells in a diffuse to granular proteinaceous background with histiocytes. Nuclei are round to oval with even chromatin; magenta-staining cilia are seen at the terminal end (DQ stain, CS). (**b**, **c**) TDC in TP shows large and small granular clumps of proteinaceous material, dispersed histiocytes, and small clusters of ciliated, columnar epithelial cells. Nuclear morphology is well preserved, and cilia stain light pink (Pap stain, TP)

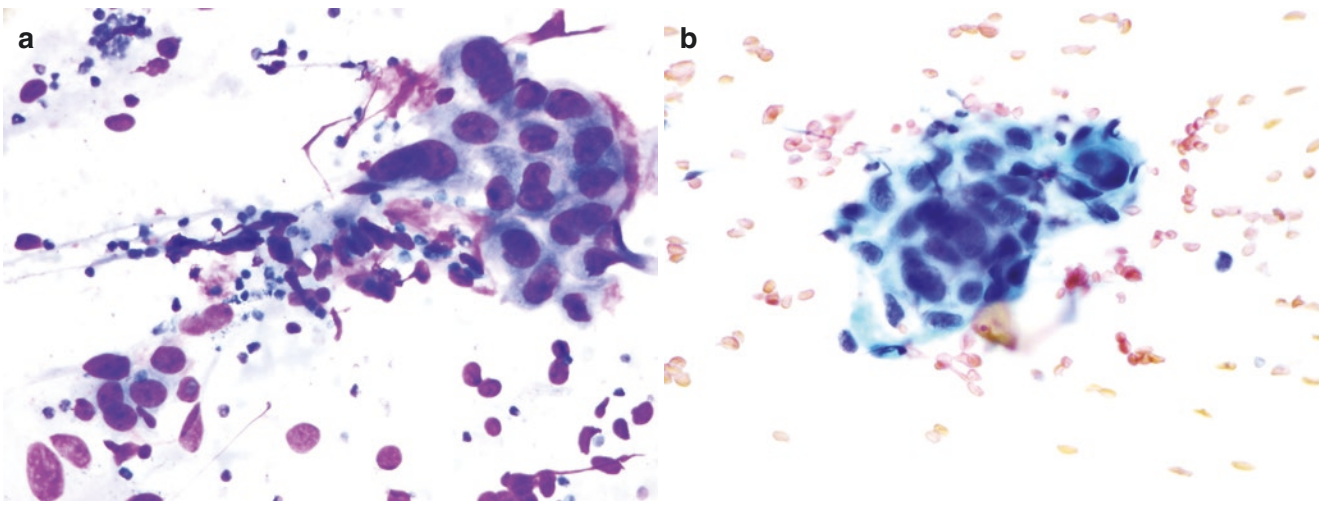

Fig. 4.10 Squamous metaplasia (SM). (**a**, **b**) In CS, SM shows two-dimensional sheets with a pulled-out appearance. Cells are enlarged, and elongated to spindled. Nuclei are enlarged with some bi-nucleation, pale to dark chromatin, and nucleoli. Intranuclear grooves occasionally can be seen, and rarely, pseudoinclusions (*not shown*). Cytoplasm is dense, squamoid, with distinct borders (**a**, DQ stain, CS; **b**, Pap stain, CS). (**c**) TP shows similar features as CS, except that the cells are in more cohesive groups with a less pulled-out 2-D appearance (Pap stain). (**d**) A histologic section of the total thyroidectomy specimen shows MNG with extensive SM. Note dilated follicles or small cysts with SM, surrounded by thyroid follicles (H&E stain)

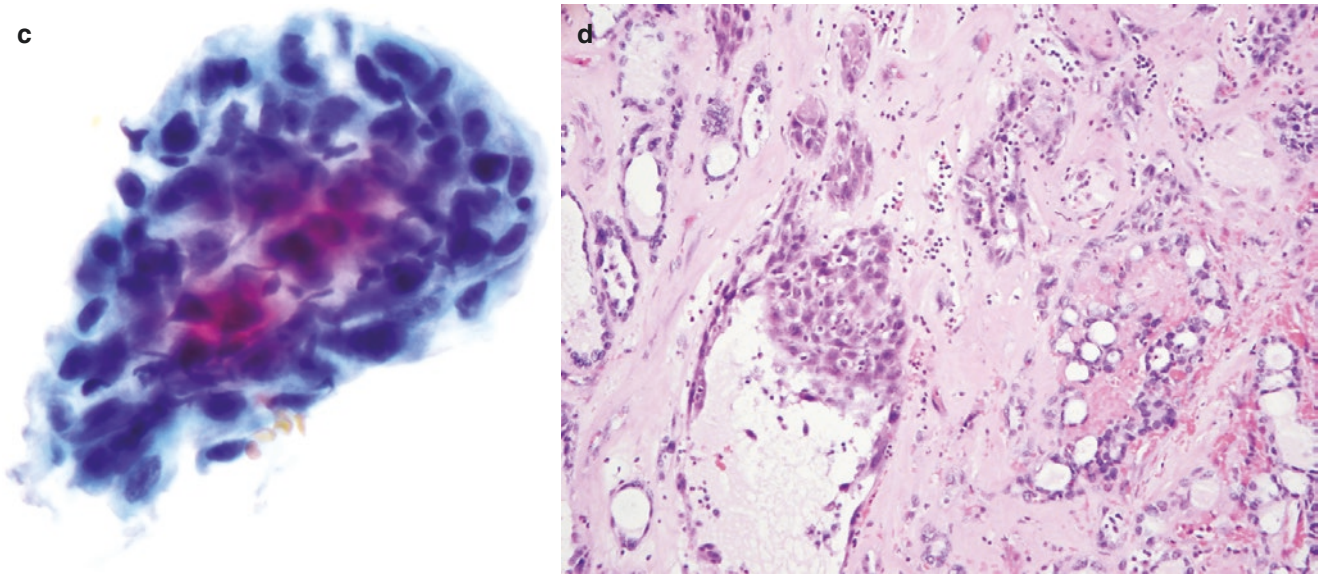

Fig. 4.10 (continued)

Hashimoto's Thyroiditis (Chronic Lymphocytic Thyroiditis)

- Hashimoto thyroiditis (HT), also known as chronic lymphocytic thyroiditis, is the most common type of lymphocytic thyroiditis.
- It is an autoimmune disease, with an incidence estimated to range from 0.3 to 1.5 cases per 1000 people.
- The disease is characterized by a cellular immune response involving T and B lymphocytic infiltration of the thyroid gland, as well as by a humoral immune response leading to the production of thyroid-specific antibodies, including antithyroid peroxidase antibodies (TPOAb).
- Grossly, the thyroid gland shows diffuse and symmetric enlargement. Occasionally it can be nodular. Cut surface is yellow-tan (Fig. 4.11a). Histologically, extensive lymphocytic infiltration with germinal center formation is seen, and some plasma cells are seen in close association with atrophic follicles lined by Hürthle cells (Fig. 4.11b). Lymphocytes are usually T-cell. Colloid is present. Giant cells and SM are also noted. HT looks similar in CS, TP, and SP.
- Diagnosis of Hürthle cell lesions is a challenge in both CS and LBP, as Hürthle cells in Hashimoto's thyroiditis, MNG/BFN, or Hürthle cell neoplasms display similar cytological appearance and may be difficult to distinguish.

Cytology of HT on LBP

- The diagnosis of HT on CS is made when increased numbers of polymorphous lymphocytes, clusters of Hürthle (oncocytic) cells, and/or thyroid follicular cells and lymphocytic infiltration of epithelial cell clusters are present in varying proportions with scanty colloid, lymphohistiocytic aggregates, lymphoid tangles, scattered plasma cells, and giant cells (Fig. 4.12a–c).
- The diagnosis of thyroiditis on TP and SP is reliable, as all characteristic findings of HT are easily identified (Figs. 4.12d–f and 4.13a–d; *see also* Fig. 3.7).
- Specimens are usually hypercellular, with both Hürthle cells and/or thyroid follicular cells and lymphocytes, noted individually and/or in clusters, lymphohistiocytic aggregates, lymphoid tangles, scattered plasma cells, and giant cells.

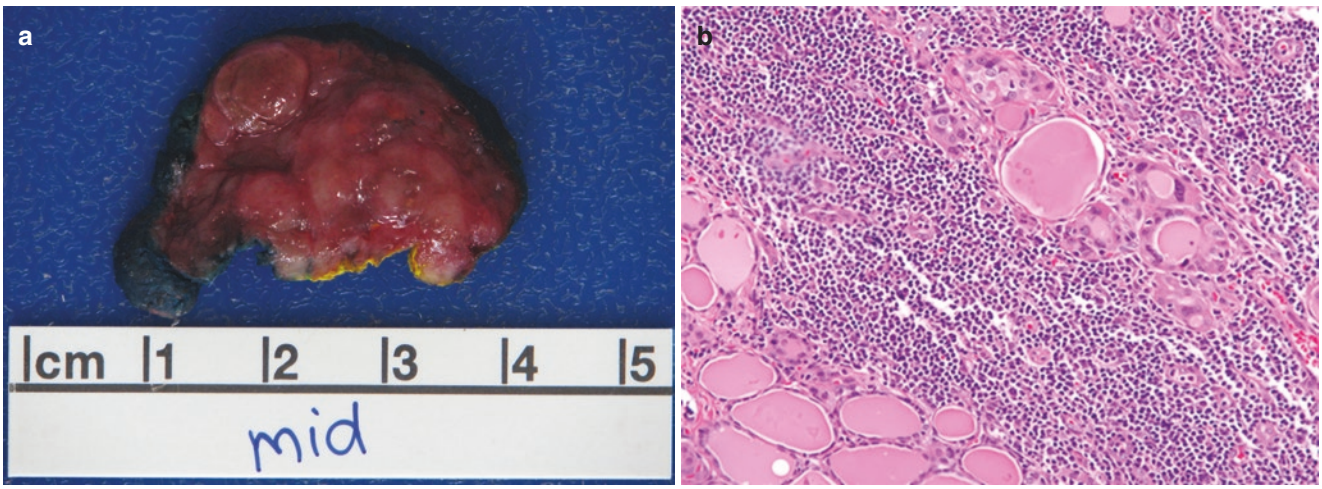

Fig. 4.11 Chronic lymphocytic thyroiditis/Hashimoto's thyroiditis (HT). (**a**) Gross specimen of a lobectomy with HT showing nodular, symmetric enlargement with a yellow-tan cut surface. (**b**) Histology shows extensive lymphocytic infiltration in close association with atrophic follicles lined by Hürthle cells. Lymphocytes are usually T cells. Colloid is present (H&E stain)

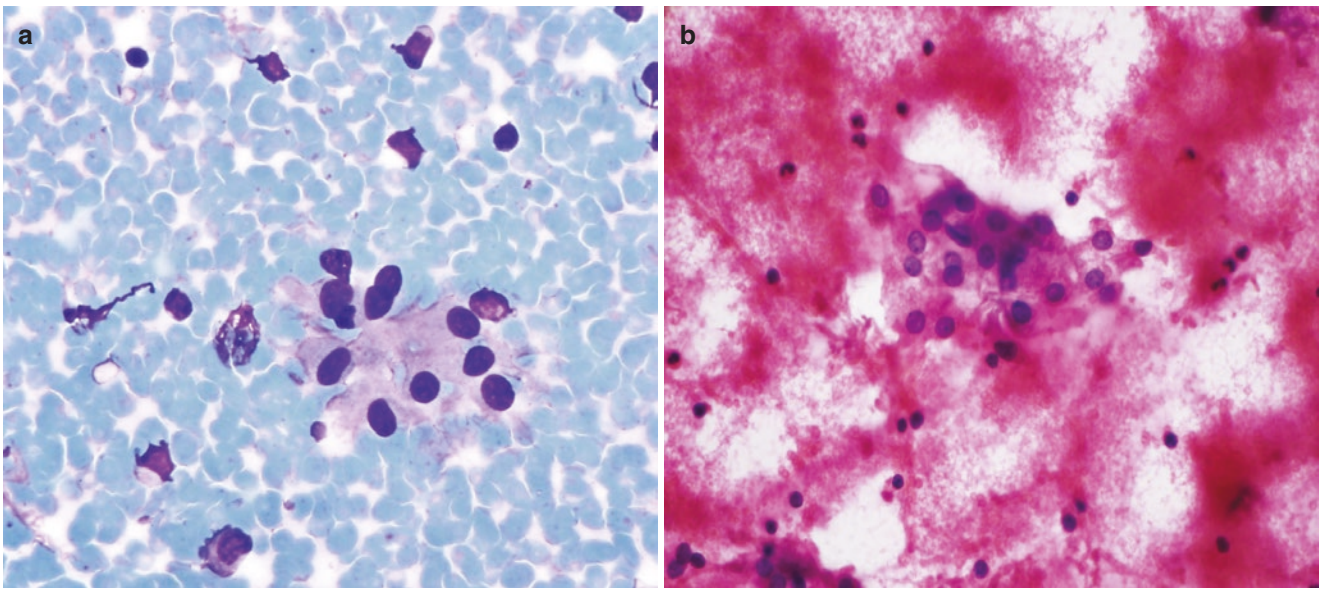

Fig. 4.12 Hashimoto's thyroiditis (HT) in CS and LBP. (**a**–**c**) Polymorphous lymphoid population, Hürthle cells, and lymphohistiocytic aggregate in HT. Note abundant blood partially obscuring cell detail in the Pap-stained CS (**a**, DQ stain CS; **b**, **c**, Pap stain CS). (**d**–**f**) TP shows a polymorphous lymphoid population, Hürthle cells, and lymphohistiocytic aggregate. Note abundant, thin tissue paper colloid, granular cytoplasm of Hürthle cells, and the crisp nuclear morphology of these cells and lymphocytes compared with the CS. Lymphohistiocytic aggregate forms a tighter cluster in TP, but the cellular morphology is similar to the CS (**d**–**f**, Pap stain TP)

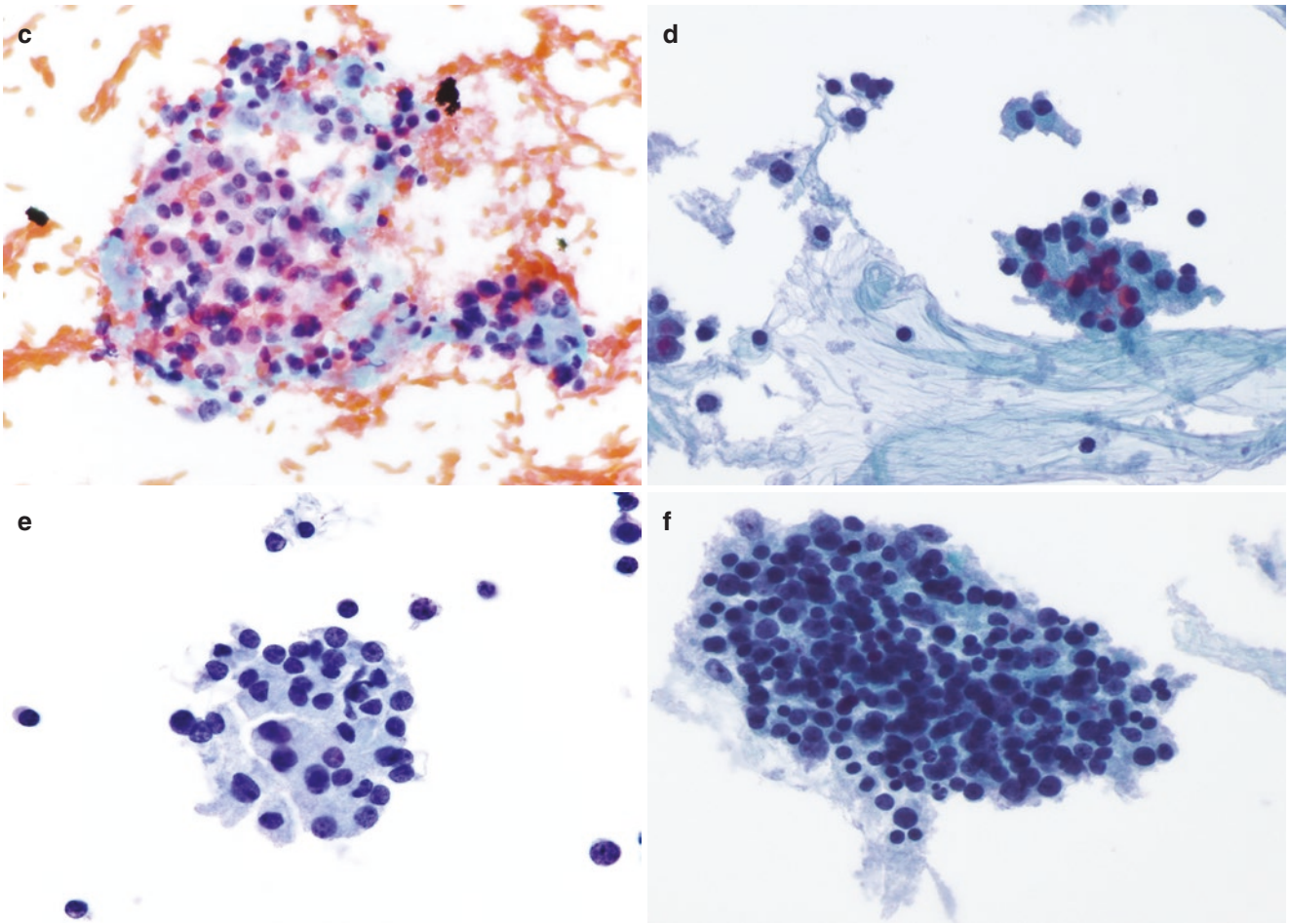

Fig. 4.12 (continued)

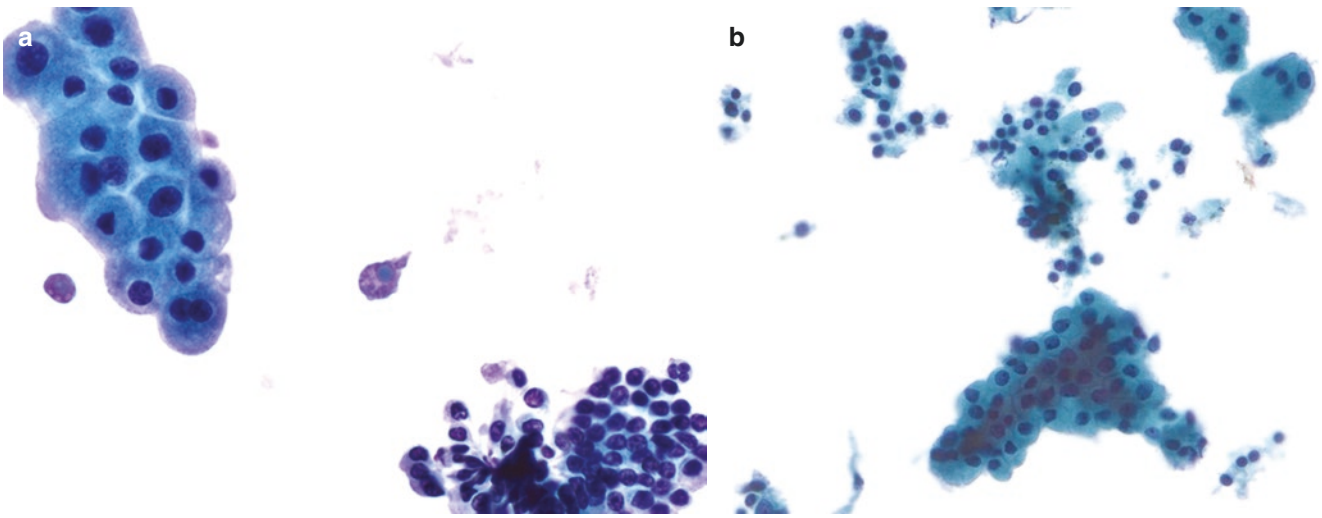

Fig. 4.13 Hashimoto's thyroiditis (HT) in TP and SP. (**a**) Characteristic cytomorphology of HT is seen on a TP slide. Lymphocytes may aggregate and clump at the periphery of the slide and mimic follicular cells (Pap stain, TP). (**b**–**d**) SP also shows the characteristic cytomorphology of HT. Note the distinct cytoplasmic walls of Hürthle cells and well-preserved morphology for these cells and lymphocytes. Lymphocytes are increased and appear in clusters, some adjacent to Hürthle cells. Note the somewhat 3-D appearance of cells; some lymphocytes appear on a different plane of focus (Pap stain, SP)

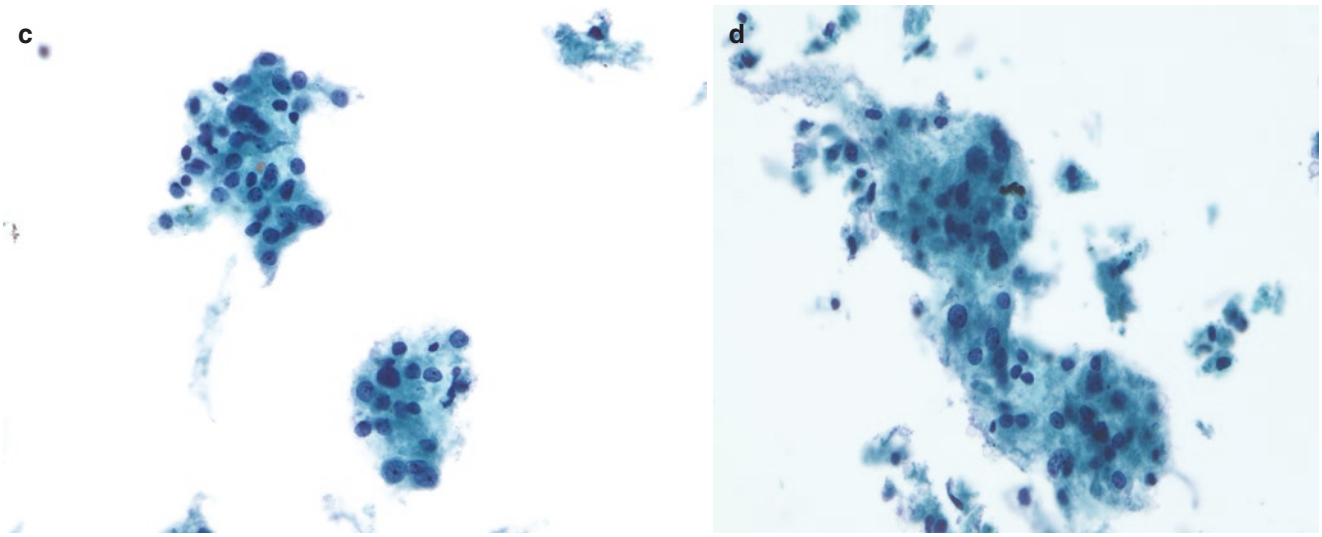

Fig. 4.13 (continued)

- The most recent TBSRTC does not require a minimum number of Hürthle cells and/or thyroid follicular cells for an adequate diagnosis of HT.
- Lymphocytes are polymorphous and dispersed as isolated cells, in clusters, and infiltrate Hürthle cells. In LBP (particularly TP), lymphocytes form clumps towards the periphery of the slide (*see* Fig. 4.13a).
- Hürthle cells are arranged in flat sheets, small clusters with infiltrating lymphocytes, or as isolated cells, showing small nuclei with or without nucleoli. The cytoplasm is well defined and granular (*see* Figs. 4.12d and 4.13a, b).
- Random cellular and nuclear atypia composed of large Hürthle cells with large nuclei and prominent nucleoli is usually present and favors a diagnosis of HT.
- Hürthle cells in HT can demonstrate atypical nuclear features, including elongation, grooves, and clearing with a less prominent HT background and can be misinterpreted as PTC.
- Plasma cells and lymphohistiocytic aggregates may be prominent and are seen in close approximation to Hürthle cell clusters.
- The appearance of HT on cytologic preparations depends on the state of the disease. In the milder early phase, LBP show follicular cell clusters infiltrated by a few lymphocytes. As the disease progresses to a more severe form, LBP show follicular cell clusters infiltrated by moderate amounts of lymphocytes. In the late phase of the disease, the background shows an increased/dense lymphocytic infiltration in various stages of transformation, with fewer Hürthle and/or follicular cells.

Salient Points for HT

- Clinical presentation is symmetric enlargement of thyroid gland.
- Diagnosis of HT is made with clinical imaging, serum thyroid peroxidase (TPO) antibody assessment, and FNA.
- Proper recognition of Hürthle cells, lymphocytes, and lymphohistiocytic aggregates virtually rules out a Hürthle cell neoplasm and prevents unnecessary surgery.
- HT may be the main cause for false-positive (FP) results on thyroid FNA. In a 2018 study by Rammeh et al. [34] of head and neck masses, all FP were reported in the thyroid group. These cases, cytologically classified suspicious for malignancy and PTC, proved to be lymphocytic thyroiditis on final histology.
- Problems in the differential diagnosis of HT may arise when there is a deviation in the proportions of the two cell components, Hürthle cells and lymphocytes. In cases of HT misdiagnosed as MNG/BFN, Hürthle cells may be present in a background of colloid with low numbers of lymphocytes. Cases of HT misdiagnosed as suspicious for PTC may show the nuclear changes described above for the cytology of HT.
- When a thyroiditis is suspected, the detection of lymphoepithelial clusters in an inflammatory background is the pivotal clue for the diagnosis in LBP.
- Neoplasia most commonly associated with HT includes PTC and non-Hodgkin's lymphoma.
- The incidence of coexisting thyroid neoplasia with HT ranges between 3% and 14%.

- PTC is the most common malignancy coexistent with HT. The mechanism underlying this association is not fully understood, but PTC coexistent with HT is associated with improved prognosis.
- In the [34] study, the only case of HT with carcinoma showed evidence of increased lymphocytes in the background, occasional thyroid follicular cell cluster infiltrated by lymphocytes, and many scattered, large atypical cells having large nuclei and intranuclear pseudoinclusions.

Main Differences Between LBP and CS in HT

- As shown in Tables 4.1 and 4.2 and Fig. 4.12, the LBP appearance of thyroiditis is similar to that in CS except that the amount of background lymphocytes in LBP can be higher than normal because of the spinning of the material before the automated process. When a thyroiditis is suspected, the detection of lympho-epithelial clusters in an inflammatory background is the pivotal clue for the diagnosis and warrants a simple follow-up for the patient.
- Lymphocytes may be more evenly dispersed, with fewer lymphohistiocytic aggregates.
- Lymphocytes may clump at the periphery of the slide (particularly in TP) and may be mistaken for follicular cells.
- Hürthle cells may be shrunken and more dissociated.

Riedel's Thyroiditis

- Riedel's thyroiditis (RT) is a rare form of chronic thyroiditis. Although the etiology is unknown, it may develop in the course of subacute thyroiditis. It may be associated with idiopathic fibrosis in other sites (retroperitoneum, lung, mediastinum, pancreas).
- Patients present with diffuse and painless enlargement of the thyroid with compressive symptoms.
- It is a fibroinflammatory process that partially destroys and replaces the thyroid parenchyma and often involves surrounding tissues.
- Grossly, the goitrous thyroid gland is hard (Fig. 4.14a). The mass may not be well defined and may involve extrathyroidal tissue, such as adjacent muscle and other structures. Cut surface is firm, yellow-tan to gray, and smooth. Histologically, spindle cells of dense fibrosis obliterate thyroid parenchyma and infiltrate adjacent skeletal muscle and other structures. Patchy perivascular and infiltrative inflammatory cells comprise lymphocytes, plasma cells, and eosinophils (Fig. 4.14b).
- On CS, FNA demonstrates moderate cellularity with fragments of fibrous tissue with bland, spindle-shaped cells, myofibroblasts, and intense inflammatory infiltrate composed of lymphocytes (Figs. 4.14c, d).
- On TP, the fibrosis forms clumps of spindle cells instead of being diffuse. Cells may be closely associated with inflammatory cells (Fig. 4.14e).
- The differential diagnosis includes a fibrous variant of HT, anaplastic carcinoma, solitary fibrous tumor, and sarcoma.
- Immunohistochemical studies (IHC) reveal a few scattered B lymphocytes (CD20 positive) and numerous scattered T lymphocytes (CD3 positive).
- RT has been claimed to be an IgG4-related disease.

Graves' Disease

- Graves' disease is an autoimmune, diffuse hyperplastic disorder that causes hyperthyroidism and is usually clinically diagnosed. It is more common in women and presents as diffuse enlargement of thyroid gland. Histologically, hyperplastic follicles with papillary infoldings without fibrovascular cores are seen. FNA is performed only when there is a dominant cold nodule that raises a suspicion for malignancy.
- On CS, Graves' disease shows a hypercellular specimen with follicular cells in large branching sheets, with thin, watery colloid in the background. The nuclei are enlarged and vesicular and may show a prominent nucleoli. Nuclear atypia may be pronounced after anti-thyroid therapies. Cytoplasm is moderate to abundant and shows small secretory vacuoles. The most distinctive feature is "flame cells" or fire-flare appearance, represented by marginal cytoplasmic vacuoles with eosinophilic frayed edges; these are best seen on DQ stain.
- In LBP, Graves' disease may be difficult to identify unless there is a clinical history. Cytology shows features similar to those in CS, including enlarged nuclei with a prominent nucleoli. Cytoplasm is moderate to abundant and shows small secretory vacuoles. The "flame cells" or fire-flare appearance, represented by marginal cytoplasmic vacuoles with frayed edges, are evident and appear different from benign follicular cells (Fig. 4.15a–c).

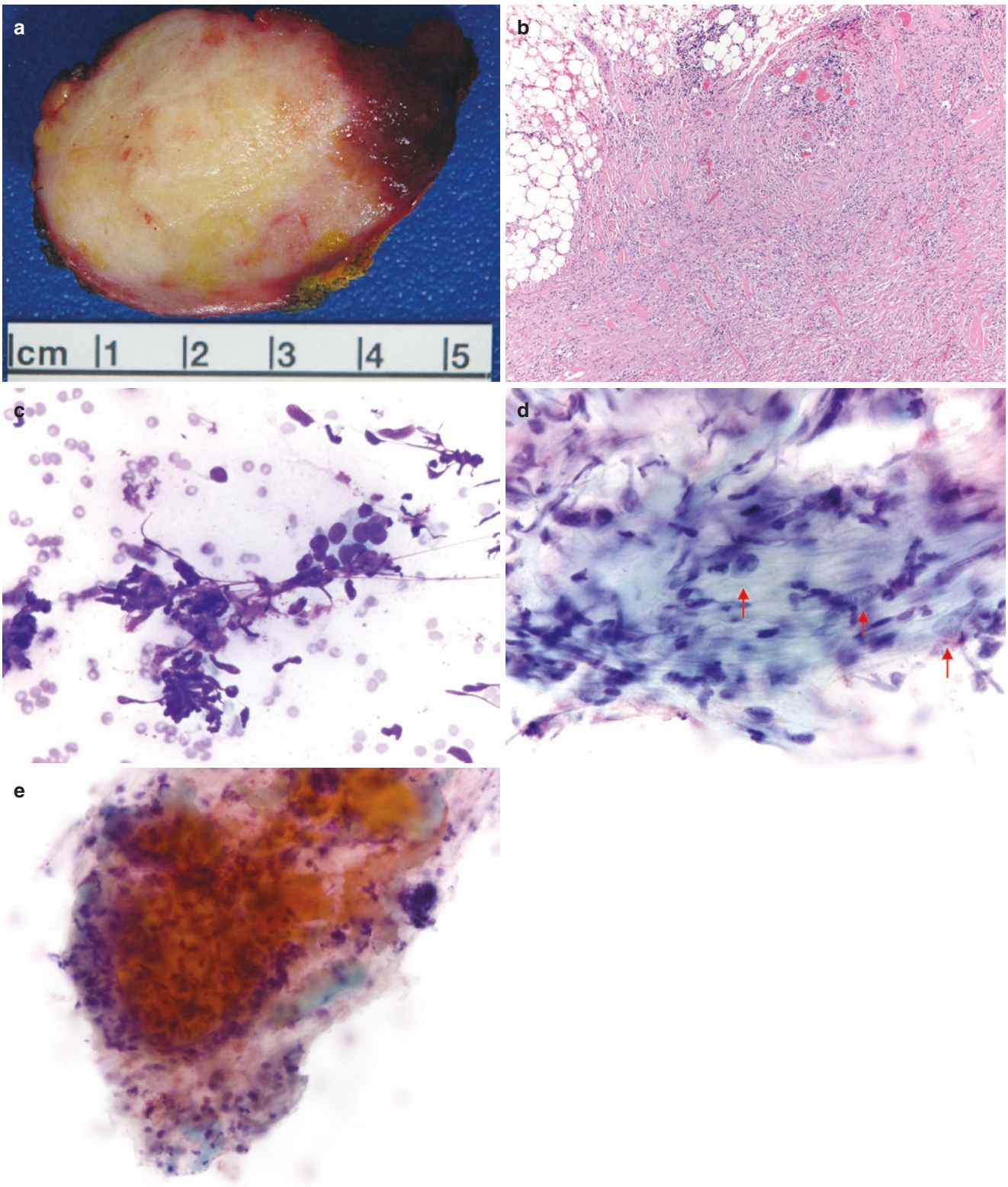

Fig. 4.14 Riedel's thyroiditis (RT). (**a**) Gross appearance of a thyroid lobe in RT appears smooth with a yellow-tan to gray cut surface. The gland was hard and firm on palpation. (**b**) Histologic section of the thyroidectomy specimen shows spindle cells of dense fibrosis with inflammatory cells obliterating thyroid parenchyma and infiltrating adjacent skeletal muscle and adipose tissue. The patchy perivascular and infiltrative inflammatory cells comprise lymphocytes, plasma cells, and eosinophils (H&E stain). (**c**, **d**) CS of RT show a moderate cellularity with loosely cohesive fragments of fibrous tissue composed of bland, spindle-shaped cells (i.e., myofibroblasts) (*arrows*). Other areas showed inflammatory infiltrate composed of lymphocytes. Note the fibrous stroma, which stains magenta in DQ (**c**) and pale green in the Pap stain (**d**). (**e**) On TP, the spindle cells of fibrosis form cohesive clumps instead of being in loosely cohesive fragments. This may occur because of the non-neoplastic nature of the lesion. Cells are closely associated with inflammatory cells (Pap stain, TP)

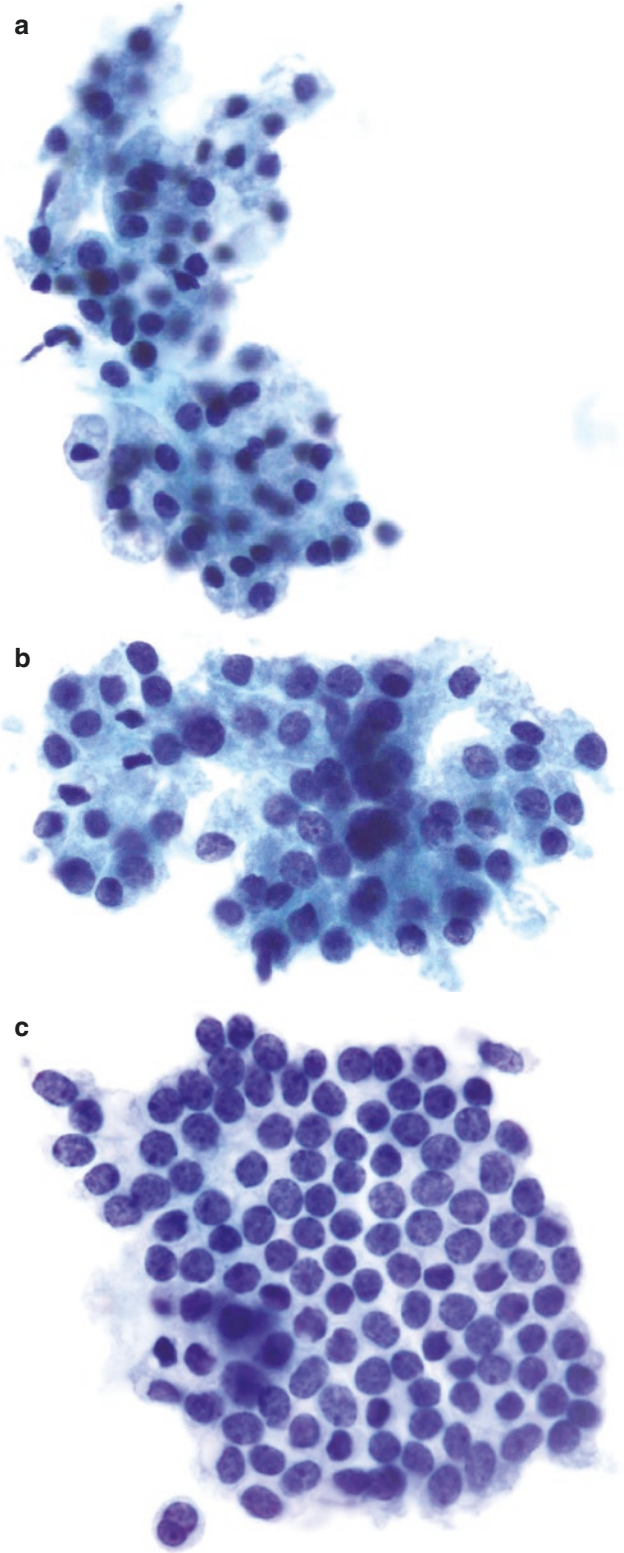

Fig. 4.15 Graves' disease. (**a**, **b**) A clinically proven case of Graves' disease shows enlarged nuclei with nucleoli. Cytoplasm is moderate to abundant and shows small secretory vacuoles. The most distinctive feature is "flame cells" or fire-flare appearance, represented by marginal cytoplasmic vacuoles with eosinophilic frayed edges; these are best seen on DQ stain. However, some peripheral cells in the two groups of follicular cells do show frayed edges. (**c**) A macrofollicle of benign follicular cells shown for comparison (**a**–**c**, Pap stain, TP)

Suggested Reading

1. Abi-Raad R, Prasad M, Baldassari R, Schofield K, Callender GG, Chhieng D, et al. The value of negative diagnosis in thyroid fine-needle aspiration: a retrospective study with histologic follow-up. Endocr Pathol. 2018;29:269–75. https://doi.org/10.1007/s12022-018-9536-5.
2. Afify AM, Liu J, Al-Khafaji BM. Cytologic artifacts and pitfalls of thyroid fine-needle aspiration using ThinPrep: a comparative retrospective review. Cancer. 2001;93:179–86.
3. Alatsakis M, Drogouti M, Tsompanidou C, Katsourakis A, Chatzis I. Invasive thyroglossal duct cyst papillary carcinoma: a case report and review of the literature. Am J Case Rep. 2018;19:757–62. https://doi.org/10.12659/AJCR.907313.
4. Ali SZ, Cibas ES. The Bethesda system for reporting thyroid cytopathology; definitions, criteria, and explanatory notes. 2nd ed. Cham: Springer International Publishing AG; 2018.
5. Alshaikh S, Harb Z, Aljufairi E, Almahari SA. Classification of thyroid fine-needle aspiration cytology into Bethesda categories: an institutional experience and review of the literature. Cytojournal. 2018;15:4. https://doi.org/10.4103/cytojournal.cytojournal_32_17.
6. Awasthi P, Goel G, Khurana U, Joshi D, Majumdar K, Kapoor N. Reproducibility of "the Bethesda system for reporting thyroid cytopathology": a retrospective analysis of 107 patients. J Cytol. 2018;35:33–6. https://doi.org/10.4103/JOC.JOC_215_16.
7. Bongiovanni M, Papadakis GE, Rouiller N, Marino L, Lamine F, Bisig B, et al. The Bethesda system for reporting thyroid cytopathology explained for practitioners: frequently asked questions. Thyroid. 2018;28:556–65. https://doi.org/10.1089/thy.2017.0685.
8. Chandanwale SS, Nair R, Gambhir A, Kaur S, Pandey A, Shetty A, et al. Cytomorphological spectrum of thyroiditis: a review of 110 cases. J Thyroid Res. 2018;2018:5246516. https://doi.org/10.1155/2018/5246516.
9. Chong Y, Ji SJ, Kang CS, Lee EJ. Can liquid-based preparation substitute for conventional smear in thyroid fine-needle aspiration? A systematic review based on meta-analysis. Endocr Connect. 2017;6:817–29. https://doi.org/10.1530/EC-17-0165.
10. Choong KC, Khiyami A, Tamarkin SW, McHenry CR. Fine-needle aspiration biopsy of thyroid nodules: is routine ultrasound-guidance necessary? Surgery. 2018;164:789–94. https://doi.org/10.1016/j.surg.2018.04.047.
11. Cibas ES, Ali SZ. The 2017 Bethesda system for reporting thyroid cytopathology. Thyroid. 2017;27:1341–6. https://doi.org/10.1089/thy.2017.0500.
12. Cipriani NA, White MG, Angelos P, Grogan RH. Large cytologically benign thyroid nodules do not have high rates of malignancy or false-negative rates and clinical observation should be considered: a meta-analysis. Thyroid. 2018. doi: https://doi.org/10.1089/thy.2018.0221. [Epub ahead of print].
13. Clark DP, Faquin WC. Thyroid cytopathology. 2nd ed. New York: Springer; 2010.
14. Cochand-Priollet B, Prat JJ, Polivka M, Thienpont L, Dahan H, Wassef M, et al. Thyroid fine needle aspiration: the morphological features on ThinPrep slide preparations. Eighty cases with histological control. Cytopathology. 2003;14:343–9.
15. Das DK, George SA, Mohammad T, John B, George SS, Behbehani AI. Papillary carcinoma in thyroglossal duct cyst: diagnosis by fine-needle aspiration cytology and immunocytochemistry. Diagn Cytopathol. 2018;46:797–800. https://doi.org/10.1002/dc.23968.
16. Duncan LD, Forrest L, Law WM Jr, Hubbard E, Stewart LE. Evaluation of thyroid fine-needle aspirations: can ThinPrep be used exclusively to appropriately triage patients having a thyroid nodule? Diagn Cytopathol. 2011;39:341–8. https://doi.org/10.1002/dc.21392.
17. Durante C, Costante G, Lucisano G, Bruno R, Meringolo D, Paciaroni A, et al. The natural history of benign thyroid nodules. JAMA. 2015;313:926–35. https://doi.org/10.1001/jama.2015.0956.

18. Fadda G, Rossi ED, Raffaelli M, Mulè A, Pontecorvi A, Miraglia A, et al. Fine-needle aspiration biopsy of thyroid lesions processed by thin-layer cytology: one-year institutional experience with histologic correlation. Thyroid. 2006;16:975–81.
19. Fischer AH, Clayton AC, Bentz JS, Wasserman PG, Henry MR, Souers RJ, et al. Performance differences between conventional smears and liquid-based preparations of thyroid fine-needle aspiration samples: analysis of 47,076 responses in the College of American Pathologists Interlaboratory Comparison Program in Non-Gynecologic Cytology. Arch Pathol Lab Med. 2013;137:26–31. https://doi.org/10.5858/arpa.2012-0009-CP.
20. Geers C, Bourgain C. Liquid-based FNAC of the thyroid: a 4-year survey with SurePath. Cancer Cytopathol. 2011;119:58–67. https://doi.org/10.1002/cncy.20125.
21. Guo HQ, Zhang ZH, Zhao H, Niu LJ, Chang Q, Pan QJ. Factors influencing the reliability of thyroid fine-needle aspiration: analysis of thyroid nodule size, guidance mode for aspiration and preparation method. Acta Cytol. 2015;59:169–74. https://doi.org/10.1159/000381412.
22. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, et al. 2015 American Thyroid Association management guidelines for adult patients with thyroid nodules and differentiated thyroid Cancer: the American Thyroid Association guidelines task force on thyroid nodules and differentiated thyroid Cancer. Thyroid. 2016;26:1–133. https://doi.org/10.1089/thy.2015.0020.
23. Harigopal M, Sahoo S, Recant WM, DeMay RM. Fine-needle aspiration of Riedel's disease: report of a case and review of the literature. Diagn Cytopathol. 2004;30:193–7.
24. Hoda RS. Non-gynecologic cytology on liquid-based preparations: a morphologic review of facts and artifacts. Diagn Cytopathol. 2007;35:621–34.
25. Hoda RS, VandenBussche C, Hoda SA. Diagnostic liquid-based cytology. New York: Springer; 2017.
26. Jung CK, Lee A, Jung ES, Choi YJ, Jung SL, Lee KY. Split sample comparison of a liquid-based method and conventional smears in thyroid fine needle aspiration. Acta Cytol. 2008;52:313–9.
27. Li W, Zhu Q, Jiang Y, Zhang Q, Meng Z, Sun J, et al. Partially cystic thyroid nodules in ultrasound-guided fine needle aspiration: prevalence of thyroid carcinoma and ultrasound features. Medicine (Baltimore). 2017;96:e8689. https://doi.org/10.1097/MD.0000000000008689.
28. Ljung BM. Thyroid fine-needle aspiration: smears versus liquid-based preparations. Cancer. 2008;114:144–8. https://doi.org/10.1002/cncr.23541.
29. Moon S, Chung HS, Yu JM, Yoo HJ, Park JH, Kim DS, et al. Associations between Hashimoto thyroiditis and clinical outcomes of papillary thyroid cancer: a meta-analysis of observational studies. Endocrinol Metab (Seoul). 2018;33:473–84. https://doi.org/10.3803/EnM.2018.33.4.473.
30. Nagarajan N, Schneider EB, Ali SZ, Zeiger MA, Olson MT. How do liquid-based preparations of thyroid fine-needle aspiration compare with conventional smears? An analysis of 5475 specimens. Thyroid. 2015;25:308–13. https://doi.org/10.1089/thy.2014.0394.
31. Pastorello RG, Destefani C, Pinto PH, Credidio CH, Reis RX, Rodrigues TA, et al. The impact of rapid on-site evaluation on thyroid fine-needle aspiration biopsy: a 2-year cancer center institutional experience. Cancer Cytopathol. 2018;126:846–52. https://doi.org/10.1002/cncy.22051.
32. Pellicer DL, Sadow PM, Stephen A, Faquin WC. Atypical squamous metaplasia in a benign cystic thyroid nodule mimicking high-grade carcinoma. Diagn Cytopathol. 2013;41:706–9. https://doi.org/10.1002/dc.22803.
33. Pusztaszeri MP, Krane JF, Cibas ES, Daniels G, Faquin WC. FNAB of benign thyroid nodules with papillary hyperplasia: a cytological and histological evaluation. Cancer Cytopathol. 2014;122:666–77. https://doi.org/10.1002/cncy.21441.
34. Rammeh S, Romdhane E, Sassi A, Belhajkacem L, Blel A, Ksentini M, et al. Accuracy of fine-needle aspiration cytology of head and neck masses. Diagn Cytopathol. 2018;47:394–9. https://doi.org/10.1002/dc.24120. [Epub ahead of print].
35. Renshaw AA, Gould EW. Characteristics of false-negative thyroid fine-needle aspirates. Acta Cytol. 2018;62:12–8. https://doi.org/10.1159/000481722.
36. Rossi ED, Morassi F, Santeusanio G, Zannoni GF, Fadda G. Thyroid fine needle aspiration cytology processed by ThinPrep: an additional slide decreased the number of inadequate results. Cytopathology. 2010;21:97–102. https://doi.org/10.1111/j.1365-2303.2009.00659.x.
37. Rossi ED, Raffaelli M, Zannoni GF, Pontecorvi A, Mulè A, Callà C, Lombardi CP, et al. Diagnostic efficacy of conventional as compared to liquid-based cytology in thyroid lesions: evaluation of 10,360 fine needle aspiration cytology cases. Acta Cytol. 2009;53:659–66.
38. Rossi ED, Zannoni GF, Moncelsi S, Stigliano E, Santeusanio G, Lombardi CP, et al. Application of liquid-based cytology to fine-needle aspiration biopsies of the thyroid gland. Front Endocrinol (Lausanne). 2012;3:57. https://doi.org/10.3389/fendo.2012.00057.
39. Sahin D, Yilmazbayhan D, Firat P, Hacisalihoglu UP, Kirimlioglu SH, Celenk E, et al. Comparison of conventional cytology and SurePath in split thyroid fine needle aspiration materials. Cytopathology. 2017;28:291–8. https://doi.org/10.1111/cyt.12430.
40. Sharma S, Agarwal S, Jain M, Singh GB, Andley M. Cytomorphological differences between liquid-based cytology and conventional smears in fine-needle aspirates of thyroid lesions. J Cytol. 2018;35:208–11. https://doi.org/10.4103/JOC.JOC_150_17.
41. Tripathy K, Misra A, Ghosh JK. Efficacy of liquid-based cytology versus conventional smears in FNA samples. J Cytol. 2015;32:17–20. https://doi.org/10.4103/0970-9371.155225.