8
Cystic Lesions of the Thyroid

Thyroid cysts are common lesions that most often result from cystic degeneration in an adenomatous nodule. However, any type of thyroid nodule can undergo cystic degeneration, including follicular adenomas, follicular carcinomas, Hurthle cell neoplasms, and papillary thyroid carcinomas (PTCs). In some studies, as many as 15–25% of solitary thyroid nodules and up to 37% of all thyroid nodules are at least partially cystic. Often the cysts evolve secondary to hemorrhagic degeneration within the nodule. In addition to cystic degeneration of follicular-derived lesions, other nonfollicular cysts including thyroglossal duct cysts, branchial cleft-like cysts, and parathyroid cysts can also occur in or near the thyroid gland and are amenable to fine needle aspiration (FNA).

The risk of malignancy in a thyroid cyst is low, occurring in less than 4% of purely cystic nodules, but the risk increases up to 14% for mixed solid and cystic lesions, cysts larger than 3–4 cm, and recurring cysts. By far, the most common type of malignant thyroid cyst is PTC. Because of problems related to specimen adequacy, FNA has a poor track record for diagnosing cystic malignancies in any anatomic site including the thyroid gland. Thus, thyroid cysts are a common cause of false-negative diagnoses. Increasing use of ultrasound guidance to sample solid components within complex cystic lesions may enhance diagnostic yield and reduce false-negative diagnoses.

D.P. Clark and W.C. Faquin, *Thyroid Cytopathology*,
Essentials in Cytopathology 8, DOI 10.1007/978-1-4419-5954-6_8,

General Diagnostic Approach

The predominant component of a cystic lesion is the macrophage that puts the FNA into the cystic arm of the diagnostic algorithm (Figure 8.1). FNA of thyroid cysts typically results in a specimen consisting of these macrophages and little if any associated epithelium to identify the type of cyst. When fewer than six groups of follicular cells, each containing ten cells, are identified amidst the macrophages, the specimen should be placed into the nondiagnostic category. If ultrasound guidance was not utilized for a nondiagnostic cystic lesion, a repeat FNA with ultrasound guidance is often indicated. The majority of thyroid cysts represent cystic degeneration of an adenomatous nodule and should be placed in the benign diagnostic category; however, a small subset are malignant, typically cystic PTCs, and these should be placed in the malignant category. Because of the paucity of follicular epithelium, diagnostic challenges often arise with cystic lesions. Focal features of PTC within the epithelium (e.g., nuclear enlargement, nuclear grooves) may place such cases into the Suspicious for Malignancy or Atypia of Undetermined Significance category. The key to evaluating FNA specimens of thyroid cysts is to obtain an adequate specimen containing follicular epithelium, and then to assess all the components, paying careful attention to the cytologic features of the epithelium to exclude PTC.

Differential diagnosis of thyroid cysts:

Follicular-derived cysts	Nonfollicular cysts
Cystic adenomatous nodule	Thyroglossal duct cysts
Cystic papillary carcinoma	Branchial cleft-like cysts
Cystic follicular neoplasm	Ultimobranchial body cysts
Cystic Hurthle cell neoplasm	Parathyroid cysts

Diagnostic Criteria

General Features

Aspirates of thyroid cysts often contain numerous macrophages but little epithelium. For diagnostic purposes, it is critical to aspirate any solid portion of the nodule, especially to obtain adequate

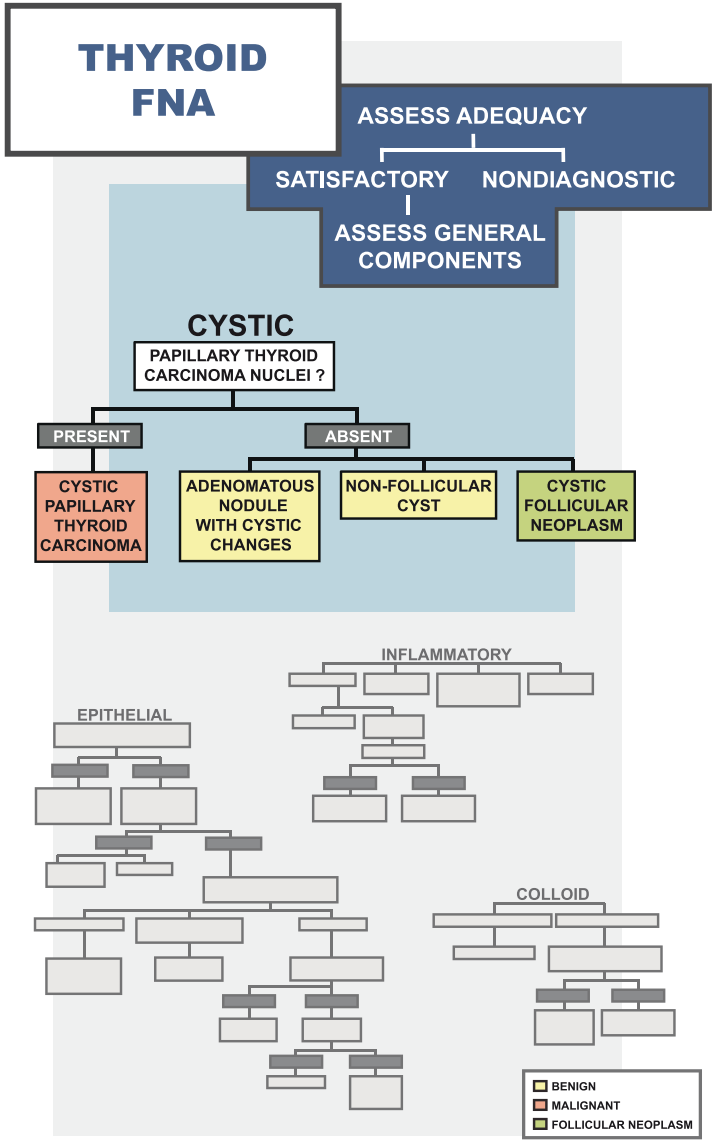

FIGURE 8.1. Algorithmic approach to cystic lesions.

material for cases of cystic follicular neoplasms. Ultrasound-guided FNA is especially useful for obtaining a sample from the solid portion of a thyroid cyst. For most types of cysts, both benign and malignant, the microscopic features of the cyst contents are similar and include a combination of abundant hemosiderin-laden macrophages, foamy histiocytes, blood, proteinaceous debris, watery colloid, and giant cells with foamy cytoplasm (Figure 8.2). Cholesterol crystals may also be present and are best visualized using Diff-Quik stains. The amount of background watery colloid will vary depending upon the nature of the cyst and may be difficult to appreciate. Cystic adenomatous nodules usually have more background watery colloid than cystic neoplasms. The cyst fluid in the aspirate can be clear yellow or bloody; however, the gross color of the fluid is not predictive of whether the cyst is benign or malignant. Adhering to specimen adequacy criteria (>6 groups of follicular epithelium, each containing at least ten cells) will help avoid making a false-negative diagnosis of a cystic PTC.

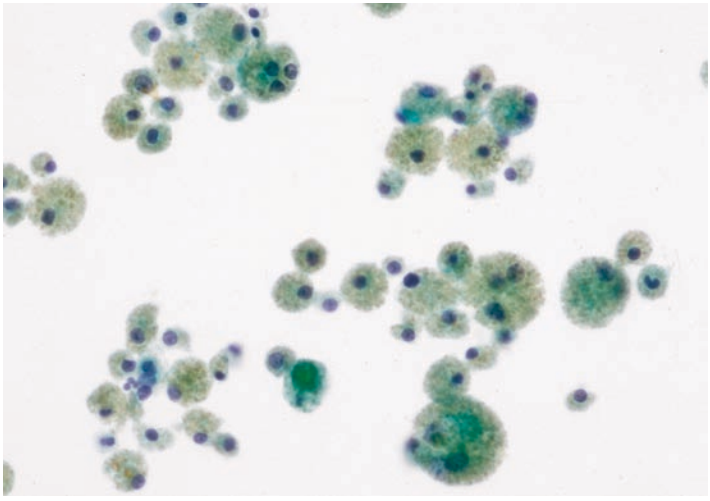

FIGURE 8.2. Cyst contents. Aspiration of thyroid cysts typically yields specimens containing abundant hemosiderin-laden macrophages and debris. When adequate epithelial cells are absent, the specimen is considered nondiagnostic. (ThinPrep, Papanicolaou.)

Nonepithelial components of cyst contents are as follows:

- Hemosiderin-laden macrophages
- Foamy histiocytes
- Blood
- Colloid
- Cholesterol crystals
- Chronic inflammation
- Giant cells with vacuolated cytoplasm

Cystic Degeneration of Follicular Nodules

Aspirates of benign thyroid nodules with cystic degenerative changes are hypocellular and include the usual cyst contents (outlined above) as well as occasional groups of cohesive cyst lining epithelial cells and scattered fragmented macrofollicles in the background (Figure 8.3). The presence of a background watery colloid together with occasional fragmented macrofollicles with

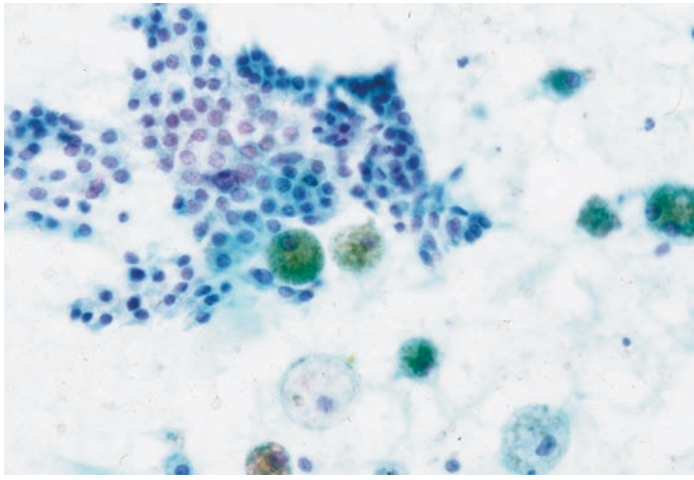

FIGURE 8.3. Benign thyroid cyst. The aspirate consists of fragmented macrofollicles in a background of hemosiderin-laden macrophages and watery colloid. (ThinPrep, Papanicolaou.)

their characteristic honeycomb arrangement of follicular cells is the essential feature favoring a benign thyroid cyst. Some thyroid cysts represent spontaneous hemorrhage into a solid nodule, and FNA will yield only blood unless a solid portion of the nodule is aspirated. Keep in mind that in addition to an adenomatous nodule, follicular or Hurthle cell neoplasms can also exhibit cystic changes, and the diagnostic cytologic features to suggest this would include a predominance of microfollicles or dyscohesive Hurthle cells in a background of cyst contents (see diagnostic approach to follicular and Hurthle cell neoplasms, Chaps. 6 and 7).

Cytologic features of benign thyroid cysts are as follows:

- Hypocellular specimen
- Cyst contents
- Watery colloid
- Fragmented macrofollicles
- Cyst lining cells
- Pertinent negative findings
  - Absence of psammoma bodies
  - Absence of papillary architecture
  - Absence of nuclear pseudoinclusions

In addition, occasional cohesive groups of cyst lining cells are often present in aspirates of cystic adenomatous nodules. These cells have a distinctive cytologic appearance reminiscent of features typically seen in reparative cells. Benign cyst lining cells form small two-dimensional groups with distinct cell borders and windows between cells, and they exhibit a streaming appearance (Figure 8.4). The cells show a cytomorphologic spectrum from elongate spindled cells with eosinophilic cytoplasm to polygonal cells with moderate amounts of dense granular eosinophilic cytoplasm (Figures 8.4 and 8.5). The nuclei of cyst lining cells can be mildly enlarged with nuclear grooves, but nuclear pseudoinclusions, psammoma bodies, and papillary arrangements are absent (Figure 8.6). Cases with only mild nuclear enlargement and rare nuclear grooves should be placed in the benign category; however, the presence of nuclear pseudoinclusions or other overt features of PTC should prompt a diagnostic category of Atypia of Undetermined Significance, Suspicious for Malignancy, or Malignant, depending on the extent of PTC features.

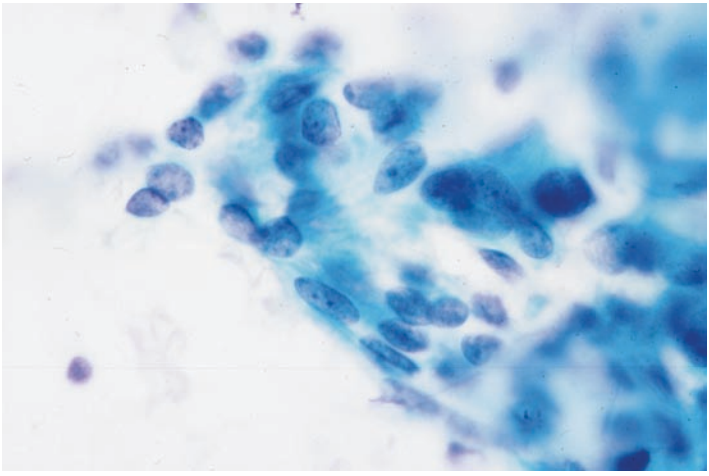

FIGURE 8.4. Benign thyroid cyst lining cells. The cells form cohesive two-dimensional groups with distinct cell borders and a "streaming" appearance reminiscent of reparative cells. (Smear, Papanicolaou.)

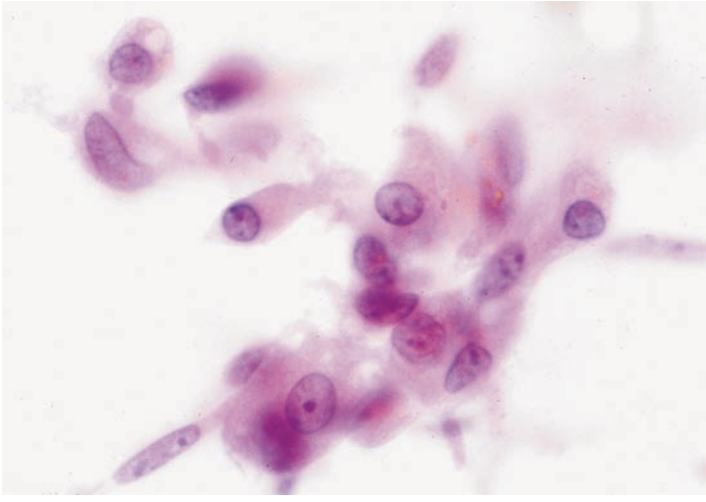

FIGURE 8.5. Benign thyroid cyst lining cells. The cells can often have a spindled appearance. (Smear, modified H&E.)

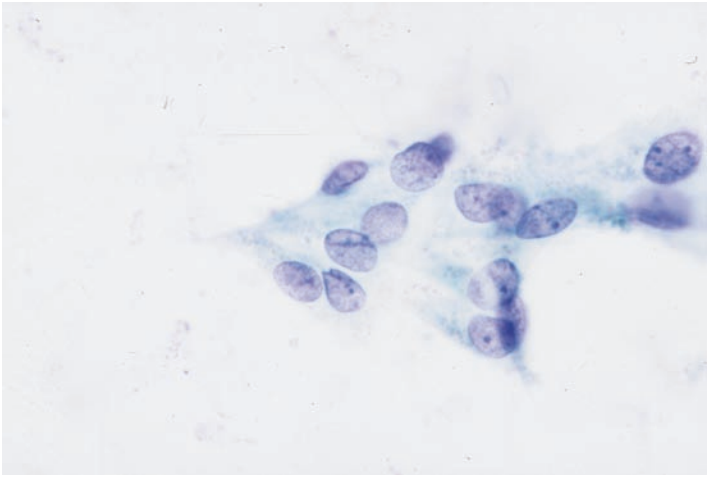

FIGURE 8.6. Benign thyroid cyst lining cells. The nuclei of cyst lining cells can sometimes be enlarged with nuclear grooves and pale chromatin, raising the possibility of papillary thyroid carcinoma (PTC). (Smear, Papanicolaou.)

Cytologic features of benign cyst lining cells are as follows:

- Spindled cells and polygonal cells with "reparative" appearance
- Small flat cohesive groups
- Distinct cell borders
- Windows between cells
- Occasional nuclear grooves

Cystic Papillary Thyroid Carcinoma

Up to 50% of PTCs are at least partially cystic, and approximately 10% of PTCs are predominantly cystic. Aspirates of cystic PTCs are hypocellular with the usual cyst contents of hemosiderin-laden macrophages, blood, debris, chronic inflammation, and cholesterol crystals. In addition, large epithelioid giant cells with dense cytoplasm and many nuclei, as well as rare psammoma bodies,

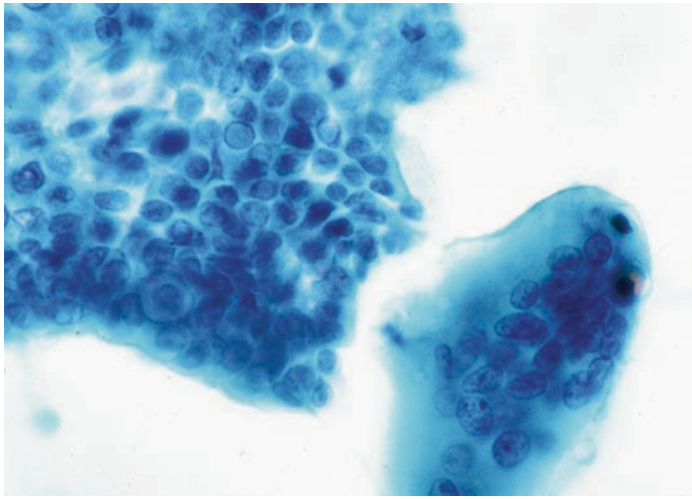

FIGURE 8.7. Cystic papillary thyroid carcinoma. Despite the hypocellularity, rare epithelial groups are identified with diagnostic nuclear features of PTC. A multinucleated giant cell is also present. (Smear, Papanicolaou.)

can sometimes be seen (Figure 8.7). The presence of either of these latter two nonepithelial features should raise suspicion of a cystic PTC.

The difficulty with FNA of cystic PTCs is that the diagnostic epithelial cells are sparse (Figure 8.8). To make a "suspicious" or definite diagnosis of PTC by FNA, epithelial cells must be identified that exhibit the classic nuclear and architectural features of PTC. These features include monolayered or papillary groups of cells with pale chromatin, dense squamoid cytoplasm, enlarged oval nuclei with nuclear grooves, and nuclear pseudoinclusions. Often, an aspirate of a cystic PTC does not contain sufficient cytologic features for a definitive diagnosis, and the FNA should be called suspicious for malignancy.

Cytologic features of cystic papillary carcinoma are as follows:

- Cyst contents
- Rare large epithelioid giant cells with dense cytoplasm

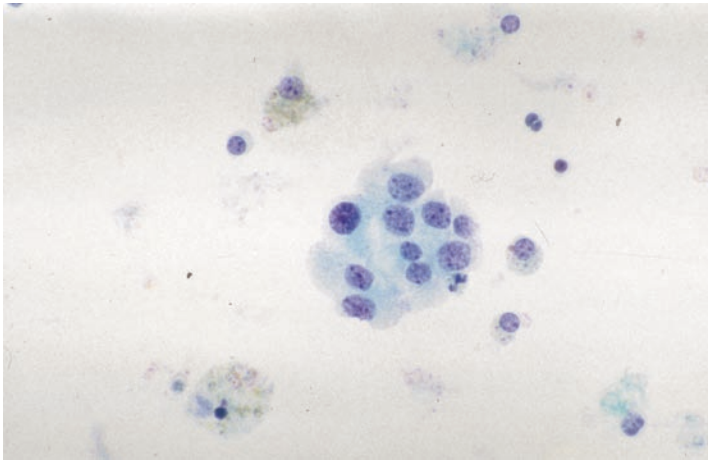

FIGURE 8.8. Cystic papillary thyroid carcinoma. This aspirate consisted primarily of macrophages and did not contain sufficient epithelial groups to make a definitive diagnosis of PTC. (Smear, Papanicolaou.)

- Rare psammoma bodies
- Rare epithelial cells with nuclear and architectural features of papillary carcinoma:
  - Monolayered or papillary groups
    (a) Pale chromatin
    (b) Nuclear grooves
    (c) Nuclear pseudoinclusions
    (d) Squamoid cytoplasm

Thyroglossal Duct Cysts

Thyroglossal duct cysts occur from embryologic remnants of the thyroglossal duct, a midline structure associated with the hyoid bone. Although more common in childhood, they can also occur in adults. The fluid often has a mucinous appearance, but it can also be proteinaceous. In contrast to thyroid cysts, however, the fluid seldom has hemorrhagic features and colloid is absent. Aspirates of thyroglossal duct cysts can have a predominance of macrophages and background debris, but they are often more cellular than cystic follicular nodules of the thyroid. The epithelial component of

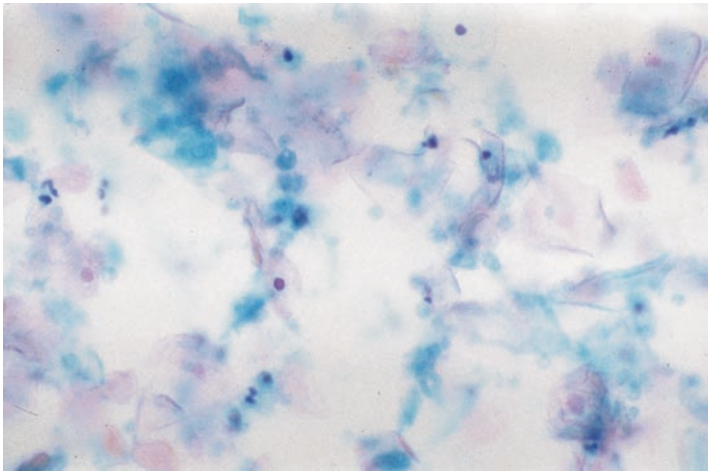

FIGURE 8.9. Thyroglossal duct cyst. The aspirate is characterized by cytologically bland squamous cells and anucleate squames in a background of debris. Nuclear hyperchromasia and atypia are absent. (Smear, Papanicolaou.)

the aspirate can include any combination of several cell types including squamous cells, glandular cells, and ciliated respiratory-type cells (Figure 8.9). The epithelial cells are cytologically bland with mild reactive-type atypia.

Cytologic features of thyroglossal duct cysts are as follows:

- Mucinous or "dirty" proteinaceous fluid
- Seldom hemorrhagic
- Absent colloid
- Abundant macrophages
- Squamous cells, glandular cells, and ciliated respiratory-type cells
- Cholesterol crystals

Branchial Cleft Cysts and Ultimobranchial Body Cysts

Branchial cleft-like cysts (lymphoepithelial cysts) and ultimobranchial body cysts (cystic solid cell nests) are rare in the thyroid gland, and when they do occur it is often in association with Hashimoto thyroiditis. Aspirates of branchial cleft cysts of the neck and

branchial cleft-like cysts of the thyroid are similar and contain turbid proteinaceous fluid and degenerate squamous cells, as well as glandular cells that may be mucin containing or ciliated. Variable amounts of background lymphocytes can be seen, but colloid and follicular cells are absent. Without clinical information, it may be impossible to distinguish a branchial cleft cyst from a thyroglossal duct cyst on the basis of cytologic features alone. An abundance of background lymphocytes and germinal center fragments favors a branchial cleft cyst, but lymphocytes are not always present.

Cytologic features of branchial cleft-like cysts are as follows:

- Turbid proteinaceous fluid
- Squamous cells, mucinous cells, ciliated cells
- Variable background lymphocytes
- Absent colloid and follicular cells

Even more rare is the ultimobranchial body cyst, which can be cytologically indistinguishable from cystic PTC. Aspirates are hypocellular and contain occasional cohesive clusters of oval to elongate cells with enlarged pale, grooved nuclei (Figure 8.10).

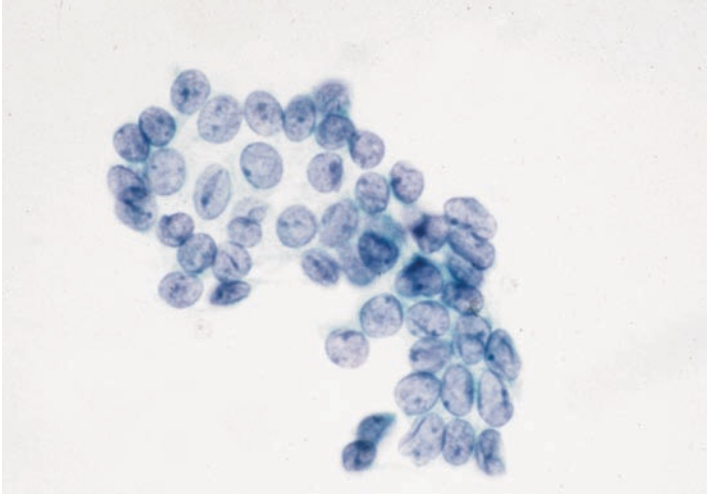

FIGURE 8.10. Ultimobranchial body cyst. The nuclei of cells from this rare thyroid cyst have pale chromatin and nuclear grooves, similar to those of PTC. (ThinPrep, Papanicolaou.)

Psammoma bodies, nuclear pseudoinclusions, and papillary architecture are absent. In contrast to PTC, aspirated cells from ultimobranchial body cysts are thyroglobulin negative and are positive for carcinoembryonic antigen (CEA).

Parathyroid Cysts

Parathyroid cysts that can be either nonfunctioning or, less commonly, functioning, are occasionally mistaken for thyroid nodules and aspirated. The fluid obtained from a parathyroid cyst has a characteristic thin, clear, colorless appearance resembling water, reflecting the absence of cells, blood, colloid, and debris. Rarely, parathyroid adenomas can be cystic and contain yellow-brown fluid with occasional groups of parathyroid cells in microfollicles, crowded clusters, or papillary arrangements suggesting a thyroid neoplasm (Figure 8.11). When a parathyroid cyst is suspected based on the gross appearance of the aspirated water clear fluid, an assay for parathormone will confirm the diagnosis.

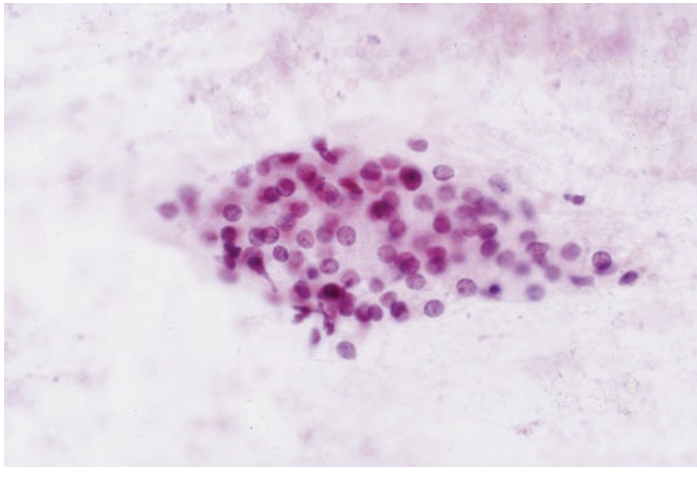

FIGURE 8.11. Cystic parathyroid adenoma. This hypocellular specimen contained clear fluid and rare cohesive clusters of cells resembling follicular cells. (Smear, Papanicolaou.)

Cytologic features of parathyroid cysts are as follows:

- Thin "water clear" fluid
- Acellular
- Absence of debris, histiocytes, colloid, blood

Differential Diagnosis and Pitfalls

As alluded to earlier, two of the greatest difficulties with aspirates of thyroid cysts are (1) obtaining a satisfactory sample and (2) avoiding a false-negative diagnosis of a cystic PTC. Cytologic features favoring a benign thyroid cyst include abundant background watery colloid and fragmented macrofollicles. In contrast, the presence of even one psammoma body, large multinucleated giant cells with squamoid cytoplasm, or epithelial cells with nuclear grooves and intranuclear pseudoinclusions, or a papillary architecture should be a warning that the aspirate may represent a cystic PTC.

When present in an aspirate, cyst lining cells are recognized as benign by their resemblance to reparative cells; however, in some cases, the nuclear features of benign cyst lining cells include enlarged pale nuclei, nuclear grooves, and squamoid cytoplasm, raising the possibility of PTC. When other features of PTC are absent and the background contains colloid and fragmented macrofollicles, the cyst lining cells can be diagnosed as benign; however, depending upon the microscopic components present, some cases may be impossible to exclude a cystic PTC and a diagnosis of Atypia of Undetermined Significance or Suspicious for PTC is made.

Thyroglossal duct cysts and branchial cleft-like cysts have overlapping cytologic features and are usually easily distinguished from follicular-derived thyroid cysts by the presence of squamous and ciliated epithelial cells. The problem that occasionally arises in evaluating these aspirates is that the squamous cells with reactive atypia (Figure 8.12) can mimic a metastatic squamous cell carcinoma, especially because some head and neck squamous cell carcinomas can be quite well differentiated. Although the finding of atypical squamous cells in a cyst of an older adult

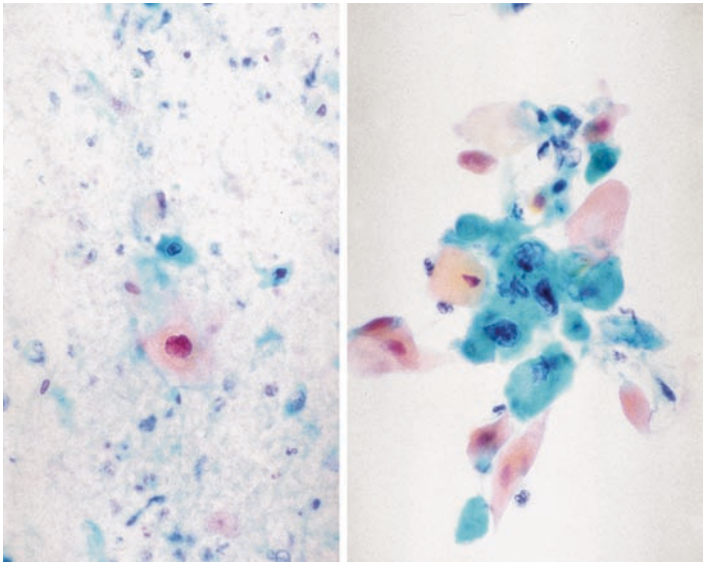

FIGURE 8.12. Some branchial cleft cysts (*left*) can have rare atypical squamous cells, but marked nuclear atypia such as in this cystic squamous cell carcinoma (*right*) should not be present. (Smear, Papanicolaou.)

patient warrants careful clinical follow-up, the key to excluding a squamous cell carcinoma is the absence of diagnostic malignant features. Even in well-differentiated squamous cell carcinomas, rare cells will show an increased N/C ratio with hyperchromatic irregular nuclei.

Ancillary Techniques

Immunocytochemical studies can be used to aid in the diagnosis of certain thyroid cysts, but, in general, ancillary techniques are not helpful. Two instances in which special studies can be applied are (1) parathyroid cysts to verify the presence of parathormone in the cyst fluid and (2) aspirates of ultimobranchial body cysts, which can be distinguished from PTC and benign thyroid cysts by their negative reactivity for thyroglobulin and positive reactivity for CEA.

Clinical Management and Prognosis

Benign thyroid cysts may disappear subsequent to FNA; however, approximately 50% of these cysts will reaccumulate fluid. Clinical options for these patients include repetitive aspiration, use of sclerotherapy, and surgery. Because the risk of malignancy is increased for patients with large cysts (greater than 4 cm), cysts with a residual solid component, and cysts that recur more than once, surgical intervention is more strongly considered in these instances. Because thyroid cysts are a well-known cause of false-negative diagnoses, careful clinical follow-up should be given.

Suggested Reading

Castro-Gomez L, Cordova-Ramirez S, Duarte-Torres R, de Ruiz PA, Hurtado-Lopez LM. Cytologic criteria of cystic papillary carcinoma of the thyroid. Acta Cytol 2003;47:590–594.

De los Santos ET, Keyhani-Rofagha S, Cunningham JJ, Mazzaferri EL. Cystic thyroid nodules: the dilemma of malignant lesions. Arch Intern Med 1990;150:1422–1427.

Meko JB, Norton JA. Large cystic/solid thyroid nodules: a potential false-negative fine needle aspiration. Surgery (St. Louis) 1995;118: 996–1003.