Chapter 3
Thyroid

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Introduction

Fine needle aspiration (FNA) is the procedure of choice for the evaluation of thyroid nodules. More recently, the implementation of ultrasonographic-guided FNAs of the thyroid has increased the overall diagnostic yield and accuracy of the procedure [1–4]. However, despite the improvement in diagnostic yield, a significant subset of thyroid FNAs continues to be inadequate for interpretation, and this leads to some uncertainty in the follow-up management for such patients.

The diagnostic yield for thyroid FNA may be affected by several factors such as the nature of the lesion (e.g., size, cystic vs. solid), needle size, skill and level of experience of the operator, as well as the level of experience of the cytopathologist [1]. Many of these factors fluctuate between different institutions; hence one would expect significant variation in FNA adequacy rates. The presence or absence of rapid on-site evaluation (ROSE) by a cytopathologist or a cytotechnologist to assess for specimen adequacy during the FNA procedure is a potential factor, which can greatly affect the yield and can be standardized between institutions. Numerous studies have been published regarding the influence of ROSE on thyroid FNA specimen adequacy, with most of the studies acknowledging that FNA is more likely to be adequate for interpretation with ROSE [2, 5, 6]. More so, ROSE has been shown to decrease the number of needle passes, increase diagnostic accuracy, and reduce the risk for a repeat procedure [7, 8]. Immediate evaluation of the material also allows the opportunity to obtain additional material for cell blocks and/or ancillary

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studies [9]. This is especially important in suspected cases of medullary thyroid carcinoma, which require immunostaining for calcitonin, and in suspected cases of lymphoma, which require additional material for flow cytometry.

Specimen Adequacy Assessment

Recommendations for optimal specimen preparation include the use of air-dried and alcohol-fixed slides, prepared for Romanowsky and Papanicolaou staining, respectively, with supplemental combinations of liquid-based or cytospin preparations, cell blocks, and RPMI for flow cytometric evaluation where appropriate and possibly sterile material for microbiology. For cyst-fluid-only specimens, only one or two smears are recommended with the remainder being processed as either cytospin or liquid-based preparations.

Examination usually starts with the review of the slides under scanning magnification. This quickly gives significant information as most benign follicular nodules are sparsely cellular, consisting predominantly of colloid. Colloid can be thin and watery, thick and opaque with sharp outlines, or extremely thick and sticky. Smears that have a high ratio of colloid to follicular cells generally indicate a benign thyroid nodule [10]. Some features are generally nonspecific. For instance, macrophages can be seen in cyst contents, benign hyperplastic nodule with cystic degeneration, as well as cystic papillary thyroid carcinoma. In a similar fashion, multinucleated giant cells can be seen in granulomatous diseases, benign hyperplastic nodule with cystic degeneration, papillary carcinoma, and anaplastic carcinoma.

A thyroid FNA specimen is deemed to be satisfactory for evaluation if it has at least six groups of benign, well-visualized follicular cells, with each group consisting at least 10 follicular cells [11, 12]. Tissue fragments with multiple follicles can be split up and counted as separate and distinct groups [13]. Exceptions to this adequacy requirement include: abundance of colloid even in the absence of six follicular groups, abundance of lymphocytes necessitating the diagnosis of lymphocytic thyroiditis, and presence of atypia [14].

Cystic Lesions of the Thyroid

Diagnostic Consideration

Thyroid FNA specimens with abundant histiocytes having few to no follicular cells are interpreted as “fluid cyst only,” under the category of “nondiagnostic” [15, 16] (Fig. 3.1). Numerous macrophages can be seen in a variety of hyperplastic and neoplastic benign and malignant thyroid nodules undergoing cystic degeneration.

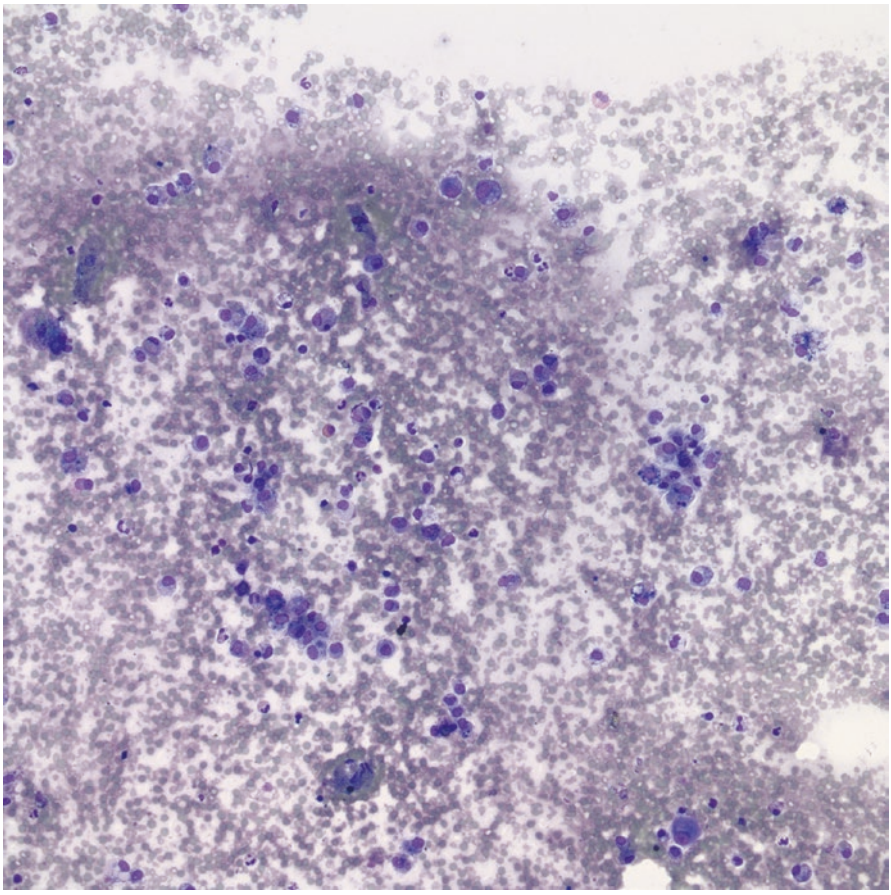

Fig. 3.1 Fluid cyst only. Abundant macrophages and no follicular cells (Diff-Quik stain, ×200)

Benign cysts arising from nodular goiters collapse after drainage. A small number may reaccumulate or bleed immediately following an FNA, necessitating reaspiration. Recurrence with hemorrhagic or chocolate-colored contents is a warning for the possibility of malignancy [17].

Cystic Degeneration in a Hyperplastic Nodule

Cytomorphologic Features

- Low cellularity.
- Abundant macrophages.
- Reactive follicular cell changes.

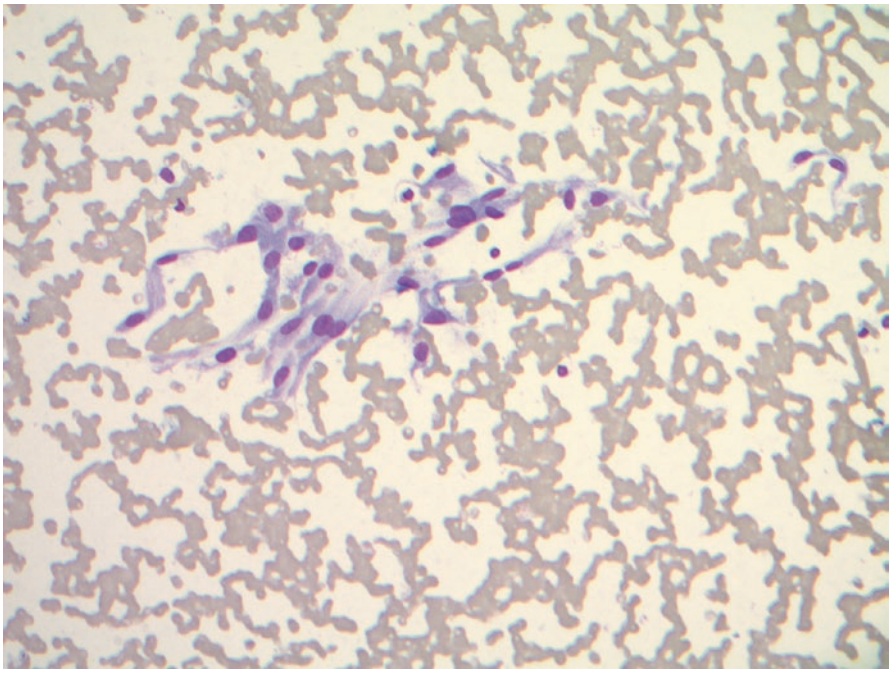

Fig. 3.2 Cystic degeneration in a hyperplastic nodule. Cyst lining cells with pulled-out appearance that mimics reparative epithelium (Diff-Quik stain, ×200)

Tips and Pitfalls

- Cyst lining cells typically show reactive changes. They have a pulled-out appearance that mimics reparative epithelium (Fig. 3.2).
- Cases may be diagnosed as FLUS/AUS because of the reparative changes.
- Dystrophic calcifications can mimic psammoma bodies.

Cystic Papillary Carcinoma

Cytomorphologic Features

- Tumor can be partially or totally cystic, unilocular or multilocular, or thin or thick walled and may contain residual tumor in the wall [18].
- Tissue fragments exhibit scalloped borders, and they are arranged in a cartwheel pattern with nuclei at the outside perimeter [17] (Fig. 3.3).

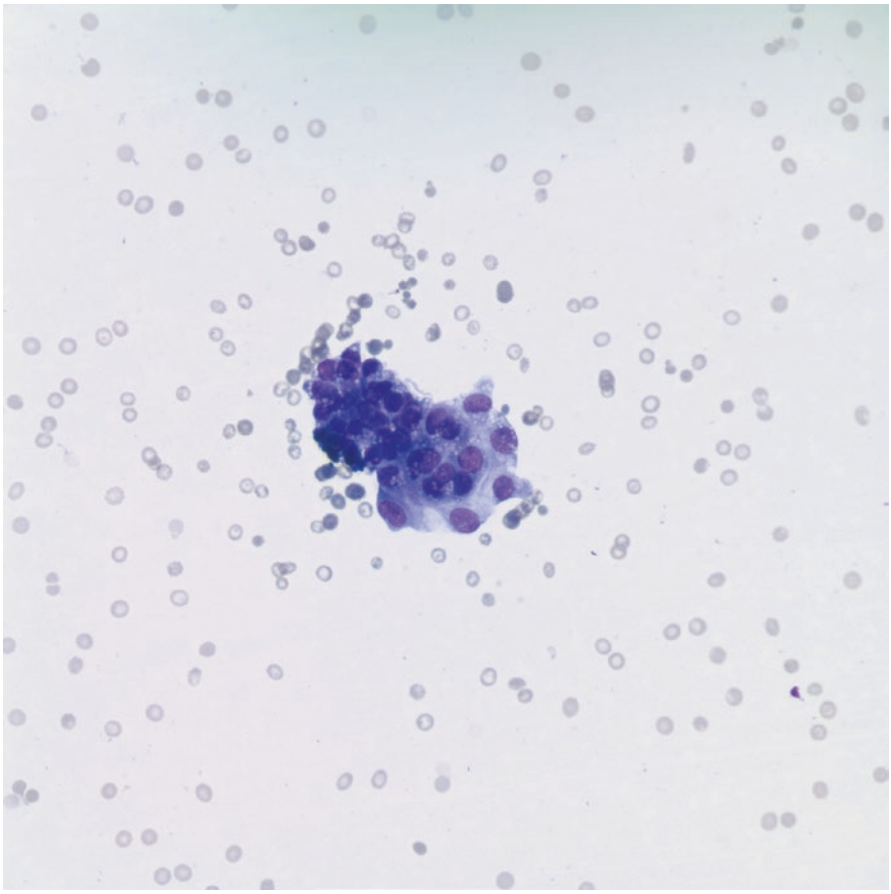

Fig. 3.3 Cystic papillary carcinoma. Tissue fragment showing scalloped borders with nuclei at the outside perimeter. Cytoplasm is vacuolated (Diff-Quik stain, ×400)

- Cytologic features commonly seen include three-dimensional fragments, anisonucleosis, nuclear crowding, nuclear enlargement, intranuclear inclusions, and cytoplasmic vacuoles [19, 20] (Fig. 3.4).

Tips and Pitfalls

- Fine, powdery chromatin of PTC may not be present because the chromatin tends to stain intensely due to degeneration.
- The combination of macrophages, hemosiderin, and cellular debris in the background may obscure distinction from cystic goiter.

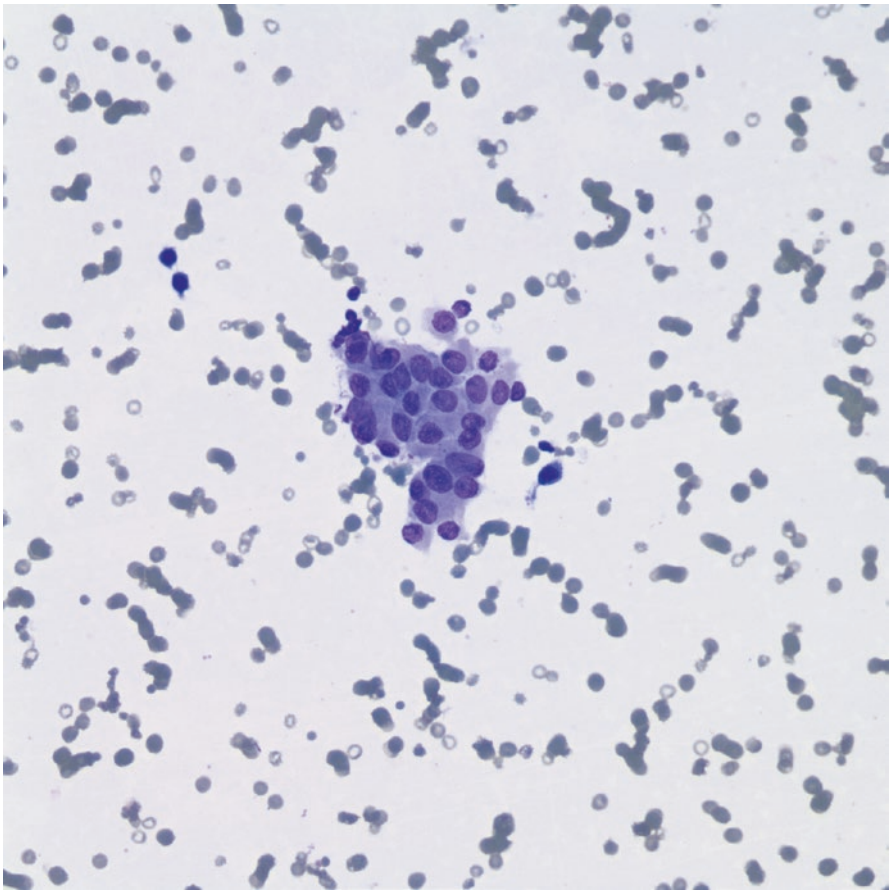

Fig. 3.4 Cystic papillary carcinoma. Cells show some of the nuclear features of papillary thyroid carcinoma, such as nuclear enlargement, nuclear elongation, and nuclear grooves (Diff-Quik stain, ×400)

- Atypical histiocytoid cells of cystic PTC may be difficult to distinguish from clusters of histiocytes with foamy cytoplasm and enlarged nuclei that are seen in cystic degeneration in goiters [21].

Lymphoepithelial Cysts

- Lymphoepithelial cysts in the thyroid bear close resemblance to their counterparts in the salivary gland.
- The cysts are lined predominantly by squamous epithelium and focally by columnar epithelium.
- The epithelium is bordered by a fibrous capsule and surrounded by lymphoid tissue, often with follicles and germinal centers [22].

Lymphocytes-Rich Lesions of the Thyroid

Diagnostic Consideration

Thyroid glands with Hashimoto thyroiditis usually show diffuse enlargement and the gland feels firm and rubbery. FNA is performed only if there is a suspicious nodule that raises the possibility of a coexisting malignancy.

Primary lymphoid neoplasms of the thyroid are uncommon. They are basically of two types: diffuse large B-cell lymphoma (DLBCL) and extranodal marginal zone B-cell lymphoma (ENMZBL) also referred to as MALT lymphomas. MALT lymphomas are low grade and often arise in a background of Hashimoto's thyroiditis.

Hashimoto Thyroiditis

Cytomorphologic Features

- Very cellular, with numerous lymphoid cells.
- The most characteristic feature is the presence of intense infiltration of the gland by polymorphous population of lymphocytes and plasma cells (Figs. 3.5 and 3.6).
- There may be occasional clusters of Hürthle cells.
- Normal follicular cells are infrequent or absent altogether.

Tips and Pitfalls

- The proportion of Hürthle cells varies widely from case to case. When it is present in abundance, the cells may proliferate to form nonneoplastic Hürthle cell nodules, with little to no lymphoid infiltrate, thereby making it difficult to distinguish from Hürthle cell neoplasm on cytologic preparations. The cells of Hürthle cell neoplasm, however, usually have more prominent nucleoli and they usually do not have a prominent lymphoid infiltrate [10].
- In florid Hashimoto thyroiditis with atrophy of the follicular cells, lymphocytes predominate, often forming follicles and germinal centers and may be difficult to distinguish from intrathyroidal lymph node sampling. Often this can also lead to a misdiagnosis of malignant lymphoma [23]. When in doubt, additional material should be collected at the time of ROSE for ancillary studies like flow cytometry.
- Occasionally, multinucleated giant cells are seen and this may lead to confusion with subacute thyroiditis.
- Syncytial tissue fragments of follicular epithelium with papillary-like architecture can often be seen in Hashimoto thyroiditis and can lead to a misdiagnosis of papillary carcinoma especially when the Hürthle cells display reactive nuclear changes like chromatin clearing, nuclear enlargement, and occasional grooves [18].

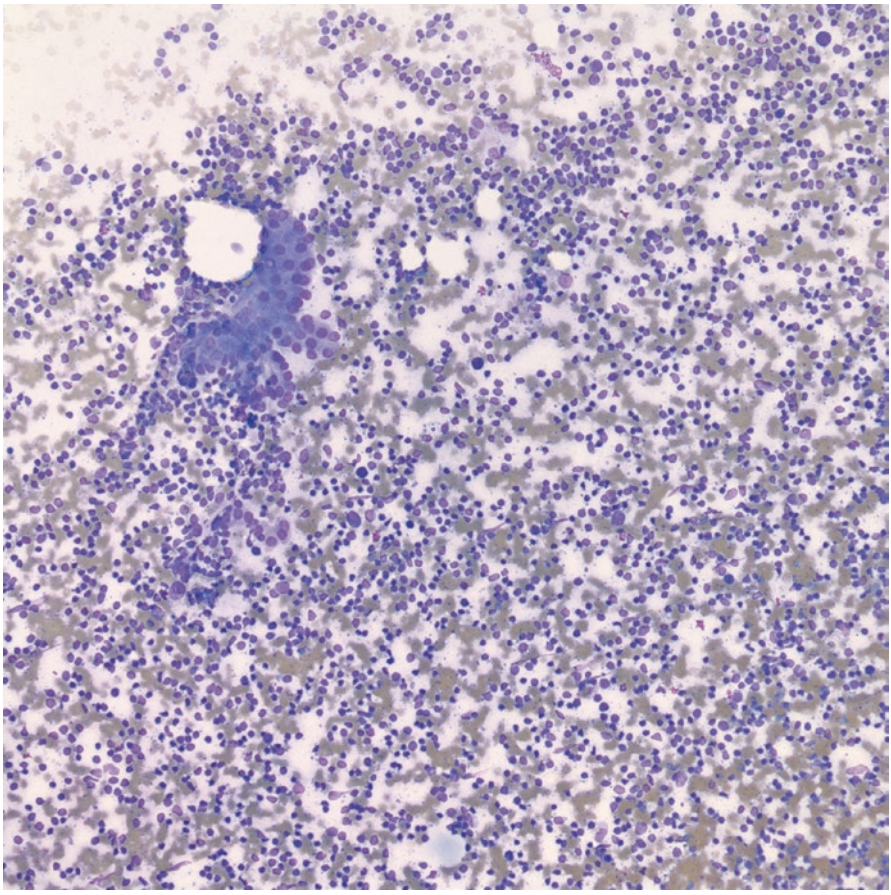

Fig. 3.5 Hashimoto thyroiditis. Polymorphous population of lymphocytes and cluster of Hurthle cells (Diff-Quik stain, ×200)

Lymphoid Neoplasms of the Thyroid

Cytomorphologic Features

Diffuse Large B-Cell Lymphoma

- Variable cellularity, usually very cellular.
- Dense and monomorphous population of poorly differentiated lymphoid cells, which are usually larger than the normal lymphocytes (Fig. 3.7).
- Cells are large, with high nuclear/cytoplasmic (N:C) ratio and finely granular chromatin.
- Nucleoli may be small or large.
- Mitotic activity is frequent and Karyorrhexis is a common feature.
- Cytomorphologic features of Hashimoto thyroiditis may be present on the smear.

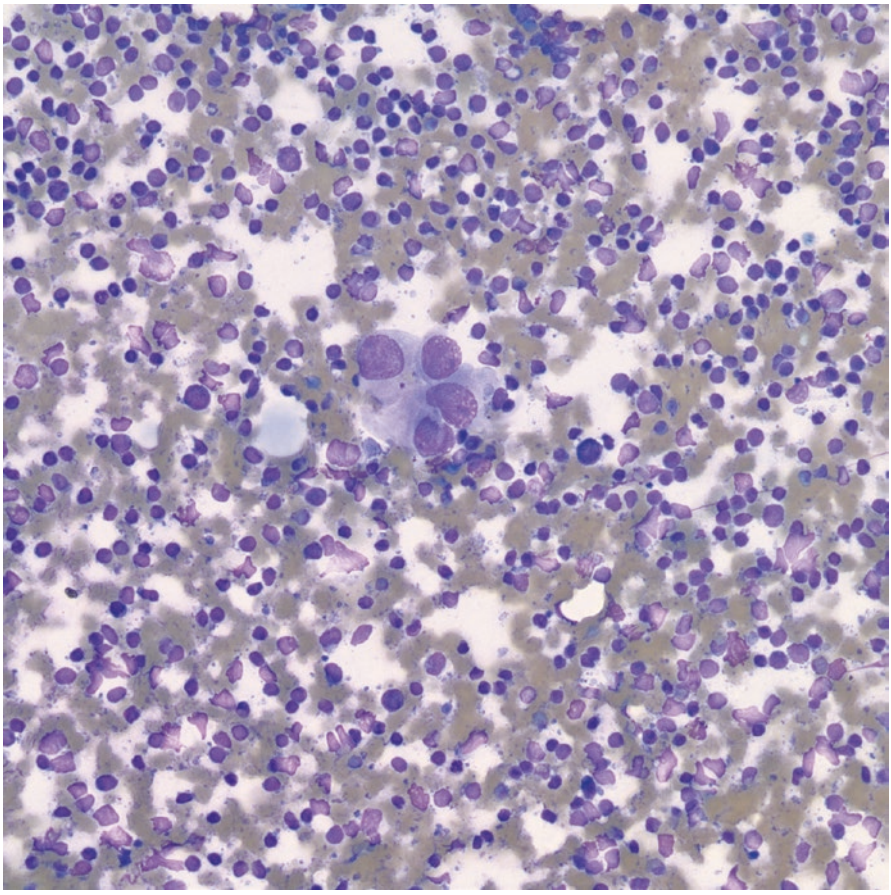

Fig. 3.6 Hashimoto thyroiditis. Polymorphous population of lymphocytes and rare Hurthle cells (Diff-Quik stain, ×400)

MALT Lymphoma

- Polymorphous population of lymphocytes and plasma cells (Fig. 3.8).

Tips and Pitfalls

- DLBCL cells are often seen in large aggregates and this may lead to misdiagnosis as an epithelial neoplasm, most notably anaplastic carcinoma and metastatic carcinoma.
- MALT lymphoma can be very difficult to differentiate from the florid lymphoid phase of Hashimoto thyroiditis because of the heterogeneous population of lymphocytes and both entities may coexist [23].
- Additional material should be obtained at the time of ROSE for immunohistochemical stains.
- Flow cytometry is an important ancillary study and additional material should be obtained at the time of ROSE in RPMI solution for flow cytometry.

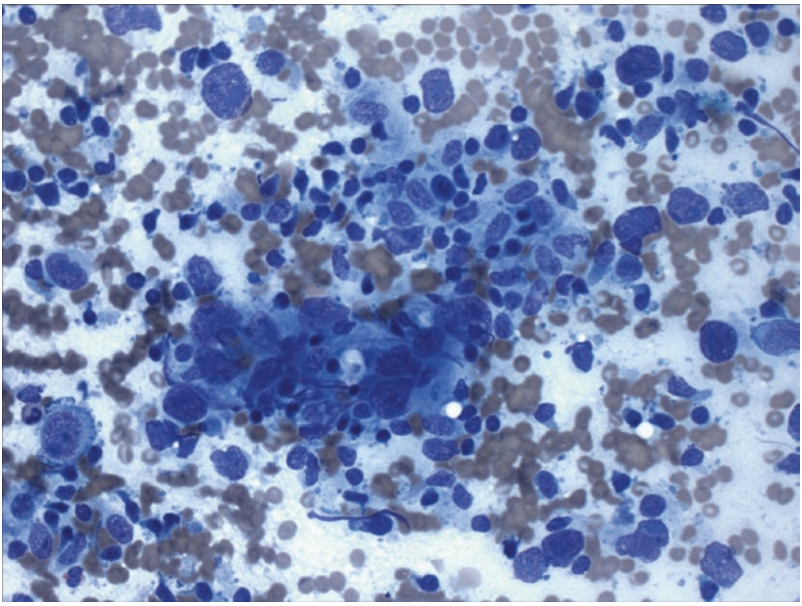

Fig. 3.7 Diffuse large B-cell lymphoma. Poorly differentiated, large lymphoid cells with high N:C ratio (Diff-Quik stain, ×400)

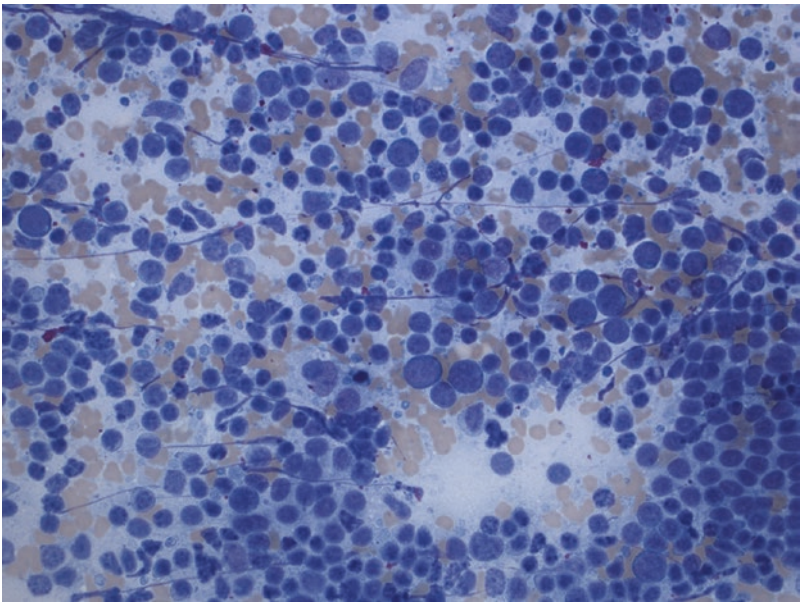

Fig. 3.8 MALT lymphoma. Polymorphous population of lymphocytes and plasma cells (Diff-Quik stain, ×400)

Papillary Thyroid Carcinoma

Diagnostic Consideration

Papillary thyroid carcinoma (PTC) is defined based on nuclear features. The classic PTC has true papillary architecture, but there are a large number of PTC variants with some having virtually no papillary architecture. It is important to be aware of these variants so that they are not confused with other neoplasms. Some of the variants have a tendency toward more aggressive clinical behavior than the classic PTC; hence it is important to be able to recognize them as such.

Cytomorphologic Features

- Smears may show papillary structures, sheets, loosely cohesive groups, or syncytial fragments (Fig. 3.9).
- Cellularity is variable. A large majority of cases is overwhelmingly cellular, whereas cellularity may be scant in tumors with desmoplastic reaction, or those with cystic change.

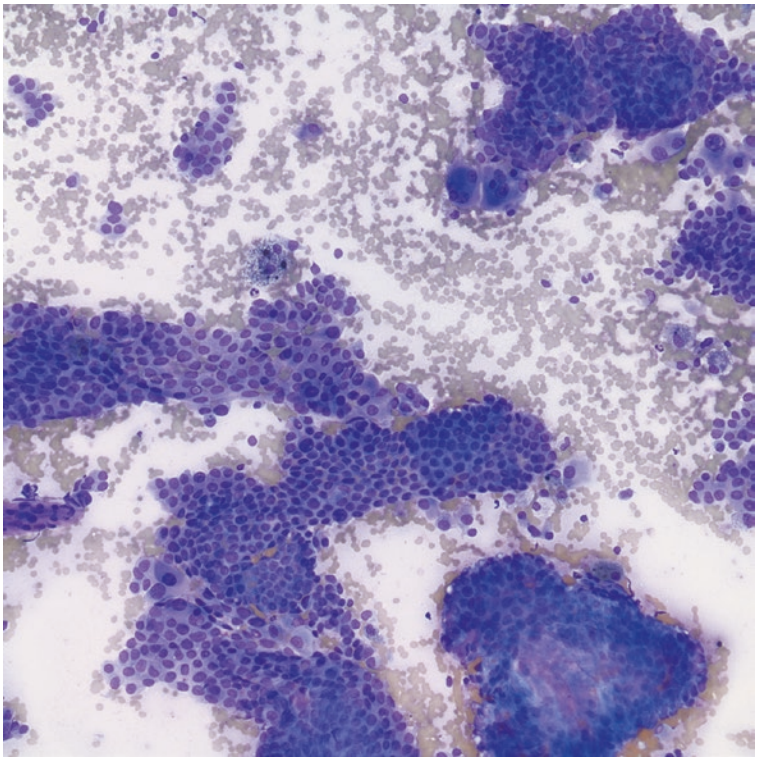

Fig. 3.9 Papillary thyroid carcinoma. Tumor arranged as papillary fragments and syncytial groups (Diff-Quik stain, ×200)

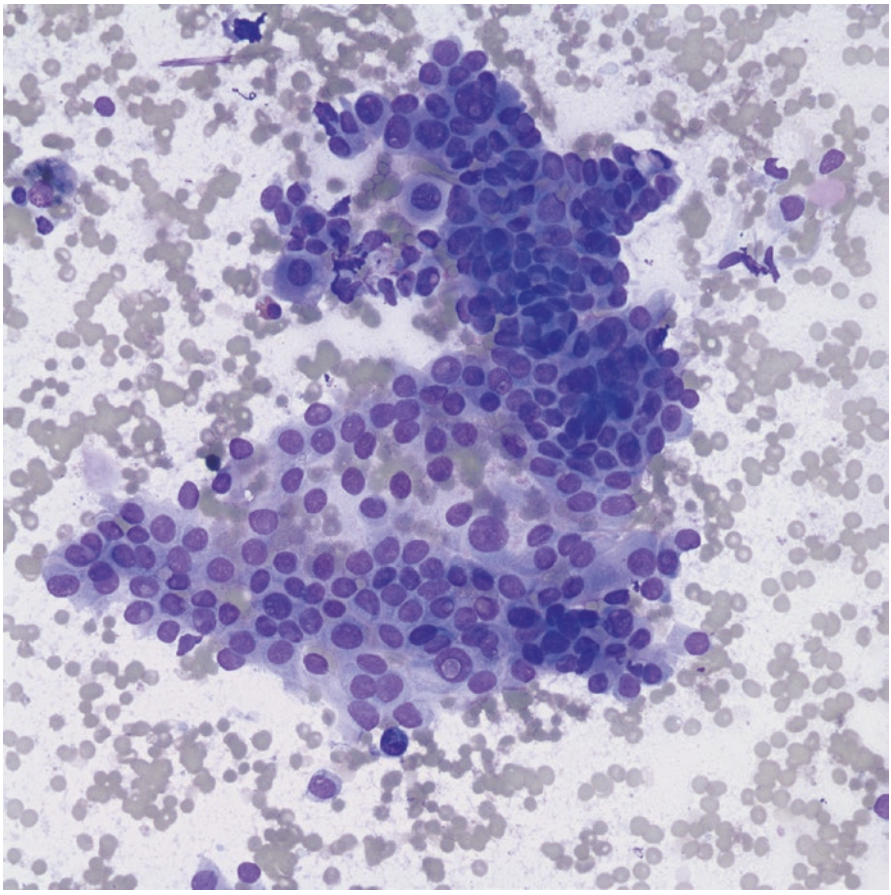

Fig. 3.10 Papillary thyroid carcinoma. Hallmark cytologic features such as nuclear enlargement, nuclear elongation, nuclear grooves, and intranuclear cytoplasmic inclusions (Diff-Quik stain, ×400)

- Nuclear crowding/overlapping.
- The hallmark feature of PTC is the presence of nuclear features such as nuclear enlargement, membrane irregularity, nuclear grooves, nuclear elongation, powdery chromatin, pseudoinclusions, and nucleoli (which may be small or large and may be single or multiple) (Fig. 3.10).
- Cytoplasm is variable – from scant in conventional PTC to abundant, squamoid, vacuolated, or Hürthle-like in other cytomorphologic variants.
- Concentric laminated calcifications also known as psammoma bodies.
- Multinucleated foreign body-type giant cells almost always present with variable number and size of nuclei.

Tips and Pitfalls

- Psammoma bodies must be distinguished from nonspecific, dystrophic calcifications, which are not laminated.
- The presence of conventional PTC nuclear features helps to distinguish oncocytic variant of PTC from Hürthle cell neoplasm. However, the presence of pale chromatin and nuclear grooves is well recognized in Hürthle cells in the absence of PTC [24].
- Tall cell variant of PTC is characterized by neoplastic cells whose height is at least twice their width and the tall cells must comprise at least 30% of the tumor cell population. The tall cells are not as prominent in cytologic preparations as they are on histology. They are frequently seen as large polygonal cells with abundant granular eosinophilic cytoplasm, thereby resembling Hürthle cells [25, 26] (Fig. 3.11).

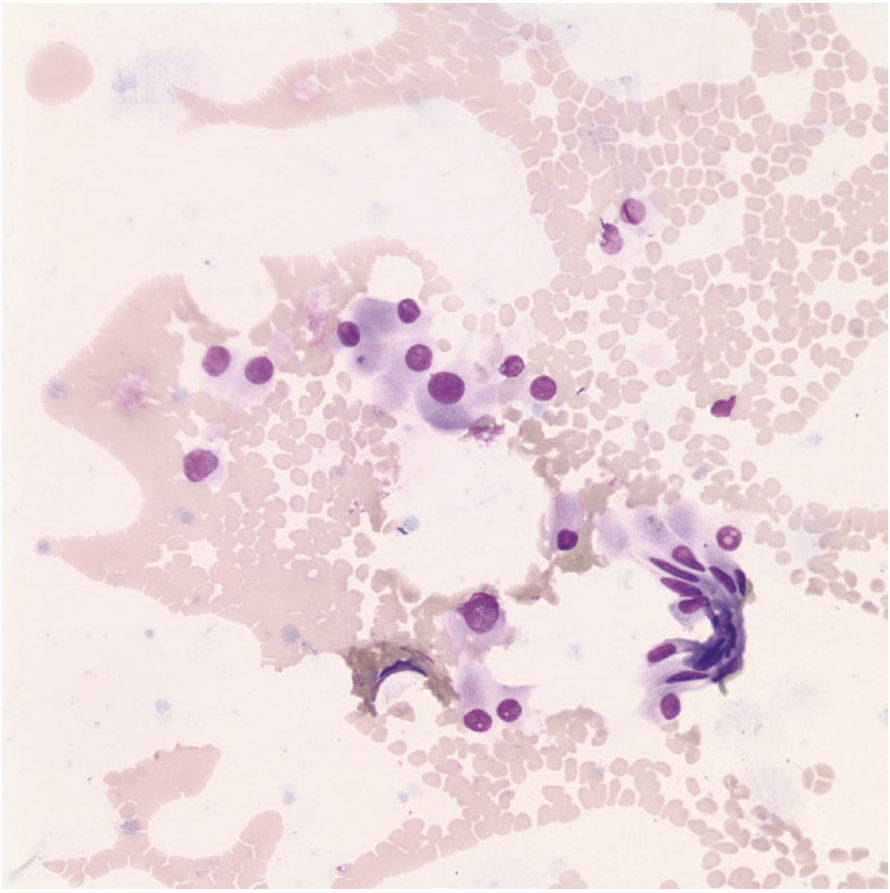

Fig. 3.11 Tall cell variant of papillary thyroid carcinoma. Neoplastic cells whose height is at least twice their width (Diff-Quik stain, ×400)

- The neoplastic cells in columnar variant of PTC are pseudostratified and columnar, but the nuclei do not necessarily demonstrate the typical nuclear features of PTC, and hence the tumor may be confused with metastatic adenocarcinoma to the thyroid.
- Although not entirely specific for the diffuse sclerosing variant of PTC, features such as numerous psammoma bodies, metaplastic squamous epithelium, and marked lymphocytic infiltration are typically seen. The presence of marked lymphocytic infiltrate can obscure the neoplastic follicular cells, mimicking lymphocytic thyroiditis.
- Papillary structures are often not present in solid variant of PTC, and the presence of cohesive syncytial-type tissue fragments, microfollicular/trabecular pattern, or dyshesive single-cell pattern may lead to misdiagnosis of other types of thyroid carcinoma such as poorly differentiated carcinoma, follicular variant of PTC, or medullary carcinoma [27, 28] (Figs. 3.12 and 3.13).

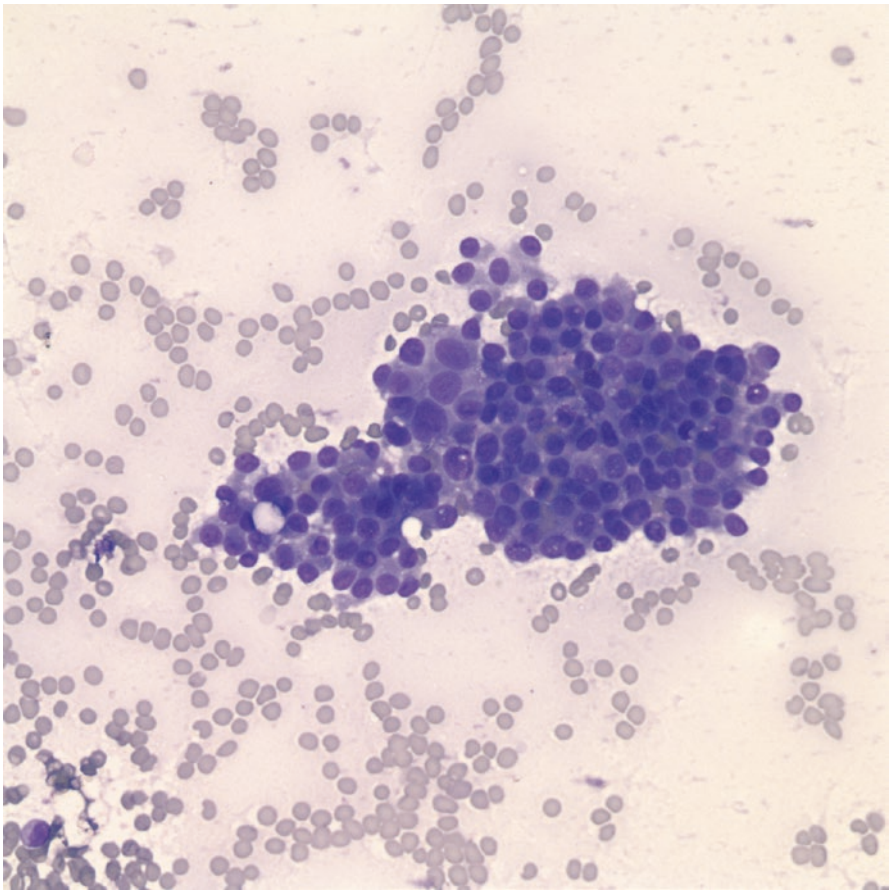

Fig. 3.12 Solid variant of papillary thyroid carcinoma. Tumor arranged as cohesive syncytial-type groups (Diff-Quik stain, ×400)

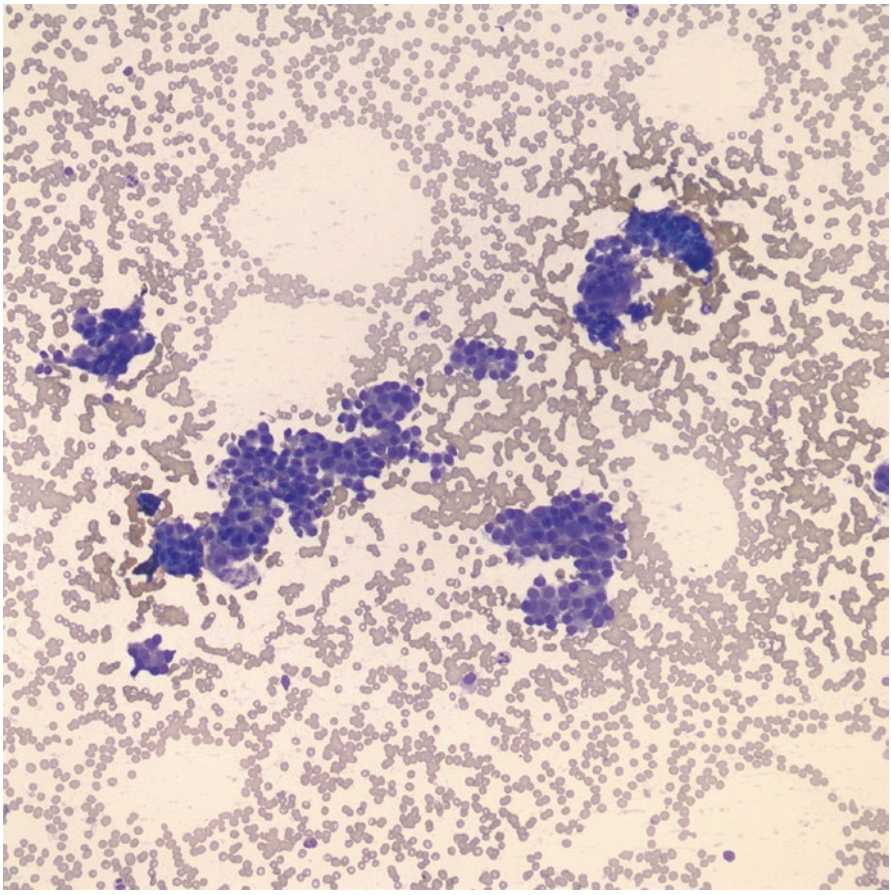

Fig. 3.13 Solid variant of papillary thyroid carcinoma. Tumor arranged in microfollicular and trabecular patterns (Diff-Quik stain, ×200)

Medullary Carcinoma

Diagnostic Consideration

Medullary carcinoma has a wide spectrum of cytomorphologic patterns and hence can mimic a variety of neoplasms. At the time of ROSE, additional pass for cell block material should be obtained if there is a suspicion of medullary carcinoma. This is important because FNA cannot always distinguish medullary carcinoma based on cytology alone, and often, immunohistochemical stain for calcitonin is a useful ancillary study.

Cytomorphologic Features

- Usually highly cellular aspirate, although scant cellularity may be seen with carcinomas containing extensive amyloid deposits and calcification.
- There is a wide spectrum of cytologic features in medullary carcinoma. It is monomorphic if only one cytomorphologic pattern is evident and polymorphic if a combination of different cytomorphologic patterns is seen.
- Tumor cells are predominantly single cells with abundant granular cytoplasm but may also be seen as sheets, loose clusters, syncytia, rosettes, cords, and papillae [29–31] (Figs. 3.14 and 3.15).

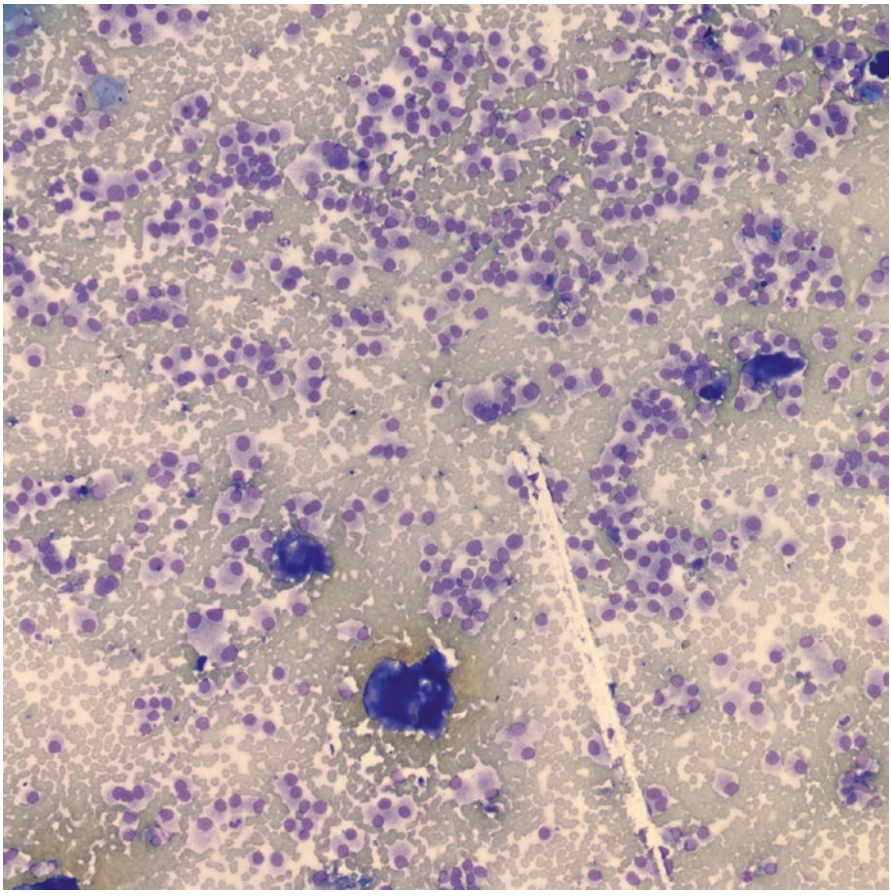

Fig. 3.14 Medullary carcinoma. Single cells with uniform size and shape and abundant granular cytoplasm (Diff-Quik stain, ×200)

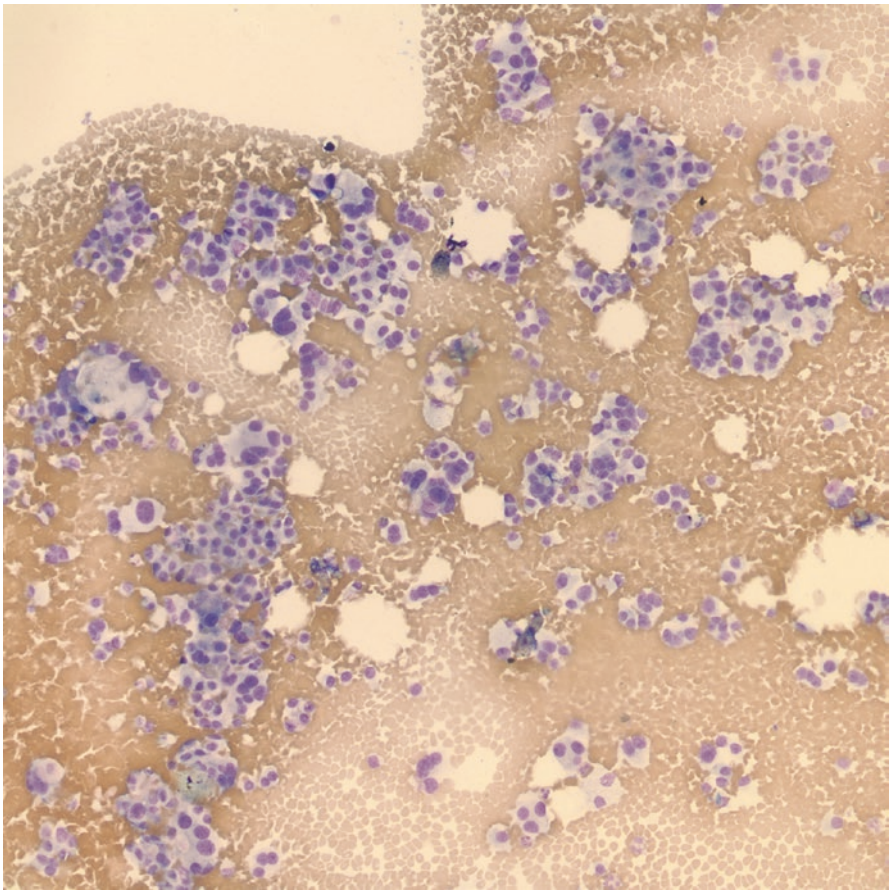

Fig. 3.15 Medullary carcinoma. Loose clusters, rosettes, and cords of tumor cells (Diff-Quik stain, ×200)

- Cells are usually uniform in size and shape but occasionally can present as large, pleomorphic cells. Nuclei are eccentrically placed, giving the cells a plasmacytoid appearance. Binucleation and multinucleation are common. Intranuclear inclusions are frequently seen (Figs. 3.16 and 3.17).

Tips and Pitfalls

- The presence of papillary architecture can mimic papillary carcinoma especially in the presence of intranuclear inclusions and psammoma bodies.

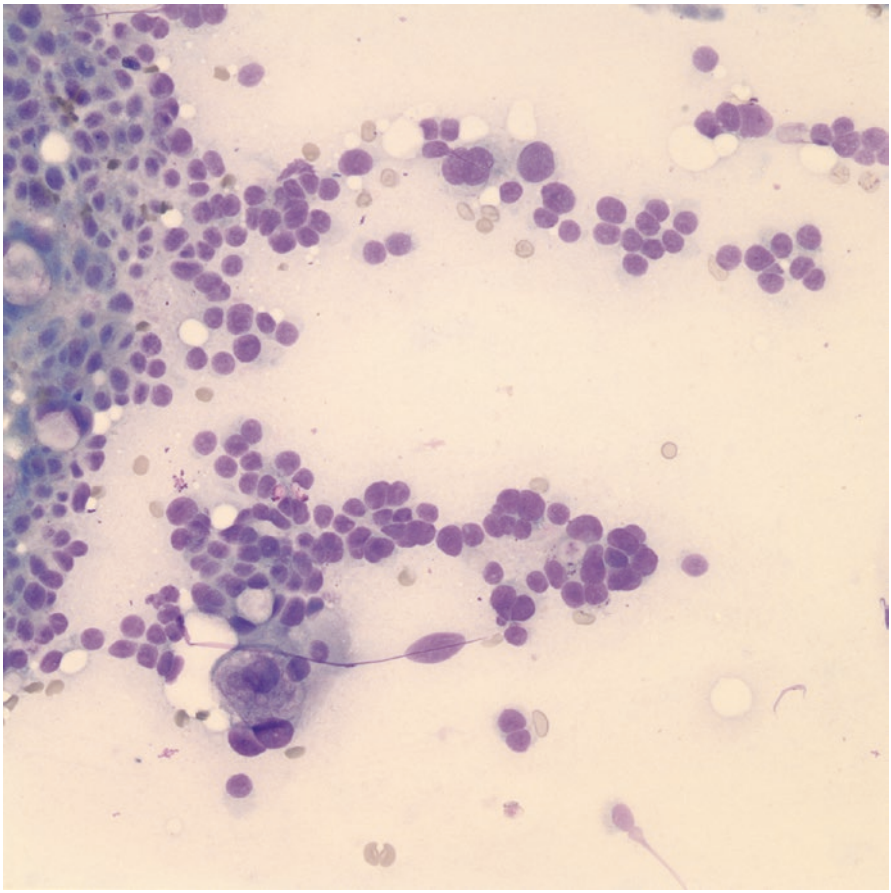

Fig. 3.16 Medullary carcinoma. Large pleomorphic cells (Diff-Quik stain, ×400)

- Tumor cell arrangement as rosettes or microfollicles can mimic a follicular neoplasm or Hürthle cell neoplasm.
- Tumor cell arrangement as cords can mimic poorly differentiated carcinoma, especially the insular type.
- Dispersed single-cell pattern can mimic a lymphoma. When the single cells have prominent plasmacytoid appearance, they can mimic a plasmacytoma.
- Tumors with a predominant spindle cell component can mimic sarcoma, melanoma, or spindle cell carcinoma.
- Amyloid can be confused with thick colloid. If in doubt, additional material should be obtained at the time of ROSE for cell block on which Congo red stain may be performed.

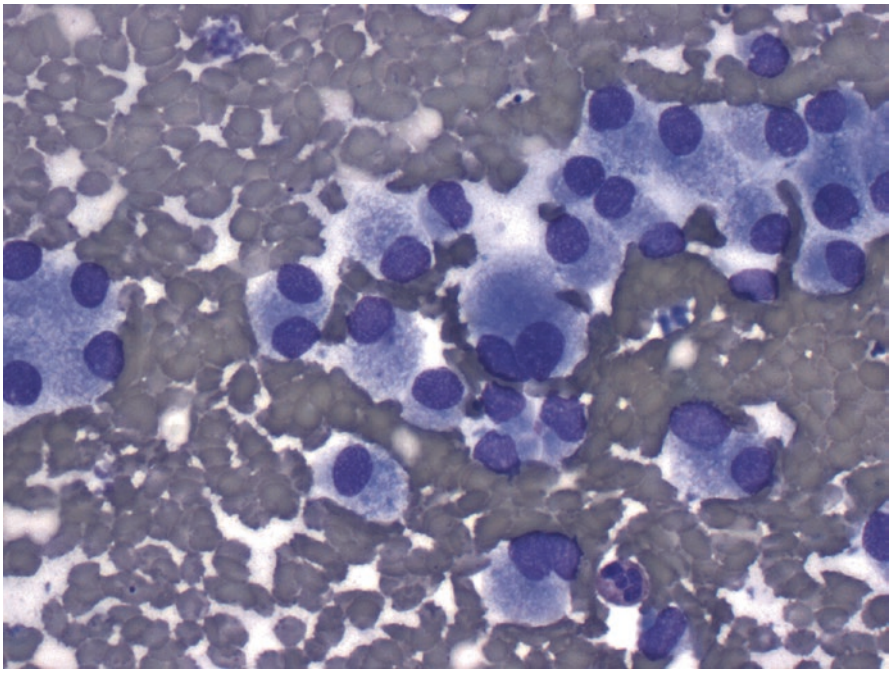

Fig. 3.17 Medullary carcinoma. Single cells with eccentrically placed nuclei. Some of the cells are binucleated (Diff-Quik stain, ×600)

Anaplastic Carcinoma

Diagnostic Consideration

The history is very important in this entity as patients present with rapidly enlarging neck mass which has often metastasized to adjacent structures by the time of diagnosis.

Cytomorphologic Features

- Usually very cellular specimen.
- Noncohesive, large cells with marked nuclear pleomorphism (Figs. 3.18 and 3.19).
- Cells may be epithelioid or spindle-shaped.
- Multinucleated giant cells are usually present.

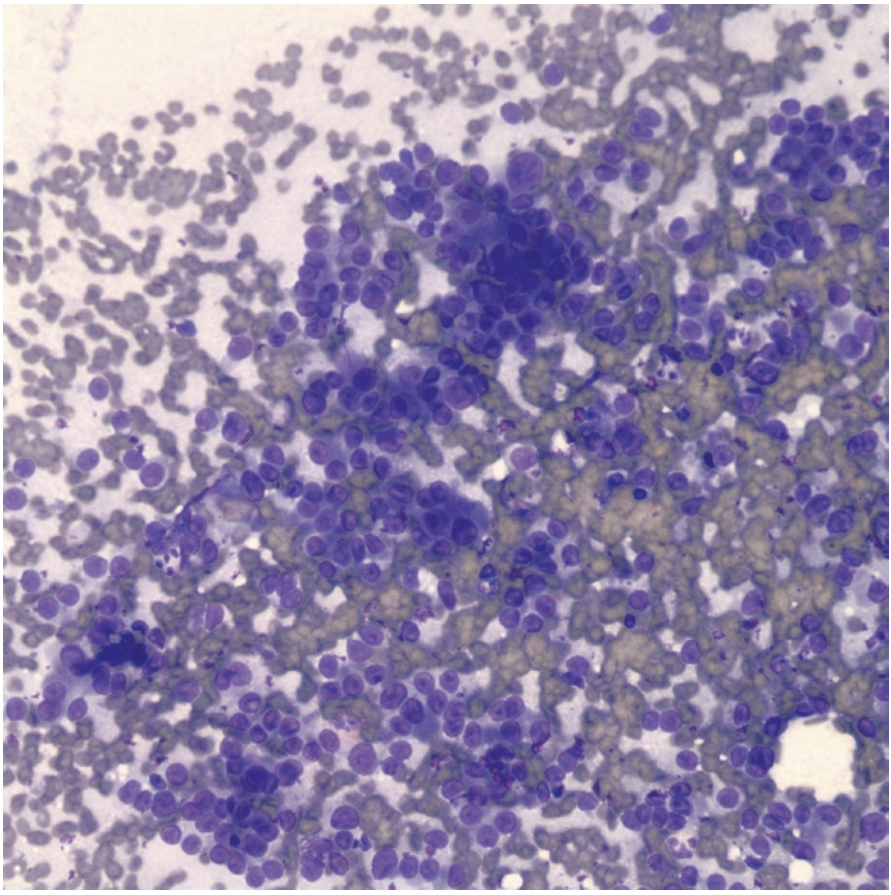

Fig. 3.18 Anaplastic carcinoma. Noncohesive large cells with nuclear pleomorphism (Diff-Quik stain, ×400)

- Extensive necrosis is common, mitoses are numerous, and the Ki67 proliferation index is high [32].
- A good number is associated with a differentiated thyroid carcinoma so marked atypia and pleomorphism may not be prevalent, depending on sampled areas of the tumor.

Tips and Pitfalls

- Anaplastic carcinoma with extensive collagen deposition can mimic Riedel's thyroiditis. The stromal spindle cells from Riedel's thyroiditis are however bland, in comparison to anaplastic carcinoma cells [18].

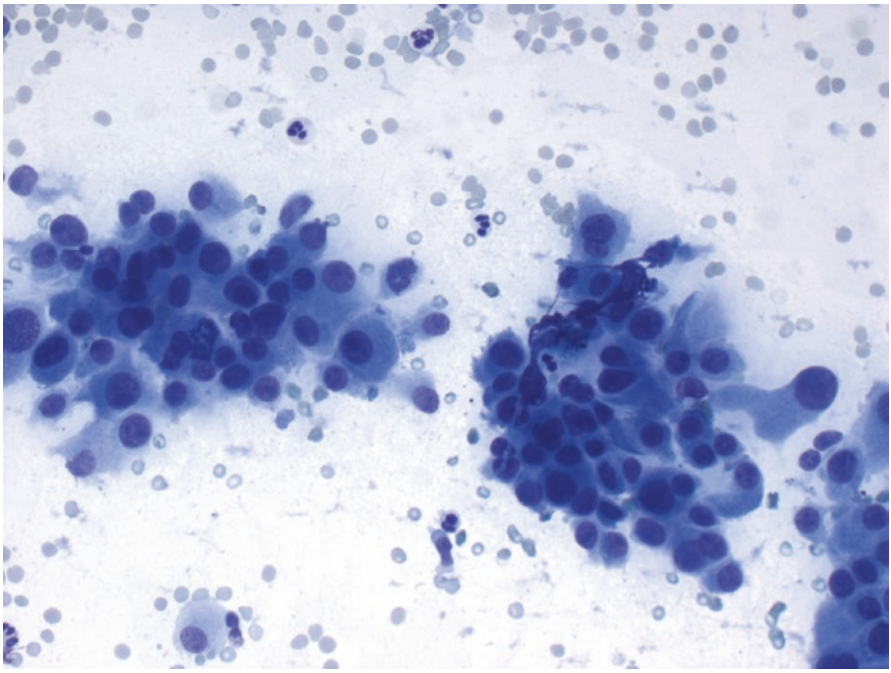

Fig. 3.19 Anaplastic carcinoma. Noncohesive large cells with marked nuclear pleomorphism (Diff-Quik stain, ×400)

- Anaplastic carcinoma cells can be confused with radioactive iodine-induced changes in benign follicular cells after treatment for Graves' disease. These changes include cytomegaly, clumped chromatin, and nucleoli.
- When ossified laryngeal or thyroid cartilage containing hematopoietic tissue is inadvertently sampled, megakaryocytes may mimic anaplastic carcinoma cells. However, megakaryocytes lack the malignant features exhibited by anaplastic carcinoma cells.
- Anaplastic carcinoma cells can mimic poorly differentiated squamous cell carcinoma from direct extension from an adjacent organ in the head and neck. Also, when anaplastic carcinoma has extensive squamous differentiation, it can be mistaken for squamous cell carcinoma [18].
- The medium to large cells of large cell lymphoma, exhibiting high N/C ratios and scant cytoplasm, can sometimes be difficult to differentiate from cells of malignant lymphoma.
- Anaplastic carcinoma can often have a spindle cell pattern, simulating cytologic features of sarcoma.
- Immunohistochemistry can be helpful in the differential diagnosis of anaplastic carcinoma, so additional material should be obtained at the time of ROSE for this purpose.

Metastatic Neoplasms to the Thyroid

Diagnostic Consideration

The possibility of metastasis should always be considered whenever a patient with a history of malignancy elsewhere in the body presents with a thyroid nodule. The thyroid may also be involved by direct extension of malignancies from the head and neck region.

Cytomorphologic Features

- The cytomorphologic pattern of a metastatic tumor depends on the manner of thyroid involvement, the histologic type, and stage of the tumor.
- Cytologic features of metastasis are distinct and different from what is usually seen in primary thyroid tumors. However, there can be an admixture of the tumor with atypical follicular cells [18].

Tips and Pitfalls

- It can be difficult to differentiate between metastatic clear cell renal cell carcinoma and dominant clear cell component within a primary thyroid follicular neoplasm. It may also be difficult to distinguish metastatic clear cell RCC with granular cytoplasm from Hürthle cell neoplasm [18].
- In a patient with a history of breast carcinoma, the presence of single-file pattern of cells and intracytoplasmic lumina is consistent with breast origin [33] (Fig. 3.20).
- Neoplastic cells from metastatic lung adenocarcinoma are usually arranged in three-dimensional clusters and gland-forming clusters. Intranuclear cytoplasmic inclusions may be present and may lead to a misdiagnosis of PTC [34] (Fig. 3.21).
- Benign metaplastic changes seen in the thyroid can mimic squamous cell carcinoma.
- Anaplastic thyroid carcinoma with prominent squamous differentiation can mimic metastatic squamous cell carcinoma.
- In metastatic malignant melanoma, cells may present with clearing of the chromatin, poorly formed nuclear grooves, and intranuclear cytoplasmic inclusions and may lead to a misdiagnosis as PTC [35].
- Whenever metastasis to the thyroid is suspected, especially when there is a history of malignant neoplasms in a different body site, additional material should be obtained at the time of ROSE for immunohistochemical stains and/or molecular studies.

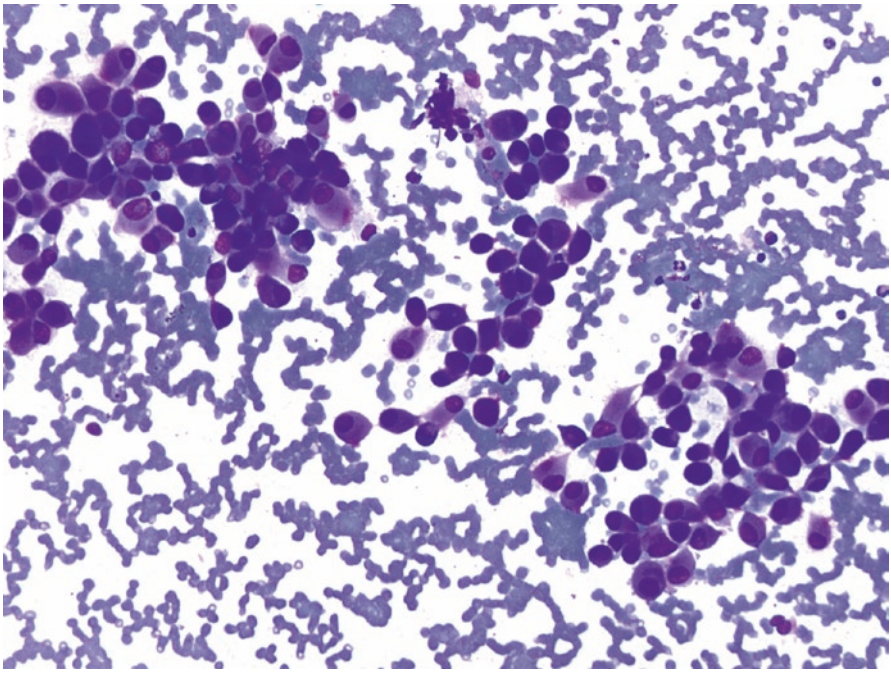

Fig. 3.20 Metastatic breast carcinoma to the thyroid. Loosely cohesive clusters and single tumor cells. The nuclei are eccentrically placed and some of the cells have intracytoplasmic lumina (Diff-Quik stain, ×200)

Parathyroid Tissue Sampling

Diagnostic Consideration

Thyroid tissue has overlapping cytomorphologic features with parathyroid tissue so it may be difficult to distinguish one from the other on FNA [36, 37].

Cytomorphologic Features

- High cellularity.
- Cells are arranged as cohesive sheets, ribbon-like cords, and occasional micro-acini (Fig. 3.22).
- Isolated cells and naked nuclei can be present.
- Round nuclei with stippled chromatin pattern (Fig. 3.23).
- Nucleoli may be absent, small, or prominent.
- Cytoplasm is scant to moderate.

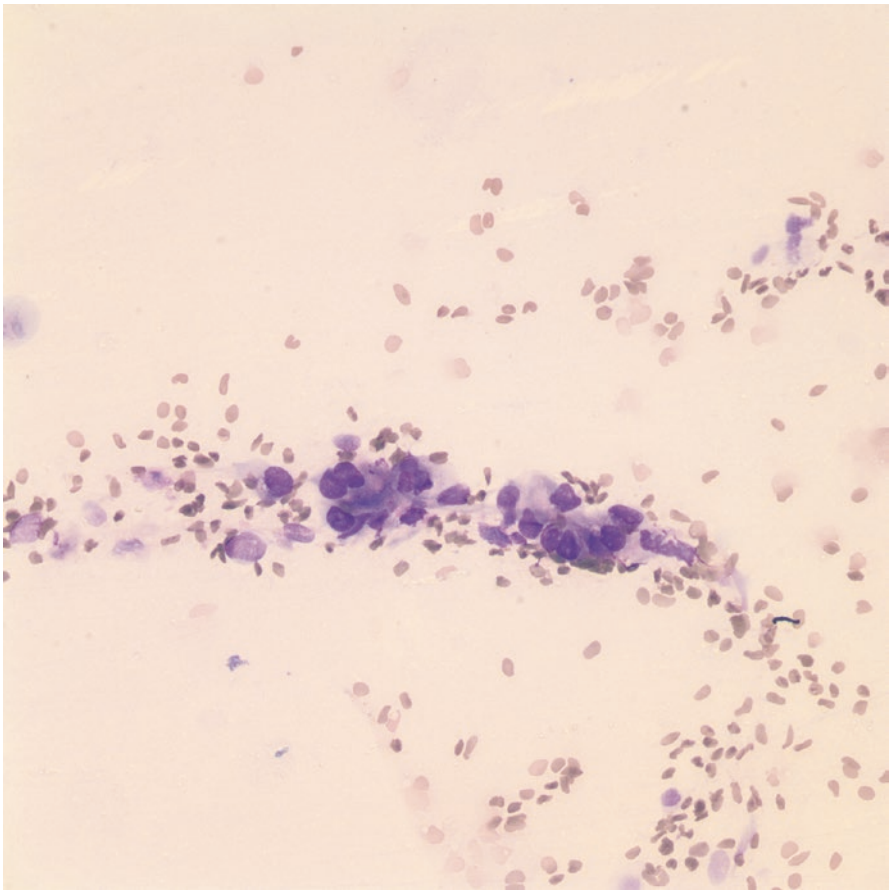

Fig. 3.21 Metastatic lung adenocarcinoma to the thyroid. Gland-forming clusters of tumor cells (Diff-Quik stain, ×400)

Tips and Pitfalls

- Colloid-like material can be produced by hyperplastic parathyroid glands and this can be confused with true colloid [38].
- Parathyroid adenoma smears can show tissue fragments with papillary-like architecture and may be misdiagnosed as papillary carcinoma (Fig. 3.24). Smears with the presence of papillary-like architecture alone without the usual nuclear features of papillary carcinoma should be read with caution [18].
- Parathyroid smears may be interpreted as follicular neoplasm when the cells present as tight, small, three-dimensional clusters in the absence of colloid.

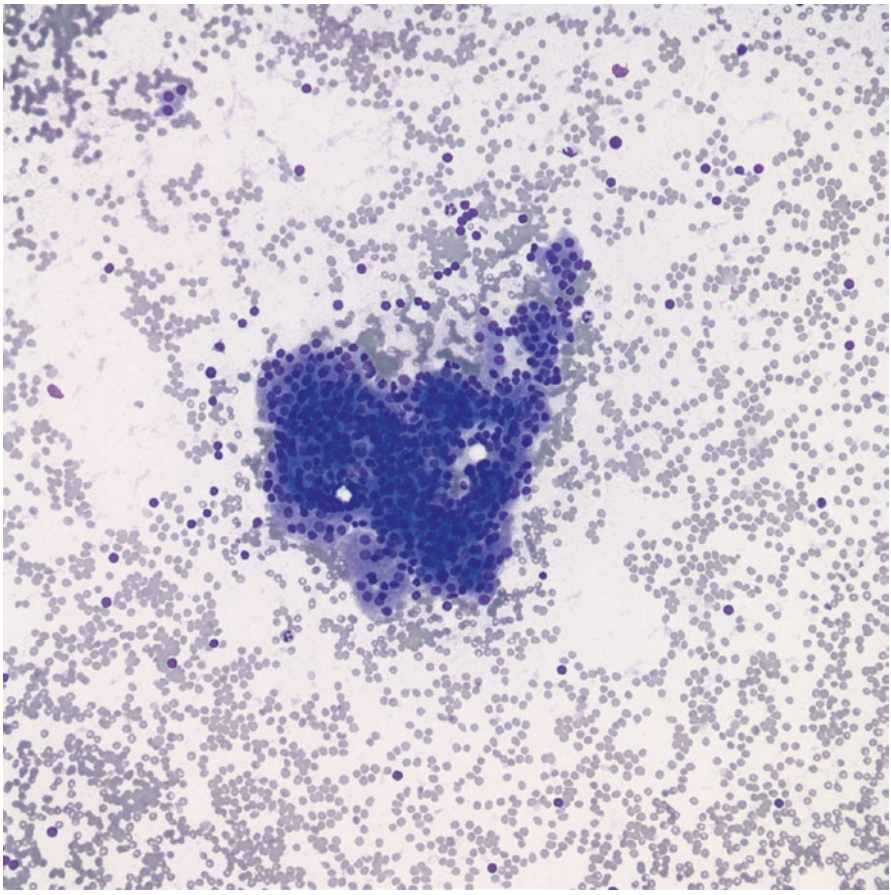

Fig. 3.22 Parathyroid tissue. Cells arranged as cohesive sheets and occasional microacini (Diff-Quik stain, ×400)

- Oncocytic parathyroid adenoma may have follicular structures and can also have colloid-like material in the background, which may lead to a misdiagnosis of Hürthle cell neoplasm. However, Hürthle cell neoplasms of the thyroid have much larger and more prominent nucleoli, and the cells tend to be more discohesive [39, 40].
- When there is a suspicion of parathyroid tissue during ROSE for a thyroid FNA, additional material should be collected for parathyroid hormone (PTH) and/or thyroglobulin immunohistochemical stains. It may also be important to send additional sample for parathyroid assay.

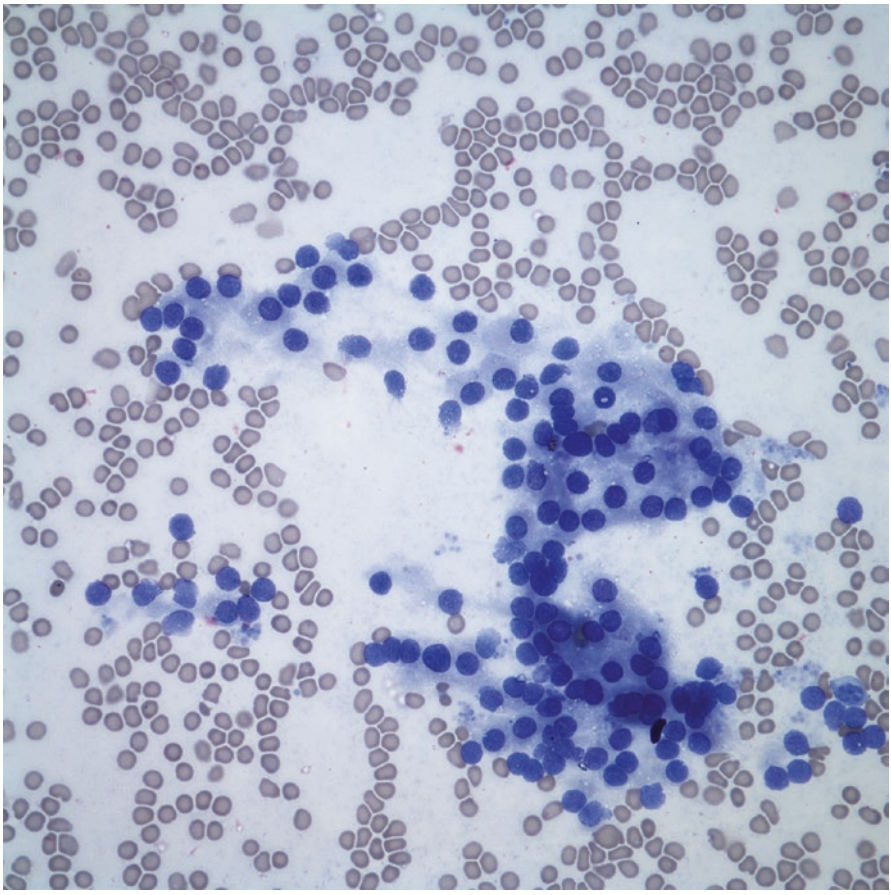

Fig. 3.23 Parathyroid tissue. Cells have round nuclei with stippled chromatin pattern (Diff-Quik stain, ×400)

Ectopic Thyroid Tissue

Diagnostic Consideration

The finding of thyroid tissue in the FNA of a neck mass that is unconnected to the thyroid gland can pose a diagnostic dilemma. The challenge is always to determine whether the aspirate represents a metastatic thyroid malignancy, ectopic thyroid tissue, or benign thyroid inclusion in a lymph node.

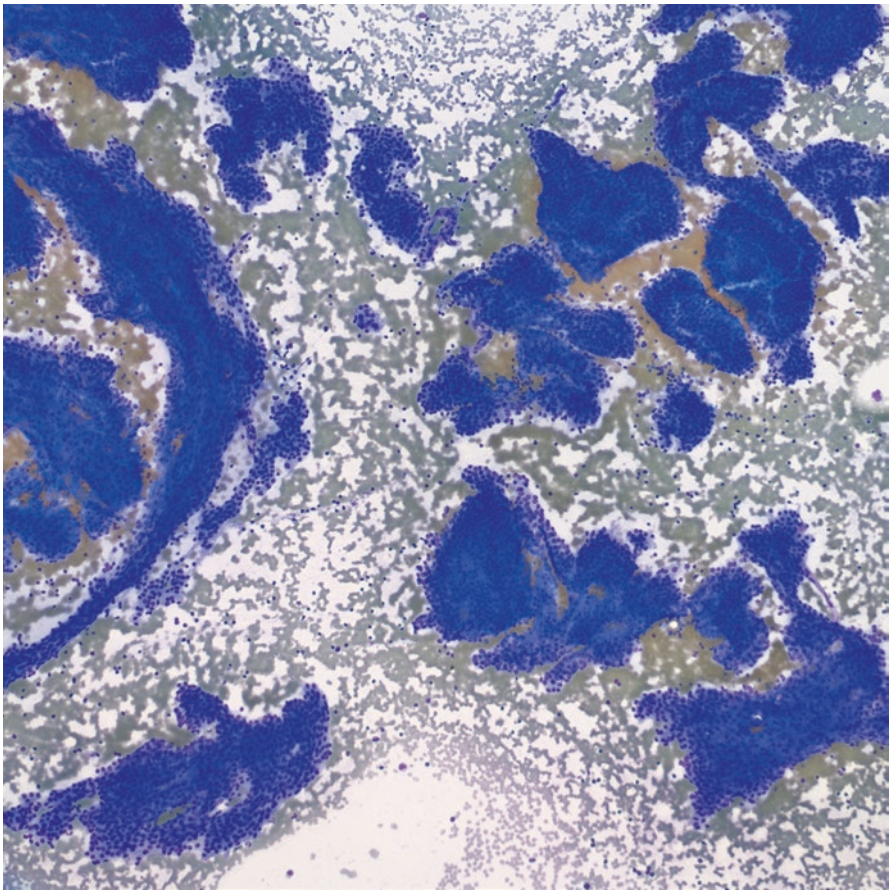

Fig. 3.24 Parathyroid adenoma. Tissue fragments with papillary-like architecture (Diff-Quik stain, ×100)

Cytomorphologic Features

- The cytomorphologic features of ectopic thyroid tissue ranges from normal-appearing follicular cells that are reminiscent of hyperplasia, presence of follicular cells and polymorphous population of lymphocytes in lymphocytic thyroiditis, to rarely, presence of cytologic features of malignancy.
- The presence of a few cytologic features such as unequivocal nuclear features of papillary carcinoma and psammoma bodies is diagnostic of metastases.

Tips and Pitfalls

- Although benign thyroid inclusions may be present in lymph nodes, the presence of thyroid tissue in lateral neck nodes almost always represents nodal metastases from a primary thyroid carcinoma [41, 42].
- The presence of cytologically benign-appearing follicular cells does not necessarily imply a benign process because the pattern of growth of certain thyroid carcinomas may be so well differentiated that they can simulate a nonneoplastic thyroid tissue.
- The presence of cytologic or architectural atypia in follicular cells, even if accompanied by a lymphoid background, does not always indicate metastatic thyroid carcinoma.

Material for Molecular Tests

Molecular testing improves the diagnostic accuracy of FNA for cases in the indeterminate category [43]. It may also provide significant prognostic and therapeutic information preoperatively [44]. The currently available molecular testing can be classified into those involving somatic mutation markers and those involving gene expression classifiers [45]. Several studies have also identified differential expression of several miRNA expressions in thyroid cancers when compared with benign thyroid tissues [45]. More recently, next-generation sequencing has emerged, thus allowing the simultaneous sequencing of large panels of genes [46].

Appropriate and adequate specimen collection at the time of ROSE is key to the success in performance of these tests. It is important to ensure that the specimen/pass evaluated at the time of ROSE is adequately represented in the material sent off for molecular tests.

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