4
Inflammatory Lesions and Lymphoma

Thyroiditis comprises a diverse group of inflammatory thyroid lesions and is one of the most common endocrine disorders in clinical practice. The most frequently encountered form is chronic lymphocytic thyroiditis (Hashimoto thyroiditis), first described in 1912, and a major cause of goiter and hypothyroidism in the United States. Clinically, patients are typically young to middle-aged women who present with a moderately enlarged nodular thyroid that is nontender. Approximately 90% of patients have high circulating antibody titers to thyroid peroxidase and, to a lesser extent, to thyroglobulin. Hashimoto thyroiditis is an autoimmune disorder that is thought to be caused by a derangement of suppressor T lymphocytes. Possible contributing factors to this disease include genetic associations with HLA-DR3, HLA-DR5, and HLA-B8; viral and infectious factors have also been proposed. Approximately 10% of cases are the fibrosing variant of Hashimoto thyroiditis that presents as severe hypothyroidism in elderly patients. Individuals with Hashimoto thyroiditis have a significantly increased relative risk of developing malignant lymphoma, and data suggest that there is also an increased risk of papillary carcinoma. Fine needle aspiration (FNA) is most often used to evaluate Hashimoto thyroiditis when a dominant nodule is present. Together with confirmatory antibody studies, FNA is an accurate means of diagnosing chronic lymphocytic thyroiditis.

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Subacute thyroiditis (de Quervain's thyroiditis, giant cell thyroiditis, subacute granulomatous thyroiditis), the pathology of which was first described in 1904 by de Quervain, is the most common cause of painful thyroid disease, and has a peak incidence in women in the third to sixth decades. Although a definite cause of subacute thyroiditis has yet to be found, a viral etiology has been proposed. In fact, patients often report a history of a recent upper respiratory tract infection. Patients present with sudden or gradually progressive pain in the region of the thyroid gland, and some patients report a viral prodrome. Symptoms are spontaneously remitting within weeks to months; clinical features of thyrotoxicosis are present in up to 50% of patients. Occasionally, subacute thyroiditis can present as a dominant nodule, and it is this subset of cases that is sampled by FNA.

Acute thyroiditis is a rare and potentially life-threatening occurrence that is most commonly due to bacterial infection or less often fungal infection. Patients present with fever, chills, malaise, thyroid pain that may radiate, and unilateral or bilateral thyroid enlargement, possibly with abscess formation. Acute thyroiditis often occurs from hematogenous spread to the thyroid of a systemic infection. The role of FNA in the evaluation of this disorder, in addition to diagnosing acute thyroiditis, is to obtain material for cultures and sensitivity testing. *Staphylococcus aureus* and *Streptococcus* sp. have been identified as the causative agent in up to 80% of cases.

Reidel thyroiditis (invasive fibrous thyroiditis) is a rare thyroid disease of unknown etiology that primarily affects middle-aged to older women. Patients who may be euthyroid or hypothyroid present with diffuse goiter that is hard to palpation, and often examination of the thyroid gland shows fixation to adjacent structures. As the clinical picture implies, the key differential diagnosis is with malignancy, particularly undifferentiated carcinoma or lymphoma. Thyroid FNA can be attempted, but samples are often nondiagnostic because of hypocellularity associated with the extensive fibrosis.

Differential diagnosis of inflammatory lesions are as follows:

- Acute thyroiditis
- Chronic lymphocytic thyroiditis
- Subacute thyroiditis
- Reidel thyroiditis
- Lymphoma

Primary lymphoma, particularly non-Hodgkin B-cell lymphoma, is rare and accounts for approximately 1–5% of thyroid malignancies. Most patients are women in their fifties, and the majority has a history of Hashimoto thyroiditis. Other lymphoproliferative disorders such as Hodgkin disease, plasmacytoma, and T-cell lymphomas have been reported in the thyroid gland but are very rare. Patients generally present with either sudden diffuse enlargement of a mass or occasionally with a solitary thyroid nodule. The thyroid is firm, and there is often fixation to and compression of surrounding thyroid structures. The role of FNA in the evaluation of thyroid lymphoma is to exclude undifferentiated carcinoma and to obtain material for immunophenotypic subtyping of the lymphoma. In patients with primary thyroid lymphoma, approximately one-third are diffuse large B-cell lymphomas (DLBCLs), one-third are extranodal marginal zone lymphomas of mucosa-associated lymphoid tissue (MALT) type, and one-third are mixed DLBCL and MALT lymphoma. Primary follicular lymphomas have also been reported but are less common.

Clinicopathologic features of primary thyroid lymphoma are as follows:

- One to five percent of thyroid malignancies
- Women in sixth decade
- History of Hashimoto thyroiditis
- Firm, diffuse thyroid mass
- Rapid onset
- Two most common subtypes:
  - Diffuse large B-cell lymphoma
  - Extranodal marginal zone lymphoma of MALT type

General Diagnostic Approach

Using the algorithm (Figure 4.1), thyroid FNAs containing a predominance of inflammatory cells are divided into subsets of disorders based on the specific types and combinations of cells present. A variety of pathologically distinct inflammatory processes that affect the thyroid can be diagnosed by FNA and are placed into the Benign category. Hashimoto thyroiditis is by far the most

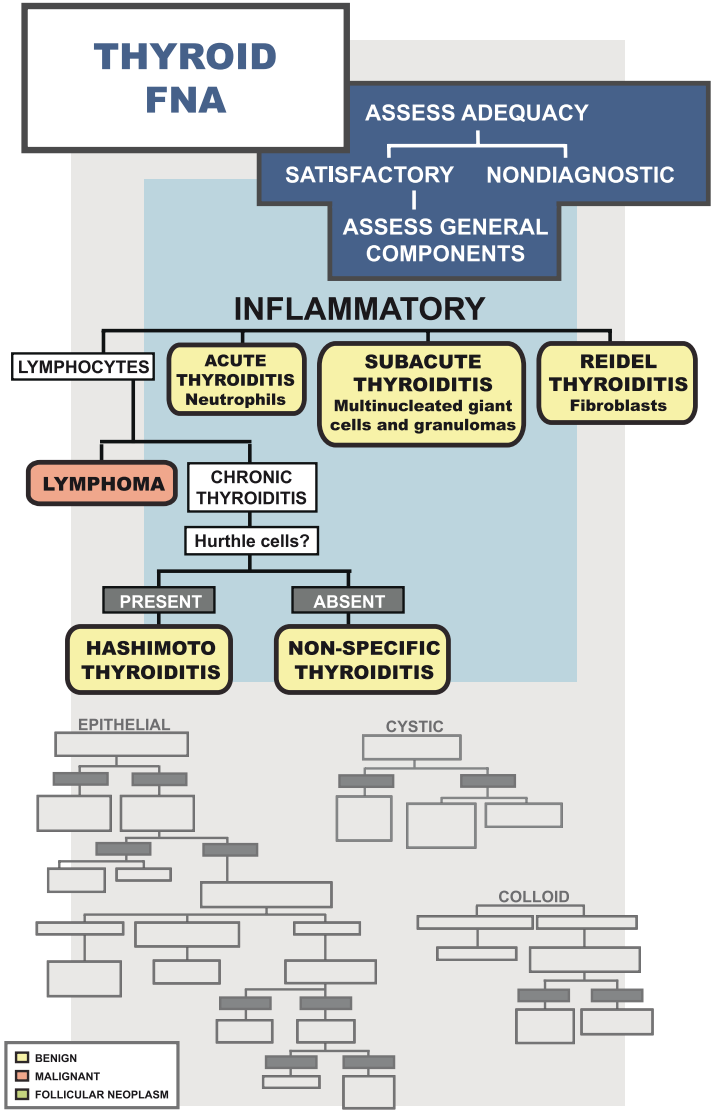

FIGURE 4.1. Algorithmic approach to inflammatory disorders and lymphoma.

frequently encountered of these lesions, but other less common inflammatory lesions that can also be seen include acute thyroiditis, subacute thyroiditis, and Reidel thyroiditis. In addition, in a small subset of cases with a predominance of lymphocytes including an increased proportion of intermediate to large lymphocytes, ancillary studies such as flow cytometry can be used to exclude the possibility of lymphoma. Using appropriate ancillary studies, most lymphomas will be accurately placed into the malignant category.

Diagnostic Criteria

Acute Thyroiditis

Microscopically, the aspirate consists of an abundance of neutrophils along with histiocytes and necrotic debris (Figure 4.2). The findings are nonspecific and generally reflect features of an abscess. Follicular epithelium is scant to absent, but when present can show reparative changes such as nuclear enlargement and prominent nucleoli.

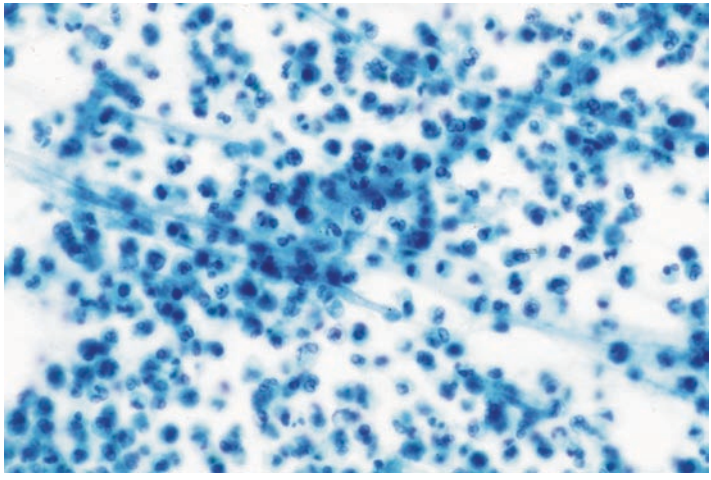

FIGURE 4.2. Acute thyroiditis. Marked acute inflammation and debris are seen, but follicular cells and colloid are absent. (Smear, Papanicolaou.)

Importantly, atypical follicular cells suggestive of undifferentiated thyroid carcinoma are not identified. Bacteria or other organisms may be seen in smears or by special stains, and often the most clinically useful information is obtained from culture and sensitivity testing of the aspirated material.
Cytologic features of acute thyroiditis are as follows:

- Abundant neutrophils
- Histiocytes
- Necrotic debris
- Few follicular cells with reparative changes

Chronic Lymphocytic Thyroiditis (Hashimoto Thyroiditis)

Aspirates are variably cellular depending upon the degree of fibrosis of the thyroid gland, and in the small subset of cases of the fibrosing variant of Hashimoto thyroiditis, the specimen is hypocellular. Aspirates of chronic lymphocytic thyroiditis are characterized by a combination of two features (1) a mixed population of lymphocytes, plasma cells, and lymphohistiocytic aggregates and (2) occasional cohesive clusters of follicular cells with oncocytic features (Hurthle cells) (Figures 4.3–4.6). The majority of Hashimoto thyroiditis cases will be diagnosed as "Benign." The inflammatory component that consists of an abundance of mature B and T lymphocytes as well as centrocytes and centroblasts generally predominates the sample. Lymphohistiocytic aggregates with associated follicular dendritic cells and tingible body macrophages are often easily identified (Figure 4.4) such that the aspirate closely resembles a reactive lymph node. Plasma cells can be seen among the mixed population of lymphocytes and, in rare cases, can be the predominant cell. Significant amounts of background colloid are not present, but small fragments of collagenous tissue can sometimes be seen, and lymphoglandular bodies (small cytoplasmic fragments of lymphocytes) are scattered in the background.

In most cases, the follicular cells that are much less abundant than the inflammatory component have enlarged, sometimes grooved, nuclei and densely granular oncocytic cytoplasm (Figures 4.5 and 4.6). Distinct nucleoli may or may not be seen. The follicular cells

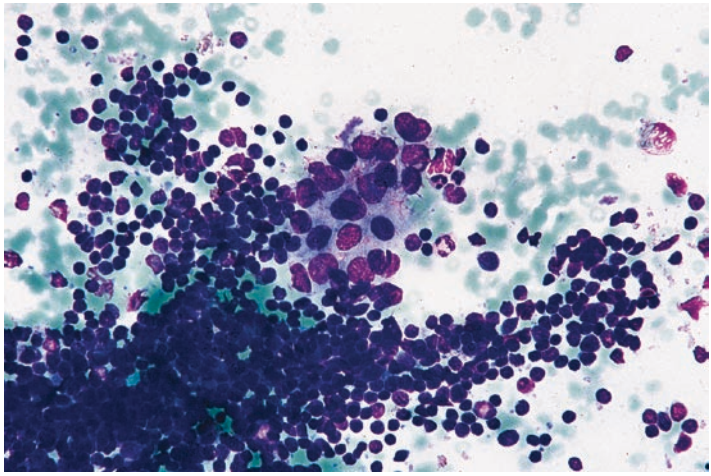

FIGURE 4.3. Chronic lymphocytic thyroiditis. Abundant mixed population of lymphocytes and occasional small groups of follicular cells with oncocytic features. (Smear, Diff-Quik.)

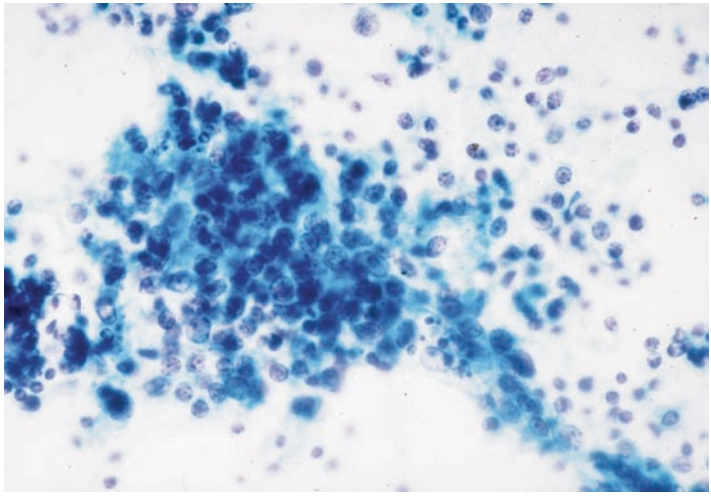

FIGURE 4.4. Chronic lymphocytic thyroiditis. Lymphohistiocytic aggregates are often present. (Smear, Papanicolaou.)

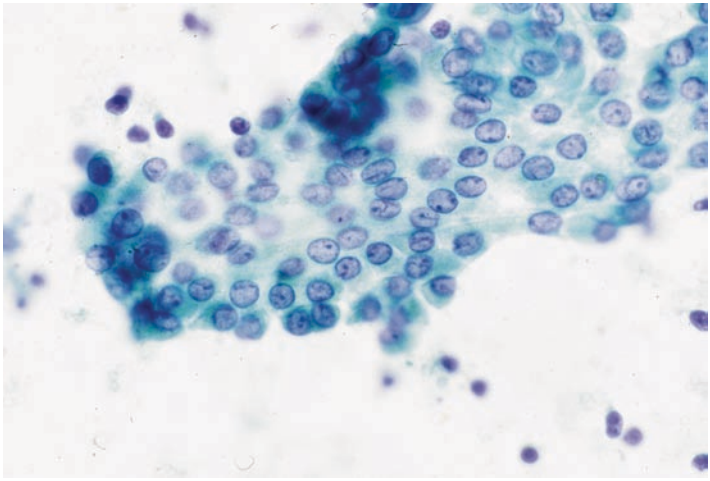

FIGURE 4.5. Chronic lymphocytic thyroiditis. The follicular cells have abundant densely granular cytoplasm, enlarged round nuclei, and form small, two-dimensional cohesive clusters. (Smear, Papanicolaou.)

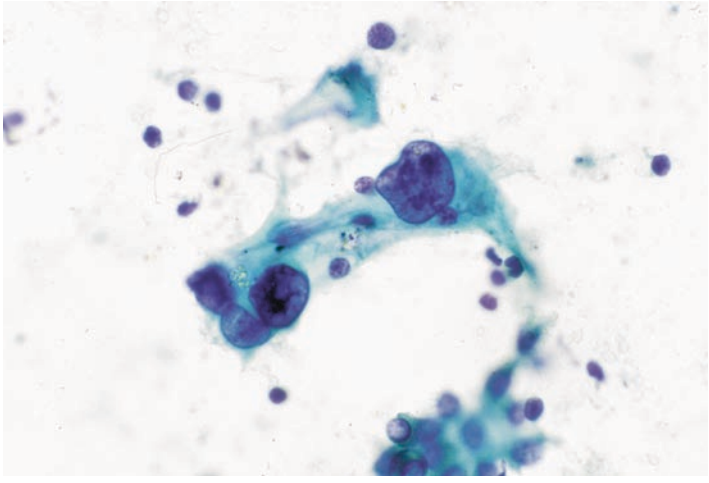

FIGURE 4.6. Chronic lymphocytic thyroiditis. Nuclear atypia in the form of nuclear grooves can often be seen. (ThinPrep, Papanicolaou.)

form small, two-dimensional cohesive clusters. Such cases should be placed into the "Benign" category. However, occasional follicular cells can display marked atypia or extensive nuclear grooves, raising the possibility of papillary carcinoma (see Figure 4.6). When this occurs, the aspirate will often be placed into the "Atypia of undetermined significance" category since papillary carcinoma cannot be excluded. Similarly, when a Hurthle cell nodule in the setting of chronic lymphocytic thyroiditis is aspirated, the specimen will sometimes consist of a pure population of Hurthle cells with a few scattered background lymphocytes. When a Hurthle cell neoplasm cannot be excluded, the aspirate will also be placed into the "Atypia of undetermined significance" category. Other cytologic features that can sometimes be seen include flame cells, squamous metaplastic cells, and giant cells.

Cytologic features of Hashimoto thyroiditis are as follows:

- Cellular aspirate
- Abundant mixed lymphocytes and plasma cells
- Lymphohistiocytic aggregates
- Follicular cells with oncocytic features (Hurthle cells) and variable nuclear atypia

Subacute Thyroiditis

Aspirates of subacute thyroiditis are usually hypocellular and consist of multinucleated giant cells that surround and engulf colloid. In addition, loose aggregates of epithelioid histiocytes (granulomas) are characteristic (Figures 4.7 and 4.8). Care should be taken not to misinterpret the epithelioid histiocytes with their curved nuclei and abundant granular cytoplasm as an epithelial neoplasm. A variable amount of background mixed inflammatory cells including lymphocytes, plasma cells, eosinophils, and neutrophils are sometimes seen. Follicular cells are generally sparse and, when present, can show oncocytic features as well as degenerative changes with reactive atypia.

Cytologic features of subacute thyroiditis are as follows:

- Hypocellular
- Multinucleated giant cells
- Loose clusters of epithelioid histiocytes
- Mixed chronic inflammation
- Scant follicular cells with reactive changes

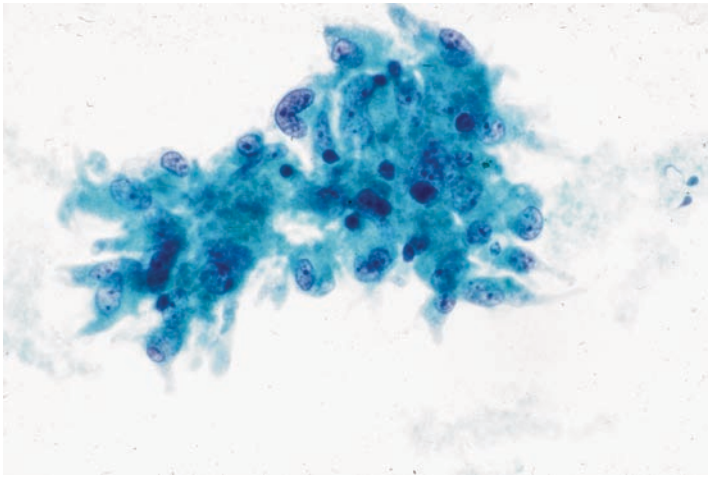

FIGURE 4.7. Subacute thyroiditis. Collections of epithelioid histiocytes (granulomas) with their curved nuclei and abundant granular to foamy cytoplasm should not be mistaken for an epithelial neoplasm. (ThinPrep, Papanicolaou.)

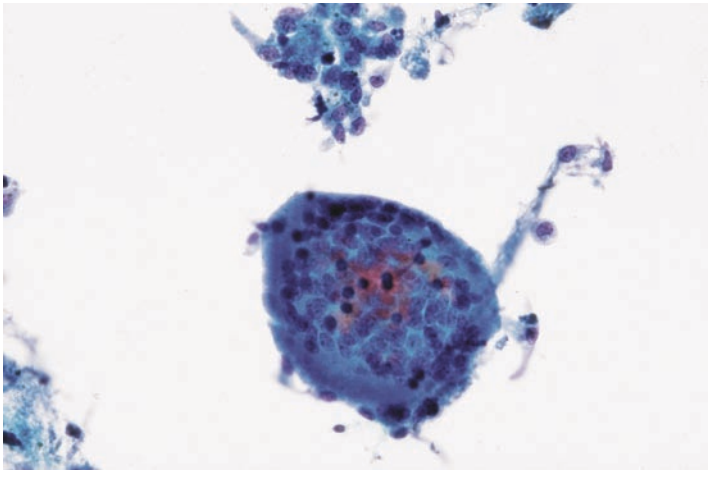

FIGURE 4.8. Subacute thyroiditis. Multinucleated giant cells, although not a specific finding, are characteristic of this lesion. (Smear, Papanicolaou.)

Reidel Thyroiditis

Aspirates of Reidel thyroiditis are hypocellular and often non-diagnostic due to scant cellularity. Microscopically, fragments of collagenous fibrous tissue, scattered cytologically bland spindle cells with plump elongate nuclei, and some background chronic inflammatory cells are seen (Figures 4.9 and 4.10). Follicular cells, lymphohistiocytic aggregates, and abundant lymphocytes are absent, helping to exclude chronic lymphocytic thyroiditis.

Cytologic features of Reidel thyroiditis are as follows:

- Hypocellular
- Collagenous fibrous tissue
- Bland spindle cells
- Mild chronic inflammation
- Absent follicular cells

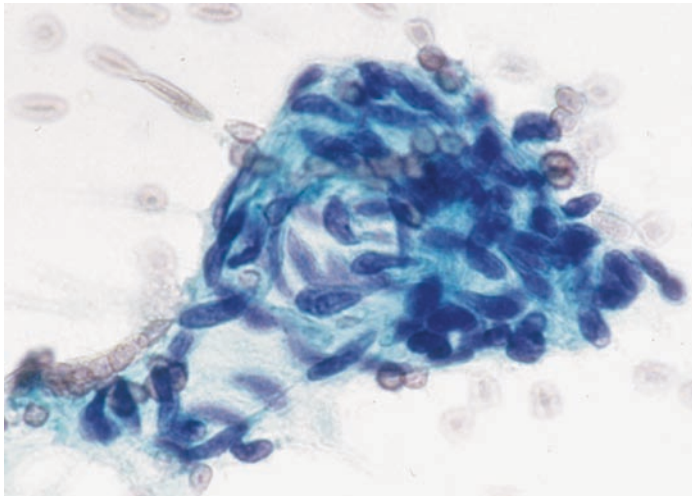

FIGURE 4.9. Reidel thyroiditis. Aspirates are hypocellular and contain occasional clusters of bland spindle cells and collagenous fibrous tissue. (Smear, Papanicolaou.)

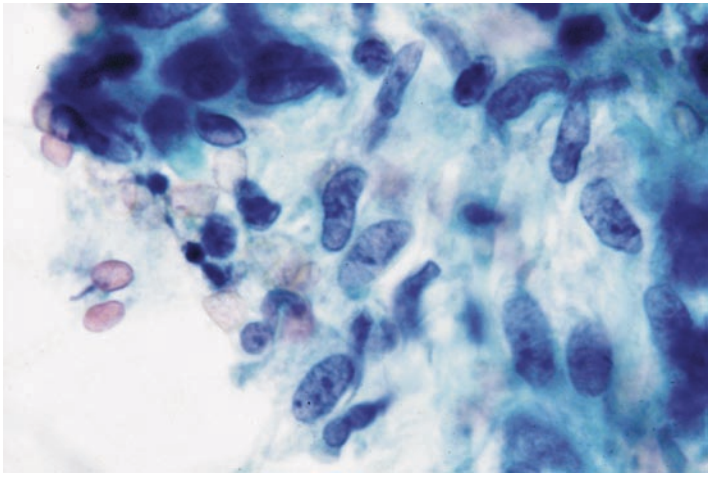

FIGURE 4.10. Reidel thyroiditis. Spindle cells form loose aggregates and have delicate cytoplasm and bland elongate nuclei with fine chromatin. (Smear, Papanicolaou.)

Lymphoma

The diagnosis of primary lymphoma of the thyroid gland is usually apparent on aspirates because a component of DLBCL is present in 50–75% of cases (pure cases of DLBCL plus mixed cases of DLBCL and extranodal marginal zone lymphoma). When diagnostic difficulties arise in the diagnosis of DLBCL, it is usually due to confusion with other nonlymphoid malignancies. The cells of DLBCL appear malignant and consist of cellular aspirates of large, highly atypical immature lymphoid cells, including a predominance of centroblast-like cells or immunoblasts in a background of scant to absent follicular cells (Figures 4.11 and 4.12). The cells are generally two to three times larger than a small mature lymphocyte and have irregular round nuclei with vesicular chromatin and basophilic cytoplasm. The centroblast-like cells have 1–3 peripheral nucleoli and scant cytoplasm, whereas the immunoblastic cells have a prominent central nucleolus and abundant cytoplasm. When immunoblastic cells predominate, they may appear plasmacytoid. Lymphoglandular bodies are

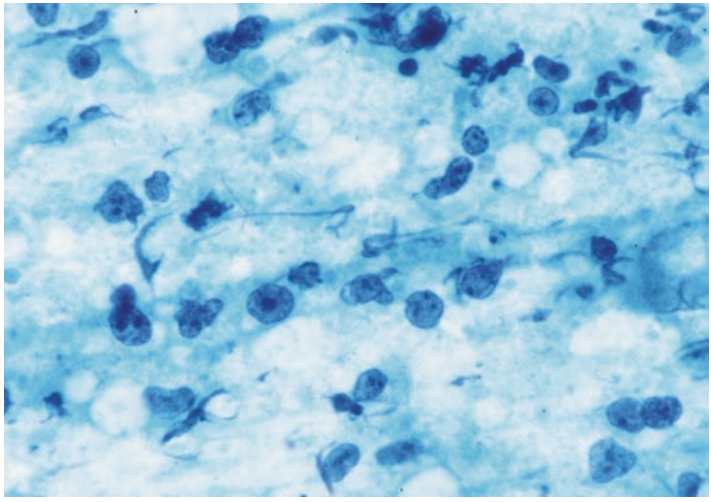

FIGURE 4.11. Diffuse large B-cell lymphoma (DLBCL). The aspirate is moderately cellular and shows a single cell pattern of atypical lymphoid cells. (Smear, Papanicolaou.)

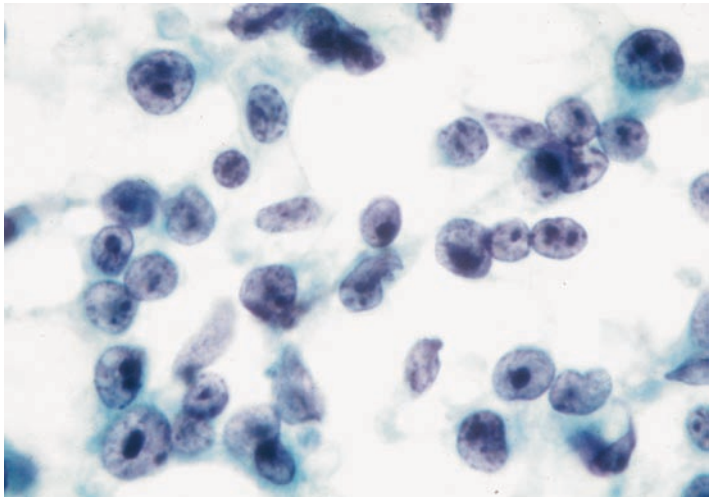

FIGURE 4.12. DLBCL. Individual immunoblastic lymphoid cells are large with a prominent central nucleolus and moderate amounts of delicate cytoplasm. (Smear, Papanicolaou.)

identifiable in the background, giving a morphologic clue that the cells are lymphoid. A grade 3 follicular lymphoma that would be unusual as a primary thyroid lymphoma would have a similar cytologic appearance and immunoprofile as DLBCL. Using flow cytometry or some other method of immunophenotypic analysis, the typical profile for DLBCL shows light chain restriction and expression of pan-B cell markers such as CD20, while other markers including CD5, CD10, and CD23 are variable but often negative.

Cytologic features of DLBCL are as follows:

- Cellular aspirate
- Large, atypical immature lymphoid cells
- Background lymphoglandular bodies
- Absent follicular cells
- Monotypic light chain restriction
- CD20+, CD45+, CD5−, CD10±

In contrast to DLBCL, which is easily recognizable as malignant, the second most common primary lymphoma of the thyroid is extranodal marginal zone lymphoma of MALT type. This is an indolent low-grade B-cell lymphoma that poses a particular diagnostic challenge because of its cytologic resemblance to a reactive lymph node or to benign inflammatory conditions such as chronic lymphocytic thyroiditis. Aspirates are composed of a heterogeneous population of cells including an increased number of small to intermediate-size lymphocytes resembling centrocytes as well as plasmacytoid cells, scattered immunoblasts, and plasma cells (Figure 4.13). A key to diagnosing this lymphoma is to recognize the absence of a spectrum of cells such that transitional forms between intermediate-size and large lymphocytes are not present. Nuclei of the intermediate-size cells are slightly irregular with condensed chromatin and indistinct nucleoli. Some cells have more abundant pale cytoplasm, giving a monocytoid appearance. Lymphohistiocytic aggregates are present, but tingible body macrophages and large activated follicle center cells are decreased (Figure 4.14). Because it may be difficult, if not impossible, to distinguish MALT lymphoma from a benign condition, immunophenotypic analysis such as flow cytometry to demonstrate light chain restriction is essential. The immunoprofile of MALT lymphomas is generally CD20+ and CD45+, but CD5−, CD10−, and CD23−. If cell block material is available, an immunostain for cyclin D1

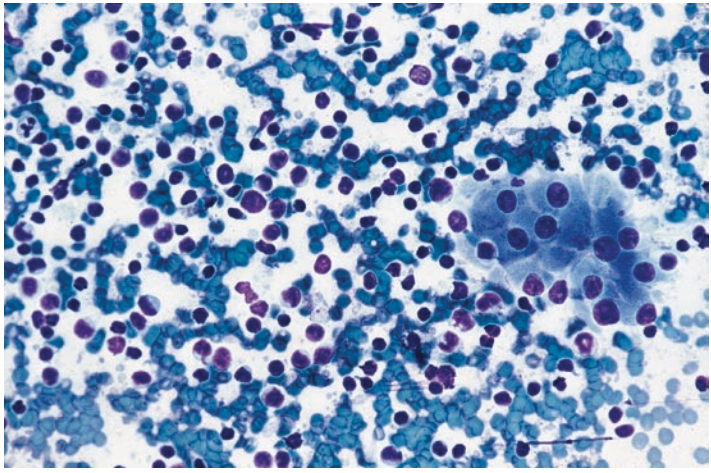

FIGURE 4.13. Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT). Cellular aspirate consisting of a heterogeneous population of small to intermediate-size lymphocytes and occasional larger immunoblasts. (Smear, Diff-Quik.)

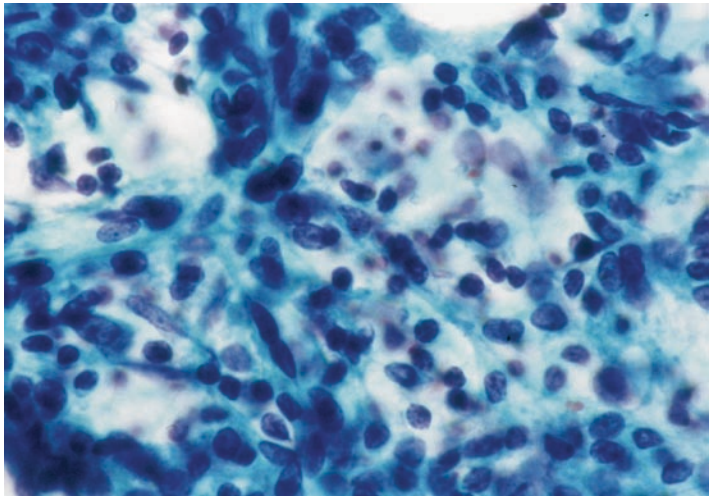

FIGURE 4.14. Extranodal marginal zone lymphoma of MALT type. Germinal center fragment showing small to intermediate-size lymphocytes and follicular dendritic cells. Tingible body macrophages are not present. (Smear, Papanicolaou.)

will be negative, excluding the unlikely possibility of a mantle cell lymphoma.

Cytologic features of MALT lymphoma are as follows:

- Cellular aspirate resembling a reactive lymph node
- Small to intermediate-size lymphocytes
- Monocytoid appearance
- Scattered immunoblasts and plasma cells
- Lymphohistiocytic aggregates
- Monotypic light chain restriction
- CD20+, CD45+, CD5−, CD10−, Bcl-2+, Bcl-6−, CD23−
- Cyclin D1−

Differential Diagnosis and Pitfalls

A challenging diagnostic problem in thyroid cytology is the distinction of Hashimoto thyroiditis from MALT lymphoma because of the heterogeneous population of lymphocytes in each. Cytologic differences between these two can be very subtle, but features favoring Hashimoto thyroiditis include a combination of lymphocytes in all stages of maturation with a predominant population of small mature lymphocytes and admixed plasma cells, and lymphohistiocytic aggregates with tingible body macrophages and activated follicle-center cells. Because of the cytologic overlap between Hashimoto thyroiditis and MALT lymphoma, the ultimate distinction between these two entities depends upon evaluation of light chain restriction through immunophenotyping by flow cytometry or immunocytochemistry. Only a small subset of Hashimoto thyroiditis cases will require further evaluation to exclude lymphoma. This small subset of cases would include those that are cellular with absent or very scant follicular cells, and an increased proportion of intermediate to large lymphocytes or atypical forms. One caveat in the evaluation of the kappa/lambda ratio of B cells in Hashimoto thyroiditis is that the ratio for CD10+ B cells can be skewed beyond that seen in reactive lymph nodes. In such cases, correlation with other markers and/or molecular studies can be useful.

Cytologic features favoring Hashimoto thyroiditis over MALT lymphoma are as follows:

- Spectrum of lymphocytes in all stages of maturation
- Lymphohistiocytic aggregates with tingible body macrophages
- Activated follicle-center cells
- Polytypic light chain expression

DLBCLs is easily distinguished from MALT lymphoma; however, it may sometimes be difficult to exclude a nonlymphoid malignancy with a single cell pattern such as malignant melanoma, small cell carcinoma, medullary carcinoma, or even undifferentiated carcinoma. The presence of small cytoplasmic fragments of lymphocytes known as lymphoglandular bodies within the background of the aspirate is a characteristic cytologic feature of lymphoid aspirates. However, the most definitive evidence that the lesion is a lymphoma is immunoreactivity for CD45 and B-cell markers together with the demonstration of light chain restriction. A panel of antibodies including cytokeratins, HMB-45 and S-100, and lymphoid markers is usually appropriate for evaluating aspirates of DLBCL where the differential diagnosis of a nonlymphoid malignancy is considered.

The presence of giant cells in thyroid aspirates raises a differential diagnosis that includes subacute thyroiditis as well as palpation thyroiditis, Hashimoto thyroiditis, papillary thyroid carcinoma (PTC), and nonspecific changes in an adenomatous nodule. Systemic granulomatous diseases such as sarcoidosis, tuberculosis, and foreign-body reactions are also included, but these are rare in the thyroid gland. Correlation between the clinical features and the microscopic pattern of cell types present can usually resolve this differential.

Occasional giant cells can be seen in adenomatous nodules and in palpation thyroiditis. Unlike Hashimoto thyroiditis, subacute thyroiditis usually contains more numerous giant cells and lacks cohesive collections of Hurthle cells, abundant lymphocytes, and lymphohistiocytic aggregates. Importantly, the presence of epithelioid giant cells with their dense cytoplasm raises the possibility of PTC, so this entity should be excluded by searching for epithelial cells with diagnostic nuclear features.

Differential diagnosis of giant cells in thyroid aspirates are as follows:

- Subacute thyroiditis
- Adenomatous nodule with degenerative changes
- Palpation thyroiditis
- Hashimoto thyroiditis
- Papillary carcinoma
- Sarcoidosis
- Tuberculosis
- Foreign-body reaction

Occasionally, aspirates of Hashimoto thyroiditis contain an increased number of follicular cells with oncocytic features, raising the possibility of a Hurthle cell neoplasm. In most cases, background lymphocytes are present and serve as the important clue that the aspirate represents a hyperplastic nodule in Hashimoto thyroiditis. Another feature favoring a hyperplastic nodule over a neoplasm is the arrangement of the follicular cells in cohesive flat, two-dimensional groups rather than as a single cell pattern. In some cases, however, it may not be possible to exclude a Hurthle cell neoplasm, and such cases will be placed into the "Atypia of undetermined significance" category.

Features favoring a hyperplastic nodule in Hashimoto thyroiditis over a Hurthle cell neoplasm are the following:

- Background lymphocytes
- Two-dimensional flat sheets of oncocytic cells
- Absence of a single cell pattern

The differential diagnosis of both acute thyroiditis and Reidel thyroiditis includes undifferentiated carcinoma. In acute thyroiditis, the abundance of neutrophils with background debris, and sometimes even necrosis, can mimic the tumor diathesis of undifferentiated carcinomas. Such aspirates should be carefully screened for malignant epithelial or spindled cells. Aspirates of acute thyroiditis usually lack an epithelial component. In Reidel thyroiditis, the clinical finding of a hard mass with fixation to extrathyroidal structures is also worrisome for undifferentiated carcinoma. The spindle cells in aspirates of Reidel thyroiditis are distinguished from those of undifferentiated carcinoma by their uniformly bland cytologic appearance, absence of mitotic activity, and absence of a background tumor diathesis.

Ancillary Techniques

The most important ancillary study for the evaluation of inflammatory conditions is immunophenotyping to exclude a lymphoma. This is especially important for cases where a low-grade lymphoma, usually MALT lymphoma, is considered in the differential diagnosis. Flow cytometry is probably the most accurate and effective means for obtaining immunophenotypic information. Alternatively, immunocytochemistry can be performed on cell blocks or air-dried cytospins. When combined with ancillary marker studies such as flow cytometry, FNA can be used to diagnose and even subclassify thyroid lymphomas according to the WHO system, which incorporates cytomorphologic features, immunophenotype, and results of molecular studies.

Clinical Management and Prognosis

For cases in which clinical hypothyroidism is present, chronic lymphocytic thyroiditis is managed by thyroid hormone replacement. Approximately 20% of patients with chronic lymphocytic thyroiditis are hypothyroid at presentation, and approximately 5% of the patients who are euthyroid progress to hypothyroidism each year. Surgical intervention is reserved for those cases in which the thyroid is so enlarged that the patient develops compressive symptoms. When dominant nodules or rapid diffuse thyroid enlargement occur in the setting of chronic lymphocytic thyroiditis, FNA is used to rule out the possibility of a neoplastic condition, particularly lymphoma and PTC.

Subacute thyroiditis is a self-remitting painful disorder that in some cases can be associated with hypothyroidism lasting up to several months. Most cases are treated with nonsteroidal antiinflammatory drugs to manage the associated pain, but in some cases the pain is so severe that oral corticosteroid therapy is needed. A small subset of patients will suffer from repeated episodes of subacute thyroiditis, and rarely, surgical intervention is necessary. Reidel thyroiditis is a progressive disorder that may lead to compressive symptoms from involvement of extrathyroidal structures requiring surgical intervention to relieve the tracheal compression.

In contrast to most other inflammatory disorders of the thyroid, acute thyroiditis is a potentially life-threatening illness. It is usually managed by hospitalization and administration of parenteral antibiotics. A delay in the initiation of antibiotic treatment can be fatal. Therefore, rapid and accurate FNA diagnosis of acute thyroiditis is essential, although in many cases acute thyroiditis is diagnosed clinically and FNA is primarily used to obtain material for culture and sensitivity testing.

Primary lymphomas of the thyroid are rare and typically occur in the setting of chronic lymphocytic thyroiditis. Because advances in subclassifying these lymphomas are recent, it is difficult to separate the clinical course of thyroid MALT lymphomas from DLBCL based on published studies. Depending upon the subtype and stage of the lymphoma, some patients may be treated with thyroidectomy alone while other patients are treated with radiotherapy or with combined radiotherapy and chemotherapy. Results of 5-year survival rates range from 13 to 92%, but in most studies the average 5-year survival is 40–60%. Stage at diagnosis appears to be the most important predictive factor, and for those patients in whom the lymphoma is confined to the thyroid gland, the recurrence rate is low.

Suggested Reading

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