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Pulmonary Lymphomas and Other Lymphoproliferative Lesions

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A variety of lymphoid lesions can occur in the lung and involve airways, blood vessels, interstitium, and pleura. Some may present as solitary lesions; others are multifocal or diffuse. Primary and metastatic nonhematopoietic malignancies may mimic lymphoid lesions. The most difficult problem confronting the pathologist is the determination of the benign or malignant potential of certain lymphoid infiltrates. Immunophenotyping may solve some problems, but newer technologies such as *in situ* hybridization, three-color flow cytometry, polymerase chain reaction, and Southern blot analysis for gene rearrangements may be necessary.

Display 55-1 summarizes the lymphoid lesions that involve the lung and other diseases that may present differential diagnostic problems. The standardized and more recently developed technologies used in the evaluation of lymphoid lesions also are reviewed in this chapter.

BRONCHUS-ASSOCIATED LYMPHOID TISSUE

The bronchus-associated lymphoid tissue (BALT) that occurs in some animals has been morphologically and functionally characterized by Bienenstock and colleagues as a part of the mucosa-associated lymphoid tissue (MALT).[1,2] BALT is not detected normally in the human lung; it develops after stimulation (see Chap. 1).[3] Hyperplasia of BALT may occur in chronic bronchitis, cystic fibrosis, chronic granulomatous disease, chronic abscesses, and adjacent to primary and secondary neoplasms (Fig. 55-1).[4] It may also occur in collagen-vascular diseases, especially rheumatoid arthritis, juvenile rheumatoid arthritis, and Sjögren syndrome.[5] If BALT hyperplasia is localized and appears as a nodule, it may be classified as a pseudolymphoma; if it is diffuse and interstitial, lymphocytic interstitial pneumonia (LIP) may be diagnosed.[5] Some pulmonary lymphomas probably arise from BALT.[6]

LYMPHOMAS AND PSEUDOLYMPHOMAS

Most lymphocytic lesions of the lung have been classified as pseudolymphoma, low-grade B-cell lymphoma, small lymphocytic lymphoma, or small lymphocytic proliferations.[7–10] These may present as single or multiple discrete masses, localized infiltrates, or bilateral interstitial infiltrates. In 1983, Koss and colleagues summarized the extensive experience at the Armed Forces Institute of Pathology, and most cases were classified as small lymphocytic proliferations, plasmacytoid lymphocytic lymphoma, or small cleaved follicular center cell lymphoma.[7] In that series, only 14% of the cases were classified as pseudolymphoma.

Table 55-1 summarizes the features Koss and associates found helpful in separating benign from malignant lymphoid lesions (*e.g.*, lymphoma *versus* pseudolymphoma). The light microscopic findings are a modification of Saltzstein's original observations, in which meticulous histologic evaluation and clinical and pathologic correlation were carried out.[11] Although light microscopic features are helpful in some cases, a definitive diagnosis using only light microscopic criteria is difficult in others.[9,12,13] Pseudolymphomas and lymphomas are characterized by proliferations of small lymphocytes, some of which may have prominent plasmacytoid features or plasma cell components. The pulmonary

DISPLAY 55-1. BENIGN AND MALIGNANT LYMPHOID LESIONS OF THE LUNG

Lymphoma and pseudolymphoma
T-cell lymphomas
Angiocentric lymphoid lesions
Lymphocytic interstitial pneumonia
Follicular bronchitis and bronchiolitis
Diffuse panbronchiolitis
Angioimmunoblastic lymphadenopathy
Angiofollicular hyperplasia
Hodgkin disease
Leukemia
Intrapulmonary thymoma
Intrapulmonary lymph nodes
Plasma cell neoplasms
Extramedullary hematopoiesis
Mast cell tumors

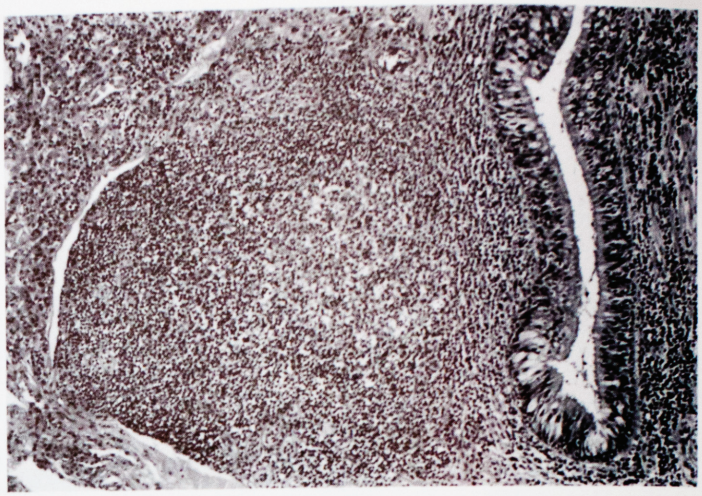

FIGURE 55-1. Hyperplasia of the bronchus-associated lymphoid tissue is present in a patient with cystic fibrosis. (H & E stain; low magnification.)

infiltrates of chronic lymphocytic leukemia are histologically indistinguishable from small lymphocytic lymphoma. Waldenström macroglobulinemia occasionally manifests itself in the lung as lymphoplasmacytic infiltrates that may be patchy or interstitial.[14,15]

In lesions classified as pseudolymphoma and lymphoma, fibrosis may be prominent, as well as germinal centers and small granulomas. In several published series, immunomicroscopy antibodies against κ and λ light chains in paraffin-embedded tissue have shown that some cases originally classified as pseudolymphoma were lymphomas, but the results of this technique were inadequate or inconclusive for many cases.[8–10,16–18] The groups led by Tubbs and Weiss emphasized many of the problems in determining monoclonality in small lymphoid infiltrates using paraffin-embedded tissue.[19,20] The difficulty in making a diagnosis of lymphoma or pseudolymphoma is indicated by the inclusion of the term "small lymphocytic proliferations" in the two large series of Koss and colleagues and Kennedy and associates.[7,9] This difficulty highlights the importance of obtaining fresh tissue for special ancillary immunotypic and genotypic studies of lymphoid lesions of the lung, but it is not clear whether these additional techniques will resolve each diagnostic problem.

Lymphoma and pseudolymphoma may contain follicles with germinal centers, some of which may be reactive (Fig. 55-2).[7,8,10,21] The infiltrate may appear monomorphic, composed predominately of mature lymphocytes, some with plasmacytoid features (Fig. 55-3). The infiltrates may appear nodular. Some investigators have commented on a pattern of distribution along lymphangitic routes.[8] Lymphoid lesions composed predominantly of small lymphocytes usually do not exhibit necrosis. Visceral pleural invasion is uncommon in pseudolymphoma, but it is often seen in lymphoma. Parietal pleural invasion is considered definitive in the diagnosis of lymphoma by Koss and colleagues.[7] Cartilage invasion is suggestive but not diagnostic of lymphoma. Lymphomas occasionally present as endobronchial masses.[22,23]

Other features that may be seen in pulmonary lymphoid proliferations include hyaline sclerosis, giant cells, noncaseating granulomas, amyloid deposition, obstructive pneumonia, organizing pneumonia, hyperplasia of type II pneumocytes, bronchiolitis

TABLE 55-1
Features Useful in the Diagnosis of Pulmonary Lymphomas and Pseudolymphomas

Feature	Lymphomas	Pseudolymphomas
Cytologic malignancy	Present in lymphomas other than those composed of small lymphocytes or plasmacytoid lymphocytes	Never present
Monomorphic infiltrate	Often present (except in PL lymphoma)	Rarely present
Reactive follicles	Often a few present	Often numerous
Pleural invasion (visceral)	Often present	Rarely present
Pleural invasion (parietal)	Infrequently present	Never present
Cartilage invasion	Often present	Occasionally present
Immunologic markers	Monoclonal	Polyclonal
Genotypic markers	Monoclonal or polyclonal	Polyclonal

FCC, follicular center cell; PL, plasmacytoid lymphocytic.
Adapted from Koss MN, Hochholzer L, Nichols PW, Wehunt WD, Lazarus AA. Primary non-Hodgkin's lymphoma and pseudolymphoma of lung: a study of 161 patients. Hum Pathol 1983;14:1024.

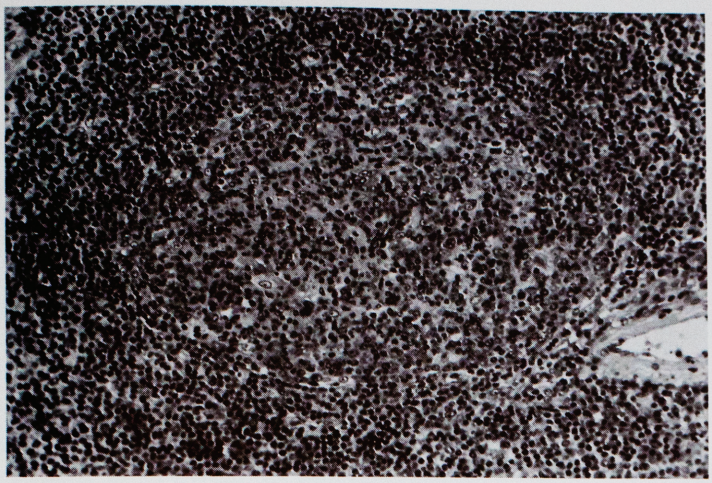

FIGURE 55-2. A lymphoid follicle is seen in a patient with pulmonary pseudolymphoma. (H & E stain; low magnification.)

obliterans, and focal interstitial fibrosis.[7,8] Some of these associated findings may obscure the nature of the lymphoid infiltrate.

The lymphoid infiltrates may be white, tan, or yellow and may be well circumscribed or diffuse.[18] Individual nodules may be as large as 11.0 cm in diameter. In the series of pulmonary lymphomas published by Li and associates, 31% were larger than 5.0 cm in diameter, and in the series of L'Hoste and colleagues, 68% were less than or equal to 6.0 cm in diameter.[10,18] Most lymphomas reported in the larger series occurred in patients in the sixth decade of life.[7–9,18] The male-to-female ratio varied from 1 : 1.73 to 1 : 1.5.[7–9,18] Many of the patients were asymptomatic, with only radiographic abnormalities detected that usually consisted of solitary nodules or multiple nodules; diffuse infiltrates were less common. Regardless of whether lesions composed of small lymphocytes were classified as lymphoma, pseudolymphoma, or small lymphocytic proliferations (*i.e.*, indeterminate for malignancy), the prognosis was good, although many of these patients developed local occurrence or disseminated disease.[7–10,18]

The concept of lymphomas arising in or associated with MALT (*i.e.*, maltomas) has been advocated by Isaacson and colleagues and has been applied to lymphoid lesions of lung and other sites, including the stomach and salivary glands.[6,10,18,21,24–26] These tumors are characterized by relatively homogeneous lymphoid infiltrates that are diffuse but sometimes nodular, and they are composed of small lymphocytes, in some cases with slightly irregular, often indented nuclei (*i.e.*, centrocytelike). Plasmacytoid elements, plasma cells, germinal centers, and lymphoepithelial lesions are common. Some of these lesions have been considered monotypic using immunoperoxidase techniques on paraffin-embedded tissue, but the monoclonal pattern appears to be limited to the plasmacytoid or plasma cell components and not the lymphoid cells. This has led some investigators to conclude that most pseudolymphomas in the lung are actually low-grade lymphomas of BALT, usually B-cell type. Lymphoid lesions initially classified as pseudolymphomas have progressed to overt lymphomas, and low-grade lymphomas have progressed to high-grade lymphomas.[10,12,27] We think that pulmonary pseudolymphoma does exist but is uncommon. The clinicians managing the patients with maltomas must understand the extremely low malignant potential of these lesions to prevent inappropriately aggressive therapy where none is indicated. The problem is confounded by the fact that some cases diagnosed as low-grade B-cell lymphoma of BALT have failed to show monotypic staining for light chains.[10]

Lymphomas other than low-grade lymphocytic or lymphocytic-plasmacytic types have been diagnosed in the lung and include a wide variety of types within the International Working Formulation.[28] Other types of lymphoma that occur in the lung are difficult to fit into the classification (Display 55-2).[29]

Less commonly, lymphomas that are not composed predominantly of small lymphocytes occur in the lung.[7–10,18] Depending on the classification used, these lymphomas include follicular center cell lymphomas, immunoblastic sarcoma, and other high-grade lymphomas (Fig. 55-4). Compared with the cases composed predominantly of small lymphocytes, these lymphomas tend to be persistent or have early recurrences with a higher death rate. The lymphoma may recur in the ipsilateral or contralateral lung, and dissemination may involve regional or systemic lymph nodes. Primary and metastatic nonhematopoietic neoplasms may mimic these lymphomas.

With the possible exception of the BALT-associated lymphoma, it is usually not possible to determine whether a lymphoma involving the lung is primary or secondary without clinical data, such as a history of previous lymphoma or information

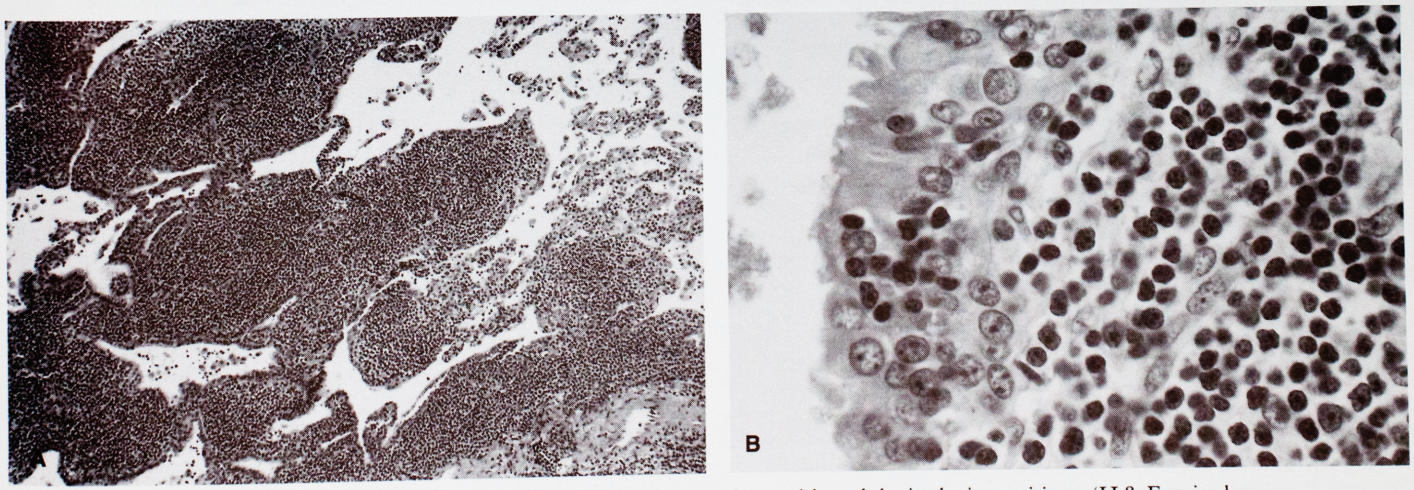

FIGURE 55-3. (**A**) Small lymphocytic lymphoma of the lung with nodules in the interstitium. (H & E stain; low magnification.) (**B**) Small lymphocytic lymphoma infiltrating the respiratory epithelium. (H & E stain; intermediate magnification.)

DISPLAY 55-2. LYMPHOMAS NOT EASILY CONFORMED TO THE WORKING CLASSIFICATION

Low-grade B-cell lymphoma of mucosa-associated lymphoid tissue
Lymphocytic lymphoma of intermediate differentiation
Mantle zone lymphoma
Monocytoid B-cell lymphoma
B-cell lymphoma with prominent infiltrating T lymphocytes (*i.e.*, T-cell–rich B-cell lymphoma)
T-cell lymphoma with prominent histiocytes

From the Non-Hodgkin's Lymphoma Pathologic Classification Project. National Cancer Institute sponsored study of classifications of non-Hodgkin's lymphomas. Summary and description of a working formulation for clinical usage. Cancer 1982;49:2112.

obtained from staging procedures. In the past, a prerequisite for the diagnosis of primary pulmonary lymphoma was a thorough search for involvement of extrathoracic sites of origin, but some investigators feel that primary lymphoma should be diagnosed if the patient presents with predominantly pulmonary manifestations. Extrathoracic lymphomas may develop in some patients with pulmonary lymphomas, especially the small lymphocytic type, including maltomas; however, these cases probably represent the development of a second lymphoreticular malignancy. Common sites of extrathoracic lymphomas occurring in patients with pulmonary lymphomas are the stomach and salivary glands.[10]

Lymphomas may present with diffuse bilateral infiltrates similar to LIP.[9,21] This pattern may be observed at the margin of a nodule or mass. Lymphomas may be angiocentric, which in the past led to confusion with lymphomatoid granulomatosis.[8,9,18,30]

T-Cell Lymphomas

Most lymphomas that have been immunophenotyped are of B-cell lineage, but a few are T-cell malignancies (*i.e.*, peripheral, postthymic).[7,10,20] Peripheral T-cell lymphomas are morphologically heterogeneous. Suchi and associates classified T-cell lymphomas based on cytologic criteria as low grade or high grade.[31] They found that the adult T-cell leukemias or lymphomas associated with the human T-cell leukemia virus-1 (HTLV-I) were predominantly high grade. Lymphomas exhibiting clear cell features were predominantly T-cell in origin. Pinkus and colleagues classified peripheral T-cell lymphomas as small lymphocytic, mixed small and large cell, large cell, lymphoepithelioid cell, angiocentric, and adult T-cell leukemia-lymphoma type.[32] They found that some cases had angioimmunoblastic or Hodgkin-like features. Although presentation in lymph nodes was more frequent, most patients demonstrated extranodal involvement during the course of their illness including the lung. In patients with pulmonary involvement, angiocentricity was a prominent feature. Seventeen percent of the cases evaluated demonstrated aberrant loss of one or more pan-T-cell markers. Poor survival was associated with mixed, large cell, angiocentric, and adult T-cell leukemia-lymphoma cases.

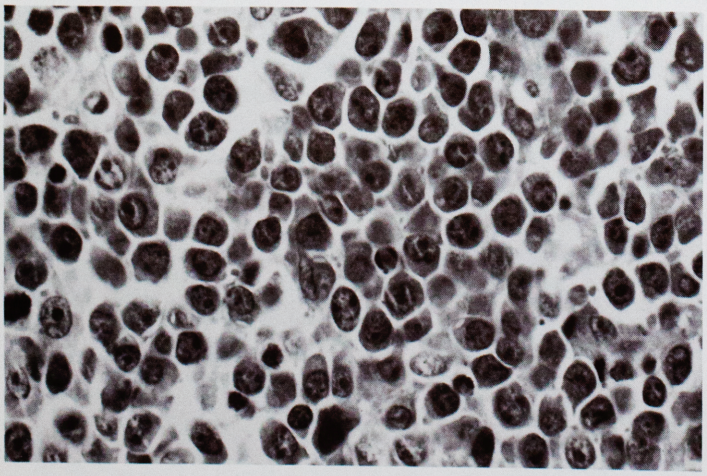

FIGURE 55-4. The large cell immunoblastic lymphoma of the lung has malignant cells exhibiting enlarged nuclei, prominent nucleoli, and abundant cytoplasm. (H & E stain; high magnification.)

Angiocentric Lymphoid Lesions

Primary and secondary lymphomas with definite atypia may infiltrate blood vessels to such an extent that they may be called angiocentric.[30,33] These lesions include lymphomatoid granulomatosis, benign lymphocytic angiitis and granulomatosis, and angiocentric lymphoma.

Lymphomatoid granulomatosis was initially thought to represent an inflammatory process or to share features of Wegener granulomatosis and lymphoma.[34,35] There is evidence that lymphomatoid granulomatosis represents a T-cell lymphoma.[36,37] It usually involves the lung, but extrapulmonary infiltrates or mass lesions may occur in the central nervous system, skin, or other organs.[35]

A smaller number of cases involving pulmonary vessels with bland lymphoid infiltrates, little cytologic atypia, and associated plasmacytoid lymphocytes and plasma cells were originally described by Saldana and associates and designated benign lymphocytic angiitis and granulomatosis.[33,37,38] The angiocentric component of the lesion consists primarily of T cells, and the lymphoplasmacytic areas reflect hyperplasia of BALT are composed predominantly of B cells.

The subdivision of angiocentric proliferative lesions into three categories, similar to benign lymphocytic angiitis and granulomatosis, lymphomatoid granulomatosis, and angiocentric lymphomas has been proposed by Lipford and associates.[39] Grade 1 in their scheme is similar to benign lymphocytic angiitis and granulomatosis (Fig. 55-5), although the former has been expanded to include cases with extranodal involvement of skin, kidneys, lung, upper respiratory system, central nervous system, and peripheral nervous system. Grade 2 probably embraces most cases of lymphomatoid granulomatosis. Grade 3 are lymphomas that are recognized as malignant by cytologic criteria. Grade 2 lesions may progress to overtly cytologically malignant lymphoma and complete remission is unusual. There may be complete remission after therapy for grade 3 lesions.

Many grade 2 lesions, most of which are probably equivalent to lymphomatoid granulomatosis, have been found to be T-cell proliferations. Grade 1 lesions consist predominantly of small lymphocytes, and grade 2 lesions consist of a polymorphic infiltrate consisting of small lymphocytes, plasma cells, macrophages, and larger pleomorphic lymphoid cells producing angioinvasion and angiodestruction (Fig. 55-6). Grade 3 lesions may represent any type of lymphoma involving lung. Mederios and colleagues

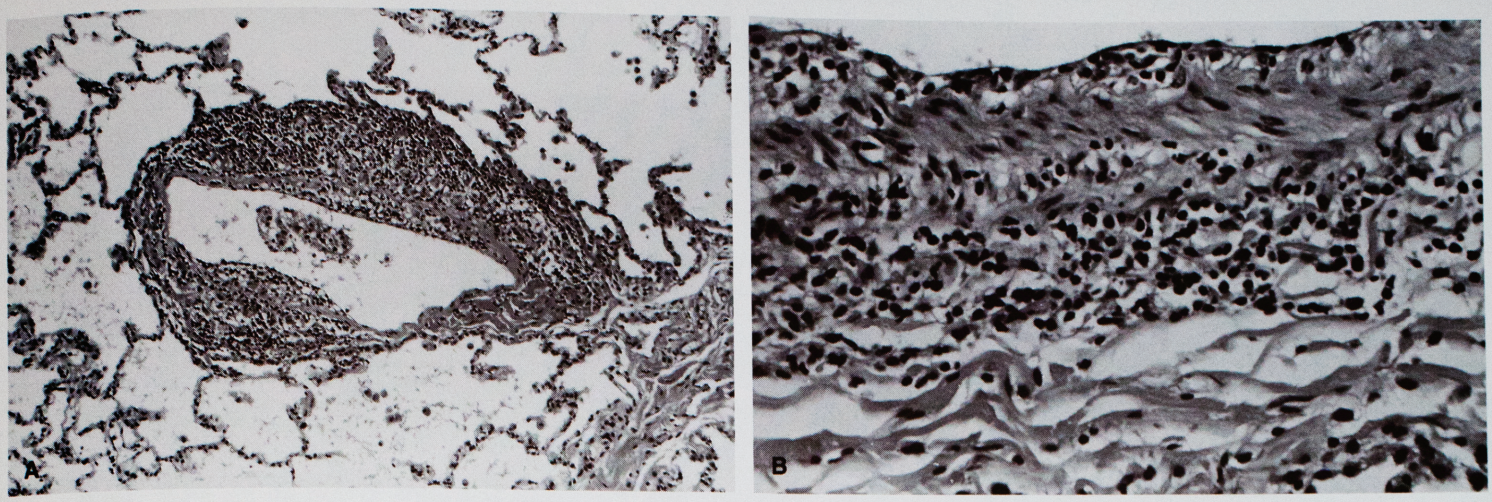

FIGURE 55-5. (**A**) In benign lymphocytic angiitis and granulomatosis, a vascular infiltrate of lymphocytes involves a pulmonary vessel. (H & E stain; low magnification.) (**B**) Small lymphocytes without atypia are present in the muscular wall and intima. (H & E stain; intermediate magnification.)

reported molecular analysis of eight cases of angiocentric immunoproliferative lesions and demonstrated only one case of grade 3 lymphoma with a clonal gene rearrangement of the T-cell receptor.[40] Analysis revealed a frequent association with Epstein-Barr genomes.

Angiotrophic Lymphomas

Another type of lymphoma that involves blood vessels is the angiotropic lymphoma, also called intravascular lymphomatosis. It was previously thought to be a malignant proliferation of endothelial cells and referred to as malignant angioendotheliomatosis.[41,42] Patients with angiotropic lymphoma may present with symptoms and signs related to the involvement of central nervous system, skin, or lung. Characteristic features are proliferation of neoplastic mononuclear cells within luminal vascular channels. Immunomicroscopic and genotypic studies have demonstrated the lymphoid nature of the vascular infiltrate in most cases to be B cell in origin; a few samples displayed a T-cell phenotype.[42]

LYMPHOCYTIC INTERSTITIAL PNEUMONIA

LIP is a chronic interstitial pneumonia characterized by interstitial infiltrates composed of small lymphocytes and plasma cells (Fig. 55-7). Plasma cells may be prominent. In some cases, small, poorly formed granulomas are found.[43] Lymphoid follicles may be observed. Some cases progress to diffuse interstitial fibrosis. Some cases appear to be idiopathic, and some arise in patients with dysproteinemia, collagen-vascular autoimmune diseases (especially Sjögren syndrome), or immunodeficiency states (see Chap. 32).[43–46]

LIP has been detected in patients, predominantly children, with the acquired immunodeficiency syndrome (AIDS; see Chap. 45).[47–49] Patterns similar to LIP occur in patients with extrinsic allergic alveolitis, drug reactions, bone marrow allograft recipients, and lung allografts undergoing cellular rejection (see Chap. 71). The question of whether LIP represents lymphoma rather than a benign reactive process has been addressed by some investigators,

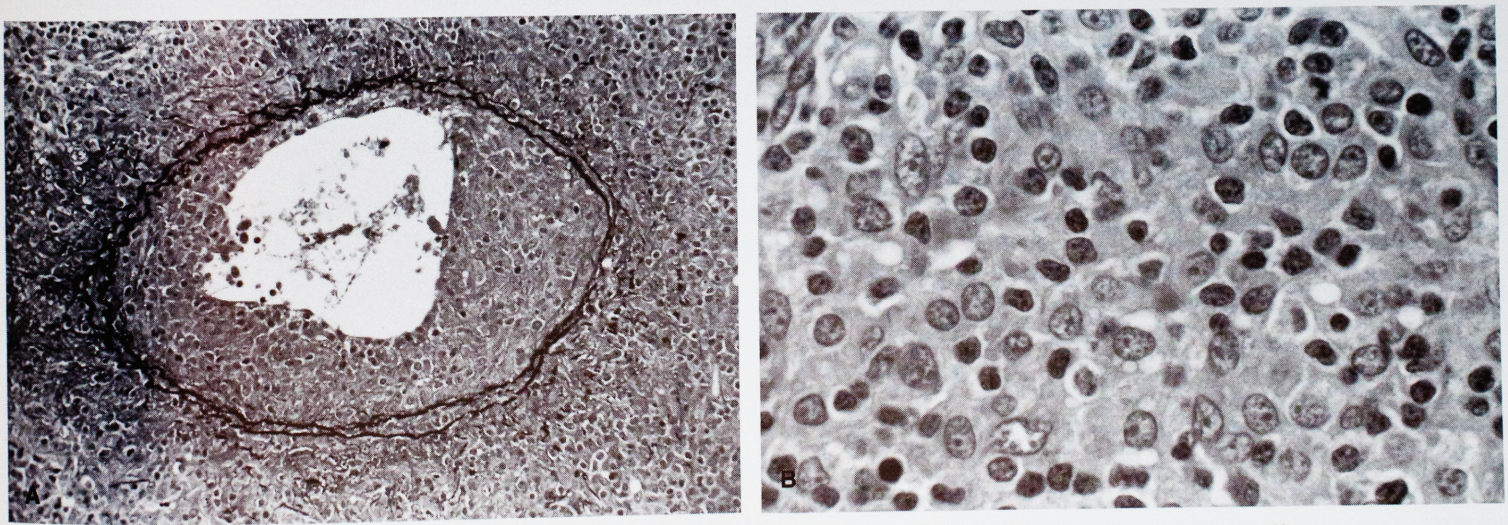

FIGURE 55-6. (**A**) Lymphomatoid granulomatosis of the lung with angiocentric infiltrates. (Verhoeff van Gieson stain for elastic tissue; intermediate magnification.) (**B**) Lymphomatoid granulomatosis of the lung with an infiltrate consisting of small lymphocytes and larger, more pleomorphic lymphoid elements. (H & E stain; high magnification.)

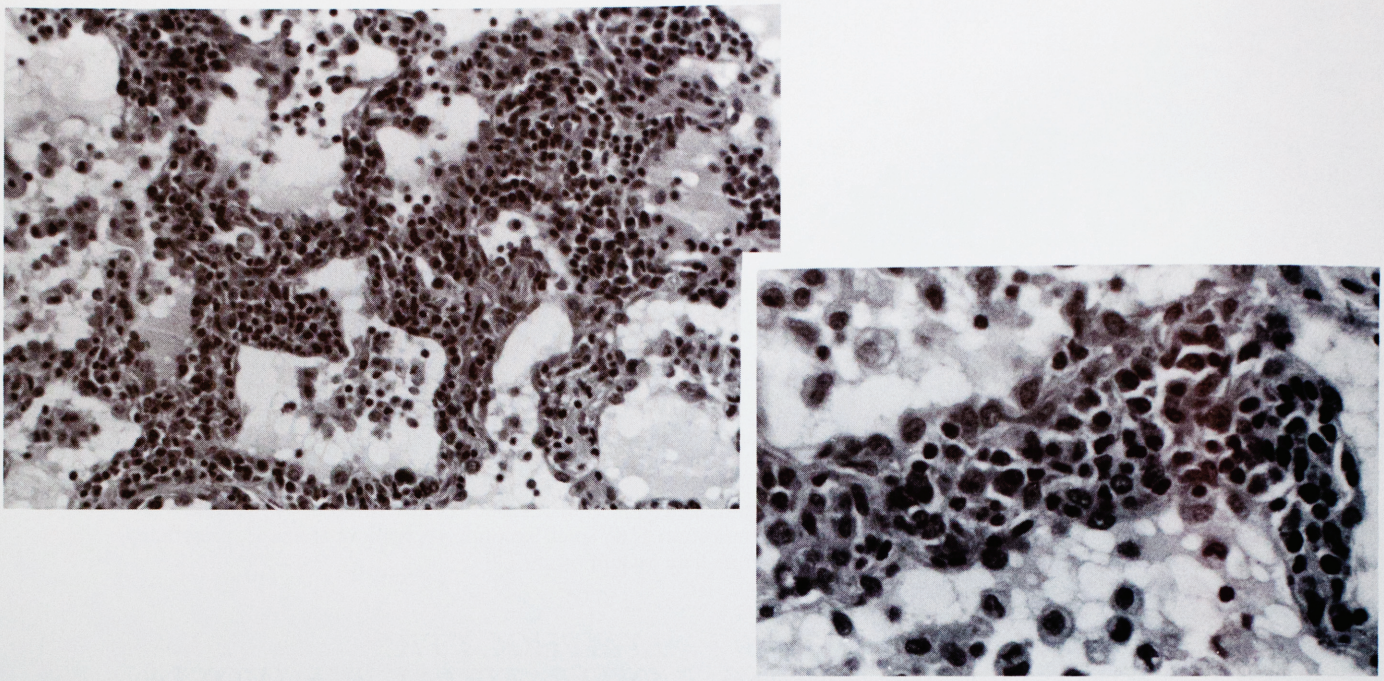

FIGURE 55-7. Lymphocytic interstitial pneumonia with rich infiltrate of lymphocytes and plasma cells. (H & E stain; low magnification.) Detail of the cellular infiltrate can be seen at higher magnification (*inset*). (H & E stain; intermediate magnification.)

but a only a small number of cases have been evaluated by immunomicroscopic methods.[50] For cases in which the lymphocytic infiltrate is monoclonal or exhibits prominent atypia, the diagnosis of lymphoma seems to be justified.

The LIP pattern may be present at the periphery of lymphomas that are predominantly nodules or masses, and cases of LIP have evolved into overt malignant lymphomas.[51,52] LIP does not always respond to therapy, which usually consists of corticosteroids or immunosuppressive agents.

FOLLICULAR BRONCHITIS AND BRONCHIOLITIS

Follicular bronchitis and bronchiolitis is characterized by large lymphoid follicles with reactive germinal centers adjacent to airways in the absence of clinical or pathologic evidence of bronchiectasis (Fig. 55-8). The process is diffuse and bilateral, with radiographic reticulonodular infiltrates. It may occur in patients with collagen-vascular diseases, especially rheumatoid arthritis and Sjögren syndrome, in those with immunodeficiency syndromes, and in patients with peripheral blood eosinophilia, suggesting hypersensitivity (see Chap. 30).[53] Steroid therapy produces inconsistent results.

Histologically, abundant hyperplastic follicles with germinal centers are adjacent to and produce compression of airways. The infiltrates frequently extend into bronchiolar epithelium. Lymphoid hyperplasia is observed along the intralobular septa, subpleural regions, and lymphatics, particularly in immunodeficient patients. The cellular infiltrate is characterized by lymphocytes and plasma cells. Suppurative exudates within the airways is observed in approximately one half of the patients. In a few patients, bronchiolitis obliterans and vascular inflammation have been observed. The finding of follicular bronchitis and bronchiolitis should lead the clinician to investigate the possibility of bronchiectasis, cystic fibrosis, collagen-vascular diseases, immunodeficiency states (*e.g.*, AIDS), and hypersensitivity.

DIFFUSE PANBRONCHIOLITIS

Diffuse panbronchiolitis is a disease largely restricted to Japan and manifested clinically by dyspnea, cough, and mucopurulent sputum.[54] Histologically, it is characterized by a suppurative bronchiolitis involving respiratory and terminal bronchioles with subsequent progression to bronchioloectasis. A few cases have been reported in North America.[55] The involved bronchioles and adja-

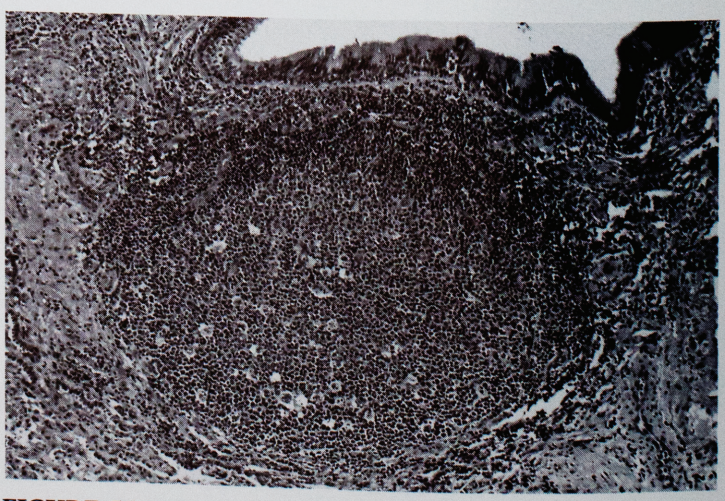

FIGURE 55-8. Follicular bronchitis or bronchiolitis with prominent lymphoid follicle associated with an airway. (H & E stain; low magnification.)

cent alveolar septa are infiltrated by neutrophils, lymphocytes, plasma cells, and histiocytes. There are no eosinophils, and there usually are no giant cells or granulomas. The inflammatory infiltrate may be intense, but blood vessels are spared (see Chap. 30).

Unlike follicular bronchitis and bronchiolitis, lymphoid follicles are not prominent in diffuse panbronchiolitis. The lumen of the involved bronchioles contain mucus and an acute inflammatory exudate. Many patients have associated chronic sinusitis. Other associated conditions include ulcerative colitis, allergic angiitis and granulomatosis, adult T-cell lymphoma, and non-Hodgkin lymphoma. Because lymphoma may infiltrate airways, it should be excluded before the diagnosis of follicular bronchitis and bronchiolitis or diffuse panbronchiolitis is rendered.

ANGIOIMMUNOBLASTIC LYMPHADENOPATHY

Angioimmunoblastic lymphadenopathy usually involves the lymph nodes and is characterized by a proliferation of arborizing small vessels, prominent immunoblasts, and amorphous acidophilic interstitial material.[56] Constitutional symptoms include fever, sweats, weight loss, rash, and generalized lymphadenopathy and hepatosplenomegaly.[56] The samples from the initial biopsies may appear benign, but in some cases, there is progression to immunoblastic sarcoma.[56,57] A few cases have been reported in which this process involved the lung.[58,59]

ANGIOFOLLICULAR HYPERPLASIA

Angiofollicular hyperplasia (*i.e.*, Castleman disease) frequently involves intrathoracic lymph nodes and may be multicentric. A few cases of intrapulmonary angiofollicular hyperplasia have been reported, but it is distinctly uncommon.[60] There are two histologic types: hyaline-vascular, characterized by small hyalinized vascular follicles and intrafollicular capillary proliferation, and plasma cell, characterized by large follicles with intervening sheets of plasma cells.[60] The latter type is associated with systemic manifestations, including fever, anemia, and hypergammaglobulinemia. The plasma cell variant may exhibit monoclonal or polyclonal features when evaluated by immunomicroscopy for light chains, but this does not appear to be of prognostic significance.[61] Malignant lymphoma may supervene in some cases.[62]

HODGKIN DISEASE

Secondary Hodgkin disease involving the lung is much more common than primary Hodgkin disease of the lung.[63] Secondary Hodgkin disease may extend from the mediastinum to involve adjacent pulmonary parenchyma and airways. Multifocal pulmonary Hodgkin disease may rarely be found at the initial evaluation of Hodgkin disease, or it may occur during relapse. Secondary Hodgkin disease in extranodal sites such as the lung (Fig. 55-9) may not contain classic Reed-Sternberg cells, which are not required for diagnosis.[64] Eosinophils may be prominent, and the case may be mistaken for eosinophilic pneumonia or eosinophilic granuloma. Granulomas may be prominent in lymph nodes in patients with Hodgkin disease whether they are involved by tumor or not. Small, loose granulomas may be observed, especially in lymph nodes and in extranodal sites. In cases of prominent granuloma formation, Hodgkin disease may be overlooked.

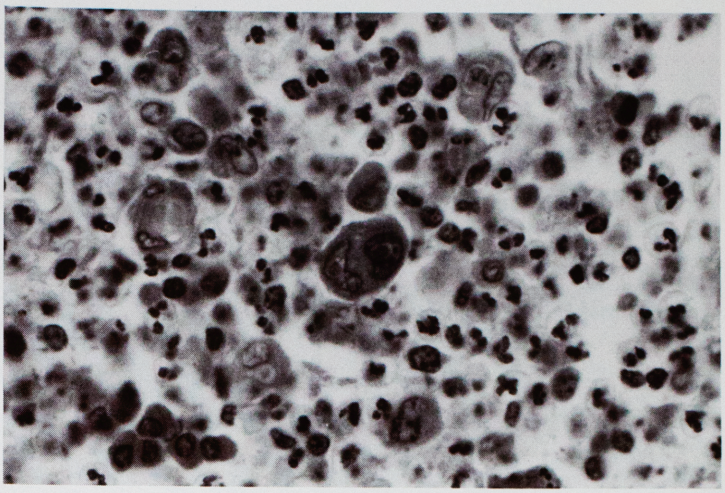

FIGURE 55-9. Hodgkin disease in the lung is indicated by a Reed-Sternberg cell surrounded by numerous neutrophils and plasma cells. (H & E stain; intermediate magnification.)

Most cases of primary pulmonary Hodgkin disease are case reports or small series. The largest series of primary Hodgkin of the lung was reported by Yousem and associates and included 15 patients.[63] The female-to-male ratio was 2 : 1, most patients were asymptomatic, and the chest radiographs frequently demonstrated one or multiple nodules in the lung. The microscopic findings of primary pulmonary Hodgkin disease were similar to those for lymph node involvement. Some patients may present with endobronchial involvement.[65]

LEUKEMIA

Most patients with leukemia develop pulmonary infiltrates during the course of the disease. Leukemic infiltrates are, however, uncommonly diagnosed during life.[66] In the clinical and radiologic differential diagnosis of leukemic involvement of lung, the following should be included: infections, chemotherapy effect, radiation effect, hemorrhage, heart failure with congestion and pulmonary edema, and diffuse alveolar damage.[67,68] In open biopsies for the evaluation of pulmonary infiltrates in leukemic patients, identification may be difficult if leukemic cells are sparse and may be overlooked (Fig. 55-10).

Chronic lymphocytic leukemia is the most frequent type of leukemia identified in lung biopsies.[69] It typically is perivascular or interstitial, but it may diffusely infiltrate bronchioles, presenting as small airway disease with obstruction.[70] Pulmonary infiltrates are common in adult T-cell leukemias.[71] In the acute leukemias, there may be severe pulmonary manifestations if the blast count is high, probably because of pulmonary leukostasis.[72,73] Diffuse alveolar damage may be secondary to lysis of leukemic cells by chemotherapy.[74] Nodule or mass formation by leukemic infiltrates is unusual.[66]

Granulocytic sarcomas may present in a variety of sites, including lung and thoracic lymph nodes, even before the develop-

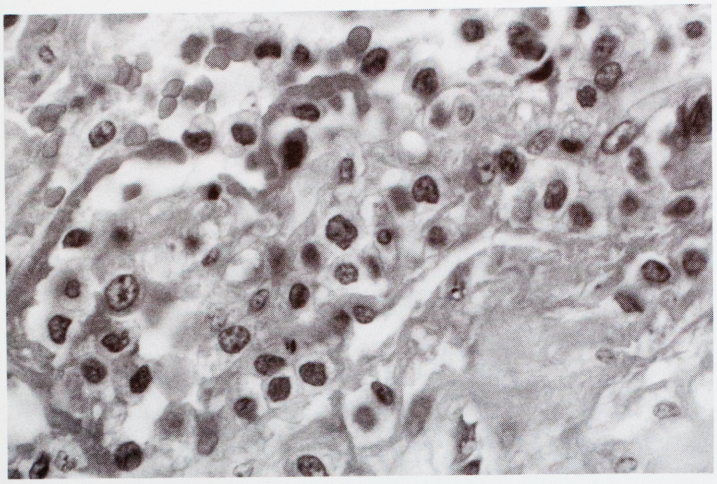

FIGURE 55-10. Acute myelomonocytic leukemia involving the lung; hyaline membranes are evident. (H & E stain; high magnification.)

ment of overt acute myelogenous or myelomonocytic leukemia.[75–78] Eosinophilic myelocytes should be searched for diligently. Without the aid of immunohistochemical evaluation, the differential diagnosis may be difficult. Detection of myeloid cytoplasmic differentiation antigens, lysozyme (muramidase), myeloperoxidase, and naphthol-ASD-chloroacetate-esterase are also helpful.[79–80]

MISCELLANEOUS CONDITIONS THAT MIMIC LYMPHOID INFILTRATES OF THE LUNG

Malignant Histiocytic Neoplasms

True malignant histiocytic neoplasms are uncommon and are usually classified as true histiocytic lymphoma or, if disseminated, as malignant histiocytosis; they may involve lung.[81–84] Many of these neoplasms exhibit extreme pleomorphism, and the diagnosis of malignant histiocytosis or true histiocytic lymphoma may not be considered. Histochemistry, immunomicroscopy, and electron microscopy help in the diagnosis of these neoplasms.

Intrapulmonary Thymoma

Thymomas may be intrapulmonary without associated mediastinal mass.[85,86] They may present as a mass lesion, as endobronchial masses or as pleural tumors.[87,88] The diagnosis may be difficult in small biopsy specimens. The cases reported in the literature exhibited typical microscopic features of thymoma. In patients with thymomas presenting as lung or pleural tumors, thymoma can be misdiagnosed as lymphoma unless the possibility of thymoma is considered. The immunophenotypic detection of CD1 (T6) in the lymphoid population and demonstration of epithelial cells and their cytoplasmic processes with antibodies to cytokeratin may provide corroborative data (see Chap. 74).

Intrapulmonary Lymph Nodes

Intrapulmonary lymph nodes are usually excised as a pulmonary nodule to exclude neoplasm. They are usually subpleural and may be multiple. The lymph nodes may be hyperplastic, and many exhibit prominent carbon deposition and crystals compatible with silicates.[89]

Plasma Cell Neoplasms

Extramedullary plasmacytomas may occur in the lung but are uncommon (Fig. 55-11).[90,91] Plasma cell infiltrates may occur in patients with established multiple myeloma. The plasma cell neoplasms usually are not clinically significant but may present with multiple nodules. In patients presenting with extramedullary plasma cell neoplasms, dissemination with the development of multiple myeloma eventually may occur.[90] Associated deposits of amyloid, nodular deposits of immunoglobulin, deposits of crystalline material, and ossification have been reported in patients with plasma cell neoplasms or plasma cell infiltrates associated with multiple myeloma.[92–94]

Included in the differential diagnosis of plasmacytomas are plasma cell granulomas and lymphoid infiltrates with plasmacytoid features, including lymphomas. Some plasma cell neoplasms are relatively undifferentiated, and the plasma cell nature of the infiltrate may be difficult to establish. Immunohistochemical and ultrastructural studies may be helpful in these cases.[95] In contrast to non-Hodgkin lymphomas, which cannot be reliably immunophenotyped in paraffin-embedded tissue, immunoglobulin in the plasma cells of plasmacytoma and plasma cell myeloma is readily detected in paraffin-embedded tissue.

Extramedullary Hematopoiesis Involving the Lung

Extramedullary hematopoiesis of the lung is rare.[96] More common sites include the liver, spleen, and lymph nodes. Extramedullary hematopoiesis frequently occurs in myeloproliferative disorders, thalassemia, and carcinomatosis. If the possibility of extramedullary hematopoiesis of the lung is kept in mind, the diagnosis is usually straightforward, but if the mixture of erythroid and megakaryocytic elements is overlooked, the erroneous diagnosis of myelocytic leukemia or of myelocytic sarcoma may be made.

Mast Cell Tumors

Mast cell tumors of the lung are rare, especially if solitary.[97] The diagnosis may be especially difficult if the granules are not prominent. The pale cells in mast cell tumors resemble sclerosing hemangioma of lung, which should be considered in the differential diagnosis (see Chap. 58). Mast cell infiltrates may be mistaken for

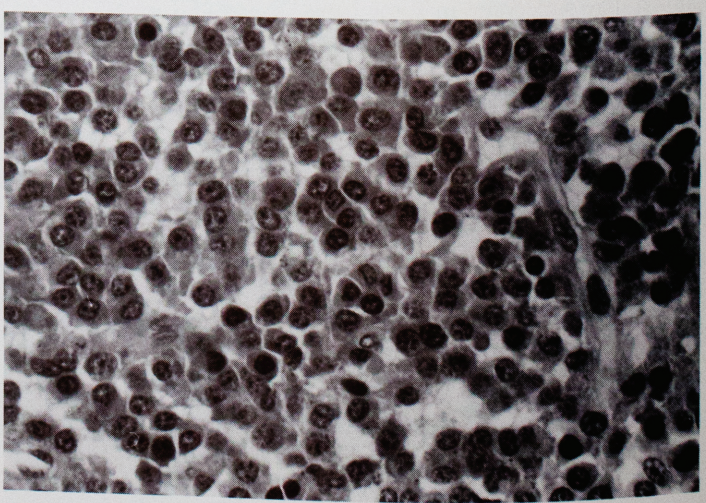

FIGURE 55-11. In pulmonary plasmacytoma, numerous plasma cells are easily recognizable. (H & E stain; high magnification.)

lymphoid neoplasms. The Giemsa stain modified for the detection of mast cells is helpful in evaluating these tumors.

EVALUATION OF LYMPHOPROLIFERATIVE DISORDERS

Display 55-3 summarizes the salient methodologic points in the laboratory evaluation of lymphoid lesions. The variety of technologies do not obviate the importance of clinical history, review of previous pathologic material, and optimal quality of hematoxylin and eosin–stained sections of paraffin-embedded material. Light microscopic evaluation must be incorporated with the results of other laboratory investigations.

Frozen section control is important to ensure adequacy of the sample and to determine the optimal method of evaluation. Ideally, there should be adequate tissue available for evaluating fresh, frozen, and paraffin-embedded specimens. Material should be saved for electron microscopy, because it may be necessary in difficult diagnostic cases, and for flow cytometry, Southern blot analysis, immunomicroscopy, *in situ* hybridization, and routine hematoxylin and eosin–stained sections. For most lymphoproliferative disorders, immunomicroscopy can be conducted in a reliable and cost-effective fashion on paraffin-embedded tissue for determining T- and B-cell lineage (Color Fig. 55-1), but it cannot provide accurate information about clonality in most cases.[98] We recommend the use of B-5 fixative and 10% neutral buffered formalin. The initial antigens evaluated should include those for B cells and T cells (*i.e.*, CD43, CD45RB, CD20). In most cases, the overall immunophenotype can be determined using this approach. If this does not yield definitive results, other antibodies that are active in paraffin-embedded tissue may be evaluated, but it is important to have frozen tissue available, because many monoclonal antibodies directed against lymphocyte differentiation antigens are optimally active in frozen tissue; clonality cannot be reliably assessed in paraffin sections.[19,20,95]

Tissue that is fresh or frozen may be used for Southern blotting in the evaluation of gene rearrangement to determine the clonality of B-cell and T-cell proliferations or multicolor flow cytometry and cytospin immunocytology.[99–105] Sample size and ice artifact have been found the two most important factors in evaluation.[102] Evaluation of the κ and λ light chain V-region subgroups by immunocytochemistry analysis of cytospin preparations has been advocated.[106] Frozen tissue and tissue embedded in paraffin may be evaluated by *in situ* hybridization.[107]

The polymerase chain reaction can increase the yield of Southern blot analysis of lymphoid tissue for the detection of T-cell receptor gene rearrangement.[108–110] The rapid-cycle polymerase chain reaction has been used to evaluate immunoglobulin gene rearrangements.[111] These technologies are rapidly evolving and should continue to be evaluated by careful clinical and histologic correlation. Ideally, the results of immunomicroscopy, *in situ* hybridization, Southern blotting, and three-color flow cytometry should be correlated. Caution should be exercised in overinterpreting an individual test result.

The current situation may be analogous to the cautions raised by Tubbs and colleagues and Warnke and Rouse with respect to interpreting the early results of immunomicroscopy using frozen and paraffin-embedded tissues.[91,113] In the extensive study by Chen and colleagues, the results of gene rearrangement analysis and immunophenotyping were correlated.[103] One subgroup of patients in this series had lymphomas immunotyped as B-cell lymphomas that also demonstrated T-cell receptor β-chain rearrangements. Problems can arise in the interpretation of biclonal B-cell lymphomas, T-cell–rich B-cell lymphomas, histiocyte-rich B-cell lymphomas, and lymphohistiocytic T-cell lymphomas.[113–118]

Lymphoid lesions composed of small lymphocytes with or without plasmacytoid features offer a challenge in determining monoclonality or polyclonality of extranodal proliferations. The predominance of κ or λ light chains in an infiltrate is easier to evaluate in fresh tissue than in paraffin-embedded tissue (Color Fig. 55-2). The immunoglobulin of the cells of the infiltrates that contain a prominent plasmacytoid or plasma cell component can be phenotyped in paraffin sections. Interpretation of the immunomicroscopic results of κ or λ light chain staining of paraffin wax-embedded material characterized by small lymphocytic proliferations is more problematic than using frozen tissue and is unreliable. Even frozen-tissue immunomicroscopy should be interpreted with caution.[19,112]

If small lymphocytic infiltrates have no associated plasmacytoid features or plasma cells, the yield for monoclonal features is low compared with polyclonal features. In dealing with this type of small lymphocytic infiltrate, the differential diagnosis usually is lymphoid hyperplasia, pseudolymphoma, or a small lymphocytic lymphoma. Three-color flow cytometry requires fresh tissue, Southern blotting for gene rearrangements requires fresh or frozen tissue, and *in situ* hybridization for messenger RNA requires frozen or paraffin-embedded tissue; any of these analyses may be definitive.[107] The goal of assigning each case a diagnosis of malignancy (*e.g.*, lymphoma) or nonmalignancy (*e.g.*, pseudolymphoma) may not be attainable, even with the variety of technologies available.[98]

DISPLAY 55-3. TECHNIQUES FOR EVALUATING LYMPHOPROLIFERATIVE DISORDERS

Frozen section control

Fresh tissue
- Three-color flow cytometry
- Cytospins
- Southern blot analysis
- Polymerase chain reaction

Frozen tissue
- Immunomicroscopy
- *In situ* hybridization
- Southern blot analysis
- Polymerase chain reaction

Paraffin-embedded tissue (*i.e.*, formalin and B-5 fixatives)
- Optimal hematoxylin and eosin–stained sections 2 μm thick
- Histochemical stains
- Immunomicroscopy
- *In situ* hybridization

Electron microscopy

LYMPHOID LESIONS IN PATIENTS WITH ALTERED IMMUNE STATUS

The spectrum of lymphoid proliferation associated with AIDS has already been described in Chapter 45. Important pulmonary lymphoid processes also are observed in patients with collagen-vascular autoimmune diseases (see Chaps. 31 and 67). This section concentrates on lymphoproliferation and the role of Epstein-Barr virus (EBV) in transplant patients.

The incidence of lymphoproliferative disorders in patients who receive organ transplants has increased with the introduction of cyclosporin A as an immunosuppressive agent.[119] These disorders may be nodal or extranodal, may occur within a relatively short time period following transplantation, and may also involve the transplanted organ, including transplanted lungs.[120] Pulmonary involvement may be the primary manifestation of lymphoproliferative disorders. The majority of these disorders are composed of B cells. Some lymphoproliferative disorders may regress with a decrease in the dosage of cyclosporin, but therapy with immunosuppressive agents may be required.[119,121] The spectrum of disease may range from B-cell hyperplasia to malignant lymphoma.[122,123] These lesions may be monoclonal, oligoclonal, or polyclonal, as identified by cell-marker or gene-rearrangement studies.[122,124] In many cases, EBV virus genes, antigens, and proteins have been identified in the proliferating lymphoid elements.[122,123,125,126]

EBV genes, antigens, and proteins have been detected in patients with B-cell or T-cell lymphoproliferative diseases,[122,127] including non-Hodgkin lymphoma and Hodgkin disease[127–130]; in patients with AIDS (see Chap. 45); in patients with congenital immunodeficiency states[128,129,131]; in lymphoproliferative lesions in allograft recipients[122,123,125,126]; and in a minority of non-immunocompromised patients.[132] These elements have also been demonstrated in angiocentric lesions.[40] Pulmonary lymphoplasmacytic infiltrates may occur in patients with acute EBV infection.[133,134]

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