CHAPTER 31

Lymphoproliferative Diseases

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Lymphoreticular diseases affecting the lung include primary and secondary lymphomas and related disorders, leukemias, and a number of lesions that are generally considered benign and hyperplastic processes. Pseudolymphoma, lymphocytic interstitial pneumonia, small (well-differentiated) lymphocytic lymphomas, and lymphomatoid granulomatosis have long been difficult lesions for pathologists.[1–5] Lymphomatoid granulomatosis, with its synonyms,[6–8] has been considered by some to be a peculiar vasculitis and by others a lymphoproliferative disorder, with the latter being the prevailing view.[8]

Classically, lymphomas comprise a monomorphous population of atypical lymphoid cells manifesting as clinically aggressive neoplasms. An immunologic definition of a lymphoma has recently been accepted: a clonal proliferation of lymphoid cells that in many cases can be identified with immunologic marker studies and subclassified as T or B lymphocytic or true histiocytic in origin.[9] The clinical and histologic spectrum of lymphomas has broadened considerably to include lesions that pursue a very indolent clinical course and those with a polymorphous cellular composition.

Normal Lymphoid Tissue and Lymphatic Routes of the Lung

Understanding the histology of lymphoreticular infiltrates in the lungs requires knowledge of the normal lymphatic routes and lymphoid tissue of the lung. The lymphatic routes are found along the bronchovascular bundles, the pulmonary veins, and in the septa and pleura.[10,11] The lymphatics themselves are barely discernible in normal lungs but are easily recognized in pathologic states such as pulmonary edema and passive congestion. Lesions that tend to show a distribution along the lymphatic routes include lymphoreticular infiltrates, lymphangitic carcinoma, sarcoidosis, and some pneumoconioses, the last reflecting lymphatic drainage of the inhaled dust.

Hilar and peribronchial lymph nodes are present in all individuals, but intrapulmonary lymph nodes are uncommon. *Intrapulmonary lymph nodes* are usually incidental findings in lobectomy specimens or at autopsy. In one study of 10 clinically recognized cases, all were adult, all were smokers, and 80% were men.[12] Intrapulmonary lymph nodes are usually below the level of the carina, well circumscribed, and less than 2 cm in diameter, and are located close to the pleura or a septum; they may be multiple, are usually anthracotic, and may contain or coexist with silicotic nodules.[12]

Bienenstock and others[13–16] have drawn attention to a relatively extensive system of pulmonary lymphoid tissue termed bronchus-associated lymphoid tissue (BALT). BALT represents lymphoid aggregates found along airways, particularly at bifurcations, as well as those along other lymphatic routes of the lung, and is thought to be part of a more generalized mucosa-associated lymphoid tissue (MALT) that is distinguished from the peripheral somatic (nodal) lymphoid tissue.[15,16] MALT synthesizes IgA and other immunoglobulins in response to mucosal surface antigens, and lymphocytes in this system have the ability to circulate and "home" to other MALT organs. The lymphoid tissue of MALT is intimately associated with the adjacent epithelium (Fig. 31–1), and lymphomas of MALT show a tendency to invade adjacent epithelium.[17–19] Lymphomas of MALT in general are indolent, low

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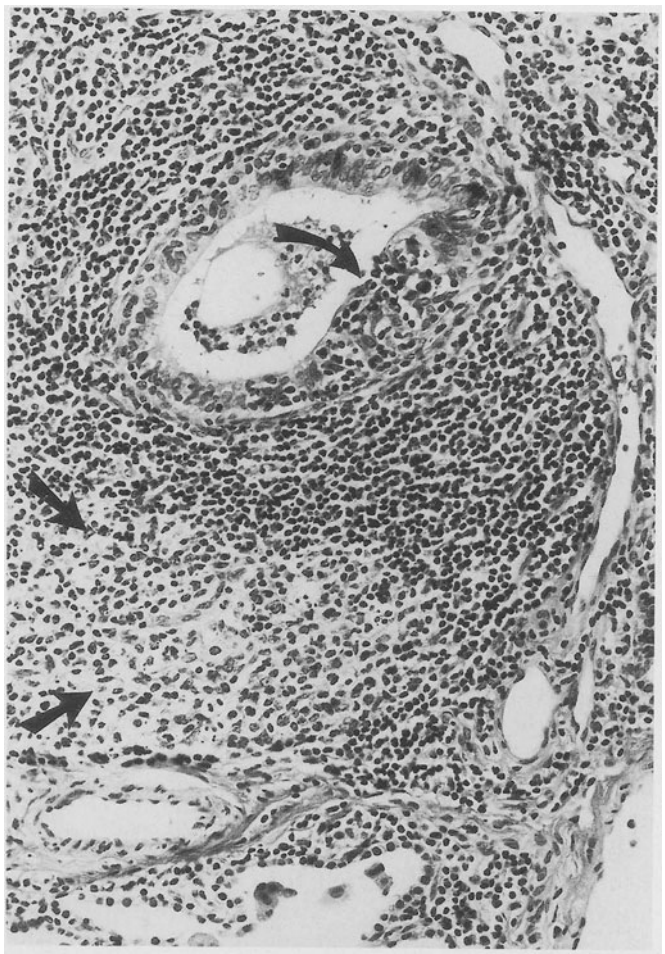


Fig. 31–1. Bronchus-associated lymphoid tissue (BALT) adjacent to bronchiole. There is a somewhat pale staining germinal center (*arrows*) with a cuff of small lymphocytes which show prominent infiltration of the epithelium of the adjacent bronchiole (*curved arrows*). H and E, ×100.

grade, and tend to remain localized for long periods of time.[14–18,20–22] In addition to the lung, other organs in the MALT system include salivary gland, intestinal tract, thyroid, cervix, endometrium, and breast.*

The radiologic manifestations of lymphoreticular infiltrates include a broad and nonspecific spectrum of changes.[24–26] The radiographic patterns of disease can often be correlated with the histologic findings: lesions that are characterized histologically by diffuse infiltrates along lymphatic routes without extensive nodular expansions produce a diffuse interstitial pattern radiographically, whereas mixed interstitial and nodular or frankly nodular patterns are associated with progressively larger nodules along the lymphatic distribution.

*References: 13–15,17,18,20–23.

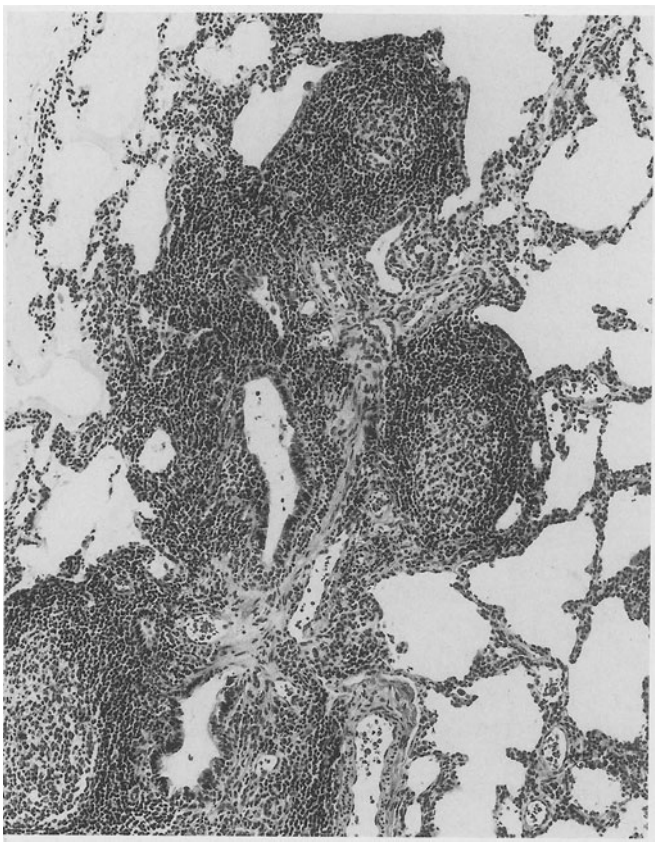


Fig. 31–2. Follicular bronchiolitis with germinal centers along a small airway from a child with an uncharacterized immunodeficiency state. H and E, ×40.

Massive infiltration with spillover into air spaces produces a pneumonic or alveolar pattern. Combinations of these patterns are common.[24–26]

Lymphoid Hyperplasias, Benign Lymphoid Infiltrates, and Related Lesions

Hyperplasia of lymphoid tissue in the lung is similar to lymphoid hyperplasia of other sites, with the production of germinal centers distributed along the normal locations of lymphatic tissue, specifically the pulmonary lymphatic routes. Exuberant lymphoid hyperplasia along the airways is termed follicular bronchitis or follicular bronchiolitis (Fig. 31–2), depending on the size of airway involved.[27] Lymphoid hyperplasia may also involve the septa and pleura.

In healthy children one may see a few lymphocytes and a rare germinal center in the lung, but in normal adults one generally does not see any significant quantity of lymphoid tissue in histologic sections[16]; when

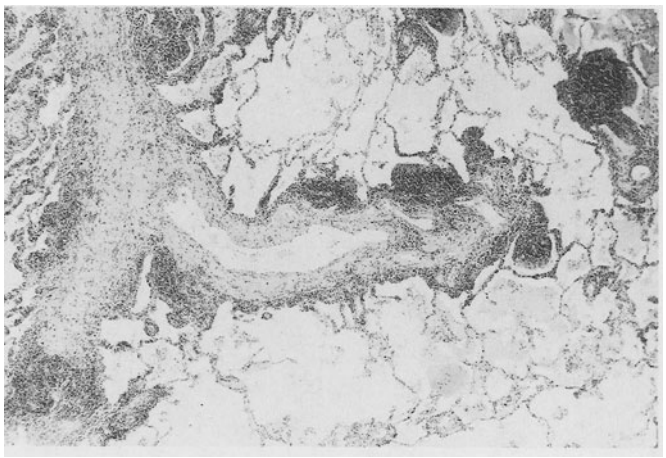


Fig. 31–3. Lymphoid hyperplasia adjacent to active tuberculosis. Septal and perivascular lymphoid follicles represent lymphoid reaction to nearby tuberculous granulomas. H and E, ×25.

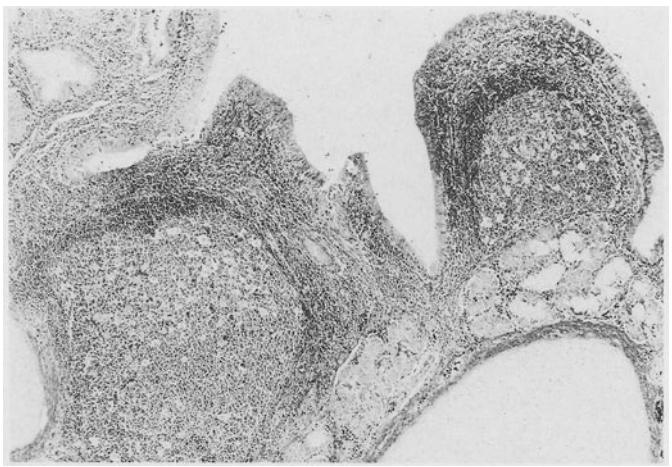


Fig. 31–4. Submucosal lymphoid hyperplasia (follicular bronchitis) in bronchiectasis. H and E, ×40.

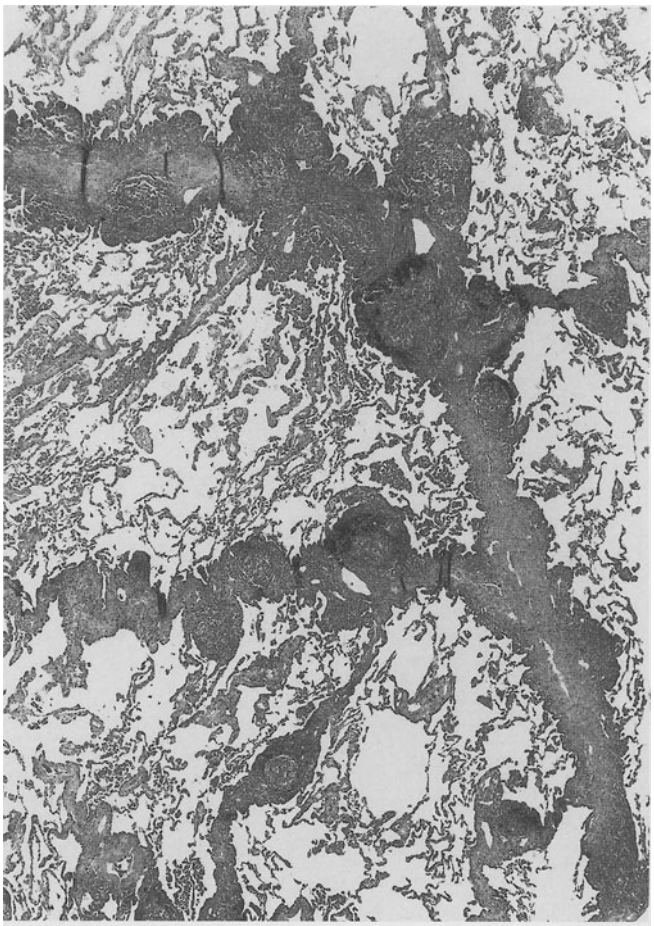


Fig. 31–5. Lymphoid hyperplasia in rheumatoid lung disease with germinal centers following septa and bronchovascular structures. The adjacent parenchyma has minor changes, and this patient's radiographic infiltrates were due to lymphoid hyperplasia. Such a lesion has also been referred to as lymphocytic interstitial pneumonia. H and E, ×10.

lymphoid tissue is prominent, a pathologic condition is usually present. Hyperplasia of lymphoid tissue in the lung is most commonly a manifestation of chronic infections, chronic bronchitis, bronchiectasis, or cystic fibrosis, or is a reaction around chronic inflammatory processess such as granulomatous infections or abscesses[28] (Figs. 31–3 and 31–4). Primary and secondary tumors can also have an associated lymphoid reaction including germinal centers, sheets of plasma cells, or granulomas, especially in foci of obstructive pneumonia. Metastases from the lymphoepithelial variant of nasopharyngeal carcinoma and primary lymphoepithelioma-like carcinomas of the lung represent particularly florid examples.

Diffuse lymphoid hyperplasia (Fig. 31–5) producing bilateral pulmonary infiltrates on chest radiographs may sometimes be the only histologic finding, particularly in collagen vascular diseases (e.g., rheumatoid arthritis, Sjögren's syndrome), congenital and acquired immunodeficiency states, and systemic hypersensitivity reactions,[27,29,30] and there is histologic overlap with lymphocytic interstitial pneumonia (see following). In collagen vascular diseases the proliferation in the lung is probably analogous to the exuberant lymphoid hyperplasia seen in lymph nodes of some of these patients.[31] The lymphoid hyperplasia may at times be most prominent along airways (follicular bronchitis/bronchiolitis) and may be associated with clinical evidence of interstitial *or* airflow obstructive disease.[27]

When first described, *angioimmunoblastic lymphadenop-*

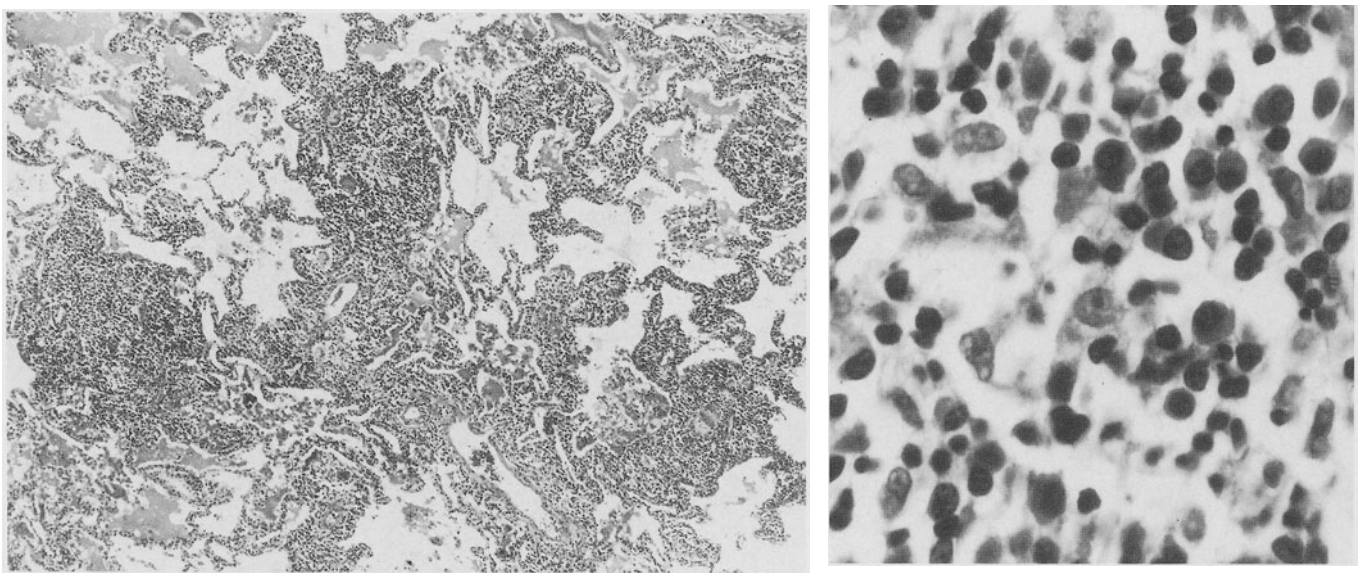


Fig. 31–6. Lymphocytic interstitial pneumonia. Note the dense diffuse polymorphous interstitial infiltrate with lymphocytes, plasma cells, and histiocytes. H and E: Left, ×40; right, ×630.

athy was thought to represent a peculiar autoimmune reaction,[32] but a significant number of cases are now recognized as T-cell lymphomas.[33] Pulmonary involvement may be a conspicuous feature of the syndrome,[32,34–36] which usually includes generalized lymphadenopathy, hepatosplenomegaly, Coombs-positive hemolytic anemia, skin rash, polyclonal hypergammaglobulinemia, and anemia.[32] Histologically, a polymorphous proliferation of immunoblasts, plasma cells, and occasionally histiocytes are found along the lymphatic routes of the lung.

Lymphocytic (lymphoid) interstitial pneumonia (LIP) is a chronic interstitial pneumonia characterized by a dense and diffuse interstitial infiltrate of cells that are histologically benign, polymorphous, and polyclonal.* These histologically diffuse interstitial lymphoid infiltrates can be distinguished from diffuse lymphoid hyperplasia, which is primarily related to the lymphatic routes, although in the literature both patterns have often been called lymphocytic interstitial pneumonia. Also, unlike lymphomas, LIP is usually more diffuse in its involvement of alveolar walls. Lymphoid follicles with or without germinal centers distributed along the lymphatic routes may be found, and when they are the dominant feature (Fig. 31–5), the term diffuse lymphoid hyperplasia is appropriately descriptive.[30]

The majority of patients are adults and have symptoms similar to other chronic interstitial pneumonias including cough, dyspnea, weight loss, and progressive shortness of breath.[1,37,38] Children may also be affected.[39] Chest radiographs show bibasilar infiltrates. Pulmonary functions reflect infiltrative lung disease with restriction and abnormal gas exchange. Dysproteinemias are a common laboratory finding, and either hyper- or hypogammaglobulinemia may be identified. A number of patients with LIP have associated conditions including collagen vascular diseases, autoimmune diseases, bone marrow transplantation, intestinal lymphoid hyperplasia, and immunodeficiency states including congenital and acquired immunodeficiency syndromes.[37–46] These associated conditions should be excluded before considering a diagnosis of idiopathic LIP.

The histology of LIP is characterized by a marked interstitial infiltrate of lymphocytes, plasma cells, and histiocytes (Fig. 31–6). Some cases have giant cells, granulomas, or reactive lymphoid follicles (Figs. 31–7 and 31–8. Interstitial fibrosis and honeycombing may be present. In contrast to lymphomas, LIP lacks large monomorphous foci of small lymphocytes or plasmacytoid lymphocytes and fails to show an overwhelming lymphatic distribution. A number of cases previously reported as LIP represented examples of diffuse bilateral small (well-differentiated) lymphocytic lymphomas presenting in the lung.[19,47,48] Immunophenotypic studies of LIP fail to show a clonal population of lymphoid cells.[38] T or B lymphocytes may predominate.[38,46]

The differential diagnosis of LIP includes nonspecific reactive changes; extrinsic allergic alveolitis, and small lymphocytic and lymphoplasmacytic lymphomas. In immunosuppressed patients, pneumocytis should be

*References: 1,4,30,37,38.

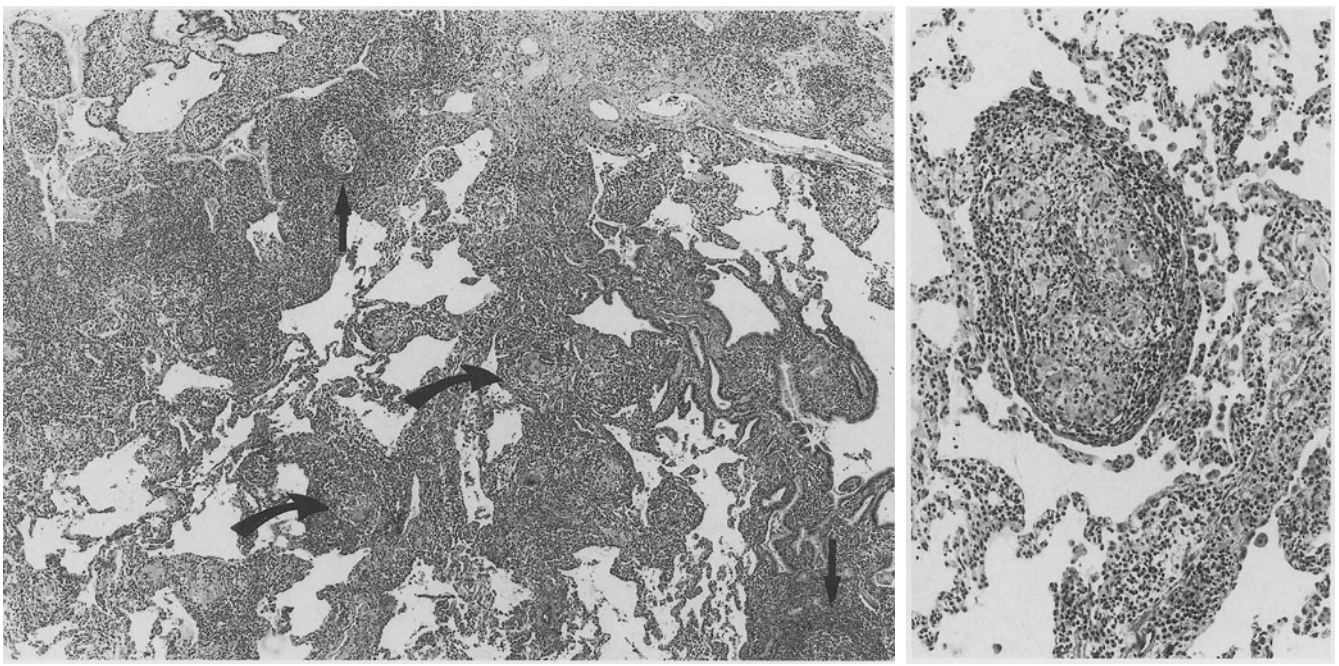


Fig. 31–7. Lymphocytic interstitial pneumonia from case of Sjögren's syndrome. Note dense diffuse lymphoid infiltrate with germinal centers (*straight arrows*) and granulomas (*curved arrows*, and *right*). H and E: left, ×25; right, ×100.

excluded. The treatment of lymphocytic interstitial pneumonia is not resolved, but a number of patients, even those with immunodeficiency states, respond to steroids.[37,49]

A *pseudolymphoma* represents a localized lymphoid proliferation in the lung that usually presents as a single nodule confined to one lobe.[30,47,50] Many of the lesions that had been called pulmonary pseudolymphoma (nodular lymphoid hyperplasia[30]) have been reinterpreted as small lymphocytic lymphomas[19,47–55] and the category of pseudolymphoma has shrunk considerably in size. Of all cases with massive accumulations of lymphocytes in the lung, roughly four of five (80%) were previously interpreted as pseudolymphomas,[56] whereas roughtly four of five (80%) are now interpreted as small lymphocytic lymphomas.[50]

Most patients are adults, and a few have a history of a prior pneumonia at the site. The majority of patients are asymptomatic and have a localized mass or infiltrate on routine chest radiography. Laboratory studies are generally noncontributory, but four cases in the series

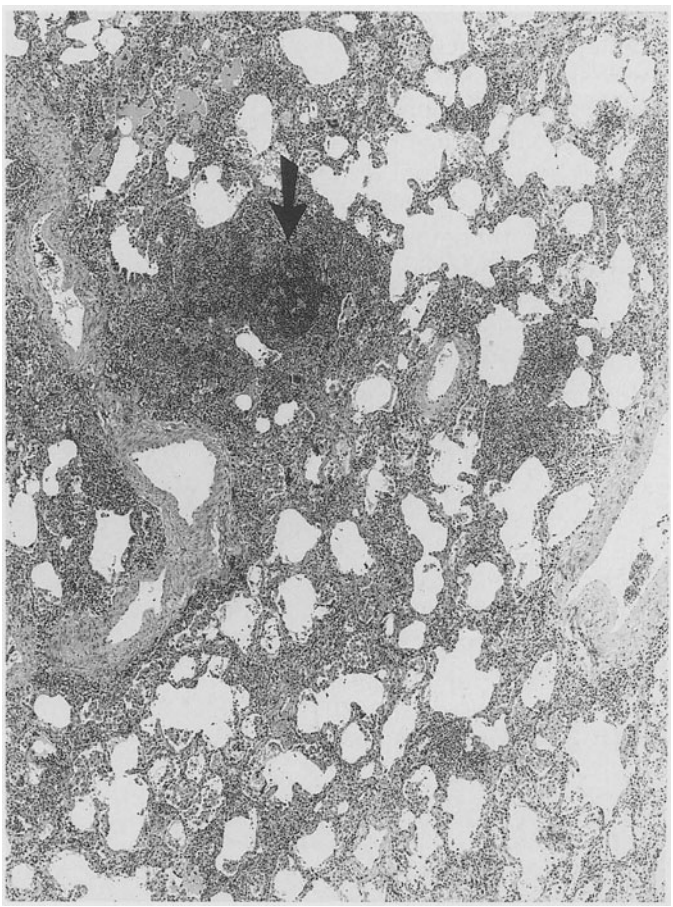


Fig. 31–8. Lymphocytic interstitial pneumonia in acquired immunodeficiency syndrome (AIDS). The moderately dense diffuse interstitial infiltrate of lymphocytes and plasma cells has occasional reactive germinal center (*arrow*). H and E, ×25.

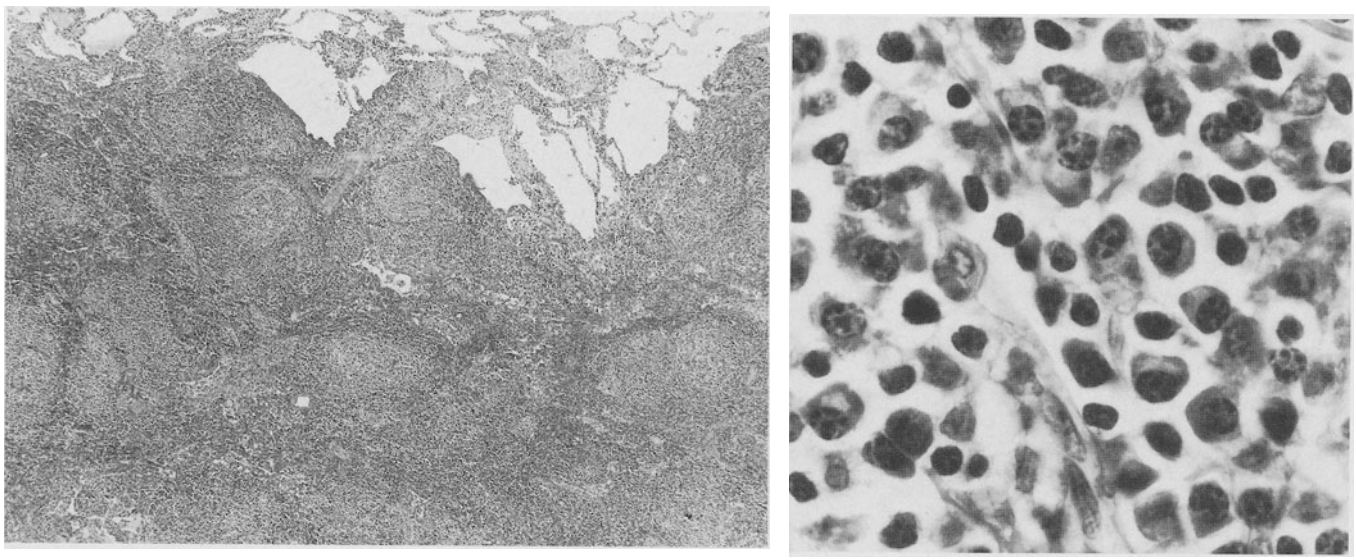


Fig. 31–9. Pseudolymphoma (localized lymphoid hyerplasia). This localized circumscribed mass of hyperplastic lymphoid tissue has numerous germinal centers and an associated mixed cellular population with lymphocytes and mature plasma cells. H and E: left, ×25; right, ×630.

of Koss et al.[50] had a polyclonal hypergammaglobulinemia.

Grossly, pseudolymphomas are tan and well circumscribed from the surrounding tissue.[30] Fibrosis within the lesion may cause retraction of tissue toward the center of the mass. The key microscopic feature in pseudolymphoma is the heterogeneity in cellular composition and variation from field to field (Fig. 31–9). Russell bodies and germinal centers may be prominent. The cellular infiltrate is mixed and generally includes lymphocytes, plasma cells, and occasional histiocytes that may form nonnecrotizing granulomas. Giant cells are seen in approximately one-third of cases. There is a variable amount of scarring that may be cellular and fibroblastic or acellular and hyaline in appearance. When fibroblastic proliferation is marked, focal or chronic organizing pneumonia may be more appropriate terms.[57] Confusion with the entity pulmonary hyalinizing granuloma should not occur. See Chapter 33 (p. 1336). Amyloid-like material may be present in pseudolymphomas. At the edge of the lesion, one does not see lymphatic tracking of a monomorphous population of cells, which characterizes lymphomas. Necrosis was found in one case reported by Koss et al.[50] Immunologic marker studies of pseudolymphomas fail to show a clonal population of cells.[50]

Castleman's disease (giant lymph node hyperplasia), particularly the hyaline vascular type, may involve nodes that are partially or completely intrapulmonary in location.[58]

In summary, much is made of distinguishing small lymphocytic lymphomas from either pseudolymphoma or lymphocytic interstitial pneumonia. In the case of pseudolymphoma, the distinction is often academic because both these lesions are usually resected for diagnosis, and solitary small lymphocytic lymphomas managed in this way rarely recur and often lack extrapulmonary involvement. It is reasonable to do noninvasive lymphoma staging procedures, but most patients will not require further therapy.

Malignant Lymphomas Presenting in the Lung

Definitions of a "primary" lymphoma occurring in an extranodal site, including the lung,[59] are somewhat arbitrary and cases that have evidence of disseminated disease are generally excluded. From a practical point of view, it is useful to divide pulmonary lymphomas into those in which the lung is the major site of involvement at presentation and those in which the lymphoma has presented at another site before secondary pulmonary involvement has occurred.[60]

A lymphatic distribution of involvement can be recognized in the majority of pulmonary lymphomas whether presenting in the lung or involving it secondarily.[47,48,60] A spectrum is encountered from diffuse infiltrates along lymphatic routes without mass formation to large necrotic masses with no discernible distribution. The lymphatic distribution is best appreciated at low power or even with naked-eye examination of the glass slide. (Fig. 31–10).

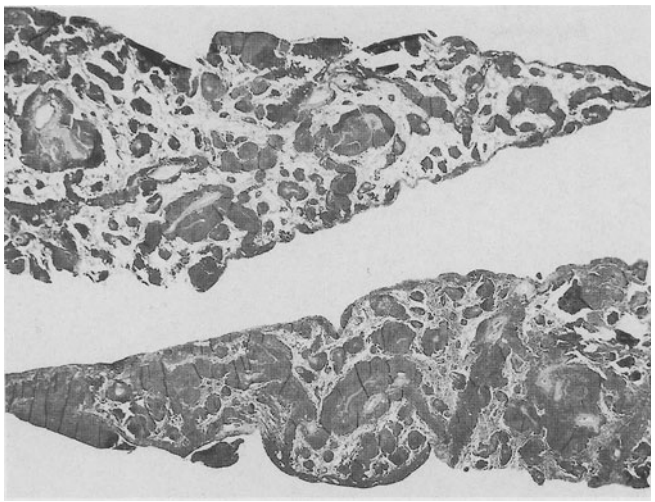


Fig. 31–10. Small lymphocytic lymphoma of lung shows diffuse involvement of lymphatic routes in pleura, septa, and along bronchovascular bundles. H and E, ×6.

Although the absence of involvement of hilar lymph nodes has been used as evidence against a diagnosis of lymphoma when evaluating a pulmonary lesion,[2,56] recent studies have emphasized that absence of hilar lymph node involvement is a frequent occurrence.[48,50,51]

If a pulmonary lymphoid lesion is suspected at the time of frozen section, the surgeon should be asked to sample hilar nodes as they may be helpful in both diagnosis and staging. Some tumor tissue should be appropriately saved (usually frozen) for immunologic marker studies, which may be helpful in confirming a light microscopic impression.[51]

Pulmonary Lymphomas Composed Predominantly of Small Lymphocytes

This category includes small (well-differentiated) lymphocytic lymphomas with or without plasmacytoid features, lymphocytic lymphomas of intermediate differentiation, and small cleaved cell lymphomas. Some cases are difficult to classify, a feature not uncommon in lymphomas of mucosa-associated lymphoid tissue.[17]

The following description is a summary of six series.[48,50,52–55] Most patients are older than 20 (mean age, approximately 55 years), although patients as young as 12 have been observed. Slightly more than half are asymptomatic with the lesion being discovered on chest radiographs. Those with symptoms describe cough, dyspnea, hemoptysis, weight loss, chest pain, and systemic complaints such as malaise. The male to female ratio is approximately 1:1.

Laboratory findings are generally nonspecific. Something less than a third of the patients are found to have a monoclonal serum protein spike either at presentation or subsequently. This finding is probably more common in patients with lymphoplasmacytic lymphomas.[54] An IgM monoclonal gammopathy is seen in cases of Waldenstrom's macroglobulinemia with lung involvement.[61–63] Cryoglobulinemia has also been reported.[64] Pulmonary function studies are rarely recorded because the majority of patients have radiographically localized disease. In the minority of patients that have diffuse bilateral disease radiographically, pulmonary function abnormalities of restriction and decreased diffusing capacity may be present.

The chest radiographic findings are quite variable, and any combination of the following may be seen: single or multiple nodules; unilateral or bilateral disease; localized alveolar and/or interstitial infiltrates; or diffuse bilateral alveolar and/or interstitial infiltrates. The most common presentation is a solitary, noncalcified nodule that may be 20 cm or more in diameter. Cavitation and hilar adenopathy are rarely observed.

Histologically, there is a monomorphous (or homogeneous) population of lymphocytes or plasmacytoid lymphocytes following lymphatic routes (see Fig. 31–10) with consolidation to masses (Figs. 31–11 and 31–12). The distribution may not be readily discernible in large masses, but tracking of the lymphoid infiltrate along lymphatic routes may be seen at their edge, and smaller satellite lesions may be found distributed along lymphatic routes. Cytologically, most cases are small lymphocytic lymphomas or lymphoplasmacytic lymphomas; lymphocytic lymphomas of intermediate differentiation and small cleaved cell lymphomas are less frequent.[48,50,52,53] Plasmacytoid differentiation is usually appreciated in patients with Waldenstrom's macroglobulinemia.[61–63] As in lymphomas of MALT at other sites, some cases show considerable cellular heterogeneity including the small lymphocytes, atypical small lymphocytes, plasmacytoid cells, plasma cells, and immunoblasts, and the term polymorphous immunocytoma is descriptively appropriate;[17,18,55] germinal centers may be numerous and be infiltrated by the neoplastic cell population.[65] Epithelial infiltration with the formation of lymphoepithelial lesions is also common (Fig. 31–13).

Pseudofollicular proliferation centers and true germinal centers are often scattered through the lesions (Fig. 31–14).[48,50–54,66] At the edge of masses one may find admixed plasma cells and histiocytes or a nonspecific intraalveolar accumulation of inflammatory cells. These foci may show a polyclonal immunostaining pattern. Granulomas, giant cells, dense sclerosis, and hyalinized material (which may or may not stain positively for amyloid) are sometimes seen. A few cases mimick nodular amyloidosis. A relatively common ap-

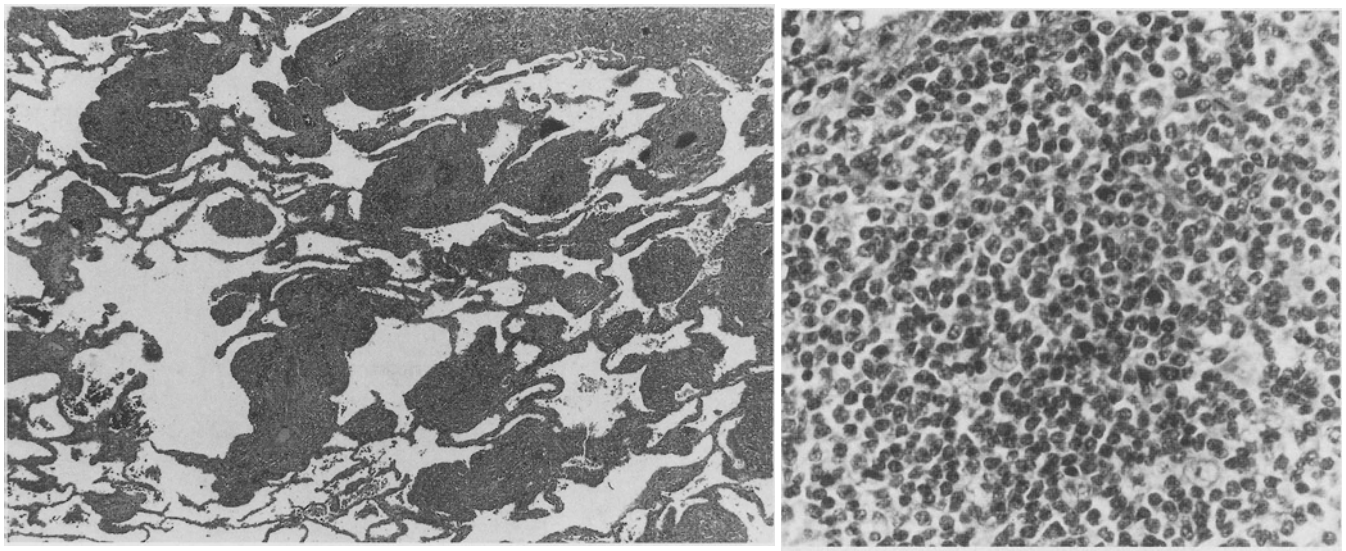


Fig. 31–11. Small lymphocytic lymphoma presenting as diffuse radiographic infiltrates. Biopsy shows pleural and perivascular monomorphous infiltrates of small lymphocytes. Involvement of alveolar walls is relatively inconspicuous compared to marked perivascular infiltrates. H and E: left, ×25; right, ×250.

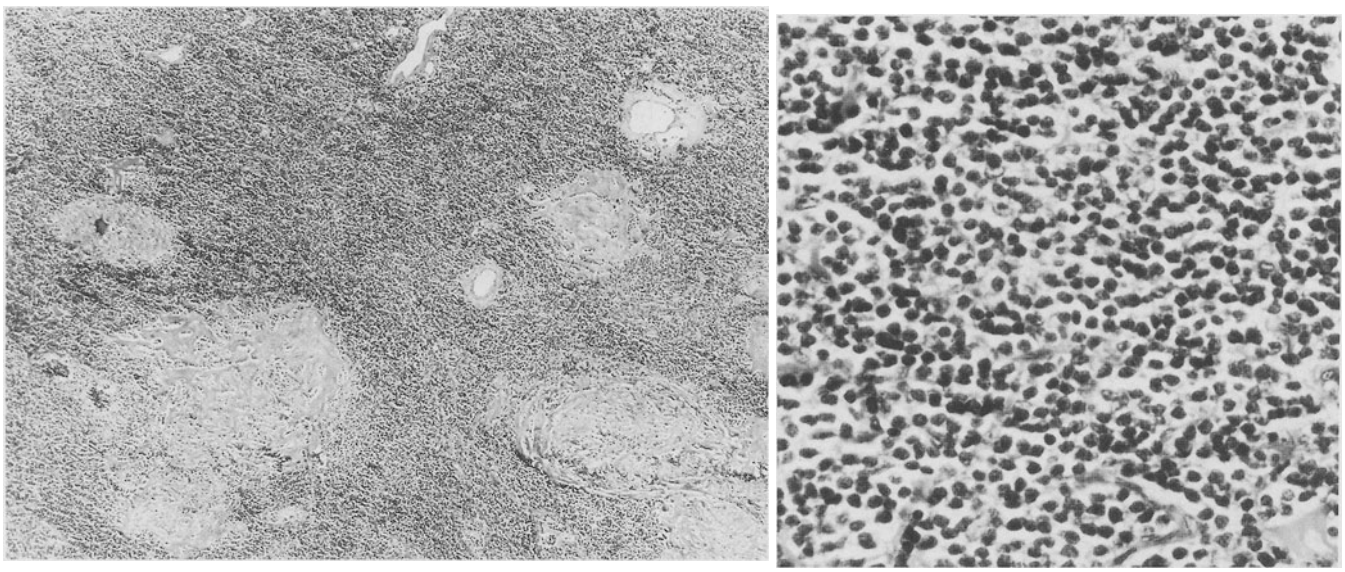


Fig. 31–12. Small lymphocytic lymphoma presenting as solitary mass. Between islands of sclerotic connective tissue are sheets of monomorphous small lymphocytes. In such cases there may be either monoclonal or polyclonal plasma cells in sclerotic regions. H and E: left, ×40; right, ×250.

pearance is bands of dense sclerosis surrounding islands of small lymphocytes with occasional plasma cells (See Fig. 31–12).

The differential diagnosis includes LIP, diffuse lymphoid hyperplasia, pseudolymphoma, other lymphomas, and chronic lymphocytic leukemia affecting the lung.

Immunologically, most small lymphocytic lymphomas are B-cell tumors.[17–19,55] A cytogenetic study of one case revealed karyotypic abnormalities with a translocation.[67]

The vast majority of these neoplasms are indolent and may be cured by surgery alone if they are localized.* Those that recur may do so within months or up to decades after initial recognition. At presentation, a

*References: 18,21,22,30,48,50,52–55.

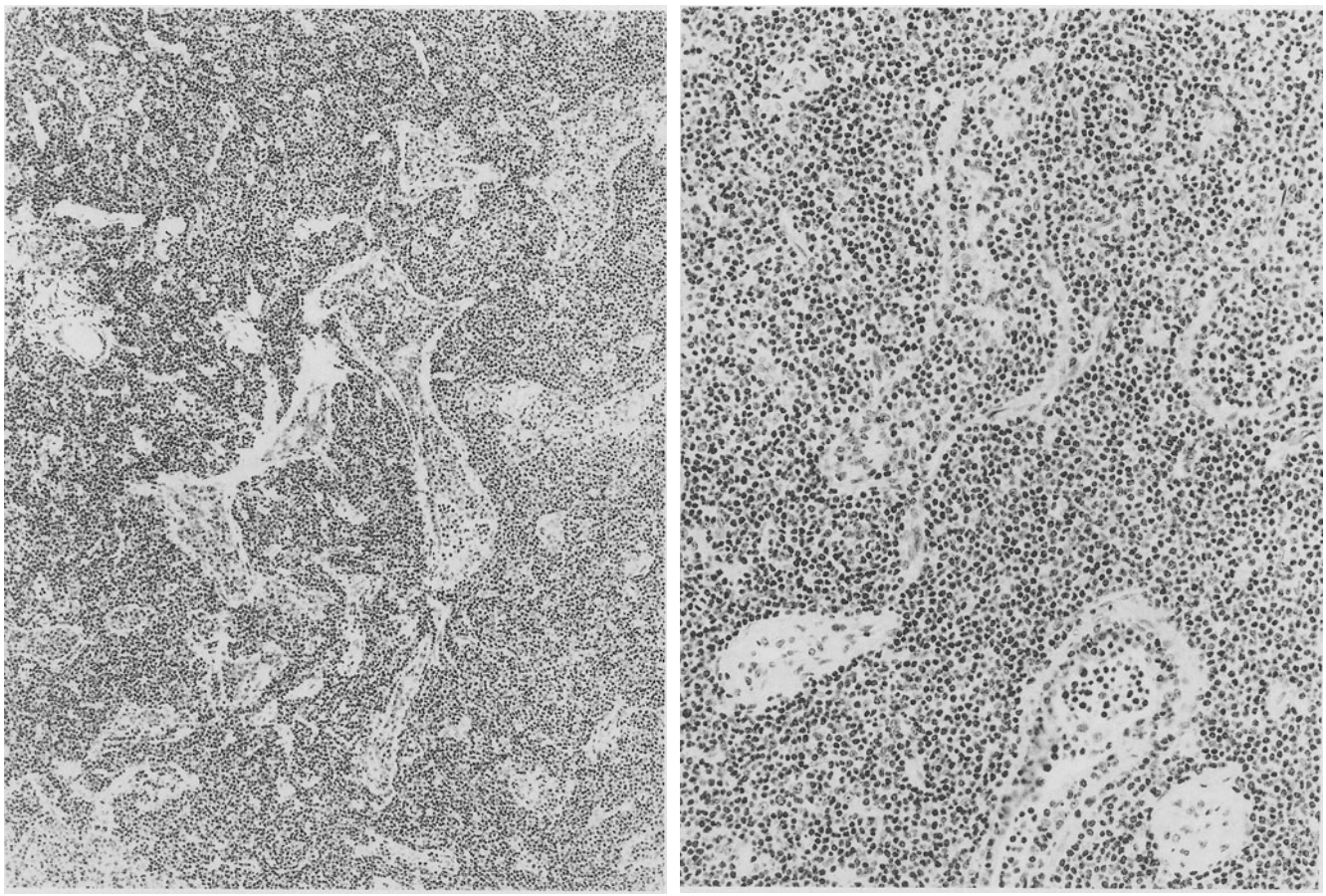


Fig. 31–13. Lymphoepithelial lesions from case of small lymphocytic lymphoma of the lung. A monomorphous population of small lymphocytes surrounds irregular-shaped islands, which represent epithelium infiltrated by lymphocytes. H and E: left, ×40; right, ×100.

minority, probably less than one-fourth, are found to have evidence of extrapulmonary lymphoma.[48] Transformation into a large-cell lymphoma, analogous to Richter's syndrome, may occur.[47,55]

Therapy and staging procedures should be tempered by the indolent nature of these lesions. Because resection alone may cure a significant number of patients, initial staging procedures should be noninvasive. The indolent behavior of these lymphomas is thought to reflect lymphomas of MALT in general.** Similarly, these lung lymphomas may be associated with gastrointestinal lymphomas or lymphomas of other MALT sites, before, after, or concurrently with the pulmonary lesions.***

Other Non-Hodgkin's Pulmonary Lymphomas

This heterogeneous group includes cases that would most often be classified as diffuse mixed-cell or large cell lymphomas if encountered in lymph nodes. It also includes a majority, if not all, of the angiocentric immunoproliferative lesions discussed separately next. As a group they are about one-fourth as common as small lymphocytic lymphomas. Both T-cell and B-cell types occur.[55] Follicular lymphomas, diffuse small noncleaved cell lymphomas, and lymphoblastic lymphomas rarely involve the lung.

The clinical and radiographic findings are summarized from two series.[50,60] Although most patients are adults, there is a wide age range and children may be affected, particularly in immunodeficiency states. Occasional patients are asymptomatic, but the majority have cough, shortness of breath, fever, and a variety of other systemic complaints. The laboratory findings are noncontributory. Either at presentation or during the course, patients may develop a variety of extrapulmonary lesions, including paraneoplastic syndromes and involvement of multiple other organ systems. Involvement of the nervous system, skin, and subcutaneous tissues is not uncommon.

Radiographically, the patients show any combination

**References: 17,18,20–22,55.
***References: 22,48,50,55,68.

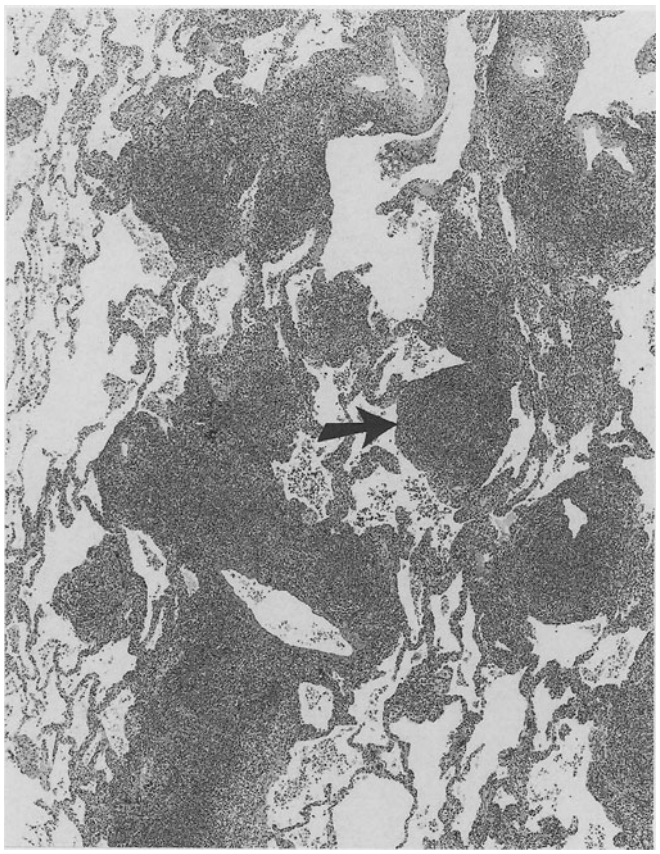


Fig. 31–14. Small lymphocytic lymphoma involving lung. An occasional germinal center (*arrow*), is seen, but elsewhere a dense monomorphous population of small lymphocytes expands septa and shows a perivascular distribution. H and E, ×40.

of nodule(s) or infiltrate(s) that may involve one or multiple lobes. Cavitation is relatively frequent, and a single cavitating mass mimicking tuberculosis may be seen. The development of infiltrates may be so rapid as to suggest an accute infection.[26,69,70]

Grossly, the lungs are consolidated by gray-tan, nodular infiltrates that may show necrosis and cavitation. When the infiltrates are not so massive, a lymphangitic pattern may be appreciated grossly. These lymphomas tend to show the broadest histologic spectrum, reflective both of the inherent heterogeneity of such a large subgroup and the frequent secondary changes in the adjacent lung parenchyma (Figs. 31–15 through 31–17). Subclassification of the lymphoma is based on identifying the neoplastic cell population: large lymphoid cells in the case of large-cell lymphoma, and a mixture of atypical small lymphocytes and large cells in the case of mixed-cell lymphomas. In the latter group there may be interspersed plasma cells and histiocytes.[33,51] Extensively necrotic lesions often have a rim of viable cytologically benign cells, and one may need to search several blocks to find foci of recognizable lymphoma. In cases that present as diffuse infiltrates along lymphatic routes without mass formation, the cellular heterogeneity may be so great that one is extremely reluctant to make a diagnosis of lymphoma. In such cases, cytologic atypia should be sought in infiltrates along pulmonary veins and in plaques of tumor in the pleura, because the peribronchial and peribronchiolar infiltrates tend to be the most polymorphous (see Fig. 31–10).

Vascular infiltration (Fig. 31–16) is common in this

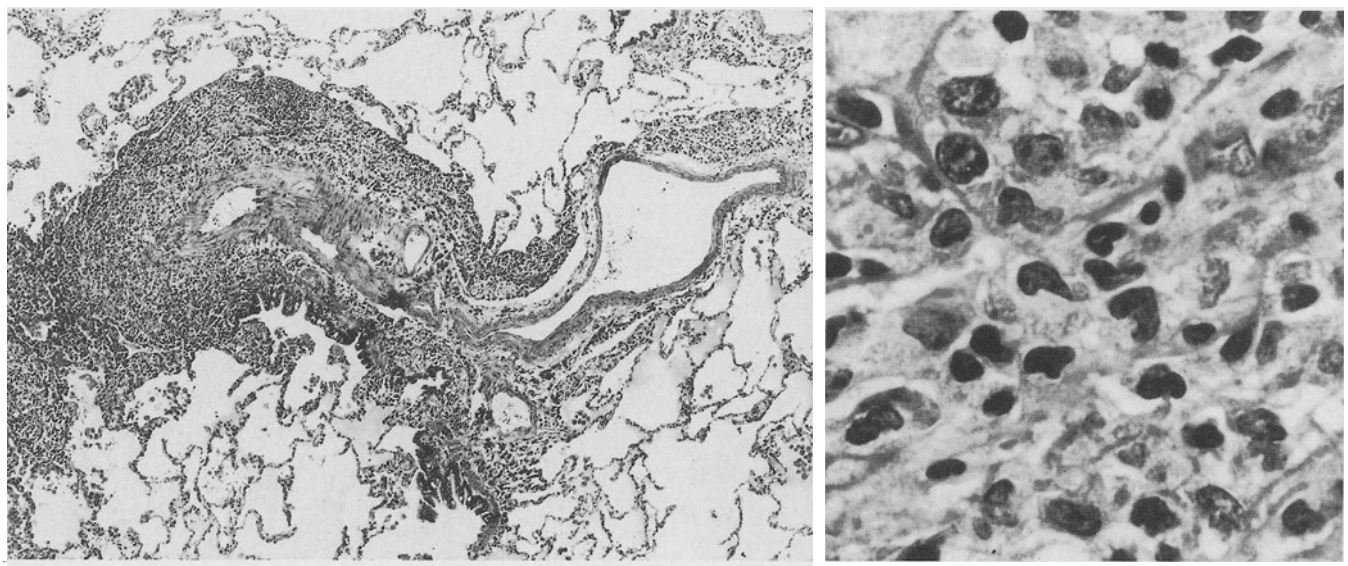


Fig. 31–15. Mixed-cell lymphoma presenting as diffuse radiograph infiltrates. The process surrounds airways and vessels and infiltrates the vessels. The mixed-cell population suggests a T-cell lymphoma with numerous atypical small lymphocytic forms. H and E: left, ×40; right, ×630.

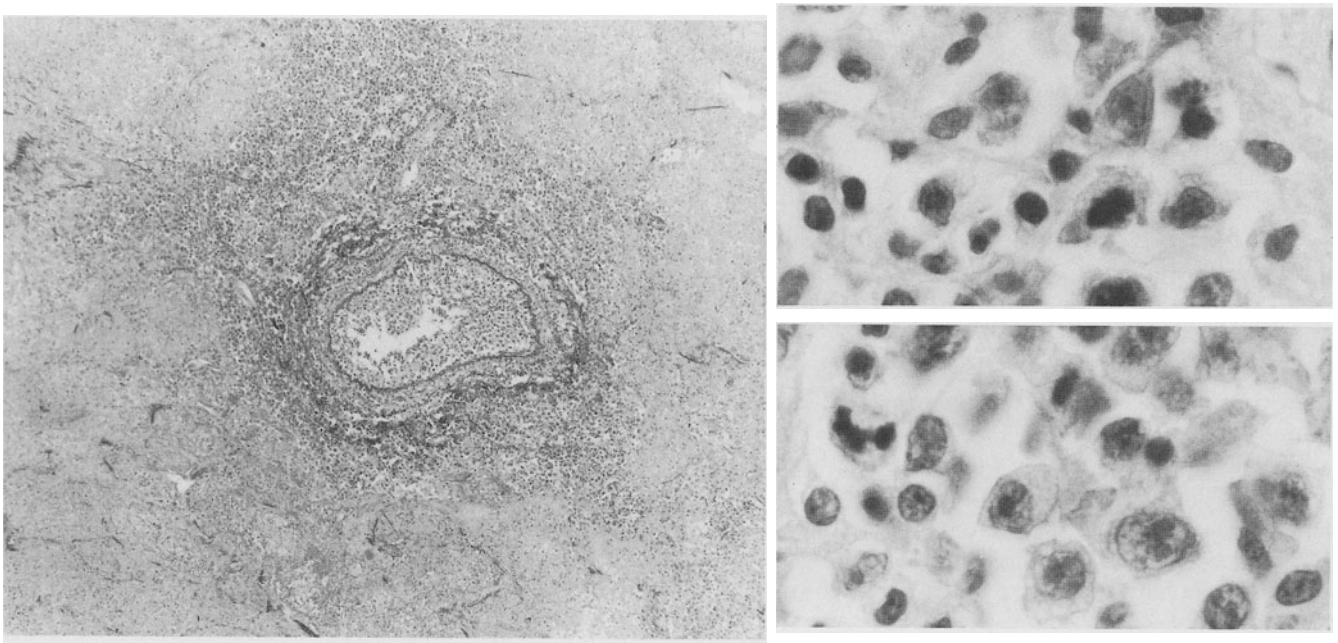


Fig. 31–16. Large cell lymphoma presenting as multiple nodules on chest radiograph. Prominent vascular infiltration is surrounded by tumor necrosis (left). The vascular infiltrate (upper right) is mixed in composition but includes atypical large cell similar to those seen among viable lymphoma (lower right). Such a case might also be interpreted as high-grade angiocentric lymphoma. H and E: left, ×40; right, upper and lower, ×630.

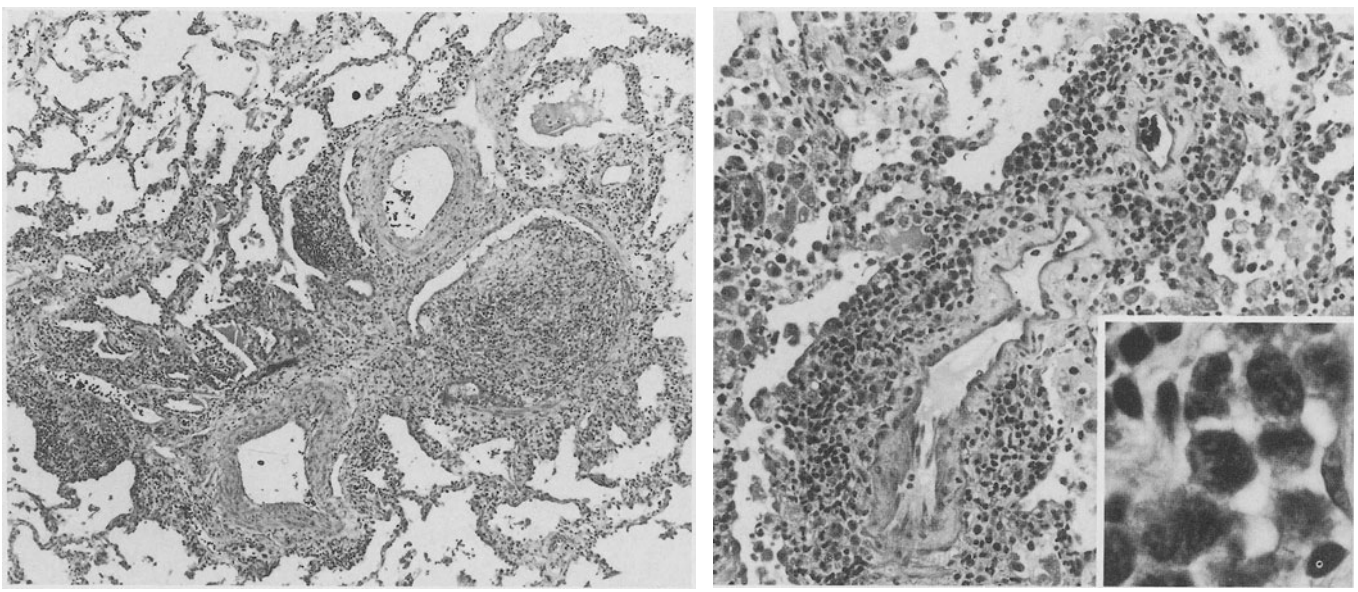


Fig. 31–17. Malignant lymphoma simulating airway inflammatory disease in patient with bilateral lower lobe infiltrates on chest radiograph, cough, and dyspnea. Small airways are surrounded by polymorphous infiltrates with some bronchiolitis obliterans (left). The neoplastic population (right inset) is most easily demonstrated along pulmonary veins (right). H and E: left, ×40; right, ×100; inset, ×630.

subgroup, although necrosis *limited to* vessel walls is unusual. When a necrotic vessel is seen, it is usually in the midst or at the edge of a large zone of tissue necrosis. Vascular infiltration may be by malignant cells, cytologically benign cells, or a mixture.

Invasion of airways (Fig. 31–17) also occurs and may produce a secondary bronchiolitis or bronchiolitis obliterans with more distal obstructive changes, including foamy macrophages in alveoli and inflammatory infiltrates in alveolar walls. An intraalveolar exudate and hyperplasia of type II pneumocytes is also common in the parenchyma adjacent to lymphomatous infiltrates. Less common secondary changes include organizing pneumonia and infarcts.

Like lymphomas presenting at other extranodal sites,[71,72] lymphomas presenting in the lung may have an associated cytologically benign infiltrate, usually at the periphery.[47,60] It is quite remarkable how extensive this infiltrate may be relative to the foci recognizable as lymphoma.

As with small lymphocytic lymphomas, a localized lymphoma in this group that is entirely resected may be cured.[54] However, the majority of patients have extensive bilateral disease, are clinically ill, and require aggressive chemotherapy that may result in either temporary or long-term remissions.[51,60]

Angiocentric Immunoproliferative Lesions (Lymphomatoid Granulomatosis)

Lymphomatoid granulomatosis was originally described as an angiocentric and angiodestructive process composed of lymphoreticular cells that showed a propensity to infiltrate blood vessels.[5] It was not clear whether it was primarily a disease of the lymphoid system, a peculiar vasculitis, or a hybrid.[5] Since the initial report, several sizable series have been published.[73,74] Other labels have also been applied to this condition, including polymorphic reticulosis,[6] benign and malignant angiitis and granulomatosis,[7] and most recently angiocentric immunoproliferative lesions.[8] This group of conditions shows considerable overlap with mixed-cell lymphomas as discussed previously.

As the histologic spectrum of lesions that are accepted as lymphomas has broadened, particularly since the recognition of T-cell lymphomas, it has become apparent that many if not most cases of lymphomatoid granulomatosis represent lymphoproliferative processes. It is acknowledged that these are somewhat different from the classical lymphomas presenting in lymph nodes.* In addition to lymphomas of T- and B-cell type,[75,76] some other lesions previously included with cases of lymphomatoid granulomatosis are pulmonary Hodgkin's disease and angioimmunoblastic lymphadenopathy involving the lung. The presence of vascular invasion, although characteristic of lymphomatoid granulomatosis, is common in many lymphoid lesions at a variety of sites,[77] most notably in primary brain lymphomas. The term vasculitis has often been used in this context but vascular invasion or infiltration is more appropriate.

This subset of lymphoproliferative diseases involving the lung is distinct and has recognizable differences from more conventional lymphomas. There are frequently infiltrates of the skin or nervous system, both central and peripheral. While one may simply call these mixed-cell lymphomas, the concept of angiocentric immunoproliferative lesions,[8] divided into low-grade and high-grade types, is appealing and preferable to continued use of the term lymphomatoid granulomatosis. Most angiocentric immunoproliferative lesions have been shown immunophenotypically to be postthymic T-cell lymphoproliferations, and the high-grade lesions, which represent the majority of cases, are designated angiocentric lymphomas.[8] Molecular studies show clonal gene rearrangements in a minority of cases, which is further evidence to segregate this group of lesions from more conventional lymphomas.[78]

The histologic features of angiocentric immunoproliferative lesions are distinctive (Figs. 31–18 through 31–20). Most commonly, there are nodular infiltrates of lymphoid cells which, when small, are seen to center on or be adjacent to vascular structures (Fig. 31–18). Less commonly, there are more diffuse infiltrates along vascular structures and within septa. As the nodular lesions enlarge, there is a central fibrinous exudation into air spaces (Fig. 31–19) and eventually central necrosis with a rim of viable tissue (Fig. 31–20A). Extremely large nodules can develop. The lymphoid infiltrate constituting the nodules is heterogeneous and includes lymphoid cells, histiocytes that may form small epithelioid clusters, plasma cells, and rarely giant cells. Variable numbers of large lymphoid cells and small and intermediate-sized lymphoid cells with atypical nuclear membranes and mitotic figures are seen in increasing numbers from low-grade to high-grade lesions. There are associated changes in the air spaces including accumulation of pulmonary alveolar macrophages that may be foamy and prominent type II cells. Vascular infiltration by the lymphoid infiltrate is a distinctive feature

*References: 6,8,30,50,60.

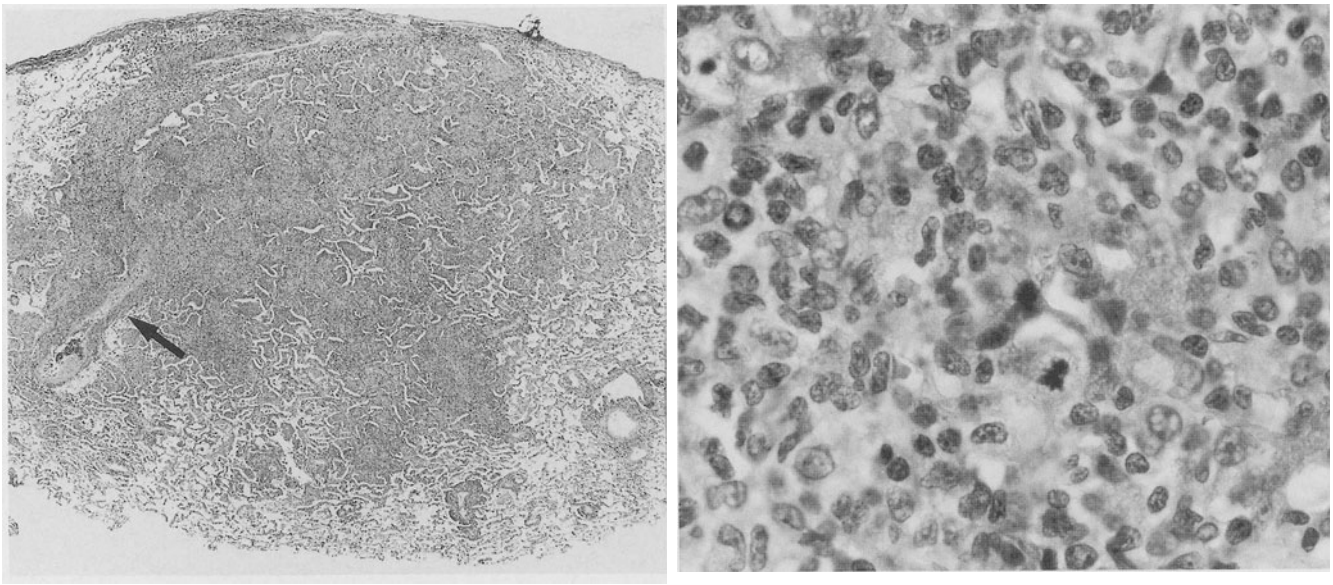


Fig. 31–18. Angiocentric lymphoma. Note the nodular infiltrate with interstitial, air space, and vessel (*arrow*) involvement. The infiltrate is composed of a mixed population of lymphoid cells (right) with relatively numerous atypical small lymphoid forms and moderate numbers of large lymphoid cells; a few histiocytes are present. The features are those of an intermediate to high-grade angiocentric immunoproliferative lesion (angiocentric lymphoma). H and E: left, ×20; right, ×250.

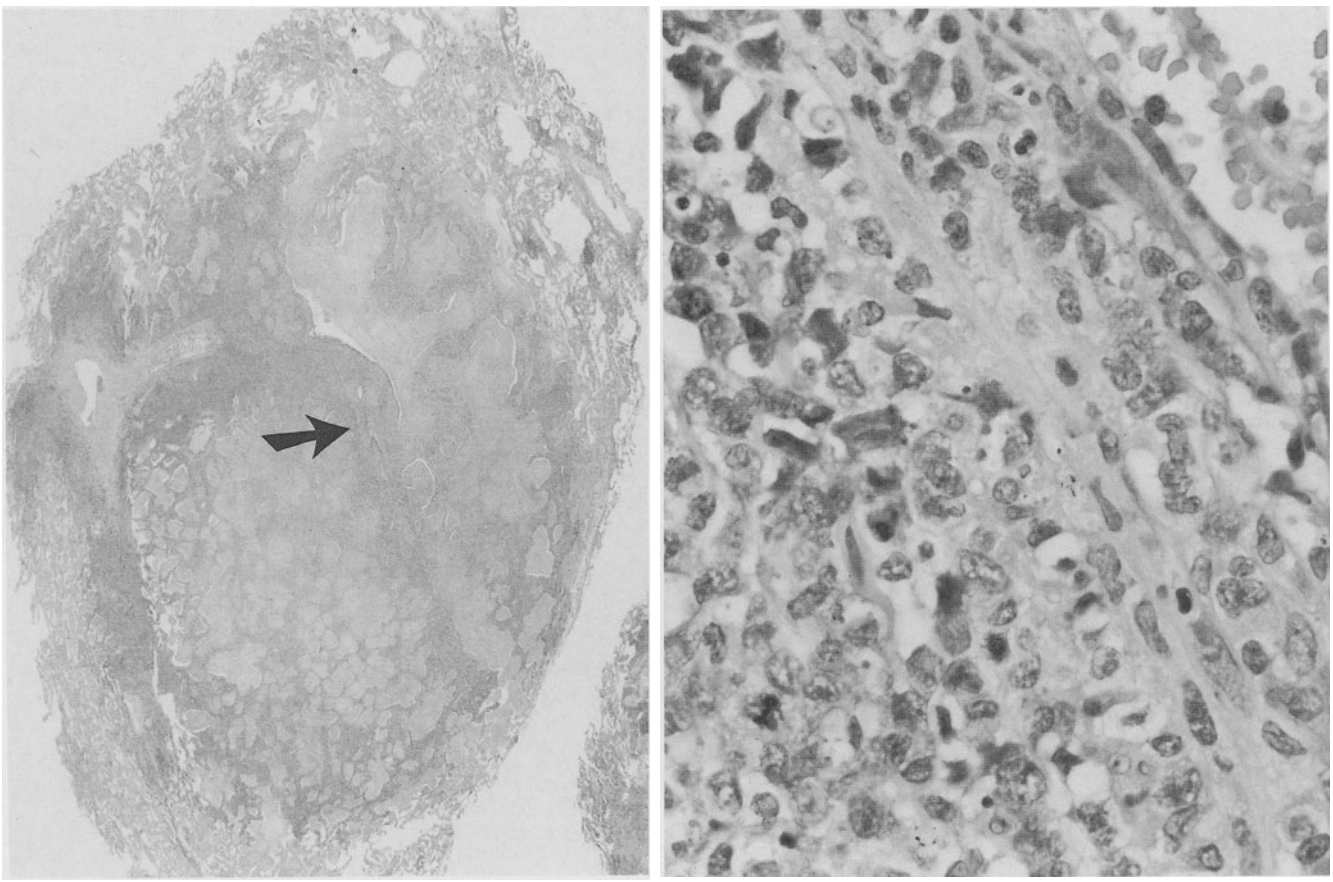


Fig. 31–19. Angiocentric lymphoma. This nodular infiltrate has central exudation into air spaces that precedes central necrosis in such cases. The neoplastic infiltrate (right) is composed of a monomorphous population of large cells. The field at the right is from an involved vessel wall (*arrow*) with the lumen at upper right. The pattern here is that of a high-grade angiocentric immunoproliferative lesion (angiocentric lymphoma). H and E: left, ×10; right, ×250.

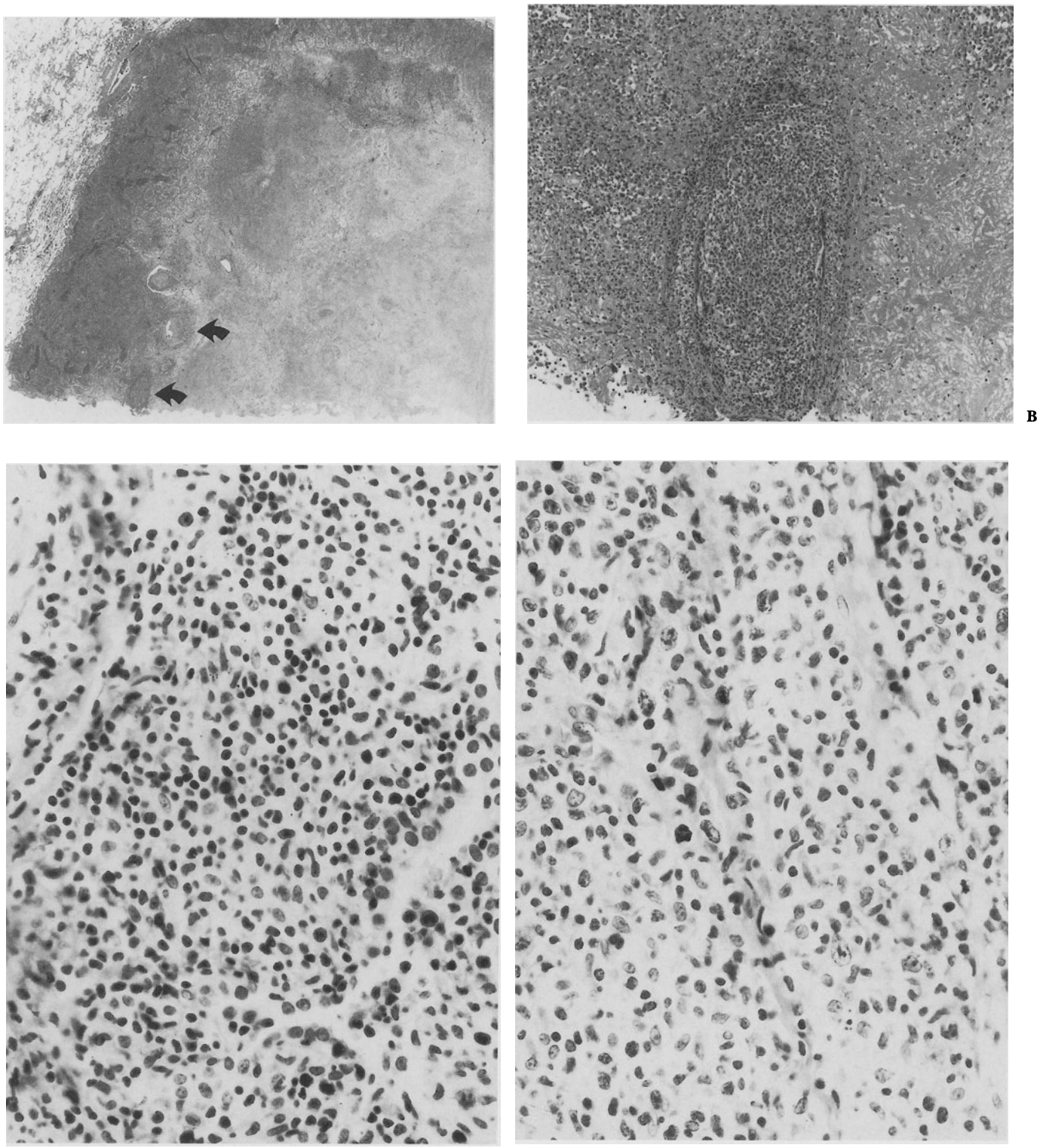


Fig. 31–20A–C. Angiocentric lymphoma. Note the large nodule with central necrosis **(A)** and vascular infiltration **(B).** The viable lymphoid infiltrate varied from a relatively bland cytologic appearance with small round small lymphocytes and modest numbers of intermediately sized cells lacking atypia (**C,** left) to a pattern characteristic of mixed-cell lymphoma with atypical small lymphocytes and large lymphoid forms (**C,** right). Based on the cytologic features **(C),** this would be classified as intermediate to high-grade angiocentric immunoproliferative lesion (angiocentric lymphoma). H and E. **A,** ×20; **B,** ×100; **C,** ×250.

(Fig. 31–20B), but is not seen in all sites of involvement and may not involve all vessels. The vascular infiltrate may be by cytologically benign cells, cytologically malignant cells, or a mixture of the two. The number of atypical cells varies from field to field (Fig. 31–20C), and one should search out the most atypical field in order to classify a given case. Not uncommonly, biopsies that show several nodules may reveal monomorphous foci of atypical large cells in only one of the nodules.

While initially a three-grade scheme for angiocentric immunoproliferative lesions was devised, a two-grade system with low-grade and high-grade categories has proved most practical.[8] At the low-grade end, one has difficulty convincing oneself of a neoplastic lymphoproliferative process. Because perivascular infiltrates are common in many conditions, a key feature is the density and mass-like character of the process; expansile nodules, central necrosis, and vascular infiltration are less common in benign lesions. At the high-grade end of the spectrum, recognition of the lymphomatous process is easy.

Early series of lymphomatoid granulomatosis suggested a poor prognosis despite chemotherapy,[5,73] with less than half of the patients living 2 years. This prognosis is similar to earlier series of large cell and mixed-cell lymphomas presenting in the lung.[60,73] More recent studies have suggested a more favorable prognosis with aggressive chemotherapy for high-grade lesions, with more than 50% long-term remissions.[8]

Lymphomatoid granulomatosis has been described in a number of clinical settings including immunodeficiency states.[60,73,79,80] Such a process in an immunocompetent individual should probably not be equated with a histologically similar process in an immunodeficient individual, but a common theme may be Epstein–Barr virus (EBV). Epstein–Barr virus has been found in a significant number of cases of lymphomatoid granulomatosis,[78,81] and it is also associated with lymphoproliferations in the acquired autoimmune deficiency syndrome and organ transplantation.[80,82–84] The significance of these findings in relationship to classical lymphomas remains to be clarified.

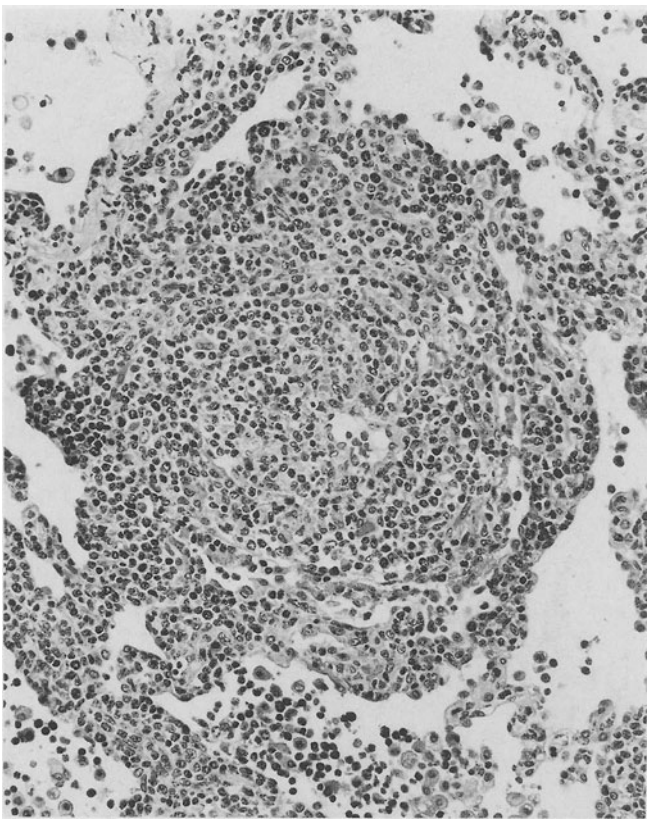
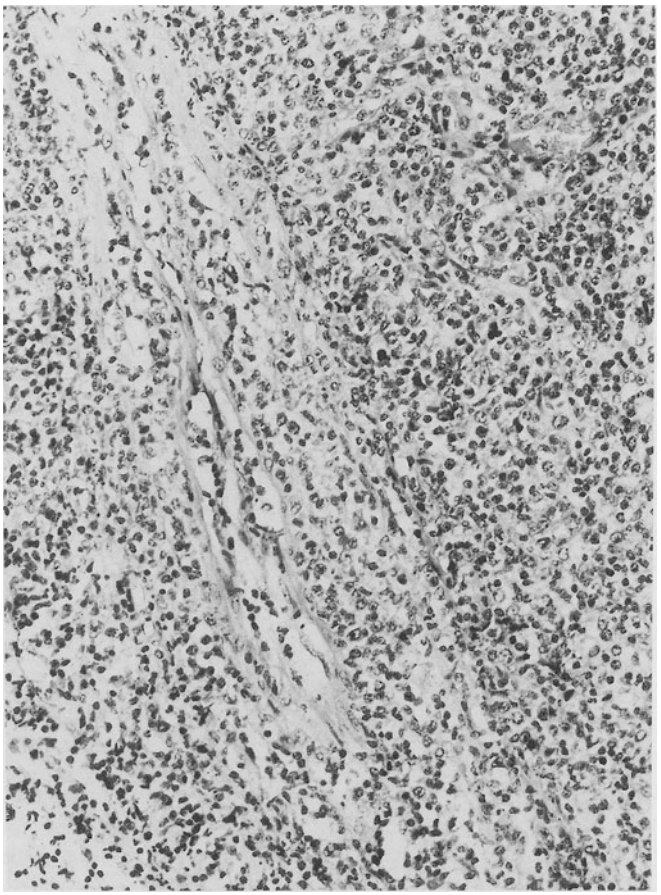


Fig. 31–21. EBV-associated lymphoproliferative lesion. This histologically polymorphous lesion composed predominantly of small lymphocytes shows marked propensity for vascular infiltration. The lesion regressed with decreased immunosuppression. H and E, ×150. (Courtesy of S.A. Yousem, M.D., University of Pittsburgh.)

Pulmonary Lymphomas and Lymphoproliferations in the Setting of Transplantation and the Acquired Immunodeficiency Syndrome

Patients who have undergone transplantation are at increased risk to develop lymphoid proliferations.[82,83] Initially these were considered lymphomas; however, many have been found to be associated with EBV, usually a primary infection by the virus after transplantation.[82,83] Clinically these patients may present with nonspecific signs and symptoms or those similar to pulmonary lymphomas, and histologically they show a spectrum from a polymorphous infiltrate of plasma cells, small lymphocytes, and histiocytes to an appearance identical to diffuse large cell lymphoma (Figs. 31–21 and 31–22). Necrosis and vascular infiltration may be prominent. Immunophenotypically, they may be polyclonal or monoclonal, with the latter usually associated with a monotonous population of immunoblasts and large lymphoid cells. In one case the proliferating cells in the allograft were shown to be recipient lymphoid cells containing the EBV genome.[83] Many of these lymphoproliferations can be directly attributed to the immunosuppressive therapy, because they often resolve when immunosuppressive therapy is decreased. Such behavior may even be seen with lesions that are proven to be monoclonal. Molecular study of these lymphoproliferations shows the EBV genome to be



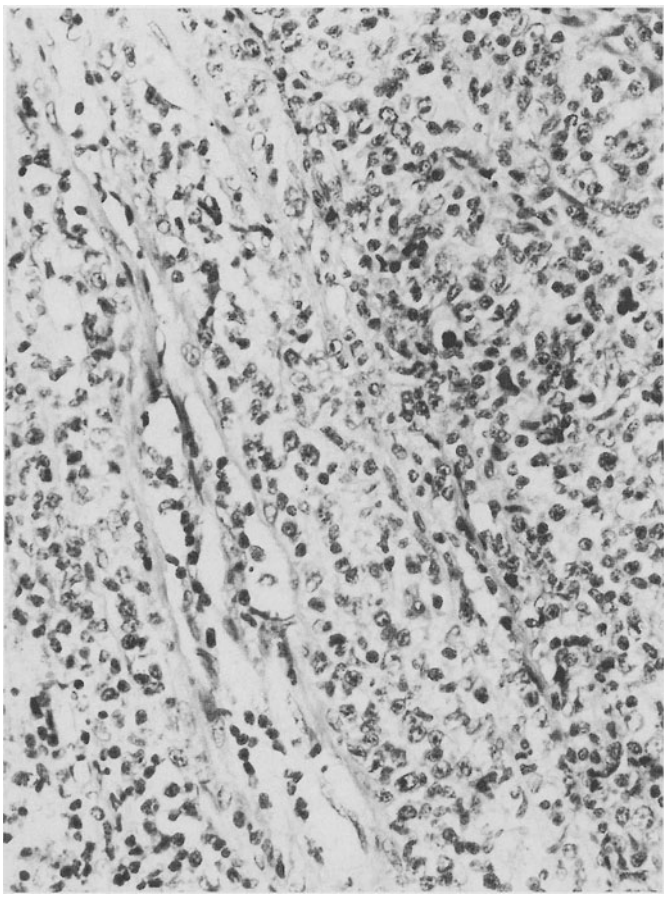


Fig. 31–22. EBV-associated lymphoproliferative lesion. There is marked vascular infiltration by cytologically malignant cells which have features of diffuse large cell lymphoma. This lesion regressed when immunosuppression was decreased. H and E: left, ×150; right, ×250. (Courtesy of S.A. Yousem, M.D., University of Pittsburgh.)

present in the neoplastic cells, although only serologic studies can determine if the infection is primary or secondary (i.e., reactivation).

Practically speaking, transplant-associated EBV lymphoproliferations often cannot be distinguished from lymphomas on morphologic or immunophenotypical grounds. Prognostication is difficult, and one often must wait for the follow-up to determine the behavior of a given lesion.

A number of pulmonary lymphoid proliferations are seen in the setting of acquired immunodeficiency syndrome (AIDS),[85,86] and EBV has been associated with a significant proportion.[60,61] Lymphocytic interstitial pneumonia (LIP) (see Fig. 30–8) may be encountered either as diffuse dense infiltration of alveolar septa by a mixed population of inflammatory cells or diffuse lymphoid hyperplasia. LIP in AIDS is more common in children than in adults. Kaposi's sarcoma of the lung is sometimes an associated lesion (see Chapter 33, p. 1400).

The lung is one of the less common sites of de novo lymphomas developing in patients with AIDS.[86]

Intravascular Lymphomatosis Presenting in the Lung

Intravascular lymphomatosis, also known as angiotropic lymphoma and malignant angioendotheliomatosis, is an uncommon form of lymphoma that has a marked propensity for intravascular growth.[87] The condition most commonly involves the central nervous system and the skin, but primary pulmonary presentation is also well described.[88,89] Patients have shortness of breath, fever, and diffuse interstitial infiltrates on chest radiographs. Histologically, there is a proliferation within vessels of atypical large lymphoid cells that at low power may mimic an interstitial pneumonia (Fig. 31–23). Cytologic evaluation reveals these cells to be distinct from endothelial cells, and immunophenotypically most cases are B cell,[87] in contrast to the angiocentric immu-

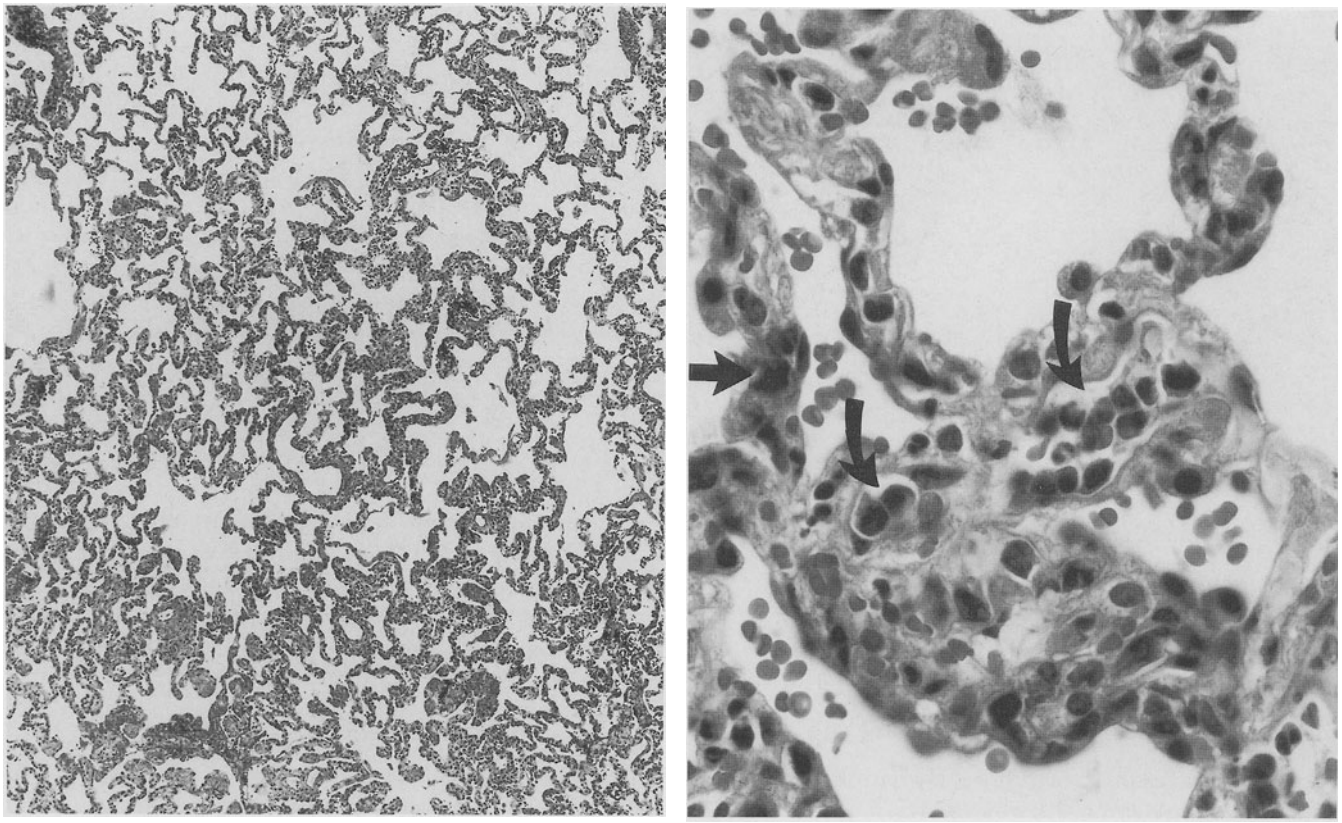


Fig. 31–23. Intravascular lymphomatosis presenting in lung. Low-power pattern (left) suggests diffuse interstitial pneumonia; however, the cytologic features (right) are those of neoplastic large lymphoid cells with intravascular location (*arrows*). H and E: left, ×40; right, ×500.

noproliferation lesions. Involved vessels are usually capillaries, although clusters of cells in larger vessels may be seen.

Because relatively few cases have been described, assessment of therapeutic intervention is difficult to analyze; some cases do show a response to chemotherapy.[89]

Hodgkin's Disease Presenting in the Lung

Primary pulmonary Hodgkin's disease is considered rare, and some have disputed its existence. Relapse of Hodgkin's disease in the lung or pleura is much more common. Nevertheless, case reports and small series of primary pulmonary Hodgkin's disease have appeared for many years,[90,91] and 61 cases in the literature were recently reviewed.[92]

Primary pulmonary Hodgkin's disease occurs more frequently in women (2:1), and patients are older than those with primary nodal Hodgkin's disease; the average age is 33 years for men and 51 years for women.[91] The majority had the following symptoms in decreasing order of frequency: cough, fever, weight loss, dyspnea, fatigue, anorexia, chest pain, and pruritis.[91] Radiographically, reticulonodular infiltrates and single or multiple nodules are described.[91,92] Cavitation is not uncommon.[92]

The histologic findings of pulmonary Hodgkin's disease are identical to those in lymph nodes: Reed–Sternberg cells in the appropriate cellular milieu are needed for the diagnosis. In small nodules and diffuse infiltrates, a lymphatic distribution of infiltration can be discerned; vascular infiltration occurs. Other patterns include a pneumonic growth pattern (in which the infiltrate fills alveoli in a consolidative fashion), endobronchial lesions, and extensive subpleural or pleural involvement.[90,91,93] Some cases may show a dramatic sarcoid-like granulomatous reaction.[94]

The patients in Yousem's series were treated with conventional chemotherapeutic protocols for Hodgkin's disease.[91] Approximately half showed a favorable response to combination chemotherapy with long-term remissions. Unfavorable prognosis was linked to "B" symptoms, age greater than 60 years, and bilateral disease.

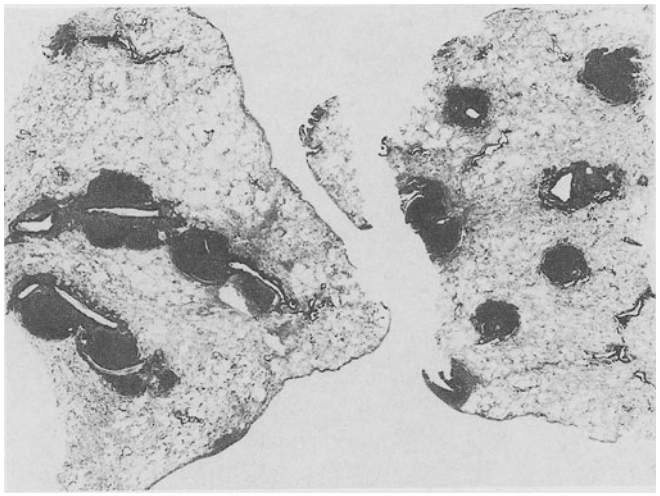


Fig. 31–24. Pulmonary relapse of large cell lymphoma presenting radiographically as a localized infiltrate. Small lymphomatous nodules are distributed along bronchovascular bundles and in the pleura. H and E, ×5.

Secondary Lymphomas Involving the Lung

Histologically, secondary pulmonary lymphomas in the lung cannot be distinguished from those presenting in the lung.[47,60] (Figs. 31–24 and 31–25). The knowledge of prior lymphoma is critical in making the diagnosis because the cytologic features may then be compared with the initial lesion. There may be transformation to a more unfavorable histology, with an increase of large cells in the case of non-Hodgkin's lymphomas and a relative increase in large cells and decrease in small lymphocytes and other inflammatory cells in Hodgkin's disease.[60]

Chronic lymphocytic leukemia involving the lung cannot be distinguished from primary or secondary small lymphocytic lymphomas. Among secondary mixed-cell and large cell lymphomas, necrosis and vascular infiltration are common findings. When Hodgkin's disease relapses in the lung, histologically diffuse infiltrates along lymphatic routes tend to be relatively frequent, and central fibrinoid necrosis with viable cells rimming vessels is quite common.

Leukemic Infiltrates in the Lung

Clinically significant leukemic pulmonary infiltrates recognized during life are quite rare, and infections, hemorrhage, heart failure, the effects of chemotherapy or radiotherapy, alveolar proteinosis, and opportunistic neoplasms should first be excluded.[95–97] Even when an unequivocal leukemic infiltrate is histologically identified in the lung, it may be incidental (although still significant) to a coexisting lesion, especially infection, that is the cause of the patient's immediate lung problem. The incidence of leukemic infiltration of the lung found histologically at autopsy, which varies from 25% to 64%,[95] is much greater than clinically significant infiltrates found during life, which occur in less than 7% percent of leukemic patients.[95,98,99] Any histologic subtype may be seen, but in the author's experience chronic lymphocytic leukemia is the type most often encountered in biopsy material. An interesting but quite rare

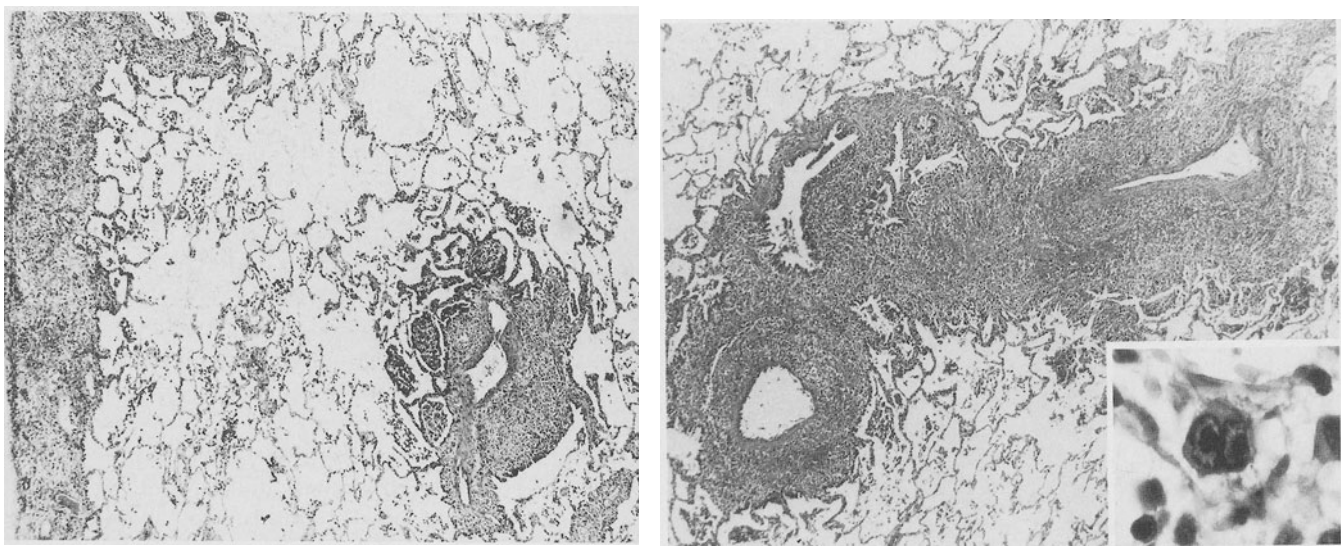


Fig. 31–25. Pulmonary relapse of Hodgkin's disease. Infiltrates are present in the pleura and along pulmonary veins and bronchovascular rays. H and E: left and right, ×25; inset, ×630.

manifestation of chronic lymphocytic leukemia is diffuse infiltration of bronchioles producing airway obstructive disease.[100]

Among acute leukemias, pulmonary infiltration is more common with nonlymphocytic leukemias,[95,101] and severe pulmonary disease may be a major initial manifestation, especially in patients with high (40% or greater) blast counts.[95]

Three unusual reactions that appear unique to leukemia are leukostasis, leukemic cell lysis pneumopathy, and hyperleukocytic reaction.[97,102,103] In leukostasis, there is vascular occlusion by aggregates of blasts in patients with peripheral leukocyte counts greater than 200,000/μl. Leukemic cell lysis pneumopathy is associated with severe hypoxemia and diffuse pulmonary infiltrates developing within 48 h after the onset of chemotherapy in patients with high leukocyte counts, generally greater than 200,000/μl. The high blast count combined with the effects of the chemotherapy on the leukemic cells is associated with aggregates of blasts within capillaries, small infarcts, hemorrhage, interstitial edema, and subsequent diffuse alveolar damage. In the hyperleukocytic reaction, a rapid increase in the peripheral blast count (generally greater than 245,000/μl) is associated with acute respiratory distress and accumulations of blast cells in small vessels with microhemorrhages and alveolar edema.

In both acute and chronic adult T-cell leukemias, clinically evident pulmonary leukemic infiltrates appear to be relatively common and were seen in 13 of 29 patients reported by Yoshioka et al. (Fig. 31–26).[104] In 6 of the 13 cases, a diagnosis of "chronic lung disease" had been carried for 2 to 6 years before this diagnosis of leukemia, and 4 of the 6 were histologically confirmed as having leukemic infiltrates, often associated with interstitial fibrosis.

Radiographically, leukemic involvement of the lung may present as localized or diffuse infiltrates, nodule(s), pleural disease, or recurrent "pneumonias."[97–100,105–108]

Histologically, leukemic infiltrates of the lung follow the lymphatic routes (Fig. 31–27). Formation of nodules is unusual.[105] The leukemic cells may be so sparse that they are easily overlooked. Special stains, such as chloroacetate esterase, may be helpful in confirming their presence and in identifying a phenotype. Both lymphoid and myeloid leukemias may involve the lung or pleura.[100,105,106]

Agnogenic myeloid metaplasia and acute myelosclerosis are occasionally associated with pulmonary involvement.[109] Infiltrates along the lymphatic routes are seen with variable amounts of fibrous tissue production. The amount of fibrous tissue may overshadow the hematopoietic cells (Fig. 31–28).

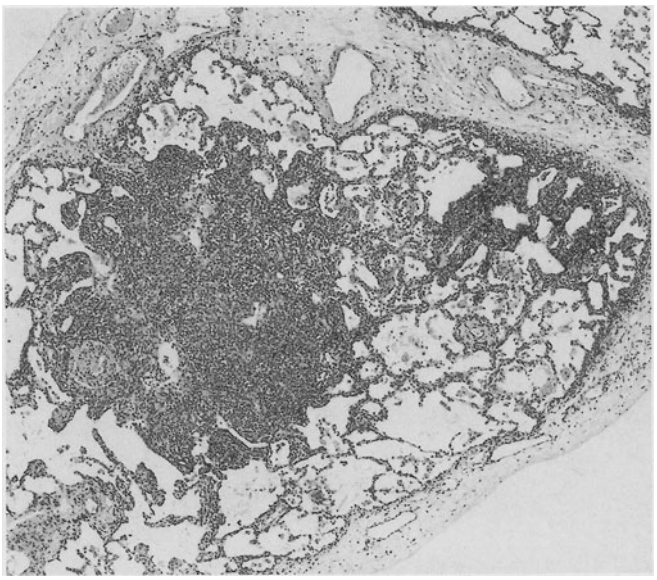


Fig. 31–26. Adult T-cell leukemia/lymphoma. Dense peribronchiolar and alveolar septal lymphoid infiltrates are seen in this biopsy from a patient who had a chronic pulmonary infiltrate. The cytological features of the cells were identical to those of the patient's lymphoreticular malignancy. H and E, ×25. (Courtesy of M. Kitaichi, M.D., Kyoto.)

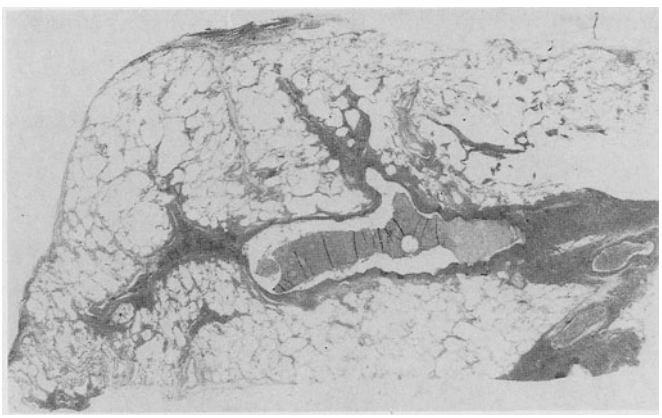


Fig. 31–27. Pulmonary infiltration by chronic myelogenous leukemia at autopsy. The infiltrate is restricted to a distribution along airways and vessels. H and E, ×4.

Malignant Histiocytosis

Malignant histiocytosis is a rare lymphoreticular malignancy caused by a systemic proliferation of neoplastic cells that resemble histiocytes,[110–113] although many cases classified as malignant histiocytosis have been reinterpreted as T-cell[114] or Ki-1 lymphomas.[115] Pulmonary involvement was described before the recognition of these latter two groups of lymphomas, and the

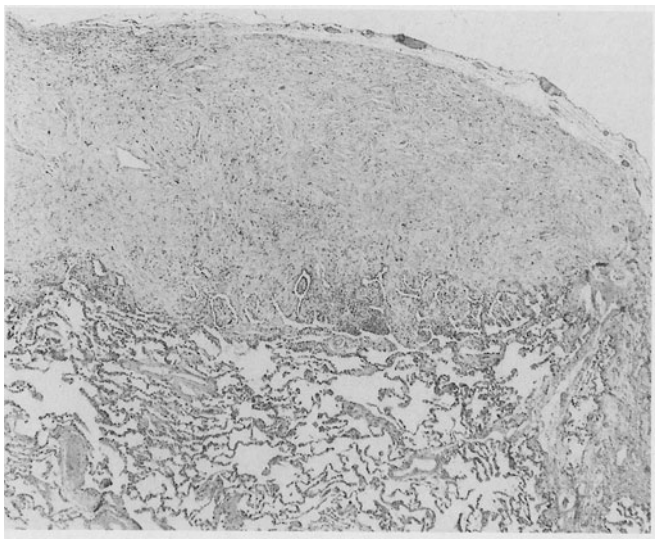


Fig. 31–28. Pleural involvement by agnogenic myeloid metaplasia. A thick pleural plaque is composed predominantly of fibrous tissue. Within this, a few islands of hematopoietic cells including megakaryocytes can be identified. This patient had a long history of agnogenic myeloid metasplasia and evidence of extramedullary myelofibrotic lesions at other sites including the pulmonary parenchyma. H and E, ×25.

features of lung involvement in malignant histiocytosis, as presently defined, are not well characterized. Pulmonary symptoms include cough, fever, and shortness of breath.[110,111,113] Pulmonary functions may show a severe restrictive deficit, and even respiratory failure.[110,111,113] Chest radiographs show bilateral interstitial infiltrates or, rarely, multiple nodules.[110]

Histologically, an infiltrate of atypical lymphoid cells (sometimes with features recognizable as histiocytic) involves lymphatic routes. There may be a variable amount of septal widening and fibrous tissue proliferation, and the cells may occur singly or in clusters. The infiltrates may expand to form nodules.

Mycosis Fungoides/ Sezary's Syndrome

The lung is the second most frequently involved extracutaneous site, after lymph nodes, in mycosis fungoides (cutaneous T-cell lymphoma)[116,117] (Fig. 31–29). Localized, diffuse, or sometimes nodular radiographic infiltrates are seen. The infiltrates are distributed along lymphatic routes, and the cytologic spectrum is similar to that seen in mycosis fungoides at other sites. Vascular infiltration and necrosis may be present.

Plasma Cell Tumors and Multiple Myeloma

Plasma cell tumors in the lung are extremely rare.[118] Pure plasmacytomas should be distinguished from other lesions with numerous plasma cells, including lymphoplasmacytoid small lymphocytic lymphomas and plasma cell granulomas. The number of cases of pulmonary plasmacytomas that have been reported is too small to make any firm statements about their behavior. Amin[119] has reported three cases that all

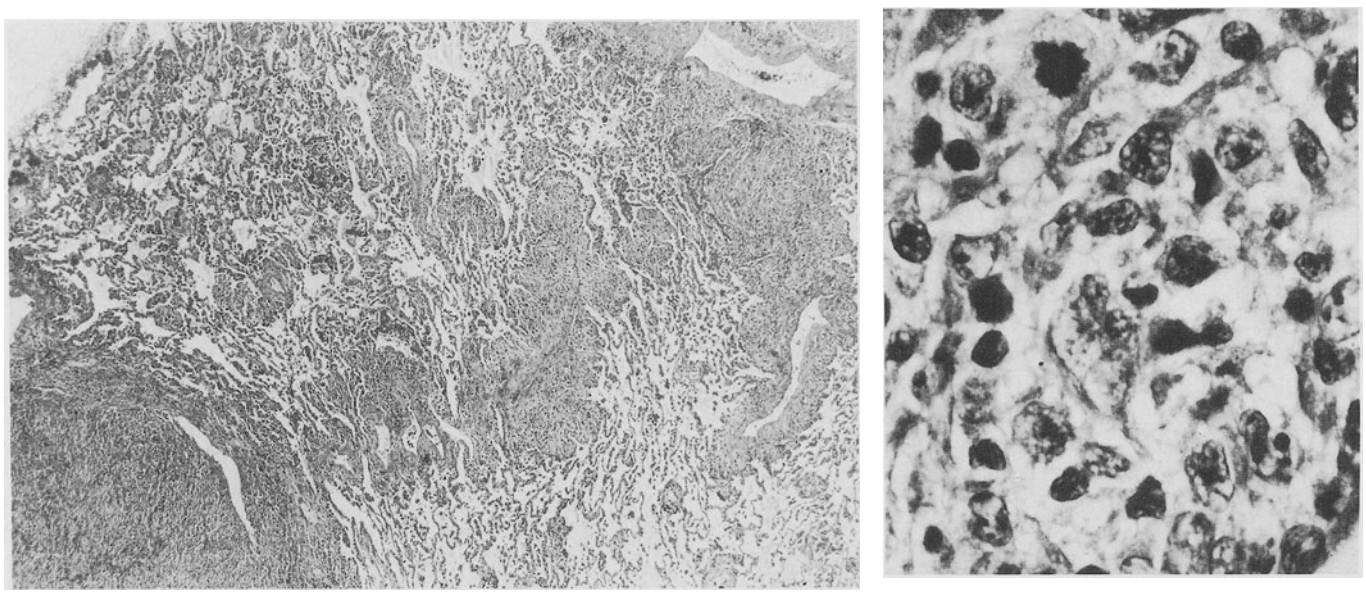


Fig. 31–29. Disseminated mycosis fungoides involving the lung shows both discrete nodules (low left) and diffuse perivascular infiltrates. A mixed cytologic composition includes cells with convoluted nuclei. H and E: left, ×25; right, ×630.

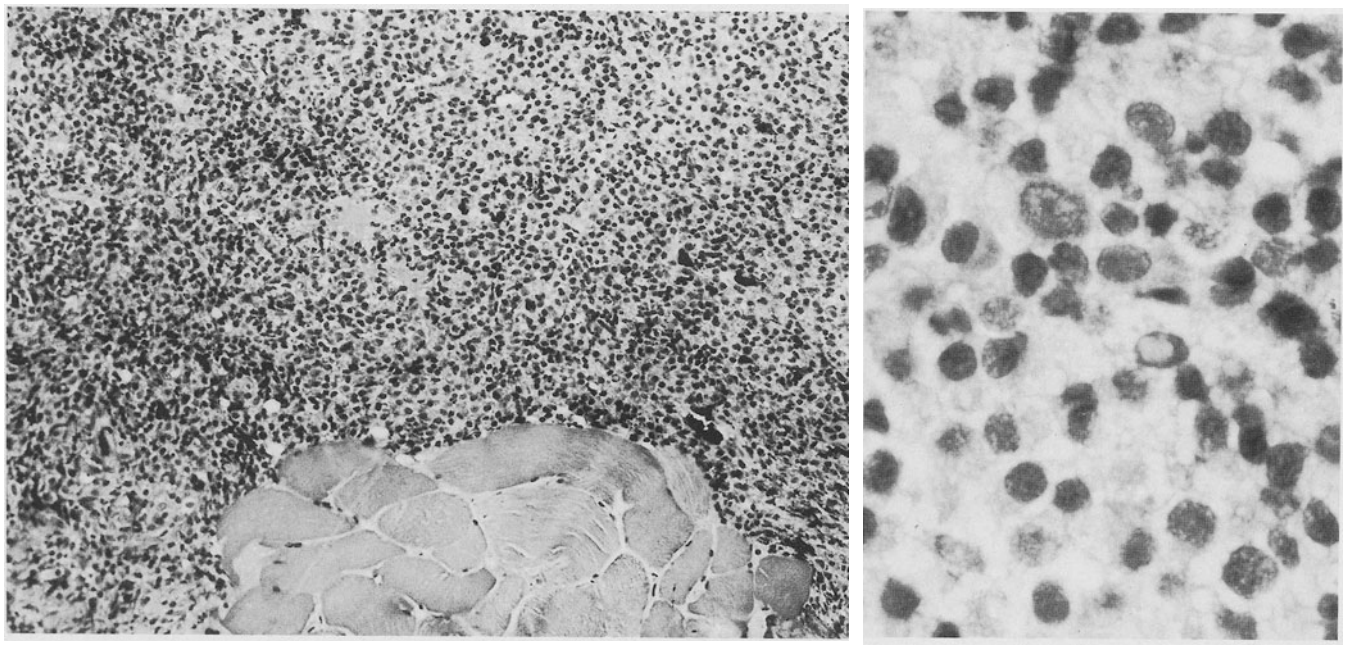


Fig. 31–30. Waldenstrom's macroglobulinemia presenting as recurrent pleural effusions. A closed pleural biopsy shows a dense infiltrate of lymphocytes and plasmacytoid lymphocytes, some with Dutcher bodies. H and E: left, ×100; right, ×630.

showed systemic dissemination within 3 years of presenting with localized or only regional lung disease. Roikjaer and Thomsen[120] described a patient with two separate pulmonary plasmacytomas occurring during a 5-year period. Both were resected, and there was no evidence of dissemination during the next 4 years.

Pulmonary involvement in patients with multiple myeloma is more frequent than is primary pulmonary plasmacytoma, although it still is not common. Most of the patients have clinically obvious disseminated myeloma, and pulmonary involvement is part of the systemic disease.[121,122] Pulmonary presentation with infiltrates resembling pneumonia has also been described.[123] Multiple nodules are more frequent than diffuse infiltrates.[123] Also in this setting, diffuse alveolar septal amyloid deposition or other forms of amyloidosis secondary to the myeloma may also be a cause of lung disease.[123] Kijner and Yousem[124] reported a case of systemic light chain disease presenting as bilateral nodular infiltrates on chest radiographs. Light chain deposition was distinguished from amyloid by electron microscopy.

Pleural Lymphoma/Leukemia

Pleural involvement by lymphomas and leukemias is not unexpected, because the pleura represents one of the lymphatic routes that these lesions generally affect. Indeed, one of the helpful features in identifying lymphocytic lymphomas is the fact that extrapleural plaques of infiltrate strongly favor a lymphoma over a benign process.[50] Elastic tissue stains may be necessary to identify the exact location of the visceral pleura in the case of massive infiltrates. Lymphomas, including Waldenstrom's macroglobulinemia, rarely present as pleural disease (Fig. 31–30). In these cases, the extensive and predominately visceral pleural infiltration is out of proportion to the relatively scant infiltration of the underlying pulmonary parenchyma.

Immunologic marker studies may be helpful ancillary aids in recognizing a clonal population of cells in effusions. Pleural effusions found at presentation in patients with Hodgkin's disease and (less commonly) non-Hodgkin's lymphomas are usually caused by lymphomatous involvement of mediastinal lymph nodes and secondary lymphatic obstruction.[125] In cases that require biopsy, the visceral pleura should be biopsied in preference to the parietal pleura, as the extent of infiltrate is usually much more severe in the visceral pleura. Widespread myeloma may cause pleural effusions.[121,122]

Practical Considerations

Overall, the majority of pulmonary lymphomas and leukemias are diagnosed on the basis of open lung biopsy or a resection specimen. Primary diagnosis by transbronchial biopsy is feasible in selected situations,

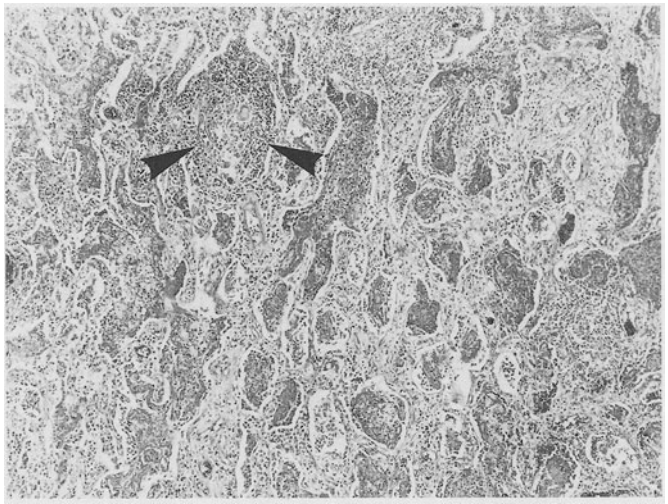


Fig. 31–31. Pulmonary parenchymal reaction adjacent to primary pulmonary Hodgkin's disease. There is extensive nonspecific interstitial widening with granulomas (*arrowheads*) and dense intraalveolar exudate; these nonspecific and apparently inflammatory changes were quantitively much more extensive than the Hodgkin's disease in this case. H and E ×40.

particularly with support of immunohistochemical studies.[126] Endobronchial involvement may be seen with both leukemias and lymphomas.[127–130] These cases are particularly amenable to biopsies through the bronchoscope. Techniques such as bronchial washings and bronchoalveolar lavage are occasionally useful in the primary diagnosis of lymphoma, but their role is probably greater in patients who already carry a histologic diagnosis and for whom a pulmonary relapse needs to be confirmed. Confirmation of pulmonary involvement by these techniques has been shown with all varieties of lymphoreticular infiltrates.[96,131–135]

A trap in the evaluation of many lung lymphomas is the presence of an associated benign or reactive-appearing infiltrate that may obscure the neoplasm population (Fig. 31–31).

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