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Primary Pulmonary Lymphoid Lesions: Radiologic and Pathologic Findings[1]

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The pulmonary lymphoid system is complex and is composed of two compartments: the pulmonary lymphatics and the bronchus-associated lymphoid tissue (BALT). Additional important cells that function in the pulmonary lymphoid system include dendritic cells, Langherhans cells, macrophages, and plasma cells. An appreciation of the normal lymphoid anatomy of the lung as well as its immunology is helpful in understanding the radiologic and pathologic findings of the primary pulmonary lymphoid lesions. Primary lymphoid lesions of the lung arise from the BALT and are uncommon. However, they are increasingly recognized within the growing number of posttransplant patients as well as other patients who are receiving immunosuppressive therapies. Primary lymphoid lesions encompass a wide range of benign and malignant lesions. Benign lymphoid lesions of the lung include reactive lymphoid hyperplasia, follicular bronchiolitis, lymphoid interstitial pneumonia, and nodular lymphoid hyperplasia. Malignant lymphoid lesions of the lung include low-grade B-cell lymphoma of mucosa-associated lymphoid tissue (MALT), other non-Hodgkin lymphomas, and Hodgkin lymphoma. Last, a miscellaneous group of primary lymphoid lesions includes lymphomatoid granulomatosis, posttransplant lymphoproliferative disorders, acquired immunodeficiency syndrome (AIDS)–related lymphoma, and intravascular lymphoma/lymphomatosis. These lesions are best evaluated with multidetector chest computed tomography. The radiologic findings of the primary lymphoid lesions are often nonspecific and are best interpreted in correlation with clinical data and pathologic findings. The purpose of this article is to review pulmonary lymphoid anatomy as well as the most common primary pulmonary lymphoid disorders.

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Abbreviations: AIDS = acquired immunodeficiency syndrome, BALT = bronchus-associated lymphoid tissue, EBV = Epstein-Barr virus, FDG = fluorodeoxyglucose, H-E = hematoxylin-eosin, HIV = human immunodeficiency virus, LIP = lymphoid interstitial pneumonia, MALT = mucosa-associated lymphoid tissue, NLH = nodular lymphoid hyperplasia, PTLD = posttransplant lymphoproliferative disorder

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SA-CME LEARNING OBJECTIVES

After completing this journal-based SA-CME activity, participants will be able to:

- Describe the components of the pulmonary lymphoid anatomy of the lungs, including BALT and the pulmonary lymphatics.
- Discuss the pathogenesis and treatments of the common primary pulmonary lymphoid lesions.
- Recognize imaging features of the common primary pulmonary lymphoid lesions.

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Introduction

The pulmonary lymphoid system is composed of bronchus-associated lymphoid tissue (BALT) and the pulmonary lymphatics. Primary lymphoid diseases of the lung arise from the BALT.

Primary lymphoid lesions of the lung encompass *(a)* nonneoplastic lymphocytic proliferations, including reactive lymphoid hyperplasia, follicular bronchiolitis, lymphoid interstitial pneumonia (LIP), and nodular lymphoid hyperplasia (NLH); *(b)* neoplastic lymphocytic proliferations, including low-grade B-cell lymphoma of mucosa-associated lymphoid tissue (MALT), other non-Hodgkin lymphomas, and Hodgkin lymphoma; and *(c)* a miscellaneous group

TEACHING POINTS

- BALT is a specific type of MALT that is present in the lungs and involved in the immune response to inhaled antigens.
- Follicular bronchiolitis is polyclonal hyperplasia and expansion of the BALT from chronic antigen stimulation, resulting in hyperplastic lymphoid follicles primarily composed of polytypic B cells, which are predominantly peribronchiolar and at bronchial bifurcations, with only minimal lymphocytic infiltration into the adjacent alveolar interstitium.
- Pleural effusion and airspace consolidation are extremely uncommon in LIP, and their presence suggests a malignant process such as lymphoma. Large nodules (>11 mm) or growing nodules also warrant suspicion for possible coexisting lymphoma.
- MALT lymphoma (MALToma) is a monoclonal lymphoid proliferation arising from a B-cell progenitor within the BALT, and is classified as low-grade marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue in the World Health Organization classification.
- PTLD encompasses a group of lymphoproliferative disorders occurring in the post stem cell and organ transplant setting that range from benign polyclonal proliferation to malignant monoclonal disease. PTLD is intimately associated with EBV infection.

of lesions, including lymphomatoid granulomatosis, posttransplant lymphoproliferative disorder (PTLD), acquired immunodeficiency syndrome (AIDS)–related lymphoma, and intravascular lymphoma/lymphomatosis (Table 1).

These lesions are best evaluated with multidetector chest computed tomography (CT) in correlation with clinical data and pathologic findings. The purpose of this article is to review pulmonary lymphoid anatomy as well as the most common primary pulmonary lymphoid disorders.

Table 1: Primary Lymphoid Lesions of the Lung

Nonneoplastic
Reactive hyperplasia
Follicular bronchiolitis
LIP
NLH
Neoplastic
Primary pulmonary lymphoma
MALT lymphoma
Other non-Hodgkin lymphoma
Hodgkin lymphoma
Miscellaneous
Lymphomatoid granulomatosis
PTLD
AIDS-related lymphoma
Intravascular lymphoma

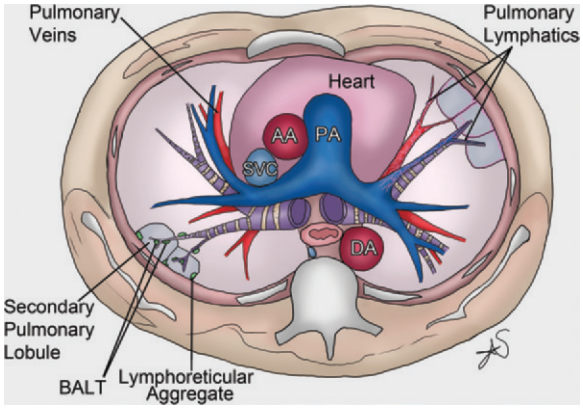

Figure 1. Pulmonary lymphatics and BALT. Illustration shows the pulmonary lymphatics draining along interlobular septa, pulmonary arteries, and pulmonary veins toward the hilum in the left lung. BALT is depicted along bronchi and bronchial bifurcations in the right lung. Pulmonary lymphoreticular aggregates are also depicted in the right lung along the interlobular septa and pleura. *AA* = ascending aorta, *DA* = descending aorta, *PA* = pulmonary artery, *SVC* = superior vena cava.

Pulmonary Lymphoid Anatomy

Pulmonary Lymphatics

The pulmonary lymphatics are made up of lymphatic pathways that are located in the pleura and interlobular septa as well as along the bronchovascular bundles and pulmonary veins. This pulmonary lymphatic network consists of two subdivisions: the superficial lymphatic system and deep lymphatic system (Fig 1).

The superficial lymphatic system, also known as the pleural lymphatics, arises in the pleural space and drains the outer portion of the lung toward the hilum along the lymphatics located within the interlobular septa. The deep lymphatic system, also known as the parenchymal lymphatics and intralobar lymphatics, arises within the secondary pulmonary lobule and drains along lymphatic channels located on the bronchovascular bundles toward the hilar nodes (1–4). Although points of communication exist between these two systems at the boundaries of lobules and lobes, for the most part they drain separately along their own lymphatic channels, which contain valves, toward the hila and subsequently into the hilar nodes (2,3).

Bronchus-associated Lymphoid Tissue

BALT is a specific type of MALT that is present in the lungs and involved in the immune response to inhaled antigens (1–3,5–8). BALT is made up of submucosal collections of lymphocytes (B and T cells) present just beneath areas of specialized bronchial epithelium throughout the airways, most commonly at areas of bronchial bifurcation (Figs 1, 2) (2,5,7).

BALT is an organized structure, composed primarily of B cells at the center with periph-

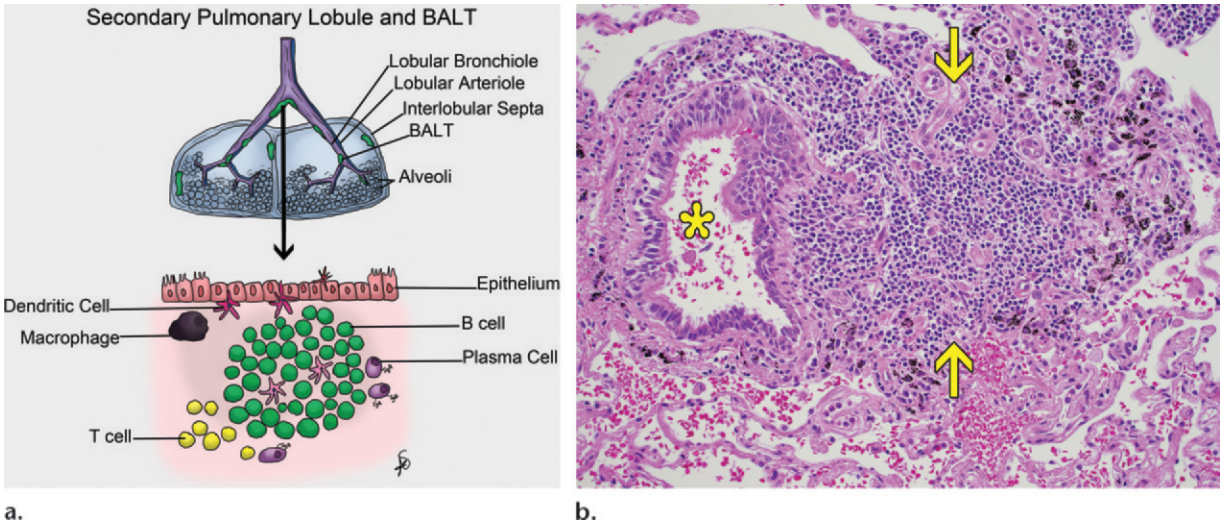

Figure 2. BALT. **(a)** Illustration shows BALT within the secondary pulmonary lobule and at the cellular level. **(b)** BALT hyperplasia in a 62-year-old woman with a 40 pack-year smoking history and histologic evidence of respiratory bronchiolitis (so-called smokers' macrophages) and emphysema. Low-power photomicrograph shows BALT hyperplasia, characterized by a collection of small lymphocytes (arrows) adjacent to the airway (*). (Original magnification, ×200; hematoxylin-eosin [H-E] stain.)

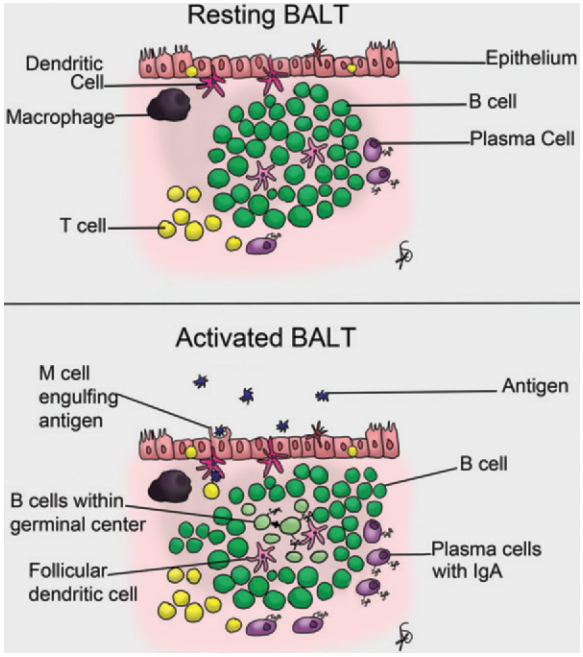

Figure 3. Illustration shows resting BALT (top) and antigenically stimulated BALT (bottom). The antigenically stimulated BALT has a germinal center present in the center of the B-cell follicle, in which B cells are actively proliferating, differentiating, and undergoing antibody class switching.

eral clusters of T cells (6,9). Compared with the normal bronchial epithelium, which is composed of ciliated columnar cells, a specialized epithelium composed of nonciliated flattened epithelial cells—also known as M cells—that are capable of phagocytosis and pinocytosis of antigens overlies areas where BALT exists or can be induced (1–3,5–7,11,12). This specialized epithelium is infiltrated by lymphocytes (T cells) and is also referred to as lymphoepithelium (Fig 2) (6,10–12).

BALT contains no afferent lymph channels, but drains via efferent lymphatic channels to regional lymph nodes (5,12). Resting BALT contains no true germinal centers, which are areas in the center of a follicle (spherical cluster of B cells) in which stimulated B cells are actively proliferating, differentiating, and changing the class of antibody that they produce (IgM, IgG, IgA, etc). However, BALT can develop follicles with distinct germinal centers when antigenically stimulated (Fig 3) (6,10).

BALT is not present at birth, develops in infants and young children, and is again absent in the normal healthy adult (2,3,5,9,11–14). BALT can reappear in adults with antigenic stimulation, such as infection, cigarette smoke, chronic inflammation (asthma), collagen vascular disease, and AIDS (2,3,5,8,11,12,14,15). The process by which BALT reappears in adults secondary to antigen stimulation is referred to as BALT induction (Fig 4).

When an antigen appears, one of the specialized nonciliated epithelial cells of the lymphoepithelium phagocytoses the antigen from the airway lumen. Next, one of two types of antigen-presenting cells within the adjacent mucosa (either a dendritic cell or Langerhans cell) receives the antigen and is stimulated. The stimulated antigen-presenting cell releases cytokines to recruit naive B and T cells to its location and presents the antigen to T cells, leading to subsequent BALT stimulation and growth, further cytokine release,

and IgA production (Fig 4) (5,12). Chronic antigenic stimulation of BALT in adulthood can result in a variety of benign and malignant lymphoid diseases, with the possibility of more than one of these diseases occasionally arising within the same patient (3,5,11,12,16).

Important Cells Involved in the Pulmonary Lymphoid System

Pulmonary Dendritic Cells and Langerhans Cells.—There are two types of dendritic cells: follicular dendritic cells located in the BALT and interdigitating dendritic cells that are located in the connective tissue of the lung around airways and in alveolar walls, interlobular septa, and the pleura. Langerhans cells are a subtype of dendritic cell derived by a process of differentiation, and small numbers are found in the bronchial epithelium (2,9,12). Both dendtritic cells and Langerhans cells detect and present inhaled antigens to T cells located within the BALT and are important in maintenance of the BALT (9,12,17). Follicular dendritic cells play an important role in sustaining the stimulated B cells (2,12).

Macrophages.—These are present along the epithelial surface of the airways, within the BALT, and within the pulmonary interstitium. Macrophages are involved in phagocytosis (1,3).

Plasma Cells.—Plasma cells are present within the mucosa of the tracheobronchial tree as well as the periphery of the BALT. Most plasma cells express surface IgA (1,5).

Pulmonary Lymphoreticular Aggregates

Pulmonary lymphoreticular aggregates are nonencapsulated collections of cells composed primarily of lymphocytes, but which also contain a few plasma cells. These are distributed around bronchi, interlobular septa, and the pleura. These are also rarely located at the centers of acini adjacent to terminal and respiratory bronchioles (Figs 1, 2) (2,3,6).

Intrapulmonary Lymph Nodes

Intrapulmonary lymph nodes are encapsulated lymph nodes that usually occur below the level of the carina at the bifurcations of large bronchi as well as in the lung periphery, subpleural in location or adjacent to interlobular septa. These are associated with dust and cigarette smoking. At imaging, they appear as single or multiple well-circumscribed, homogeneous nodules that are round or ovoid. Resection of intrapulmonary lymph nodes occurs when the intrapulmonary lymph node is mistaken for lung malignancy. This usually happens in older patients who have risk factors for lung cancer such as a history of smoking (1–3,7,18).

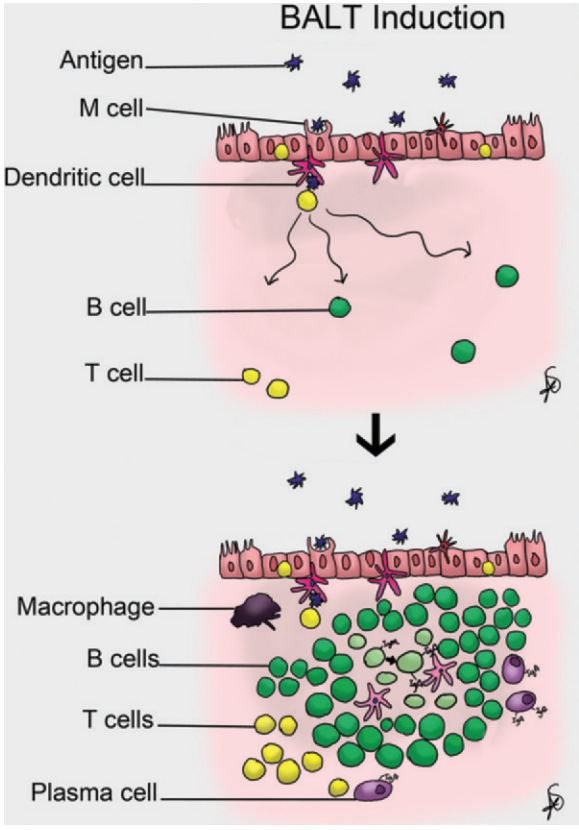

Figure 4. Illustration shows BALT induction. Top: An M cell within the lymphoepithelium phagocytoses the antigen, which is subsequently picked up by a dendritic cell (antigen-presenting cell). The dendritic cell releases cytokines that recruit naive B and T cells to its location, then presents the antigen to T cells. Bottom: Cytokine release leads to subsequent BALT stimulation and growth, further cytokine release, and IgA production.

Nonneoplastic Lymphocytic Proliferations

Nonneoplastic lymphocytic proliferations include reactive lymphoid hyperplasia, follicular bronchiolitis, LIP, and NLH.

Reactive Lymphoid Hyperplasia

Reactive lymphoid hyperplasia of the BALT occurs in response to multiple diseases, including infection, malignancy, allergic lung diseases such as hypersensitivity pneumonitis, as well as interstitial lung diseases. It is a reactive phenomenon seen in histopathologic specimens, not a disease in itself (19).

Follicular Bronchiolitis

Follicular bronchiolitis (Table 2) is polyclonal hyperplasia and expansion of the BALT from chronic antigen stimulation, resulting in hyperplas-

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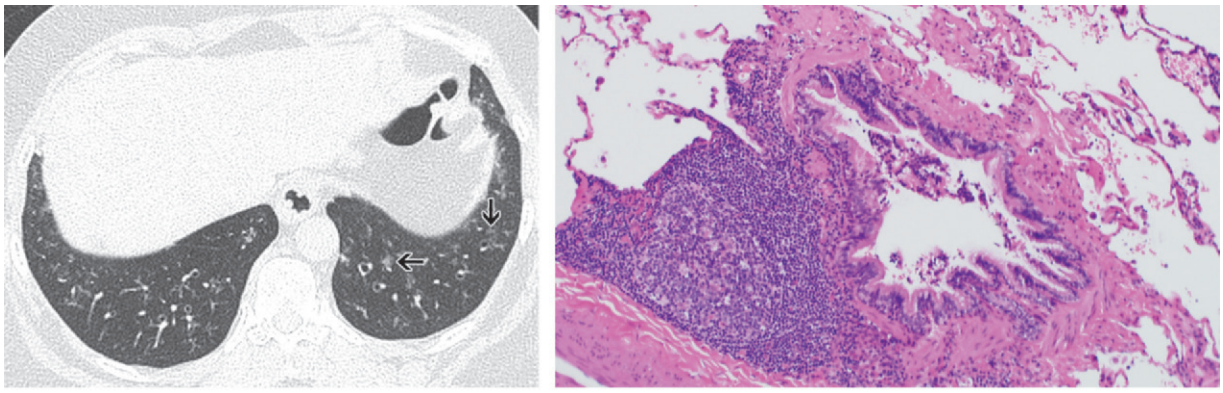
Table 2: Features of Follicular Bronchiolitis

Clinical data	Associated with collagen vascular disease, particularly rheumatoid arthritis, and immunodeficiency
Histopathologic findings	Polyclonal hyperplasia of the BALT
	Peribronchiolar in distribution
	No more than minimal lymphocytic infiltration into adjacent alveolar septa
Main imaging findings	Radiography: radiograph usually normal; subtle lower lung nodular opacities
	CT: small centrilobular nodules (usually 1–3 mm in size); tree-in-bud configuration
	PET/CT: given small size of lesions, PET/CT unhelpful
Differential diagnosis	Infection, hypersensitivity pneumonitis, respiratory bronchiolitis

Note.—PET = positron emission tomography.



a. b.

Figure 5. Follicular bronchiolitis in a 53-year-old woman with a history of Sjögren syndrome. **(a)** Axial CT image of the lower lungs shows multiple ground-glass centrilobular nodules (arrows). Note the bronchial dilatation in the left lower lobe. (Courtesy of Tan-Lucien H. Mohammed, MD, FCCP, Gainesville, Fla.) **(b)** Photomicrograph shows bronchi and bronchioles associated with hyperplastic polyclonal lymphoid follicles with reactive germinal centers compressing the lumina. (Original magnification, ×40; H-E stain.)

tic lymphoid follicles primarily composed of polytypic B cells, which are predominantly peribronchiolar and at bronchial bifurcations, with only minimal lymphocytic infiltration into the adjacent alveolar interstitium (6,18,20–23). It is associated with collagen vascular diseases, particularly rheumatoid arthritis, congenital or acquired immunodeficiency disorders such as IgA deficiency, AIDS, and common variable immunodeficiency, as well as with hypersensitivity disorders associated with peripheral eosinophilia (6,18,20–25).

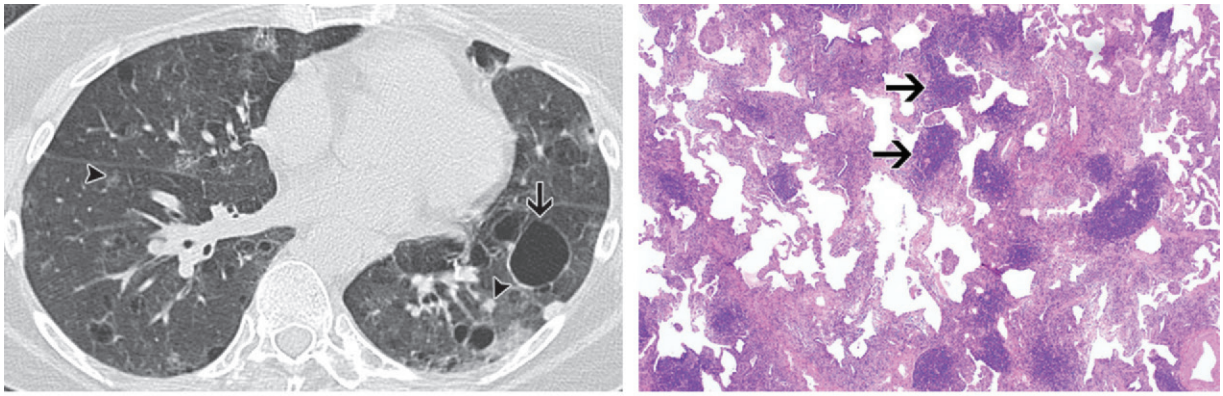
Radiographically, these hyperplastic lymphoid follicles may not be apparent, or may appear as subtle nodular opacities in a lower lung distribution. CT of the lung shows centrilobular nodules and ground-glass opacities, which can range from 1 to 12 mm in size but are most commonly 1–3 mm (Fig 5). The centrilobular nodules sometimes demonstrate a tree-in-bud configuration (6,18,20–24). Less common findings include nodules along the septa and pleura, which may actually represent small lymphoreticular aggregates (20,24,25).

Infrequent findings include bronchiectasis, bronchial wall thickening, and peribronchovascular consolidation (20,22,24,25). Interlobular septal thickening has been described in several cases, but has been postulated by Howling et al (20) to possibly be an incidental finding due to its apparent lack of relationship to the histologic findings of follicular bronchiolitis. Given the small size of the nodules present in follicular bronchiolitis, fluorodeoxyglucose (FDG) PET/CT is of little value in the workup of this disease (20,24).

The differential diagnosis for follicular bronchiolitis includes other diseases that manifest as centrilobular nodules at CT, including infection, hypersensitivity pneumonitis, and respiratory bronchiolitis. Eliciting clinical information such as presence of infectious symptoms, environmental exposures, smoking history, and history of collagen vascular disease and immunodeficiency is helpful. Infectious symptoms would suggest an infectious process. A history of environmental exposure would suggest hypersensitivity pneumonitis. Smoking is associated with respiratory bronchiolitis. A history of collagen vascular disease, particularly rheumatoid arthritis, or immunodeficiency would point toward follicular

Table 3: Features of LIP

Clinical data	Associated with autoimmune disease, chronic infections, and several miscellaneous conditions (see Table 4) Dysgammaglobulinemia present in up to 60% of patients
Histopathologic findings	Infiltration of polyclonal lymphocytes (predominantly T cells) into the alveolar interstitium
Main imaging findings	Radiography: radiograph often normal; lower lung reticular and nodular opacities CT: perivascular cysts, centrilobular nodules, ground-glass attenuation, lower lung distribution of disease, patchy interlobular septal thickening, lymphadenopathy PET/CT: limited data available; nodules in LIP can be hypermetabolic if >11 mm
Differential diagnosis	Infection, pulmonary amyloidosis, pulmonary lymphoma



a. b.

Figure 6. LIP in a 70-year-old woman. **(a)** Axial CT image shows multiple well-defined thin-walled cysts (arrow) on a background of ground-glass attenuation. In addition, multiple pulmonary nodules are present (arrowheads). (Courtesy of Jeffrey P. Kanne, MD, Madison, Wis.) **(b)** Photomicrograph shows lung parenchyma with a dominant interstitial pattern of distribution of lymphocytes, which are primarily T cells intermixed with polytypic B cells and plasma cells (confirmed with CD3 and CD20 immunostains, respectively [not shown]), commonly seen in adults and children with altered immune status. Multiple lymphoid follicles are also present in the interstitium (arrows). (Original magnification, ×40; H-E stain.)

bronchiolitis. Ultimately, surgical lung biopsy is usually necessary to establish a diagnosis of follicular bronchiolitis, especially in the absence of a suggestive clinical history (21,24).

Patients usually present in middle age, although cases in children have been reported. Symptoms include insidious onset of shortness of breath, dyspnea, cough, and weight loss (18,23,24). The prognosis for this disease is generally good but can be variable with younger age, as younger patients are more likely to have worsening disease despite adequate treatment (6,18,21,23,24). Treatment involves management of the underlying disease, steroids, and immunosuppressants (6,18,21,24).

Lymphoid Interstitial Pneumonia

LIP is a rare benign polyclonal lymphoproliferative disorder of the lung parenchyma (Table 3). Compared with follicular bronchiolitis, it is a much more extensive and diffuse disease. In LIP, there is diffuse infiltration of lymphocytes (predominantly T cells intermixed with some polytypic B cells) and plasma cells into the alveolar interstitium, resulting in expansion of the alveolar septa (7,10,16,18,20–23,25–29). Ill-defined granulomas and giant cells have been found in 20%–50% of cases (6,7,10,18,22,23,27). Lymphoid follicles primarily composed of B cells are often present (19). LIP can also be complicated by amyloidosis, especially in the case of Sjögren syndrome (6,7,23,27,30).

Radiographic findings are nonspecific and range from nodular or reticular opacities in the lower lungs to an absence of findings (6,7,10,16,18,22,26,27). CT shows ground-glass opacity, centrilobular nodules and ground-glass opacities, bronchovascular bundle thickening, and peribronchovascular cysts predominantly in the lower lungs (Fig 6) (10,16,18,22,23,25,28–30). Cyst formation in LIP has been postulated to be secondary to a ball-valve mechanism involving small bronchioles that become obstructed or partially obstructed by the adjacent lymphocyte infiltration (23).

Interlobular septal thickening secondary to infiltration of the interlobular septa with lympho-

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Table 4: Diseases Associated with LIP

Diseases related to the immune system
Common variable immunodeficiency
Sjögren syndrome
Systemic lupus erythematosus
Rheumatoid arthritis
Primary biliary cirrhosis
Celiac sprue
Crohn disease
Myasthenia gravis
Hashimoto thyroiditis
Autoerythrocyte sensitization
Autoimmune hemolytic anemia
Pernicious anemia
Dysproteinemia
Infections
HIV/AIDS
Epstein-Barr virus (EBV) infection
Human herpesvirus 8
Chronic active hepatitis
Legionella pneumonia
Pneumocystis jirovecii
Tuberculosis
Miscellaneous
Dilantin (phenytoin)–induced
Allogenic bone marrow transplant
Graft versus host disease

Note.—HIV = human immunodeficiency virus

cytes and plasma cells has also been described, but can be a less prominent feature at CT and is often mild and patchy when present (16,25,28–30). Lymphadenopathy can be variably present. Pleural effusion and airspace consolidation are extremely uncommon in LIP, and their presence suggests a malignant process such as lymphoma. Large nodules (>11 mm) or growing nodules also warrant suspicion for possible coexisting lymphoma (6,7,10,16,23,26,28,30). There are case reports of increased metabolic activity at FDG PET/CT in nodules found in LIP that are larger than 11 mm (31).

The differential diagnosis of LIP includes infection, primary pulmonary lymphoma, and pulmonary amyloidosis. LIP patients are often receiving immunosuppressive therapies, predisposing them to infection, thus a history of infectious symptoms is suggestive of infection. However, follow-up to resolution is always necessary, as nonresolving areas of consolidation or large nodules at CT may represent other underlying processes, particularly primary pulmonary lymphoma. Amyloidosis can also manifest with cysts and nodules. The presence of calcification in the nodules at CT suggests amyloidosis, although tissue confirmation is often necessary, as primary pulmonary lymphoma can coexist.

Primary pulmonary lymphoma is well known to coexist with LIP, and differentiating these two entities is important but can be challenging. CT findings that point toward primary pulmonary lymphoma include areas of consolidation and the presence of pleural effusion. Large nodules (>11 mm) or growing nodules also warrant concern for primary pulmonary lymphoma. PET/CT is of questionable diagnostic value, as both large nodules in LIP (>11 mm) as well as primary pulmonary lymphoma can demonstrate increased metabolic activity. Ultimately, definitive pathologic diagnosis of LIP typically requires surgical biopsy, with immunohistochemical studies necessary to determine the polyclonal nature of the lymphocytes and distinguish LIP from lymphoma (10,23,29,31–33).

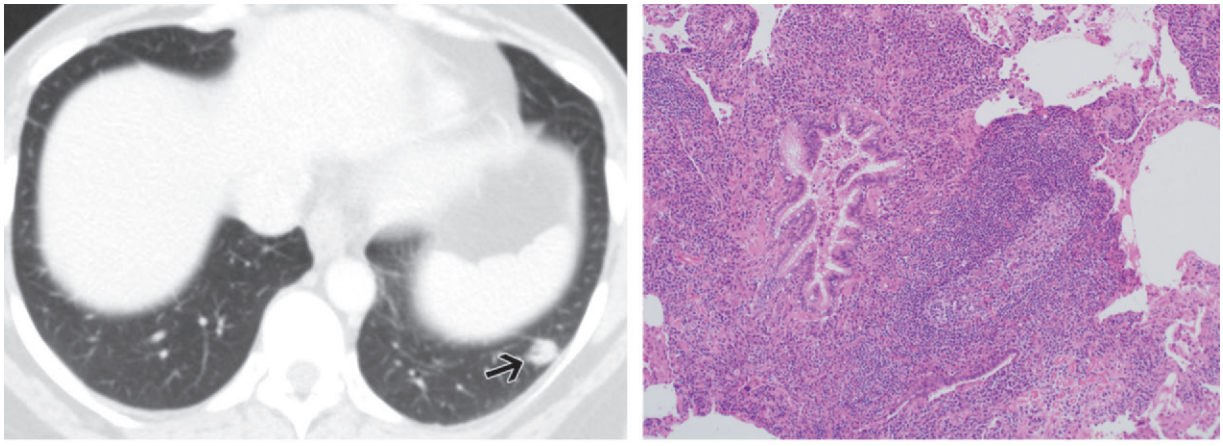
LIP has been associated with multiple diseases including many autoimmune diseases, AIDS in the pediatric population, common variable immunodeficiency, collagen vascular diseases such as Sjögren syndrome, and Castleman disease (Table 4) (6,7,10,16,18,22,23,25–29,34,35). It has been associated with the presence of EBV and human herpesvirus 8 and is also a known complication of graft versus host disease in bone marrow transplantation patients (10,18,22,23,27,36,37). The presence of LIP has been used to establish a diagnosis of AIDS in a child less than 13 years old with HIV infection (10,23,26,27).

LIP arises most commonly between the fourth and seventh decades and has higher prevalence in women than in men. Symptoms include insidious onset of cough, dyspnea, and weight loss (6,7,10,18,22,26,27,35). Approximately 60% of patients with LIP have dysproteinemia, which is usually some form of dysgammaglobulinemia, hypergammaglobulinemia being more common than hypogammaglobulinemia (6,7,10,18,22,26,27,35).

Treatment involves corticosteroids as well as treatment of the underlying disease, and outcomes are variable. At least one-third of patients are reported to have progressive disease despite therapy, with a few rarely progressing to end-stage lung disease and honeycombing (6,10,16,18,22,25,26,28). Death is usually a complication of infection secondary to immunosuppressive treatments. Malignant lymphoma complicates approximately 5% of LIP cases. Transformation of LIP to lymphoma remains a controversial subject, and the prevailing belief is that these patients also have separate areas of malignant pulmonary lymphoma from the outset (10,16,22,23,27,28).

Table 5: Features of NLH

Clinical data	Usually found in asymptomatic patients May be associated with collagen vascular disease or dysgammaglobulinemia
Histopathologic findings	Localized infiltration of polyclonal lymphocytes (predominantly T cells); "focal LIP" Polymorphous population of B and T cells with multiple germinal centers
Main imaging findings	Radiography: nodule, mass, or masslike opacity; single or multiple CT: nodule, mass, or masslike area of consolidation; single or multiple; air bronchograms PET/CT: no significant data available given rarity of this disease
Differential diagnosis	Lung cancer, metastasis, primary pulmonary lymphoma



a. b.

Figure 7. NLH in a 52-year-old woman. **(a)** Axial CT image shows a solitary pulmonary nodule in the left lower lobe (arrow). **(b)** Photomicrograph of the nodule shows a mixture of polyclonal B and T lymphocytes admixed with plasma cells. Lymphoepithelial lesions are commonly seen in these nodules, which can be either B or T cells. (Original magnification, ×40; H-E stain.)

Nodular Lymphoid Hyperplasia

NLH, formerly referred to as pseudolymphoma, is an uncommon localized polyclonal lymphoid hyperplasia in the pulmonary lung parenchyma (Table 5) (23,38). It has also been described previously as a localized, masslike form of LIP by Bragg et al (26).

NLH is composed of a polymorphous population of lymphoid cells (both B and T cells), multiple germinal centers, as well as infiltration and expansion of the alveolar interstitium by lymphocytes (T cells) and plasma cells. Variable amounts of fibrosis may also be present in the lesion as well as occasional giant cells (6,7,18,22,23,26,38). Invasion of the bronchial epithelium by lymphoid cells, referred to as a lymphoepithelial lesion, is common in NLH as well as other nonneoplastic lymphoid proliferative diseases. Russell bodies—immunoglobulin-containing cytoplasmic inclusions within plasma cells—may also be present. Focal, limited lymphangitic spread around the bronchovascular bundles and interlobular septa is present more often than not (38).

Unlike LIP, which diffusely involves the lungs, NLH involves a small area of lung and appears as a nodule, mass, or focal area of masslike consolidation within the lung at chest radiography and CT (Figs 7, 8) (6,7,18,22,23,26,38). Lesions are usually single but can be multiple (23,35). Air bronchograms are often present within the lesion at CT. NLH is often subpleural in location but can also be peribronchial.

NLH lesions show no invasion or destruction of the adjacent pleura or bronchus, a behavior often exhibited by malignant lymphoma (6,22,23,35,38). Mediastinal and hilar lymphadenopathy as well as pleural effusion are typically absent in NLH, and if present should raise the possibility of lymphoma. As these lesions are extremely rare, significant data are not available on the utility of FDG PET/CT in the workup of NLH (7,18,22,26,35).

Differential diagnostic considerations for NLH include primary lung malignancy, metastasis, and primary pulmonary lymphoma. The presence of mediastinal and hilar lymphadenopathy, pleural effusion, or invasion of an adjacent bronchus or pleural space should raise suspicion for malignancy. However, the radiographic and CT appearance of NLH, metastasis, lung malignancy,

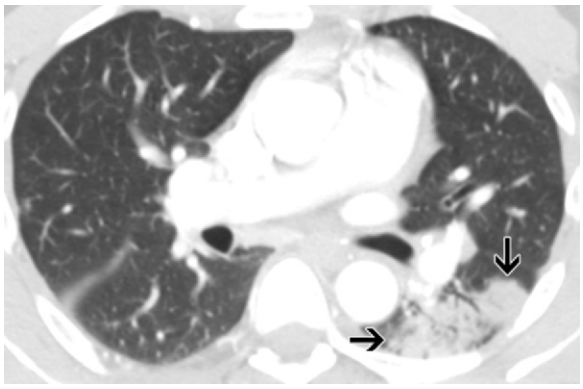


Figure 8. NLH in a 48-year-old man. Axial CT image shows a masslike area of consolidation in the left lower lobe with air bronchograms (arrows).

and primary pulmonary lymphoma can be very similar, ultimately necessitating surgical biopsy.

NLH can be associated with collagen vascular disease and dysgammaglobulinemia, but much more commonly occurs as an isolated finding in asymptomatic individuals (7,38). When symptoms are present, they include cough and dyspnea (22).

Definitive diagnosis is made with surgical biopsy. Extreme care must be taken to differentiate NLH from MALT lymphoma (discussed later), which is more common (7,18). Immunohistochemical studies are necessary to determine the polyclonal population of the lymphocytes and plasma cells, as well as molecular genetic analysis to ensure that no rearrangements of the immunoglobulin light or heavy chains are present (7,18,22,35). Intranuclear inclusions (Dutcher bodies) that are variably present in MALT lymphoma are absent in NLH (38). Glickenstein et al (35) have described NLH as a premalignant lesion, but this view remains controversial. Treatment is surgical resection. Gibson and Hansell (6) have described instances of recurrence after resection (6,18,22).

Neoplastic Lymphocytic Proliferations

Primary Pulmonary Lymphoma

Primary pulmonary lymphoma is a malignant, monoclonal lymphoid proliferation within the lung parenchyma. Primary pulmonary lymphomas can be MALT lymphoma (low-grade marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue), other non-Hodgkin lymphomas, or Hodgkin lymphoma. MALT lymphoma is by far the most common, comprising the majority (up to 90%) of cases of lymphoma involving the pulmonary parenchyma. However, it remains a fairly rare disease, representing approximately 3%–4% of extranodal lymphomas and less than 1% of all malignancies involving the lung (8,22,39–41).

Much rarer causes of primary pulmonary lymphoma comprising the remaining pulmonary lymphomas include other non-Hodgkin lymphomas, with diffuse large B-cell lymphoma being the second most common subtype after MALT lymphoma. Hodgkin lymphoma is the least common form of primary pulmonary lymphoma; parenchymal involvement occurs more commonly from direct extension of mediastinal disease (8,22,23,39,40).

MALT Lymphoma

MALT lymphoma (MALToma) is a monoclonal lymphoid proliferation arising from a B-cell progenitor within the BALT, and is classified as low-grade marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue in the World Health Organization classification (Table 6) (22,25,39–48). Histologically, MALT lymphoma is a lesion comprised of sheets of monoclonal lymphocytes with occasional interspersed plasma cells (22,25,41,43,46). These plasma cells often contain intranuclear inclusions of immunoglobulins known as Dutcher bodies. Similar to benign, reactive lymphoid lesions, MALT lymphoma lesions also commonly contain giant cells, granulomas, and reactive germinal centers, which can cause confusion in the diagnostic process.

In addition, invasion of the bronchial epithelium by lymphoid cells, referred to as a lymphoepithelial lesion, is common in both MALT lymphoma and in nonneoplastic lymphoid proliferations. There is lymphangitic spread at the periphery of these lesions (along pleura, interlobular septa, and bronchovascular bundles), and invasion into the adjacent pleura, vessels, and airways can occur (8,22,23,25,41). Bone marrow involvement is not common, but monoclonal gammopathy has been reported in up to 40% of patients and is likely produced by the lymphoma cells (22,41). Amyloid deposits are present in up to 10% of lesions (8,22,41,42,46,47).

Radiography shows nodules, masses, and/or consolidation. The disease can be bilateral or unilateral (22,23,40–44,46,49). CT shows multiple nodules, masses, and/or nodular/masslike areas

Table 6: Features of MALT Lymphoma

Clinical data	Often asymptomatic May coexist with pulmonary amyloidosis and LIP Associated with autoimmune disease, smoking, HIV
Histopathologic findings	Sheets of monoclonal lymphocytes Plasma cells and germinal centers present; Dutcher bodies present Lymphangitic spread at the periphery of lesions Can invade adjacent airways, vessels, pleura May be associated with trisomy 3, bcl-10 mutations, and t(11;18)(q21;q21)
Main imaging findings	Radiography: nodule, mass, and/or consolidation; single or multiple lesions CT: nodules, masses, and/or areas of consolidation; single or multiple lesions; bronchovascular distribution; air bronchograms often present; mediastinal and hilar lymphadenopathy up to 30% of the time PET/CT: hypermetabolic lesions present about half of the time
Differential diagnosis	Granulomatosis with polyangiitis, sarcoidosis, infection, metastatic disease

of ground-glass attenuation or consolidation (or a mix of both), which tend to be in a bronchovascular distribution and often show air bronchograms (Figs 9–11). The air bronchograms within these lesions may be dilated (22,23,25,40,42–44,46,47,49). More rarely, MALT lymphoma manifests as patchy large areas of ground-glass attenuation throughout the lungs (25,42,43,49).

In addition, the MALT lymphoma can infiltrate along the airways, resulting in a mosaic attenuation pattern resulting from small airway disease, also seen in other diseases such as hypersensitivity pneumonitis (43). Hilar and mediastinal lymphadenopathy can be present up to 30% of the time. The CT angiogram sign, which is an enhancing vessel on a background of consolidation, may be present in MALT lymphoma but is extremely nonspecific, as it is present in multiple other conditions including primary lung malignancy and infection. Pleural effusions are uncommon (23). MALT lymphoma lesions are hypermetabolic at PET/CT approximately half of the time (32).

The differential diagnosis for MALT lymphoma includes other entities that can manifest in a peribronchovascular distribution at CT: granulomatosis with polyangiitis (formerly Wegener granulomatosis), sarcoidosis, perilymphatic spread of metastatic disease, and infection. Clinical information can be helpful in narrowing the differential diagnosis. Symptoms of fever and leukocytosis suggest an infectious cause. Hemoptysis and poor kidney function point to granulomatosis with polyangiitis.

A history of a prior malignancy raises the possibility of metastatic disease. CT findings such as lymphadenopathy can be seen with sarcoidosis or metastatic disease. However, they are nonspecific, and biopsy—either transbronchial or surgical—is ultimately necessary. MALT lymphoma can coexist with LIP, and findings of consolidation, presence of pleural effusion, and large (>11 mm) or growing nodules in a patient with LIP should raise suspicion for lymphoma (10,23,29).

Patients tend to present around the 6th decade, although rare cases in younger patients have been reported. MALT lymphoma results from chronic inflammation of the BALT and has been associated with multiple autoimmune diseases such as Sjögren syndrome, rheumatoid arthritis, common variable immunodeficiency, chronic inflammation from smoking, and infections such as HIV and hepatitis C. Most patients who develop MALT lymphoma are former or active smokers (8,22,39,41–47).

MALT lymphoma has been associated with trisomy 3, bcl-10 mutations, and multiple translocations, of which t(11;18)(q21;q21) has been found most commonly (8,19,22). MALT lymphoma has been found in patients with concurrent LIP (10,16,22,27,28,46). Findings suggestive of MALT lymphoma in a patient with LIP include areas of consolidation, presence of large nodules (>11 mm), growing nodules, and pleural effusion (23). Symptoms include cough, dyspnea, hemoptysis, and weight loss; however, approximately one-half of patients are asymptomatic (8,22,23,39,41,42,44–47,49).

Definitive diagnosis requires tissue sampling with immunohistochemical studies to confirm a monoclonal B-cell population, which is positive for pan–B-cell antigens CD19, CD20, PAX-5, and occasionally CD43; lacks expression of CD5, CD10, CD23, and cyclin D1; and demonstrates light chain restriction. Light chain restriction refers to a cell population producing only one of the two types of light chain (either κ or λ) that occur in a monoclonal cell population. Flow cytometric immunophenotyping as well as molecular genetic studies to assess for light and heavy chain rearrangements can be helpful in confirming the

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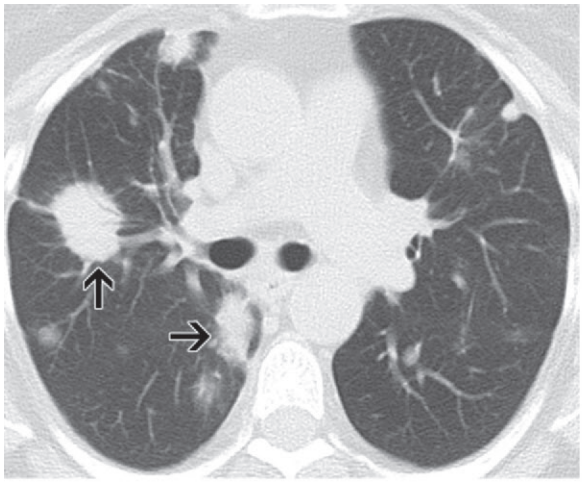

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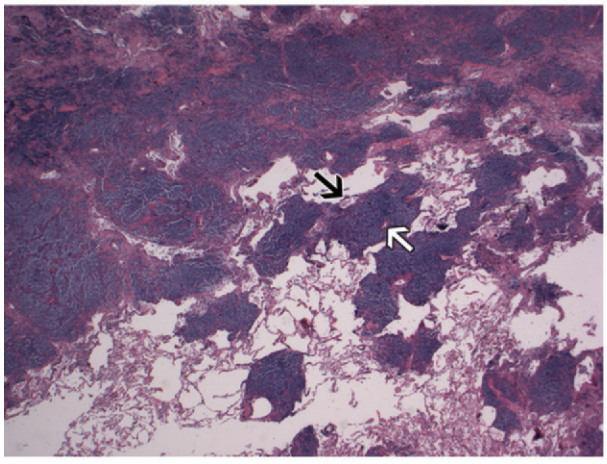

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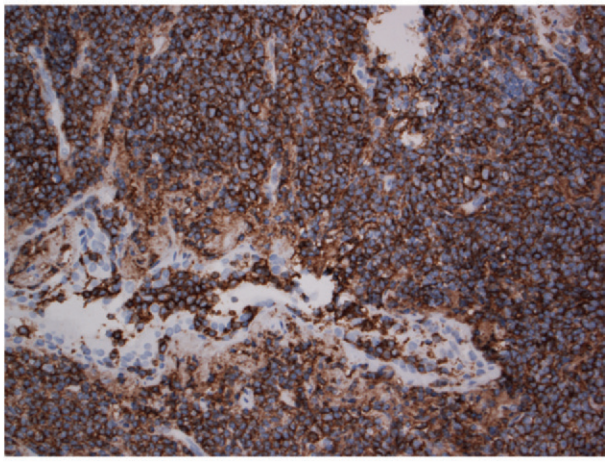
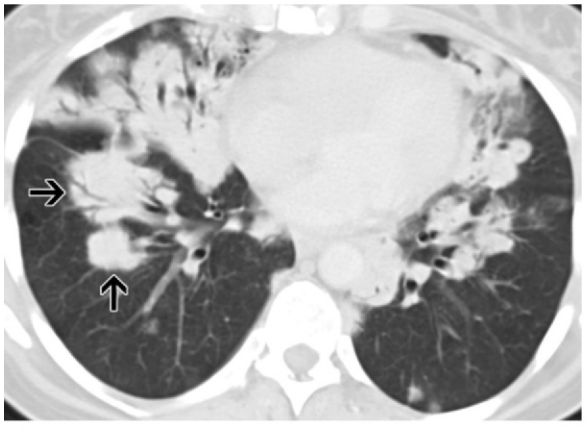


c.

Figure 9. MALT lymphoma in a 63-year-old woman. **(a)** Axial CT image shows multiple nodules and masses within the lungs (arrows), some of which have air bronchograms. **(b)** Photomicrograph shows lung parenchyma with solid, dense nodules of lymphoid infiltrate spreading along the interstitium in the periphery and frequently invading the bronchi (white arrow) and blood vessels (black arrow). (Original magnification, ×20; H-E stain.) **(c)** CD20 immunostaining (brown color) highlights the predominant B cells in the lymphoid infiltrate, which are monotypic (expressing λ immunostain only [not shown]). (Original magnification, ×200; CD20 immunostain.)



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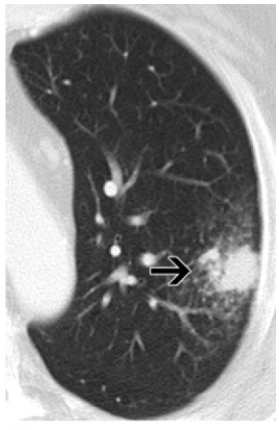


11.

Figures 10, 11. **(10)** MALT lymphoma in a 60-year-old woman. Axial CT image shows nodular masslike areas of consolidation with air bronchograms in the lower lungs (arrows). **(11)** MALT lymphoma in a 71-year-old man. Axial CT image of the left lung shows a pulmonary nodule with surrounding ground-glass attenuation and satellite nodules (arrow).

diagnosis as well as offering positive evidence for both malignancy and the B-cell origin of these neoplasms (8,22,39–42,44–47).

Transbronchial biopsy has a lower yield relative to surgical biopsy; however, recently many patients have been diagnosed via transbronchial biopsy and also via CT-guided percutaneous transthoracic biopsy. A surgical biopsy may still ultimately be necessary if minimally invasive procedures fail to achieve a definitive diagnosis (8,46).

Treatment is usually with chemotherapy or immunotherapy (rituximab). Surgery and radiation therapy are options available for localized disease and could be considered after staging and evaluation of all other mucosal sites have been performed. The prognosis is good, with 5- and

Table 7: Features of Lymphomatoid Granulomatosis

Clinical data	EBV infection Associated with immunosuppressive medications, particularly azathioprine, autoimmune diseases, HIV/AIDS Patients highly symptomatic: cough, fever, skin rash
Histopathologic findings	Angioinvasive/angiodestructive, usually oligoclonal or monoclonal proliferation of CD20-positive B cells (some of which are infected with EBV) among a background of polyclonal, reactive CD3-positive T cells
Main imaging findings	Radiography: nodules, masses, and/or areas of consolidation CT: nodules, masses, and/or areas of consolidation in a peribronchovascular distribution; air bronchograms, cavitation, or ground-glass halo may be present; pleural effusion possible PET/CT: lesions are avidly hypermetabolic
Differential diagnosis	Vasculitis, sarcoidosis, necrotizing sarcoid granulomatosis, multifocal lung malignancy, metastatic disease, primary pulmonary lymphoma, angioinvasive aspergillosis

10-year survival rates ranging from 84% to 88% (22,23,39,41,42,44–46,49). However, MALT lymphoma tends to recur in the lung in up to one-half of patients within the first years after diagnosis as well as within other areas containing MALT, such as the gastrointestinal tract.

Regional involvement of hilar lymph nodes is variable and does not affect prognosis. The presence of an associated pleural effusion or amyloid within the tumor is uncommon and signifies a poorer prognosis (22,40,46). Rarely, it is associated with paraneoplastic syndromes including transverse myelitis, cerebellar ataxia, and peripheral neuropathy (22,41). Approximately 20% of MALT lymphomas are complicated by diffuse large B-cell lymphoma (22,41,47).

Miscellaneous Pulmonary Lymphoid Lesions

Miscellaneous primary pulmonary lymphoid lesions are rare and include lymphomatoid granulomatosis, PTLD, AIDS-related lymphoma, and intravascular lymphoma/lymphomatosis. Of these, the two most common are lymphomatoid granulomatosis and PTLD.

Lymphomatoid Granulomatosis

Lymphomatoid granulomatosis is an angioinvasive/angiodestructive, usually oligoclonal or monoclonal proliferation of CD20-positive B cells (some of which are infected with EBV) among a background of polyclonal, reactive CD3-positive T cells (Table 7) (22,23,25,40,50–55). This disease was originally described by Liebow, who recognized it as a malignant lymphoproliferative B-cell process with an angiocentric distribution reminiscent of granulomatosis with polyangiitis (formerly Wegener granulomatosis). It has also been referred to as angiocentric immunoproliferative lesion in the past (22,25,50–52,56). It tends to involve the lungs, skin, and central nervous system (CNS) most commonly, although other organ systems can become involved. CNS involvement has a very poor prognosis (8,22,23,25,26,35,52,55–57).

Histologically, lymphomatoid granulomatosis shows nodular replacement of the lung parenchyma by a mixed mononuclear cell infiltrate around the muscular arteries and veins, with invasion of these vessels and areas of necrosis present later in the disease process. This cellular infiltrate is composed of large atypical B cells, small lymphocytes, histiocytes, and plasma cells. The large atypical B cells stain positive for CD20, CD79a, and EBV; positive or negative for CD30; and negative for CD15 (8,22,25,35,50,54,55). The small lymphocytes are reactive polyclonal T cells (CD4-positive cells > CD8-positive cells). The recent World Health Organization classification classifies lymphomatoid granulomatosis lesions into three grades based on the number of large atypical B cells, number of EBV-infected large B cells, and amount of necrosis (8,22,52,54,55).

Grade 1 is the rarest grade and consists of rare large B cells among a background of polyclonal T cells, with less than 5 EBV-infected B cells per high-power field and minimal if any necrosis. This B-cell proliferation is polyclonal (22,52,54,55).

Grade 2 is the most frequently encountered grade and has more large B cells among a background of polyclonal T cells, with 5–20 EBV-infected B cells per high-power field and multiple foci of necrosis. B-cell proliferation in this grade is oligoclonal or monoclonal (22,52,54,55).

In Grade 3, there are many EBV-infected large B cells present in sheets (>50 per high-power field) among a background of polyclonal T cells and extensive necrosis. Grade 3 lymphomatoid granulomatosis is a monoclonal population of B

RadioGraphics

cells and is consistent with angiocentric large B-cell lymphoma (22,52,54,55).

Radiography and CT show nodules, masses, or an area of consolidation in a perilymphatic (predominantly peribronchovascular) distribution (Figs 12, 13). Cavitation is sometimes present (22,23,25,35,50,51,55,56,58). Lesions may contain air bronchograms and a peripheral ground-glass halo (50,51). Mediastinal lymph node enlargement is rare (22,26,35,50,55). Pleural effusion is sometimes present (26). FDG PET/CT shows avid FDG uptake in these lesions (51).

Differential diagnostic considerations for lymphomatoid granulomatosis are broad and include vasculitis such as granulomatosis with polyangiitis, sarcoidosis, necrotizing sarcoid granulomatosis, multifocal lung malignancy, metastatic disease, primary pulmonary lymphoma, and infections such as angioinvasive aspergillosis. The presence of peripheral ground-glass halos around the lesions at CT, which is sometimes present in lymphomatoid granulomatosis, can occur with many of these diseases, including vasculitis, hemorrhagic metastatic disease, and angioinvasive aspergillosis. The presence of air bronchograms within the lesions of lymphomatoid granulomatosis may also be seen in primary lung malignancy and primary pulmonary lymphoma. When both cavitation and ground-glass halos are present in lymphomatoid granulomatosis, the disease appears most similar to granulomatosis with polyangiitis at imaging. Thus, as with several other primary pulmonary lymphoid lesions, biopsy is necessary.

Lymphomatoid granulomatosis tends to manifest in middle age and is more common in men (8,22,26,51,55,56,59,60). It can be idiopathic or occur in the setting of congenital or acquired immunosuppression, including both immunodeficiency diseases such as AIDS, hypogammaglobulinemia, and common variable immunodeficiency as well as patients who are receiving immunosuppressive therapies (22,51,53,55,57,59–61). There is also an association with autoimmune diseases such as Sjögren syndrome, inflammatory bowel disease, and rheumatoid arthritis. Patients are usually very symptomatic at presentation. Symptoms include cough, dyspnea, fever, rash, and weight loss (26,35,51,55,56,60). Skin rash is a common clinical symptom and may precede radiologic abnormalities in the chest (56).

Definitive diagnosis is made with tissue sampling using both immunohistochemical and molecular genetic studies to assess for B-cell clonality, presence of EBV-infected B cells, and light and heavy chain rearrangements. Transbronchial biopsy has been shown to have much lower yield relative to surgical biopsy, and surgical biopsy is the preferred method of tissue sampling (8,22,51,56,60). Prognosis is variable and depends on the grade of the lesion, with both grades 2 and 3 having a poorer prognosis (22,57). Progression to malignant large B-cell lymphoma involving lymph nodes, spleen, and bone marrow has been reported (22,26,40,50,52,59,60). Overall, median survival is 2 years (22,23,26,35). Treatment options include interferon-α-2b for lower grades and chemotherapy or combination chemoimmunotherapy for grade 3 lymphomatoid granulomatosis (22,26,50,52,56,60). Rituximab has also been used with variable success (51,59,60).

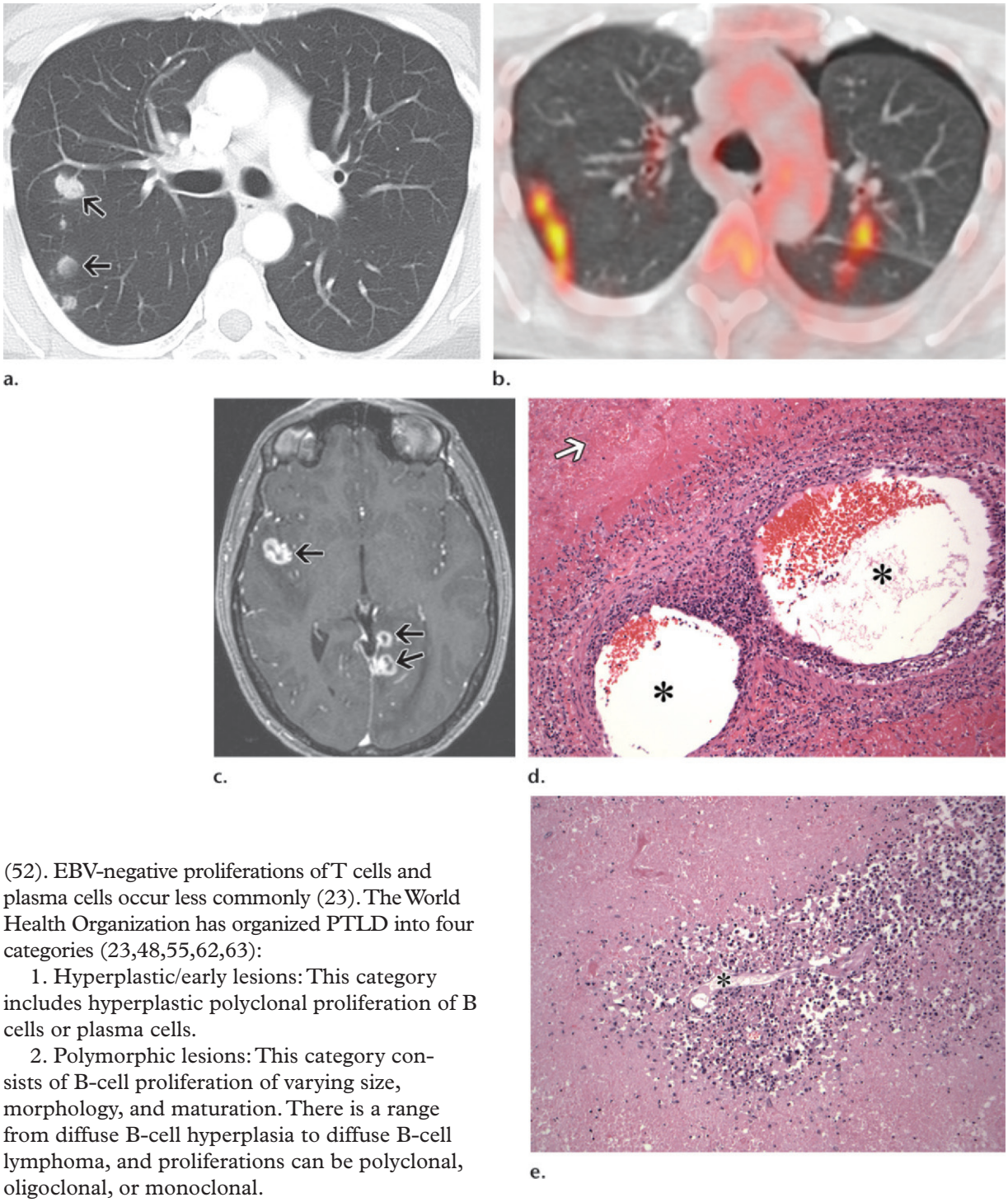
Posttransplant Lymphoproliferative Disorder

PTLD encompasses a group of lymphoproliferative disorders occurring in the post stem cell and organ transplant setting that range from benign polyclonal proliferation to malignant monoclonal disease (Table 8) (8,23,26,40,55,62–65). PTLD is intimately associated with EBV infection. Greater than 80% of PTLD cases consist of EBV-infected B-cell proliferations occurring within the first 2 years after transplant as a result of decreased anti-EBV cellular immunity (decreased T-cell immunity) secondary to iatrogenic immunosuppression after transplant. EBV-negative T-cell and plasma cell proliferations make up the small remaining percentage of PTLD cases, which usually occur much later (23,26,40,55,62,64–66).

PTLD development occurs with EBV seroconversion in the transplant patient. Causes of EBV seroconversion in the transplant patient include oral secretion transmission of the virus, residual EBV DNA within the BALT lymphocytes of the donated allograft, and via blood transfusion containing EBV-infected B cells (63). Any tissue in the body can become involved, with extranodal disease being more common than nodal disease (40,55). The lungs are a common site of PTLD involvement in heart-lung transplant recipients (62,63).

Histologically, PTLD is a spectrum of lymphoid proliferation. The majority of PTLD cases are composed of proliferation of EBV-infected B cells that range from benign polyclonal proliferation to malignant monoclonal proliferation (8,23). The proliferation of EBV-infected B cells is reminiscent of lymphomatoid granulomatosis. However, unlike lymphomatoid granulomatosis, there is no background of polyclonal reactive T cells, angioinvasion/angiodestruction, or necrosis present, which are key distinguishing features between these two diseases

Figure 12. Lymphomatoid granulomatosis in a 44-year-old woman. **(a)** Axial CT image shows multiple pulmonary nodules (arrows), some of which have a subtle ground-glass attenuation halo. **(b)** PET/CT image shows multiple hypermetabolic lesions in the lungs. Pneumothorax on the left is from recent biopsy of a lesion in the left lung. **(c)** Axial postcontrast T1-weighted image of the brain shows multiple peripherally enhancing lesions (arrows), which represent central nervous system involvement by lymphomatoid granulomatosis. **(d)** Photomicrograph from lung wedge biopsy shows nodular replacement of the lung parenchyma by a mixed mononuclear cell infiltrate, with prominent invasion of vessels (*) and areas of necrosis (arrow) surrounded by a rim of viable cells. (Original magnification, ×100; H-E stain.) **(e)** Photomicrograph from brain biopsy shows similar lesions, with tumor cells surrounding the vessels (*) and areas of necrosis. (Original magnification, ×40; H-E stain.)



(52). EBV-negative proliferations of T cells and plasma cells occur less commonly (23). The World Health Organization has organized PTLD into four categories (23,48,55,62,63):

1. Hyperplastic/early lesions: This category includes hyperplastic polyclonal proliferation of B cells or plasma cells.

2. Polymorphic lesions: This category consists of B-cell proliferation of varying size, morphology, and maturation. There is a range from diffuse B-cell hyperplasia to diffuse B-cell lymphoma, and proliferations can be polyclonal, oligoclonal, or monoclonal.

3. Monomorphic lesions: malignant monoclonal proliferation of B cells or T/natural killer cells including diffuse large B-cell lymphoma, Burkitt lymphoma, plasma cell myeloma, and T-cell lymphoma.

4. Classic Hodgkin-like PTLD: This category includes lymphocytic proliferations with morphologic characteristics similar to Hodgkin lymphoma, including Reed-Sternberg cells.

Radiography and CT show nodules, masses, patchy airspace consolidation, and mediastinal and

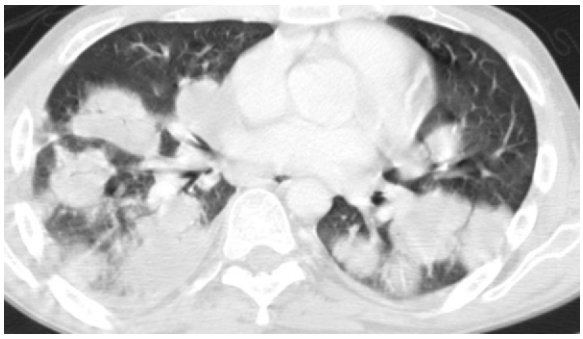


Figure 13. Lymphomatoid granulomatosis in a 68-year-old woman. Axial CT image shows multiple nodular masslike areas of consolidation in the lower lungs as another form of presentation of lymphomatoid granulomatosis. Also noted is right hilar and subcarinal lymphadenopathy. A right pleural effusion is also present.

Table 8: Features of PTLD

Clinical data	Post stem cell and organ transplant patients Associated with EBV infection
Histopathologic findings	Proliferation of EBV-infected B cells Spectrum of polyclonal to monoclonal proliferation
Main imaging findings	Radiography: multiple pulmonary nodules, masses, and/or airspace consolidation; mediastinal and hilar lymphadenopathy CT: multiple pulmonary nodules, masses, and/or airspace consolidation with or without ground-glass halo; perilymphatic distribution; mediastinal and hilar lymphadenopathy; air bronchograms, septal thickening, invasion into adjacent structures, and pleural effusion may be present PET/CT: lesions are avidly hypermetabolic
Differential diagnosis	Angioinvasive aspergillosis

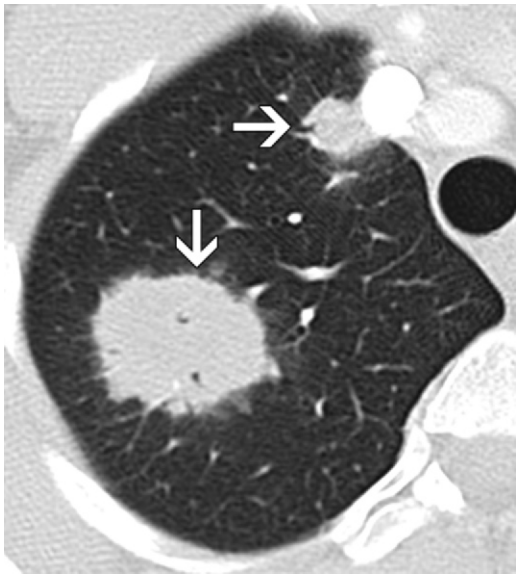


Figure 14. PTLD of the lung as a complication of liver transplant for autoimmune hepatitis in a 35-year-old woman. Coned-down view of the right upper lobe shows masslike areas of consolidation (arrows), some of which contain air bronchograms.

hilar lymphadenopathy (Fig 14). Multiple pulmonary nodules are the most common finding, and they can sometimes have a peripheral ground-glass halo—resulting from less dense infiltration of cells into the adjacent interstitium—that mimics angioinvasive aspergillosis. The nodules are usually peribronchovascular, subpleural, or both (perilymphatic distribution). Air bronchograms may be present within the nodules. Halo signs are sometimes present.

PTLD can also sometimes appear as a solitary mass in the lungs (23,26,40,62–67). Septal thickening has been reported in approximately one-third of cases (23,40,67). Pleural effusions can be present. Involvement of the chest wall, thymus, and pericardium has also been reported to occur, but less commonly (26,40,62,65). FDG PET/CT shows avid FDG uptake in PTLD lesions and is useful in defining the extent of disease (62).

The main differential diagnosis for PTLD in the immunosuppressed population is angioinvasive aspergillosis. Unfortunately, clinical scenarios and imaging findings at radiography, CT, and PET/CT are similar for both PTLD and angioinvasive aspergillosis, necessitating tissue sampling.

PTLD involves approximately 2% of transplant cases overall; however, incidence varies with each type of transplant. It usually develops within the first 2 years after transplant, but has been reported to occur decades later, usually with a much poorer prognosis (23,40,62,64–67).

Risk factors for developing PTLD after transplant include organ type, age, increased amount or frequency of immunosuppressive medications (azathioprine and cyclosporine posing most risk), cytomegalovirus infection, HLA mismatch, and EBV status before transplantation.

Children are more likely to develop PTLD than adults. PTLD occurs most commonly after multiorgan transplant such as heart-lung transplant (up to 33%), followed by small bowel, lung, heart, liver, pancreas, renal, and stem cell transplant (23,26,40,62,63,68). Patients with EBV seronegative status before transplant are more likely to develop PTLD (63). Symptoms are variable and include fever, weight loss, lymphadenopathy, flulike symptoms, and diarrhea (23,63,66).

Definitive diagnosis is made with tissue sampling, either surgical biopsy or transthoracic needle biopsy with both immunohistochemical and molecular genetic studies to assess for B-cell clonality, presence of EBV-infected B cells, and light and heavy chain rearrangements (particularly light chain restriction) (26,62,63,66,67). Early, less aggressive polyclonal/hyperplastic PTLD can be treated with a combination of decreased immunosuppression and antiviral agents directed against the EBV, such as acyclovir (23,62,63,66,67,69). Decrease or cessation of immunosuppression is essential to treatment (23,62,65,66,68).

Rituximab has been reported to be helpful but not useful alone, and aggressive disease often requires combination immunochemotherapy of rituximab and chemotherapy agents used in treatment of lymphoma (55,62,65,67,69). Studies exploring the adoptive transfer of EBV-specific cytotoxic T cells from the donor have preliminarily shown promise in restoring immune balance and treatment of PTLD; however, this approach is time-consuming and costly, and more investigation is needed (69). The prognosis of PTLD is variable, with widespread disease and late-onset disease (after the first 2 years) having overall poor prognosis (26,66).

Conclusion

Primary pulmonary lymphoid diseases arise from the BALT and encompass a wide spectrum of nonneoplastic, neoplastic, and miscellaneous lymphoid proliferations. Although rare, these diseases are becoming more commonly recognized in immunosuppressed populations. These diseases are best evaluated with imaging (Table 9), particularly multidetector chest CT, in correlation with clinical data and pathologic findings.

References

1. Breeze R, Turk M. Cellular structure, function and organization in the lower respiratory tract. Environ Health Perspect 1984;55:3–24.
2. Corrin B, Nicholson AG. The structure of the normal lungs. In: Corrin B, Nicholson AG, eds. Pathology of the lungs. 3rd ed. London, England: Churchill Livingstone, 2011; 1–37.
3. Tomashefski JF, Farver CF. Anatomy and histology of the lung. In: Tomashefski JF, ed. Dail and Hammar's pulmonary pathology. 3rd ed. New York, NY: Springer, 2008; 20–48.
4. Sozio F, Rossi A, Weber E, et al. Morphometric analysis of intralobular, interlobular and pleural lymphatics in normal human lung. J Anat 2012;220(4):396–404.
5. Bienenstock J, McDermott MR. Bronchus- and nasal-associated lymphoid tissues. Immunol Rev 2005;206:22–31.
6. Gibson M, Hansell DM. Lymphocytic disorders of the chest: pathology and imaging. Clin Radiol 1998;53(7):469–480.
7. Kradin RL, Mark EJ. Benign lymphoid disorders of the lung, with a theory regarding their development. Hum Pathol 1983;14(10):857–867.
8. William J, Variakojis D, Yeldandi A, Raparia K. Lymphoproliferative neoplasms of the lung: a review. Arch Pathol Lab Med 2013;137(3):382–391.
9. Halle S, Dujardin HC, Bakocevic N, et al. Induced bronchus-associated lymphoid tissue serves as a general priming site for T cells and is maintained by dendritic cells. J Exp Med 2009;206(12):2593–2601.
10. Swigris JJ, Berry GJ, Raffin TA, Kuschner WG. Lymphoid interstitial pneumonia: a narrative review. Chest 2002;122(6):2150–2164.
11. Sato A, Hayakawa H, Uchiyama H, Chida K. Cellular distribution of bronchus-associated lymphoid tissue in rheumatoid arthritis. Am J Respir Crit Care Med 1996;154(6 Pt 1):1903–1907.
12. Foo SY, Phipps S. Regulation of inducible BALT formation and contribution to immunity and pathology. Mucosal Immunol 2010;3(6):537–544.
13. Tschernig T, Kleemann WJ, Pabst R. Bronchus-associated lymphoid tissue (BALT) in the lungs of children who had died from sudden infant death syndrome and other causes. Thorax 1995;50(6):658–660.
14. Tschernig T, Pabst R. Bronchus-associated lymphoid tissue (BALT) is not present in the normal adult lung but in different diseases. Pathobiology 2000;68(1):1–8.
15. Richmond I, Pritchard GE, Ashcroft T, Avery A, Corris PA, Walters EH. Bronchus associated lymphoid tissue (BALT) in human lung: its distribution in smokers and non-smokers. Thorax 1993;48(11):1130–1134.
16. Johkoh T, Müller NL, Pickford HA, et al. Lymphocytic interstitial pneumonia: thin-section CT findings in 22 patients. Radiology 1999;212(2):567–572.
17. Chu T, Jaffe R. The normal Langerhans cell and the LCH cell. Br J Cancer Suppl 1994;23:S4–S10.
18. Travis WD, Galvin JR. Non-neoplastic pulmonary lymphoid lesions. Thorax 2001;56(12):964–971.
19. Corrin B, Nicholson AG. Lymphoproliferative disease. In: Corrin B, Nicholson AG, eds. Pathology of the lungs. 3rd ed. London, England: Churchill Livingstone, 2011; 653–676.
20. Howling SJ, Hansell DM, Wells AU, Nicholson AG, Flint JD, Müller NL. Follicular bronchiolitis: thin-section CT and histologic findings. Radiology 1999;212(3):637–642.
21. Aerni MR, Vassallo R, Myers JL, Lindell RM, Ryu JH. Follicular bronchiolitis in surgical lung biopsies: clinical implications in 12 patients. Respir Med 2008;102(2):307–312.
22. Koss MN. Malignant and benign lymphoid lesions of the lung. Ann Diagn Pathol 2004;8(3):167–187.
23. Hare SS, Souza CA, Bain G, et al. The radiological spectrum of pulmonary lymphoproliferative disease. Br J Radiol 2012;85(1015):848–864.
24. Exley CM, Suvarna SK, Matthews S. Follicular bronchiolitis as a presentation of HIV. Clin Radiol 2006;61(8):710–713.
25. Do KH, Lee JS, Seo JB, et al. Pulmonary parenchymal involvement of low-grade lymphoproliferative disorders. J Comput Assist Tomogr 2005;29(6):825–830.
26. Bragg DG, Chor PJ, Murray KA, Kjeldsberg CR. Lymphoproliferative disorders of the lung: histopathology, clinical manifestations, and imaging features. AJR Am J Roentgenol 1994;163(2):273–281.
27. Fishback N, Koss M. Update on lymphoid interstitial pneumonitis. Curr Opin Pulm Med 1996;2(5):429–433.

Table 9: Imaging Findings of Primary Pulmonary Lymphoid Lesions

Disease	Radiography	CT	PET/CT
Follicular bronchiolitis	Common: radiographs show no abnormality Less common: lower lung nodular opacities	Common: centrilobular nodules, tree-in-bud configuration Less common: nodules along pleura and interlobular septa, bronchiectasis, bronchial wall thickening, peribronchovascular consolidation	No findings
LIP	Common: radiographs show no abnormality Less common: reticular and nodular opacities in the lower lungs	Common: ground-glass opacity, centrilobular nodules, and perivascular cysts in the lower lungs Less common: patchy lower lung interlobular septal thickening, lymphadenopathy	Hypermetabolic activity may be present in nodules >11 mm
NLH	Nodule, mass, or focal area of masslike consolidation; can be single or multiple lesions	Nodule, mass, or focal area of masslike consolidation; air bronchograms; can be single or multiple lesions	No significant data available regarding evaluation with PET/CT
MALT lymphoma	Bilateral or unilateral nodules, masses, and/or consolidation	Common: bilateral or unilateral nodules, masses, and/or consolidation in a bronchovascular distribution; air bronchograms in lesions Less common: patchy ground-glass attenuation; hilar/mediastinal lymphadenopathy Uncommon: pleural effusion	Lesions are hypermetabolic half of the time
Lymphomatoid granulomatosis	Nodules, masses, and/or consolidation	Common: nodules, masses, and/or consolidation in perilymphatic distribution Less common: air bronchograms, ground-glass halo, pleural effusion, cavitation Uncommon: mediastinal lymph node enlargement	Lesions are avidly hypermetabolic
PTLD	Nodules, masses, patchy airspace consolidation; mediastinal and hilar lymphadenopathy	Common: nodules, masses, patchy airspace consolidation in a perilymphatic distribution; mediastinal and hilar lymphadenopathy Less common: air bronchograms; halo sign; septal thickening; pleural effusion; invasion of chest wall, thymus, and pericardium	Lesions are avidly hypermetabolic; PET/CT extremely useful to establish extent of disease

28. Johkoh T, Ichikado K, Akira M, et al. Lymphocytic interstitial pneumonia: follow-up CT findings in 14 patients. J Thorac Imaging 2000;15(3):162–167.
29. Lynch DA, Travis WD, Müller NL, et al. Idiopathic interstitial pneumonias: CT features. Radiology 2005;236(1):10–21.
30. Koyama M, Johkoh T, Honda O, et al. Pulmonary involvement in primary Sjögren's syndrome: spectrum of pulmonary abnormalities and computed tomography findings in 60 patients. J Thorac Imaging 2001;16(4):290–296.
31. Vale J, Silva E, Melo V, Jones J, Nunes R, Torres AS. Lymphocytic interstitial pneumonia: two cases of unusual presentation. Eur Respir J 2011;38(suppl 55):639.
32. Paes FM, Kalkanis DG, Sideras PA, Serafini AN. FDG PET/CT of extranodal involvement in non-Hodgkin lymphoma and Hodgkin disease. RadioGraphics 2010;30(1):269–291.
33. Baqir M, Kluka EM, Aubry MC, et al. Amyloid-associated cystic lung disease in primary Sjögren's syndrome. Respir Med 2013;107(4):616–621.
34. Tanaka N, Kim JS, Bates CA, et al. Lung diseases in patients with common variable immunodeficiency: chest radiographic and computed tomographic findings. J Comput Assist Tomogr 2006;30(5):828–838.
35. Glickstein M, Kornstein MJ, Pietra GG, et al. Nonlymphomatous lymphoid disorders of the lung. AJR Am J Roentgenol 1986;147(2):227–237.
36. Kaan PM, Hegele RG, Hayashi S, Hogg JC. Expression of bcl-2 and Epstein-Barr virus LMP1 in lymphocytic interstitial pneumonia. Thorax 1997;52(1):12–16.
37. Kramer MR, Saldana MJ, Ramos M, Pitchenik AE. High titers of Epstein-Barr virus antibodies in adult patients with lymphocytic interstitial pneumonitis associated with AIDS. Respir Med 1992;86(1):49–52.
38. Abbondanzo SL, Rush W, Bijwaard KE, Koss MN. Nodular lymphoid hyperplasia of the lung: a clinicopathologic study of 14 cases. Am J Surg Pathol 2000;24(4):587–597.
39. Lee WK, Duddalwar VA, Rouse HC, Lau EW, Bekhit E, Hennessy OF. Extranodal lymphoma in the thorax: cross-sectional imaging findings. Clin Radiol 2009;64(5):542–549.
40. Lee KS, Kim Y, Primack SL. Imaging of pulmonary lymphomas. AJR Am J Roentgenol 1997;168(2):339–345.

41. Kurtin PJ, Myers JL, Adlakha H, et al. Pathologic and clinical features of primary pulmonary extranodal marginal zone B-cell lymphoma of MALT type. Am J Surg Pathol 2001;25(8):997–1008.
42. Kinsely BL, Mastey LA, Mergo PJ, et al. Pulmonary mucosa-associated lymphoid tissue lymphoma: CT and pathologic findings. AJR Am J Roentgenol 1999;172(5):1321–1326.
43. Lee IJ, Kim SH, Koo SH, et al. Bronchus-associated lymphoid tissue (BALT) lymphoma of the lung showing mosaic pattern of inhomogeneous attenuation on thin-section CT: a case report. Korean J Radiol 2000;1(3):159–161.
44. Arnaoutakis K, Oo TH. Bronchus-associated lymphoid tissue lymphomas. South Med J 2009;102(12):1229–1233.
45. Au V, Leung AN. Radiologic manifestations of lymphoma in the thorax. AJR Am J Roentgenol 1997;168(1):93–98.
46. Ahmed S, Kussick SJ, Siddiqui AK, et al. Bronchial-associated lymphoid tissue lymphoma: a clinical study of a rare disease. Eur J Cancer 2004;40(9):1320–1326.
47. Huang H, Lu ZW, Jiang CG, Li J, Xu K, Xu ZJ. Clinical and prognostic characteristics of pulmonary mucosa-associated lymphoid tissue lymphoma: a retrospective analysis of 23 cases in a Chinese population. Chin Med J (Engl) 2011;124(7):1026–1030.
48. Campo E, Swerdlow SH, Harris NL, Pileri S, Stein H, Jaffe ES. The 2008 WHO classification of lymphoid neoplasms and beyond: evolving concepts and practical applications. Blood 2011;117(19):5019–5032.
49. Wislez M, Cadranel J, Antoine M, et al. Lymphoma of pulmonary mucosa-associated lymphoid tissue: CT scan findings and pathological correlations. Eur Respir J 1999;14(2):423–429.
50. Lee JS, Tuder R, Lynch DA. Lymphomatoid granulomatosis: radiologic features and pathologic correlations. AJR Am J Roentgenol 2000;175(5):1335–1339.
51. Chung JH, Wu CC, Gilman MD, Palmer EL, Hasserjian RP, Shepard JA. Lymphomatoid granulomatosis: CT and FDG-PET findings. Korean J Radiol 2011;12(6):671–678.
52. Katzenstein AL, Doxtader E, Narendra S. Lymphomatoid granulomatosis: insights gained over 4 decades. Am J Surg Pathol 2010;34(12):e35–e48.
53. Destombe S, Bouron-DalSoglio D, Rougemont AL, et al. Lymphomatoid granulomatosis: a unique complication of Crohn disease and its treatment in pediatrics. J Pediatr Gastroenterol Nutr 2010;50(5):559–561.
54. Colby TV. Current histological diagnosis of lymphomatoid granulomatosis. Mod Pathol 2012;25(suppl 1):S39–S42.
55. Dunleavy K, Roschewski M, Wilson WH. Lymphomatoid granulomatosis and other Epstein-Barr virus associated lymphoproliferative processes. Curr Hematol Malig Rep 2012;7(3):208–215.
56. Pisani RJ, DeRemee RA. Clinical implications of the histopathologic diagnosis of pulmonary lymphomatoid granulomatosis. Mayo Clin Proc 1990;65(2):151–163.
57. Katzenstein AL, Carrington CB, Liebow AA. Lymphomatoid granulomatosis: a clinicopathologic study of 152 cases. Cancer 1979;43(1):360–373.
58. Seo JB, Im JG, Chung JW, et al. Pulmonary vasculitis: the spectrum of radiological findings. Br J Radiol 2000;73(875):1224–1231.
59. Castrale C, El Haggan W, Chapon F, et al. Lymphomatoid granulomatosis treated successfully with rituximab in a renal transplant patient. J Transplant 2011;2011:865957.
60. Roschewski M, Wilson WH. Lymphomatoid granulomatosis. Cancer J 2012;18(5):469–474.
61. Mittal K, Neri A, Feiner H, Schinella R, Alfonso F. Lymphomatoid granulomatosis in the acquired immunodeficiency syndrome: evidence of Epstein-Barr virus infection and B-cell clonal selection without myc rearrangement. Cancer 1990;65(6):1345–1349.
62. Borhani AA, Hosseinzadeh K, Almusa O, Furlan A, Nalesnik M. Imaging of posttransplantation lymphoproliferative disorder after solid organ transplantation. RadioGraphics 2009;29(4):981–1000; discussion 1000–1002.
63. Cadranel J, Naccache J, Wislez M, Mayaud C. Pulmonary malignancies in the immunocompromised patient. Respiration 1999;66(4):289–309.
64. Carignan S, Staples CA, Müller NL. Intrathoracic lymphoproliferative disorders in the immunocompromised patient: CT findings. Radiology 1995;197(1):53–58.
65. Conces DJ Jr. Noninfectious lung disease in immunocompromised patients. J Thorac Imaging 1999;14(1):9–24.
66. Rappaport DC, Chamberlain DW, Shepherd FA, Hutcheon MA. Lymphoproliferative disorders after lung transplantation: imaging features. Radiology 1998;206(2):519–524.
67. Collins J, Müller NL, Leung AN, et al. Epstein-Barr-virus-associated lymphoproliferative disease of the lung: CT and histologic findings. Radiology 1998;208(3):749–759.
68. Harris KM, Schwartz ML, Slasky BS, Nalesnik M, Makowka L. Posttransplantation cyclosporine-induced lymphoproliferative disorders: clinical and radiologic manifestations. Radiology 1987;162(3):697–700.
69. Carbone A, Gloghini A, Dotti G. EBV-associated lymphoproliferative disorders: classification and treatment. Oncologist 2008;13(5):577–585.