# Chapter 8
# Lymphoid Interstitial Pneumonia and Follicular Bronchiolitis


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## Abbreviations

| | |
|---|---|
| AIDS | acquired immune deficiency syndrome |
| BAL | bronchoalveolar lavage |
| CVID | common variable immunoglobulin deficiency |
| DILS | diffuse infiltrative lymphocytic syndrome |
| FB | follicular bronchiolitis |
| GLILD | granulomatous-lymphocytic interstitial lung disease |
| GPA | granulomatosis with polyangiitis |
| HIV | human immunodeficiency virus |
| HRCT | high-resolution chest computed tomography |
| IPAF | interstitial pneumonia with autoimmune features |
| LDH | lactate dehydrogenase |
| LIP | lymphoid interstitial pneumonia |
| NLH | nodular lymphoid hyperplasia |
| PFT | pulmonary function test |
| RA | rheumatoid arthritis |
| SS | Sjögren's syndrome |

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## Introduction

Follicular bronchiolitis (FB) and lymphoid interstitial pneumonia (LIP) represent a pathophysiological continuum of lymphocytic infiltration from hyperplasia of bronchus-associated lymphoid tissue to cellular expansion of the interstitium with fibrosis [1]. In other words, LIP is a clinicopathologic term that describes diffuse involvement of the lung parenchyma by reactive pulmonary lymphoid tissue, whereas FB refers to a pattern of lymphoid follicular hyperplasia centered on airways, vessels, and interlobular septa consistent with a lymphatic distribution [2]. Although LIP can be difficult to distinguish from FB, we will review the clinical, radiologic, and pathologic presentation of both entities in this continuum. We will also review what little is known regarding their etiopathogenesis and treatment.

## Lymphoid Interstitial Pneumonia

LIP was first described by Carrington and Liebow in 1966 [3]. It is a benign lymphoproliferative disorder that is characterized by diffuse infiltration of small mature lymphocytes, plasma cells, and histiocytes that spread diffusely into the alveolar septae.

### *Clinical Presentation*

LIP is an uncommon disorder that is rarely idiopathic; rather, it is thought to be an expression of systemic immunologic disorders in the lung [4]. The diagnosis of LIP should be considered in anyone with lung cysts and an immunologic abnormality (Table 8.1). A thorough evaluation for an underlying systemic condition, especially autoimmune and immunodeficiency states, should be undertaken after a radiological or histopathological diagnosis of LIP is established [5].

LIP has a bimodal distribution. In children less than 13, LIP is generally associated with human immunodeficiency virus (HIV) and is an acquired immunodeficiency syndrome (AIDS)-defining illness [6]. Whereas in adults, LIP most commonly affects women in the fourth to sixth decade with an underlying autoimmune disorder or immunodeficiency [7, 8]. The female to male prevalence in adults is 2:1 [8]. Most non-HIV adults presenting with LIP are white [8], whereas in the context of HIV, LIP is more commonly seen in those of black African or Afro-Caribbean origin, particularly those from Haiti [9].

**Table 8.1** Clinical and radiologic features of follicular bronchiolitis and lymphoid interstitial pneumonia

| | Follicular bronchiolitis | Lymphoid interstitial pneumonia |
|---|---|---|
| **Common associations** | **Immune deficiencies**<br>Congenital<br>CVID<br>HIV<br>**Connective tissue disorders**<br>SS<br>RA<br>**Interstitial pneumonias**<br>Hypersensitivity pneumonitis<br>LIP<br>NSIP | **Immune deficiencies**<br>Congenital<br>CVID<br>HIV<br>**Connective tissue disorders**<br>SS<br>RA<br>SLE<br>**Interstitial pneumonias**<br>IPAF<br>**Viruses**<br>EBV<br>HIV<br>HHV-8<br>Hepatitis B<br>Hepatitis C |
| **Pulmonary function test** | Obstructive, reduced FEF25–75<br>Air trapping<br>Diffusion limitation<br>Restriction<br>Mixed, nonspecific, or normal | Diffusion limitation<br>Restriction |
| **Nodules** | 1–3 mm common, >12 mm uncommon<br>Centrilobular, tree-in-bud<br>Peribronchial<br>Ground-glass nodules | Mixed, nonspecific, or normal<br>Micronodules, but up to 2 cm<br>Centrilobular, subpleural, perilymphatic<br>Ground-glass nodules |
| **Airways** | Bronchial wall thickening<br>Bronchiolectasis<br>Mosaicism, air trapping | Bronchial wall thickening |
| **Cysts** | Rounded or oval<br>5 mm to 5 cm<br>Diffuse or basilar<br>Perivascular, internal septation | Round, thin walled<br>5 mm to 5 cm<br><10% of parenchyma<br>Present in 60%–80%<br>Occur randomly in all lung zones<br>Peribronchovascular |
| **Septal/interstitial abnormality** | Minimal or none unless coexisting with another pattern | Basilar reticulation<br>Honeycombing rare<br>Present in approximately 65% |

*CVID* common variable immune deficiency, *HIV* human immunodeficiency virus, *EBV* Epstein-Barr virus; *HHV-8* human gammaherpesvirus 8, *RA* rheumatoid arthritis, *SS* Sjögren's syndrome, *SLE* systemic lupus erythematosus, *LIP* lymphoid interstitial pneumonia, *NSIP* nonspecific interstitial pneumonia, *IPAF* interstitial pneumonia with autoimmune features, *FEF25–75* forced expiratory flow at 25-75%, *mm* millimeter, *cm* centimeter

Patients may have constitutional symptoms including fevers, chills, night sweats, weight loss, and fatigue [7, 10]. Patients may also present with pleuritic chest pain possibly indicating a pneumothorax [11]. On examination, patients may have bibasilar end inspiratory crackles [12], or the chest may be silent as it often is in children. Clubbing of the fingers and toes frequently occurs in children, but may not be present in adults [13–15]. Splenomegaly is commonly associated with LIP in the setting of common variable immune deficiency (CVID) [16]. When LIP occurs in the setting of HIV, it may be associated with other features of diffuse infiltrative lymphocytic syndrome (DILS) including xerophthalmia and xerostomia, nontender parotid and salivary gland involvement, widespread lymphadenopathy, hepatosplenomegaly, or discomfort after eating if lymphocytic gastritis is a feature. There may also be facial numbness or weakness caused by seventh cranial nerve palsy. Patients may also present neck stiffness and headache due to aseptic meningitis [9].

Pulmonary function may show a restrictive ventilatory defect with a reduced diffusion [17]. Approximately 80% of patients with LIP have serum dysproteinemias; most commonly hypergammaglobulinemia [8] but hypogammaglobulinemia can occur in the setting of CVID. The cause of this is unknown but likely reflects chronic systemic autoimmune inflammation [18]. Serum lactate dehydrogenase (LDH) may be elevated, but this is a nonspecific finding [9].

## Associated Conditions

Many affected patients have immune dysregulation or an underlying autoimmune disease, and thus, LIP is thought to represent a nonspecific response to multiple stimuli or antigens [7, 19]. Tertiary lymphoid neogenesis, which is associated with chronic inflammatory conditions, is seen in the distinct B- and T-cell areas of cellular proliferation found in LIP [20, 21]. Although the specific immunologic pathogenesis for LIP is unknown, an immunologic pathogenesis is further supported by an association with major histocompatibility complex antigens [9] and the presence of immune complex deposition [22].

## Viral Associations

Chronic antigenic stimulation as a cause of LIP is suggested by the association of several viruses (EBV, HIV, HHV-8, hepatitis B, hepatitis C) with LIP [19, 23]. Epstein-Barr virus (EBV) is frequently found in the lungs of children and some adults with LIP [24]. EBV infects B lymphocytes, inducing proliferation of these cells, and patients with various types of immunodeficiency are at increased risk for developing a sustained EBV-related proliferation response, resulting in B-cell lymphoproliferative disorders [25]. EBV is also often found in the lungs of children with LIP and AIDS [26], and the titers of EBV antibodies are significantly higher in adult patients with AIDS and LIP compared to AIDS patients without LIP [27]. The

predilection for EBV and/or HIV being associated with LIP in children is likely due to the presence of bronchus-associated lymphoid tissue, which is less commonly seen in healthy adult lungs [15]. Viral-related LIP may be associated with a cellular immune response against the viral antigen as CD8+ lymphocytes, in particular, are considered to play a major role in the pathology of LIP, with increased CD8+ lymphocytes found in BAL fluid [15].

### Autoimmune Disease

Another hypothesis suggests that LIP is due to loss of self-tolerance; a clonality of autoreactive T cells develops in response to lung antigens [28]. This is most evident by the strong association between LIP (and follicular bronchiolitis) and Sjögren's syndrome (SS): nearly 1% of adults with SS have LIP, and 30% to 60% of adults with LIP have SS [29–32]. LIP is also associated with a number of other autoimmune disorders including rheumatoid arthritis, systemic lupus erythematosus, autoimmune thyroid disease, primary biliary cirrhosis, myasthenia gravis, hemolytic and pernicious anemia, idiopathic thrombocytopenic purpura, erythrocyte sensitization syndrome, autoimmune glomerulonephritis, ulcerative colitis, celiac sprue, and diabetes mellitus [7, 8, 33–37]. Because of this strong association with autoimmune disease, the presence of LIP is one of the criteria for the new entity "interstitial pneumonia with autoimmune features (IPAF)," which describes patients with an idiopathic interstitial pneumonia and features suggestive of, but not definitive for, a connective tissue disease [38].

### Immunodeficiencies

A polyclonal hypergammaglobulinemia is typically present when LIP is associated with an underlying autoimmune condition. However, LIP also occurs in the setting of other immunodeficiencies in addition to that seen in HIV/AIDS, and dysgammaglobulinemia syndrome is frequently linked to LIP.

LIP may be seen in approximately 10% of patients with CVID [16, 39]. Pathologic specimens from patients with CVID frequently contain both granulomatous and lymphoproliferative histopathologic patterns, otherwise called granulomatous-lymphocytic interstitial lung disease (GLILD). Lymphoid hyperplasia, follicular bronchiolitis, and LIP may "represent different ends of a spectrum of the same disease" [5, 16, 40]. The presence of GLILD decreases survival by 50% compared to patients with CVID and no evidence of GLILD [16].

LIP may occur after allogeneic hematopoietic stem cell transplantation, often following a viral infection or in the context of chronic graft versus host disease [41–43]. LIP may also be seen in the immunodeficiency syndrome ataxia-telangiectasia [44].

### Other Associations

LIP has also been associated with Castleman disease, another rare lymphoproliferative disorder, which may result in systemic inflammatory symptoms, lymphadenopathy, and multi-organ involvement [45]. This has been reported primarily in patients with Asian ancestry [8, 53].

## *Radiology*

The classic radiologic findings of LIP are bilateral interstitial infiltrates of the lower lobes. Alveolar and reticulonodular infiltrative patterns are also seen [8]. However, the chest radiograph is neither sensitive nor specific for LIP and may miss characteristic imaging findings that may be detected by high-resolution computed tomography (HRCT) of the chest.

HRCT typically shows a combination of ill-defined centrilobular and subpleural micronodules, ground-glass opacities, basilar reticulation, peribronchovascular interstitial thickening, and pulmonary cysts. Cysts are present in 60%–80% of patients and are thin walled and regular shaped (round) (Fig. 8.1). They vary in size and are often large (up to 3 cm) [46]. Typically, cysts comprise <10% of the lung parenchyma. They occur randomly in all lung zones but are often basilar and subpleural or along the peribronchovascular bundle [47]. Cysts are postulated to be a consequence of bronchiolar obstruction by lymphocytic infiltrates accompanied by postobstructive ectasia/dilatation [5]. Ischemia is another process that can induce cystic change in the lungs. The obstruction of small capillaries that supply the terminal bronchiole leads to necrosis of the airways and ischemic dilatation.

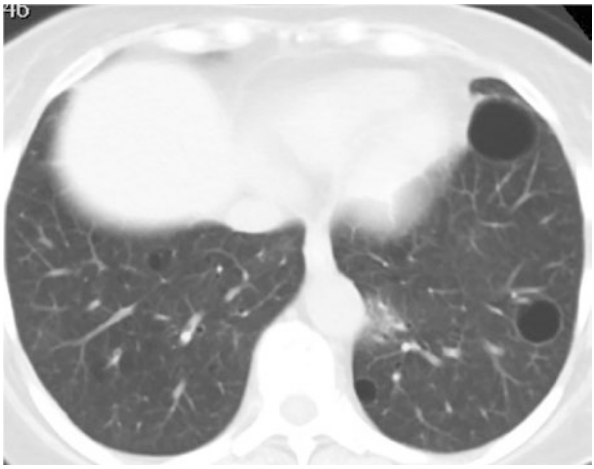

**Fig. 8.1** High-resolution chest computed tomography of a patient with lymphoid interstitial pneumonia showing multiple thin-walled round cysts

Ground-glass opacities may represent areas of alveolar septal infiltrates, whereas centrilobular nodules represent foci of peribronchiolar infiltrates [13]. Although micronodules are characteristic, 40% of patients may have larger nodules up to 2 cm. Nodules are typically subpleural and in a perilymphatic distribution [48]. Ground-glass opacities and nodules may evolve into consolidation, architectural distortion, and honeycombing [9]. The reverse halo sign (atoll sign) may be seen [49]. Mediastinal and hilar adenopathy are also seen in approximately 65% of patients with LIP [13, 50–52]. The regular (as opposed to bizarre) shape of the cysts, presence of adenopathy, and septal thickening help to distinguish LIP from pulmonary Langerhans cell histiocytosis, whereas the presence of centrilobular nodules allows differentiation of LIP from lymphangioleiomyomatosis [47, 50].

Radiologic findings may wax and wane with a chronic, indolent course [5]. Radiologic findings that may be reversible include ground-glass attenuation, airspace consolidation, centrilobular small nodules, subpleural small nodules, large nodules, thickening of the interlobular septa, thickening of bronchovascular bundles, and lymph node enlargement [52], whereas cysts and architectural distortion may stay stable or progress on imaging follow-up. Often, new cysts develop in areas of previous centrilobular nodules [52].

## *Diagnosis*

LIP should be considered when there is a characteristic HRCT in the correct clinical context. However, in the absence of a clearly diagnosed systemic disease, it is recommended that the diagnosis of LIP be confirmed histologically [2, 53].

Bronchoscopy is most useful for establishing an alternative diagnosis. Bronchoalveolar lavage (BAL) will reveal a lymphocytosis with a shift in favor of CD3 T lymphocytes, often with a mild increase in eosinophils and alveolar macrophages [33]. More importantly, the BAL should be negative for viral, bacterial, and fungal pathogens and neoplastic (clonal) cells [9].

As the yield of transbronchial biopsies is low in making a diagnosis of LIP, surgical lung biopsy (Fig. 8.2) is the procedure of choice. The macroscopic appearance of the lung may be normal, but histopathologic examination generally shows a diffuse interstitial inflammatory infiltrate composed of mature small lymphocytes, plasma cells, and occasional histiocytes [12]. This pattern is most characteristically present in the areas surrounding lymphatic channels, such as the alveolar septa, interstitial septa, peribronchovascular regions, and subpleural lung [7]. Alveolar aggregates of lymphoid tissue may cause bronchiolitis and small airway plugging leading to cysts [9]. The interstitial lymphoid cells are mainly T cells (CD3+) mixed with histiocytes and plasma cells, while B cells (CD20+) are more prominent in peribronchial germinal centers [54]. Scattered multinucleated giant cells or ill-formed granulomas are seen in the lymphoid infiltrates in about half of the cases [9, 12]. There is no evidence of vasculitis or necrosis. Hyperplasia of type II pneumocytes is commonly seen, and fibrosis may develop in more advanced cases [9, 12].

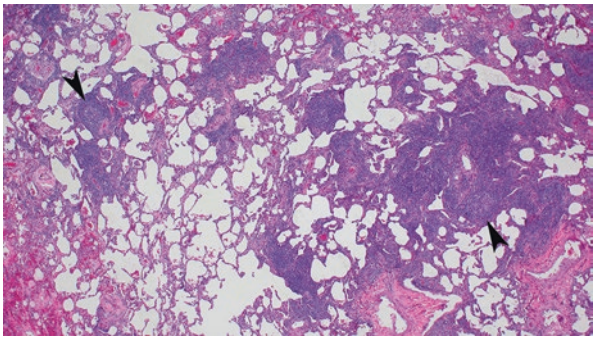

**Fig. 8.2** Lymphoid interstitial pneumonia. Chronic lymphoplasmacytic inflammation extends from the bronchovascular area to the adjacent lobule. Germinal centers can be seen both around the airway and also in more distal areas of the lobule (arrowheads). Hematoxylin and eosin: 20×

The histopathologic differential diagnosis of LIP includes lymphomatoid granulomatosis, hypersensitivity pneumonitis, small lymphocytic lymphoma, and MALTomas [5, 18]. Immunohistochemical studies and flow cytometry should be performed in order to distinguish between the polyclonal populations of lymphocytes seen in LIP and a monotypic cell population seen in malignant lymphoproliferative disorders. In the past, LIP was considered a risk factor for the development of malignant lymphoma; however, many of the previously described cases were reclassified as lymphoma, and only a small number of definite LIP cases are felt to have undergone malignant transformation. Due to its association with immunocompromised states, stains for *Pneumocystis jiroveci* pneumonia (PJP) must be carried out in all patients.

## *Treatments*

The natural history of LIP is variable, and it may often be stable for many months without specific treatment, although approximately one-third of cases may progress to pulmonary fibrosis and respiratory failure [12, 52]. The reported median survival times range from 5 years [5] to 11.5 years [53].

Patients with mild or indolent disease may not require therapy [55]. However, treatment should be considered in patients with disabling symptoms or a progressive decline in pulmonary function [39]. There are no randomized, placebo-controlled clinical trials to inform treatment decisions. Instead, treatment recommendations are based on case reports and case series. Approximately 50% to 60% of patients stabilize or improve with corticosteroids [8]. Suggested prednisone regimens range from 1 to 2 mg/kg/day for 2 to 12 weeks followed by a slow taper over another 6–12 weeks [56]. Variable improvement and treatment responses have also been reported with hydroxychloroquine, azathioprine, rituximab, cyclophosphamide, and

chlorambucil [8, 39, 55, 57–59]. There may be a role for gamma globulin therapy in patients with hypogammaglobulinemia [8, 60]. LIP associated with HIV often resolves with highly active antiretroviral drug treatment [61].

## Follicular Bronchiolitis

Follicular bronchiolitis (FB) is considered one of the reactive lymphoid disorders that affect the lungs, along with nodular lymphoid hyperplasia (NLH) – which is synonymous with pseudolymphoma, and LIP [62].

Histologically, FB is characterized by nonneoplastic, polyclonal [63] lymphoid hyperplasia of the bronchus-associated lymphoid tissue (BALT). Lymphoid follicles containing reactive germinal centers lie in the walls of the small airways (<2 mm, non-cartilaginous) leading to progressive narrowing and eventual obliteration of the bronchioles. There is little to no extension to the alveolar septa and interstitium. BALT is itself not native to adult human airways and can be considered an ectopic lymphoid tissue that appears to develop as a result of antigenic stimulation [64]. This might suggest that FB reflects a pathologically exaggerated inflammatory response with BALT and lymphoplasmacytic infiltration in the susceptible host with an aberrant immune system (Table 8.1). NLH and LIP share the same reactive lymphoid and plasmacytic inflammation but are distinguished from each other based on the diffuseness and the predominant compartments of the lung affected. Whereas FB is primarily bronchiolocentric, LIP is characterized by more extensive interstitial involvement. However, these entities are not mutually exclusive, and FB may coexist with LIP and NLH, which can dominate over FB in the affected patient's clinical and radiographic presentation.

### *Clinical Presentation*

Clinically, FB is most commonly associated with connective tissue diseases (CTD), particularly rheumatoid arthritis (RA) and Sjögren's syndrome (SS), as well as congenital and acquired immunodeficiencies such as HIV infection and CVID. Other associations include hypersensitivity reactions, diffuse panbronchiolitis, granulomatosis with polyangiitis (GPA), interstitial pneumonias, multicentric Castleman disease, infections, and bronchiectasis [65–68]. Infrequently, FB may exist in a "primary" idiopathic form without any identifiable associated conditions or derangements of the immune system [68]. However, as a result of overlapping clinical features, multiple clinical associations, and the need for a biopsy for definitive confirmation of FB, its precise prevalence and epidemiology remain unknown and are dependent on the underlying associated condition. For example, FB will be

more prevalent in the pediatric population among those with congenital immune deficiency syndromes, whereas it may be more prevalent later in life in adult women affected by SS. Most, but not all, series appear to indicate FB being identified after recognition of the associated disorder [65, 68], although FB as a presenting manifestation of SS has been described [78].

Attributable respiratory symptoms are commonly cough and dyspnea. However, they may be mild or, in some cases, asymptomatic. Among those with respiratory symptoms, evidence of small airway disease can be found in over half of the patients with SS [69, 70]; however, it is not clear how many may be asymptomatic or have only mild impairment [68, 69, 71, 72].

Pulmonary function testing (PFT) should include both lung volumes and diffusion capacity, in addition to the standard spirometry. As with other causes of bronchiolitis where the small airways are predominantly affected, obstructive physiology by classic definitions may not always be present as might be expected, but depending on the severity of the disease and the specific type of bronchiolitis, the PFTs may be normal, restricted, and nonspecific or have mixed defects [60, 68, 72, 73]. Lung volumes may demonstrate air trapping, and the diffusion capacity for carbon monoxide may be reduced, which may be the most sensitive indicator [68]. Among the newer techniques, impulse oscillometry may be a promising technique to detect peripheral airway disease, but is not readily available [74].

## *Radiology*

Short of a lung biopsy, the most specific objective clues for FB are found radiographically. However, a plain chest radiograph is typically inadequate, as it may be normal. In the symptomatic patient suspected of, or at risk for, having bronchiolitis, HRCT imaging is required (Fig. 8.3). Micronodules ranging from 1 to 3 mm are universal, with up to half between 3 and 12 mm [75]. They can be greater than a centimeter but are less common prompting consideration for other processes. They are most commonly diffuse and less commonly basilar predominant or equally

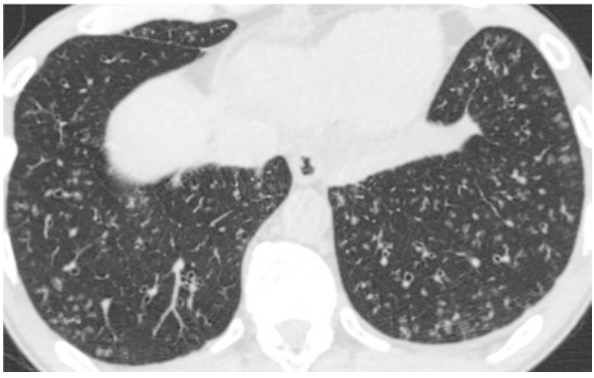

**Fig. 8.3** High-resolution chest computed tomography of a patient with follicular bronchiolitis showing multiple solid and ground-glass nodules in a peribronchial distribution and tree-in-bud distribution. Bronchial wall thickening, bronciolectasis, and bronchiectasis are also present

distributed [75]. They can appear solid and also with ground-glass opacities, often in a centrilobular, tree-in-bud, or peribronchial distribution [75, 76]. Additional evidence of airway disease can be appreciated with bronchial wall thickening and dilation (i.e., bronchiolectasis), sometimes evolving into more obvious features of bronchiectasis. Indirect features of small airway disease typically include evidence of air trapping suggested by mosaicism that can be accentuated on expiratory CT imaging. Although this is fairly characteristic in constrictive bronchiolitis and bronchiolitis of hypersensitivity pneumonitis, it does not appear to be a common feature for follicular bronchiolitis [75, 77]. A more unique feature to FB and LIP among the different types of bronchiolitis and idiopathic interstitial pneumonias is that patients can present with diffuse cystic lung disease, particularly in the clinical context of SS [71, 78]. In a series of four patients with SS who presented with cystic lung disease, SSA was positive in all, and surgical lung biopsy in three showed two cases of FB and one case of LIP [78]. These rounded or oval cysts were described to be variable in size (5 mm to 5 cm), basilar predominant if not diffuse, perivascular, and sometimes with internal septations. The authors propose that these characteristic findings in established SS may obviate the need for a biopsy to confirm FB or LIP. However, lymphoma and amyloid can complicate cystic lung disease and should be considered in the context of associated nodularity [79, 80]. Cystic lung disease in FB may not be as common of a finding when associated with other disorders such as RA or in immunodeficiencies [75, 81], but is considered a common feature of LIP [52].

## *Diagnosis*

Although the CT features in the appropriate clinical context may suggest the presence of FB, a formal diagnosis still requires a surgical lung biopsy (Fig. 8.4). The decision to do a biopsy may lie largely on the clinical context of whether alternative considerations that have important prognostic or treatment

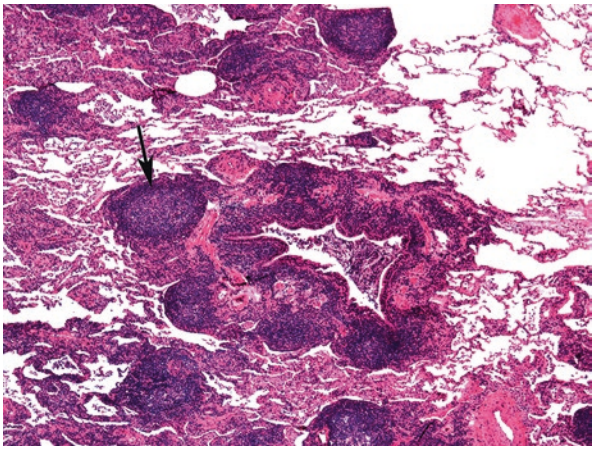

**Fig. 8.4** Follicular bronchiolitis. Thoracoscopic wedge excision reveals chronic bronchiolitis with germinal centers (arrow) adjacent to small airways, features consistent with follicular bronchiolitis. Hematoxylin and eosin: 200×

implications are being considered, such as lymphoma or amyloid. Progressive disease may also prompt the need for definitive histologic diagnosis, especially if there is no specific context such as SS to guide the clinician. As surgical lung biopsy is associated with some morbidity and mortality, a period of observation may also be appropriate. Increasing expertise and availability of bronchoscopic transbronchial cryobiopsy may prove to be a more cost-effective, if not a safer, alternative to a surgical lung biopsy, particularly since the FB abnormalities are airway centered [82, 83]. The diagnostic yield may further improve with a multidisciplinary review.

If there is no clinical pressure to achieve a firm histological diagnosis, a confident working diagnosis might be achieved based on the clinical context and HRCT features, as described previously. Thus, it is imperative to evaluate thoroughly for clues to underlying connective tissue disease, immune deficiency states, hypersensitivity exposures, and other associated disorders.

### *Treatment*

As most cases of FB are secondary to another primary disorder, treatment is often related to treating the underlying disease. Although no formal randomized controlled trials exist specifically targeting FB, there are observational data to support that treating the underlying immune derangement may be of benefit, particularly in acquired immunodeficiency syndromes such as HIV [84, 85] and CVID [86]. However, in some cases, treatment targeting the underlying disorder may be ineffective including in systemic inflammatory disorders such as in RA [73] and SS [29]. Many have treated empirically, regardless of the mechanism, with prednisone or cytotoxic agents including azathioprine, mycophenolate, and cyclophosphamide, with anecdotal benefit [64, 68, 71, 87]. As with the literature in diffuse panbronchiolitis and bronchiectasis, macrolides may be of help in idiopathic FB or possibly even when associated with other disorders [46, 68, 88–91]. Finally, there is rationale for, but little experience with, more specific targeted therapies such with rituximab and other biologic agents that target the lymphoplasmacytic inflammation [56].

## Conclusion

Follicular bronchiolitis and lymphoid interstitial pneumonia represent a pathologic continuum arising from benign reactive lymphoid reaction of the BALT leading to formation of nodules and luminal narrowing and to expansion of the interstitium with fibrosis and, in some cases, cyst formation. Multiple disorders have been associated with LIP and FB including autoimmune disorders and immunodeficiencies, but they can also occur in an idiopathic form. Additionally, LIP and FB may be overshadowed by other features of these other disorders or by other injury patterns, such as interstitial pneumonias, that may coexist and

dominate the clinical and radiographic presentation. Diagnostic evaluation thus requires a careful evaluation for associated conditions, and given the variable patterns on pulmonary function testing and an insensitive chest radiograph, HRCT imaging is necessary to identify the suggestive features for FB and LIP. Cystic disease in well-established SS may be specific for FB and/or LIP, but a definitive diagnosis in most other contexts requires a surgical biopsy. Treatment should initially target any underlying conditions, and in refractory or idiopathic variants, prednisone, macrolides, cytotoxic medications, and biologic agents have been used with variable success.

**Key Learning Points**

- Follicular bronchiolitis and lymphoid interstitial pneumonia are characterized by polyclonal infiltration of the lung by mature lymphocytes. Follicular bronchiolitis is primarily bronchiolocentric, whereas lymphoid interstitial pneumonia extends into the interstitium with fibrosis.
- Follicular bronchiolitis and lymphoid interstitial pneumonia are rarely idiopathic and are generally associated with an immunodeficiency or autoimmune condition.
- Lymphoid interstitial pneumonia is an AIDS-defining illness in children.
- There is a strong association between lymphoid interstitial pneumonia and follicular bronchiolitis and Sjögren's syndrome with nearly 1% of Sjögren's syndrome patients having LIP or FB and 30%–60% of patients with LIP having Sjögren's syndrome.
- The diagnosis of LIP should be considered in anyone with lung cysts and an immunologic abnormality.
- The diagnosis of follicular bronchiolitis should be considered in anyone with micronodules in a peribronchial distribution with an underlying immunologic abnormality.
- Treatment of follicular bronchiolitis and lymphoid interstitial pneumonia is focused on treating the underlying/associated condition.

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## References

1. Gupta N, Vassallo R, Wikenheiser-Brokamp, FX MC. Diffuse cystic lung disease. Part II. Am J Respir Crit Care Med. 2015;192(1):17–29.
2. Guinee DG Jr. Update on nonneoplastic pulmonary lymphoproliferative disorders and related entities. Arch Pathol Lab Med. 2010;134(5):691–701.
3. Carrington CB, Liebow AA. Lymphocytic interstitial pneumonia. Amer J Path. 1966;48:36a.
4. Takata T, Nagafuchi S, Tsuda H, Uehira K, Kondo S, Ueda A, et al. Lymphocytic interstitial pneumonia associated with a marked increase in monoclonal IgM-κ-type rheumatoid factor and serum CA19-9. Jpn J Med. 1991;30(1):92–6.

5. Swigris JJ, Berry GJ, Raffin TA, Kuschner WG. Lymphoid interstitial pneumonia: a narrative review. Chest. 2002;122:2150–64.
6. WHO Case definitions of HIV for surveillance and revised clinical staging and immunological classification of HIV-related disease in adults and children. WHO 2006. http://www.who.int/hiv/
7. Filipek MS, Thompson ME, Wang PL, Gosselin MV, L Primack S. Lymphocytic interstitial pneumonitis in a patient with systemic lupus erythematosus. J Thorac Imaging. 2004;19(3):200–3.
8. Strimlan CV, Rosenow EC III, Weiland LH, Brown LR. Lymphocytic interstitial pneumonitis: review of 13 cases. Ann Intern Med. 1978;88(5):616–21.
9. Doffman SR, Miller RF. Interstitial lung disease in HIV. Clin Chest Med. 2013;34(2):293–306.
10. Jawad H, Walker CM, Wu CC, Chung JH. Cystic interstitial lung diseases: recognizing the common and uncommon entities. Curr Probl Diagn Radiol. 2014;43(3):115–27.
11. Parker JS, Shellito J, Pei LA, Mason CM. Lymphocytic interstitial pneumonitis presenting as recurrent pneumothoraces. Chest. 1991;100(6):1733–5.
12. Koss MN, Hochholzer L, Langloss JM, Wehunt WD, Lazarus AA. Lymphoid interstitial pneumonia: Clinicopathological and immunopathological findings in 18 cases. Pathology. 1987;19(2):178–85.
13. Johkoh T, Műller NL, Pickford M, Hartman TE, Ichikado K, Akira M, et al. Lymphocytic interstitial pneumonia: thin-section CT findings in 22 patients. Radiology. 1999;212(2):567–72.
14. Zar HJ. Chronic lung disease in human immunodeficiency virus (HIV) infected children. Pediatr Pulmonol. 2008;43(1):1–10.
15. Saito M, Hatakeyama S, Wakabayashi Y, Yanagimoto S, Takemura T, Yotsuyanagi H. A pathologically proven case of adult-onset HIV-related lymphocytic interstitial pneumonia with acute exacerbation treated with steroid and antiretroviral therapy. J Infect Chemother. 2015;21(12):868–72.
16. Bates CA, Ellison MC, Lynch DA, Cool CD, Brown KK, Routes JM. Granulomatous-lymphocytic lung disease shortens survival in common variable immunodeficiency. J Allergy Clin Immunol. 2004;114(2):415–21.
17. Panchahbai TS, Farver C, Highland KB. Lymphocytic interstitial pneumonia. Clin Chest Med. 2016;37(3):463–74.
18. Dalvi V, Gonzalez EB, Lovett L. Lymphocytic interstitial pneumonitis (LIP) in Sjögren's syndrome: a case report and a review of the literature. Clin Rheumatol. 2007;26(8):1339–43.
19. Fishback N, Koss M. Update on lymphoid interstitial pneumonitis. Curr Opin Pulm Med. 1996;2(5):429–33.
20. Randall TD. Bronchus-associated lymphoid tissue (BALT0 structure and function). Adv Immunol. 2010;107:187–241.
21. Maglione PJ, Ko HZB, Beasley MB, Strauchen JA, Cunningham-Rundles C. Tertiary lymphoid neogenesis is a component of pulmonary lymphoid hyperplasia in patients with common variable immunodeficiency. J Allergy Clin Immunol. 2014;133(2):535–42.
22. DeCoteau WE, Tourville D, Ambrus M, Montes M, Adler R, Tomasi TB Jr. Lymphoid interstitial pneumonia and autoerythrocyte sensitization syndrome. Arch Intern Med. 1974;134(3):519–22.
23. Park JH, Levinson AI. Granulomatous-lymphocytic interstitial lung disease (GLILD) in common variable immunodeficiency (CVID). Clin Immunol. 2010;134(2):97–103.
24. Malamou-Mitsi V, Tsai M, Gal A, Koss MN, O'Leary TJ. Lymphoid interstitial pneumonia not associated with HIV infection: role of Epstein-Barr virus. Mod Pathol. 1992;5(5):487–91.
25. Mueller GA, Pickoff AS. Pediatric lymphocytic interstitial pneumonitis in an HIV-negative child with pulmonary Epstein-Barr virus infection. Pediatr Pulmonol. 2003;36(5):447–9.
26. Marzouk K, Corate L, Saleh S, Sharma OP. Epstein-Barr-virus-induced interstitial lung disease. Curr Opin Pulm Med. 2005;11(5):456–60.
27. 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.

28. Levinson AI, Hopewell PC, Stites DP, Spitler LE, Fudenberg HH. Coexistent lymphoid interstitial pneumonia, pernicious anemia, and agammaglobulinemia. Arch Intern Med. 1976;136(2):213–6.
29. Shi JH, Liu HR, Xu WB, Feng RE, Zhang ZH, Tian XL, et al. Pulmonary manifestations of Sjögren's syndrome. Respiration. 2009;78:377–86.
30. Alkhayer M, McCann BG, Harrison BD. Lymphocytic interstitial pneumonitis in association with Sjogren's syndrome. Br J Dis Chest. 1988;82:306–9.
31. Sarkar PK, Patel N, Furie RA, Talwar A. Pulmonary manifestations of primary Sjögren's syndrome. Chest Duis Allied Sci. 2009;51:93–101.
32. Constantopoulos SH, Papadimitrioo CS, Moutsopoulos HM. Respiratory manifestations in primary Sjögren's syndrome. A clinical, functional and histologic study. Chest. 1985;88:226–9.
33. Khardori R, Eagleton LE, Soler NG. Lymphocytic interstitial pneumonitis in autoimmune thyroid disease. Am J Med. 1991;90(5):649–52.
34. Rodriguez-Rosin R, Pares A, Bruguera M, Coll J, Picado C, Agusti-Vidal A, et al. Pulmonary involvement in primary biliary cirrhosis. Thorax. 1981;36(3):208–12.
35. Schuyler MR, Niewochner DE, Inkley SR, Kohn R. Abnormal lung elasticity in juvenile diabetes mellitus. Am Rev Respir Dis. 1976;11391:37–41.
36. Garcia D, Young L. Lymphocytic interstitial pneumonia as a manifestation of SLE and secondary Sjogren's syndrome. BMJ Case Rep. 2013; https://doi.org/10.1136/bcr-2013-009598.
37. Benisch B, Peison B. The association of lymphocytic interstitial pneumonia and systemic lupus erythematosus. Mt Sinai J Med. 1979;46(4):398–01.
38. Fischer A, Antoniou KM, Brown KK, Cadranel J, Corte TJ, du Bois RM, et al. An official European Respiratory Society/American Thoracic Society research statement: interstitial pneumonia with autoimmune features. Eur Respir J. 2015;46(4):976–87.
39. Prasse A, Kayser G, Warnatz K. Common variable immunodeficiency-associated granulomatous and interstitial lung disease. Curr Opin Pulm Med. 2018;19(5):503–9.
40. Katzenstein A. Katzenstein's and Askin's surgical pathology of non-neoplastic lung disease. 3rd ed. Philadelphia: W. B. Saunders; 1997.
41. Bergeron A, Bengoufa D, Feuillet S, Meignin V, Peffault de Latour R, Rybojad M, et al. The spectrum of lung involvement in collagen vascular-like diseases following allogeneic hematopoietic stem cell transplantation. Medicine. 2011;90(2):146–57.
42. Kotloff RM, Alhya VN, Crawford SW. Pulmonary complications of solid organ and hematopoietic stem cell transplantation. Am J Respir Crit Care Med. 2004;170(1):22–48.
43. Bolaños-Meade J, Ioffe O, Hey JC, Vogelsang GB, Akpek G. Lymphocytic pneumonitis as the manifestation of acute graft-versus-host disease of the lung. Am J Hematol. 2004;79(2):132–5.
44. Tangsinmankong N, Wayne AS, Howenstine MS, Washington KR, Langston C, Gatti RA, et al. Lymphocytic interstitial pneumonitis, elevated IgM concentration, and hepatosplenomegaly in ataxia-telangiectasia. J Pediatr. 2001;138(6):939–41.
45. Chan KL, Lade S, Prince HM, Harrison SJ. Update and new approaches in the treatment of Castleman disease. J Blood Med. 2016;7:145–58.
46. Ichikawa Y, Kinoshita M, Koga T, Oizumi K, Fujimoto K, Hayabuchi N. Lung cyst formation in lymphocytic interstitial pneumonia: CT features. J Comput Assist Tomogr. 1994;18(5):745–8.
47. Baldi BG, Carvalho CRR, Dias OM, Marchiori E, Hochhegger B. Diffuse cystic lung diseases: differential diagnosis. J Bras Pneumol. 2017;43(2):140–9.
48. Becciolini V, Gudinchet F, Cheseaux JJ, Schnyder P. Lymphocytic interstitial pneumonia in children with AIDS: high-resolution /CT finings. Eur Radiol. 2001;11(6):1015–20.
49. Freeman MD, Grajo JR, Karamsadkar ND, Steffensen TS, Hazelton TR. Reversed halo sign on CT as a presentation of lymphocytic interstitial pneumonia. Radiol Case. 2013;7(10):51–6.
50. Grant LA, Babar J, Griffin N. Cysts, cavities, and honeycombing in multisystem disorders: differential diagnosis and findings on thin-section CT. Clin Radiol. 2009;64(4):439–48.
51. Desai SR, Nicholson AG, Stewart S, Twentyman OM, Flower CD, Hansell DM. Benign pulmonary lymphocytic infiltration and amyloidosis: computed tomographic and pathologic features in three cases. J Thorac Imaging. 1997;12(3):215–20.

52. Johkoh T, Ichikado K, Akira M, Honda O, Tomiyama N, Mihara N, et al. Lymphocytic interstitial pneumonia: follow-up CT findings in 14 patients. J Thorac Imaging. 2000;15(3):162–7.
53. Cha SL, Fessler MB, Cool CD, Schwarz ML, Brown KK. Lymphoid interstitial pneumonia: clinical features, associations and prognosis. Eur Respir J. 2006;28(2):364–9.
54. Nicholson AG, Wotherspoon TC, Diss DM, Hansell DM, Du Bois R, Sheppard MN, et al. Reactive pulmonary lymphoid disorders. Histopathology. 1995;26(5):405–12.
55. Parambil JG, Myers JL, Lindell RM, Matteson EL, Ryu JH. Interstitial lung disease in primary Sjögren's syndrome. Chest. 2006;130(5):1489–95.
56. Devauchelle-Pensecd V, Pennec Y, Morvan J, Pers JO, Daridon C, Jousse-Joulin S, et al. Improvement of Sjögren's syndrome after two infusions of rituximab (anti-CD20). Arthritis Rheum. 2007;57:310–7.
57. Schupp JC, Köhler T, Müller-Quernheim J. Usefulness of cyclophosphamide pulse therapy in interstitial lung diseases. Respiration. 2016;91:296–301.
58. Okada M, Suzuki K, Matsumoto M, Nakashima M, Nakanishi T, Takada K, et al. Intermittent intravenous cyclophosphamide pulse therapy for the treatment of active interstitial lung disease associated with collagen vascular diseases. Mod Rheumatol. 2007;17:131–6.
59. Swartz MA, Vivino FB. Dramatic reversal of lymphocytic interstitial pneumonitis in Sjögren's syndrome with rituximab. JCR J Clin Rheumatol. 2011;17:454.
60. Popa V. Lymphocytic interstitial pneumonia in common variable immunodeficiency. Ann Allergy. 1988;60:203–6.
61. Dufour V, Wislez M, Bergot E, Mayaud C, Cadranel J. Improvement of symptomatic human immunodeficiency virus-related lymphoid interstitial pneumonia in patients receiving highly active antiretroviral therapy. Clin Infect Dis. 2003;36:e127–30.
62. Poletti V, Ravaglia C, Tomassetti S, Gurioli C, Casoni G, Asioli S, et al. Lymphoproliferative lung disorders: clinicopathological aspects. Eur Respir Rev. 2013;22(130):427–36.
63. Tashiro K, Ohshima K, Suzumiya J, Yoneda S, Yahiro M, Sugihara M, et al. Clonality of primary pulmonary lymphoproliferative disorders; using in situ hybridization and polymerase chain reaction for immunoglobulin. Leuk Lymphoma. 1999;36(1–2):157–67.
64. Randall TD. Bronchus-associated lymphoid tissue (BALT) structure and function. Adv Immunol. 2010;107:187–241.
65. Yousem SA, Colby TV, Carrington CB. Follicular bronchitis/bronchiolitis. Hum Pathol. 1985;16(7):700–6.
66. Couture C, Colby TV. Histopathology of bronchiolar disorders. Semin Respir Crit Care Med. 2003;24(5):489–98.
67. Travis WD, Hoffman GS, Leavitt RY, Pass HI, Fauci AS. Surgical pathology of the lung in Wegener's granulomatosis. Review of 87 open lung biopsies from 67 patients. Am J Surg Pathol. 1991;15(4):315–33.
68. 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):307–12.
69. Kakugawa T, Sakamoto N, Ishimoto H, Shimizu T, Nakamura H, Nawata A, et al. Lymphocytic focus score is positively related to airway and interstitial lung diseases in primary Sjogren's syndrome. Respir Med. 2018;137:95–102.
70. Kampolis CF, Fragkioudaki S, Mavragani CP, Zormpala A, Samakovli A, Moutsopoulos HM. Prevalence and spectrum of symptomatic pulmonary involvement in primary Sjogren's syndrome. Clin Exp Rheumatol. 2018.;36 Suppl;112(3):94–101.
71. Lu J, Ma M, Zhao Q, Meng F, Wang D, Cai H, et al. The clinical characteristics and outcomes of follicular bronchiolitis in Chinese adult patients. Sci Rep. 2018;8(1):7300.
72. Yuksekkaya R, Celikyay F, Yilmaz A, Arslan S, Inanir A, Inonu H, et al. Pulmonary involvement in rheumatoid arthritis: multidetector computed tomography findings. Acta Radiol. (Stockholm, Sweden: 1987. 2013;54(10):1138–49.
73. Devouassoux G, Cottin V, Liote H, Marchand E, Frachon I, Schuller A, et al. Characterisation of severe obliterative bronchiolitis in rheumatoid arthritis. Eur Respir J. 2009;33(5):1053–61.

74. McNulty W, Usmani OS. Techniques of assessing small airways dysfunction. Eur Clin Respir J. 2014;1:25898-http://dx.doi.org/10.3402/ecrj.v1.25898.
75. Howling SJ, Hansell DM, Wells AU, Nicholson AG, Flint JD, Muller NL. Follicular bronchiolitis: thin-section CT and histologic findings. Radiology. 1999;212(3):637–42.
76. Kang EY, Woo OH, Shin BK, Yong HS, Oh YW, Kim HK. Bronchiolitis: classification, computed tomographic and histopathologic features, and radiologic approach. J Comput Assist Tomogr. 2009;33(1):32–41.
77. Pipavath SJ, Lynch DA, Cool C, Brown KK, Newell JD. Radiologic and pathologic features of bronchiolitis. AJR Am J Roentgenol. 2005;185(2):354–63.
78. Gupta N, Wikenheiser-Brokamp KA, Fischer A, McCormack FX. Diffuse cystic lung disease as the presenting manifestation of Sjogren syndrome. Ann Am Thorac Soc. 2016;13(3):371–5.
79. Borie R, Wislez M, Antoine M, Copie-Bergman C, Thieblemont C, Cadranel J. Pulmonary mucosa-associated lymphoid tissue lymphoma revisited. Eur Respir J. 2016;47(4):1244–60.
80. Do KH, Lee JS, Seo JB, Song JW, Chung MJ, Heo JN, et al. Pulmonary parenchymal involvement of low-grade lymphoproliferative disorders. J Comput Assist Tomogr. 2005;29(6):825–30.
81. Weinman JP, Manning DA, Liptzin DR, Krausert AJ, Browne LP. HRCT findings of childhood follicular bronchiolitis. Pediatr Radiol. 2017;47(13):1759–65.
82. Lentz RJ, Fessel JP, Johnson JE, Maldonado F, Miller RF, Rickman OB. Transbronchial cryobiopsy can diagnose constrictive bronchiolitis in veterans of recent conflicts in the middle east. Am J Respir Crit Care Med. 2016;193(7):806–8.
83. Ussavarungsi K, Kern RM, Roden AC, Ryu JH, Edell ES. Transbronchial Cryobiopsy in diffuse parenchymal lung disease: retrospective analysis of 74 cases. Chest. 2017;151(2):400–8.
84. Rasmussen LD, Pedersen C, Madsen HD, Laursen CB. Follicular bronchiolitis in an HIV-infected individual on combination antiretroviral therapy with low CD4+ cell count but sustained viral suppression. BMJ Case Rep. 2017;2017:bcr2017221025.
85. Shipe R, Lawrence J, Green J, Enfield K. HIV-associated follicular bronchiolitis. Am J Respir Crit Care Med. 2013;188(4):510–1.
86. Tashtoush B, Memarpour R, Ramirez J, Bejarano P, Mehta J. Granulomatous-lymphocytic interstitial lung disease as the first manifestation of common variable immunodeficiency. Clin Respir J. 2018;12(1):337–43.
87. Romero S, Barroso E, Gil J, Aranda I, Alonso S, Garcia-Pachon E. Follicular bronchiolitis: clinical and pathologic findings in six patients. Lung. 2003;181(6):309–19.
88. Hayakawa H, Sato A, Imokawa S, Toyoshima M, Chida K, Iwata M. Bronchiolar disease in rheumatoid arthritis. Am J Respir Crit Care Med. 1996;154(5):1531–6.
89. Thalanayar PM, Holguin F. Follicular bronchiolitis in primary ciliary dyskinesia. Australas Med J. 2014;7(7):294–7.
90. Kobayashi H, Kanoh S, Motoyoshi K, Aida S. Tracheo-broncho-bronchiolar lesions in Sjogren's syndrome. Respirology. 2008;13(1):159–61.
91. Ichikawa Y, Ninomiya H, Koga H, Tanaka M, Kinoshita M, Tokunaga N, et al. Erythromycin reduces neutrophils and neutrophil-derived elastolytic-like activity in the lower respiratory tract of bronchiolitis patients. Am Rev Respir Dis. 1992;146(1):196–203.