DOI: 10.7860/JCDR/2015/13873.6496

Review Article

Internal Medicine Section

Follicular Bronchiolitis: A Literature Review

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ABSTRACT

Follicular bronchiolitis (FB) also known as hyperplasia of the bronchial associated lymphoid tissue (BALT), or bronchiolar nodular lymphoid hyperplasia, is an entity characterized by the development of lymphoid follicles with germinal centers in the walls of small airways. FB is thought to be caused by antigenic stimulation of BALT, followed by a polyclonal lymphoid hyperplasia. It is currently classified as one of the reactive pulmonary lymphoid disorders in a group known as the lymphoproliferative pulmonary diseases (LPDs).

FB is a pathological diagnosis that can be seen in several clinical settings, including connective tissue diseases, immunodeficiency states, autoimmune diseases, infections, obstructive airway diseases, as well as several types of interstitial lung diseases (ILDs). Its characteristics need to be carefully identified and differentiated from other closely related diseases in the group of LPDs due to significant differences in treatment and prognosis.

Keywords: BALT, Lymphoid follicles, Lymphoproliferative pulmonary diseases, Small airways

BACKGROUND

For over half a century, clinicians and pathologists have recognized a group of pulmonary diseases associated with an accumulation of lymphoid follicles in the walls of bronchi and bronchioles. This entity was first described in patients with bronchiectasis, a disease characterized by extensive airway mural inflammation, where lymphocytic hyperplasia in the walls of small airways formed part of the inflammatory picture. However, in a group of patients, pathologists were able to confirm that sub-epithelial accumulation of lymphoid follicles was the primary pathology affecting the bronchioles [1]. These enlarged follicles would often distort the architecture of the bronchial tree, merely due to their size, projecting into the bronchial lumen and causing partial bronchial and bronchiolar obstruction.

In 1947, the first reference to this entity was made by Engel et al., who coined the term “nodal bronchiolitis”, describing thickened bronchioles, with well formed lymphoid follicles in their walls in the absence of a diffuse inflammatory infiltrate [2].

In 1952, Whitewall studied 200 consecutive lung specimens mainly from lobectomies and pneumonectomies of patients with advanced bronchiectasis. He described this feature as “follicular bronchiectasis”, where the most prominent microscopic finding was an extensive formation of lymphoid follicles and lymph nodes in the walls of affected bronchi and bronchioles [1].

In 1979, Epler et al., described an association between bronchiolitis and the administration of D-penicillamine in 2 patients with rheumatoid arthritis and eosinophilic fasciitis. The chronic inflammatory bronchiolar disorder seen was characterized by extensive proliferation of lymphoid tissue, occurring as follicles in the bronchiolar walls and was given the name "follicular bronchiolitis" (FB) [3].

Currently, FB is classified as one of the non-neoplastic (reactive) pulmonary lymphoid disorders in a group known as the lymphoproliferative pulmonary diseases (LPDs) [Table/Fig-1]. It is mainly distinguished from other reactive pulmonary lymphoid diseases in its group such as lymphocytic interstitial pneumonia (LIP) and nodular lymphoid hyperplasia (NLH) by the pattern and extent of pulmonary parenchymal involvement.

PATHOPHYSIOLOGY

Bronchioles are small airway divisions arising from the tertiary bronchi with an average internal diameter of 1mm, where the airway becomes devoid of hyaline cartilage. The term bronchiolitis refers to inflammation of the bronchioles with considerable sparing of the larger airways and lung parenchyma. FB is characterized by the presence of hyperplastic lymphoid follicles that are prominent and well-defined reactive germinal centers distributed along bronchovascular bundles and associated with minimal interstitial disease [3].

Lymphoproliferative Pulmonary Diseases (LPDs)
Reactive/non-neoplastic lymphoid lesions: classified based on the pattern of pulmonary involvement • Nodular lymphoid hyperplasia (NLH): focal • Follicular bronchiolitis (FB): peribronchial • Lymphoid interstitial pneumonia (LIP): diffuse with pulmonary cyst
Malignant parenchymal lymphoproliferative lesions **Primary (0.5% of all primary lung neoplasms)** • Extranodal marginal zone lymphoma of MALT origin (MALT lymphoma) • Diffuse large B-cell lymphoma (DLBCL) • lymphomatoid granulomatosis (LYG)
Secondary • Non-Hodgkin lymphoma (NHL) • Hodgkin lymphoma (HL)
Lymphoproliferative disorders in the immunocompromised • Acquired immune deficiency syndrome (AIDS)- related lymphoma (ARL) • Post-transplantation lymphoproliferative disorder (PTLD)

[Table/Fig-1]: Classification of lymphoproliferative pulmonary diseases

Bronchus-associated lymphoid tissue (BALT) is a dense cluster of lymphocytes with follicular structures commonly distributed in a reticular network of stromal cells associated with specialized airway epithelium. BALT is characterized by three main features; 1) Development of a stromal cell network with separation of B and T cell areas; 2) Aggregation of follicular dendritic cells (FDCs) in the B cell follicles; 3) Development of high endothelial venules (HEVs) and lymphatics in the follicular structures [4].

In 1973, the term “BALT” was introduced by Bienenstock et al., as they described the morphologic and functional characteristics

of lymphoid aggregates in the respiratory tract of rabbits [5]. In rabbits, BALT is constitutively present in the lungs, seen along the bronchial tree, interlobular septa and within the subpleural nodes. This structure is comparable to the gastric mucosal associated lymphoid tissue (MALT) and intestinal associated lymphoid tissue (Peyer's patches).

Studies in humans, however, show that BALT does not exist constitutively as a normal structural component of the airways, but rather an ectopic lymphoid tissue that develops in the lungs in response to antigenic stimulation through inflammation or infection, in a process known as "lymphoid-neogenesis" [6,7]. Once formed, BALT seems to persist in the lungs for up to 3 months after clearance of an infection. During pulmonary inflammation, the perivascular spaces become densely packed with lymphocytes, a process referred to as "perivascular cuffing". Since pulmonary arteries run parallel to the small airways, lymphocytic inflammation may extend into the airways forming "Induced-BALT" [8].

Induced BALT collects airway antigens and primes naive B cells and T cells. These airway germinal centers can generate memory T cells and plasma cells that remain in the airway and bone marrow, where they respond locally to a secondary challenge, promoting a rapid and efficient immune response to pulmonary pathogens [9].

BALT can be seen in association with many chronic pulmonary diseases, such as asthma, COPD, malignancy, rheumatoid lung disease, and tuberculosis [10-12].

CLASSIFICATION

FB can be generally classified based on its underlying aetiology into a primary and secondary form.

Secondary follicular bronchiolitis is a relatively common disease that occurs in association with many systemic and pulmonary diseases summarized in [Table/Fig-2]. Idiopathic (Primary) form of follicular bronchiolitis is a rare disease that occurs without an associated primary immunodeficiency state, inflammatory, autoimmune, infectious, or connective tissue disease.

Connective tissue disease
Sjögren's syndrome [13,14] Rheumatoid arthritis [15,16] Systemic lupus erythematosis [17,18]
Other immunological disorders
Evans Syndrome (Autoimmune haemolytic anaemia and immune thrombocytopenia) [19,20] Pernicious anaemia [21]
Immunodeficiency
AIDS, particularly in children [22] Common variable immunodeficiency (CVID) [23,24]
Infections
Pneumocystis Jirovicci pneumonia [25] *Legionella pneumonia* [26] Active hepatitis [27]
Interstitial lung diseases [24, 28-30]
LIP Respiratory bronchiolitis-ILD (RB-ILD) Desquamative interstitial pneumonia (DIP) Hypersensitivity pneumonitis (HP) Cryptogenic organizing pneumonia (COP) Granulomatous lymphocytic-ILD (GLILD)
Airway inflammatory diseases [10,11]
Bronchiectasis Asthma COPD
Familial [31,32]
Idiopathic (primary)

[Table/Fig-2]: Diseases associated with follicular bronchiolitis

CLINICAL PRESENTATION

Secondary follicular bronchiolitis may occur at any age, while the idiopathic form is most commonly seen in middle-aged and elderly patients.

FB can be generally classified into three clinicopathalogical groups based on the patients' clinical presentation and the presence or absence of underlying systemic diseases [16,33,34]: Group 1 includes patients with an underlying connective tissue disease, most commonly rheumatoid arthritis (RA) and Sjögren's syndrome (SS), who often present in their 5th decade with progressively worsening dyspnea as the main symptom in almost all cases and in 88% of patients the diagnosis of connective tissue disease proceeds the respiratory manifestations.

Group 2 includes patients with an immunodeficiency, either congenital or acquired, e.g. Common variable immune deficiency (CVID) and acquired immunodeficiency syndrome (AIDS), respectively, where the clinical presentation is that of a teenager or young adult with recurrent pneumonias and progressive dyspnea.

Group 3 constitutes a heterogeneous group of patients, middle age and elderly, who have no known immunodeficiency and no clinical or serological evidence of a connective tissue disease, often presenting with a chronic cough and peripheral eosinophilia, suggesting an underlying hypersensitivity reaction. This group has also been referred to as "idiopathic (primary) follicular bronchiolitis" [35,36].

Pulmonary function testing in patients with FB is often nonspecific, and can reveal a normal, restrictive, obstructive or mixed pattern of airflow limitation.

RADIOLOGICAL FINDINGS

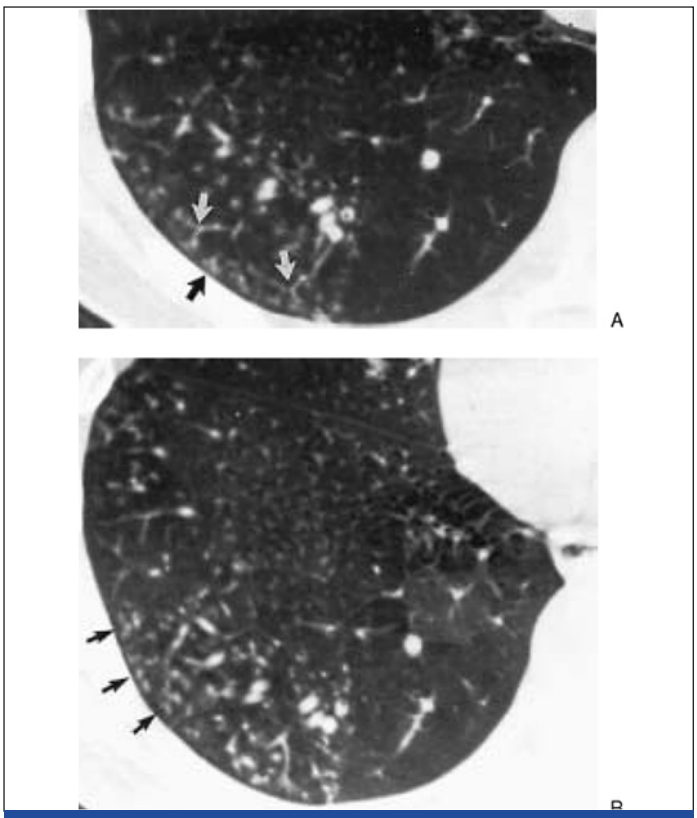
Chest radiography is often normal in primary FB, but may reveal lung hyperinflation due to air trapping, small nodules, reticular, or reticulonodular infiltrates in a severe bronchiolar disease [37]. The most common features of FB on high resolution computed tomography (HRCT) scan are small centrilobular nodules (1–3 mm) in diameter often associated with bilateral patchy ground-glass opacities [38].

One of the most common distinctive signs of bronchiolar disease on HRCT is a "Tree-in-bud" pattern, representing bronchiolar impaction with exudative material secondary to infection or inflammation [39] [Table/Fig-3]. The presence of peribronchial inflammation and peribronchial lymphoid follicle formations can give a unique fluffy appearance to the tree-in-bud on HRCT, as the lymphoid follicles become densely concentrated in the interstitium adjacent to the bronchioles and fade away from the interstitium furthest from the airway. We here in describe this unique pattern which may assist in differentiating follicular bronchiolitis from other types of infectious or inflammatory bronchiolitis on HRCT as a "cotton-in-bud" appearance [Table/Fig-4].

Air trapping due to bronchiolar obstruction can also produce a mosaic pattern of lung attenuation (geographic areas of variable densities) often depicted on expiratory HRCT imaging. [Table/Fig-5] illustrates the main features of FB on HRCT scan.

HISTOPATHOLOGY

Diagnosing FB on pathological specimens requires demonstrating two fundamental features, first, the presence of well formed lymphoid follicles in the walls of bronchioles and the second is narrowing or complete obliteration of the bronchiolar lumen [Table/Fig-6a-c]. In these pathological specimens the main distinguishing feature between FB and LIP is the extension of lymphoid follicles along the interlobular septa with substantial sparing of the alveolar septa in FB, where as extensive alveolar septal involvement is considered the hallmark of LIP [23,27,34]. Nonetheless, many pathologists today describe these two entities as a continuum of



[Table/Fig-3]: Infectious bronchiolitis with a tree-in-bud appearance and small well-defined centrilobular nodules (arrows). These reflect the presence of exudate-filled centrilobular bronchioles

[Table/Fig-4]: In Follicular bronchiolitis, dilated and thick-walled bronchioles (white arrows) are seen in association with a fluffy tree-in-bud "Cotton-in-bud" appearance. These findings correlate pathologically with bronchiolar follicular obstruction and peribronchiolar interstitial lymphoid follicles, respectively

reactive pulmonary lymphoid diseases, in which the distinction in many cases is somewhat arbitrary. Secondary features that can be associated with FB on pathologic specimens include foci of organizing pneumonia, foci of obstructive pneumonia and bronchiolar intraluminal neutrophilic infiltrate [40].

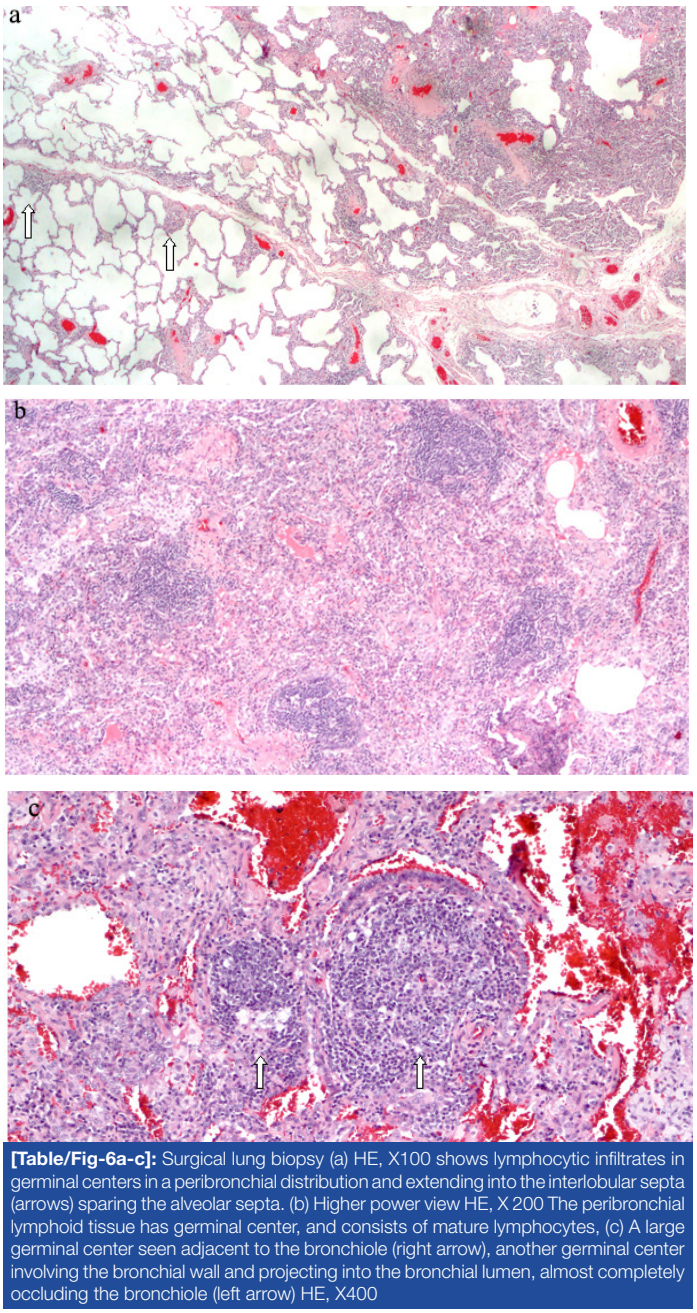
Immunohistochemistry in FB is essential to rule out malignancy. In the absence of a primary immunodeficiency state, FB lesions often reveal CD20 and CD79a positive B cells predominantly within peribronchial lymphoid aggregates and CD3 positive T cells predominantly in the alveolar interstitium when overlapping with LIP [41,42].

DIFFERENTIAL DIAGNOSIS

A pathologic diagnosis of FB is aetiologically non-specific, as it may represent a primary condition, or a secondary pathological finding associated with other pulmonary or systemic diseases. Hence, a clinical diagnosis after establishing FB on pathological evaluation requires correlating the pathology with clinical and radiographic findings.

Main CT features of FB
• Bilateral 1–3 mm nodules—centrilobular/peribronchial distribution
• Bilateral patchy ground-glass opacities (mosaic pattern)
• Fluffy tree-in-bud "Cotton-in-bud" peribronchiolar opacities
• Bronchial dilatation
• Disease is limited to the airways (i.e. no diffuse interstitial involvement)

[Table/Fig-5]: Cardinal HRCT features of follicular bronchiolitis



[Table/Fig-6a-c]: Surgical lung biopsy (a) HE, X100 shows lymphocytic infiltrates in germinal centers in a peribronchial distribution and extending into the interlobular septa (arrows) sparing the alveolar septa. (b) Higher power view HE, X 200 The peribronchial lymphoid tissue has germinal center, and consists of mature lymphocytes, (c) A large germinal center seen adjacent to the bronchiole (right arrow), another germinal center involving the bronchial wall and projecting into the bronchial lumen, almost completely occluding the bronchiole (left arrow) HE, X400

The main differential process from a clinical standpoint is a stepwise approach that entails identifying the distinctive features of FB from other closely related diseases in the LPDs group, this step requires recognizing the unique patterns of bronchiolar and pulmonary involvement on HRCT and close microscopic evaluation of airway and parenchymal follicular extensions, along with immunohistochemistry staining to rule out malignancy. Next step is differentiating between primary and secondary FB by recognizing other clinical features or multiple organ involvement, with the aid of serological and immunodeficiency testing.

TREATMENT AND PROGNOSIS

In secondary FB, management is usually aimed at treating the underlying condition. FB associated with HIV has been shown to improve with the initiation of anti-retroviral therapy [43], and when associated with a connective tissue disease, FB is generally approached with the same treatment modalities of the primary

disease, which often involves the use of immunosuppressant therapy.

In FB with underlying CVID, intravenous immunoglobulin replacement therapy can significantly reduce the frequency and severity of pulmonary infections. In recent studies the use of rituximab and azathriprine (combination chemotherapy) has demonstrated a functional and radiographic pulmonary improvement in this group of patients [23,44,45].

In the less common form of the disease, Idiopathic (primary) FB, corticosteroids have been used with anecdotal reports of general improvement in clinical symptoms and resolution of radiographic abnormalities [30]. This is considered as supportive evidence of a hypersensitivity type reaction, or an undiagnosed connective tissue disease with primary respiratory manifestations as the likely aetiology in many cases of idiopathic FB. However, no treatment guidelines have yet been established for the treatment of primary FB, where a relapse of the disease with cessation of therapy and subsequent remission with reinstitution of corticosteroid treatment is commonly seen [33,34]. Macrolide antibiotics have also been used in the treatment of primary FB, with symptomatic improvement possibly related to their anti-inflammatory properties [46].

The prognosis of patients with FB appears to be dependent on two factors, the age at time of presentation and the underlying primary disease. Among all patients with FB middle age and elderly patients diagnosed with primary FB have the most favourable prognosis, while patients under 30 years of age with an underlying immunodeficiency tend to develop a more progressive disease with a higher mortality [47].

CONCLUSION

Follicular bronchioitis is a benign lymphoproliferative small airway disease and a ubiquitous pathological finding, where the constellation of clinical, radiographic and pathological characteristics is essential for establishing the best course of treatment and predicting disease prognosis. In this article we summarize the stepwise approach in classifying the disease while highlighting its main pathological and radiographic characteristics.

ACKNOWLEDGMENT

We would like to thank Dr. Jay H. Ryu from the Department of Pulmonary and Critical Care Medicine at Mayo Clinic, Rochester, Minnesota, for his contribution in reviewing this article and providing valuable guidance and thank Dr. Pablo Bejarano from the Department of Pathology at Cleveland Clinic Florida for his effort in providing and reviewing the pathology images included in this article.

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FINANCIAL OR OTHER COMPETING INTERESTS: None.

Date of Submission: **Mar 06, 2015**
Date of Peer Review: **May 23, 2015**
Date of Acceptance: **Jun 18, 2015**
Date of Publishing: **Sep 01, 2015**