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Follicular bronchiolitis in surgical lung biopsies: Clinical implications in 12 patients

Michelle R. Aerni[a], Robert Vassallo[a,*], Jeffrey L. Myers[b], Rebecca M. Lindell[c], Jay H. Ryu[a]

[a]*Division of Pulmonary and Critical Care Medicine, Desk East 18, Mayo Clinic, 200 1st St. SW, Rochester, MN, USA*
[b]*Department of Laboratory Medicine and Pathology, University of Michigan, Ann Arbor, MI, USA*
[c]*Department of Radiology, Mayo Clinic, Rochester, MN, USA*

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Summary
Background: Follicular bronchiolitis is a histopathologic finding that occurs in diverse clinical contexts. The current study was conducted to characterize clinico-radiologic features, and assess outcomes associated with follicular bronchiolitis.
Subjects and methods: Twelve subjects with follicular bronchiolitis on lung biopsy were seen over a 9-year period, between 1996 and 2005. Medical records, biopsy and radiographic findings, and details of outcome at the time of last follow-up were recorded.
Results: The study population included 4 men and 8 women; the median age at diagnosis was 54 years (range, 33–81 years). Four patients had underlying systemic diseases that included: 2 with common variable immunodeficiency, 1 Sjögren's syndrome and 1 undifferentiated connective tissue disease. The diagnosis was obtained by surgical lung biopsy in all cases. Follicular bronchiolitis was the major histologic pattern in 9 patients; organizing pneumonia, nonspecific interstitial pneumonia and usual interstitial pneumonia was seen in 1 patient each with follicular bronchiolitis being an associated secondary histopathologic component. Computed tomographic findings included reticular opacities, small nodules and ground-glass opacities. Clinical course was characterized by relative stability with partial response to immunosuppressive agents. During a median follow-up period of 47 months, only one death occurred—out of 9 patients where the outcome information was available—and was unrelated to lung disease.
Conclusions: The histologic lesion of follicular bronchiolitis may be seen as the predominant finding or a relatively minor feature in interstitial pneumonias. The clinical

Abbreviations: AIDS, acquired immunodeficiency syndrome; CT, computed tomography; CTD, connective tissue disease; CVID, common variable immunodeficiency; DIP, desquamative interstitial pneumonia; FB, follicular bronchiolitis; NSIP, nonspecific interstitial pneumonia

*Corresponding author. Tel.: +1 507 284 5398; fax: +1 507 266 4372.
E-mail address: vassallo.robert@mayo.edu (R. Vassallo).

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course and prognosis for most patients with follicular bronchiolitis is relatively good, and progressive lung disease is uncommon.

Introduction

Follicular bronchiolitis is an uncommon bronchiolar disorder characterized by the presence of hyperplastic lymphoid follicles with reactive germinal centers distributed along bronchovascular bundles.[1–3] Follicular bronchiolitis can also occur as a secondary finding in a variety of lung diseases. When it occurs in isolation, follicular bronchiolitis is a form of primary airway-centered lymphoid hyperplasia that is often associated with systemic diseases such as connective tissue disease or immunodeficiency syndromes.[1–4] Relatively little is known regarding prognostic implications and treatment of follicular bronchiolitis. Additionally, the relationship of follicular bronchiolitis to idiopathic interstitial pneumonias remains to be clarified.

In an effort to further characterize the clinical features and outcomes associated with follicular bronchiolitis, we identified 12 patients with follicular bronchiolitis on surgical lung biopsies and examined the clinical and radiologic presentation of these subjects, as well as their clinical course and outcome.

Subjects and methods

We conducted a computer-assisted search of the Mayo Clinic database to identify cases of follicular bronchiolitis seen in adults (21 years of age or older) at our institution over a 9-year period, June 1, 1996 through May 31, 2005. Twelve patients were identified; relevant medical records and imaging studies were reviewed. Surgical lung biopsy specimens were reviewed by one of us (J.L.M.) to confirm the histopathologic diagnosis of follicular bronchiolitis. Histologic diagnosis of follicular bronchiolitis required the presence of hyperplastic lymphoid follicles limited to distal cartilaginous airways and bronchioles without histologic or immunophenotypic evidence of malignant lymphoma.

Eventual clinical outcome was assessed at the time of the last available follow-up and categorized as improved, stable or worsened using the changes in respiratory symptoms, radiologic findings and pulmonary function measurements (total lung capacity, vital capacity, diffusing capacity to carbon monoxide and oxygen saturation or PaO_2) as described in a consensus statement from the American Thoracic Society/European Respiratory Society.[5] This study was approved by the Mayo Foundation institutional review board. Patients who did not authorize the use of their medical records for research were excluded from this study.

Results

Underlying systemic disease was present in 4 patients and included common variable immunodeficiency syndrome in 2 patients, and 1 patient each with Sjögren's syndrome and undifferentiated connective tissue disease (Table 1). No cause or associated systemic disease could be identified, or developed, in the remaining 8 patients, i.e. these were idiopathic cases. Four of these 8 patients had an elevated antinuclear antibody titer or rheumatoid factor in the serum but there were no clinical features of connective tissue disease (Table 1). Three patients (25%) were current smokers at the time of diagnosis, 2 patients were prior smokers (17%), while the majority (7 out of 12 or 58%) were lifelong non-smokers.

Ten patients had pulmonary function results available, including 6 obtained prior to initiating treatment. Four patients (40%) had a restrictive pattern of ventilatory limitation and 3 other patients (30%) had a nonspecific pattern of abnormalities (reduced diffusing capacity). Three remaining patients (30%) had normal pulmonary function results; an obstructive pattern was not observed. Overall, the most common pulmonary function abnormality was a reduced diffusing capacity which was observed in 7 of 10 patients. Pulmonary function test results were available in 6 of the 8 patients with idiopathic follicular bronchiolitis and are summarized in Table 2.

Chest radiography was available in 10 patients and demonstrated relatively nonspecific findings consisting of bilateral interstitial changes in most patients (Table 3). Two patients (20%) had normal chest radiographs. Eleven of the 12 patients had CT scans performed and all were abnormal. CT findings were variable and included reticular opacities, nodules, ground-glass opacities and patchy consolidation. Five patients (45%) had mediastinal or hilar lymphadenopathy (Table 3). Two patients had traction bronchiectasis seen on CT; patients with nonspecific interstitial pneumonia and usual interstitial pneumonia, respectively. In 2 patients with normal chest radiograph, CT scan revealed micronodular infiltrates and patchy ground-glass opacities, respectively. Among 9 patients in whom follicular bronchiolitis was the predominant histopathologic finding, 8 had CT scans available and demonstrated ground-glass opacities and/or small nodules (Figure 1A and B) in all except one patient.

Most patients were treated with prednisone, sometimes in combination with azathioprine, with a generally favorable response (Table 1). Eight of the 12 patients (67%) underwent a trial of prednisone treatment with a median daily dose of 40 mg (range, 20–60 mg). Symptomatic improvement (improved cough, dyspnea or both) with prednisone treatment was noted in 6 of these patients (75%). Objective improvement with prednisone treatment, as evidenced by improvement in pulmonary function measurements or parenchymal infiltrates seen on chest radiography or CT, was noted in all 8 patients. A trial of macrolide therapy (azithromycin 250 mg orally once every Monday, Wednesday and Friday) was administered in one of these patients who had had become corticosteroid-dependent. On macrolide treatment, the corticosteroid dose was gradually discontinued, and the patient experienced continued subjective and objective improvement. One patient was asymptomatic

Table 1 Demographic, clinical and histologic features for 12 patients with follicular bronchiolitis.

Age, sex	Underlying disease	Major histologic finding	Minor histologic finding	Treatment	Outcome
51, female	–	FB	–	Prednisone	Not available
61, male	–	FB	–	Prednisone, azathioprine, mycophenolate	Improved at 54 months
58, female	Sjögren's syndrome	FB	Non-necrotizing granulomas	Prednisone	Inactive disease at 103 months
81, male	–	OP	FB	None	Died of metastatic melanoma at 46 months
36, male	CVID	FB	DIP	Prednisone	Improved infiltrates at 10 months
33, female	–	FB	Carcinoid tumorlets	Prednisone, azathioprine	Stable at 52 months
48, male	–	FB	Emphysema	None	Stable at 50 months
60, female	Undifferentiated CTD	UIP	FB	Prednisone, azathioprine	Improved at 48 months
46, female	–	NSIP	FB	Prednisone	Not available
45, female	–	FB	–	Prednisone, azithromycin	Improved at 17 months
79, female	–	FB	–	Prednisone, azathioprine	Slow decline at 107 months
53, female	CVID	FB	–	None	Not available

FB, follicular bronchiolitis; DIP, desquamative interstitial pneumonia; CVID, common variable immunodeficiency; CTD, connective tissue disease; NSIP, nonspecific interstitial pneumonia.
The mean duration of follow-up after histopathologic diagnosis was 47 months.

at presentation with normal pulmonary function results, and continues to remain stable on no therapy at 50 months follow-up after initial abnormal CT scan.

There were no deaths related to follicular bronchiolitis or progressive respiratory disease. One patient died from metastatic melanoma at 4 years after the diagnosis of follicular bronchiolitis. Development of secondary pulmonary lymphoma did not occur in any of the patients in this series.

Discussion

Follicular bronchiolitis is an uncommon pulmonary disorder characterized by expansion of lymphoid tissue in the peribronchiolar regions associated with mild degrees of lymphocytic and monocytoid cell infiltration in the interstitium.[1,2,4,6,7] The histologic lesion of follicular bronchiolitis may be seen as the predominant finding or a relatively minor feature in interstitial pneumonias. Objective improvement in lung function is commonly observed with corticosteroid therapy. The current report suggests that macrolide therapy may be an alternative to corticosteroids in some patients with follicular bronchiolitis. The clinical course and prognosis for most patients with follicular bronchiolitis is relatively good, and progressive lung disease is uncommon.

Most of the patients in the current series presented with respiratory symptoms and abnormal chest radiographs of nonspecific character. Pulmonary function testing demonstrated either a nonspecific or restrictive pattern of abnormalities; none had an obstructive defect. CT scan findings were variable but follicular bronchiolitis was associated mainly with findings of small nodules and/or ground-glass opacities as previously reported by Howling et al.[3] However, we note that the radiologic findings in our study were more heterogeneous than those described by Howling. This is likely explained by inclusion of only those patients in whom the follicular bronchiolitis was the sole or predominant histologic abnormality in Howling's study, whereas we included patients in whom follicular bronchiolitis was not the predominant histologic finding. The distribution of nodular infiltrates may suggest the possibility of bronchiolar disease in some of these patients, but the CT appearance is by no means specific for follicular bronchiolitis.[1,3]

In previous studies, the majority of patients with follicular bronchiolitis had identifiable underlying diseases including connective tissue diseases, other autoimmune disorders, inflammatory bowel disease and immunodeficiency

Table 2 Pulmonary function.

Characteristic	Idiopathic FB ($N = 6$)*	Entire group ($N = 10$)†
Total lung capacity—% predicted		
Mean	83.6	82
Range		60–105
Residual volume—% predicted		
Mean	118.6	107
Range		49–163
FVC—% predicted		
Mean	72	77.9
Range		47–117
FEV_1—% predicted		
Mean	71.2	78
Range		50–112
Carbon monoxide diffusing capacity—% predicted		
Mean	61.8	66.9
Range		44–85

*For the subgroup of patients with primary follicular bronchiolitis, total lung capacity and residual volume measurements were available in 5 out of 6 patients.

†Total lung capacity values were available for 7, residual volume for 6, FVC and FEV_1 values for 9 and carbon monoxide diffusing capacity for 10 patients.

Table 3 Radiologic features.

Characteristic	No. (%)
Chest radiographic findings*	
Bilateral interstitial	7 (70)
Mixed alveolar and interstitial infiltrates	1 (10)
Normal	2 (20)
CT findings†	
Reticular opacities	6 (55)
Centrilobular nodules	5 (45)
Ground-glass opacities	5 (45)
Mediastinal or hilar lymphadenopathy	5 (45)
Traction bronchiectasis	2 (18)
Airspace consolidation	2 (18)
Emphysema	1 (9)

*Chest radiograph was available in 10 patients.

†CT chest was available in 11 patients.

syndromes.[3,6] For example, Howling's study,[3] consisted of 12 patients with follicular bronchiolitis all of whom had systemic diseases that included connective tissue disease in 10 (rheumatoid arthritis in 8), "autoimmune disorder" in 1, and acquired immunodeficiency syndrome (AIDS) in the remaining patient. However, Romero et al.,[4] recently described 6 patients with follicular bronchiolitis diagnosed by surgical lung biopsy with only 1 patient having an underlying disease, AIDS. Of the remaining 5 patients, 4 were idiopathic and 1 had prolonged exposure to polyethylene flock. Similarly, we were unable to identify an underlying disease in two-thirds of our 12 patients with follicular bronchiolitis. Thus, absence of an identifiable systemic disease should not dissuade consideration of follicular bronchiolitis in the differential diagnosis for a patient with suggestive clinico-radiologic features.

As in any other cause of bronchoilitis, bronchoscopy appears to have a minor role in the diagnosis of follicular bronchiolitis. The vast majority of patients with follicular bronchiolitis described in previous reports have had their diagnosis confirmed by surgical lung biopsy.[2,4,8] All of our 12 patients underwent surgical lung biopsy for diagnosis; bronchoscopic biopsy in 6 patients had been nondiagnostic. As in virtually every cause of primary bronchiolar disease, bronchoscopic biopsy is unlikely to be diagnostic due to sampling error [patchy nature of the disease], and insufficient amount of representative tissue obtained.

Most of the patients described in previous reports as well as in our study were treated with corticosteroids, sometimes in combination with another immunosuppressive drug such as azathioprine or methotrexate.[2,4] In general, patients with follicular bronchiolitis appear to respond favorably to corticosteroid therapy. Initial improvement may be followed by relapse of the disease as the corticosteroid dose is tapered. The role of other immunosuppressive drugs in the treatment of follicular bronchiolitis remains unclear. One of our patients was treated with macrolide therapy (azithromycin) with favorable results. Macrolides have been used for their immuno-modulatory and anti-inflammatory properties in several respiratory diseases including asthma, cystic fibrosis and diffuse panbronchiolitis.[9–13] Diffuse panbronchiolitis is a disease that has been described mainly in Japanese adults and rarely in the Western hemisphere.[13,14] It is a distinct clinicopathologic syndrome that is characterized by bronchiolar inflammation and chronic sinusitis. Although the pathogenesis of diffuse panbronchiolitis is not known, prolonged treatment with erythromycin improves respiratory symptoms, lung function and survival.[13–16] Hayakawa et al.[17] described significant improvement of symptoms with erythromycin therapy in several rheumatoid patients with inflammatory bronchiolar lesions consistent with follicular bronchoilitis, although in their series, macrolides were found to be more effective in the management of the control group with diffuse panbronchiolitis. A variety of macrolides have been demonstrated to alter immune responses in both *in vitro* and *in vivo* models of inflammation.[9,13] These studies suggest a role for macrolides as potentially useful pharmacologic agents in the treatment of inflammatory lung diseases such as follicular bronchiolitis. The role of macrolide therapy in the treatment of follicular bronchiolitis deserves to be explored further.

Histologic features of follicular bronchiolitis can overlap with other lymphoproliferative lesions, most notably lymphoid interstitial pneumonia. Distinction between lymphoid interstitial pneumonia and follicular bronchiolitis is based mainly on the extent of lymphocytic infiltration. In follicular bronchiolitis, the lymphoid follicles and mononuclear cell infiltration are predominantly peribronchial and peribronchiolar. However, in lymphoid interstitial pneumonia, the interstitial infiltration is more diffuse and expands alveolar septa. Follicular bronchoilitis and lymphoid interstitial pneumonia sometimes have to be carefully distinguished

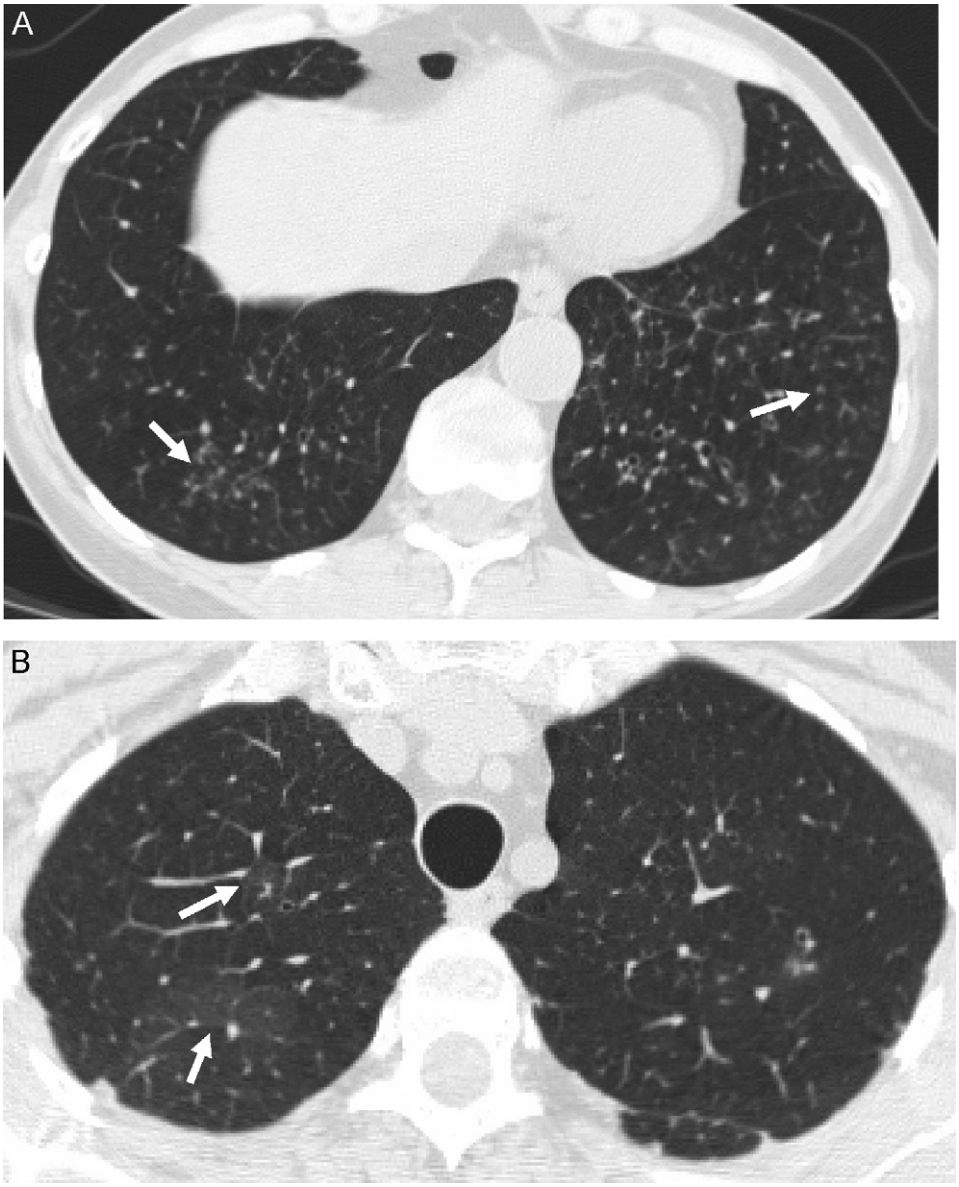

Figure 1 High-resolution CT of a 53-year-old woman with follicular bronchiolitis confirmed on surgical lung biopsy. (A) This image demonstrates numerous micronodules (arrows) suggestive of bronchiolar disease in both lower lobes. (B) Patchy ground-glass opacities (arrows) are seen in the apices, particularly on the right side.

from a low-grade lymphoma. This distinction usually requires immunohistochemical analysis and molecular gene rearrangement studies to determine clonal rearrangement of the immunoglobulin heavy chain gene.

Similar to previous reports,[2,4] follicular bronchiolitis was associated with a generally good prognosis and appeared to respond favorably to corticosteroid therapy. No deaths occurred from respiratory causes among our 12 patients. We conclude that follicular bronchiolitis can occur without underlying connective tissue disease or immunodeficiency syndrome and is associated with a relatively favorable clinical course. Corticosteroid therapy has been used most commonly and appears to provide clinical benefit for patients with follicular bronchiolitis. The role of macrolides in the treatment of follicular bronchiolitis should be explored further.

Conflict of interest

None of the authors have any conflict of interest to declare.

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References

1. Ryu JH, Myers JL, Swensen SJ. Bronchiolar disorders. *Am J Respir Crit Care Med* 2003;**168**:1277–92.
2. Yousem SA, Colby TV, Carrington CB. Follicular bronchitis/bronchiolitis. *Hum Pathol* 1985;**16**:700–6.

3. Howling SJ, Hansell DM, Wells AU, Nicholson AG, Flint JD, Muller NL. Follicular bronchiolitis: thin-section CT and histologic findings. *Radiology* 1999;**212**:637–42.
4. 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**:309–19.
5. American Thoracic Society. Idiopathic pulmonary fibrosis: diagnosis and treatment. International consensus statement. American Thoracic Society (ATS), and the European Respiratory Society (ERS). *Am J Respir Crit Care Med* 2000;**161**:646–64.
6. Nicholson AG, Wotherspoon AC, Diss TC, et al. Reactive pulmonary lymphoid disorders. *Histopathology* 1995;**26**:405–12.
7. Poletti V, Zompatori M, Cancellieri A. Clinical spectrum of adult chronic bronchiolitis. *Sarcoidosis Vasc Diffuse Lung Dis* 1999;**16**: 183–96.
8. Benesch M, Kurz H, Eber E, et al. Clinical and histopathological findings in two Turkish children with follicular bronchiolitis. *Eur J Pediatr* 2001;**160**:223–6.
9. Stover DE, Mangino D. Macrolides: a treatment alternative for bronchiolitis obliterans organizing pneumonia? *Chest* 2005;**128**: 3611–7.
10. Gerhardt SG, McDyer JF, Girgis RE, Conte JV, Yang SC, Orens JB. Maintenance azithromycin therapy for bronchiolitis obliterans syndrome: results of a pilot study. *Am J Respir Crit Care Med* 2003;**168**:121–5.
11. Khalid M, Al Saghir A, Saleemi S, et al. Azithromycin in bronchiolitis obliterans complicating bone marrow transplantation: a preliminary study. *Eur Respir J* 2005;**25**:490–3.
12. Clement A, Tamalet A, Leroux E, Ravilly S, Fauroux B, Jais JP. Long term effects of azithromycin in patients with cystic fibrosis: a double blind, placebo controlled trial. *Thorax* 2006;**61**:895–902.
13. Keicho N, Kudoh S. Diffuse panbronchiolitis: role of macrolides in therapy. *Am J Respir Med* 2002;**1**:119–31.
14. Poletti V, Chilosi M, Casoni G, Colby TV. Diffuse panbronchiolitis. *Sarcoidosis Vasc Diffuse Lung Dis* 2004;**21**:94–104.
15. Kadota J, Mukae H, Ishii H, et al. Long-term efficacy and safety of clarithromycin treatment in patients with diffuse panbronchiolitis. *Respir Med* 2003;**97**:844–50.
16. Kudoh S, Azuma A, Yamamoto M, Izumi T, Ando M. Improvement of survival in patients with diffuse panbronchiolitis treated with low-dose erythromycin. *Am J Respir Crit Care Med* 1998;**157**: 1829–32.
17. Hayakawa H, Sato A, Imokawa S, et al. Diffuse panbronchiolitis and rheumatoid arthritis-associated bronchiolar disease: similarities and differences. *Intern Med* 1998;**37**:504–8.