Int J Clin Exp Pathol 2021;14(4):526-532
www.ijcep.com /ISSN:1936-2625/IJCEP0125757

Case Report

Pediatric follicular bronchiolitis with severe atelectasis: a case report

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Received November 6, 2020; Accepted January 21, 2021; Epub April 15, 2021; Published April 30, 2021

Abstract: Follicular bronchiolitis is a rare pulmonary disorder characterized by the presence of multiple hyperplastic lymphoid follicles with a peribronchiolar distribution. An 11-year-old girl with total atelectasis of the right middle lobe (RML) and diffuse multiple small nodules at both lung bases presented to our hospital with frequent upper respiratory infections and pneumonia. The disease progressed during a 3-month period of macrolide therapy, and thoracoscopic biopsy with lobectomy of the atelectatic RML was performed. The histopathologic diagnosis was follicular bronchiolitis. The patient's pulmonary function improved dramatically after oral steroid treatment. It can be difficult to diagnose follicular bronchiolitis based solely on clinical, laboratory, and radiologic findings; the disorder must be confirmed histopathologically. A patient with longstanding irreversible atelectasis and resulting recurrent respiratory infection may require lobectomy for the diagnosis and treatment of follicular bronchiolitis.

Keywords: Follicular bronchiolitis, pediatrics, atelectasis, lobectomy

Introduction

Follicular bronchiolitis is a rare non-neoplastic bronchiolar disorder characterized by the presence of hyperplastic lymphoid follicles with reactive germinal centers spread along the bronchovascular bundles [1]. This condition is thought to be caused by the antigenic stimulation of bronchial-associated lymphoid tissue (BALT), which in turn induces polyclonal lymphoid hyperplasia. Follicular bronchiolitis is associated with inflammatory conditions of the respiratory tract such as collagen vascular disease, immunodeficiency disease, hypersensitivity, bronchiectasis, and other infections [2]. With the aim of improving awareness about these poorly recognized entities, we herein report a case of follicular bronchiolitis in a child with total atelectasis of the right middle lobe (RML) and diffuse multiple small nodules at both lung bases who underwent RML lobectomy.

Case report

An 11-year-old girl who had been admitted several times per year over a period of several years for the treatment of frequent upper respiratory infections (URIs) and pneumonia presented to our hospital with fever, chronic cough, and sputum. She was slightly dyspneic with exercise but had no limitations in her daily activities. Chest radiography showed multiple poorly defined nodular lesions in both lower lung fields (**Figure 1**). Thoracic computed tomography (CT) revealed total atelectasis with bronchial dilatation in the RML and diffuse multiple centrilobular nodules with bronchial dilatation and wall thickening in both lower lobes, indicating bronchiectasis with bronchiolitis (**Figure 2**).

The neutrophil and eosinophil counts and C-reactive protein level were within normal limits. Sputum cultures showed no growth of any pathogenic organisms, including acid-fast bacilli and fungus. Test results for mycoplasma antibodies and HIV antibodies were also negative. Autoimmune tests, including FANA, ANCA, RF, anti-CCP Ab, cold agglutinin, AIT, and anticentromere Ab, yielded normal results. The patient's pulmonary function test (PFT) results indicated a moderate-to-severe restrictive pattern of ventilatory limitation with a predicted

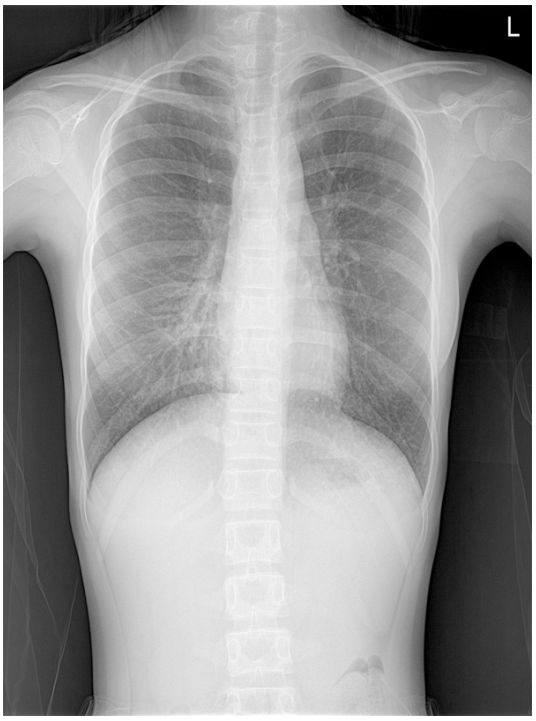

Figure 1. Chest radiograph shows multiple poorly defined nodular lesions in both lower lung fields.

forced expiratory volume in one second (FEV1) of 55%, a forced vital capacity (FVC) of 60%, a peak expiratory flow of 39%, and an FEV1/FVC of 79%.

Because CT findings suggested the presence of diffuse panbronchiolitis, macrolides were prescribed for 3 months; however, the disease continued to progress, and a histopathologic diagnosis became necessary. Thoracoscopic lung biopsy (wedge resection) of the right lower lobe and lobectomy of the atelectatic RML were performed. There were no pleural adhesions or effusions, but mild fibrosis and perihilar tissue thickening were found. The RML had fully collapsed, and a large amount of thick, purulent mucous discharge was drained from the cut bronchus. The resected lung was slightly firm upon palpation, and the cut surface of the pathologic specimen exhibited multiple small, dispersed, yellowish nodules (**Figure 3A**).

Microscopic examination revealed diffuse interstitial infiltration of lymphocytes and plasma cells with follicular lymphoid hyperplasia in the peribronchus and peribronchioles. Infiltration of foamy macrophages was noted in the interstitium and intra-alveolar spaces, and bronchioloectasis and bronchiectasis were also present (**Figure 3B-D**). Surprisingly, the consolidated atelectatic RML and multiple small, diffuse nodular lesions at both lung bases shared the same histopathologic pattern.

The patient was discharged on postoperative day 7 without any morbidity. Her symptoms, including frequent URIs, sputum, and dyspnea on exertion, improved postoperatively. A PFT revealed gradual improvement following steroid treatment for 1 year postoperatively and remained steady thereafter. To date, inhalation steroid therapy has been maintained.

The patient's predicted FEV1, which improved dramatically from 55% to 78% after 4 months of postoperative oral steroid treatment, declined to 72% after 2 months of steroid dose reduction. The FVC, which improved from 60% to 81% after oral steroid treatment, declined to 70% after dose reduction. However, the FEV1 increased to 82%, and the FVC again increased to 81% after six cycles of methylprednisolone pulse therapy over a 6-month period. Thereafter, the patient remained well for 7 months without oral steroid treatment, and her FEV1 and FVC remained steady at > 80%. Her FEV1 remained steady 7 years after surgery, between 72 and 77%, and her FVC was between 79-95%. Her diffusing capacity of the lungs for carbon monoxide declined from 86% at the time of surgery to 76% 7 years after surgery.

This study was approved by the Institutional Review Board (IRB) of Daegu Catholic University Medical Center (IRB No: CR-20-226), and the requirement for written informed consent from the patient was waived by the IRB.

Discussion

Follicular bronchiolitis is a lymphoproliferative interstitial lung disease associated with the expansion of lymphoid tissue in the area around the bronchioles [1, 3-5]. The disorder is characterized by infiltration of lymphocytic and monocytoid cells in the interstitium and alveoli [1, 4, 5]. Although uncommon, it more often affects adults and is rarely reported in children [6, 7]. Although several radiologic and pathologic studies have been proposed to characterize this disease, the full spectrum of etiologic factors is not fully understood [8]. In adults, this condition is typically found in patients with con-

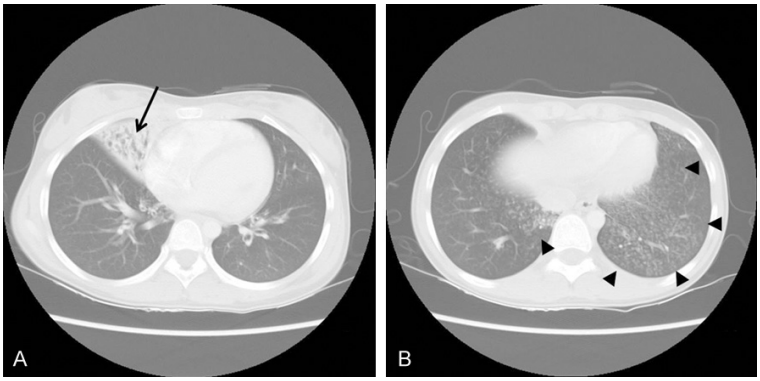

Figure 2. Chest computed tomography shows atelectasis (arrow) and bronchial dilatation in the right middle lobe (A) and multiple centrilobular nodules (arrow heads) and bronchiectasis in both lower lobes (B).

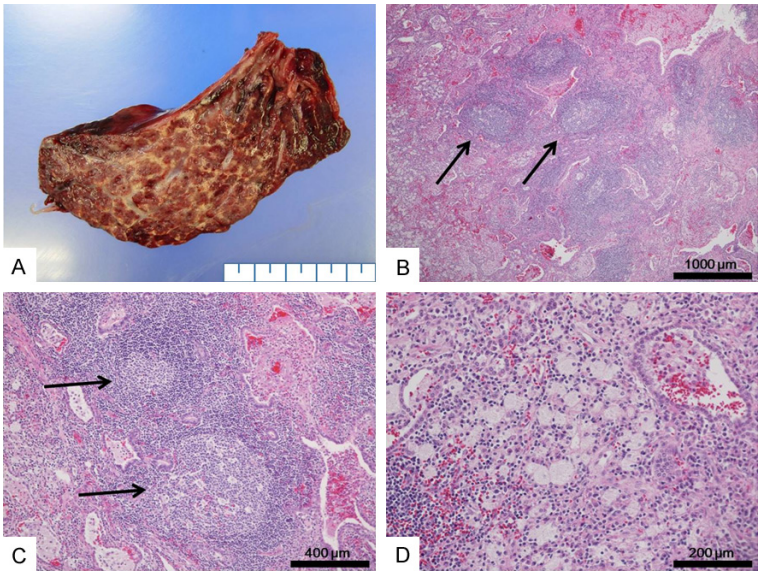

Figure 3. The macro- and microscopic findings of the resected lung. The cut surface of the right middle lobe exhibits scattered small yellowish nodules (A). There is diffuse infiltration of inflammatory cells and lymph follicles (arrows) (hematoxylin and eosin [H&E], ×40) (B). Chronic inflammatory cells and well developed lymph follicles (arrows) are located in peribronchiolar area (H&E, ×100) (C). The infiltrated chronic inflammatory cells are composed of small lymphocytes and plasma cells. Interstitial infiltration of foamy macrophages is focally identified (H&E, ×200) (D).

nective tissue disorders (particularly rheumatoid arthritis and Sjogren's syndrome); congenital or acquired immunodeficiency states (such as acquired immune deficiency syndrome, IgA deficiency, and common variable immunodeficiency); a hypersensitivity reaction; or non-specific, airway-centered inflammation (e.g., bronchiectasis and infections), and following lung transplant [2, 9-12]. In children, it is thought to be caused by intrauterine respiratory diseases, respiratory viral infections, or immunologically-mediated disorders [13]. Less frequently, it can be idiopathic, without any other associated diseases [14]. In our case, no evidence of connective tissue disorders, an immunodeficient state, infections, or hypersensitivity reactions were found. Although the precise cause of follicular bronchiolitis in our patient remains unknown, it may represent a polyclonal hyperplasia of BALT in response to intrinsic or extrinsic antigenic stimuli. Idiopathic follicular bronchiolitis mostly occurs in middle-aged and older patients, while the secondary form can occur at any age [14].

The clinical presentation of pediatric follicular bronchiolitis ranges from respiratory distress in infancy to incidental findings in older children [4, 9]. Common clinical findings are nonspecific and include cough, fever, moderate respiratory distress, fine crackles, recurrent pneumonia, weight loss, and fatigue [11]. Failure to thrive, recurrent hemoptysis, and tachypnea may also be associated with the disorder [15]. Multiple PFTs have demonstrated obstructive, restrictive, and mixed patterns. In our case, the tests revealed a severe, restrictive pattern, which improved with steroid therapy.

Chest radiographic findings generally include small bilateral nodular or reticulonodular infiltrates with intrathoracic adenopathy [16]. The CT findings vary but mainly include small centrilobular or peribronchial nodules and/or ground-glass opacities, which are typically bilateral and diffuse. The most common features of follicular bronchiolitis on high-resolution CT (HRCT) scans are multiple small centrilobular nodules (1-3 mm in diameter), which are often

associated with patchy ground-glass opacities at both lung bases [16]. The presence of peribronchial inflammation with peribronchial lymphoid follicles has a unique, fluffy, tree-in-bud appearance on HRCT as the interstitium adjacent to the bronchioles becomes densely concentrated by lymphoid follicles, which fade away from the interstitium furthest from the airway [14]. In some cases, bronchial dilatation and thickening are present, as in our case [17].

Open lung biopsy is necessary for a definitive diagnosis of follicular bronchiolitis, despite the presence of clinical and radiological findings suggestive of bronchiolitis. Diagnosing follicular bronchiolitis by histopathologic examination is based on two key findings: the presence of well-formed lymphoid follicles in the bronchiolar walls and the narrowing or complete obstruction of the bronchiolar lumen [14]. Histopathologic findings include numerous reactive lymphoid follicles with germinal centers and a peribronchiolar distribution that may result in small airway disease, which in turn can cause airway lumen compression and obstruction [18]. Peribronchiolar and peribronchial nodular aggregations of lymphoid cells, including lymphocytes and plasma cells, containing reactive germinal centers are present by microscopic evaluation [4]. Secondary obstructive changes caused by the narrowing of the small airway induce infiltration of foamy macrophages and organizing pneumonia.

It is necessary to carefully identify the characteristics of follicular bronchiolitis and differentiate it from other similar diseases in the group of lymphoproliferative interstitial lung diseases, including diffuse panbronchiolitis and other lymphoproliferative disorders. This is particularly important for lymphoid interstitial pneumonia because there are significant differences in the treatment and prognoses of these conditions [14]. Diffuse panbronchiolitis is predominantly observed in East Asian populations and is rarely reported in the Western Hemisphere [19]. Characterized by chronic airway infection with diffuse bilateral micronodular lung lesions, the disease has distinct features of bronchiolar inflammation and chronic sinusitis. In patients with nonallergic chronic paranasal sinusitis, the main symptoms are a large amount of sputum and progressive exertional dyspnea. Long-term treatment with macrolides is known to be effective [20].

Treatment for follicular bronchiolitis is typically directed at the underlying cause, and idiopathic cases are generally treated with bronchodilators and corticosteroids; there are anecdotal reports of general improvement of clinical symptoms and resolution of radiographic abnormalities [1, 21]. Such reports are considered supportive evidence for characterizing follicular bronchiolitis as hypersensitivity type reaction or a hidden connective tissue disease with primary respiratory manifestations [14]. However, treatment guidelines for the treatment of idiopathic follicular bronchiolitis are not established yet, and disease relapse with cessation of treatment and subsequent remission with reinstitution of corticosteroid therapy is commonly observed [4, 5, 14]. Macrolide antibiotics have also been used in the treatment of primary follicular bronchiolitis, with symptomatic improvement possibly associated with their anti-inflammatory properties [22]. In our case, however, the patient was resistant to macrolide therapy. Dias et al. reported the case of a child with left upper lobe atelectasis and recurrent respiratory infections who required lobectomy for the diagnosis and treatment of follicular bronchiolitis [17]. Our case, which required a lobectomy of the chronic atelectatic lobe due to follicular bronchiolitis, was extremely rare. To the best of our knowledge, this is the third pediatric case of a lobectomy of the chronic atelectatic lobe due to follicular bronchiolitis reported in the English literature [17, 23]. The clinical, radiologic, and pathologic characteristics of these three cases are summarized in **Table 1**. After lobectomy, we treated the patient successfully with oral steroid for 6 months and subsequently with six cycles of methylprednisolone pulse therapy. The child's symptoms and PFT results improved dramatically and remained stable for > 1 year after treatment.

The prognosis of patients with follicular bronchiolitis is likely dependent on two factors: the age at the time of disease onset and the underlying primary disease [14]. The prognosis of this disorder is generally considered to be favorable, although a more progressive disease can be found when it presents at a younger age with an underlying immunodeficiency [1, 2, 24]. The presence of organizing pneumonia alongside follicular bronchiolitis does not portend a poorer prognosis as it typically resolves with little or no scarring [25].

Table 1. Clinicopathologic characteristics of pediatric follicular bronchiolitis with severe atelectasis

Case	1 [17]	2 [23]	Present case
Age/sex	21 Mo/M	9 Mo/F	11 Yr/F
Clinical presentation	Persistent wheezing and recurrent respiratory infections	Persistent cough, fever, respiratory distress, and poor weight gain	Frequent respiratory infections
Underlying condition	Unremarkable	Unremarkable	Unremarkable
Pulmonary function	N/A	N/A	Severe restrictive pattern of ventilatory limitation
Radiologic findings	Chest radiography: atelectasis HRCT: diffuse GGO, atelectasis and mild bronchial dilation	Chest radiography: collapse and mediastinal shift Chest CT: consolidation with extensive air bronchogram and compensatory hyperinflation	Chest radiography: multiple poorly defined nodules in both lower lung fields Chest CT: atelectasis and diffuse multiple centrilobular nodules with bronchiectasis
Location	LUL	LUL	RML
Pathologic findings	Numerous reactive lymphoid follicles in the peribronchus and peribronchioles	Dense peribronchiolar and interstitial lympho-plasma cell infiltrates Reactive lymphoid follicles in the peribronchus and peribronchioles Organizing pneumonia	Diffuse interstitial lympho-plasma cell infiltration Follicular lymphoid hyperplasia in the peribronchus and peribronchioles Bronchiectasis and bronchioloectasis
Operation (age)	LUL lobectomy (3 Yr)	LUL lobectomy (2 Yr)	RLL open biopsy and RML lobectomy (11 Yr)
Post-operational care	Inhaled short acting β2-agonist and corticosteroid	N/A	Oral to inhaled steroid
Clinical outcome (age)	Relapse (10 Yr)	Symptom-free (3 Yr)	Symptom-free (18 Yr)

Abbreviations: CT; computed tomography, GGO; ground-glass opacity, HRCT; high resolution computed tomography, LUL; left upper lobe, Mo; months old, N/A; not available, RLL; right lower lobe, RML; right middle lobe, RUL; right upper lobe, Yr; years old.

In summary, this report describes the case of a child with total atelectasis in the RML and diffuse multiple small nodules at both lung bases who was initially misdiagnosed with diffuse panbronchiolitis based on CT findings. The patient was resistant to macrolide therapy but recovered after 6 months of oral steroid therapy and subsequent pulse therapy with methylprednisolone after diagnostic confirmation of follicular bronchiolitis by thoracoscopic biopsy and RML lobectomy of the lesion. It can be difficult to diagnose follicular bronchiolitis solely based on clinical, laboratory, and radiologic findings; the diagnosis must be confirmed histopathologically. The prognosis can be favorable when appropriate medication is introduced at an appropriate time. A patient with long-standing irreversible atelectasis and resulting recurrent respiratory infection may require lobectomy for the diagnosis and treatment of follicular bronchiolitis.

Acknowledgements

We would like to thank Editage (www.editage.co.kr) for English language editing.

Disclosure of conflict of interest

None.

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References

[1] Ryu JH, Myers JL and Swensen SJ. Bronchiolar disorders. Am J Respir Crit Care Med 2003; 168: 1277-1292.

[2] Travis WD and Galvin JR. Nonneoplastic pulmonary lymphoid lesions. Thorax 2001; 56: 964-971.

[3] Weinman JP, Manning DA, Liptzin DR, Krausert AJ and Browne LP. HRCT findings of childhood follicular bronchiolitis. Pediatr Radiol 2017; 47: 1759-1765.

[4] Yousem SA, Colby TV and Carrington CB. Follicular bronchitis/bronchiolitis. Hum Pathol 1985; 16: 700-706.

[5] Romero S, Barroso E, Gil J, Aranda I, Alonso S and Garcia-Pachon E. Follicular bronchiolitis: clinical and pathologic findings in six patients. Lung 2003; 181: 309-319.

[6] Nicholson AG. Pulmonary lymphoproliferative disorders. Curr Diagn Pathol 2000; 6: 130-139.

[7] Dai YW, Lin L, Tang HF and Jiang KW. Follicular bronchiolitis in a child. World J Pediatr 2011; 7: 176-178.

[8] Burgel PR, Bergeron A, de Blic J, Bonniaud P, Bourdin A, Chanez P, Chinet T, Dalphin JC, Devillier P, Deschildre A, Didier A, Kambouchner M, Knoop C, Laurent F, Nunes H, Perez T, Roche N, Tillie-Leblond I and Dusser D. Small airways diseases, excluding asthma and COPD: an overview. Eur Respir Rev 2013; 22: 131-147.

[9] Kinane BT, Mansell AL, Zwerdling RG, Lapey A and Shannon DC. Follicular bronchitis in the pediatric population. Chest 1993; 104: 1183-1186.

[10] Bramson RT, Cleveland R, Blickman JG and Kinane TB. Radiographic appearance of follicular bronchitis in children. AJR Am J Roentgenol 1996; 166: 1447-1450.

[11] Jeong Y, Bang YH and Kim YK. Migrating persistent pulmonary consolidation in a child: a case of follicular bronchiolitis. Pediatr Pulmonol 2017; 52: e22-e25.

[12] Benesch M, Kurz H, Eber E, Varga EM, Göpfrich H, Pfleger A, Popper H, Setinek-Liszka U and Zach MS. Clinical and histopathological findings in two Turkish children with follicular bronchiolitis. Eur J Pediatr 2001; 160: 223-226.

[13] Reittner P, Fotter R, Lindbichler F, Tillich M, Varga EM, Zach M and Popper H. HRCT features in a 5-year-old child with follicular bronchiolitis. Pediatr Radiol 1997; 27: 877-879.

[14] Tashtoush B, Okafor NC, Ramirez JF and Smolley L. Follicular bronchiolitis: a literature review. J Clin Diagn Res 2015; 9: OE01-05.

[15] Exley CM, Suvarna SK and Matthews S. Follicular bronchiolitis as a presentation of HIV. Clin Radiol 2006; 61: 710-713.

[16] Pipavath SJ, Lynch DA, Cool C, Brown KK and Newell JD. Radiologic and pathologic features of bronchiolitis. AJR Am J Roentgenol 2005; 185: 354-363.

[17] Dias Â, Jardim J, Nunes T, Souto Moura C and Vaz L. Follicular bronchiolitis: a rare cause of persistent atelectasis in children. Respir Med Case Rep 2013; 10: 7-9.

[18] Guinee DG Jr. Update on pulmonary and pleural lymphoproliferative disorders. Diagn Histopathol 2008; 14: 474-498.

[19] Keicho N and Kudoh S. Diffuse panbronchiolitis: role of macrolides in therapy. Am J Respir Med 2002; 1: 119-131.

[20] Kudoh S and Keicho N. Diffuse panbronchiolitis. Clin Chest Med 2012; 33: 297-305.

[21] Ryu JH. Classification and approach to bronchiolar diseases. Curr Opin Pulm Med 2006; 12: 145-151.

[22] Aerni MR, Vassallo R and Ryu JH. Successful teatment of follicular bronchiolitis with macrolide. Chest 2005; 128: 428S.
[23] Ikeri NZ, Umerah GO, Ugwu CE, Olusoji O, Adeyomoye A, Ekure E and Daramola AO. Follicular bronchiolitis in a Nigerian female child: a case report and review of the literature. Case Rep Pediatr 2016; 2016: 1096953.
[24] Bates CA, Ellison MC, Lynch DA, Cool CD, Brown KK and Routes JM. Granulomatous-lymphocytic lung disease shortens survival in common variable immunodeficiency. J Allergy Clin Immunol 2004; 114: 415-421.
[25] Allen TC. Pathology of small airways disease. Arch Pathol Lab Med 2010; 134: 702-718.