

Case Report

A functionally improved case of obstructive impairment caused by systemic lupus erythematosus

A 67-year-old Asian woman presented with dyspnoea on exertion and wheezing. She had been diagnosed with systemic lupus erythematosus (SLE) and bronchial asthma at the ages of 42 and 50 years, respectively. Her SLE was stable with the use of 1 mg of daily prednisolone for more than 5 years. To control her bronchial asthma a combination of a low-dose inhaled corticosteroid (ICS) and long-acting β_2 -agonist (LABA) (125/5 μ g of fluticasone/formoterol), 10 mg of montelukast and 400 mg of theophylline were prescribed. She had a smoking history of 28 pack-years and quit smoking at the age of 45 years.

4 weeks before presentation, segmentectomy of segment 9 of the right lung was performed for nodular lesions suspected to be lung cancer or malignant (figure 1). The nodule in the right lower lung was identified as a faint nodular opacity 4 years before the referral. She was finally referred

to our respiratory centre as the size and density of the lesion gradually increased. Histopathological examination of specimens of nodular lesions measuring 2.5×2.0 cm and 1.0×0.7 cm revealed the pathological findings shown in figure 2.

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Task 1

Which of the following choices is the most appropriate pathological diagnosis for a nodular lesion?

- a) Poorly differentiated lung carcinoma
- b) Mucosa-associated lymphoid tissue lymphoma
- c) IgG4-related disease
- d) Nodular lymphoid hyperplasia
- e) Lymphoid interstitial pneumonia (LIP)

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Pulmonary lymphoproliferative diseases are often associated with collagen diseases. In addition to treatment of the primary disease, additional treatments may be considered depending on the pathology presented in the case. <https://bit.ly/3vKqsls>



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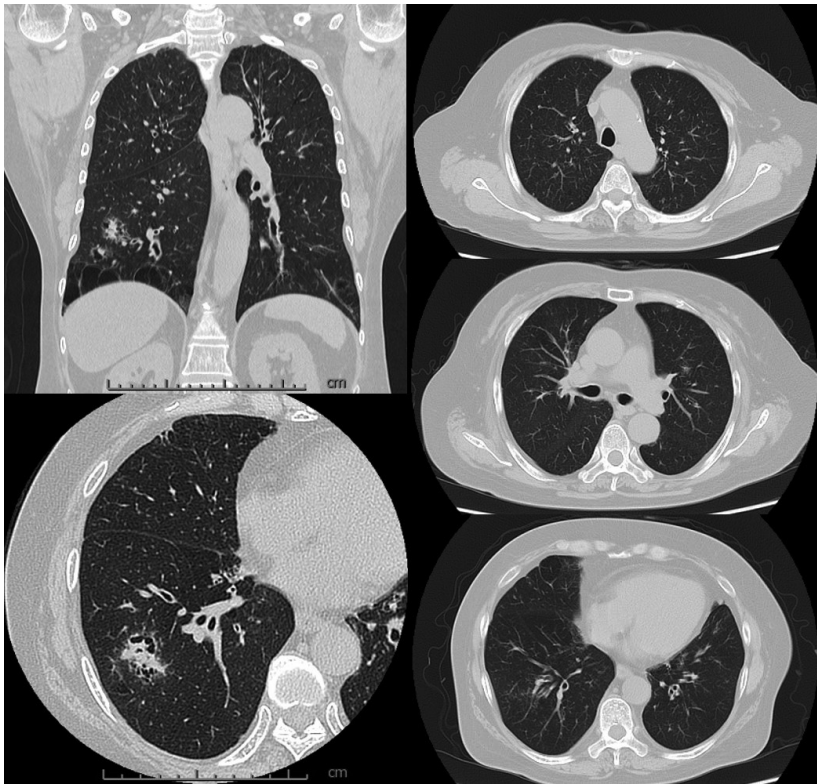


Figure 1 Chest computed tomography (CT) images before surgical biopsy. Small centrilobular nodules and bilateral patchy ground-glass opacities are observed in the whole lung. Cystic lesions are also observed in the bilateral basal parts.

Answer 1

d. Nodular lymphoid hyperplasia

HE staining of a nodular lesion showed advanced inflammatory cell infiltration (figure 2a and b). Immunostaining showed that the lesions consisted of mixed CD3- and CD20-positive T- and B-cells (figure 2b). The ratio of kappa- and lambda-positive cells in CD79α-positive cells was not significant, suggesting no monoclonality of B-cells (figure 2c). Although CD79α-positive cells were also positive for IgG, almost no IgG4-positive cells were present (figure 2d). The IgG4:IgG ratio was <0.2, which was incompatible with the pulmonary involvement of IgG4-related disease. These findings were consistent with those of pulmonary nodular lymphoid hyperplasia.

The patient had been hospitalised for bacterial pneumonia a week before presentation. Despite radiological and laboratory improvements with sulbactam/ampicillin treatment, she continued to have dyspnoea on exertion and wheezing. As she had a history of asthma and smoking, bronchial asthma or COPD exacerbation was suspected. A systemic corticosteroid, oral daily 30 mg of prednisolone for 5 days, and an on-demand short-acting β2-agonist (SABA) were insufficient to improve her dyspnoea and wheezing. To suggest other appropriate treatments, re-evaluation of chest

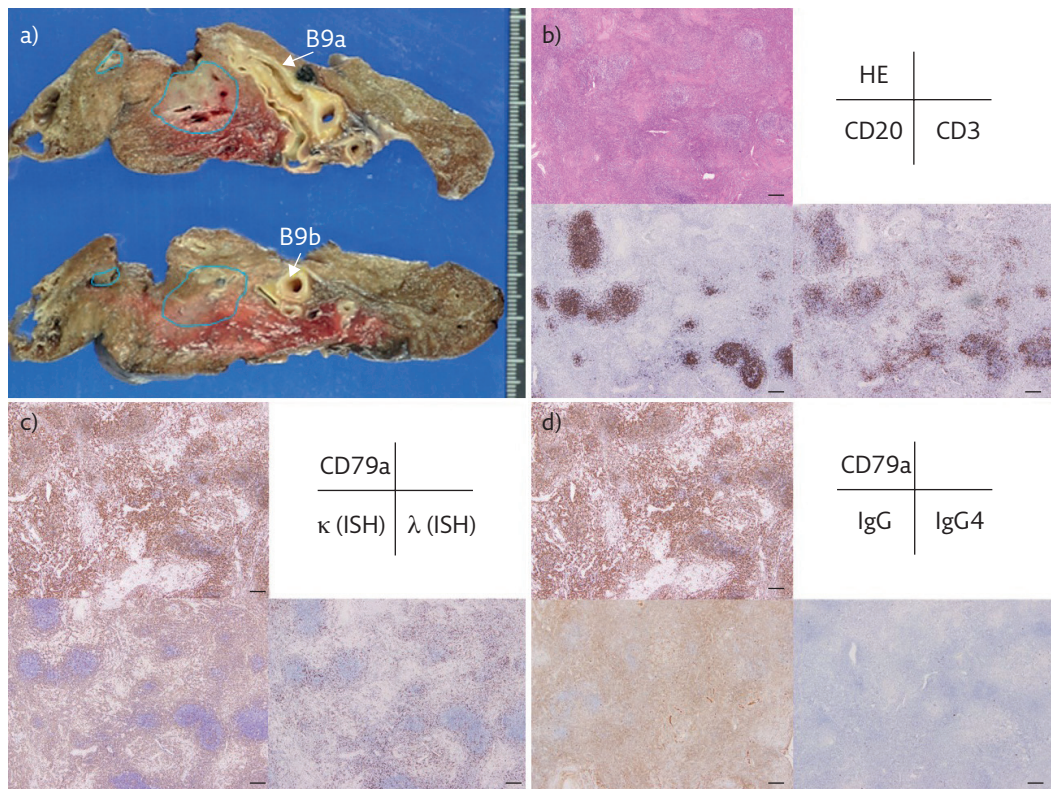


Figure 2 Macroscopic, pathological and immunohistochemical analyses of lung nodules. a) Macroscopic appearance of the resection of segment 9 of the right lower lobe. b) Haematoxylin and eosin (HE) stain, CD20 and CD3 immunohistochemistry (IHC) staining (Magnification of 40x). c) CD79a, kappa and lambda light-chain IHC staining (Magnification of 40x). d) CD79a, IgG and IgG4 IHC staining (Magnification of 40x). Scale bars=200 μm.

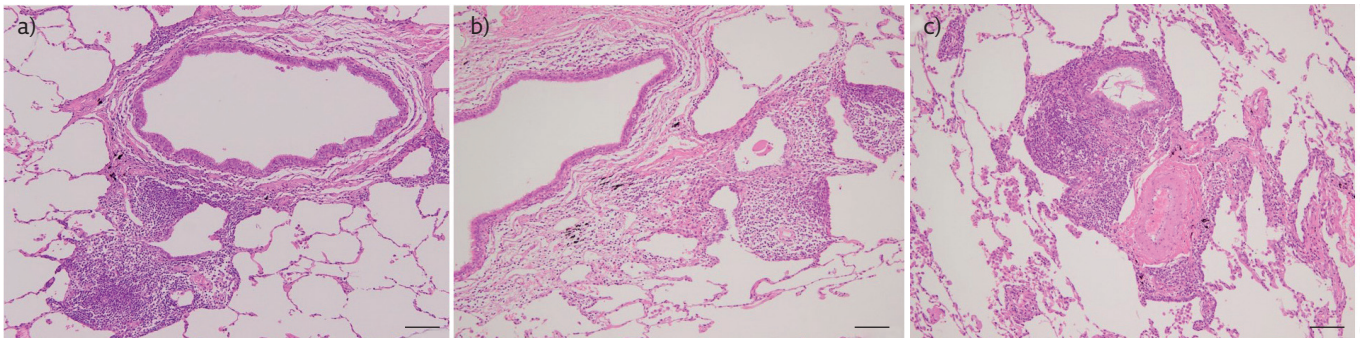


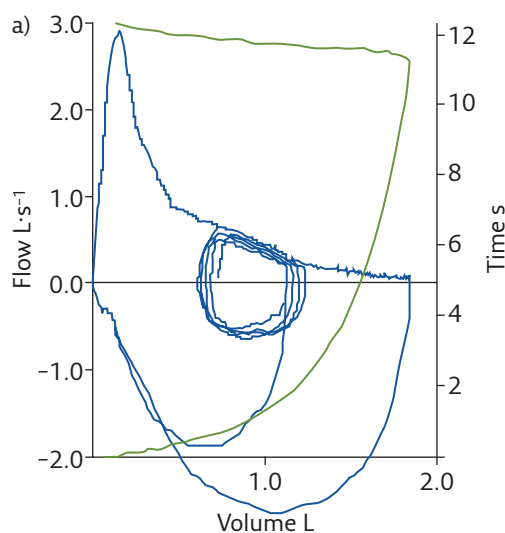
Figure 3 Pathological findings of the bronchiole. a, b) Well-formed lymphoid follicles in the walls of bronchioles. c) Large germinal centre adjacent to the bronchiole narrows or incompletely obliterates the bronchiolar lumen. No extensive alveolar septal involvement, mucous gland hyperplasia, basement membrane thickening, and smooth muscle hypertrophy are observed. Scale bars=100 μ m.

CT findings (figure 1), surgical pathology specimens (figure 3) and respiratory function tests were performed (figure 4).

Task 2

What is the diagnosis based on imaging and pathological findings?

- a) Bronchiolitis obliterans
- b) Follicular bronchiolitis (FB)
- c) Bronchial asthma
- d) Diffuse panbronchiolitis
- e) LIP



	Pretreatment
TLC	3.41 L
RV	1.56 L
VC	1.85 L
FVC	1.85 L
ATI	0.14 %
FEV₁	0.9 L
FEV₁/FVC	49.0 %
PEF	2.93 L·s ⁻¹
MMF	0.31 L·s ⁻¹
D_{LCO}	13.07 mL·min ⁻¹ ·mmHg ⁻¹
D_{LCO}/V_A	6.07 mL·min ⁻¹ ·mmHg ⁻¹ ·L ⁻¹
F_{ENO}	20 ppb

Figure 4 a) Flow-volume curve and b) pulmonary function test results. TLC: total lung capacity; RV: residual volume; VC: vital capacity; FVC: forced vital capacity; ATI: air trapping index; FEV₁: forced expiratory volume in 1 s; PEF: peak expiratory flow; MMF: maximum mid-expiratory flow; D_{LCO}: diffusing capacity for carbon monoxide; V_A: alveolar volume; F_{ENO}: fractional exhaled nitric oxide.

Answer 2

b. Follicular bronchiolitis (FB)

Chest CT before the segmentectomy showed diffuse centrilobular nodules, bronchial wall thickening and bilateral basal cystic lesions, in addition to the nodular shadow (figure 1). To explore the pathophysiological causes of airway obstruction, re-evaluation of the specimen obtained by segmentectomy, particularly other than the nodule, was performed. Well-formed lymphoid follicles were observed in the walls of the bronchioles (figure 3a and b). A large germinal centre adjacent to the bronchiole narrowed or incompletely obliterated the bronchiolar lumen (figure 3c). Alveolar septal involvement of lymphocytes was not observed. Pathological features of asthma, such as mucous gland hyperplasia, basement membrane thickening and smooth muscle hypertrophy, were not observed. Although obstructive impairment was observed on the respiratory function test, there was no deterioration in the diffusion capacity test or F_{ENO} . These findings suggested inconsistencies between COPD and bronchial asthma (figure 4). Given these pathological and clinical features, a diagnosis of SLE-associated FB was confirmed.

Task 3

Which of the following choices are unusual for the treatment of FB?

- a) Systemic corticosteroids
- b) Azathioprine
- c) Rituximab
- d) Tocilizumab
- e) Macrolide

Answer 3

d. Tocilizumab

Common treatments specific for FBs have not been established. In primary FB cases, corticosteroids have been used to treat symptoms and radiographic abnormalities. Although rituximab and azathioprine have demonstrated functional and radiographic improvements in FB patients with common variable immune deficiency (CVID) [1, 2], management of the underlying condition is generally employed in secondary FB cases. In this case, the dose of prednisolone was returned to the original SLE maintenance dose as the other symptoms of SLE were under control. Therefore, despite secondary FB, treatment with a high-dose ICS/LABA combination (200/25 µg of fluticasone furoate/vilanterol) and a long-acting muscarinic antagonist (LAMA; 5 µg of tiotropium) was initiated for severe airflow limitation instead of treatment with systemic corticosteroids and/or immunosuppressants. These treatments resulted in symptomatic and functional improvements, particularly in the reduction of residual volume (table 1); however, dyspnoea on exertion persisted. Based on a previous study showing the efficacy of macrolide antibiotics in FB [3], treatment with 200 mg of clarithromycin improved of the symptoms and pulmonary function (table 1).

Discussion

Follicular bronchiolitis is a reactive pulmonary lymphoid disorder. It is characterised by the presence of polyclonal hyperplastic lymphoid follicles with germinal centres in the walls of small

Table 1 Results of respiratory function tests

	Pretreatment	High-dose ICS/LABA and LAMA	Clarithromycin 200 mg·day ⁻¹ add on
TLC L	3.41	3.55	N/A
RV L	1.56	1.29	N/A
VC L	1.85	2.26	2.40
FVC L	1.85	2.19	2.38
ATI %	0.14	3.21	0.83
FEV₁ L	0.9	1.04	1.18
FEV₁/FVC %	49.0	47.5	49.6
PEF L·s⁻¹	2.93	3.65	3.65
MMF L·s⁻¹	0.31	0.32	0.38
D_{LCO} mL·min⁻¹·mmHg⁻¹	13.07	11.98	N/A
D_{LCO}/V_A mL·min⁻¹·mmHg⁻¹·L⁻¹	6.07	4.2	N/A
F_{ENO} ppb	20	N/A	N/A

TLC: total lung capacity; RV: residual volume; VC: vital capacity; FVC: forced vital capacity; ATI: air trapping index; FEV₁: forced expiratory volume in 1 s; PEF: peak expiratory flow; MMF: maximum mid-expiratory flow; D_{LCO}: diffusing capacity for carbon monoxide; V_A: alveolar volume; F_{ENO}: fractional exhaled nitric oxide; N/A: not applicable.

airways [1, 4], occasionally causing airway narrowing [5]. FB has been aetiologically categorised into three groups: primary/idiopathic, congenital/acquired immunodeficiency-related, and autoimmune or collagen vascular disease-related subtypes [1, 6]. Although Yousem *et al.* [6] have reported that the major FB-related autoimmune or collagen vascular diseases are rheumatoid arthritis and Sjögren syndrome [6, 7], FB can occur in association with a variety of autoimmune diseases, as in this case. Owing to nonspecific symptoms, such as chronic progressive dyspnoea, cough, fever and fatigue, FB is less likely to be considered in autoimmune disease patients with these symptoms. FB is often misdiagnosed with recurrent chest infections [8]. In this case, the patient was previously diagnosed with bronchial asthma and was suspected of having COPD based on her smoking history and lung cystic lesions, despite CT findings being compatible with FB. Due to corticosteroid-refractory symptoms and a previous history of pulmonary nodular lymphoid hyperplasia, FB was considered and finally confirmed using histological re-examination.

The most common features of FBs on CT are small centrilobular nodules with bilateral patchy ground-glass opacity (GGO). Air trapping by FB lesions occasionally causes a mosaic pattern of lung attenuation. These FB-prevalent findings could also be observed in this case. Since FB can cause restrictive, obstructive and mixed patterns of airflow limitation it is occasionally difficult to diagnose using pulmonary function tests. The main pathological feature of FB, hyperplastic lymphoid follicles in the walls of small airways, cause the stenosis of the peripheral airway, leading to obstructive impairment. However, FB occasionally presents with pleural lesions and fibrotic reactions [1], leading to restrictive or mixed impairment.

Although combination chemotherapy using rituximab and azathioprine has demonstrated a functional and radiographic improvement in FB patients with CVID [1, 2], treatments for underlying diseases are generally conducted for secondary FB, including immunosuppressant therapy in addition to systemic corticosteroid

therapy. In this case, the patient's SLE status was stable with 1 mg of prednisolone daily for a long time. Furthermore, systemic administration of 30 mg of prednisolone daily for suspected asthma and/or COPD exacerbation did not improve her symptoms. Since FB is a small airway inflammatory disease, administration of active agents, particularly bronchodilators, through the airway was considered. Therefore, treatment with a high-dose ICS/LABA and a LAMA was initiated instead of treatment with systemic corticosteroids and immunosuppressants. These treatments improved her symptoms and lung function; however, they were insufficient. Since macrolide antibiotics have been reported to improve FB symptoms, 200 mg of daily clarithromycin was initiated as an additional treatment, leading to improvement in symptoms and lung function. Despite the ability to modulate inflammation and immunity [3], the mechanisms of action of macrolides in FB are unclear. Macrolides have been reported to inhibit the clearance of methylprednisolone, leading to the enhancement of corticosteroids [9, 10]. Owing to the insufficient efficacy of systemic prednisolone, this property of clearance was less likely to contribute to the improvement in this case.

Surgical biopsy specimens examined for a nodular lesion helped confirm the presence of FB. While the lesion was initially suspected to be lung cancer, the histopathological and immunohistochemical diagnosis was pulmonary nodular lymphoid hyperplasia (PNLH). The latter is also a lymphoproliferative pulmonary disease and can generally be distinguished from FB based on the pattern of pulmonary involvement. A previous report of PNLH cases with multiple nodules and GGOs has revealed the coexistence of FB and PNLH as in this case [11].

In conclusion, we have presented a case of FB associated with SLE. Low-dose macrolide combined with a high-dose ICS/LABA and a LAMA provided additional improvement in symptoms and respiratory function in this case. Low-dose macrolide can be used as a supplemental treatment in conventional treatment plans for cases of FB.

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Conflict of interest

None declared.

References

1. Tashitouch B, Okafor NC, Ramirez JF, *et al.* Follicular bronchiolitis: a literature review. *J Clin Diagn Res* 2015; 9: OE01-OE05.
2. Chase NM, Verbsky JW, Hintermeyer MK, *et al.* Use of combination chemotherapy for treatment of granulomatous

- and lymphocytic interstitial lung disease (GLILD) in patients with common variable immunodeficiency (CVID). *J Clin Immunol* 2013; 33: 30–39.
3. Aerni MR, Vassallo R, Ryu JH. Successful treatment of follicular bronchiolitis with macrolide. *Chest* 2005; 128: 428S.
 4. Kusume K, Kitaichi M, Hoshino T, *et al.* An open lung biopsy case of follicular bronchiolitis in rheumatoid arthritis. *Nihon Kyobu Shikkan Gakkai Zasshi* 1990; 28: 906–912.
 5. Epler GR, Snider GL, Gaensler EA, *et al.* Bronchiolitis and bronchitis in connective tissue disease. A possible relationship to the use of penicillamine. *JAMA* 1979; 242: 528–532.
 6. Yousem SA, Colby TV, Carrington CB. Follicular bronchitis/bronchiolitis. *Hum Pathol* 1985; 16: 700–706.
 7. Kitasato Y, Matsunaga K, Hoshino T, *et al.* A case of follicular bronchiolitis preceding rheumatoid arthritis. *Ann Jpn Respir Soc* 2006; 44: 104–110.
 8. Duarte AC, Cordeiro A, Soares J, *et al.* Follicular bronchiolitis, a frequently misdiagnosed condition. *Pulmonology* 2019; 25: 62–64.
 9. Amayasu H, Yoshida S, Ebana S, *et al.* Clarithromycin suppresses bronchial hyperresponsiveness associated with eosinophilic inflammation in patients with asthma. *Ann Allergy Asthma Immunol* 2000; 84: 594–598.
 10. Spahn JD, Fost DA, Covar R, *et al.* Clarithromycin potentiates glucocorticoid responsiveness in patients with asthma: Results of a pilot study. *Ann Allergy Asthma Immunol* 2001; 87: 501–505.
 11. Kajiwaru S, Sakai S, Soeda H, *et al.* Multifocal nodular lymphoid hyperplasia of the lung. *J Thorac Imaging* 2005; 20: 239–241.