【 CASE REPORT 】

# Idiopathic Obliterative Bronchiolitis in a Young Woman: A Rare Case of a Transbronchial Lung Biopsy Contributing to the Diagnosis

Naoko Yoshii [1], Hiroshi Kamoi [2], Erika Matsui [1], Kanako Sato [1], Toshiyuki Nakai [1],
Kazuhiro Yamada [1], Tetsuya Watanabe [1], Kazuhisa Asai [1], Hiroshi Kanazawa [1] and
Tomoya Kawaguchi [1]

**Abstract:**

Idiopathic obliterative bronchiolitis (OB) is a rare disease that usually requires a surgical lung biopsy. A 25-year-old woman with progressive exertional dyspnea for several months showed a severe mixed restrictive and obstructive pattern on spirometry. Chest computed tomography showed a mosaic pattern, and pulmonary ventilation-perfusion scintigraphy showed a matched defect. The bronchoscopic specimens obtained from both the alveolar and bronchiolar regions of the predicted lesion area contributed to the diagnosis of OB. She had no underlying causes of secondary OB, and she was diagnosed with idiopathic OB. Since lung transplantation was indicated, she was referred to a lung transplantation-certified hospital.

**Key words:** idiopathic obliterative bronchiolitis, bronchoscopy, transbronchial lung biopsy

## Introduction

Obliterative bronchiolitis (OB) or constrictive bronchiolitis is characterized by subepithelial inflammatory and fibrotic narrowing of small airways (1). OB is primarily a disorder of progressive air trapping due to involvement of bronchioles without lung parenchymal involvement, and it should be distinguished from bronchiolitis obliterans with organizing pneumonia (BOOP) or cryptogenic organizing pneumonia (COP). BOOP/COP is more common, showing predominantly parenchymal lesions with alveolar infiltration and intraluminal polyps in the respiratory bronchioles (2). These may be further confused with the term, bronchiolitis obliterans syndrome (BOS). BOS is a term used for progressive obstructive respiratory dysfunction that develops mainly after hematopoietic stem cell transplantation (HSCT) or organ transplantation (1). BOS after transplantation is defined by a decrease in forced expiratory volume in 1 second (FEV1)

and usually does not require a lung biopsy (3, 4).

OB has various causes, most commonly lung transplantation and HSCT, as described above. Other rare causes are connective tissue disorders, particularly rheumatoid arthritis (RA), infections, notably *Mycoplasma pneumoniae* and viral infections, exposure to fumes or inhalational toxins, and drugs, including anti-rheumatic drugs and *Sauropus androgynus*. It is regarded as idiopathic when it occurs with no identifiable cause (1, 2, 5).

The clinical manifestations of patients with OB are mostly progressive dyspnea and cough over weeks to months. Unless the patient has a medical history causing OB, initially, they are often diagnosed and treated as having bronchial asthma or chronic obstructive pulmonary disease (COPD). When OB is suspected without an apparent cause, a histological diagnosis is necessary to distinguish it from other lung diseases. Although a surgical lung biopsy is generally superior to bronchoscopic approaches due to OB lesion's heterogeneity and scattered distribution (2, 6), it is

$[\dot{V}-V]$

| | |
|---|---|
| FEV1 (% predicted) | 0.58 L (20.4%) |
| FVC (% predicted) | 1.03 L (32.2%) |
| FEV1/ FVC ratio | 56.31% |
| TLC (% predicted) | 2.38 L (61.8%) |
| RV (% predicted) | 1.14 L (129.5%) |
| DLco (% predicted) | 7.10 mL/min/mmHg (30.5%) |

FLOW [L/s]

L (ATPS)

RV (BTPS) : 1.14

FVC (BTPS) : 0.00    RV' (BTPS) : 1.35
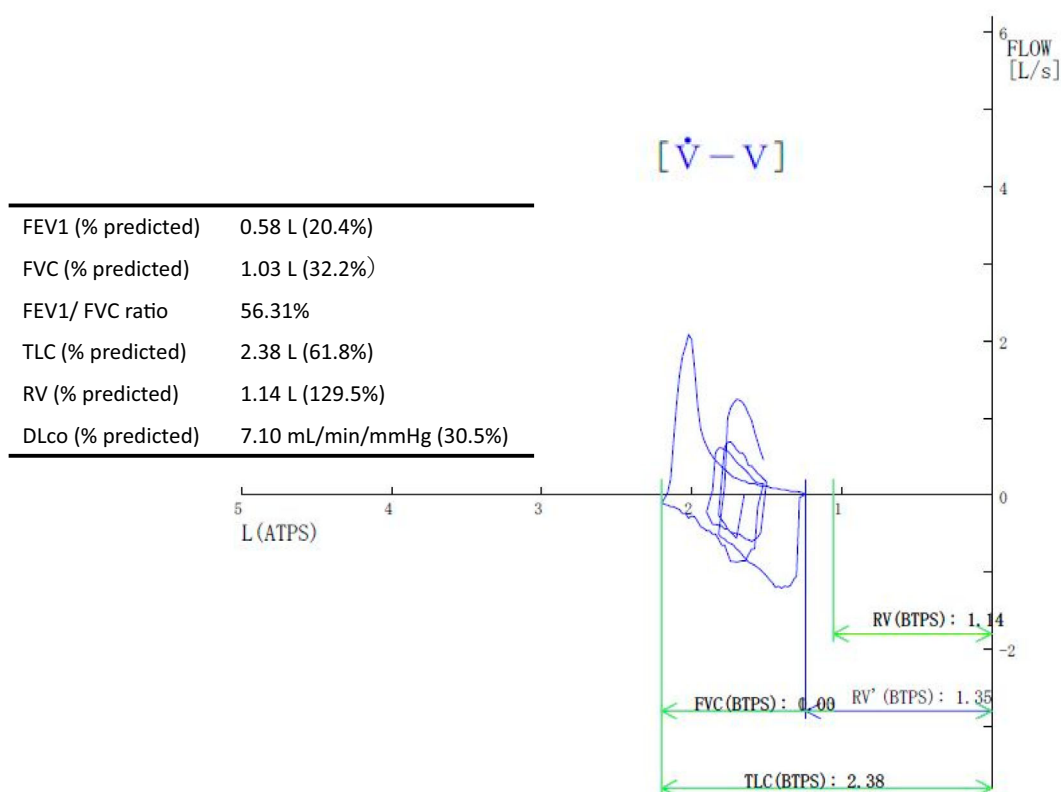
TLC (BTPS) : 2.38

**Figure 1.**   **Pulmonary function test shows a severe mixed restrictive/obstructive pattern on spirometry.**



**Figure 2.**   **Chest X ray on admission shows no infiltrates.**

often difficult to perform for OB patients with a decreased respiratory function in the clinical setting.

We herein report a young woman with idiopathic OB in whom bronchoscopic biopsy specimens helped make the diagnosis.

## Case Report

A 25-year-old woman developed exertional dyspnea 5 months before admission. She was diagnosed with bronchial asthma at a local clinic and used inhaled corticosteroid (ICS)/long-acting β2-agonist (LABA) and anti-allergic

agents along with short-term oral prednisolone. However, her symptoms gradually worsened over several months, and she was referred to our hospital for detailed examinations. On admission, percutaneous oxygen saturation (SpO₂) was 88% on room air. On auscultation, there were diminished breath sounds in both lungs. She had never smoked and had no history of bone-marrow transplantation, lung transplantation, or exposure to occupational or environmental toxins. She had no history of taking *Sauropus androgynus*. She also had no history of collagen diseases or apparent respiratory infections preceding the development of exertional dyspnea.

She had neither arthralgia nor rash suggestive of connective tissue diseases, and serum antinuclear antibodies and anti-cyclic citrullinated peptide antibody were negative. She was also negative for antibodies to human T-lymphotropic virus (HTLV-1) in her serum.

Pulmonary function tests showed a severe obstructive and restrictive mixed pattern (Fig. 1), with forced vital capacity (FVC) of 1.03 L (32.2% predicted), FEV1 of 0.58 L (20.4% predicted), FEV1/FVC ratio of 56.3%, total lung capacity of 61.8% predicted, residual volume of 129.5% predicted, and a diffusing capacity of the lung for carbon monoxide (DLco) of 30.5% predicted. The bronchodilator reversibility test, a widely used method to identify patients with asthma by measuring the change in FEV1 after the administration of a short-acting bronchodilator, showed no significant change in FEV1 following bronchodilator inhalation, which indicated no airway reversibility.

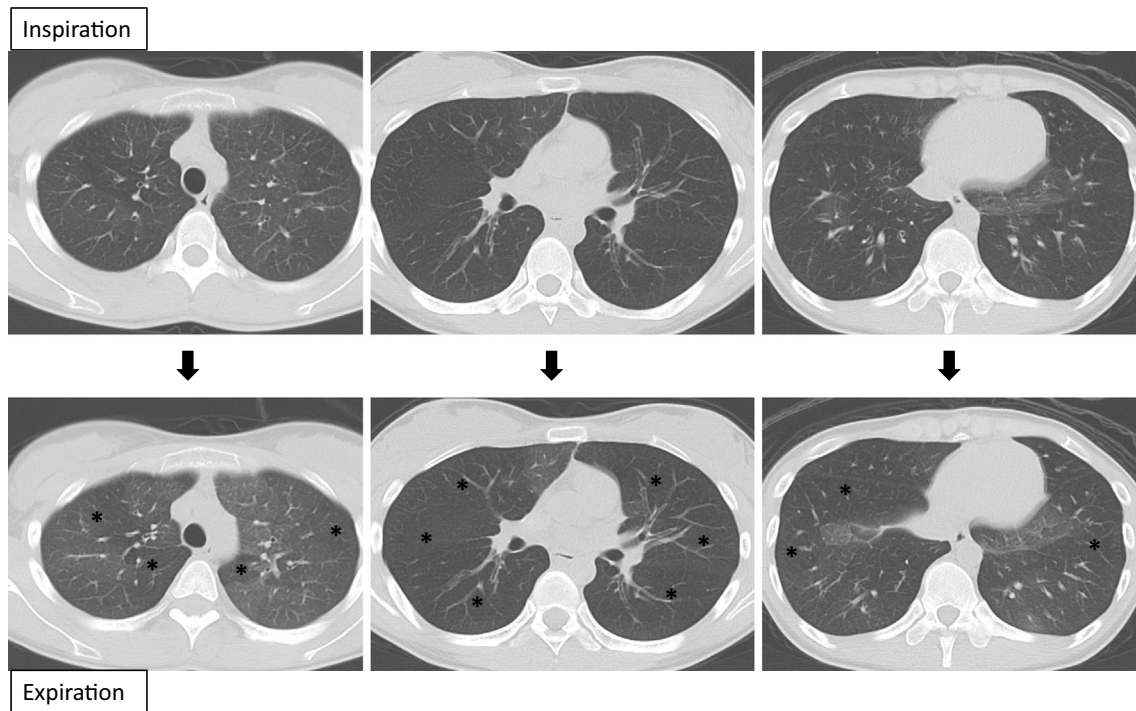Chest X-ray showed no infiltrates (Fig. 2). Chest com-

**Figure 3.** Chest CT shows a mosaic pattern of air trapping that is enhanced in the expiratory phase. The asterisk shows areas of air trapping.
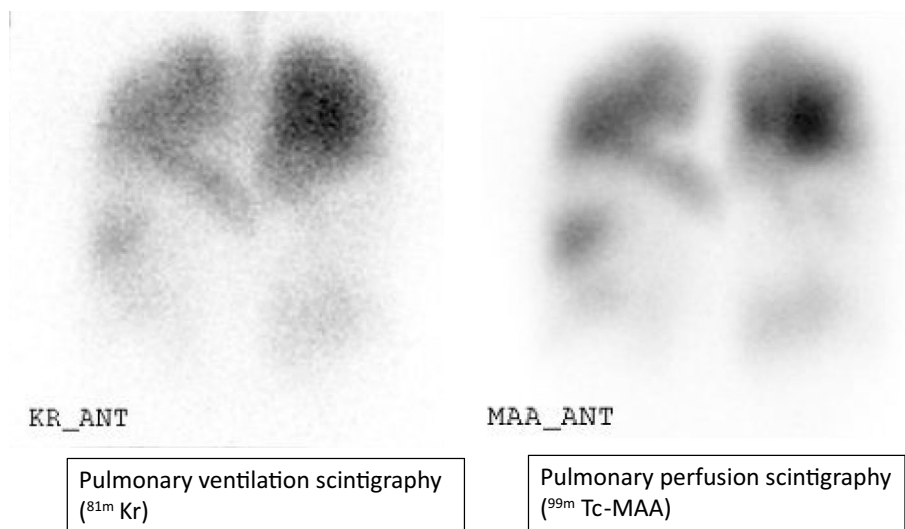


**Figure 4.** Pulmonary ventilation-perfusion scintigraphy with $^{81m}$Kr and $^{99m}$Tc-MAA shows extensive matched ventilation-perfusion defects, mainly in both lower lobes.

puted tomography (CT) showed mosaic attenuation areas that were enhanced during the expiratory phase compared to the inspiratory phase, indicating the presence of scattered air trapping in bilateral lungs (Fig. 3). Pulmonary ventilation-perfusion scintigraphy with $^{81m}$Kr and $^{99m}$Tc-MAA showed matched ventilation-perfusion defects, consistent with the air-trapped areas seen on chest CT (Fig. 4).

On a bronchoscopic examination, specimens were collected from the bronchioles and alveolar areas. A transbronchial lung biopsy (TBLB) was performed in the right S8 region suspected to be a lesion based on CT and pulmonary ventilation-perfusion scintigraphy. A biopsy of bronchioles

was also performed just proximal to the same bronchus. In specimens from the respiratory bronchiole region, proliferation of fibroblasts with mucin deposition was observed, and infiltration of inflammatory cells, mainly lymphocytes, was also found (Fig. 5a). As the sample had been obtained by a TBLB, the specimens had crushed by forceps, and we were unable to identify the part of the endobronchial space it had been retrieved from or the muscle layer on histopathology. In contrast, in the alveolar specimen, no interstitial fibrosis was observed, and inflammatory cell infiltration was very slight (Fig. 5b). Although a surgical lung biopsy was not performed due to her impaired pulmonary function, idi-
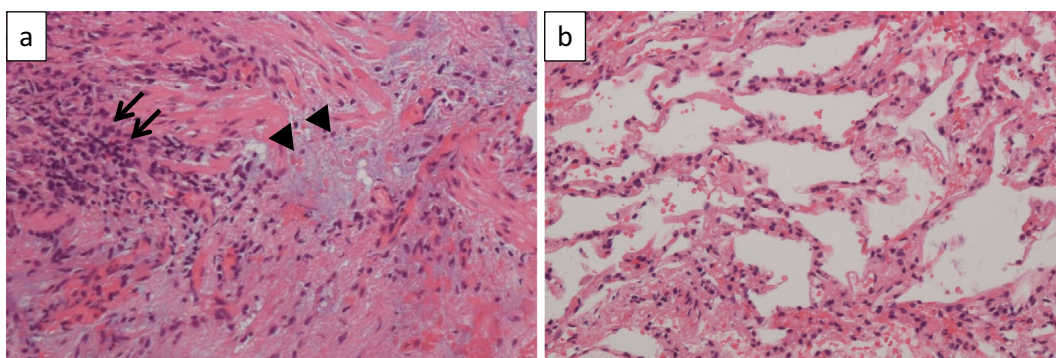
**Figure 5.** **(a) The histopathological findings of specimens from the respiratory bronchiole region. This image shows inflammatory thickening of the bronchiole wall. Proliferation of fibroblasts with mucin deposition is observed (arrowheads), and infiltration of inflammatory cells, mainly lymphocytes, is also found (arrows). (b) In contrast, in the alveolar specimen, no interstitial fibrosis is observed, and inflammatory cell infiltration is very slight.**

opathic OB was diagnosed based on her progressive symptoms and the results of these examinations.

She continued an inhaled long-acting muscarinic antagonist (LAMA)/LABA combination and oral macrolide and started home oxygen therapy after discharge. Since lung transplantation was indicated, she was referred to a lung transplantation-certified hospital. When she underwent the various examinations for registration as a potential lung transplant recipient, a sliding esophageal hiatal hernia was diagnosed, and an oral proton pump inhibitor was added to her medication. Her respiratory function has not improved in the second year since her diagnosis, although it has not shown any deterioration from the initial pulmonary function tests. In this two-year period, she has not developed any collagen diseases or malignancies.

## Discussion

In the present case, a young woman with progressive exertional dyspnea for several months showed a severe mixed restrictive and obstructive pattern on spirometry. Although she had been treated for bronchial asthma for several months, her symptoms did not improve, but worsened. The mosaic pattern in both lungs on end-expiration CT presenting air trapping and the finding of matched defects on lung ventilation-perfusion scintigraphy confirmed the lung lesion sites with constriction in respiratory bronchioles. Although a surgical lung biopsy was not possible due to her decreased lung function, the bronchoscopic specimens obtained from both the alveolar and respiratory bronchiolar regions of the lung lesion area contributed to the diagnosis of OB.

She had no history of transplantation, collagen disease, viral infection, or exposure to fumes or gas that might have caused OB, and she was diagnosed with idiopathic OB. Idiopathic OB is a rare disease that has been reported in patients aged 38 to 80 years, most of whom are women. Parambil et al. examined 29 adult patients with non-transplant OB (5). They reported that 15 patients (52%) had auto-immune diseases (including 10 RA, 2 Sjögren syndrome, and others), and the 9 with no underlying causes had idiopathic OB. Eight of the nine idiopathic patients were women, and six did not show any significant disease progression during one to five years of follow-up. Kraft et al. also reported four cases of idiopathic OB (7). The patients were all women, and none had experienced significant progression of their disease over several years of follow-up.

However, none of the idiopathic OB patients in either report had any apparent improvement in the follow-up period, despite treatment with an oral or inhaled corticosteroid or macrolide therapy. In the present case, similar to most previous cases of idiopathic OB, no apparent deterioration of the respiratory function or symptoms was observed during the two-year follow-up period after the diagnosis, nor was any improvement obtained with inhaled bronchodilators and macrolide therapy. The patient had to continue home oxygen therapy with inhalation of $O_2$ at 2 L/min.

Our patient's pulmonary function tests showed a severe obstructive and restrictive mixed pattern and decreased DLco. The pulmonary function test of this patient was conducted several times and showed the same pattern every time. Typically, in OB patients, the significant findings on spirometry are a normal or slightly decreased FVC, a reduced FEV1, and a reduced ratio of FEV1 to FVC. The response to inhaled bronchodilators is generally poor. However, the respiratory function of the OB patient may show various patterns. Some patients show a normal pattern, and some show a mixed pattern of obstruction and restriction. The DLco is initially normal but may decrease with disease progression. A decreased DLco is caused by damage to the interstitial tissue between the alveoli and capillaries and a decline in alveolar ventilation or decreased blood flow in the pulmonary capillaries. We considered the decreased DLco to reflect the reduced alveolar ventilation and alveolar blood flow in the present case.

Several studies have described the association of gastroesophageal reflux disease (GERD) and BOS after lung

transplantation (8, 9). Capel et al. reported a case of a non-transplant OB patient with a large volume of gastro-esophageal reflux and considered GERD to be associated with the development of OB (10). They also suggested that GERD might account for some of the cases of idiopathic OB. Previous reports have suggested that repeated aspiration of gastric contents might be one of the causes of post-transplant lung injury in the association between GERD and post-transplant patients. However, it has also been reported that Proton-pump inhibitor (PPI) therapy does not prevent aspiration of gastric contents, and no report has described a case of a PPI inhibiting progression of OB (8). In the present case, the patient had a mild esophageal hiatal hernia; therefore, the possibility that GERD might have affected the development of OB cannot be ruled out. However, the prevalence of GERD in Japan is around 15%, so it is unlikely to have been the main factor influencing the development of so rare a lung disease as non-transplant OB (11).

Diseases that must be differentiated from OB include bronchial asthma, COPD, diffuse panbronchiolitis, follicular bronchiolitis, respiratory bronchiolitis with interstitial lung disease, and diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH) (12). DIPNECH, which is considered a preneoplastic lesion in the spectrum of pulmonary neuroendocrine tumors, is also a rare disorder that occurs predominantly in women and is not associated with smoking (13). DIPNECH is very similar to OB in that the patients have exertional dyspnea and show an obstructive or obstructive/restrictive defect on spirometry and a mosaic pattern on chest CT. Therefore, it is difficult to distinguish DIPNECH and non-transplant OB based solely on the manifestations and radiological features.

The histopathologic lesion of OB is characterized by a pure lesion of the bronchioles, with few changes in the distal parenchyma (14). Therefore, specimens were obtained from the alveolar region and the bronchiolar region. In specimens from the bronchiolar region, proliferation of fibroblasts with mucin deposition and infiltration of inflammatory cells were observed. In contrast, in the alveolar specimen, inflammatory cell infiltration was very slight. These results contributed to the diagnosis in this case.

In this present case, end-expiration CT confirmed that the lesion with air trapping matched the defect on ventilation-perfusion scintigraphy. These results allowed us to predict the location of the lung lesion in advance. A diagnosis of non-transplant OB usually requires a surgical lung biopsy to distinguish it from other lung diseases. However, a surgical lung biopsy is often difficult to perform in OB patients with a decreased pulmonary function. A TBLB, which can obtain much smaller specimens, has less sensitivity for an OB diagnosis than a surgical lung biopsy due to the patchy and heterogeneous nature of the lesion (2, 14). However, as in the present case, even a transbronchial biopsy may also contribute to the diagnosis. To obtain specimens useful for the diagnosis, it is essential to predict the location of obstructive lesions using end-expiration CT and ventilation-perfusion

scintigraphy and to collect specimens from both alveolar and bronchiolar areas.

In recent years, the usefulness of a transbronchial cryobiopsy, which can obtain larger, less crushed tissue than a traditional TBLB, in the diagnosis of OB and diffuse parenchymal lung disorders has been reported (15, 16). A cryobiopsy may be a viable alternative to a surgical lung biopsy for the histologic diagnosis of OB. However, even if a cryobiopsy is performed for a patient suspected of having OB, an adequate assessment of the lesion site by imaging in advance is necessary, due to the heterogeneous and patchy distribution of lesions and the alveolar area showing almost normal findings in OB patients.

One limitation of this case is that the patient had no apparent symptoms of lower respiratory tract infection that preceded the onset of exertional dyspnea. However, the presence of infection with *Mycoplasma pneumoniae* or a virus was unclear.

Non-transplant OB is a rare disease. Therefore, some patients may be misdiagnosed with more common diseases, such as bronchial asthma. Idiopathic OB should also be considered in the differential diagnosis of patients with an obstructive respiratory disorder that does not respond to treatment with bronchodilators or corticosteroids. A lung biopsy is important in such patients.

As in the present case, even in suspected OB, a surgical lung biopsy may be difficult due to the patient's decreased pulmonary function. Less invasive bronchoschopic lung biopsies of both the alveolar and bronchiolar regions from the lesion predicted by end-expiration CT and ventilation-perfusion scintigraphy would aid in not only the differentiation of other lung diseases but also the diagnosis of OB.

## References

1. Barker AF, Bergeron A, Rom WN, Hertz MI. Obliterative bronchiolitis. N Engl J Med **370**: 1820-1828, 2014.
2. Aguilar PR, Michelson AP, Isakow W. Obliterative bronchiolitis. Transplantation **100**: 272-283, 2016.
3. Verleden GM, Glanville AR, Lease ED, et al. Chronic lung allograft dysfunction: definition, diagnostic criteria, and approaches to treatment - a consensus report from the Pulmonary Council of the ISHLT. J Heart Lung Transplant **38**: 493-503, 2019.
4. Jagasia MH, Greinix HT, Arora M, et al. National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host Disease: I. The 2014 diagnosis and staging working group report. Biol Blood Marrow Transplant **21**: 389-401.e381, 2015.
5. Parambil JG, Yi ES, Ryu JH. Obstructive bronchiolar disease identified by CT in the non-transplant population: analysis of 29 consecutive cases. Respirology **14**: 443-448, 2009.
6. Ryu JH, Myers JL, Swensen SJ. Bronchiolar disorders. Am J Respir Crit Care Med **168**: 1277-1292, 2003.
7. Kraft M, Mortenson RL, Colby TV, Newman L, Waldron JA Jr., King TE Jr. Cryptogenic constrictive bronchiolitis. A clinicopathologic study. Am Rev Respir Dis **148**: 1093-1101, 1993.
8. Wood RK. Esophageal dysmotility, gastro-esophageal reflux dis-

ease, and lung transplantation: what is the evidence? Curr Gastroenterol Rep **17**: 48, 2015.

9. Hartwig MG, Appel JZ, Li B, et al. Chronic aspiration of gastric fluid accelerates pulmonary allograft dysfunction in a rat model of lung transplantation. J Thorac Cardiovasc Surg **131**: 209-217, 2006.

10. Capel K, Shih RD. Constrictive bronchiolitis presenting with a mixed obstructive and restrictive pattern, associated with acid reflux. BMJ Case Rep **2017**: bcr2017221438, 2017.

11. Chiba H, Gunji T, Sato H, et al. A cross-sectional study on the risk factors for erosive esophagitis in young adults. Intern Med **51**: 1293-1299, 2012.

12. Ryu JH, Azadeh N, Samhouri B, Yi E. Recent advances in the understanding of bronchiolitis in adults. F1000Res **9**: 568, 2020.

13. Rossi G, Cavazza A, Spagnolo P, et al. Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia syndrome. Eur Respir J **47**: 1829-1841, 2016.

14. Colby TV. Bronchiolitis: pathologic considerations. Am J Clin Pathol **109**: 101-109, 1998.

15. Ussavarungsi K, Kern RM, Roden AC, Ryu JH, Edell ES. Transbronchial cryobiopsy in diffuse parenchymal lung disease: retrospective analysis of 74 cases. Chest **151**: 400-408, 2017.

16. Sirol Aflah Syazatul S, Piciucchi S, Tomassetti S, Ravaglia C, Dubini A, Poletti V. Cryobiopsy in the diagnosis of bronchiolitis: a retrospective analysis of twenty-three consecutive patients. Sci Rep **10**: 10906, 2020.