

[ CASE REPORT ]

## Unilateral Autoimmune Pulmonary Alveolar Proteinosis with Polymyositis-related Interstitial Lung Disease

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### Abstract:

A 61-year-old patient with cystic bronchiectasis and bronchial artery hyperplasia in the left lung was diagnosed with polymyositis-related interstitial lung disease. After nine months of immunosuppressive therapy, he developed unilateral autoimmune pulmonary alveolar proteinosis (APAP) in the right lung with respiratory failure. After bronchial artery embolization to prevent massive hemoptysis, whole-lung lavage was performed using veno-venous extracorporeal membrane oxygenation. His respiratory condition improved, and he was discharged from the hospital with supplemental oxygen. Three reported cases of APAP with polymyositis-related interstitial lung disease, including the present case, were all positive for anti-glycyl tRNA synthetase antibody and were under immunosuppressive treatment.

**Key words:** anti-glycyl tRNA synthetase antibody, polymyositis, pulmonary alveolar proteinosis, interstitial lung disease, bronchiectasis, whole-lung lavage

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### Introduction

Pulmonary alveolar proteinosis (PAP) is a rare disease characterized by the accumulation of surfactant lipoproteins in the alveoli. Autoimmune PAP (APAP) is the most frequent form of PAP, and anti-granulocyte-macrophage colony-stimulating factor (GM-CSF) antibody is associated with its pathogenesis (1). A common computed tomography (CT) feature of PAP is a smoothly thickened septal line pattern on a background of widespread ground-glass opacities (GGOs) in the bilateral lungs, termed the “crazy-paving” pattern (2, 3). Although asymmetric or patchy patterns have also been reported, a disease extent limited to the unilateral lung occurs in only 1% of PAP cases (4, 5). Patients with PAP are vulnerable to infections, and approximately 5% of patients with APAP present with opportunistic infections. Lung infections with unusual microbial pathogens, such as *Aspergillus*, *Mycobacteria*, and *Nocardia*, have also been re-

ported (6).

Although APAP is an autoimmune disorder, only a few cases complicated with other autoimmune diseases have been reported (7). We herein report a case of polymyositis (PM)-related interstitial lung disease (PM-ILD) involving the development of unilateral APAP during immunosuppressive treatment.

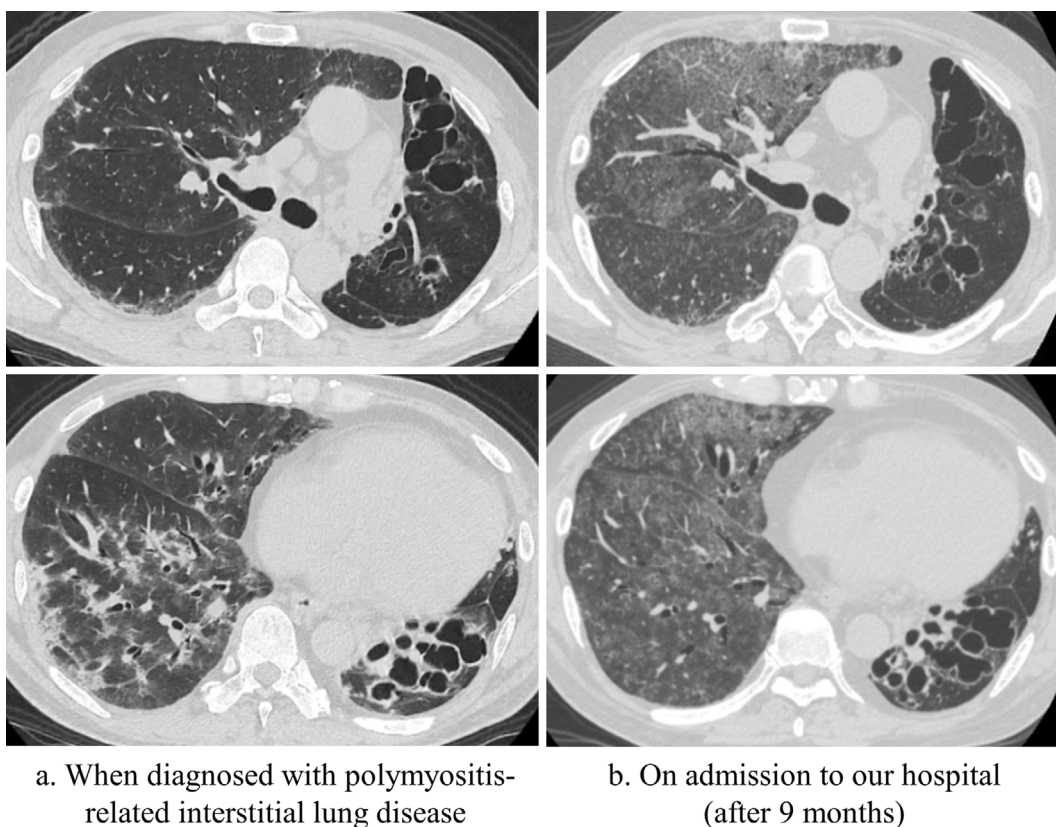
### Case Report

A 61-year-old man with a medical history of left bronchiectasis due to severe pneumonia in his childhood and a smoking history of 21 pack-years developed a persistent fever and myalgia in both lower limbs 9 months before admission to our hospital. Since laboratory data showed the elevation of serum creatine phosphokinase (700 U/L) and positive results for anti-aminoacyl-tRNA synthetase (ARS) antibody (index 139.0), his condition met the diagnostic criteria of PM established by the Ministry of Health, Labour and Wel-

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**Figure 1.** a: Chest computed tomography revealed lower lung-predominant peribronchovascular ground-glass or reticular opacities in the right lung when the patient was diagnosed with polymyositis-related interstitial lung disease. Cystic bronchiectasis and thickened bronchial wall were observed in the left lung. b: On admission to our hospital, thickened reticular lines superimposed on areas of ground-glass opacities appeared only in the right lung.

fare's Autoimmune Disease Research Group of Japan. In addition, his serum Krebs von den Lungen-6 (KL-6) level was increased (1,860 U/mL), and chest CT revealed lower lung-predominant peribronchovascular ground-glass or reticular opacities in the right lung (Fig. 1a). Thus, he was diagnosed with PM-ILD and started taking daily oral corticosteroids, tacrolimus, and monthly intravenous cyclophosphamide therapy (IVCY) for five courses.

However, three months prior to admission, chest CT revealed new GGOs in the right lung. Since serum anti-*Aspergillus fumigatus* antibody was positive, he was clinically diagnosed with chronic pulmonary aspergillosis and started on antifungal therapy. Despite treatment, his dyspnea on exertion worsened, and the GGOs expanded. A pulmonary function test showed restrictive ventilatory defects with a low diffusing capacity (Table 1). Bronchoalveolar lavage (BAL) was performed three weeks prior to admission, and he was diagnosed with APAP based on the pathological findings of BAL fluid and a positive result for serum anti-GM-CSF antibody (31.8 U/mL). The main cell type was macrophages (Table 1). He was subsequently referred to our center.

A physical examination revealed a height of 171.8 cm, body weight of 66.8 kg, blood pressure of 136/91 mmHg, pulse rate of 93 beats/min, body temperature of 36.5°C, res-

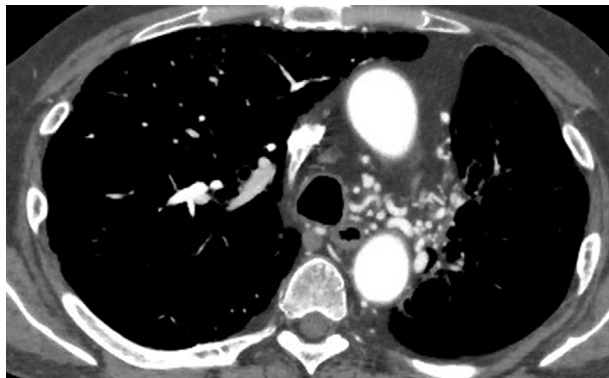
piratory rate of 18/min, and percutaneous oxygen saturation of 94% at rest ( $O_2$  2 L/min, nasal administration). He required a reservoir mask at 15 L/min on exertion. Fine crackles were heard in the right lower lung on inhalation, while no skin lesions or muscle weakness was observed. Laboratory data showed elevation of lactate dehydrogenase (594 U/L), KL-6 (4,470 U/mL) and surfactant protein D (841.5 ng/mL), while blood eosinophils (34/ $\mu$ L), serum creatine kinase (68 U/L) and C-reactive protein (0.05 mg/dL) were within the normal ranges. Immunoblotting was positive for serum anti-glycyl tRNA synthetase (EJ) antibody and anti-SS-A/Ro-52 antibody using EUROLINE. An arterial blood gas analysis showed a partial pressure of oxygen of 49.5 Torr on ambient room air (Table 1); the disease severity score of APAP was 5 (7).

Chest CT revealed thickened reticular lines superimposed on areas of GGO only in the right lung (Fig. 1b). Enhanced CT revealed left bronchial artery hyperplasia in the left bronchiectatic lung (Fig. 2). He had several instances of small amounts of bloody sputum before developing PM-ILD. Before treatment for APAP, bronchial artery embolization (BAE) was performed twice to reduce the risk of severe hemoptysis. We subsequently performed whole-lung lavage (WLL) of the right lung assisted by veno-venous extracorporeal membrane oxygenation (VV-ECMO) and biphasic cui-

**Table 1. Laboratory Data before Whole-lung Lavage.**

<b>Pulmonary function test</b>		
VC (% of predicted value)	2.61 L	(72.9)
FVC (% of predicted value)	2.58 L	(72.1)
FEV <sub>1</sub> (% of predicted value)	2.00 L	(69.0)
FEV <sub>1</sub> /FVC	77.5 %	
DL <sub>CO</sub> (% of predicted value)	7.44 mL/min/mmHg	(37.4)
DL <sub>CO</sub> /VA (% of predicted value)	2.60 mL/min/mmHg/L	(55.7)
<b>Bronchoalveolar lavage fluid (right middle lobe bronchus)</b>		
Collection rate	33 %	
Total cells	17.3×10 <sup>5</sup> /mL	
Percent of total cells (%)		
Macrophages	81 %	
Lymphocytes	12.5 %	
Neutrophils	3.5 %	
Eosinophils	3.0 %	
CD4/CD8 rate	1.26	
<b>Arterial blood gas analysis (ambient room air)</b>		
pH	7.43	
PCO <sub>2</sub>	32.1 Torr	
PO <sub>2</sub>	49.5 Torr	
HCO <sub>3</sub> <sup>-</sup>	20.7 mmol/L	

DL<sub>CO</sub>: diffusing capacity of the lung for carbon monoxide, FEV<sub>1</sub>: forced expiratory volume in one second, FVC: forced vital capacity, PCO<sub>2</sub>: partial pressure of carbon dioxide, PO<sub>2</sub>: partial pressure of oxygen, VA: alveolar volume, VC: vital capacity



**Figure 2. Enhanced computed tomography of the chest revealed left bronchial artery hyperplasia.**

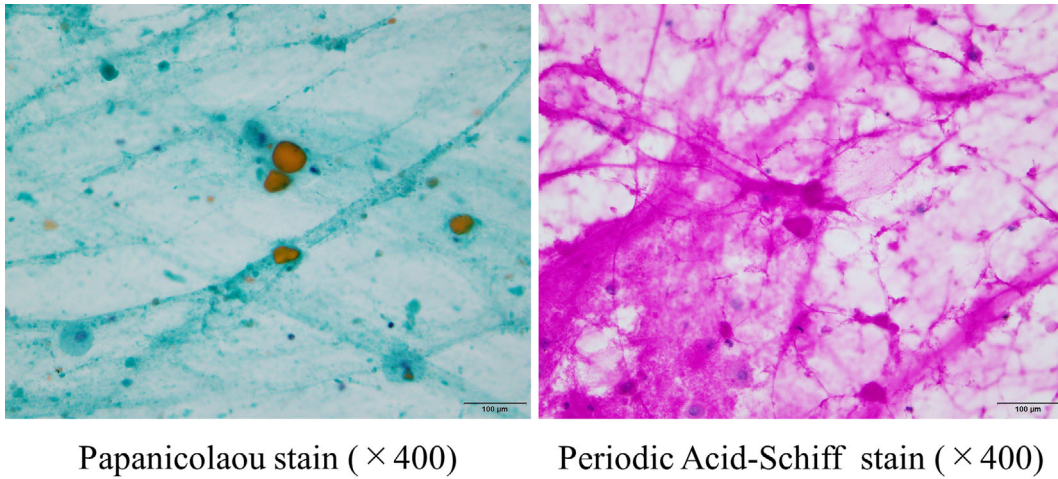
rass ventilator (RTX<sup>®</sup>, IMI, Koshigaya, Japan). The right lung was rinsed with a total of 16,840 mL of warm saline, and 15,090 mL was collected (implying 1,750 mL was absorbed). The fluid appeared cloudy, and eosinophilic globules, stained positively with periodic acid-Schiff, were observed in a Papanicolaou-stained smear (Fig. 3). *Aspergillus* species and *Mycobacterium avium* were isolated from WLL specimens. The patient continued taking voriconazole, and observation without medication was conducted for *M. avium* infection. After WWL along with prednisolone (PSL) attenuation, the CT findings significantly improved (Fig. 4, 5). He was discharged from the hospital under oxygen therapy (1 L/min, at rest; 5 L/min, on exertion). No recurrence oc-

curred in the following six months.

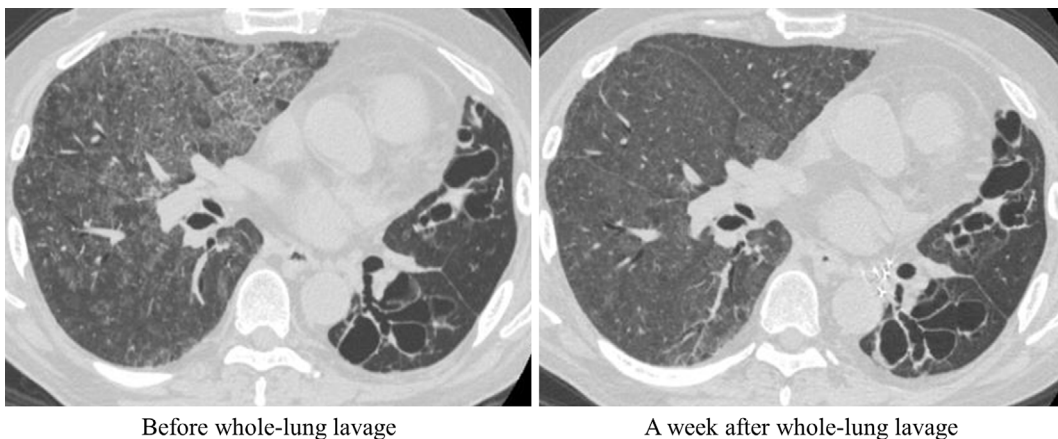
## Discussion

We herein report a rare case of unilateral APAP that developed during immunosuppressive treatment for PM-ILD. Despite treatment for PM-ILD, new GGOs were observed in the right lung on chest CT. The BAL fluid findings and the positive serum anti-GM-CSF antibody result led to a diagnosis of APAP. He was also complicated with cystic bronchiectasis and bronchial artery hyperplasia in the left lung. Thus, BAE was performed to prevent severe hemoptysis before WLL in the right lung, assisted by VV-ECMO. *Aspergillus* species and *M. avium* were isolated from the WLL fluid. After WLL, in addition to PSL attenuation and antifungal therapy, the APAP and infection were well controlled.

Despite being the most frequent form of PAP, APAP is relatively rare, with incident estimates of 0.49 cases per million people in Japan (7). Most patients with PAP present with exertional dyspnea of insidious onset, with or without nonspecific respiratory symptoms (2). Diffuse GGO with superimposed interlobular septal thickening and intralobular lines on chest CT scan, called a “crazy-paving pattern,” is a well-known feature of PAP (2). However, it is not a specific finding, and the diseases underlying a “crazy-paving pattern” are varied, including nonspecific interstitial pneumonitis, organizing pneumonia, and pneumocystis pneumonia (8). Since treatments for ILD and PAP are incompatible, an ac-



**Figure 3.** Cytological findings of the whole-lung lavage fluid revealed eosinophilic globules in the Papanicolaou-stained smear ( $\times 400$ ). Globules stained positive with Periodic Acid-Schiff were also observed ( $\times 400$ ).



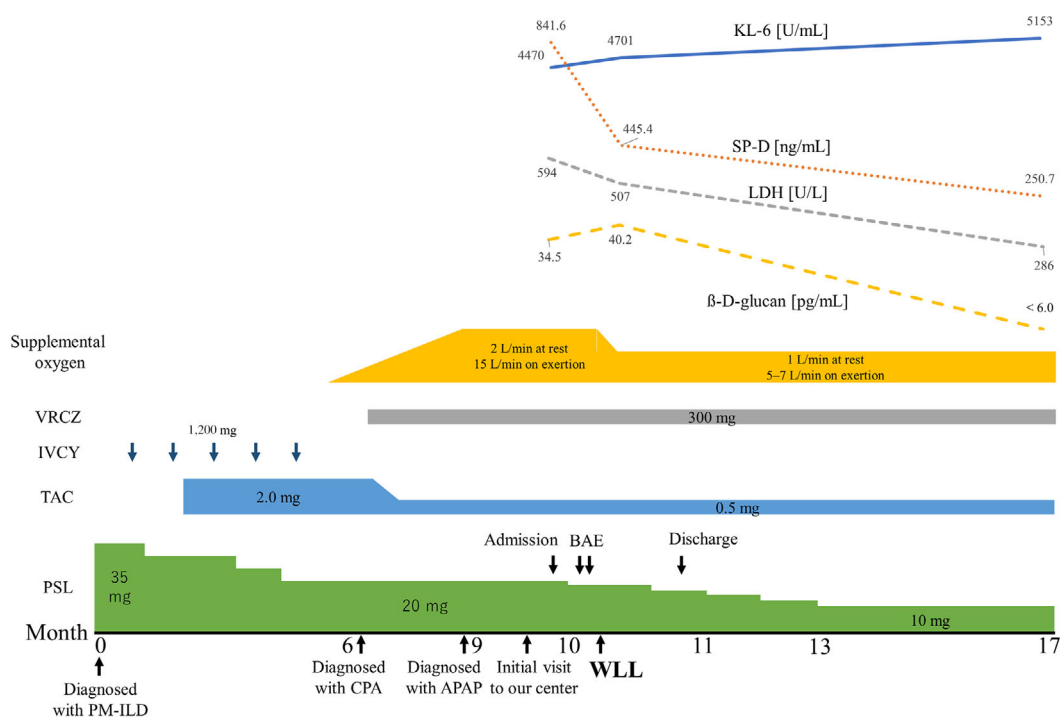
**Figure 4.** The reticular lines with ground-glass opacities, which had been observed on chest computed tomography on admission, improved a week after whole-lung lavage in the right lung.

curate diagnosis is important. A previous single-center retrospective cohort study showed that the incidence of acute exacerbation was approximately 6% per year in patients with connective tissue disease-related ILD (9). A small retrospective study further suggested that acute exacerbation of dermatomyositis (DM)-related interstitial lung disease showed a relatively slow onset (10). Thus, differentiating PAP from acute exacerbation of ILD was difficult in the present case. Although acute exacerbation of ILD was often accompanied by deterioration of extrapulmonary symptoms, there was no muscle weakness in the present case. The final diagnosis of PAP was made from the findings of the BAL fluid.

PAP lesions appeared only in the right lung in the present case. This is a prominent feature of this case, since a unilateral disease extent is observed in only 1% of PAP cases (4, 5). The detailed mechanism underlying unilateral PAP remains unclear; however, we considered the possibility that the cystic bronchiectasis might have prevented the left lung from developing APAP. A review suggested that significant respiratory infection in childhood prevents lung devel-

opment and promotes persistent infection, which causes bronchiectasis (11). The dysfunction of type II pneumocytes, which are a part of the lung structure producing surfactant protein, may have allowed the left lung to avoid developing APAP. In addition, circulatory insufficiency of the left lung may have been associated with the pathogenesis of unilateral APAP. A study using a ventilation/perfusion lung scan and pulmonary angiography in 17 patients with bronchiectasis showed that perfusion was hardly maintained in cases of cystic bronchiectasis but was preserved in cylindrical bronchiectasis (12).

Although WLL is yet to be fully evaluated in a prospective study, it is the gold-standard therapy for PAP. The indications for WLL vary among centers but include a decline in the respiratory condition and radiographic worsening (13). In the present case, the patient developed respiratory failure, but there were no PAP lesions in the left lung. Thus, WLL was considered for only the right lung. Because one-lung ventilation was difficult due to cystic bronchiectasis in the left lung, we performed WLL assisted by VV-ECMO. VV-



**Figure 5.** Clinical course of the patient after being diagnosed with polymyositis-related interstitial lung disease. APAP: autoimmune pulmonary alveolar proteinosis, BAE: bronchial artery embolization, CPA: chronic pulmonary aspergillosis, IVCY: intravenous cyclophosphamide, KL-6: Krebs von den Lungen-6, LDH: lactate dehydrogenase, PM-ILD: polymyositis-related interstitial lung disease, PSL: prednisolone, SP-D: surfactant protein D, TAC: tacrolimus, VRCZ: voriconazole, WLL: whole-lung lavage

**Table 2.** Characteristics of Three Cases of APAP Complicated with PM/DM.

	Case 1 <sup>[17]</sup>	Case 2 <sup>[18]</sup>	Our case
Gender	Female	Female	Male
Age at APAP diagnosis	58	52	61
PM/DM	DM	PM	PM
Myositis-specific autoantibodies	ARS	ARS	ARS
Types of anti-ARS antibodies	EJ	EJ	EJ
Presence of underlying ILD	Yes	Yes	Yes
Treatment for PM/DM	PSL+CyA+IVCY	PSL+CyA	PSL+TAC+IVCY
Duration of the treatments	3.5 years	15 years	9 months
Serum levels of anti-GM-CSF antibody at APAP diagnosis	1.8 U/mL	80.1 U/mL	31.8 U/mL
Treatments for APAP	PSL attenuation	PSL attenuation and WLL	PSL attenuation and WLL

APAP: autoimmune pulmonary alveolar proteinosis, ARS: aminoacyl tRNA synthetase, CyA: cyclosporine, DM: dermatomyositis, EJ: glycyl tRNA synthetase, GM-CSF: granulocyte-macrophage colony-stimulating factor, ILD: interstitial lung diseases, IVCY: intravenous cyclophosphamide, PM: polymyositis, PSL: prednisolone, TAC: tacrolimus, WLL: whole-lung lavage

ECMO requires anticoagulation, and massive hemoptysis is a rare but possible complication, with a reported frequency of 2.5% (14). The patient had a relatively high risk of massive hemoptysis due to hyperplasia of the left bronchial artery, as observed on enhanced chest CT, and several previous instances of small amounts of bloody sputum. BAE was performed before WLL, and WLL was successfully completed without any complications.

Patients with PAP are vulnerable to pulmonary infection, and approximately 5% of PAP patients also present with op-

portunistic infections (6). Lung infections with unusual microbial pathogens, such as *Aspergillus*, *Mycobacteria*, and *Nocardia*, have also been reported (15). In the present case, *Aspergillus* species and *Mycobacterium avium* were isolated from WLL fluid. In addition to PAP, immunosuppressive therapy for PM-ILD and left bronchiectasis also led the patient to become vulnerable to respiratory infection. After WLL in the right lung, voriconazole was continued for the treatment of aspergillosis. The patient's infection was well-controlled in the following six months.

In the present case, APAP was complicated with PM-ILD under immunosuppressive therapy. APAP accompanied by other autoimmune diseases is very rare, with one review showing that only 1.7% of PAP patients had co-existing autoimmune disorders or positive autoimmune serology (16). Only two cases of APAP with PM/DM have been reported. The two previously reported cases and our case of APAP complicated with PM/DM are reviewed in Table 2 (17, 18). All three patients developed APAP during immunosuppressive treatment for PM/DM. A retrospective study revealed that corticosteroid therapy worsened PAP in a dose-dependent manner (19). Thus, immunosuppressive therapies may have caused APAP in these cases. In both Case 1 and our case, the time between the initiation of treatment for PM/DM and the development of APAP was shorter than that in Case 2. It is also possible that stronger immunosuppressive therapy, including IVCY, contributed to the early development of APAP.

Interestingly, in all the three cases, serum anti-EJ antibody was positive. Anti-EJ antibody is an anti-ARS antibody, and it accounts for <5% of PM/DM cases (20). ILD and muscle weakness, but not skin involvement, are common clinical features in patients positive for anti-EJ antibody (21). ILD responds well to immunosuppressive treatment but often relapses (22). Whether or not patients with anti-EJ antibody are more likely to develop APAP than those with other anti-ARS antibodies remains unclear. However, it is notable that all three cases of APAP complicated with PM/DM were positive for anti-EJ antibody.

## Conclusions

We herein report a case of unilateral APAP accompanied by PM-ILD. After prophylactic BAE, WLL in the right lung was performed using VV-ECMO. After WLL in addition to PSL attenuation, APAP was well-controlled. Three reported cases of APAP with PM/DM-ILD, including the present case, were all positive for anti-EJ antibody and were under immunosuppressive treatment.

**The authors state that they have no Conflict of Interest (COI).**

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