

[CASE REPORT]

Pulmonary Alveolar Proteinosis with Severe Respiratory Failure Improved by Segmental Lung Lavage with Fiberoptic Bronchoscopy under General Anesthesia

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Abstract:

Pulmonary alveolar proteinosis (PAP) is a rare disorder in which lipoproteinaceous materials accumulate in the alveolar compartments. A 72-year-old man was diagnosed with autoimmune PAP with severe respiratory failure. We decided to perform segmental lung lavage (SLL) with fiberoptic bronchoscopy under general anesthesia. If improvement was not significant, whole-lung lavage (WLL) would be done. SLL improved the respiratory failure and computed tomography findings. This case showed improvement in not only the area where lavage was done but also the non-lavaged area. SLL with fiberoptic bronchoscopy under general anesthesia might be an appropriate treatment option for patients with severe PAP.

Key words: pulmonary alveolar proteinosis, segmental lung lavage, fiberoptic bronchoscopy

(Intern Med 61: 389-393, 2022)

(DOI: 10.2169/internalmedicine.7432-21)

Introduction

Pulmonary alveolar proteinosis (PAP) is a rare disease in which lipoproteinaceous materials accumulate in the terminal bronchioles and alveolar compartments (1). PAP can be classified as congenital or acquired. Acquired PAP is further classified as secondary PAP or autoimmune PAP. Secondary PAP includes patients with underlying disorders, such as dust exposure, infection, and hematological malignancies (2, 3). In contrast, patients with autoimmune PAP have autoantibodies against granulocyte-macrophage colony-stimulating factor (GM-CSF) that are detected in the serum or bronchoalveolar lavage fluid (2). Approximately 90% of

patients with PAP have autoimmune PAP (4).

Patients with PAP exhibit symptoms such as cough and dyspnea and show typical high-resolution computed tomography (HRCT) findings, such as ground-glass opacities and a crazy-paving appearance (2, 5, 6). Pulmonary function tests show a mild restrictive ventilatory defect and reduced diffusion capacity of CO (DL_{CO}), even in cases with modest impairment of the vital capacity (2). The bronchoalveolar lavage fluid (BALF) of patients with PAP can be opaque, milky, and with an increased number of lymphocytes. Furthermore, the accumulated lipoproteins are positive on periodic acid-Schiff staining (2). These BALF findings can be used to establish the diagnosis of PAP (2).

The standard treatment for PAP is whole-lung lavage

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Received: February 26, 2021; Accepted: June 13, 2021; Advance Publication by J-STAGE: August 6, 2021

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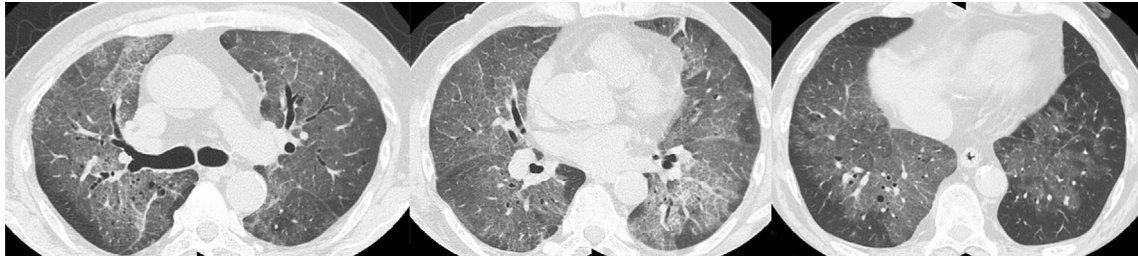


Figure 1. Computed tomography on the day before segmental lung lavage. Diffuse bilateral ground-glass opacities and a crazy-paving appearance were identified.

(WLL), which is performed to remove accumulated lipoproteinaceous materials in the alveolar compartment, resulting in the improvement of clinical, physiological, and radiographic findings (2). However, WLL can exacerbate hypoxemia due to the large volume of saline administered to the whole lungs. Therefore, patients with severe hypoxia need extracorporeal membrane oxygenation (ECMO) to maintain adequate oxygenation. However, ECMO is invasive, labor-intensive, and associated with increased morbidity (7).

Several previous reports have shown that segmental lung lavage (SLL) with fiberoptic bronchoscopy was able to remove accumulated lipoproteinaceous materials in patients with respiratory failure due to PAP (8-13). In addition, there has been only one case of SLL performed in PAP patients with severe respiratory failure under general anesthesia (13).

We herein report the second case wherein SLL with fiberoptic bronchoscopy improved respiratory failure under general anesthesia in a patient with extremely severe hypoxemia. Furthermore, this case also showed the first unique course of improvement in not only the lavaged area but also the non-lavaged area of the patient's lungs.

Case Report

A 72-year-old man presented to the hospital with an abnormal shadow on a chest radiograph and no other symptoms in November 2018. He had a 45-pack-year history of smoking and hypertension. He had never been exposed to occupational dust. CT revealed localized ground-glass opacities in the middle lobe of the right lung and the inferior lobe of the left lung. Therefore, the patient was observed without any further examination or treatment.

After five months, he developed progressive dyspnea, and CT showed an increase in abnormal chest shadows in the whole lung. Bronchoscopy was performed, and the BALF at the medial segment of the right lung (Segment V) revealed a milky turbid appearance. In addition, the serum anti-GM-CSF antibody test result was positive. Based on these findings, the patient was diagnosed with autoimmune PAP.

Due to his progressive exertional dyspnea and worsening CT findings, he was admitted to the hospital in July 2019. Upon admission, a physical examination revealed a respiratory rate of 20/min and oxygen saturation of 93% on 7 L/min of O₂ by nasal prong, with clear breath sounds. Labora-

tory findings showed an elevated lactate dehydrogenase (LDH) level of 404 IU/L and a KL-6 level of 7,936 U/mL. The arterial blood gas analysis findings on room air were as follows: pH 7.451, PaCO₂ 35.6 torr, PaO₂ 47.0 torr, HCO₃ 24.4 mEq/L, and SaO₂ 83.3%. CT showed a crazy-paving appearance with diffuse bilateral ground-glass opacities (Fig. 1). Spirometry findings and the lung volume were normal. However, the DL_{CO} was decreased (36.2% of the predicted value).

Due to severe hypoxia, ECMO was required in order to perform WLL. Therefore, prior to these invasive treatments, we decided to perform SLL with fiberoptic bronchoscopy. If improvement was not significant following SLL, then WLL would be performed. Before this decision, the patient was informed that WLL was the standard treatment and apprised of the advantages and disadvantages of SLL, and we obtained his written informed consent.

We performed SLL with endotracheal intubation and mechanical ventilation under general anesthesia. SLL was done in the superior and inferior lingular segment (Segment IV and V) of the left lung (Fig. 2A). A total of 1,250 mL saline solution was instilled via a syringe in 50-ml aliquots into each segment, and then 852 mL of fluids was suctioned out. Lavage was deemed to have been completed in each segment when the returned fluid became clear (Fig. 2C). Before this procedure, the tidal volume was 500 mL with pressure control ventilation [positive end-expiratory pressure (PEEP), 10 cmH₂O; inspiratory pressure (above PEEP), 20 cmH₂O]. However, the tidal volume decreased to 350 mL when the bronchoscope was inserted into the main carina and decreased even further to 150-200 mL with lung lavage. In addition, a blood gas analysis showed respiratory acidemia (PaCO₂ 69 mmHg, pH 7.21). We therefore had to discontinue SLL temporarily.

Two days later, SLL was resumed in the anterior segment of the right lung (Segment III) (Fig. 2B). A total of 1,000 mL saline solution was instilled, and 780 mL of fluids was suctioned out. During this procedure, SLL was discontinued once due to low tidal volume and acidemia, similar to what happened during the first SLL procedure. On the first day after the second SLL procedure, the PaO₂/F_iO₂ ratio improved from 224 at admission to 300. Chest X-ray showed improvement in the bilateral lower lung fields. Therefore, the patient was extubated and switched to a high-flow nasal

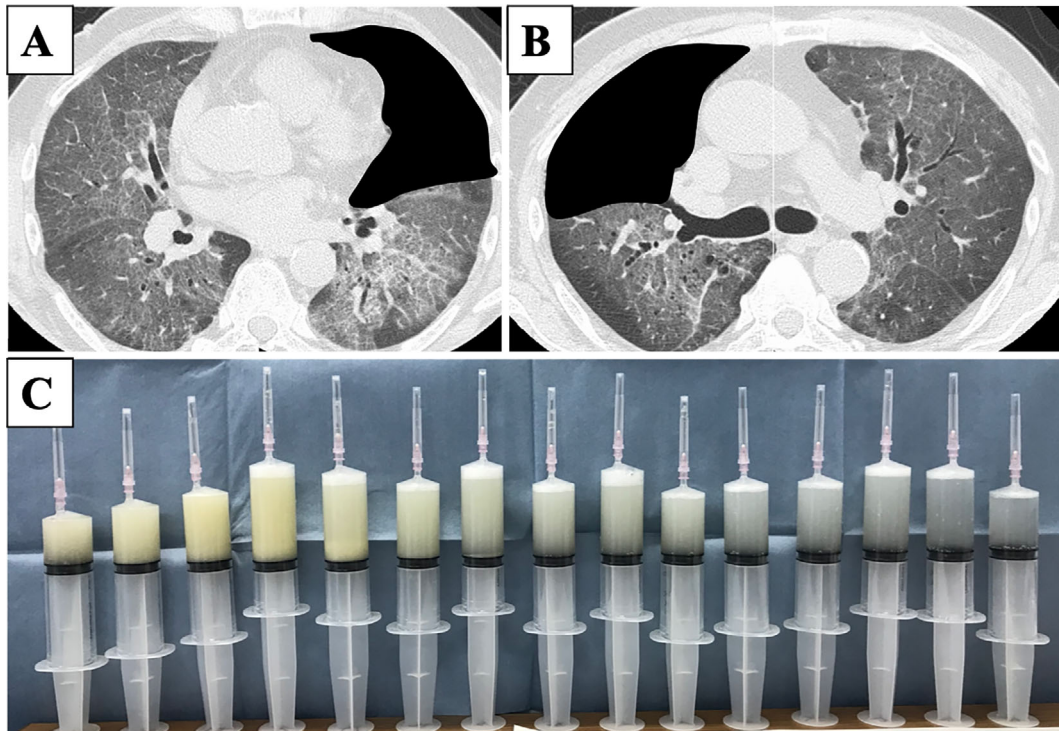


Figure 2. (A) First SLL at segment IV and V of the left lung (black area). (B) Second SLL at segment III of the right lung (black area). (C) Appearance of bronchoalveolar lavage fluid at the superior lingular segment (Segment IV) of the left lung. The turbidity of the lavage recovery solution gradually improved.

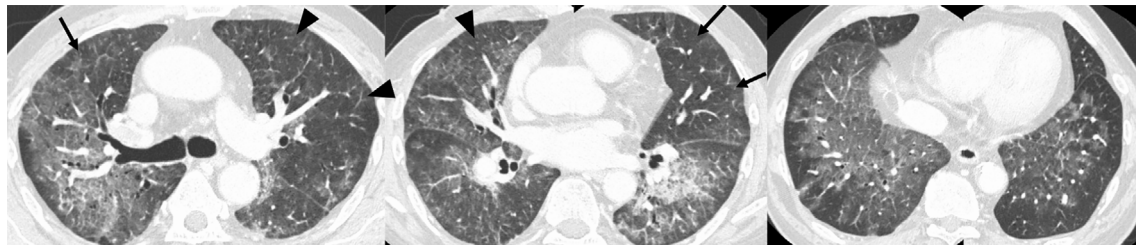


Figure 3. Contrast-enhanced computed tomography after the second SLL. Partial improvement of ground-glass opacities in the lavaged areas (arrows) and non-lavaged areas of the entire upper lobe of the left lung (arrowheads) and part of the middle lobe of the right lung (arrowhead) was seen.

cannula.

On day 8 after the second SLL, CT showed improvement of interstitial shadows in not only the lavaged area but also the non-lavaged areas of the entire upper lobe of the left lung and part of the upper and middle lobes of the right lung. CT was performed using contrast agent since the purpose of the scan was to search for pulmonary embolism due to the elevation of the D-dimer level (Fig. 3). On day 17, his oxygen saturation was 94% on 1 L/min of O₂, and he was subsequently discharged from the hospital. Two months after SLL, the DL_{CO} improved (from 36.1% to 46.9%), and CT showed further improvement (Fig. 4). The patient had no symptoms, and the PAP lesion did not develop for 17 months despite no additional treatment.

Discussion

We encountered a second case of autoimmune PAP with extremely severe hypoxemia where SLL with fiberoptic bronchoscopy improved respiratory failure and CT findings under general anesthesia without WLL. In addition, this case presented a unique course; the radiological findings of PAP improved in not only the lavaged area but also the non-lavaged area.

To date, the standard treatment for PAP has been WLL. However, this procedure requires one-lung ventilation using general anesthesia, and a large amount of lavage fluid must be injected. Since part of the lavage fluid remains in the lungs, this may result in exacerbation of hypoxemia and changes in hemodynamics (14). Therefore, in cases of se-

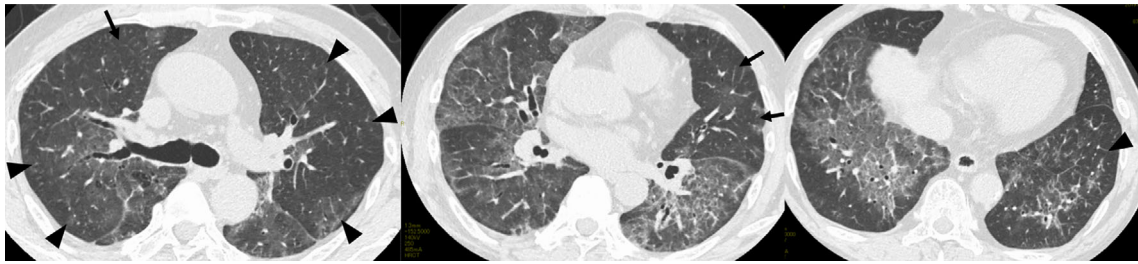


Figure 4. Computed tomography two months after SLL. The interstitial shadows in the lavaged areas (arrows) and non-lavaged areas including part of the lower lobe of the left lung (arrowheads) were improved.

vere respiratory failure, careful respiratory and circulatory management using ECMO is required. In contrast, SLL under general anesthesia is less invasive than WLL. Thus, SLL may be an appropriate treatment method for patients with severe PAP prior to WLL. However, from the perspective of respiratory management, WLL under ECMO may be superior to SLL under general anesthesia. Therefore, informed consent should be obtained from the patient before deciding on these treatments.

We conducted multiple searches on different platforms and databases, including PubMed and Google Scholar, and found six previous reports on the effectiveness of SLL for PAP patients (8-13). However, there was only 1 case of SLL performed in a PAP patient with severe respiratory failure ($\text{PaO}_2 < 50$ mmHg) under general anesthesia. Therefore, this case is the second case of successful SLL in a patient with severe PAP.

This is the first case to show improvement on the interstitial shadows in not only the lavaged area but also the non-lavaged area after SLL, as seen on CT. The following mechanism can be considered to underlie the improvement in the non-lavaged areas after SLL: autoimmune PAP is caused by the inhibition of macrophage maturation due to the disruption of GM-CSF signaling by anti-GM-CSF antibody, which reduces the ability to remove surfactant from macrophages (2). SLL decreases the total amount of accumulated surfactant and anti-GM-CSF antibody in the lungs, resulting in the promotion of macrophage maturation in the lavage area. A previous study showed that bone marrow-derived monocytes are recruited to the lung when alveolar macrophages are damaged by stimulation, such as infection, and these monocytes differentiate into alveolar macrophages (15, 16). We therefore hypothesized that the change in macrophage status after SLL would promote an increase in bone marrow-derived macrophages with a normal function in the lungs. As a result of these events, the surfactant processing capacity of macrophages exceeds the production of surfactant, resulting in the improvement of abnormal shadows in the non-lavaged area. However, in the long-term follow-up, a re-increase in anti-GM-CSF antibody may inhibit macrophage maturation and cause a relapse of the disease. Separately, another mechanism is considered to underlie the improvement in the non-lavaged areas in this case.

Previous studies have shown an acquired clonal disorder of hematopoietic progenitor cells in patients with autoimmune PAP (17). Displacement of this abnormal clone from the hematopoietic cells would lead to an improvement in PAP in both lavaged and non-lavaged areas. Further studies will be required to confirm these mechanisms.

The standard procedure for SLL has not yet been established. For one, the amount of saline used for SLL may vary among patients. We propose that lavage with 50 mL of normal saline be repeated until turbidity clears up in the lavage recovery solution, as shown in Fig. 2C. In our case, SLL was performed under intubation for approximately one hour. Therefore, we suggest the use of a wide intubation tube to maintain the tidal volume during SLL. Bronchoscopy reduces the area of the intubation tube and results in reduced tidal volume. In fact, in the present patient, a slightly larger tube was used (bronchoscopy size: 5.9 mm, endotracheal tube size: 8.5 mm). Nevertheless, the tidal volume decreased from 500 mL to 150-200 mL, and the blood gas analysis showed respiratory acidemia. We recommend a larger number of cases be evaluated in future studies to establish the standard method of SLL.

A nasal high-flow system is superior to endotracheal intubation and mechanical ventilation, as it does not reduce the tidal volume during SLL. However, it was expected that a nasal high-flow system would not be sufficient to maintain oxygenation in our case, due to the remaining saline administered for washing. Therefore, we chose SLL with endotracheal intubation and mechanical ventilation to maintain oxygenation using PEEP, resulting in a decrease in the remaining saline in the lungs.

PAP was remarkably improved after SLL in our case. However, it should be noted that autoimmune PAP has been reported to improve spontaneously in about 30% of cases (18). In this case as well, especially in the non-lavaged area, PAP may have spontaneously improved regardless of SLL. However, the disease showed a remarkable improvement on day 17 after SLL was performed, suggesting the influence of SLL rather than spontaneous improvement. However, further studies will be needed to prospectively investigate whether or not SLL is effective for severe PAP patients.

Conclusion

In the present report, we showed that SLL using fiberoptic bronchoscopy under general anesthesia improved severe respiratory failure without performing WLL and ECMO in patients with PAP. In addition, the radiological findings due to PAP improved in not only the lavaged area but also the non-lavaged area in our case. Based on these observations, SLL might be an alternative treatment method to WLL, which leads to further respiratory failure in patients with severe PAP.

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

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