Int J Clin Exp Med 2015;8(10):19556-19560
www.ijcem.com /ISSN:1940-5901/IJCEM0013532

*Case Report*

# Alveolar proteinosis in extremis: a critical case treated with whole lung lavage without extracorporeal membrane oxygenation

Wen-Liang Guo*, Yu Chen*, Nan-Shan Zhong, Zhu-Quan Su, Chang-Hao Zhong, Shi-Yue Li

*Department of Respiratory Medicine, State Key Laboratory of Respiratory Disease, Guangzhou Institute of Respiratory Disease, The First Affiliated Hospital of Guangzhou Medical University, Guangzhou, China. *Equal contributors.*

Received July 27, 2015; Accepted September 28, 2015; Epub October 15, 2015; Published October 30, 2015

**Abstract:** Pulmonary alveolar proteinosis is a rare idiopathic lung disease characterized by the accumulation of lipoproteinaceous material within the alveoli, which impairs gas transfer and decreases the ventilation/perfusion ratio, and can lead to respiratory failure. Whole lung lavage is the most effective therapy for pulmonary alveolar proteinosis, but may not be tolerated by patients with severe respiratory failure. Extracorporeal membrane oxygenation support is advocated for such patients to ensure appropriate oxygenation during lung lavage. We report a case of a 39-year-old patient with pulmonary alveolar proteinosis and severe life-threatening respiratory failure, with an oxygen index of 51 when under mechanical ventilation. The patient was successfully treated with bilateral whole lung lavage without extracorporeal oxygenation. The results suggest that there is improved ventilation and perfusion matching when one lung is ventilated while the other is lavaged, may be the mechanism of which severe respiratory failure patient due to pulmonary alveolar proteinosis can complete whole lung lavage under one lung ventilation.

**Keywords:** Pulmonary alveolar proteinosis, severe respiratory failure, whole lung lavage, ventilation/perfusion, extracorporeal membrane oxygenation, treatment

## Introduction

Pulmonary alveolar proteinosis (PAP) is a syndrome arising from altered surfactant homeostasis. Pathophysiologically, the major changes involve impaired pulmonary diffusion and ventilation/perfusion mismatch, which may result in respiratory failure [1]. Whole lung lavage (WLL) is considered the standard treatment for progressive PAP leading to respiratory compromise [2]. In very rare cases where the patient has developed critical respiratory failure and cannot tolerate single-lung ventilation, extracorporeal membrane oxygenation (ECMO) may be required to facilitate WLL [2, 3]. However, our experience with WLL over the past 15 years suggests that oxygen saturation may be improved rather than significantly reduced during lavage. This may bring up a question whether ECMO or hyperbaric conditions are always essential for WLL in PAP patients with critical respiratory failure. We present a life-threatening case of PAP requiring mechanical ventilation in which the patient was successfully managed by bilateral WLL under single lung ventilation alone. ECMO was nevertheless set up beforehand.

## Case description

A 39-year-old man complained of worsening dyspnea over the past one year. He had a > 10-year history of cigarette smoking (20/day) and worked as a cementer during the past 3 years. In April 2011 he was referred to Beijing Hospital with shortness of breath. Open-lung biopsy demonstrated pulmonary alveolar proteinosis and culture of sputum showed growth of Marseille mycobacterium. He was treated with ethambutol, minocycline and azithromycin according to susceptibility testing. However, he did not improve and exacerbation of the lesions was observed on computed tomography (CT) after two months. Therefore, bilateral WLL was

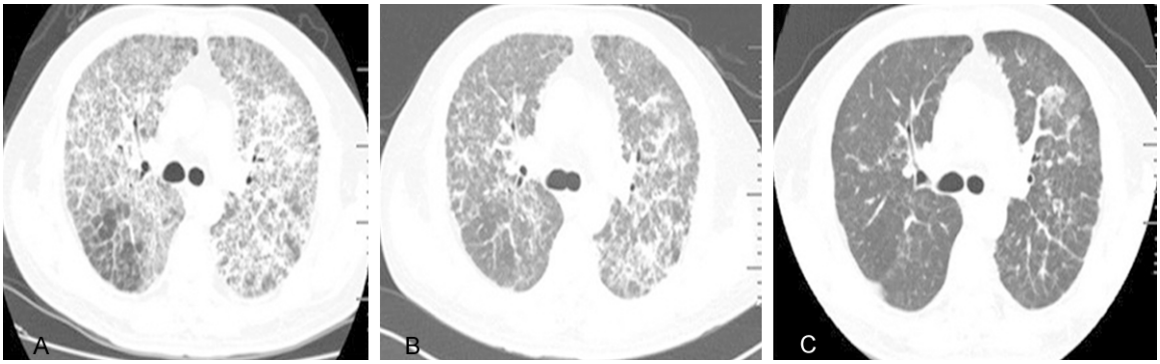


**Figure 1.** CT image on admission showing ground-glass changes, reticular pattern, and geographic distribution (A). CT images at matched anatomic levels two weeks (B) and one month (C) after whole-lung lavage demonstrate significant improvement.

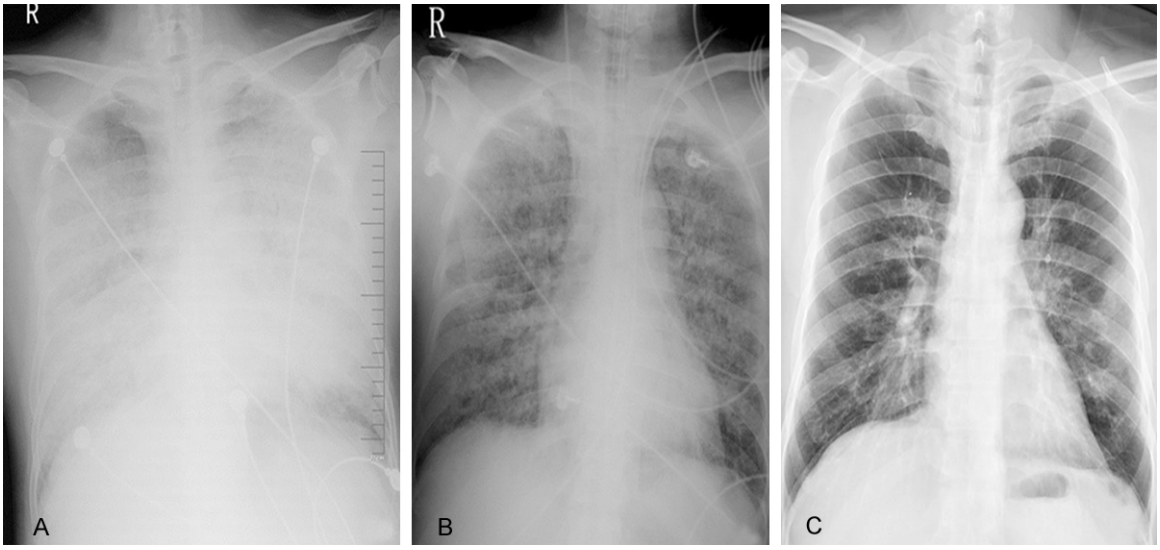


**Figure 2.** Chest X-ray on admission (A). Chest X-ray one month (B) and 29 months (C) after whole-lung lavage.

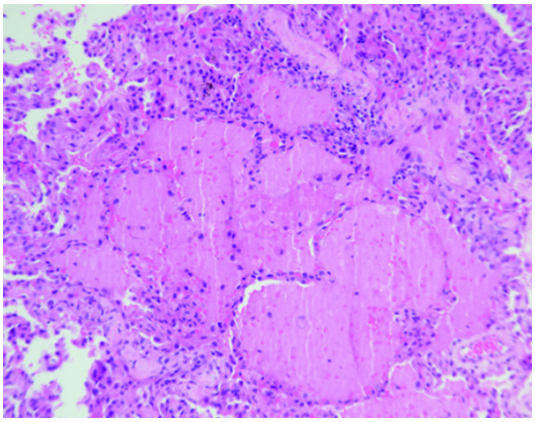

**Figure 3.** Photomicrograph of lung biopsy section (hematoxylin-eosin stain, 200×) showing preservation of alveolar architecture and filling of alveoli with lipoproteinaceous material.

performed in November, but achieved only temporary relief. The patient was subsequently referred to Shanghai Hospital in January 2012. He was treated with corticosteroid and itraconazole because of invasive pulmonary fungal infection diagnosed by G test, and subcutaneous GM-CSF for PAP. However, he still showed no improvement and was referred to our hospital on February 9. On physical examination, blood pressure was 119/65 mmHg; pulse, 108 beats per minute; respiratory rate, 24 breaths per minute at rest. Arterial blood gas analysis revealed a pH of 7.43, $PaCO_2$ of 33 mmHg, and $PaO_2$ of 52 mmHg on 8 l/min oxygen administered by rebreathing face mask. Oxygenation index was 98. White blood cell count was 15,870/μl, and hemoglobin level was 18 g/dl.

**Table 1.** Changes of oxygen saturation and vital signs during WLL*

| | $FiO_2$ | $SpO_2$ (%) | BP (mmHg) | HR (BPM) | CVP ($cmH_2O$) |
|---|---|---|---|---|---|
| Before left lung lavage (double lung ventilation) | 1 | 88 | 114/70 | 80 | 12 |
| Before left lung lavage (single lung ventilation) | 0.9 | 81 | 104/58 | 96 | 12 |
| During left lung lavage | 0.9 | 78-85 | 92-104/55-60 | 98-109 | 12-15 |
| After left lung lavage | 0.9 | 83 | 95/58 | 107 | 17 |
| Before right lung lavage (double lung ventilation) | 0.9 | 90 | 100/60 | 108 | 15 |
| Before right lung lavage (single lung ventilation) | 0.9 | 88 | 105/55 | 107 | 14 |
| During right lung lavage | 0.9 | 85-95 | 97-110/52-60 | 80-100 | 12-15 |
| After right lung lavage | 0.9 | 93 | 108/53 | 87 | 10 |

*WLL = whole-lung lavage, $FiO_2$ = fractional concentration of inspired oxygen, BP = blood pressure, HR = heart rate, BMP = bite per minute, CVP = central venous pressure.

**Table 2.** Changes of oxygen saturation and oxygen index before and after bilateral WLL*

| | Ventilation mode | $FiO_2$ (%) | $PaO_2$ (mmHg) | $SpO_2$ (%) | OI |
|---|---|---|---|---|---|
| Before WLL | Mechanical ventilation | 100 | 51 | 82 | 51 |
| One day after WLL | Mechanical ventilation | 100 | 88 | 97 | 88 |
| Four days after WLL | Noninvasive ventilation | 50 | 71 | 92 | 142 |
| One month after WLL | Nasal cannula | 33 | 87 | 96 | 264 |

*WLL = whole-lung lavage, $FiO_2$ = fractional concentration of inspired oxygen, $PaO_2$ = partial pressure of arterial oxygen, OI = oxygen index.

Concentrations of procalcitonin and D-dimer were 0.25 ng/ml and 189 ng/ml, respectively. All cultures were negative except for Pseudomonas aeruginosa. CT and radiographic images of the chest were obtained (**Figures 1A** and **2A**). The patient underwent transbronchial lung biopsy, and histological findings were typical of PAP (**Figure 3**). Under treatment with antibiotics and noninvasive ventilation, his respiratory status continued to worsen, and he was intubated and received mechanical ventilator support in the ICU on February 14. The ventilator settings were as follows: PCV mode; pressure of 22 cm $H_2O$, fractional concentration of inspiratory oxygen ($FiO_2$) of 100%, rate of 18 and positive end expiratory pressure (PEEP) of 10 mm $H_2O$. Oxygen saturation remained at 90-95%.

After multidisciplinary discussion, it was decided to perform WLL without ECMO if oxygen saturation could be maintained within the safe range under single-lung ventilation. Nevertheless, ECMO was to be prepared before the procedure to facilitate WLL if oxygen saturation fell below desirable levels. On February 17 2012, arterial blood gas analysis demonstrated a pH of 7.39, $PaCO_2$ of 43 mmHg, and $PaO_2$ of 51 mmHg on 100% $O_2$ mechanical ventilation before lavage. WLL was performed [4] using a double-lumen endobronchial tube under general anesthesia. Aliquots of warm saline (800-1000 mL) were introduced into the lung and drained by negative pressure (0.02-0.03 kpm) until the effluent was clear. The left lung received 11,600 ml of saline lavage with a return of 10,600 ml, after which it was carefully suctioned and its re-expansion was performed, initially by bilateral ventilation followed by unilateral ventilation. After 30 minutes, the tidal volume could be maintained above 300 ml under left lung ventilation, and then the contralateral WLL was initiated, repeating the procedures described above. The right lung received 14,600 ml of saline lavage with a return of 13,600 mL. The changes in oxygen saturation and vital signs during WLL are showed in **Table 1**. Bilateral WLL was successfully completed under single-lung ventilation with ECMO standby.

The post-WLL treatment continued with antibiotics and mechanical ventilation, and the patient's condition improved rapidly. Four days later, he was extubated and the mechanical ventilation was switched to noninvasive mode. His $SpO_2$ remained at 93-96% on 50% $O_2$ noninvasive ventilation, and he was transferred to the general ward. Prior to his discharge from

hospital at one month after WLL, the patient's CT and radiography revealed significant improvement in chest imaging (**Figures 1C** and **2B**). He gradually relieved in shortness of breath and could walk while breathing room air (**Table 2**). At present (29 months after the last lavage), the patient leads a normal life with good exercise tolerance. Although his radiography images show increased lung markings with discrete, scattered, patchy shadows in the both lower lobes (**Figure 2C**).

## Discussion

PAP is a rare lung disease first described by Rosen in 1958 [5]. There is no radical cure for PAP because the pathogenesis of PAP remains unclear, and WLL is the preferred technique for respiratory compromised patients [3]. WLL removes the phospholipidic material present in the alveoli, elevates diffusion capacity and offers remarkable symptom relief within a short period of time. The patient was diagnosed with PAP by histopathological examination of material from open-lung biopsy and transbronchial lung biopsies. Under treatment with antibiotics and noninvasive ventilation, neither clinical nor radiological findings improved. Furthermore, oxygenation deteriorated rapidly and mechanical ventilation was required, hence, the patient needed WLL.

Most PAP patients with relatively mild to moderate respiratory failure may undergo WLL uneventfully. Yet, for patients with severe respiratory failure who require mechanical ventilation, severe hypoxemia can be present during double-lung ventilation and would be much likely to become exacerbated and life-threatening with single-lung ventilation. Therefore, for such patients, ECMO or hyperbaric conditions may be advised to facilitate WLL [2, 3]. These two life-support methods, ECMO and hyperbaric conditions, can effectively ensure adequate oxygen saturation during WLL and make it an uncomplicated procedure. However, both methods have certain shortcomings. The major setback of hyperbaric conditions is oxygen toxicity and pneumothorax caused by barotraumas, whereas ECMO is invasive and associated with risks of bleeding, infection, thromboembolism, hemolysis and lower limb malperfusion. Furthermore, ECMO is expensive and requires technical skills and a professional team.

Nearly 80 cases of WLL have been performed for treatment of PAP in our institution. According to our previous observations, the oxygen saturation was not dramatically reduced in single-lung ventilation compared with that in the ventilation of both lungs; moreover, the oxygen saturation may show some increase after a certain duration of lung lavage with constant setting of the ventilator. We found that ventilation/perfusion could change at any time despite no change in diffusion of the ventilated lung. When the lung on one side is lavaged and the other ventilated, pulmonary vasoconstriction due to a chemoreceptor reflex in the lavaged lung, reduces perfusion of the lavaged lung and improves the ventilation/perfusion [6], which can counteract the reduction in oxygen saturation due to decreased diffusion area with single-lung ventilation. Additionally, intrapulmonic pressure increases when lavage fluid is introduced into the bronchus and alveoli, leading to pulmonary capillary contraction and shunting of pulmonary blood flow through the ventilated lung [7, 8], which also counteracts the loweringoxygen saturation. This conforms to previous studies [9, 10].

Based on the above experience and considerations, we aimed to perform WLL without ECMO if oxygen saturation could be maintained in a safe range under single-lung ventilation, otherwise ECMO could be used to facilitate WLL as it had been ready at hand. During the lavage procedure of this patient, oxygen saturation decreased at the beginning of single-lung ventilation, but not much, and oxygen saturation could be maintained in a safe range (85%-95%) throughout the procedure. In addition, the phenomenon that oxygen saturation increased (from 3% to 8%) during the filling phase and decreased during the emptying phase in this patient was consistent with our speculation described above.

Besides diffusion and the ratio of ventilation/perfusion, blood volume and cardiac function are important factors affecting oxygen saturation during WLL. During lavage, vasoconstriction, positive pressure ventilation, increased hydrostatic pressure of the lavaged lung, and lavage fluid absorption can induce fluid overload and cardiac insufficiency. Therefore, cardiac function, input and output, central venous pressure, and urinary production require close

monitoring during lavage, and diuretics and other symptomatic treatment are required when necessary. Additionally, the lavage sequence should be considered such that the more severely affected side is lavaged first to lessen the effect on oxygen saturation.

In summary, the observation in this case and many others suggests a potential treatment protocol by which a patient with severe respiratory failure due to PAP can complete bilateral WLL under single-lung ventilation without ECMO. Despite reduced diffusion area with single-lung ventilation, oxygen saturation can be maintained in a safe range through improved ventilation/perfusion during WLL. Last but not least, ECMO must be prepared beforehand.

## Disclosure of conflict of interest

None.

**Address correspondence to:** Dr. Shi-Yue Li, State Key Laboratory of Respiratory Disease, Guangzhou Institute of Respiratory Disease, The First Affiliated Hospital of Guangzhou Medical University, 151 Yanjiangxi Road, Guangzhou, Guangdong Province, China. Tel: +86-13902233925; Fax: +86-020-8306-2885; E-mail: lishiyue@188.com

## References

[1] Rogers RM, Levin DC, Gray BA, Moseley LW Jr. Physiologic effects of bronchopulmonary lavage in alveolar proteinosis. Am Rev Respir Dis 1978; 118: 255-264.

[2] Leth S, Bendstrup E, Vestergaard H, Hilberg O. Autoimmune pulmonary alveolar proteinosis: treatment options in year 2013. Respirology 2013; 18: 82-91.

[3] Luisetti M, Kadija Z, Mariani F, Rodi G, Campo I, Trapnell BC. Therapy options in pulmonary alveolar proteinosis. Ther Adv Respir Dis 2010; 4: 239-48.

[4] Michaud G, Reddy C, Ernst A. Whole-Lung Lavage for Pulmonary Alveolar Proteinosis. Chest 2009; 136: 1678-81.

[5] Rosen SH, Castleman B, Liebow AA. Pulmonary alveolar proteinosis. N Eng J Med 1958; 258: 1123-42.

[6] Gong Q, Yang Z, Wei W. The change of pulmonary blood flow in non-ventilated lung during one lung ventilation. J Clin Monit Comput 2010; 24: 407-12.

[7] Smith JD, Millen JE, Safar P, Robin ED. Intrathoracic pressure, pulmonary vascular pressures and gas exchange during pulmonary lavage. Anesthesiology 1970; 33: 401-5.

[8] Hedenstierna G. Pulmonary perfusion during anesthesia and mechanical ventilation. Minerva Anestesiol 2005; 71: 319-24.

[9] Cohen E, Eisenkraft JB. Bronchopulmonary lavage: effects of oxygenation and hemodynamics. J Cardiothorac Anesth 1990; 4: 609-15.

[10] Aquinaqa MA, Santos P, Renes E, Alvaro PF, Lorente JA, Maudes A, Diaz RR, Landin L, Liste D. Hemodynamic changes during whole bronchoalveolar lavage in two cases of pulmonary alveolar proteinosis. Intensive Care Med 1991; 17: 421-3.