

A case series of pulmonary alveolar proteinosis: Response differently to whole lung lavage

Boon Hau Ng, MMed (UKM)¹, Hsueh Jing Low, MMed (UKM)², Nik Nuratiqah Nik Abeed, MMed (UKM)¹, Mohamed Faisal Abdul Hamid, MMed (UKM)¹, Abdul Shokri Ahmad Fairuz, MMed (UKM)², Mohd Shahrir Mohamed Said, MMed (UKM)³, Andrea Ban Yu-Lin, MMed (UKM)¹

¹Respiratory Unit, Department of Internal Medicine, Pusat Perubatan Universiti Kebangsaan Malaysia, ²Department of Anaesthesiology and Critical Care, Pusat Perubatan Universiti Kebangsaan Malaysia, ³Rheumatology Unit, Department of Internal Medicine, Pusat Perubatan Universiti Kebangsaan Malaysia

SUMMARY

Pulmonary alveolar proteinosis (PAP) is a rare disease and its prognosis can be improved by whole lung lavage (WLL). Herein, we present three cases with idiopathic PAP treated successfully with either single or double WLL in the same setting. All three of them presented with exertional dyspnoea with radiographic findings of pulmonary infiltrates. They showed a marked clinical and physiologic improvement post WLL. Two of them were in remission. These three cases were diagnosed using different lung biopsy modalities, including video-assisted thoracoscopic lung biopsy, computed tomography-guided percutaneous transthoracic tru-cut needle lung biopsy, and transbronchial forceps lung biopsy (TBLB), respectively. The current cases have shown that TBLB may provide adequate diagnostic yield, and the invasive surgical lung biopsy may not be necessary to achieve a definitive diagnosis.

INTRODUCTION

PAP is caused by defective alveolar macrophages that lead to alveolar accumulation of surfactants. PAP may result from mutations in granulocyte macrophage-colony stimulating factor receptor (GS-CSF) genes, autoimmune, toxic inhalation, or haematological disorders. We report case series PAP that responded to WLL at different degrees.

CASE REPORT

Case 1

A 41-year-old female presented in February 2011 with a 3-month history of cough and progressive shortness of breath on exertion. She was treated as a bronchial asthma but did not respond to the combination of inhaled budesonide and formoterol. She had a history of recurrent pneumonia and required bilevel positive airway pressure (BiPAP) six months before the clinic review.

Physical examination, routine blood tests, and antinuclear antibodies (ANA) were normal. Oxygen saturation was 95% in room air. A chest radiograph showed bilateral pulmonary reticulation. Spirometry showed a moderate restrictive ventilatory defect with forced expiratory volume in 1 s (FEV1) equal to 1.59 L (70.4% predicted), and forced vital capacity (FVC), 1.67 L (63.4% predicted). Static lung volume measurements revealed a total lung capacity (TLC) of 1.42 L

(38.8% predicted) and residual volume of 0.16 L (14% predicted). Diffusing capacity for carbon monoxide (DLCO) was reduced at 1.06 L (18% predicted).

Contrasted chest computed tomography (CT) showed bilateral pulmonary infiltrates and thickened interlobular septa, a 'crazy paving' pattern (Figure 1A). Bronchoscopy revealed normal airways, and bronchoalveolar lavage (BAL) showed plaques of granular amphophilic in a background containing numerous bronchial lining cells, alveolar macrophages, and occasional squamous cells. Subsequent video-assisted thoracoscopic surgery (VATS) biopsy confirmed PAP.

The patient required WLL with saline solution in March 2012 (left lung 11.5L; right lung 13L), December 2012 (left lung 9L), March 2014 (left lung 13L; right lung 11L), and July 2019 (left lung 6L; right lung 6L). She had a marked ventilatory and radiological improvement after each WLL. To date, she remains asymptomatic with a stable lung function test.

Case 2

A 46-year-old female was first presented in 2010 with chronic cough and progressive dyspnoea on exertion for 12 months. She was being treated for bronchial asthma, but her symptoms were not a response to inhaled budesonide. She had two episodes of pneumonia, and she was dependent on home oxygen after the second episode of pneumonia.

Contrasted chest CT showed bilateral pulmonary infiltrates and thickened interlobular septa (Figure 1B). Bronchoalveolar lavage (BAL) revealed a milky white fluid. Microbiological analyses of BAL were negative. CT guide lung biopsy confirmed PAP. Her spirometry showed restrictive ventilatory defect with FEV1 equal to 1.35 L (48% predicted), FVC 1.37 L (42% predicted), and a normal FEV1/FVC ratio of 98%. Her TLC was 1.94 L (46.5% predicted) and DLCO 0.88 L (16% predicted). The 6 min walking distance was reduced to 294 m.

She has required eight WLL since the diagnosis of PAP, and the last WLL was in 2018. A follow-up chest radiograph and high-resolution computed tomography showed evident regression of the ground glass opacities and interlobular septal thickening. To date, she remains asymptomatic with a stable lung function test.

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Corresponding Author: Andrea Ban Yu-Lin

Email: andreaban@gmail.com

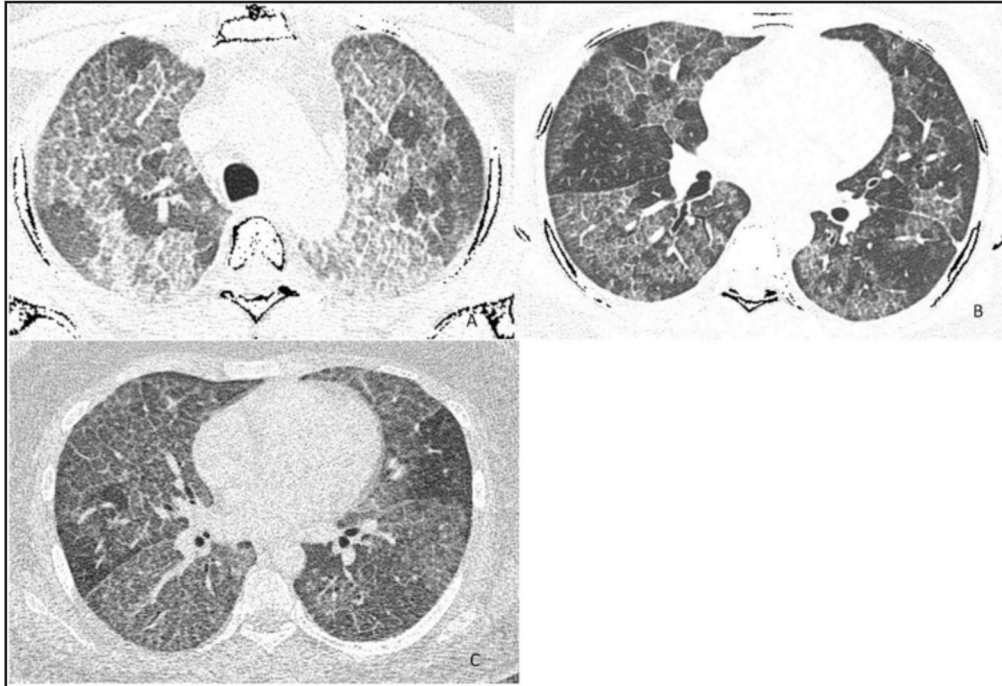


Fig. 1: Axial view CT thorax in lung window demonstrating cases of pulmonary alveolar proteinosis. (A) Case 1, (B) Case 2, (C) Case 3 with all scans showing patchy, "geographic" pattern of ground glass opacification superimposed on interlobular septal thickening in multiple lobes.

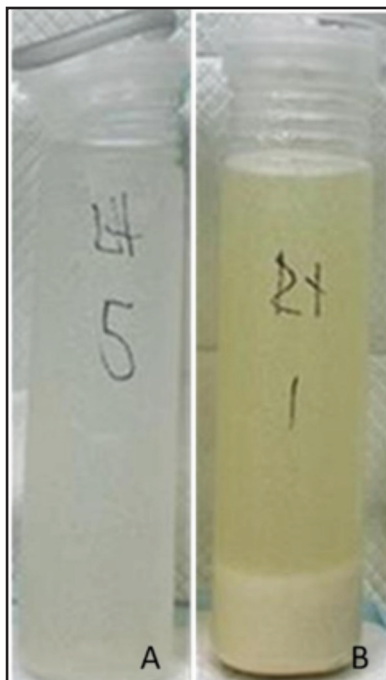


Fig. 2: Bronchoalveolar lavage specimens. (A) Normal BAL effluent. (B) Effluent obtained by WLL in pulmonary alveolar proteinosis, showing sedimentation of the proteinaceous materials at the bottom of the bottle.

Case 3

An 18-year-old girl was presented in September 2021 with intermittent cough and dyspnoea for two months with one week of fever. She was empirically treated as pulmonary

miliary tuberculosis based on clinical symptoms and chest radiograph of diffuse miliary nodules. Her dyspnoea was not improved after two weeks, and she was subjected to chest CT followed by bronchoscopy with transbronchial forceps lung biopsy (TBLB). The CT showed a bilateral crazy paving pattern (Figure 1C).

BAL showed milky effluent. The BAL for mycobacterium tuberculosis cartridge-based nucleic acid amplification test and cultures were negative. Serum ANA was positive titres of 1:160, and extracted nuclear antibody was negative. Pulmonary function test showed restrictive ventilatory defects with the ratio of 98%, FEV1 of 1.89 L (65% predicted), FVC of 1.93 L (60% predicted), and reduced DLCO of 32%.

She underwent bilateral WLL in the same settings. Following the induction of general anaesthesia, she was intubated with a double-lumen endobronchial tube. Warm (36–37°C) sterile saline (0.9% saline) was instilled from the 1 L reservoir bag for each cycle. The WLL began with the left lung and repeats until the effluent is completely clear (Figure 2 A&B). She required ten cycles of lavage on the left lung and eight cycles on the right lung. After WLL, her oxygen saturation improved from 92% to 98% in room air. Repeated spirometry at one week showed improvements in FVC of 2.23 L (70% predicted) and DLCO of 36%.

DISCUSSION

PAP is classified into three categories: congenital, autoimmune or idiopathic, and secondary. The congenital forms are caused by mutations in the genes encoding surfactant protein B or C or the receptor for GM-CSF. Autoimmune PAP is associated with the presence of anti-GM-

CSF. Secondary PAP can be associated with infection, hematologic malignancies, or exposure to inhaled chemicals. Autoimmune PAP represents 90% of all PAP cases, and it is rarely associated with another autoimmune disease.¹ In all three of our patients, PAP is most likely to be the autoimmune PAP as there is no history of exposure to chemicals, and BAL excluded infection. They responded to the WLL at varying degrees. Two of the patients had achieved remission and did not require further WLL.

The diagnosis of PAP can be made with confidence based on typical HRCT thorax features in conjunction with milky BAL fluid. Transbronchial lung biopsy, VATS, or image-guided biopsy specimens provide a pathological feature that strengthens the diagnosis. Chest radiography generally reveals non-specific symmetric bilateral alveolar opacities. The major CT abnormalities are patchy, 'geographic' patterns of ground glass opacification superimposed on interlobular septal thickening in multiple lobes. The level of radiographic severity and clinical symptoms are often discrepant.² BAL typically has a milky appearance and may reveal foamy macrophages containing eosinophilic granules, with extracellular globular hyaline material and positive on periodic acid-Schiff (PAS) staining. Lung biopsy pathognomically demonstrates intra-alveolar filled eosinophils, lipoproteinaceous materials with periodic acid-Schiff-positive and preserved alveolar architecture. A pulmonary function test assesses disease severity and monitors the treatment response. The predominant abnormality is a restrictive ventilatory defect with a reduction in TLC and DLCO.

GM-CSF regulates surfactant homeostasis, macrophages maturation, and phagocytosis. Disrupted GM-CSF signalling by neutralizing GM-CSF autoantibodies is the aetiology of autoimmune PAP. This has led to ineffective alveolar macrophages clearance of the accumulated surfactant. The detection of anti-GM-CSF antibodies in peripheral blood and BAL using ELISA (enzyme-linked immunosorbent assay) can be used to diagnose autoimmune PAP. No association has been observed between anti-GM-CSF antibody levels and severity of autoimmune PAP, in terms of the decline in lung functions, decline in partial pressure of oxygen, or clinical symptoms.¹

WLL is the first-line treatment of choice for PAP. WLL improves exercise tolerance, symptoms, pulmonary functions, arterial oxygenation, and macrophages function.³ Radiological improvement occurs more gradually after the WLL and the time period varying between individuals.⁴ WLL is indicated in a patient with limitation in daily activities because of dyspnoea, desaturation on the 6-min walking test, or PaO₂ of less than 70 mmHg or a P(A-a) O₂ of more than 40 mmHg as they are more likely to progress.⁵

WLL is a procedure for removing lipoproteinaceous material from pulmonary alveoli, thus improving macrophage function, arterial oxygenation, and shunt fraction. WLL is performed under general anaesthesia. The patient is intubated with a double-lumen endotracheal tube, with the non-lavage lung mechanically ventilated. Aliquots (1 L) of

warmed (36–37°C) sterile saline is infused at a rate of approximately 100 mL/min into the lung and is allowed to drain to gravity. Manual or mechanical chest percussion is performed during the WLL. The process is repeated until the effluent is clear. The total volumes of saline required can range from 15 L to 40 L. Upon completing the procedure, bronchoscopic suction is performed to remove the residual isotonic sodium chloride solution. The contralateral lung may be lavage 24–48 h later.

PAP that responded to WLL generally carries a good prognosis. The patient may exhibit a different progression pattern, either a spontaneous improvement, stable disease, or worsened disease that requires frequent WLL.¹ The course of the disease varies, and severe pulmonary fibrosis is rare. Approximately 10% of patients experience complete spontaneous remission.⁵ Granulocyte-macrophage colony-stimulating factor (GM-CSF), plasmapheresis, and rituximab can be considered an alternative therapy for refractory PAP.^{6,7} Corticosteroids should not be used for PAP because of their potential to exacerbate opportunistic infections.

CONCLUSION

BAL, GM-CSF autoantibody levels plus tissues HPE is diagnostic in almost all cases. TBLB is a helpful adjunct as compared to invasive VATS or image-guided lung biopsy to obtain a histological diagnosis of PAP in conjunction with detailed clinical and radiological data. WLL is well tolerated and should be considered the first treatment modality in an experienced centre. Although PAP is a rare condition, recognizing the radio-pathological features and prompt diagnosis with WLL may improve the outcome.

CONFLICT OF INTEREST

The authors state that there is none to declare.

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