Management of primary pulmonary alveolar proteinosis: A multicentric experience

Vikas Marwah¹, CDS Katoch¹, Sarvinder Singh², Ajay Handa², Vasu Vardhan³, AK Rajput⁴, MS Barthwal⁵, D Bhattacharyya⁶, SP Rai⁸

¹Department of Pulmonary, Critical Care and Sleep Medicine, Army Institute of Cardio-Thoracic Sciences (AICTS), Pune, Maharashtra, India, ²Department of Pulmonary, Critical Care and Sleep Medicine, Army Hospital (RR), Delhi Cantonment, Delhi, India, ³Department of Pulmonary Medicine, INHS Asvini, Mumbai, Maharashtra, India, ⁴Senior Consultant (Resp Medicine), Department of Pulmonary Medicine, Army College of Medical Sciences, Delhi Cantonment, Delhi, India, ⁵Department of Respiratory and Sleep Medicine, Artemis Hospital, Gurugram, Haryana, India, ⁶Department of Respiratory Medicine, Dr DY Patil Medical College, Hospital & Research Centre, Pimpri, Pune, Maharashtra, India, ⁷Department of Pulmonary Medicine, ILBS Hospital, New Delhi, India, ⁸Department of Pulmonary Medicine, Kokilaben Dhirubhai Ambani Hospital & Medical Research Institute, Mumbai, Maharashtra, India

ABSTRACT

Background: Pulmonary alveolar proteinosis (PAP) is a rare disease characterized by alveolar accumulation of surfactant material with reduced lung function and resulting hypoxemia. It is characterized by a variable clinical course, and whole lung lavage (WLL) is the standard treatment. Herein, we report our multicentric experience of management of primary PAP. Materials and Methods: This retrospective study included patients with PAP managed at various armed forces respiratory centers from 2009 to 2019. The diagnosis of primary PAP was based on histopathologic confirmation on transbronchial lung biopsy or open lung biopsy and absence of causes of secondary PAP. We analyzed the response to WLL in these patients as well as the safety of the procedure. Results: During the above-specified period, ten patients with a diagnosis of PAP were admitted to various armed forces respiratory centers. The median age of the patients was 34.5 years (range 23–59); there were nine males (90%). The mean duration (± standard deviation) of symptoms was 10.8 (±2.70) months. For management, WLL was done for eight patients with a median volume of 23.5 L (range 18–45) per patient. All the patients showed significant symptomatic response as well as improvement in physiological parameters with no major complications. The median follow-up of all patients was 18 (range 5–44) months. Conclusions: WLL is a safe, effective therapy in an experienced setting in patients with PAP and provides long-lasting benefits.

KEY WORDS: Pulmonary alveolar proteinosis, transbronchial lung cryobiopsy, whole lung lavage

INTRODUCTION

Pulmonary alveolar proteinosis (PAP) is a rare disease characterized by accumulation of surfactant, which is comprised of lipoproteinaceous material within alveoli. It is usually seen in the third or fourth decade of life with predominance seen in males. PAP occurs due to...
disorders of either surfactant production or its clearance. PAP due to disorders in surfactant clearance is further divided into three: auto-immune (primary) PAP, secondary PAP, or congenital PAP[4,5]. Congenital PAP is usually seen in children, caused by an autosomal dominant, autosomal recessive, or X-linked recessive pattern of gene mutation with the radioclinical presentation dependent on the mutated gene. Secondary PAP is usually due to reduced number or function of alveolar macrophages secondary to chronic infections, chronic inflammatory or immune-deficiency syndromes, dust exposure, or hematological disorders. Adult forms of PAP constitute majorly of primary PAP[2,6] and have high concentration of neutralizing antigranulocyte-macrophage colony-stimulating factor (GM-CSF) IgG antibodies. These bind to the GM-CSF, preventing their function of surfactant clearance.[7,8]

Patients of PAP usually present with progressive dyspnea but may also have complaints of cough, chest pain, loss of weight, and fatigue.[2-3] Due to the modification of function of neutrophils and lymphocytes, they may initially present with a superadded infection.[2] Chest radiograph shows bilateral alveolar opacities, with a peri-hilar distribution. High-resolution computed tomography (HRCT) scanning of the chest shows ground glass opacities with thickened intralobular and interlobular septae, forming a “crazy paving pattern.”[9] The morphological features on bronchoscopy are normal, but bronchoalveolar lavage usually is milky white. Transbronchial lung biopsy (TBLB) shows preserved architecture with thickened alveolar septa and periodic acid–Shiff-positive proteinaceous material in the background of eosinophilic granulomas [Figure 1]. Elevated levels of anti-GM-CSF antibodies are diagnostic with almost 100% sensitivity and 98% specificity for primary PAP.[10]

Whole lung lavage (WLL) remains the gold standard of therapy for PAP as it provides long-lasting benefits in the majority of patients.[11] It is indicated in symptomatic patients with pulmonary function impairment, whereas asymptomatic patients with no functional deficit require close observation with radiological and pulmonary function surveillance.[12] In past, a median duration of clinical benefit of 15 months was reported with WLL,[6] however, the technique has improved considerably over the years and the results are much better nowadays. We analyzed the therapeutic response to WLL as well as the safety of the procedure in this retrospective review. To the best of our knowledge, this study is the largest case series of management of PAP with WLL from India.

**MATERIALS AND METHODS**

This is a retrospective analysis of data collected between January 2009 and January 2019 at four armed forces respiratory centers across India. The study protocol was approved by the ethics review committee of all the participating centers. Patients with clinicoradiological features of PAP were extensively evaluated for any underlying secondary cause. The serum of all the patients was analyzed for lactate dehydrogenase (LDH) levels, and they also underwent HRCT of the chest. The diagnosis of PAP was confirmed by lung biopsy (either bronchoscopic or surgical) in all the cases. When TBLB was inconclusive, they underwent transbronchial lung cryobiopsy (TBLC) or surgical lung biopsy for confirmation of diagnosis. Attempts to test serum GM-CSF autoantibody testing were made for all patients, but the assay is not available locally. GM-CSF autoantibody testing was done using enzyme-linked immunosorbent assay at Translational Pulmonary Science Center Laboratory, Cincinnati, Ohio, USA.

Treatment of all patients was based on symptoms which included dyspnea or cough related to PAP.[2] Symptoms were classified using the Dyspnea Severity Score (DSS)[3] which ranges from 1 to 5. Patients who were asymptomatic with PaO₂ ≥70 mmHg were classified as DSS 1; symptomatic patients with PaO₂ ≥70 mmHg were classified as DSS 2; patients with PaO₂ from 60 to ≤70 mmHg were classified as DSS 3; patients with PaO₂ from 50 to ≤60 mmHg were classified as DSS 4; and patients with PaO₂ <50 mmHg were classified as DSS 5. Patients with no or mild symptoms were kept under close follow-up with every 6 months (earlier, if required) assessment of symptoms and physiological parameters. Patients with moderate-to-severe symptoms (DSS 3 or more), those with progressive symptoms, and those with alveolar-arterial oxygen [(A-a) O₂] gradient >40 were offered WLL.

WLL was performed after putting double-lumen tracheal tube (DLT) under general anesthesia in operation theater, with continuous physiological monitoring by a team of interventional pulmonologists, anesthetists, and a team of interventional pulmonologists, anesthetists,
and physiotherapist. Extracorporeal membrane oxygenation (ECMO) backup was kept arranged. We followed the same protocol at all the centers for WLL. Our preferred method is to lavage one lung at a time, with the patient in lateral decubitus position, ventilation of the dependent lung and lavage of the nondependent lung, and repeating cycles of drainage and instillation of warm saline with chest percussion until the effluent is clear. This choice reduces blood flow to the lavaged lung (thus giving a better ventilation/perfusion ratio) and allows easy access to the same lung for chest wall percussion. A left-sided double-lumen endotracheal tube (DLT, BronchoCath®, Mallinckrodt Medical, Inc., Livermore, CA, USA) was placed to achieve lung isolation during lavage. The position of the tube was confirmed by introducing the fiberoptic bronchoscope. Before lavage, a 20-min test of one-lung ventilation of the dependent lung was performed, with a high inspiratory oxygen fraction (up to 1) and low positive end-expiratory pressure (PEEP), while the nondependent lung was actively deflated and degassed as much as possible. After the test, the lavage was started with 750–1000 mL aliquots of saline warmed to body temperature, both delivered and drained by gravity through a large-bore tubing system. When the outflow, initially milky, became clear, chest wall percussion was added, which greatly enhanced the removal of proteinaceous material. Lavage and percussion were continued until the outflow fluid became definitively clear [Figure 2], which may take 3 h and a total of 15–20 L saline for a single lung. After the lavage, as much fluid as possible was drained and then careful thoracic suction was applied using fiberoptic bronchoscopy; ventilation with positive end-expiratory pressure was started, first in the lateral decubitus and then in the supine position. The DLT was then replaced with a single-lumen endotracheal tube. Diuretics were used to help in clearing the fluid from the lung. The patients were monitored in the recovery unit for an hour on mechanical ventilation. At the end of the recovery time, the patients were awakened and extubated.

The lavage of the second lung was performed with the patient in the opposite lateral decubitus, using the same procedure usually after an interval of 2 weeks. Following WLL, for evaluation of response DSS, arterial blood gas analysis, pulmonary function test, 6-min walk test, and chest radiographs were performed and compared with the baseline.

### RESULTS

During the study period, ten patients with primary PAP were admitted to various armed forces respiratory centers. Eight symptomatic patients were treated with sequential bilateral WLL in different sessions usually after an interval of 2–3 weeks. The median age of patients included was 34.5 (range 23–59) years; there were nine males (90%). The patient characteristics are reported in Table 1. The mean duration (± standard deviation) of symptoms was 10.8 (±2.7) months. The most common presenting complaint was dyspnea followed by cough. Other symptoms are shown in Table 2. Two patients were reformed smokers, and a total of 15–20 L saline for a single lung. After the lavage, as much fluid as possible was drained and then careful thoracic suction was applied using fiberoptic bronchoscopy; ventilation with positive end-expiratory pressure was started, first in the lateral decubitus and then in the supine position. The DLT was then replaced with a single-lumen endotracheal tube. Diuretics were used to help in clearing the fluid from the lung. The patients were monitored in the recovery unit for an hour on mechanical ventilation. At the end of the recovery time, the patients were awakened and extubated.

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While one was current smoker. Four of the patients had received ATT before reporting to our center in view of pulmonary opacities. Five patients had hypoxemia at presentation (lowest saturation 80% at room air), while one patient had clubbing. All patients had bi-basal crackles on auscultation. Elevated serum LDH levels were present in six out of ten patients (60%), and all patients had “crazy-paving” pattern on HRCT of chest [Figure 3]. Anti-GM-CSF antibodies were elevated in both the patients who were tested for it. TBLB confirmed the diagnosis of PAP in five cases, while TBLC [Figure 1] and surgical lung biopsy confirmed the diagnosis in two and three cases, respectively.

None of the patients required more than one session of WLL per lung. A median WLL volume of 23.5 L (range 18–45) was required per patient. The highest cumulative WLL volume was 35 L. All the patients showed significant symptomatic improvement along with improvement in oxygenation and stable spirometric parameters following bilateral WLL [Table 3]. Complications associated with WLL were fever (n = 3); hypoxemia (n = 2); visible fluid in the ventilating side of WLL (n = 1); and hospital-acquired pneumonia (n = 1). There were no instances of pneumothorax, salvage requirement of ECMO, DLT displacement, or death. No patient needed prolonged mechanical ventilation.

All patients were followed up for a median period of 18 (range 5–44) months. Significant improvement was achieved in all the patients with therapeutic bilateral WLL. All the patients managed with WLL have shown persistent response to treatment, without any evidence of symptomatic or radiologic worsening [Figure 4] with stable spirometric and 6-min walk test variables on follow-up till date. Conservative management was done for two patients, and both remained stable clinicoradiologically on follow-up. One of the patients (patient 7) developed pulmonary tuberculosis on follow-up and was treated with ATT in 2016.

**DISCUSSION**

In this study, we describe our experience of managing patients with primary PAP for the last 10 years. WLL to physically remove the proteinaceous material from the affected lung is the gold standard treatment even though it is quite labor intense. Since its original description in 1963,[12] there have been increasing numbers of WLL procedures done worldwide with variable benefits on follow-up. We have analyzed our results of bilateral WLL in this study as the technique has been modified and refined over the years.[13]

![Figure 3: High-resolution computed tomography chest of a patient with pulmonary alveolar proteinosis demonstrating characteristic “crazypaving” appearance](image)

![Figure 4: High-resolution computed tomography chest of a patient with primary pulmonary alveolar proteinosis before and after whole lung lavage](image)

| Table 3: Patient parameters pre- and post-whole lung lavage and on follow-up |
|---------------------------------------------------------------|
| **Case** | **Treatment** (Lung lavage volume per patient in Litres) | **Parameters (Pre and Post Whole Lung Lavage)** | **Follow up** | **Chest radiograph** |
|-----------|--------------------------------------------------------|---------------------------------|--------------|-------------------|
| **Blood gas** | **Pre** | **Post** | **Pre** | **Post** | **Pre** | **Post** | **Pre** | **Post** | **Pre** | **Post** | **Pre** | **Post** |
| **SpO2 (%)** | | | | | | | | | | | | | |
| **PaO2 (mmHg)** | | | | | | | | | | | | | |
| **A-a DO2 (mmHg)** | | | | | | | | | | | | | |
| **Pulmonary function** | | | | | | | | | | | | | |
| **FVC (% predicted)** | | | | | | | | | | | | | |
| **6MWT (lowest saturation, %)** | | | | | | | | | | | | | |
| **DLCO (%)** | | | | | | | | | | | | | |
| **Case 1** | WLL (18 L) | 84 | 92 | 52 | 65 | 155 | 53 | 54 | 62 | 76 | 86 | 48 | 50 | 6 | Improved |
| **Case 2** | WLL (24 L) | 89 | 94 | 58 | 70 | 78 | 48 | 58 | 60 | 80 | 90 | 56 | 60 | 5 | Improved |
| **Case 3** | WLL (45 L) | 93 | 96 | 68 | 76 | 58 | 36 | 66 | 69 | 76 | 91 | 65 | 68 | 5 | Improved |
| **Case 4** | WLL (24 L) | 80 | 90 | 34 | 53 | 147 | 74 | 100 | - | 94 | - | 72.6 | - | 44 | Improved |
| **Case 5** | Conservative | 96 | - | 77 | - | 18 | - | - | - | - | - | - | - | 18 | Static |
| **Case 6** | Conservative | 94 | - | 73 | - | - | - | 82 | - | 87 | - | 76 | - | 18 | Improved |
| **Case 7** | WLL (23) | 83 | 91 | 47 | 61 | 112 | 57 | 78 | 82 | - | 88 | 72 | 75 | 18 | Improved |
| **Case 8** | WLL (24 L) | 92 | 96 | 64 | 72 | 56 | 45 | 75 | 78 | 86 | 90 | 87 | 88 | 36 | Static |
| **Case 9** | WLL (18 L) | 98 | 98 | 74 | 76 | 44 | 40 | 84 | 86 | 92 | 94 | 82 | 83 | 5 | Improved |
| **Case 10** | WLL (20 L) | 90 | 95 | 60 | 70 | 62 | 38 | 61 | 64 | 82 | 91 | 62 | 65 | 18 | Static |

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The main indication for WLL is limitation in daily activities due to dyspnea. In our study also, all patients who had significant symptoms and progressive decline in lung function and oxygenation underwent bilateral WLL. Some authors have suggested that patients with PaO\textsubscript{2} of <70 mmHg on room air or an A-a oxygen gradient of more than 40 mmHg are more likely to progress and hence require WLL. Current indications vary from one center to another. In one survey of twenty worldwide centers that perform WLL in adults, the most common indications were declining lung function, declining oxygenation, and radiographic worsening. The median time from the diagnosis of PAP to performing WLL in our series was 3 months. In a series of 92 cases, the median time from diagnosis of PAP to performing WLL was 2 months; however, some patients did not require therapy for up to 17 years. The majority of patients (79%) underwent WLL within 12 months of diagnosis. In another study of 33 patients who underwent WLL, the median period between diagnosis and WLL was 7 months (range 0–60 months).

When done in experienced centers, WLL provides long-lasting benefit in the majority of patients. Seymour and Presnell reported a median duration of clinical benefit of 15 months, with 20% of patients followed beyond 3 years remaining free of recurrent PAP manifestations. In our study, no patient required repeat WLL during follow-up even though they continued to have mild impairment in DLCO. In another series of 21 patients with idiopathic PAP, in which patients underwent WLL in the 1990s, a median duration of overall benefit from WLL of 3 years was reported, with 70% of patients followed beyond 3 years remaining free of recurrent PAP manifestations. Our results can be explained as the procedure of WLL has been refined over the years, and also due to more invasive monitoring during anesthesia allowing longer lung lavage times. Other series also reported that residual gas exchange abnormalities and exercise intolerance were common, even in the absence of recurrent PAP. A review of Indian literature has shown that WLL as a therapeutic modality was used in 60% (18/30), and all of those showed satisfactory response, but long-term follow-up data on effects of WLL in these patients are not available. We have previously reported good response to bilateral WLL in two patients.

WLL is a safe procedure in experienced centers, but complications have been reported. We also evaluated the safety of the procedure in our study. In our series, fever was the most common postprocedural complication seen in three of the patients, followed by hypoxemia which improved by ventilation with high inspired oxygen concentration. In a survey by Campo et al. that included thirty centers, the most common complications were fever (18%) followed by hypoxemia (14%), wheezing (6%), pneumonia (5%), and fluid leakage (4%). Pleural effusion and pneumothorax occurred in 3.1% and 0.8%, respectively. We encountered spillage of lavage fluid into the ventilated lung in one case, probably due to malpositioning of the double-lumen endobronchial tube. This has been reported in other series as well. Barotrauma related to rapid instillation of large volumes of fluid can result in hydro-pneumothorax, subcutaneous emphysema, and pleural fluid collections. We fortunately did not come across any pleural complications. While performing the WLL, one should be ready for salvage requirement of ECMO, in case of severe compromise of ventilation. During the study period, we did not come across any such complication; however, we had ECMO backup facility. In Indian studies, only one of the patients required ECMO during WLL.

Patients with PAP have macrophage and neutrophil dysfunction, which predisposes them to increased risk of superinfection with organisms such as Nocardia, mycobacteria, and fungi. In our study, one patient developed pulmonary TB during follow-up. However, four (40%) patients were given empirical antitubercular therapy before diagnosis. Inappropriate use of ATT is associated with adverse effects and increased risk of multidrug-resistant mycobacteria. Although PAP is a rare condition, physicians treating such patients should not make the diagnosis of tuberculosis on radiologic basis alone as it is inappropriate to treat these patients with ATT in the absence of microbiological confirmation. Progressive dyspnea, worsening oxygenation, high serum LDH, and typical “crazy-paving” pattern on radiology may be a helpful clue.

There is difficulty in evaluating therapeutic interventions in PAP as the natural history is variable and spontaneous resolution is known. Significant spontaneous improvement has been described in 7.9% of patients. In the present study, two patients with mild disease did not show any clinicoradiologic deterioration. In the largest series of PAP asymptomatic patients with mild disease were most likely to have a stable to improving course, with only 8% worsening during follow-up.

The major limitation of this study apart from the small size is the lack of demonstration of anti-GM-CSF antibodies in all the patients. Due to lack of availability of the assay locally, we were able to perform this test only on two patients who could afford the sample being sent abroad. The other limitation is that it is a retrospective study. As PAP is a rare disease, it is difficult to have prospective studies to elucidate the response in terms of the onset and duration of the benefit of WLL.

**CONCLUSIONS**

WLL is a safe and effective therapy in an experienced setting in patients with primary PAP. Therapeutic sequential bilateral WLL provides long-lasting benefits as the procedure has been refined over the years.

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Declaration of patient consent
The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest
There are no conflicts of interest.

REFERENCES

1. Rosen SH, Castleman B, Liebow AA. Pulmonary alveolar proteinosis. N Engl J Med 1958;238:1123-42.
2. Inoue Y, Trapnell BC, Tazawa R, Arai T, Takada T, Hizawa N, et al. Characteristics of a large cohort of patients with autoimmune pulmonary alveolar proteinosis in Japan. Am J Respir Crit Care Med 2008;177:752-62.
3. Kariman K, Kylstra JA, Spock A. Pulmonary alveolar proteinosis: Prospective clinical experience in 23 patients for 15 years. Lung 1984;162:223-31.
4. Shah PL, Hansell D, Lawson PR, Reid KB, Morgan C. Pulmonary alveolar proteinosis: Clinical aspects and current concepts on pathogenesis.
5. Kumar A, Abdelmalak B, Inoue Y, Culver DA. Pulmonary alveolar proteinosis in adults: Pathophysiology and clinical approach. Lancet Respir Med 2018;6:554-65.
6. Seymour JF, Presnell JJ. Pulmonary alveolar proteinosis: Progress in the first 44 years. Am J Respir Crit Care Med 2002;166:215-35.
7. Trapnell BC, Whitsett JA. GM-CSF regulates pulmonary surfactant homeostasis and alveolar macrophage-mediated innate host defense. Annu Rev Physiol 2002;64:775-802.
8. Kitamura T, Tanaka N, Watanabe J, Uchida, Kanegasaki S, Yamada Y, et al. Idiopathic pulmonary alveolar proteinosis as an autoimmune disease with neutralizing antibody against granulocyte/macrophage colony-stimulating factor. J Exp Med 1999;190:875-80.
9. Lee KN, Levin DL, Webb WR, Chen D, Storto ML, Golden JA. Pulmonary alveolar proteinosis: High-resolution CT, chest radiographic, and functional correlations. Chest 1997;111:989-95.
10. Kitamura T, Uchida K, Tanaka N, Tsuchiya T, Watanabe J, Yamada Y, et al. Serological diagnosis of idiopathic pulmonary alveolar proteinosis. Am J Respir Crit Care Med 2000;162:638-62.
11. Leth S, Bendstrup E, Vestergaard H, Hillberg O. Autoimmune pulmonary alveolar proteinosis: Treatment options in year 2013. Respirology 2013;18:82-91.
12. Ramerez J, Schultz RB, Dutton RE. Pulmonary alveolar proteinosis: A new technique and rationale for treatment. Arch Intern Med 1963;112:419-31.
13. Campo I, Luisetti M, Griese M, Trapnell BC, Bonella F, Grutters J, et al. Whole lung lavage therapy for pulmonary alveolar proteinosis: A global survey of current practices and procedures. Orphanet J Rare Dis 2016;11:115.
14. Gay P, Wallaert B, Nowak S, Yserbyt J, Anevlas S, Hermant C, et al. Efficacy of Whole-Lung Lavage in Pulmonary Alveolar Proteinosis: A Multicenter International Study of GELF. Respiration 2017;93:198-206.
15. Beccaria M, Luisetti M, Rodi G, Corsico A, Zoia MC, Colato S, et al. Long-term durable benefit after whole lung lavage in pulmonary alveolar proteinosis. Eur Respir J 2004;23:526-31.
16. Kunal S, Gera K, Pilaniya V, Jain S, Gothi R, Shah A. “Crazy-paving” pattern: A characteristic presentation of pulmonary alveolar proteinosis and a review of the literature from India. Lung India 2016;33:335-42.
17. Bhattacharyya D, Barthwal MS, Katcoh CD, Rohatgi MG, Hasnain S, Rai SP, et al. Primary alveolar proteinosis-A report of two cases. Med J Armed Forces India 2013;69:90-3.
18. Sivitanidis E, Tosson R, Wiebalck A, Laczkovics A. Combination of extracorporeal membrane oxygenation (ECMO) and pulmonary lavage in a patient with pulmonary alveolar proteinosis. Eur J Cardiothorac Surg 1999;15:370-2.
19. Hadda V, Tiwari P, Madan K, Mohan A, Gupta N, Bharti SJ, et al. Pulmonary alveolar proteinosis: Experience from a tertiary care center and systematic review of Indian literature. Lung India 2016;33:626-34.
20. Marwah V, Barthwal MS, Rajput AK. Are pulmonary opacities a marker of pulmonary tuberculosis? Med J Armed Forces India 2014;70:22-5.