Original Article

Pulmonary alveolar proteinosis: Experience from a tertiary care center and systematic review of Indian literature

Vijay Hadda, Pawan Tiwari, Karan Madan, Anant Mohan, Nishkarsh Gupta[1], Sachidanand Jee Bharti[1], Vinod Kumar[1], Rakesh Garg[1], Anjan Trikha[1], Deepali Jain[2], Sudheer Arava[2], Gopi C Khilnani, Randeep Guleria

Departments of Pulmonary Medicine and Sleep Disorders, [1]Anaesthesiology and [2]Pathology, All India Institute of Medical Sciences, New Delhi, India

ABSTRACT

Background: Pulmonary alveolar proteinosis (PAP) is a rare disorder characterized by deposition of lipoproteinaceous material within alveoli, with a variable clinical course. Here, we report an experience of management of PAP at our center. A systematic review of previously reported cases from India is also included in the article. **Materials and Methods:** This study included patients with primary PAP managed at our center from 2009 to 2015. Diagnosis of primary PAP was based on histopathologic diagnosis on bronchoalveolar lavage or transbronchial lung biopsy and absence of causes of secondary PAP. For systematic review of Indian publications, the literature search was performed using PubMed and EMBASE databases using the terms "pulmonary alveolar proteinosis'" or "alveolar proteinosis" and "India" or "Indian." **Results:** During the above-specified period, five patients with diagnosis of PAP were admitted at our center. Median age of patients was 32 years (interquartile range [IQR] 30.5–59); 80% were female. Mean duration (± standard deviation) of symptoms was 6.2 (±1.79) months. Anti-granulocyte-macrophage colony stimulating factor (GM-CSF) antibodies were elevated in 4 out of 5 patients (80%). For management, whole lung lavage (WLL) was done for four patients with median volume of 32.5 (IQR 18–74) L per patient. All the patients showed significant symptomatic as well as improvement in physiological parameters. Subcutaneous GM-CSF and ambroxol were given to 3 patients and 1 patient, respectively. The median follow-up of all patients was 18 (IQR 5–44) months. A systematic review of all Indian studies of PAP revealed thirty publications. **Conclusions:** WLL is the most common, effective, and safe therapy in patients with PAP. GM-CSF administration is an efficacious treatment for patients with incomplete response after WLL.

KEY WORDS: Granulocyte-macrophage colony stimulating factor, pulmonary alveolar proteinosis, whole lung lavage

Address for correspondence: Dr. Vijay Hadda, Department of Pulmonary Medicine and Sleep Disorders, All India Institute of Medical Sciences, New Delhi - 110 029, India. E-mail: vijayhadda@yahoo.com

INTRODUCTION

Pulmonary alveolar proteinosis (PAP) is a rare clinical syndrome associated with deposition of lipoproteinaceous material within alveoli, leading to varied clinical presentations ranging from being asymptomatic to respiratory failure. Exact incidence PAP is not known; estimated prevalence is approximately 1–2 per million people. It predominantly affects men, with male to female ratio 3:1, in the third and fourth decades of life.[1,2]

Three forms of PAP are recognized – congenital, secondary, and acquired or primary. Among these, primary PAP remains the most common, constituting up to 90% of all reported cases. The most common clinical manifestation is progressive dyspnea (50–80%).[2,3]

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Other symptoms of PAP include dry cough, fatigue, and low-grade fever.[2,3] Due to macrophage and neutrophil dysfunction, there is increased risk of superinfection in PAP with organisms such as *Nocardia*, mycobacteria, and endemic or opportunistic fungi.[1,2] Patients can have polycythemia, hypergammaglobulinemia, increased lactate dehydrogenase (LDH), and various tumor marker levels. Diagnosis is suspected based on the presence of homogeneous ground-glass opacities (GGOs), with thickened intralobular and interlobular septa in typical polygonal shapes, referred to as "crazy-paving" on high-resolution computed tomography (HRCT) of the chest.[4,5] Fiberoptic bronchoscopy and bronchoalveolar lavage (BAL) and transbronchial lung biopsy (TBLB) are diagnostics. Characteristic BAL findings of PAP include opaque or milky appearance, which settles on standing. Lung biopsy shows preserved alveolar architecture, slight thickening of alveolar septa, little or no inflammatory cell infiltration, and presence of PAS-positive proteinaceous material in a background of eosinophilic granules in terminal bronchioles and alveoli. Electron microscopy of BAL fluid or lung tissue shows concentrically laminated structures called lamellar bodies. These bodies are comprised phospholipids and are probably derived from the Type II alveolar epithelial cells. Granulocyte-macrophage colony stimulating factor (GM-CSF) autoantibodies have been casually linked to autoimmune or primary PAP, and elevated levels are diagnostic, with almost 100% sensitivity and 98% specificity for primary PAP.[6]

Treatment options for PAP include observation and close follow-up, whole lung lavage (WLL), GM-CSF, and rituximab. Asymptomatic patients with little or no physiologic impairment are usually closely followed up with periodic symptom assessment, pulmonary functions tests, and imaging. Those with mild symptoms and mild hypoxemia on exertion can be treated symptomatically or with oxygen supplementation. Patients with severe symptoms and severe impairment on physiologic testing are treated with WLL. The patients with progressive disease despite WLL or those not tolerating WLL are treated with GM-CSF. Rituximab is used as the last resort.[7]

PAP being a rare disease, the experience of managing such patients in our country is limited only to case reports and small case series.[8-33] It should also be noted that the facility and expertise for management of PAP may not be available at all centers. We hereby report the experience of treatment of PAP from our center. In addition, we performed a systematic review of all previously reported cases of PAP from India.

MATERIALS AND METHODS

This study includes all patients of PAP admitted at our center from January 2009 to July 2015. Patients with clinicoradiological features of PAP underwent BAL and TBLB to establish the diagnosis. All patients were evaluated

for secondary causes of PAP, including BAL cultures to rule out infections and hematologic malignancies. Attempts to test serum GM-CSF autoantibody testing were made for all patients. GM-CSF autoantibody testing was done using enzyme-linked immunosorbent assay at Translational Pulmonary Science Center Laboratory, Cincinnati Ohio, USA (Courtesy: Dr. Bruce C. Trapnell; supported in part by National Heart, Lung and Blood Institute grant HL985453 to Dr. Bruce C Trapnell).

Selection of treatment modality

Treatment of all patients was based on symptoms which included dyspnea or cough related to PAP.[2] Symptoms were classified using dyspnea severity score (DSS) which ranges from 1 to 5. Patients who were asymptomatic with $PaO_2 \geq 70$ mmHg were classified as DSS 1; symptomatic patients with $PaO_2 \geq 70$ mmHg were classified as DSS 2; patients with PaO_2 from 60 mmHg to ≤70 mmHg were classified as DSS 3; patients with PaO_2 from 50 mmHg to ≤60 mmHg were classified as DSS 4; and patients with $PaO_2 < 50$ mmHg were classified as DSS 5.

Patients with no or mild symptoms were kept under close follow-up with every 6 monthly (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 ($[A\text{-}a]O_2$) gradient >40 were offered WLL.

WLL was performed after putting double-lumen tracheal tube (DLT) under general anesthesia in operation theater or interventional bronchoscopy suite using the standard guidelines[34,35] by a team of interventional pulmonologists, anesthetists, and physiotherapist. Extracorporeal membrane oxygenation (ECMO) backup was kept arranged. Following WLL, for evaluation of response DSS, arterial blood gas analysis, pulmonary function test (PFT), 6 min walk test, chest radiograph, and HRCT of the chest were performed and compared with the baseline. Patients with residual symptoms, elevated $(A\text{-}a)O_2$ gradient, and residual GGOs on HRCT were treated with subcutaneous GM-CSF.

Systematic review of Indian studies

We performed a systematic review of all reported cases of PAP from India. For systematic review, the literature search was performed using PubMed and EMBASE databases using the terms "pulmonary alveolar proteinosis" or "alveolar proteinosis" and "India" or "Indian".

RESULTS

During the above-specified period, five patients with PAP were admitted under our unit. Median age of patients included was 32 (interquartile range [IQR] 30.5–59) years. The youngest patient was 27 years of age at diagnosis and the oldest patient was 71 years of age. Mean duration (± standard deviation) of symptoms was 6.2 (±1.79)

months. Dyspnea and cough were the presenting complaints. Four patients had symptoms and hypoxemia at admission while one patient was asymptomatic. Elevated LDH levels were present in 4 out of 5 patients (80%). Other baseline characteristics are shown in Table 1.

All patients were diagnosed as primary PAP on the basis of clinicoradiological and histopathological findings and absence of causes of secondary PAP. Anti-GM-CSF antibodies were elevated in all four patients who were tested for it.

All four symptomatic and hypoxemic patients were treated with WLL. All patients required more than one session of WLL. Two patients required two sessions and two patients required three sessions. A median WLL volume of 32.5 (IQR 18–74) L was required per patient. The highest cumulative WLL volume lavage was 85 L in three sessions (Case 4). All the patients showed significant symptomatic improvement along with improvement in oxygenation and spirometric parameters, following WLL [Table 2]. Complications associated with WLL include hypoxemia or hypotension ($n = 2$); DLT displacement ($n = 1$); visible fluid in the ventilating side of WLL ($n = 1$); and ineffective ventilation with DLT (requiring DLT replacement/repositioning [$n = 1$]). There were no instances of pneumothorax, hemodynamic compromise, salvage requirement of ECMO, ventilator-associated pneumonia, or death.

Three patients were treated with subcutaneous GM-CSF therapy. One patient was treated initially with GM-CSF for 6 weeks, with partial improvement in symptoms and required WLL. Two patients were treated with GM-CSF after WLL [Table 2].

All patients were followed up for a median period of 18 (IQR 5–44) months. One patient developed leukocytosis with total leukocyte counts of 90,000/dl, following GM-CSF and required dose adjustment. Significant improvement was achieved in all the patients with therapeutic WLL and/or GM-CSF. All the patients have shown persistent response to treatment, without any evidence of symptomatic or radiologic worsening with stable spirometric and 6 min walk test variables on follow-up till date.

Case details
Case 1
A 27-year-old homemaker, resident of Delhi, presented with progressive dyspnea and dry cough for 8 months. There was no history of fever, other constitutional symptoms, exposure to dust or fumes, arthralgias, oral ulcers, photosensitivity, or recurrent lower respiratory tract infections. There was no history of hematologic malignancy, chemotherapy, or immunosuppressant drug intake. At presentation, she was hypoxemic (SpO$_2$ 81%) on room air. The examination of the chest revealed bilateral scattered crepitations. Her chest radiograph showed bilateral middle and lower zone interstitial

Table 1: Baseline characteristics of the study participants

Features	Study participants				
	Case 1	Case 2	Case 3	Case 4	Case 5
Age (years)	27	32	30	47	71
Gender	Female	Male	Female	Female	Female
Duration of symptoms (months)	8	6	8	4	5
Oxygenation parameters					
SpO$_2$ (%)	81	95	78	76	80
PaO$_2$ (mm of Hg)	50	82	51	48	46
(A-a)O$_2$ gradient	125	32	187	128	96
Pulmonary functions					
FEV1/FVC	94	78	-	78	84
FEV1 (% predicted)	0.95 (29.5)	2.54 (74)		1.54 (63)	1.15 (54)
FVC (% predicted)	0.99 (33.6)	2.6 (76)		2.1 (69)	1.36 (60)
Corrected DLCO (% predicted)	-	64		58	54
6 MWTD (m)	210	450	-	340	344
LDH (U/L)	554	350	220	540	432
Anti GM-CSF antibodies	Not done	Positive	Positive	Positive	Positive

SpO$_2$: Oxygen saturation, PaO$_2$: Partial pressure of oxygen, (A-a) O$_2$ gradient: Alveolar-arterial oxygen gradient, FEV1: Forced expiratory volume 1st s, FVC: Forced vital capacity, DLCO: Diffusion capacity for carbon monoxide, 6 MWTD: 6 min walk test distance, LDH: Lactate dehydrogenase, GM-CSF: Granulocyte-macrophage colony-stimulating factor

Table 2: Comparison of important clinical and laboratory features before and after whole lung lavage

Features	Study participants				
	Case 1	Case 2	Case 3*	Case 4	Case 5
Treatment	GM-CSF and WLL	None	WLL	WLL and GM-CSF	WLL and GM-CSF
Follow duration (months)	60	28	18	6	4
Blood gas parameters					
SpO$_2$ (%)	81 versus 94	95 versus 94	78 versus 97	76 versus 92	80 versus 94
(A-a) O$_2$ gradient	125 versus 16	32 versus 18	187 versus 14	128 versus 43	96 versus 40
Pulmonary functions					
FEV1 (%predicted)	29.5 versus NA¥	74 versus 78	NA versus 87	63 versus 74	54 versus 68
FVC (%predicted)	33.6 versus NA	76 versus 81	NA versus 89	69 versus 78	60 versus 71
DLCO corrected (% predicted)	NA	64 versus 72	NA versus 68	58 versus 66	54 versus 68
6 MWTD (m)**	210 versus 450	450 versus 520	- versus 398	340 versus 320	344 versus 392
Lowest SpO$_2$ (%) during 6MWT**	78 versus 92	93 versus 93	- versus 95	81 versus 89	81 versus 89

*Patient could not perform 6 MWT, ¥NA: Not available. Values shown are at baseline versus follow-up. SpO$_2$: Oxygen saturation; PaO$_2$: Partial pressure of oxygen; (A-a) O$_2$ gradient: Alveolar-arterial oxygen gradient, FEV1: Forced expiratory volume 1st s, FVC: Forced vital capacity, DLCO: Diffusion capacity for carbon monoxide, 6 MWTD: 6 min walk test distance, WLL: Whole lung lavage, GM-CSF: Granulocyte macrophage colony stimulating factor

infiltrates. HRCT of the chest showed bilateral GGOs, more in the left lung fields as compared to the right, with interlobular septal thickening (crazy-paving). TBLB showed PAS-positive diastase-resistant material suggestive of PAP. Workup for secondary PAP was negative. Spirometry (though poorly performed due to poor effort) revealed severe restriction (forced expiratory volume in one second/forced vital capacity [FEV1/FVC] 99; FEV1 29.5%; FVC 33.6%), and diffusion for carbon monoxide (DLCO) could not perform. Initial (A-a)O$_2$ gradient was 125. She refused to undergo WLL; therefore, subcutaneous GM-CSF was started (5 μg/kg/day). There was partial symptomatic response, and (A-a)O$_2$ gradient was still elevated (96) after 6 weeks of GM-CSF. Counseling of the patient and relatives was done again. This time, all agreed and patients underwent two sessions of therapeutic WLL augmented with chest physiotherapy under general anesthesia. There was significant improvement in symptoms as well as physiological and radiological parameters. She has been asymptomatic without any radiologic progression on follow-up for the last 5 years.

Case 2

A 32-year-old nonsmoker man, working in petrochemicals in Assam, was referred for evaluation of bilateral alveolar infiltrates on the chest radiograph done for routine yearly medical examination. He had no symptoms even on severe exertion. His history was unremarkable. Clinical examination did not reveal any abnormality. HRCT of the chest showed bilateral alveolar opacities, predominantly in bilateral lower lobes, with GGOs and septal thickening. BAL fluid was milky and cytology and TBLB both showed typical finding of PAP. Serum anti-GM-CSF antibody was positive (88.7 μg/ml). Workup for secondary PAP was negative. Spirometry revealed FEV1/FVC 78%; FEV1 74%; FVC 76%; and DLCO 64%. Room air saturation was 98% and (A-a)O$_2$ gradient was 18. In view of the absence of symptoms and physiological abnormality, he was kept under close follow-up, with a plan for WLL or GM-CSF therapy in the event of progression of disease. However, he continues to be asymptomatic without any worsening in (A-a)O$_2$ gradient, radiologic or spirometric variable on follow-up for the last 2 years.

Case 3

A 30-year-old homemaker, from Nepal, presented with productive cough and progressive dyspnea (modified Medical Research Council II to IV) for the last 8 months. Symptoms started during the third trimester of pregnancy. These symptoms were attributed to being pregnancy related and no further evaluation was done. She had relatively uneventful peripartum course and had full-term normal delivery 5 months back. However, her symptoms continued to progress; she developed Type I respiratory failure for the last 2 months before presentation. She had no history of fever, other constitutional symptoms, exposure to dust or fumes, arthralgias, oral ulcers, photosensitivity, or recurrent lower respiratory tract infections. Her history was unremarkable. On examination, she was tachypneic

and bilateral scattered crepitations were present on auscultation of the chest. Her oxygen saturation and PaO$_2$ while breathing at room air were 78% and 51 mmHg, respectively. The (A-a)O$_2$ gradient was 187. She could not perform spirometry. Her chest radiograph showed bilateral middle and lower zone interstitial infiltrates. HRCT of the chest showed bilateral crazy-paving pattern. Workup for secondary PAP was negative. Diagnosis of PAP was confirmed on both BAL and TBLB. Serum GM-CSF antibody test was positive (271.3 μg/ml). She underwent three sessions of WLL under general anesthesia with significant improvement in symptoms, (A-a)O$_2$ gradient, and radiology. She was able to perform PFT and 6 min walk test. She has been asymptomatic without any radiologic progression on follow-up for the last 18 months.

Case 4

A 65-year-old homemaker presented with complaints of dry cough and dyspnea started 4 months ago. The dyspnea was rapidly progressive, and at presentation, she was dyspneic even at rest. She had no fever, chest pain, or hemoptysis. She had diabetes mellitus, hypertension, and hypothyroidism diagnosed 5, 5, and 3 years back, respectively. On examination, she was tachypneic and chest examination revealed bilateral scattered inspiratory crepitations. Chest radiograph showed bilateral reticular and alveolar opacities in the bilateral middle and lower zones. HRCT of the chest showed bilateral middle and lower lobe predominant GGOs, with interlobar septal thickening. Arterial blood gas (ABG) showed pH 7.47 with pCO$_2$ 30 mmHg and PO$_2$ 72 (FiO$_2$ 35%), suggestive of respiratory alkalosis with hypoxemia, and (A-a)O$_2$ gradient was 128. PFT showed FEV1/FVC 78%; FEV1 63%; FVC 69%; and DLCO 58%. BAL and TBLB revealed features of PAP. Workup for secondary PAP was negative. Serum GM-CSF antibody test was positive (62.9 μg/ml). She underwent three sessions of WLL. With WLL, she had partial relief in symptoms and still had elevated (A-a) O$_2$ gradient. In view of this, we started subcutaneous GM-CSF (3 μg/kg/day; increased to 5 ug/kg/day). In view of neutrophilic leukocytosis, the dose of GM-CSF was adjusted and she received 300 μg on alternate days. With this, she showed improvement in symptoms, radiology, physiological parameters, and 6 min walk distance.

Case 5

A 71-year-old homemaker presented with productive cough and progressive dyspnea for the past 4 months. For the last 2 months, she had respiratory failure and requiring continuous supplemental oxygen to maintain saturation. She had no constitutional symptoms. She had systemic hypertension and hypothyroidism diagnosed 7 and 5 years ago, respectively. There was no other significant history. On examination, she was tachypneic, with bilateral inspiratory crepitations on chest examination. ABG was suggestive of respiratory alkalosis, with hypoxemia and elevated (A-a)O$_2$ gradient. PFT showed moderate restriction (FEV1/FVC 84; FEV1 54%; FVC 60%; DLCO 54%). HRCT of the chest, BAL, and TBLB revealed features of PAP.

Workup for secondary PAP was negative. Serum GM-CSF antibody test was positive (29.2 μg/ml). She underwent two sessions of WLL. First, WLL was performed on the right lung with 28 L of saline. Six days later, she underwent WLL with 13 L of saline on the left lung. With WLL, she had partial improvement in symptoms and borderline (A-a)O_2 gradient. Therefore, she was initiated on GM-CSF therapy (3 μg/kg/day) along with ambroxol (45 mg/day). Currently, she is able to do all daily chores without difficulty, with improvement in (A-a)O_2 gradient and 6 min walk distance.

Systematic review of Indian cases of pulmonary alveolar proteinosis

A total of 69 citations were identified (28 in PubMed and 41 on EMBASE). After initial screening, thirty studies were excluded either because of duplicate citations ($n = 24$) or not related to PAP ($n = 6$).[36-41] Remaining 39 studies were selected for further analysis. Among these, 5 studies were not from India,[42-46] seven studies were review articles,[47] meta-analysis,[48] laboratory experiments,[49,50] comments,[51] replies to previous comments,[52] or quiz[53] and they were excluded from the study. No abstract or full text was available for two citations[10,54] and both were also excluded. Finally, 25 studies were selected for systematic review [Table 3].

The median age of patients was 34.5 (IQR 19–45) years at diagnosis. Among these, two were infants and three were adolescents. There were 23 (76.7%) men. Four patients were smokers. The common reported symptoms were dyspnea (83.3%), cough with or without expectoration (70%), fever (26.7%), loss of weight or appetite (16.67%), bilateral pneumothorax (6.6%), and pleuritic chest pain (3.3%). One-third of the patients (33.3%) presented to hospital with respiratory failure. Median duration of symptoms (reported by 25 studies) was 4 months (IQR 3-9). History of pulmonary tuberculosis was present in 3 (10%) patients.

Diagnosis of PAP was based on BAL cytology (23.3%), TBLB (26.6%), VATS-guided lung biopsy (3.3%), thoracoscopic lung biopsy (3.3%), open lung biopsy (33.3%), and postmortem lung biopsy (6.6%). Anti-GM-CSF antibody testing was done only in one case. One report did not mention the mode of diagnosis. Majority of patients, i.e., 24 (80%) had primary PAP. Remaining six patients were labeled as secondary PAP related to cyclosporine/ mycophenolate (1), cotton dust exposure (2), sandstone exposure (1), glass cutting and fiber exposure (1), or *Nocardia* (1). Concomitant infections were seen in four (*Mycobacterium tuberculosis* [$n = 2$] and *Pneumocystis jiroveci* [$n = 2$]) patients.

Among these, two patients (6.67%) did not receive any treatment for PAP. WLL was performed for 17 (56.67%) patients. The details of WLL were reported in 14 studies. WLL was performed for both lungs ($n = 5$) during the same session (simultaneous WLL) or one lung followed by other ($n = 9$) after variable interval (sequential WLL). Complications reported with WLL include need for ECMO ($n = 1$)[12] and tension pneumothorax ($n = 1$).[12] Other procedures described for treatment of PAP include serial lobar lung lavage using flexible bronchoscopy for 3 (10%) patients[20,22,25] and large volume bronchoscopic[29] and nonbronchoscopic BAL[18] for one each (both for children).

Medical treatment including subcutaneous GM-CSF therapy was given to 9 (30%) patients. The dosage and duration were variable. Other medications which were used include n-acetylcysteine ($n = 1$) and intravascular immunoglobulin ($n = 2$, both infants).[18,29] Five patients received specific antimicrobial therapy – anti-tubercular therapy ($n = 2$, both BAL showed acid-fast bacilli)[17,22] and co-trimoxazole (2 for PCP[17,22] and one for nocardiosis[12]). Long-term oxygen therapy (LTOT) was prescribed to two patients at discharge.[16,29] Among all cases, 5 (16.7%) patients were given empirical anti-tubercular therapy before diagnosis.[15,20,31,32]

All patients who were treated with either WLL or GM-CSF along with other treatment showed significant symptomatic and radiologic improvement at discharge. Two (6.6%) patients died during index admission.[9,32] One patient died 1 week postdischarge on LTOT.[29] The reported follow-up duration is variable, ranging from 2 weeks to 3 years. No details regarding follow-up after discharge could be found for 9 studies.[11,15,19,20,26,27,30,31] One study mentioned symptomatic improvement on follow-up (duration not mentioned).[20] One patient required two more sessions of WLL over during 2.5 years along with GM-CSF administration and was asymptomatic during additional 1 year of follow-up.[13]

DISCUSSION

In this study, we describe our experience of managing patients with PAP for the last 6 years. During this period, five patients got admitted with the diagnosis of PAP. Among these, 4 patients were treated by WLL. WLL has been described as early as in the 1960s. Since then, it has remained the most effective therapeutic option for treatment of PAP. WLL is an invasive procedure which is done under general anesthesia and quite labor intense procedure. The procedure requires a multidisciplinary team consisting pulmonologists, anesthetist, and respiratory therapist/physiotherapist and may take many hours to get the desired results. However, based on its efficacy, it is the "standard of care" for the treatment of PAP, especially for patients with respiratory failure. In this study also, all patients showed significant improvement in symptoms, oxygenation, and radiology. Notably, all these patients had respiratory failure. Our results are consistent with the previous case reports. WLL, although time-consuming, is a relatively safe procedure for these patients. As described in this study, complications associated with WLL include hypoxemia or hypotension, DLT displacement, visible fluid

Table 3: Summary of the case studies included for the systematic review

Authors (year of publication)	Age/sex	Treatment	Comments
Baro *et al.* (2015)[17]	10/female	WLL Hydroxychloroquine (5 mg/kg/day) and prednisolone (1 mg/kg/day)	Details of WLL NR. Diagnosis of PAP was made after no response to ATT for 3 months. After WLL ATT was stopped after 6 months
Davis *et al.* (2015)[25]	33/female	WLL and GM-CSF GM-CSF (for 2 weeks)	WLL was performed sequentially on alternate side with 2-2.5 L. Patient was able to do routine activities on 1 year follow-up
Hasan *et al.* (2014)[16]	36/female	LTOT Cyclosporine and MMF stopped	Off oxygen with radiologic clearance after 2 years
Bhattacharyya *et al.* (2013)[15]	28/male	WLL Empirical ATT prior to diagnosis	WLL with 20 L for each lung done at interval of 2 days. Marked improvement after WLL; further follow-up NR
Bhattacharyya *et al.* (2013)[15]	33/male	WLL Empirical ATT prior to diagnosis	WLL with 9 L for each lung at an interval of 2 weeks apart. Marked improvement after WLL; further follow-up NR
Shende *et al.* (2013)[13]	58/male	WLL	WLL for both lung in a single setting using 8.5 L and 6 L saline for right and left lung, respectively. Required 2 more sessions of WLL and GM-CSF over next 2.5 years
Bansal and Sikri (2013)[8]	54/male	WLL GM-CSF N-acetyl cysteine	WLL at two sessions with 15.5 L and 20 L each for left and right lung, respectively. Asymptomatic at 8 months of follow-up
Baldi *et al.* (2013)[22]	38/male	WLL, steroids, co-trimoxazole, ATT, GM-CSF (for 3 weeks)	Four sessions of WLL were performed sequentially over 54 days. Total volume of saline used was 23.4 L. Asymptomatic at 18 months
Raj *et al.* (2013)[18]	8 months/female	BAL, co-trimoxazole, steroids, IVIG	Therapeutic bronchoscopic BAL weekly (volume and number of sessions NR) Discharged after 120 days
Babu *et al.* (2013)[26]	30/male	WLL	Details of WLL not mentioned. Symptomatic and radiologic clearance post-WLL
Tousheed *et al.* (2013)[27]	56/male	WLL and GM-CSF	Details of WLL not mentioned Symptomatic and radiologic improvement
Jayaraman *et al.* (2010)[28]	26/male	WLL	WLL with 30 L on right lung (30 L) followed by left lung after 5 days Asymptomatic at two weeks follow-up and clearance on chest X-ray
Khan *et al.* (2012)[12]	34/male	GM-CSF	Symptomatically improved at 6 months; no radiologic improvement
Khan *et al.* (2012)[12]	28/male	Co-trimoxazole	Asymptomatic on follow-up at 2.5 years
Khan *et al.* (2012)[12]	38/male	WLL and GM-CSF	Sequential WLL (13 L on right; 12 L on left side); GM-CSF (5 µg/kg/day) for 3 months Asymptomatic at 2 years follow-up
Khan *et al.* (2012)[12]	42/male	WLL and GM-CSF	Sequential WLL (13 L on right; 12 L on left side); Tension pneumothorax 2 days after GM-CSF (5 µg/kg/day) for 3 months Asymptomatic at 2 years follow-up
Khan *et al.* (2012)[12]	46/female	WLL and GM-CSF	WLL of both lungs with 26.8 L with ECMO support. Asymptomatic on follow-up till 3 years
Nandkumar *et al.* (2009)[19]	43/male	GM-CSF and WLL	WLL with 12.5 L and 17 L for left and right lung, respectively, at 4 days interval Asymptomatic; off oxygen at discharge
Thind (2009)[9]	24/male	Antibiotics	Died 16 days after admission
Garg *et al.* (2009)[29]	4 months/male	BAL Intravascular immunoglobulin	Large volume BAL (volume NR) Discharged on LTOT 68 days after admission; expired 1 week later
Udwadia and Jain (2007)[14]	45/male	WLL	WLL with 12 L and 16 L for left and right lung, respectively. Asymptomatic at 3 months
Indira *et al.* (2007)[23]	53/male	WLL	WLL with 12.4 L and 13.6 L for left and right lung, respectively. Asymptomatic after 6 months
Sengupta *et al.* (2007)[24]	36/female	WLL	WLL with 11 L and 13 L for left and right lung, respectively Symptomatic improvement at discharge
Kumar P *et al.* (2007)[11]	45/female	WLL	B/L simultaneous WLL; volumes not mentioned Improvement in symptoms and oxygenation
Udwadia *et al.* (1998)[20]	33/male	WLL	WLL done sequentially with 10 L and 16 L for left and right lung, respectively Able to climb 3 sets of stairs without dyspnea at discharge
Dixit *et al.* (1998)[30]	14/male	WLL	WLL with 9.5 L and 9 L for left and right lung, respectively
Sangani *et al.* (1993)[31]	14/male	None	NR
Arora *et al.* (1992)[32]	26/male	ATT	Expired after 48 h
Chauhan *et al.* (1988)[21]	35/male	None	Asymptomatic at 6 weeks
Maharaj *et al.* (1986)[33]	49/female	None	Stable after 3 years

NR: Not reported, WLL: Whole lung lavage, GM-CSF: Granulocyte-macrophage colony-stimulating factor, BAL: Bronchoalveolar lavage, ATT: Anti-tuberculous therapy, B/L: Bilateral, LTOT: Long-term oxygen therapy, MMF: Mycophenolate mofetil, IV: Intravenous, PAP: Pulmonary alveolar proteinosis

in the ventilating side of WLL, and ineffective ventilation with DLT. All these complications may be managed easily. Other major complications which may occur in these patients include pneumothorax, hemodynamic compromise, ventilator-associated pneumonia, or death.[34] While performing the WLL, one should be ready for salvage requirement of ECMO, in case severe compromise of ventilation.[55] During the study period, we did not come across any such complication; however, we had ECMO backup facility. Our systemic review of Indian studies also showed that among patients who required treatment, WLL was offered to 56.67% (17/30) and all of those showed improvement; one of the patients required ECMO during WLL.[12]

Some authors, especially for children, have used BAL instead of WLL as a therapeutic modality though results were variable. One child was managed with large volume (exact volume not mentioned) BAL every week and was discharged after 4 months from the hospital. However, this patient also received co-trimoxazole, steroids, and intravenous immunoglobulin (IVIG).[18] Other child who treated with BAL also stayed in hospital for more than 2 months and died after 1 week of discharge.[29] Both these reports suggest that BAL with or without other drugs (co-trimoxazole, steroids, IVIG) is not an optimum treatment for PAP.

Among medical management options, subcutaneous GM-CSF is the most commonly used drug.[48] Considering the fact that reduced GM-CSF effect (e.g. due to altered receptor function or antibodies) contributes to PAP pathophysiology, GM-CSF therapy should have a significant role. In this study, three patients received GM-CSF. One patient received it as the first-line treatment; however, despite treatment, the patient did not improve and WLL was done later. Other two patients received GM-CSF due to the suboptimal improvement following WLL. Indicating that response to GM-CSF may be variable. The factors which may be responsible for variable response include the neutralizing capability of endogenous GM-CSF antibodies and penetration of subcutaneous GM-CSF to reach the site of action, i.e., alveoli. Whatever may be the reason, however, it seems that GM-CSF alone is not an effective therapy for PAP. Therefore, it should be reserved for the patients where either WLL is not possible or there is suboptimal improvement following WLL. Other drugs which have been used for treatment of PAP include rituximab[56] and ambroxol.[57] A reasonable approach for treatment of PAP is patients with severe symptoms, and impairment on physiologic testing should be treated with WLL; patients with progressive disease or those not tolerating WLL should be treated with subcutaneous GM-CSF; and rituximab should be used as the last resort.[7]

Long-term prognosis is unclear. Significant spontaneous improvement has been described in 7.9% of patients.[2] No simple biochemical or clinical parameters are in routine use as prognostic variables. Only 10–15% patients may

die directly from PAP-induced pulmonary failure. A recent study noted a PAP recurrence rate of <30% at 7 years after successful WLL; residual gas exchange abnormalities and exercise intolerance were common, even in the absence of recurrent PAP.[58] In our study, no patient required WLL during follow-up till date.

One of the important features of PAP is presence of macrophage and neutrophil dysfunction which predisposes these patients to increased risk of superinfection with organisms such as *Nocardia*, mycobacteria, and endemic or opportunistic fungi.[1,2] In our systematic review of Indian studies also, 4 (13.33%) patients had concomitant infections (*M. tuberculosis*[17,22] and *P. jiroveci*,[17,22] two each). However, it should be noted that 5 (16.7%) patients were given empirical anti-tubercular therapy before diagnosis.[15,20,31,32] Inappropriate use of ATT is associated with adverse effects and increased risk of multidrug-resistant mycobacteria. Although this is a rare condition, physicians treating such patients should be aware of this differential diagnosis so that appropriate management may be initiated and unnecessary medications may be avoided. Progressive respiratory failure and typical crazy-paving pattern on radiology may be a helpful clue. Such patients should be referred to higher centers with experience in treating such patients.

One of our patients (Case 3) had onset of symptoms in the third trimester of pregnancy. Although she did not have any peripartum complication, her symptoms progressed to Type I respiratory failure. The relationship between pregnancy and PAP is not known. There are only few case reports describing PAP during pregnancy.[59-62] Its presence may lead to perinatal or postnatal complications.[59-62] Whether physiologic changes in pregnancy or alteration in levels of various growth factors predispose to PAP is not known.[63]

This study reports one of the largest case series of PAP from India. Similar to this study, Khan *et al.* also published a case series from another tertiary care hospital.[12] Although the results of both studies are comparable, in this study we were able to demonstrate anti-GM-CSF antibodies in 4 out of 5 patients, therefore confirming the diagnosis of primary PAP. Being a rare disease, it is less likely that the number of patients in any study is going to be huge. This study has given a good overview of clinical profile and management issues of patients with PAP.

CONCLUSIONS

Our study indicates that the PAP is rare disease entity with an incidence of approximately 5 per 1100 hospital admission in respiratory unit at a tertiary care center. The presentation may vary from progressive respiratory failure to totally asymptomatic radiological abnormality. Crazypaving pattern on the chest computed tomography scan is quite typical of PAP. Flexible bronchoscopy can make diagnosis in almost all patients. WLL is safe and the most effective treatment for patients with PAP. A

few patients may require experimental therapy such as GM-CSF, rituximab, and ambroxol.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Seymour JF, Presneill JJ. Pulmonary alveolar proteinosis: Progress in the first 44 years. Am J Respir Crit Care Med 2002;166:215-35.
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. Shah PL, Hansell D, Lawson PR, Reid KB, Morgan C. Pulmonary alveolar proteinosis: Clinical aspects and current concepts on pathogenesis. Thorax 2000;55:67-77.
4. Holbert JM, Costello P, Li W, Hoffman RM, Rogers RM. CT features of pulmonary alveolar proteinosis. AJR Am J Roentgenol 2001;176:1287-94.
5. Ishii H, Trapnell BC, Tazawa R, Inoue Y, Akira M, Kogure Y, *et al.* Comparative study of high-resolution CT findings between autoimmune and secondary pulmonary alveolar proteinosis. Chest 2009;136:1348-55.
6. 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(2 Pt 1):658-62.
7. Leth S, Bendstrup E, Vestergaard H, Hilberg O. Autoimmune pulmonary alveolar proteinosis: Treatment options in year 2013. Respirology 2013;18:82-91.
8. Bansal A, Sikri V. A case of pulmonary alveolar proteinosis treated with whole lung lavage. Indian J Crit Care Med 2013;17:314-7.
9. Thind GS. Acute pulmonary alveolar proteinosis due to exposure to cotton dust. Lung India 2009;26:152-4.
10. Gandhe U, Gandhe R, Nandkumar S, Butani M. Anaesthetic management of a patient undergoing whole lung lavage for pulmonary alveolar proteinosis. Ann Card Anaesth 1998;1:53-5.
11. Sengupta S, Kumar P, Rudra A, Ramasubban S, Mukhopadhyay A. Bilateral whole lung lavage in the treatment of pulmonary alveolar proteinosis. J Anaesthesiol Clin Pharmacol 2007;23:79.
12. Khan A, Agarwal R, Aggarwal AN, Bal A, Sen I, Yaddanapuddi LN, *et al.* Experience with treatment of pulmonary alveolar proteinosis from a tertiary care centre in north India. Indian J Chest Dis Allied Sci 2012;54:91-7.
13. Shende RP, Sampat BK, Prabhudesai P, Kulkarni S. Granulocyte macrophage colony stimulating factor therapy for pulmonary alveolar proteinosis. J Assoc Physicians India 2013;61:209-11.
14. Udwadia ZF, Jain S. Images in clinical medicine. Pulmonary alveolar proteinosis. N Engl J Med 2007;357:e21.
15. Bhattacharyya D, Barthwal MS, Katoch 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.
16. Hasan A, Ram R, Swamy T. Pulmonary alveolar proteinosis due to mycophenolate and cyclosporine combination therapy in a renal transplant recipient. Lung India 2014;31:282-4.
17. Baro A, Shah I, Chandane P, Khosla I. Pulmonary alveolar proteinosis in a 10-year-old girl masquerading as tuberculosis. Oxf Med Case Reports 2015;2015:300-2.
18. Raj D, Bhutia TD, Mathur S, Kabra SK, Lodha R. Pulmonary alveolar proteinosis secondary to *Pneumocystis jiroveci* infection in an infant with common variable immunodeficiency. Indian J Pediatr 2014;81:929-31.
19. Nandkumar S, Desai M, Butani M, Udwadia Z. Pulmonary alveolar proteinosis with respiratory failure-anaesthetic management of whole lung lavage. Indian J Anaesth 2009;53:362-6.
20. Udwadia ZF, Patel DB, Kapadia FN, Gandhe UM, Butani M. Pulmonary alveolar proteinosis with respiratory failure – Therapeutic role of bronchoscopic and whole lung lavage. J Assoc Physicians India 1998;46:738-9.
21. Chauhan MS, Jayaswal R, Rajan RS, Chopra RK, Bhalla IP, Tewari SC. Pulmonary alveolar proteinosis (with review of literature). J Assoc Physicians India 1988;36:445-6.
22. Baldi MM, Nair J, Athavale A, Gavali V, Sarkar M, Divate S, *et al.* Serial lobar lung lavage in pulmonary alveolar proteinosis. J Bronchology Interv Pulmonol 2013;20:333-7.
23. Indira KS, Rajesh V, Darsana V, Ranjit U, John J, Vengadakrishnaraj SP, *et al.* Whole lung lavage: The salvage therapy for pulmonary alveolar proteinosis. Indian J Chest Dis Allied Sci 2007;49:41-4.
24. Sengupta S KP, Rudra A, Ramasubban S, Mukhopadhyay A. Bilateral whole lung lavage in the treatment of pulmonary alveolar proteinosis. J Anesth Clin Pharmacology 2007;23:79-81.
25. Davis KR, Vadakkan DT, Krishnakumar EV, Anas AM. Serial bronchoscopic lung lavage in pulmonary alveolar proteinosis under local anesthesia. Lung India 2015;32:162-4.
26. Babu VA NS, Subramanian S. Rapid dianosis and management of pulmonary alveolar proteinosis. Lung India 2013;30:S44-68.
27. Tousheed S ST, Mohan M, Karnati A, Gupta V. Pulmonary alveolar proteinosis due to chronic cotton dust exposure and hepatitis C infection. Chest 2013;144:439A.
28. Jayaraman S, Gayathri AR, Senthil Kumar P, Santosham R, Santosham R, Narasimhan R. Whole lung lavage for pulmonary alveolar proteinosis. Lung India 2010;27:33-6.
29. Garg G, Sachdev A, Gupta D. Pulmonary alveolar proteinosis. Indian Pediatr 2009;46:521-3.
30. Dixit R, Chaudhari LS, Mahashur AA. Anaesthetic management of bilateral alveolar proteinosis for bronchopulmonary lavage. J Postgrad Med 1998;44:21-3.
31. Sangani BK, Prabhudesai PP, Tandon SP, Vidyeeswar P, Bijur S, Mahashur AA. Pulmonary alveolar phospholipoproteinosis. Indian Pediatr 1993;30:917-9.
32. Arora VK, Seetharaman ML, Veliath AJ. Silicotic alveolar proteinosis with bilateral spontaneous pneumothorax. J Assoc Physicians India 1992;40:760-2.
33. Maharaj B, Singh GP, Pudifin DJ. Pulmonary alveolar proteinosis. A case report. S Afr Med J 1986;70:692-3.
34. Michaud G, Reddy C, Ernst A. Whole-lung lavage for pulmonary alveolar proteinosis. Chest 2009;136:1678-81.
35. Abdelmalak BB, Khanna AK, Culver DA, Popovich MJ. Therapeutic Whole-Lung Lavage for Pulmonary Alveolar Proteinosis: A Procedural Update. J Bronchology Interv Pulmonol 2015;22:251-8.
36. Jayaram Subhashchandra B, Ismailkhan M, Chikkaveeraiah Shashidhar K, Gopalakrishna Narahari M. A rare case of non-small cell carcinoma of lung presenting as miliary mottling. Iran J Med Sci 2013;38:65-8.
37. Moitra S, Puri R, Paul D, Huang YC. Global perspectives of emerging occupational and environmental lung diseases. Curr Opin Pulm Med 2015;21:114-20.
38. Senturk A, Karalezli A, Soyturk AN, Hasanoglu HC. A rare cause of crazy-paving and mediastinal lymphadenopathy: congestive heart failure. J Clin Imaging Sci 2013;3:30.
39. Kulkarni AP. An overview of critical care in cancer patients. Indian J Crit Care Med 2007;11:4-11.
40. Kant S BP. Bronchoalveolar lavage. J Intern Med India 2003;6:99-104.
41. Bhagwat AG DS, Conen PE. Natural history of experimental adjuvant induced pneumonia (EAIP). A histological, histochemical and ultrastructural study of an experimental model of dip in man. Bull Postgrad Inst Med Educ Res Chandigarh 1975;9:68-75.
42. al Khayat A, Nafday S. Pulmonary alveolar proteinosis. Indian J Pediatr 1993;60:827-9.
43. Lee MG, Spencer H, Clarke WF, Rao BN, Lowe M, Nelson M. Pulmonary alveolar proteinosis in Jamaica. West Indian Med J 1982;31:103-10.
44. Kojima J HH, Numata T, Shimizu K, Kawaishi M, Saito K, Arya J, *et al.* Secondary pulmonary alveolar proteinosis associated with IgG4-related disease. European Respiratory Journal 2013;42 (Suppl 57):P2371.
45. Bella A QH, Gupta R, Aleissa M, Syed E. Sirolimus and the "crazy" pneumonia: A case report and review of the literature. Chest 2013;142:460A.
46. El-Dawlatly A, Hajjar W, Alnassar S, Alsafar R, Abodonya A. Continuous positive airway pressure ventilation during whole lung lavage for treatment of alveolar proteinosis - A case report and review of literature. Saudi J Anaesth 2011;5:76-8.
47. Khan A, Agarwal R. Pulmonary alveolar proteinosis. Respir Care 2011;56:1016-28.
48. Khan A, Agarwal R, Aggarwal AN. Effectiveness of granulocyte-macrophage colony-stimulating factor therapy in autoimmune pulmonary alveolar proteinosis: A meta-analysis of observational studies. Chest 2012;141:1273-83.

49. Dodagatta-Marri E, Qaseem AS, Karbani N, Tsolaki AG, Waters P, Madan T, *et al*. Purification of surfactant protein D (SP-D) from pooled amniotic fluid and bronchoalveolar lavage. Methods Mol Biol 2014;1100:273-90.

50. Strong P, Kishore U, Morgan C, Lopez Bernal A, Singh M, Reid KB. A novel method of purifying lung surfactant proteins A and D from the lung lavage of alveolar proteinosis patients and from pooled amniotic fluid. J Immunol Methods 1998;220:139-49.

51. Sharma V, Chatterjee S, Debnath J. Diagnosing pulmonary alveolar proteinosis: Is there any role of radiology? Med J Armed Forces India 2013;69:199-200.

52. Bhattacharyya D. Reply. Med J Armed Forces India 2013;69:200-1.

53. Ravi R MA, Meenal J, Sridharan K. Radiological quiz – Chest. Indian J Radiol Imaging 2006;16:983-4.

54. Udani PM, Mukerji S. Pulmonary alveolar proteinosis. Indian J Child Health 1963;12:256-8.

55. 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.

56. Kavuru MS, Malur A, Marshall I, Barna BP, Meziane M, Huizar I, *et al*. An open-label trial of rituximab therapy in pulmonary alveolar proteinosis.

57. Oda N, Tamai K, Suzuki Y, Yoshimatsu H, Matsuoka H, Matsumoto Y, *et al*. Marked improvement in autoimmune pulmonary alveolar proteinosis with severe hypoxemia in a patient treated with ambroxol: a case report. J Med Case Rep 2015;9:100.

58. 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.

59. Thompson JC, Kishima M, Gomes MU, Menezes Mde A, Perandre Neto J, Pereira PT. Pulmonary alveolar proteinosis: four cases. J Bras Pneumol 2006;32:261-6.

60. Crocker HL, Pfitzner J, Doyle IR, Hague WM, Smith BJ, Ruffin RE. Pulmonary alveolar proteinosis: two contrasting cases. Eur Respir J 2000;15:426-9.

61. Canto MJ, Vives MA, Carmona F, Agusti C, Cararach V, Iglesias X. Successful pregnancy after spontaneous remission of familial pulmonary alveolar proteinosis. Eur J Obstet Gynecol Reprod Biol 1995;63:191-3.

62. Belchior I, Cerdeira AS, Santos M, Braga JS, Aragao I, Martins A. [Successful pregnancy in a severely hypoxemic patient with pulmonary alveolar proteinosis]. Rev Port Pneumol 2011;17(3):139-42.

63. Freymond N, Cottin V, Cordier JF. Infiltrative lung diseases in pregnancy. Clin Chest Med 2011;32:133-46, ix.

Eur Respir J 2011;38:1361-7.