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Whole Lung Lavage in Autoimmune Pulmonary Alveolar Proteinosis: Unique Challenges in a Resource-Limited Setting

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ABSTRACT

Autoimmune pulmonary alveolar proteinosis (PAP) is characterized by antibodies to granulocyte–macrophage colony-stimulating factor (GM-CSF), alveolar macrophage dysfunction, and surfactant accumulation. Whole lung lavage (WLL) is the treatment of choice in patients with PAP and severe hypoxemia. In resource-limited settings, WLL can be performed in the intubated, anesthetized patient who is being one lung ventilated using a Y-type bladder irrigation catheter for saline instillation and drainage.

JEL Classification: Respiratory Medicine

1 | Introduction

Pulmonary alveolar proteinosis (PAP) is a diffuse lung disease characterized by accumulation of lipoproteinaceous materials in the alveoli and terminal airways [1]. It occurs due to impairment of surfactant clearance and defects in alveolar macrophage and neutrophil-mediated host defense. There is little or no lung inflammation and a preserved lung architecture on histopathology [2]. PAP may be primary, secondary, or congenital. Primary PAP includes the autoimmune or hereditary variants. Autoimmune PAP is characterized by circulating autoantibodies against granulocyte–macrophage colony-stimulating factor (GM-CSF). Secondary PAP occurs due to exposure to high level of dust, infection, or malignancy. Congenital PAP occurs due to defects in surfactant production.

Most of the patients present in their fourth or fifth decade of life with symptoms of progressive dyspnea, cough, fatigue, and weight loss [1, 3]. Whole lung lavage (WLL) is the treatment of choice in patients with respiratory failure. We hereby report a case of 28-year-old lady with severe autoimmune PAP and hypoxic respiratory failure. She was successfully treated with three sessions of sequential WLL. There were multiple challenges in her treatment due to financial constraints and limited resources.

2 | Case History/Examination

A 28-year-old unmarried lady presented to our hospital with a history of shortness of breath and cough for 1 year with occasional scanty sputum production. She was referred to the Emergency Department with worsening dyspnea for last 2 weeks as she required supplemental oxygen to maintain saturation while breathing room air. There was no chest pain, hemoptysis, palpitation, limb swelling, fever, or weight loss. There was no

history of exposure to household or environmental fumes and dust or drugs.

On physical examination, she was conscious, oriented, and alert. Heart rate was 96 bpm and regular; respiratory rate was 36/min, and pulse oximetry saturation (SpO_2) was 62% at room air. Oxygen saturation improved to 89% with supplemental oxygen of 15 L/min ($FiO_2 = 60\%$) delivered through a venturi mask. Chest auscultation revealed diffuse bilateral crackles. The rest of the physical examination was unremarkable.

3 | Methods (Investigations, Differential Diagnosis, and Treatment)

Lab investigations revealed a hemoglobin of 14 g/dL, total leukocyte count of 8000/cumm, and a platelet count of 250×10^3/cumm. Peripheral blood smear was normal; so were the liver and the renal function tests. Antinuclear antibody and HIV serology were negative. Arterial blood gas (ABG) analysis showed partial pressure of oxygen (PaO_2) 44 mmHg and the alveolar-arterial gradient (A-a gradient) of 458 mmHg. Chest X-ray revealed bilateral interstitial and alveolar opacities predominant in the middle and lower lung fields (Figure 1A). Sputum smear microscopy for acid-fast bacilli and Xpert MTB/RIF assay were negative. Transthoracic echocardiography was normal. A high-resolution computed tomography (HRCT) scan of chest was done which showed diffuse and widespread areas consolidation and ground glass opacities (GGOs) with superimposed smooth interstitial thickening giving a "crazy paving" pattern (Figure 2A).

The differential diagnosis at this point included PAP, acute pulmonary edema, acute respiratory distress syndrome, and *Pneumocystis jirovecii* pneumonia. Our patient had longstanding symptoms, no immunocompromising condition, and a normal cardiac examination and echocardiographic findings. Based on the clinical-radiological features, a strong suspicion of PAP was made. Serum sample for anti-GM-CSF antibodies was sent to pulmonary alveolar proteinosis laboratory at Cincinnati Children's Hospital, Ohio, USA. GM-CSF autoantibody concentration was 238.9 mcg/mL (normal < 3.1 mcg/mL). Initially, flexible bronchoscopy with diagnostic bronchoalveolar lavage (BAL) was deferred as patient had severe hypoxemia. Based on clinical-radiological features and a positive anti-GM-CSF antibody, a provisional diagnosis of autoimmune PAP was made, and the patient was planned for WLL.

BAL was performed during the first WLL session. BAL return was thick and milky white with sediment formation on standing. BAL fluid was sent for cytology, cultures, acid-fast bacilli (AFB), and Xpert MTB/RIF assay. Bronchoalveolar lavage (BAL) cytology results revealed amorphous, eosinophilic materials along with few scattered macrophages. Periodic acid–Schiff (PAS) stain was positive (Figure 3). AFB, Xpert MTB/RIF assay, and cultures were negative. A diagnosis of autoimmune PAP was established.

4 | Whole Lung Lavage Procedure

WLL was done under general anesthesia. She was intubated with a double-lumen endotracheal tube (DLT) of size 35 Fr. The correct position of DLT was confirmed by a flexible bronchoscope. Initially, both lungs were ventilated for approximately 5 min to oxygenate the patient adequately. Then, one lung ventilation (OLV) was performed for 5 min and the side of the lung to undergo WLL was clamped and placed in a dependent position to maintain oxygen saturation above 90%. Bair Hugger was used to warm the body during the procedure. Y type TUR bladder irrigation catheter with stopcock (Figure 4) connected to the DLT was used for instillation of saline and collection of effluent. The vertical limb was used for instillation of saline. One limb was connected to the DLT for inflow of saline and the other limb directed to the collecting bottles. Each cycle consisted of instillation of aliquots of 1 L saline warmed to the body temperature (37°C). After instillation, chest percussion was performed for 5 min by clamping both limbs of the Y connector. Then, gravity-dependent drainage of the effluent was done by elevating the foot end of the bed (Trendelenburg position) and unclamping of limb directed to the collecting bottles. Several cycles were repeated until the effluent was clear or as tolerated by the patient. Serial effluent was less turbid during each cycle of WLL (Figure 5A).

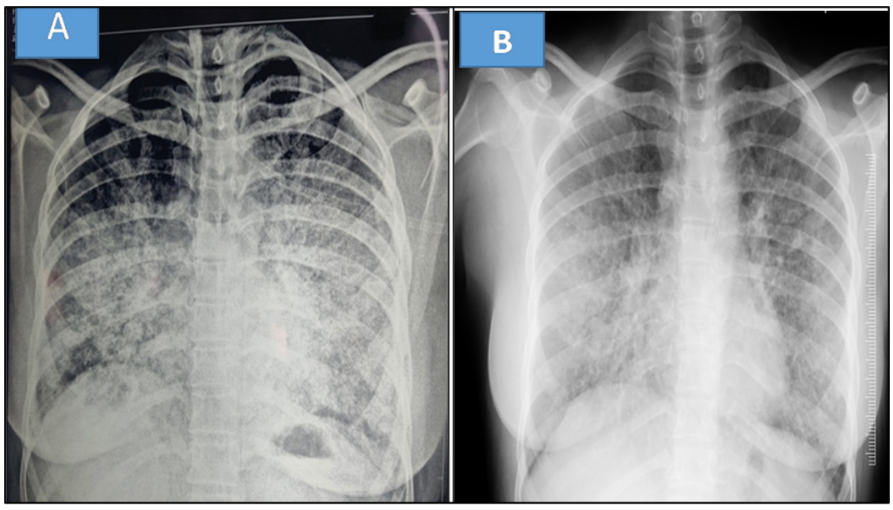

FIGURE 1 | (A) Shows chest X-ray taken at the time of presentation and (B) after three sessions of whole lung lavage.

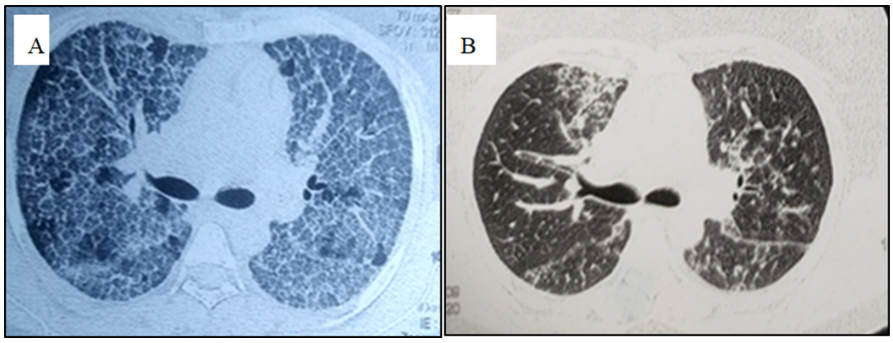

FIGURE 2 | HRCT chest showing diffuse ground glass opacities and consolidation with superimposed smooth interstitial thickening giving "crazy paving" pattern at presentation (A), significant clearing of GGO's and interlobular septal thickening after three sessions of WLL (B).

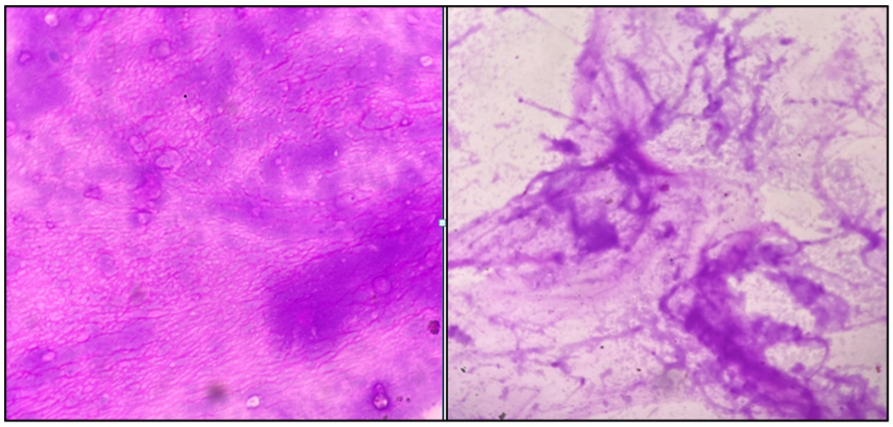

FIGURE 3 | BAL fluid cytology showing periodic acid–Schiff (PAS) stain-positive amorphous, eosinophilic material along with few scattered macrophages.

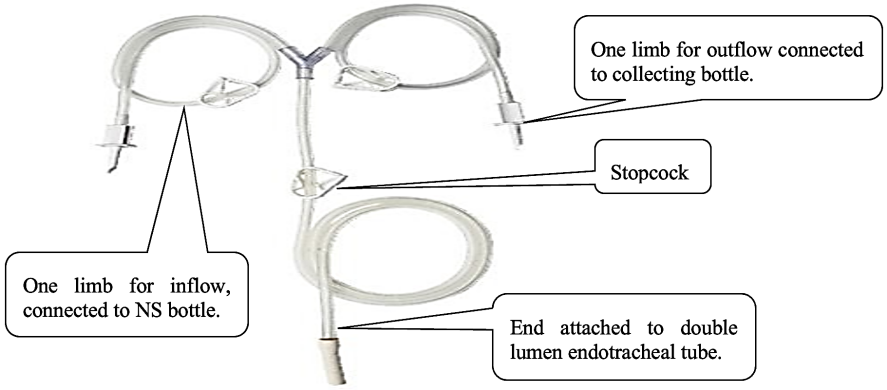

FIGURE 4 | Y type TUR bladder irrigation catheter. The labels show catheter attachments during WLL procedure.

Our patient underwent three sessions of WLL. The first session was performed on the left side using 6500 mL of warm normal saline. Aliquots of 500–1000 mL were instilled. Transient desaturations, with SPO_2 falling below 85%, were encountered during the instillation—drainage cycles. The saturation improved when the patient was placed in reverse Trendelenburg position. However, after 10 cycles, there was persistent desaturation below 85% which did not improve by patient positioning and the procedure was terminated. After the procedure, the patient was observed in the ICU and was extubated after 10 h. Manual chest physiotherapy along with positioning maneuvers was continued. After the first session of WLL, patient improved clinically, and oxygen saturation was maintained with supplemental oxygen via 40% Venturi mask. The alveolar-arterial gradient improved to 193 mmHg.

Second session of WLL was planned after 2 weeks of the first procedure on the right side. However, during the procedure, left lung ventilation resulted in persistent hypoxemia ($SPO_2 < 85\%$). Hence, an on-table decision to repeat the lavage of the left lung was made as the oxygen saturation was maintained during right lung ventilation. Second session of WLL was done using 14 L of saline on the left side (Figure 5B). Third session was performed after 3 weeks in the right side with 10 L of saline (Figure 5C).

FIGURE 5 | Serial lavage samples showing milky effluent fluid with sedimentation obtained during WLL. First session (A), second session (B), and third session (C). Serial aliquots show progressive clearing.

TABLE 1 | Summary of WLL sessions.

Monitored parameters	First session (Left)	Second session (Left)	Third session (Right)
Instilled volume (mL)	6500	14,000	10,000
Drained volume (mL)	6100	13,100	9400
Retained volume (mL)	400	900	600
Procedure time	2 h 40 min	3 h 30 min	2 h 40 min
Preprocedure			
A-a gradient	459 mmHg	229 mmHg	113 mmHg
Postprocedure (24 h)			
SPO2	92% with 40% FiO_2	90% with 28% FiO_2	92% with 21% FiO_2
PaO2	48 mmHg	58 mmHg	67 mmHg
A-a gradient	193 mmHg	105 mmHg	12.9 mmHg

The patient tolerated the second session and the third session well, and WLL was terminated after there was a significant clearing of the effluent without significant sediment in each session. The parameters monitored before, during, and after the WLL sessions are provided in Table 1.

5 | Conclusion and Results (Outcome and Follow-Up)

After three sessions of WLL, there was a significant improvement in the dyspnea and her SpO_2 improved to 92% at room air. Chest X-ray and HRCT chest showed significant resolution of consolidation and GGOs (Figures 1B and 2B). ABG showed PaO_2 67 mmHg and A-a gradient 12.9 mmHg. She was discharged with advice to follow up regularly and report back if the symptoms recurred. At the time of discharge, she was explained about the risk of recurrence and need for regular monitoring. At 3 months of follow-up, she was asymptomatic with a SPO_2 of 95%, PaO_2 88 mmHg, and A-a gradient 2 mmHg breathing room air. Spirometry showed a normal FEV_1, FVC, and FEV_1/FVC ratio. At 1-year follow-up, she reported no respiratory symptoms, a normal SpO_2, and chest X-ray. We have advised her to follow up regularly and explained the possible need for a repeat procedure if hypoxemia recurs.

6 | Discussion

PAP is a rare diffuse lung disease with a reported incidence of 0.37 per 100,000 population [4]. Ninety percent of patients have

an autoimmune etiology. Nearly a third of the patients are asymptomatic. Symptoms when present are nonspecific [3]. HRCT scan is characterized by the presence of widespread GGOs and consolidation with superimposed smooth interstitial thickening imparting a "crazy paving pattern" [5]. Crazy paving is also seen in acute pulmonary edema, *Pneumocystis jirovecii* pneumonia, viral pneumonia, and ARDS. Clinical history, cardiac evaluation, sputum, and BAL examination are used to distinguish these conditions. In our case, BAL fluid was milky and formed sediments on standing indicating the presence of excess surfactant proteins and phospholipids. Cytology smears of the sediment showed the presence of periodic acid–Schiff (PAS) stain-positive amorphous, eosinophilic material establishing a diagnosis of PAP. In PAP, lung biopsy shows little or no inflammation and a preserved parenchymal architecture. We did not perform a lung biopsy in our patient as there was a high risk of worsening respiratory failure and need of mechanical ventilation. Autoimmune PAP is characterized by the presence of anti-GM-CSF antibody, which binds to GM-CSF, decreases its level and biological activity, and plays a key role in the pathogenesis [6]. Our patient had a raised anti-GM-CSF antibody levels indicating an autoimmune etiology. Anti-GM-CSF antibody positivity has high sensitivity and specificity for autoimmune PAP [7].

Whole lung lavage is performed in PAP for decline in lung function, decrease in resting PaO2 < 70 mmHg, alveolar-arterial O2 gradient ≥ 40 mmHg, or severe dyspnea and hypoxemia at rest or exercise [8]. Our patient met all the above criteria, and whole lung lavage was mandatory and would be lifesaving for her. We planned a sequential WLL procedure in view of severe respiratory failure. The management of this case posed multiple unique challenges to us. We had a previous experience of performing WLL during our training (fellowship), but this was the first procedure being done at our center. Our anesthesiologists, although well versed with providing GA with one lung ventilation for thoracic surgeries, were concerned regarding the tolerability of the procedure, risks of hypoxia, and its complications. There was a high risk of failure to maintain SPO_2 during the procedure, hence an unsuccessful attempt. In such cases, a veno-venous extracorporeal membrane oxygenation (ECMO) support is needed to correct the hypoxemia and complete the procedure [9]. However, ECMO services were not available at our center then. In view of severe disease with severe hypoxemia, the patient and her father were explained in detail about our limitations and were given the option of visiting other centers with better facilities and ECMO services, which is usually abroad. The patient declined to visit other center due to financial constraints. Hence, we decided to proceed with WLL at our center with a high-risk consent. Our hospital is government-owned referral hospital in Nepal, and we performed the procedure free of cost to this indigent patient.

WLL was first described by Ramirez and colleagues in 1965, and Wasserman and coworkers modified it later in 1968 [10]. WLL is the most effective treatment for PAP and leads to immediate improvement [11]. Meticulous monitoring and charting of correct position of the DLT, oxygenation, capnography, dynamic lung compliance, and volumes of saline infused and recovered are essential during the procedure. We chose to lavage the left side first for two reasons. First, the right lung is larger than the left and OLV may be better tolerated on the right side. Additionally, our patient had more radiological involvement of the left side. Despite this, the patient developed severe desaturations leading to premature termination of the first WLL session. Severe disease and poor pulmonary reserve were the major reasons that led to an inadequate procedure. The patient was placed in the Trendelenburg position during the drainage to ensure complete drainage and avoid fluid overload. This might have contributed to worsening of oxygenation due to cranial migration of saline and flooding of upper lobes.

During the second session, we had to repeat the lavage on the left side as the first session was inadequate. Most of the studies report a sequential WLL, in separate sessions, spaced two to three weeks apart [12]. However, in milder cases, bilateral lung lavage can be performed in a single session [13]. Several procedural aspects of WLL like number and interval between sessions, choice of the side, amount of fluid, and use of percussion device are not well defined and vary from center to center [14].

Inhaled recombinant human GM-CSF may be considered in severe autoimmune PAP as it has shown to improve gas exchange. If used before WLL, it may result in improvement of hypoxia and better tolerance of the WLL procedure. Subcutaneous or inhaled GM-CSF is also sometimes used postprocedure to prevent recurrence [15]. A randomized controlled trial of inhaled GM-CSF showed a modest improvement in oxygenation in autoimmune PAP. However, there were no clinical benefits in patients with mild-to-moderate hypoxemia [16]. We did not use GM-CSF in our patient as it is not readily available in our country and is expensive.

Repeated partial or unilateral lung lavage using a flexible bronchoscope may also be an option for treatment of PAP in resource-limited settings. However, this approach has only been reported in a few cases with milder disease in the literature [17, 18]. We did not plan flexible bronchoscopic lavage in our patient due to two reasons. First, the volume of saline aliquots instilled through a flexible bronchoscope would be very small and the procedure time would be longer. Second, there is a risk of spillage of infused saline into the non or less involved lung regions and further worsening of oxygenation. The greatest advantage of one lung ventilation is that it prevents the spillage of saline to the side being ventilated.

PAP is reported to recur in some patients due to reaccumulation of surfactants with recurrence of the symptoms. Studies report that around 70% of patients remain free from recurrent PAP at 7 years after WLL [19]. We have informed this aspect to the patient, advised her to follow up regularly and explained the possible need for a repeat procedure if it recurs. Our case highlights the challenges of treating severe PAP for the first time in a resource-limited setting. Meticulous planning with a team approach is the key to success.

Author Contributions

Ashesh Dhungana: conceptualization, data curation, investigation, supervision, validation, writing – original draft, writing – review and editing. **Buddhi Sagar Lamichhane:** data curation, writing – original draft, writing – review and editing. **Prajowl Shrestha:** data curation, investigation, supervision, writing – original draft, writing – review and editing. **Deepa Kumari Shrestha:** data curation, validation, writing

– original draft, writing – review and editing. **Ritamvara Oli:** data curation, writing – original draft. **Shreya Dhungana:** data curation, writing – original draft. **Pratibha Bista:** data curation, writing – review and editing.

Ethics Statement

The authors have nothing to report.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images in accordance with the journal's patient consent policy.

Patient consent statement: Available.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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