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Pulmonary Alveolar Proteinosis- Report of a Rare Case in a 28 Year Old Male

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I. Introduction

Pulmonary alveolar proteinosis (PAP)[1,2] is a rare disease affecting the lung. It is a diffuse lung disease characterized by the accumulation of periodic acid-Schiff (PAS)-positive lipoproteinaceous material in the distal air spaces. Rosen, Castleman and Liebow [3] first described PAP. Normally surfactant present in lungs helps to reduce alveolar surface tension and thereby preventing alveolar collapse. Surfactant catabolism [4] occurs in alveolar macrophages and the process requires GM-CSF (granulocyte-macrophage colony-stimulating factor). Disruption in the level of GM-CSF leads to accumulation of lipoproteinaceous material. The accumulated substance causes interference to normal gas exchange as well as lung expansion and may results in respiratory failure.. Patients usually presents with progressive dyspnoea on exertion without much findings on examination. Here we are reporting a case of Pulmonary Alveolar Proteinosis in 28 year old male patient.

II. Case Report

This 28 years old non smoker male patient presented with progressive exertional dyspnoea and dry cough for 2 years. Modified Medical Research Council (mMRC) dyspnoea scale of the patient at the time of presentation was Grade 2. There was no history of exposure to pets, chemicals and no history of connective tissue disease. Past medical history was uneventful. On examination, his vitals status were stable and the oxygen saturation at room air was 93%. General examination and Pulmonary system examination was normal.

He was investigated further. Chest X ray showed bilateral lower zone reticular shadows. HRCT(High Resolution CT) chest showed bilateral crazy pavement pattern in all the three lobes(Figure 1). There was moderate restriction (FEV1/FVC-89.6,FEV1- 67.3%,FVC-62.9% and TLC-48.4%) in spirometry with severe impairment of DLCO (diffusing capacity of the lungs for carbon monoxide) 33.7%. He had oxygen desaturation upto 83% during 6 minute walk test and covered a distance of 688 meters. ANA profile was negative. Bronchoscopy BAL (Broncho Alveolar Lavage) and TBLB(Trans bronchial lung biopsy) done from right lower lobe which showed milky fluid. Microscopy revealed PAS stain positive macrophages suggestive of pulmonary alveolar proteinosis. BAL differential count showed 85% lymphocytes, 2% neutrophils and rest macrophages. It was negative for atypical cells. TBLB showed mucosa only. BAL AFB (Acid Fast Bacilli), culture, cytology and PCP(Pneumocystis Pneumonia) staining was negative. Based on his clinicoradiological and bronchoscopic picture diagnosis of pulmonary alveolar proteinosis was made. Even though we were unable to perform serum or BAL GM CSF (Granulocyte-macrophage colony-stimulating factor) level.

Since patient was not affording for treatment with GM CSF, we decided for lung lavage. Considering the complications and extensive need for more resources and monitoring for whole lung lavage, we decide to do sequential lobar lavage(Figure 2). First lavage was done from right lower lobe. It was done under general anaesthesia with 8.5 size ET (Endotracheal) tube. Fibre optic bronchoscope was passed through the adapter attached over ET tube. Then bronchoscope was wedged first in medial basal segment. 50 ml warm saline (37 degree C) was instilled through the working channel followed by retrieval using wall suction. We instilled 1500 ml warm saline (37 degree C) in 50 ml aliquots and 1200ml milky white fluid aspirated. During procedure there was no complications. Post procedure after extubation, he had desaturation. It was managed by using CPAP(Continuous positive airway pressure) with 10cm pressure along with oxygen. Along with that intravenous FUROSEMIDE 40mg was also given. CPAP was continued for 4 hours and was able to keep him without oxygen support. He was discharged next day. Similarly sequential lobar lavage was done from left lower lobe, right middle lobe and left upper lobe and lingua at 1 week interval(Table 1). It was done using 3000ml warm saline and around 2500ml milky white fluid aspirated which showed gradual clearing fig. Each procedure was well tolerated by patient. Post procedure period was well managed by using CPAP and diuretics

After four sequential lobar lavage patient had significant improvement in dyspnoea and cough. Saturation improved to 97% room air from baseline 93%. Follow up CT chest also showed marked clearing of both lower lobes, lingua and right middle lobe (fig 3)

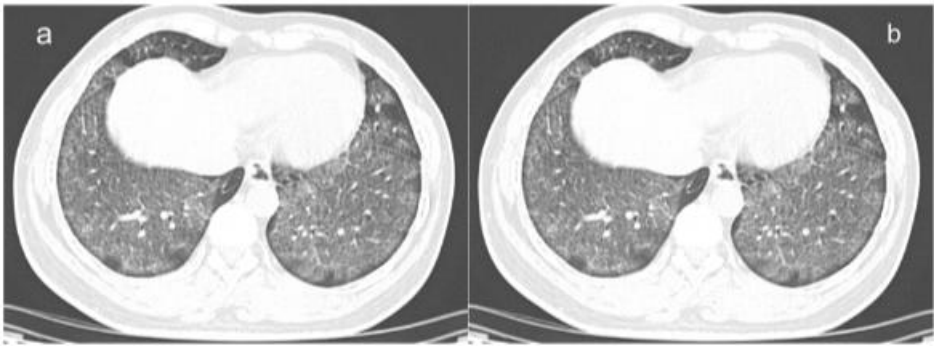

Figure1. HRCT showing bilateral (a) lower lobe (b) right middle lobe and Lingula crazy pavement pattern at presentation

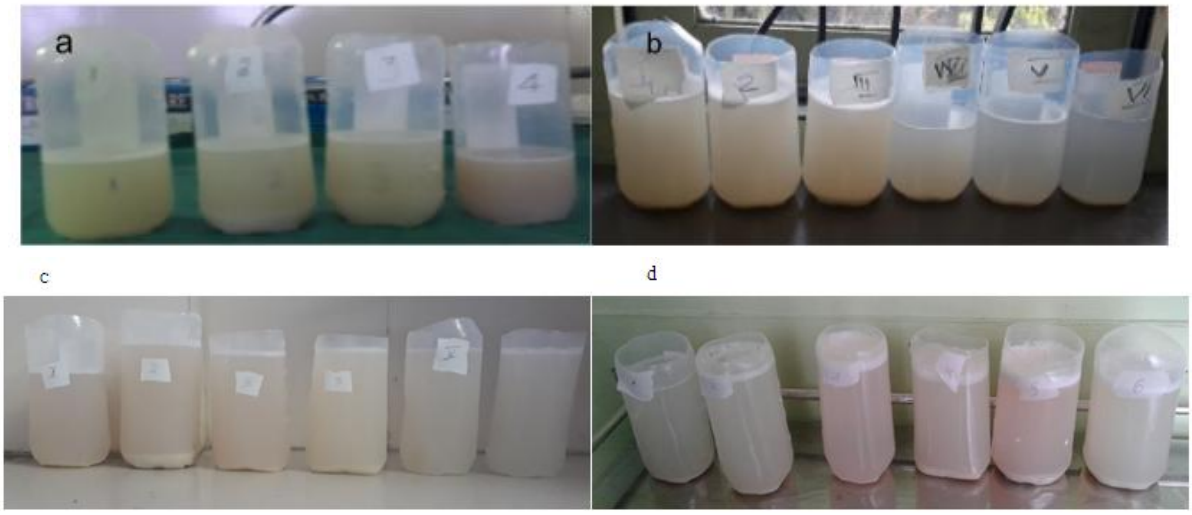

Fig 2 Shows sequential lobar lavage from right lower lobe(a), left lower lobe (b), right middle lobe (c) and left upper lobe and Lingula (d)

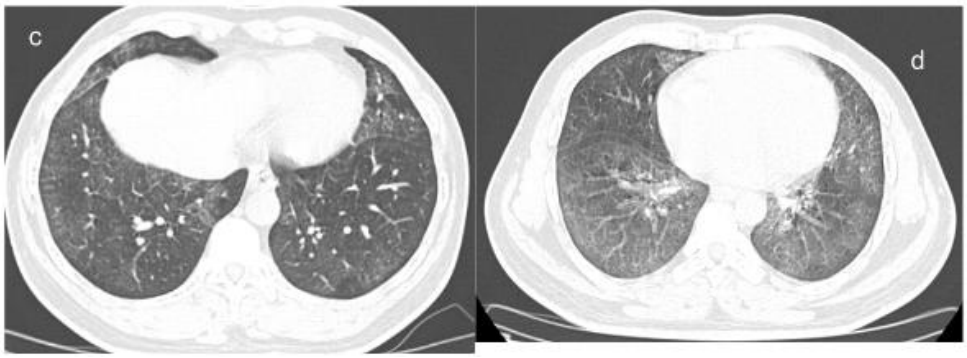

Figure 3. Follow up HRCT with significant clearing of (c) lower lobe (d) right middle lobe and Lingula

TABLE 1.The site and amount Lobar lavage

Day	Site	Input (ml)	Output (ml)
1	Right LL	1500	1200
8	Left LL	3000	2200

18	Right ML	3000	2400
30	Left UL/Lingula	3000	2400
Total	-	10500	8200

LL indicates lower lobe, ML middle lobe, UL-upper lobe

III. Discussion

PAP is caused by a group of disorders that Impairs the production and clearance of Surfactant. It has an incidence of 0.36 cases per million population worldwide. There are three main types of PAP. First one is autoimmune and hereditary PAP which is caused by disruption of granulocyte-macrophage colony-stimulating factor signalling (GM-CSF) [5,6,7,8]. Second one is congenital PAP due to disorders of surfactant production. The last one is secondary PAP, the secondary form of PAP develops in adulthood and is found in association with high level dust exposures, haematologic malignancies and after allogeneic haematopoietic cell transplantation for myeloid malignancies.

The clinical presentation of disease in patients with PAP are variable. It ranges from Asymptomatic patients, to progressive dyspnoea on exertion with dry cough as in our case to fatal respiratory failure. It may even predispose to lung infection with various organisms.

Investigation of choices includes HRCT chest shows crazy pavement pattern, Spirometry shows restrictive pattern along with disproportionately low DLCO and definitive diagnosis of PAP is based on the presence of PAS positive lipoproteinaceous material in BAL sample and on a trans bronchial or surgical lung biopsy.

The mainstay of treatment for PAP is Whole lung lavage [9] (WLL). It is done under general anaesthesia via a double-lumen endotracheal tube. WLL requires a multidisciplinary team consisting pulmonologists, anaesthetist, and respiratory therapist. It may take many hours for the desired result. Careful charting and monitoring of oxygenation, correct position of the double-lumen endotracheal tube, dynamic lung compliance, and recovery of the infused saline are important for preventing complications. Complications of WLL include malpositioning of the endotracheal tube, saline spillover into the ventilating side, hypoxaemia or hypotension, ineffective ventilation with DLT(double-lumen tube), pneumothorax, haemodynamic compromise, ventilator-associated pneumonia, or death.

Use of recombinant GM-CSF [10,11] by inhalation or subcutaneous route remains off-label for autoimmune PAP. Initial studies suggests that the proportion of responders to GM-CSF is less compared to WLL. Other Therapies such as Rituximab [12 ,13] which kills B-cells responsible for GM-CSF auto antibodies. Therapeutic plasma exchange [14, 15] which is used to remove GM-CSF auto antibodies from blood also have been employed in individual patients; further data are needed before routinely recommending these options.

Another alternative procedure is selected lobar lavage [16] by using flexible bronchoscopy. It is very safe procedure and also is simple and cost effective treatment for PAP. It can be performed in mild diseases, severe diseases which are not stable to undergo WLL and also not only in milder disease, but also when extracorporeal membrane oxygenation is not available.

When all of the other treatment modalities have failed or patient develops significant pulmonary fibrosis, then only lung transplantation become an option and the disease may also recur in the transplanted lung as well.

The outcome of Pulmonary alveolar proteinosis after treatment also variable. It ranges from stable disease with recurrences, spontaneous remission and some may even go to progressive impairment of respiratory function despite adequate treatment. In our case, the patient has spontaneous remission till date.

IV. Differential Diagnosis

Differential diagnosis of Pulmonary alveolar proteinosis includes Pulmonary, Pneumocystis pneumonia and Atypical mycobacteria pneumonia.

a) Pulmonary edema has a homogenous appearance and lacks the granularity typical of PAP

b) The exudate of pneumocystis pneumonia has a frothy or foamy appearance due to the negative image of the cyst form of *Pneumocystis jirovecii*

c) Atypical Mycobacteria Pneumonia- Alveolar macrophages more prominent than fluid, Mycobacterial stains positive

V. Conclusion

In conclusion, this case of pulmonary alveolar proteinosis shows characteristic x-ray and CT findings. It also highlights BAL and lung biopsy as the best tool for definitive diagnosis and the effectiveness of Whole

lung lavage as one of the best treatment modalities. It is noteworthy that further researches are essential for understanding more about this disease.

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