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PULMONARY ALVEOLAR PROTEINOSIS - A CASE REPORT AND REVIEW OF LITERATURE

Medicine

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ABSTRACT

Pulmonary alveolar proteinosis (PAP) is a rare disorder characterised by accumulation of lipoproteinaceous material in the alveolar air spaces. Diagnosis depends on histopathological and radiological features. Treatment includes whole lung lavage (WLL) and GM-CSF therapy. We present a case report of primary idiopathic PAP treated with bilateral whole lung lavage. A 50 year old female presented with history of progressive breathlessness and recurrent lower respiratory tract infection. There were bilateral basal fine crepitations on auscultation and she was maintaining saturation of 70% at room air. Serial chest radiographs showed persistent bilateral alveolar opacities. HRCT thorax showed crazy paving pattern involving both lungs. BAL fluid showed lipoproteinaceous material which was PAS stain positive. Patient was subsequently treated with bilateral WLL following which there was radiological and clinical improvement.

KEYWORDS

Pulmonary alveolar proteinosis, crazy paving pattern, whole lung lavage.

INTRODUCTION

Pulmonary alveolar proteinosis (PAP), is an extremely rare disorder first described by Rosen et al in 1958[1].Since then more than 260 case reports have been reported till date[2]. The annual incidence of PAP is 0.36-0.49 and prevalence is 3.7–6.2 cases per million population[2].

In PAP, lipoproteinaceous periodic acid Schiff (PAS) positive material which is amorphous and insoluble gets accumulated in the alveolar spaces, and leads to defective gas exchange[1]. Granulocyte Monocyte colony stimulating factor (GM-CSF) plays a substantial role in homeostasis of pulmonary surfactant. PAP has been divided into primary PAP, secondary PAP, and congenital PAP based primarily on pathogenesis involved.

We present a case of pulmonary alveolar proteinosis in a 35 year old female treated with bilateral whole lung lavage.

CASE REPORT

The patient presented with history of breathlessness which was insidious in onset and had gradually progressed from grade 1 to grade 3 MMRC over a course of last 4-5 months. The patient also gave history of repeated respiratory tract infections associated with cough with expectoration and fever for which she was treated with intravenous antibiotics following which there was some improvement in cough but the breathlessness continued to worsen over time.

There was no history of allergic symptoms, no childhood history of episodic breathlessness or wheezing suggestive of asthma. No history of smoking or exposure to biomass fuels. There was no history of tuberculosis or hematogenous disease. No history of joint pains , rash or photosensitivity. Patient was currently not on any medications. The patient had no environmental and occupational organic or inorganic dust exposure.

On physical examination the patient was having pulse-108/min, BP-110/70 mmHg ,RR-34 breaths per minute, and on auscultation bilateral basilar fine crepitations were heard. She was maintaining spo2 of 89% on O2 at 4L/min and was desaturating to spo2 70% at room air. Arterial blood gas showed moderate hypoxemia with hypocapnia. CBC showed Hb of 17.6g/dl, total count of 15000 , platelet count of 2.4 lacs , haematocrit of 55.3 %.RFTs and LFTs were normal. Pulmonary function tests could not be performed as the patient was too breathless.

2D ECHO was normal with ejection fraction of 55%. Chest x-ray(Figure 2) was showing alveolar opacities in bilateral midzone and lower zone and was showing increase in number of opacities compared to the chest x-rays taken previously when the patient was treated as pneumonia.

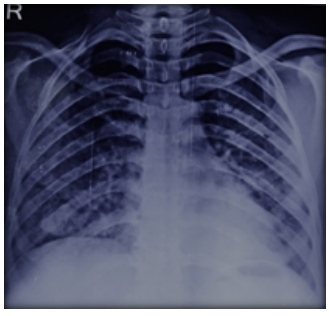

Figure 1

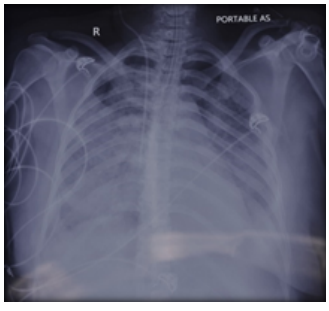

Figure 2

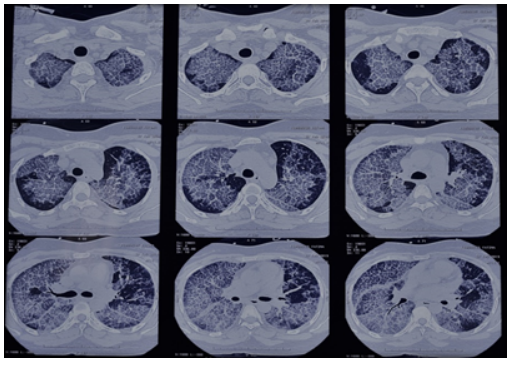

Figure 3

High resolution CT scan of thorax showed patchy areas of ground glass opacities with interlobular septal thickening within these areas in both lungs throughout suggestive of crazy paving pattern(Figure 3) .

Relative subpleural sparing seen . No evidence of consolidation or pleural effusion seen. Few pre vascular nodes seen largest measuring 13 into 7 mm.

C reactive protein was 48mg/dl . Anti nuclear cytoplasmic antibody was negative.sBronchoalveolar lavage fluid had a thick waxy appearance(Figure 4) and smear showed plenty of pulmonary alveolar and foamy macrophages against a granular fluid background showing a few lymphocytes , neutrophils and a few eosinophils. PAS stain showed PAS positive material and PAS positive globules within the cytoplasm of alveolar macrophages.These findings were consistent with pulmonary alveolar proteinosis(Figure 5). The patient was diagnosed as a case of primary idiopathic PAP as testing for anti GM-CSF autoantibodies was not available to prove it as autoimmune PAP.

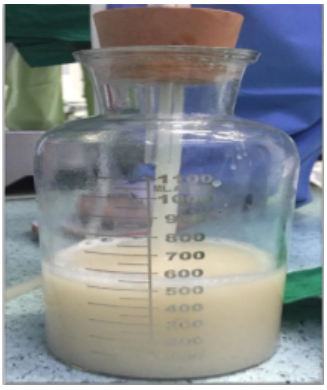

Figure 4

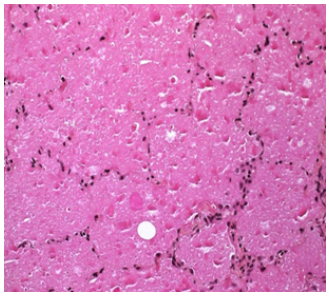

Figure 5

The patient was admitted in ICU and put on non invasive ventilation. After the diagnosis of PAP was confirmed , left sided whole lung lavage was done . About of 4.5L of normal saline was infused with an output of 2.8 L . The procedure had to be stopped as the patient began to desaturate and the saturation had dropped to 75% which was not improving. Right side whole lung lavage was attempted after few days where 8L of normal saline was infused. Following this the patient developed rigth sided pleural effusion(Figure 6), which is a common complication of whole lung lavage and was started on intravenous diuretics for the same.

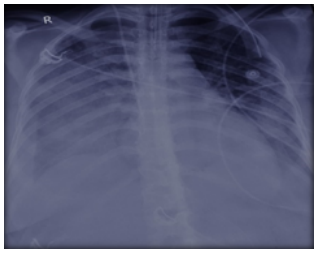

Figure 6

The patient then started developing fever and total counts had increased to 24000. Blood culture showed growth of enterobacter cloacae and the patient was started on antibiotics according to the sensitivity pattern. Patient responded well to the antibiotics and the fever subsided , with total counts decreasing from 24000 to 7800.

Repeat x-ray chest was showing decrease in the number of alveolar opacities post lavage. Repeat HRCT thorax done after whole lung lavage was also showing reduction in ground glass opacities bilaterally (Figure 7).

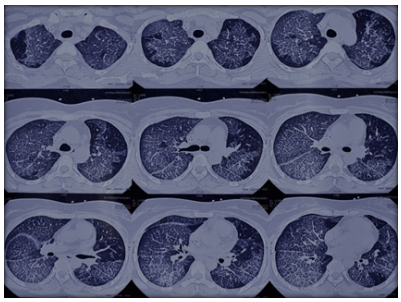

Figure 7

Patient's condition improved gradually and the oxygen requirement also came down. On ABG, pO2 improved from 59.3mmHg at admission to 73.2mmHg at discharge.

Patient was hemodynamically stable and maintaining saturation with oxygen at 1L/min which she was advised to continue at home as long term oxygen therapy. Patient had significantly improved symptomatically post whole lung lavage with improved saturation and markedly reduced breathlessness. She was advised to discontinue long term oxygen therapy as she was maintaining SPO2 of 99% at room air. Patient was followed up at the end of 1 month and 6 months with PFT, DLCO. HRCT thorax and ABG was repeated at the end of 6 months. FVC increased from 59% to 62% and DLCO increased from 28% to 53.9%. HRCT showed further reduction in ground glass opacities (Figure 8).

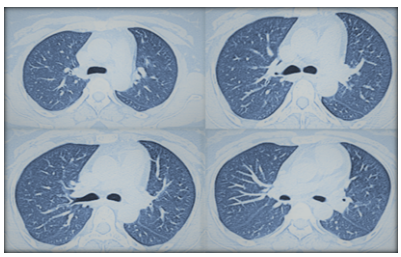

Figure 8 HRCT

CASE DISCUSSION

PAP is a rare disorder in which there is abnormal surfactant deposition in the alveoli. This surfactant is composed of lipids, proteins and small amount of carbohydrates. The most important pathogenetic factor is impaired functioning of GM-CSF signalling which affects the terminal differentiation of the alveolar macrophages affecting their function and causing abnormal clearance of surfactant leading to its alveolar accumulation[3].

PAP is primarily divided in the following three types based on the pathogenetic process
1) Primary PAP
2) Secondary PAP
3) Congenital PAP

Primary PAP: It is further divided into Hereditary PAP and Autoimmune PAP. In hereditary PAP there is defect in genes encoding for GM-CSF receptor alpha chain, that is the CSF2RA and the beta chain which is encoded by CSF2RB gene. The various types of mutations that can cause hereditary PAP include missense mutations, nonsense mutations, small insertions and deletions, exon deletion, and gene deletion[3].

Autoimmune PAP occurs due to production of GM-CSF autoantibodies which affect the functioning of the GM-CSF signalling. These auto antibodies are mainly of G subclass mostly consisting of IgG_1 and IgG_2 They have very good affinity towards GM-CSF and cause destruction of their biological activity[4]. If the cause is unknown it is also called as idiopathic PAP.

Secondary PAP: Secondary PAP occurs either due decrease in

number or decrease in function of alveolar macrophages which in turn affects surfactant clearance. The various causes and conditions associated with secondary PAP are listed below

- Hematological malignancies
- Primary myelodysplasia
- Infectious diseases
- Organ transplantation followed by immunosuppression
- Immunodeficiency disorders such as SCID or IgA deficiency
- Heavy exposure to inorganic dusts such as silica, titanium[5].

Congenital PAP: It occurs in neonates and infants due to abnormal production of surfactant. There are different types of defects in the genes encoding SP-B, SP-C, ABCA3 – which is a lipid transporter expressed in type II alveolar epithelial cells, or TTF-1 – a transcription factor essential for lung development and surfactant expression.[6-7]

Clinical Presentation

Symptoms of autoimmune PAP usually start between age of 20-50 years. They include progressive dyspnoea which is insidious in onset, cough, fatigue and fever and sputum production if there is concurrent secondary infection. Usually patients present as having slowly resolving or non-resolving pneumonia. Findings on physical examination are usually normal but on auscultation bilateral basal fine crepitations can be heard.

Radiological Appearance

Chest x-ray in a PAP patient shows alveolar opacities which are bilateral and symmetrical mainly seen in the middle and lower zones in perihilar region similar to batwing appearance in pulmonary edema.
High resolution computed tomography shows thickened smooth inter and intralobular septum which are superimposed on geographical opacities resembling ground glass opacity giving rise to something called as crazy paving pattern. This pattern is seen in various conditions such as acute interstitial pneumonia, pulmonary edema , radiation pneumonitis , pulmonary alveolar proteinosis, non-specific interstitial pneumonia[8]. Hence is it highly suggestive of PAP but not a diagnostic for it.

Investigations

Blood routine work up and complete hemogram are normal in patients with primary PAP but will be abnormal in patients with secondary PAP due to blood dyscrasias or haematological malignancies. Serum LDH is elevated 2-3 times the normal level and goes hand in hand with the severity of the disease. Detection of GM-CSF auto antibodies is highly specific and sensitive of autoimmune PAP. Arterial blood gas analysis shows hypoxemia. Pulmonary function test will show restrictive pattern.

Airways visualised on bronchoscopy appear normal and the bronchoalveolar lavage (BAL) has a milky appearance which if kept standing forms a thick layer of sediment at the bottom. The fluid consists of large eosinophilic bodies in granular material which readily stains with PAS and is highly diagnostic of PAP. Histopathology shows eosinophilic material accumulation in alveoli and distal air spaces.

Management

Treatment of PAP depends on the type of the PAP. In autoimmune PAP the treatment mainly consists of whole lung lavage or lobar lung lavage to drain out all the lipoproteinaceous substance accumulated in the lungs along with administration of GM-CSF therapy or combined use of both methods for better treatment outcomes. The treatment of secondary PAP includes treating the underlying cause like haematological malignancy although whole lung lavage might be required to reduce the symptoms. For congenital PAP the treatment modality is lung transplant.

Whole Lung Lavage (WLL)

It remains the gold standard of treatment for PAP resulting in radiological clearance and symptomatic improvement[9].Diagnosis of PAP by biopsy and hypoxemia with PaO2 <60 mm Hg; A-aDO2 gradient >40 mm Hg; shunt fraction >10% to 12%; or severe dyspnea at rest or with exercise are indications of doing a whole lung lavage[3].

The procedure is done with general anaesthesia, bronchoscopy and a double lumen fibreoptic endotracheal tube which allows ventilation of one lung while lavage is being done in the other simultaneously with saline.

Studies have shown that 42%-62% of patients undergoing lavage have shown significant improvement[10]. Study conducted by Seymour et al showed that the survival rates following whole lung lavage at 2, 5 and 10 years are 78.9%, 74.7%, and 68.3%, respectively[2].

As said earlier WLL can lead to severe refractory hypoxemia as only one lung is ventilated during the procedure. A safe alternative to this is sequential lobar lavage but there are not many studies regarding the same. Sequential lobar lavage can be done under lighter sedation and allows better oxygenation and ventilation of the other segments of the lung. Currently whole lung lavage is the standard modality of treatment in autoimmune PAP.

GM-CSF Therapy

This is based on the fact that surfactant clearance is dependent on GM-CSF mediated activity on alveolar macrophages which is disrupted by anti GM-CSF auto antibodies. It can either be given subcutaneously or in aerosolised form. Formal studies of inhaled GM-CSF therapy have not been done. Dosage of subcutaneous form is escalating doses 5 to 20 μg/kg/day over a 3-month period [3]. Study conducted by Seymour et al showed an overall response rate of 43% in these patients.

CONCLUSION

Pulmonary alveolar proteinosis is a rare and fascinating disorder whose combined diagnosis depends upon history and clinical symptoms, lung function tests, radiological features, evidence of bronchoalveolar lavage consisting of lipoproteinaceous material and histopathological diagnosis. This patient was diagnosed as primary idiopathic PAP based on her symptoms, radiological features and properties of BAL fluid being consistent with PAP and also she did not have any symptoms since childhood and neither had any history of exposure to any substance which could lead to secondary PAP.

The patient showed very good response to bilateral whole lung with marked improvement in her oxygenation and alleviation of symptoms. This case report further strengthens the fact that whole lung lavage is the standard treatment of choice for autoimmune or idiopathic PAP as further research about GM-CSF therapy is still underway.

REFERENCES

1) S. H. Rosen, B. Castleman, and A. A. Liebow, "Pulmonary alveolar proteinosis,"The New England Journal of Medicine, vol. 258, no. 23, pp. 1123–1142, 1958.
2) Seymour JF, Presneill JJ (2002) Pulmonary alveolar proteinosis: Progress in the first 44 years. Am J Respir Crit Care Med 166: 215- 235.
3) Carey B, Trapnell BC. The molecular basis of pulmonary alveolar proteinosis. Clin Immunol. 2010;135(2):223–235.
4) Uchida K, Nakata K, Trapnell BC, et al. High-affinity autoantibodies specifically eliminate granulocyte-macrophage colony- stimulating factor activity in the lungs of patients with idiopathic pulmonary alveolar proteinosis. Blood. 2004;103(3): 1089–1098.
5) Ishii H, Tazawa R, Kaneko C, et al. Clinical features of secondar pulmonary alveolar proteinosis: pre-mortem cases in Japan. Eur Respir J. 2011;37(2):465–468.
6) Galambos C, Levy H, Cannon CL, et al. Pulmonary pathology in thyroid transcription factor-1 deficiency syndrome. Am J Respir Crit Care Med. 2010;182(4):549–554.
7) Whitsett JA, Wert SE, Trapnell BC. Genetic disorders influencing lung formation and function at birth. Hum Mol Genet. 2004;13 Spec No 2:R207–R215.
8) HRCT Findings: Parenchymal Opacification , High-Resolution CT of the Lung , Fifth edition , LIPPINCOTT WILLIAMS & WILKINS, a WOLTERS KLUWER business , 2015 page 149
9) Juvet S, Hwang D, Waddell TK, Downey GP. Rare lung disease II: pulmonary alveolar proteinosis. Can Respire J. 2008;15(4):203-210.
10) Cheng SL, Chang HT, Lau HP, et al: Pulmonary alveolar proteinosis: treatment by bronchofiberscopic lobar lavage. Chest 122:1480– 1485, 2002.