CASE REPORT

# PRIMARY ALVEOLAR PROTEINOSIS

**Abdul Rab Khan, Aamir Sulaman, Munir Ahmad Abbasi, Muhammad Jehanzeb***

**Department of Pulmonology, *Radiology, Ayub Medical College, Abbottabad, Pakistan**

A 35 years old man presented with primary pulmonary alveolar proteinosis who was admitted to chest unit of ATH through casualty department. Before he came to our ward he was treated with different antibiotics including anti-tuberculosis drugs for a month at least. But his symptoms did not improve rather his dyspnoea got worse. He was misdiagnosed till histopathology revealed that he has pulmonary alveolar proteinosis. With this background we briefly review clinical features, diagnosis and treatment of this rare disease.

**Keywords:** Pulmonary alveolar proteinosis, Dyspnoea, anti-tuberculosis drugs

## INTRODUCTION

Pulmonary alveolar proteinosis (PAP) is a rare disorder first described in 1958 and characterised by alveolar filling with a lipid rich proteinaceous material (positive to PAS stain). Its incidence is 0.2–0.5 new cases per 1,000,000 persons each year and its prevalence is 2–6 cases per 1,000,000 persons.[1]

PAP is most common in adult males particularly between 30 and 60 years of age, although cases have been seen in children including neonates and up to the age of 72 years.[2] About 50–70% are cigarette smokers and the male predominance could be due to the higher frequency of smoking in males.

Nearly 3 decades after its original description we still do not know the aetiology of PAP. However because disease is restricted to lungs, except for the systemic effects of pulmonary insufficiency it seems likely that it is an alveolar response to an inhaled agent.

## CASE REPORT

A 35 years old male was admitted to chest unit Ayub Teaching Hospital through Emergency Department. The patient developed progressive dyspnoea for the last 2 years and he had class 3 dyspnoea based on the New York Heart Association classification. He also had dry cough with no haemoptysis and chest pain. He had low grade fever with generalised weakness, lethargy for the last six months. He had been repeatedly visiting general practitioners who had tried all sorts of antibiotics. He was started even on ATT on trial basis, which he took for one month.

On examination he had few crackles at lung basis. No other abnormality was found. On examination of CNS, CVS and abdomen no abnormality was detected. He had no previous history of any major illness in the past. Family history was unremarkable. He was farmer by profession, unmarried and with no history of addiction to any drugs.

The X-ray Chest showed bilateral symmetrical alveolar opacities located in mid and lower lung zones with a peri-hilar predominance.

Spirometry revealed restrictive pattern. Blood CP with absolute eosinophil count was normal. LFT's and RFT's were normal. ANF and RA-factors, HCV and Hbs-Ag were negative. Oxygen saturation was 88%. Echo done was normal. PT, and APTT were in normal range. CT Scan Chest Showed a geographical pattern of ground glass appearance with superimposed interlobular septal thickening consistent with crazy paving appearance.

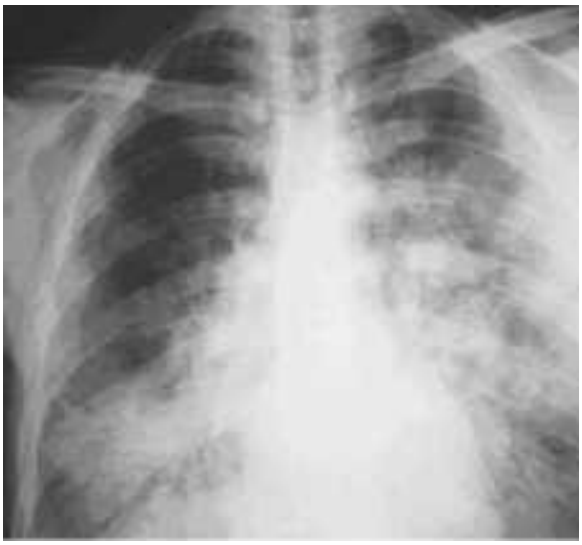

**Figure-1: Bilateral symmetrical opacification in mid and lower lung zones**

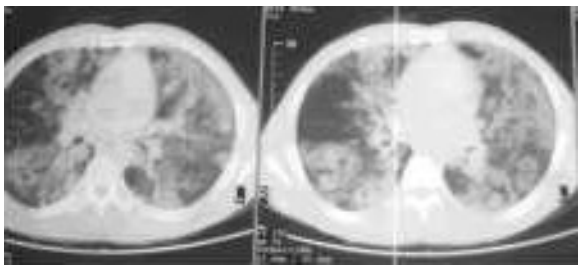

**Figure-2: A geographical pattern of ground glass appearance with superimposed interlobular septal thickening**

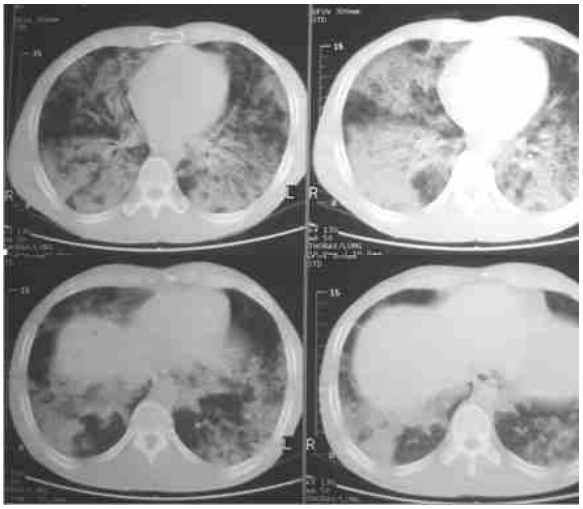

**Figure-3: CT Scan chest showing fine reticular pattern superimposed on areas of ground-glass opacity**

Bronchoscopy was done with normal findings with exception of bronchial wash, which appeared slightly milky, the wash was sent for culture and sensitivity, malignant cells, ZN staining, PAS+methanine silver staining, Also culture for Mycobacterium TB and Fungi were sent. Reports were negative for ZN, PAS and methanine silver stains, No malignant cells were seen in the bronchial wash. The BAL was negative for PAS.

**Figure-4: PAS staining of eosinophillic proteinaceous material filling the alveolar spaces**

In view of high suspicion, clinical findings and CT report, the patient was re-scoped for transcronchial lung biopsy. The biopsy report showed alveolar spaces filled with eosinophilic proteinaceous material that stained positive on PAS, thus diagnosis of pulmonary alveolar proteinosis was made.

**Figure-5: Alveolar spaces filled with eosinophilic proteinaceous material**

Surprisingly, the patient improved symptomatically although he was given supportive treatment only in ward including IV antibiotics, oxygen inhalation and Salbutamol nebulisation. His oxygen saturation was 95% without oxygen therapy and no fever was recorded. He had now class 2 dyspnoea which on presentation was class 3. Presently he is on regular monthly follow up in outpatient department.

## DISCUSSION

Based on clinical, Histopathological and pathogenic differences PAP may be divided into three distinct forms, i.e., primary or autoimmune PAP, secondary PAP, congenital PAP and Hereditary PAP.

Primary or autoimmune PAP account for 90% of all cases of pulmonary alveolar proteinosis. It is a disease of unknown aetiology believed to result from decreased surfactant clearance by alveolar macrophages. It is a disease of unknown aetiology believed to result from decreased surfactant clearance by alveolar macrophages. Both congenital and primary PAP are associated with deficiency or impaired function of granulocyte-macrophage colony stimulating factor (GM-CSF) which regulates surfactant homeostasis and immune defence.[3] GM-CSF activates alveolar macrophages and increases the rate of surfactant clearance. Secondary PAP is seen in association with dust and chemical exposure, infections and haematologic malignancies.[4]

Congenital or familial PAP may occur due to a specific homozygous defect in the genes encoding SP-B, SP-C or ABCA3.[5] It presents at birth. Mutation in the SFTB is uniformly fatal at birth. Hereditary PAP is caused by the mutations of GM-CSF receptor genes. Hereditary PAP can present between ages 1–11 yrs. It is rare and poorly studied.

The major symptoms of PAP are shortness of breath and dyspnoea on exertion. Some patients have mild cough with occasional white and sticky sputum production. Chest pain and haemoptysis are extremely unusual but weight loss, fatigue and malaise are common. Fever may suggest super infection. There are few physical signs. Breath sounds are usually normal with occasional rales.

PAP is one of condition in which symptoms and signs may be mild in face of striking imaging signs. Lab findings are that about 70% of population have elevated serum LDH. The serum level of surfactant apoproteins A and D (SR-A, SP-D) are markedly elevated though non-specific.

BAL shows characteristic eosinophilic granuloma PAS positive lipoproteinaceous material in washings. A recent report suggests that elevated serum level of SP-D in washings may be specific for PAP.[6] It may occasionally be necessary to obtain a trans-bronchial lung biopsy for histologic study.

On chest X ray there is symmetrical alveolar opacities located centrally in mid and lower lung zones often with peri-hilar predominance resembling the bat wing appearance of pulmonary oedema. On HRCT, the superimposition of reticular pattern formed by thickened interlobular septae on a background of ground glass abnormality produces the characteristic crazy paving pattern. PAP improves spontaneously in about 10% of patients. Most of the remaining patients will require treatment and the standard treatment up to recently has been unilateral or bilateral saline whole lung lavage. Lavage has virtually eliminated the mortality and results in complete remission in 75% of patients.

Recently small scale clinical trials of GM-CSF have resulted in clinical improvement in 35–70% of cases but the value of this treatment remains unclear.[7] Besides lung lavage other therapeutic approaches for autoimmune PAP include plasmapheresis, GM-CSF therapy (subcutaneous and inhaled) and B-lymphocyte depletion therapy. Rituximab is a drug which depletes autoantibody producing B lymphocyets. Recently Inhaled GM-CSF therapy has been tried for treatment of PAP in some patients with good results.[8] Patients were given either high or low dose of GM-CSF via inhalers. High dose therapy: 250 µg of GM-CSF via inhalers on days 1–8, none on day 9–14; six cycles for 12 weeks. Low dose therapy: 125 µg of GM-CSF via inhalers on days 1–4, none on days 5–14; six cycles for 12 weeks. Both of these doses resulted in a sustained therapeutic effect in patients.

## REFERENCES


1. Inove Y, Trapnell BC, Tazwa R, Arai T, Takada T, Hizawa N, *et al*, Characteristics of large cohort of patients with autoimmune pulmonary alveolar proteinosis in Japan. Amj Respir Crit Care Med 2008;177:752–62.
2. Seymour JF, presnell JJ. Pulmonary alveolar proteinosis progress in the first 44 years. Amj Respir crit care Med 2002;166:215–35.
3. Frazier AA, Franks TJ, Cook Eo, Mohammed TL, Pugatch RD, Galvin JR. From the archives of AFIP; Pulmonary alveolar proteinosis Radiographics 2008;28:883–99.
4. Suratt PM, winn WC Jr, Brody AR, Brody AR, Bolton WK, Giles RD. Acute silicosis in tomb stone sand blasters. Am Rev Respir dis 1977;115:521–9.
5. Doan ML,Guillerman RP, Dishop MK, Nogee LM, Langston C, Mallory GB, *et al*. Clinical, radiological and pathological features of ABCAz mutation in children. Thorax 2008;63:366–73.
6. Wang BM, Stern EJ, Schmidt RA, Pierson DJ. Diagnosing pulmonary alveolar proteinosis. A review and an update. Chest 1997;111:460–6.
7. Venkateshiah SB, Yan TD, Bonfield TL, Thomassen MJ, Meziane M, Czich C, *et al*. An open label trial of granulocyte macrophage colony stimulating factor therapy for moderate symptomatic pulmonary alveolar prteinosis. Chest 2006;130;227–37.
8. Tazawa R, Trapnell BC, Inoue Y, Arai T, Takada T, Nasuhara Y, *et al*. Inhaled Granulocyte/macrophage colony stimulating factor as therapy for pulmonary alveolar proteinosis. Am J Respi Crit Care med 2010;181(12):1345–54.



## Address for Correspondence:

**Prof. Abdur Rab Khan,** Department of Pulmonology, Ayub Medical College, Abbottabad, Pakistan. **Cell:** +92-334-8987788
**Email:** abdurrabkhan@hotmail.com