PULMONARY ALVEOLAR PROTEINOSIS: A CASE REPORT

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ABSTRACT

Pulmonary Alveolar Proteinosis (PAP) is a rare disease of the lung with long term, non specific clinical symptoms. The disease process usually affects both lungs relatively in a uniform manner. Chest x-ray shows diffuse bilateral alveolar infiltrates with loss of vascular pattern. Characteristic High Resolution Computed Tomography of the chest shows airspace shadowing in a geographical distribution, alternating with areas of normal lung with superimposed interlobular septal thickening, called as Crazy Paving pattern. The condition is commonly misdiagnosed as Interstitial Lung Disease with super added Infection. Lung biopsy is still the most reliable way to establish the diagnosis. Whole lung lavage is the most effective treatment for PAP and should be considered in unstable patient with progressive and worsening symptoms of the disease. We are reporting a case of 22 years old married lady, who presented with shortness of breath, fever, dry cough, malaise and weight loss. This disease was complicated by super added infection of the chest.

Key Words: *Pulmonary alveolar proteinosis, Lung biopsy, Whole lung lavage*

INTRODUCTION

Pulmonary Alveolar Proteinosis (PAP) is an uncommon, idiopathic and relatively recently identified disease actively being altered by time, improved techniques, and knowledge[1]. PAP is an alveolar filling defect affecting around 3 per million people and was first described in 1958[2].It is difficult to determine its exact frequency because of the absence of national registry. The peak age of onset of the disease is 30-50 years, but cases may have been reported in neonates, infants, children and elderly. Male to female ratio is 4:1 and there is increased incidence among smokers. Rare familial cases have also been reported. In 1969, only 139 cases of PAP had been reported worldwide; by 1980, approximately 260 cases were recognized. Even now fewer than 500 cases have been reported.

PAP is due to failure of alveolar macrophages to clear spent surfactant, leading to the filling of alveoli with a Periodic acid Schiff (PAS) positive phospholipid proteinaceous material. Such accumulation leads to an elevated shunt fraction and respiratory failure[3].These PAS positive, amorphous, granular acellular eosinophilic material, rich in lipids, is deposited in alveolar spaces, rising up into the bronchioles in severe cases. It is thought that the defect has an autoimmune basis, due to the presence of antibodies to granulocyte-macrophage colony-stimulating factor (GM-CSF), which cause inhibition of normal alveolar macrophage function, leading to abnormalities of surfactant homeostasis[4].

Three variants of the disease have been recognized: Congenital, Secondary and Primary (acquired or idiopathic).Whole lung lavage is still the most effective treatment for PAP[5]. Whole Lung Lavage should be considered in patients with deteriorating lung functions and also in those cases that are having progressive symptoms of the disease.

CASE REPORT

This was a case of a young 22 years married female with no kids, who is living in District Nowshera, located 45 kilometer from Peshawar city, which is the capital of North West Frontier Province of Pakistan. She was admitted to Department of Pulmonology, Lady Reading Hospital Peshawar on March 03, 2008 with the complaints of low grade fever for the last three

years, and also dry cough sometimes associated with scanty mucoid sputum, shortness of breath and malaise for the last one and half years. Weight loss was also noted. She is married for the last two and half years with no issue. She is a house wife and her socioeconomic conditions are satisfactory. She was not a smoker and there was no history of exposure to birds or any obvious dust. She had a full course of Anti Tuberculous Therapy one year back because of the same ailment on empirical basis. She had frequently consulted many doctors and was taking tablets prednisone, antibiotics and bronchodilators (Inhalers) on irregular basis. When she was admitted in our unit, she was also on steroids at that time. On general physical examination she was healthy looking and lying in her bed with ease. Oxygen Saturation was 89% at room air with fever of 100^0F. Pulse rate of 100/minute regular, and Blood Pressure was recorded 100/ 70 mmHg.Clubbing was also present. On systemic examination Chest was of normal shape. Chest expansion was bilaterally symmetrical and percussion notes were resonant. Basal end inspiratory crackles, more on the right side were heard on auscultation. Cardiovascular System, Central Nervous System and abdominal examinations were unremarkable. Chest radiographsat the time of presentation showed bilateral diffuse alveolar infiltrates with loss of vascular pattern involving all zones, but were more pronounced in the middle and lower zones (Figure 1). Heart size was normal and heart borders were shaggy with loss of lung volume. On the basis of history, clinical examination and chest x-ray; we made a provisional diagnosis of Interstitial Lung Disease with super added Infection. We extensively investigated the patient (Table 1 and 2). The result of full blood count was normal except for slightly raised Haemoglobin (Hb) and Packed Cell Volume (PCV), which was most likely because of hypoxemia. Blood Chemistry was also within normal limits with the exception of raised serum LDH level. Arterial Blood Gases (ABGs) report showed chronic compensated respiratory alkalosis. Other laboratory workup did not reveal any significant abnormality (Table 1). Echocardiography was performed which showed only mitral leaflet prolapse with no evidence of right ventricular enlargement**.** Pulmonary Function Tests were also performed and the result showed

Table 1: Laboratory Investigations done on March 04, 2008

(a) Blood complete: Hb: 16.2 g/dl WBC: 4800/cmm Neutrophils: 55% Lymphocytes: 40% Monocytes: 01% Eosinophils: 04 % Platelets: 99000/cmm ESR: 22 mm in 1st hour PCV: 48.7%	**(b) Biochemistry:** Blood urea: 29 mg/dl Serum Creatinin:0.1 mg/dl Serum LDH: 785 IU/L Random Blood Sugar:101 mg/dl ALT: 31 IU/L Alkaline Phosphatase:108 IU/L **Serum Electrolytes:** Na^+ :133mmol/L K^+ : 3.51mmol/L Cl^- :102mmol/L
(c) Arterial Blood Gases(ABGs): pH : 7.41 So_2: 90.7% PO_2: 78.7 mmHg PCO_2: 26.2 mmHg HCO^-_3 :19.4 mmol/L	**(d) Others:** RA Factor: Negative Anti Nuclear Factor(ANF): Negative Sputum smear for AFB : Negative 3 times Sputum Cultures : No growth seen HIV: Negative

Table 2: Pulmonary Function Tests (PFTS) Performed on March 07, 2008.

Forced Vital Capacity (FVC)----------:	(% predicted) 68
Forced Expiratory Volume in one second (FEV1) -------:	(% predicted) 64
FEV_1/FVC Ratio----------:	(% predicted) 99
LUNG VOLUMES Slow Vital Capacity (SVC)	: 67
Inspiratory Capacity (IC)	: 73
Expiratory Reserve Volume (ERV)	: 56
Lung Transfer Factor for Carbon monooxide TLCO(% Predicted): 58	

restrictive defect with reduced Lung Volumes and also reduced lung transfer factor (Table 2). HRCT Scan of the chest (Figure 2 and 3) was done and reported by the Radiologist. Report of HRCT chest showed Crazy Paving ground glass opacitity with superimposed septal thickening both lungs with no evidence of pleural effusion. Radiologist hmade a list of differential diagnosis of Crazy Paving pattern and mentioned Alveolar Proteinosis on the top, followed by Sarcoidosis, Organizing Pneumonia, Cryptogenic Organizing Pneumonia, Broncholitis Obliteran Organizing Pneumonia and lastly Infections. At this stage we had started thinking about Pulmonary Alveolar Proteinosis (PAP). We requested radiologist for image guided biopsy of the lung and biopsy was performed on March 11, 2008. Biopsy was reported on March 16, 2008. Microscopic Examination of Biopsy report (Figure 4) revealed lung consisting of alveoli filled by acellular eosinophilic structureless material containing, a few foamy and rare pigmented macrophages which is consistent with Alveolar Proteinosis. Thus, our final tissue biopsy based diagnosis was Pulmonary Alveolar Proteinosis (PAP).

Steroids were tapered and ultimately stopped, and started the patient on infusion Moxifloxacin. We also counseled the husband of the patient about whole lung Lavage which is still the main stay of treatment, but the patient and her husband were not willing. Her fever was subsided after 10 days of Moxifloxacin. Our patient was stable but symptomatic, but fortunately symptoms were not deteriorating and were not progressive. Whole lung lavage was thus postponed and we are observing her in the hope of spontaneous

Figure 1: Chest X-rays showing bilateral diffuse alveolar infiltrates involving all zones more pronounced in the middle and lower zones with loss of vascular pattern. Heart size is normal but borders are shaggy. (March 03, 2008)

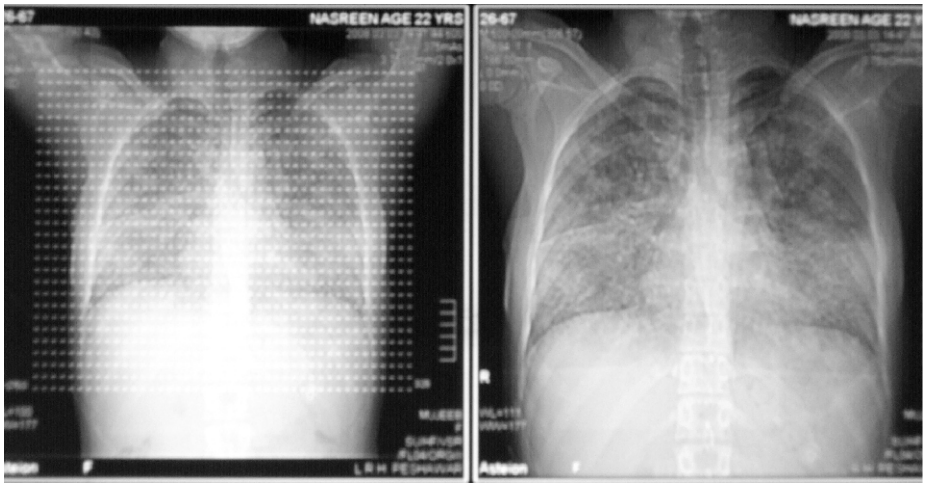


Figure 2 : HRCT findings of PAP include ground glass opacities with superimposed interlobular septal thickening and intralobular interstitial thickening. (March 03, 2008)

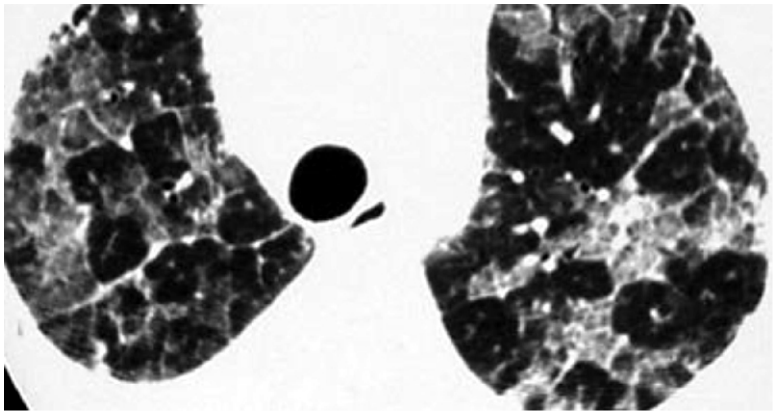


Figure 3: Another HRCT slice of the same patient showing the typical "Crazy Paving Pattern" (March 03,2008)

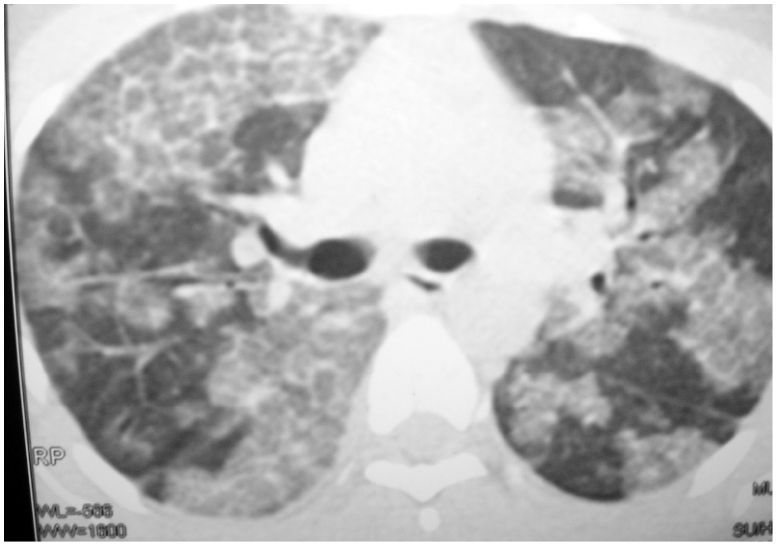
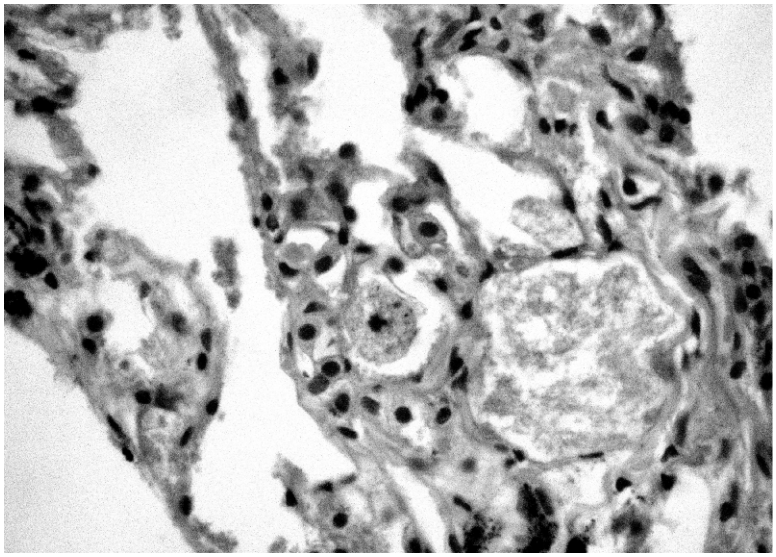


Figure 4: Microscopic View of Histopathology Slide of our patient with PAP



remission. She was discharged with an advice to have healthy lifestyle regarding diet, refraining from dust, smoke and steroids. She was also counseled that she should avoid pregnancy at the moment and report on monthly basis for follow up chest x-rays.

DISCUSSION

PAP also referred to as Alveolar Lipoproteinosis is a rare disease of the lung and this clinical syndrome was first described in 1958 by Rosen et al [6].They reported a series of 27 cases of a pulmonary disease which was characterized by the accumulation of a proteinaceous material in the alveoli. This material, rich in lipid, yields a positive reaction to periodic acid-schiff stain. The material affects the lungs in patches, taking on an acinar distribution in appearance. Honey combing is absent and the pleural surfaces appear regular and smooth. Less typically, thickened septa and interstitial fibrosis may be present, although this is probably due to repeated or chronic infection as opposed to the underlying PAP [7].

The etiology of primary PAP is unknown. The accumulation in alveolar spaces is probably caused by defective clearance of phospholipid proteinaceous material by macrophages [8, 9]. Recent data suggest that granulocyte-macrophage colony-stimulating factor (GM-CSF)may be important in the pathogenesis of PAP.

Secondary PAP could be associated with 4 main conditions:

1. Exposure to inhaled chemicals and minerals, e.g., fumes, dusts, silica, aluminum, insecticides leads to surfactant hyper-secretion, which exceed the lungs, normal clearance mechanism.
2. Hematological malignancies like acute and chronic myeloid leukemias, multiple myeloma, waldenstrom's disease and other conditions that alter the patient's immune status, e.g., lymphoma. Mechanism is uncertain in these conditions, but it is thought that the lipoprotein may be generated from degenerating alveolar cells.
3. Amphiphilic drugs, e.g., amiodarone, chlorphenetermine. Amiodarone lung toxicity in human has some features of lung phospholipidosis.
4. Infections of the lung, most commonly with nocardia asteroids, followed by Pneumocystis carinii and atypical mycobacteria. The material filling alveolar spaces in secondary PAP is mainly cell debris.

Sputum cultures were negative of our patient. We did her HIV status, which fortunately came out to be negative. She was not smoker, not exposed to any noticeable dust or chemicals. No evidence of infections, immunosuppression or any hematological abnormalities were found in our patient, though steroid induced immunosuppression was noted.

Clinical symptoms of our patient were non specific and of long duration[10].Among symptoms shortness of breaths on exertion, dry cough and fever were the most prominent. Lung biopsy was the gold standard investigation for the diagnosis of PAP[10].

At the time of admission to our unit, patient was already on steroids and steroids had been started on irregular basis by some local physician in her area .When we tapered the steroids dose and eventually stopped it ,and started our patient on respiratory quinolone (Moxifloxacin), her fever settled and she improved. This means that there is no benefit from treatment with steroids, and they may exacerbate opportunistic infections[11]. Patient with PAP will have raised serum LDH (Lactate dehydrogenase) concentration. This test is not specific for the diagnosis of PAP, it is actually a good prognostic test, which shows the activity of the disease. In our patient, there was a 3-fold rise in Serum LDH, suggesting that she is having active disease. PCV and Hb of our patient was high probably because of hypoxemia. ABGs in patient with PAP indicates reduced oxygen tension and saturation. Carbon dioxide tension is also reduced, but PH is normal, reflecting a chronic compensated respiratory alkalosis. The ABGs report of our patient was similar to one mentioned in literature.

PFTs shows restrictive defect with reduced lung volumes and transfer factor. In patient with PAP, although high-resolution CT correlates more closely with pulmonary function, plain radiographs should be sufficient for follow up[12].

On plain Chest X-ray, there is dense diffuse bilateral alveolar infiltrates with loss of vascular pattern and presence of air bronchograms. Heart size is normal but heart borders are shaggy and there is loss of lung volumes as well .So air bronchograms were not a prominent feature in this case and were not seen on plain radiographs. The typical bat's wing appearance seen in patient with PAP was not present. In bat's wing appearance the infiltrates are generally more pronounced in the peri-hilar regions in up to 50% cases and less dense peripherally with thickened interlobular septa [6,8,9,12].

Characteristic HRCT appearance is of air space shadowing in geographical distribution alternating with areas of normal lung with superimposed interlobular septal thickening and intra-lobular interstitial thickening, the so called “Crazy Paving” pattern which is mainly seen in patient with PAP, was very classic in our patient [9,13].Despite the predominance of air-space patterns, air bronchograms were not seen. The findings of HRCT chest of our patient is so characteristic that they strongly suggest the diagnosis, but we were lacking confidence, because we were not used to see such type of HRCT chest. Although the Crazy Paving appearance is highly suggestive of PAP, it is not specific and has also been described in Pneumocystis Carinii Pneumonia, Usual Interstitial Pneumonia, Organizing Pneumonia, Cryptogenic Organizing Pneumonia, Broncholitis Obliteran Organizing Pneumonia, Pulmonary Hemorrhage, Acute Radiation Pneumonitis, ARDS, Drug Induced Pneumonitis, Alveolar Cell Carcinoma and Exogenous Lipoid Pneumonia. That is why we had requested a radiologist for image guided biopsy of the lung, because lung biopsy is still the most reliable way to establish the diagnosis of PAP.

Whole Lung Lavage is the most effective treatment currently available for the patients with PAP, who have progressive and worsening symptomatology and are unstable[14]. Even though bone marrow transplantation and lung transplantation has also been suggested[8,15]. Bone marrow transplantation still needs more experiments and recurrence after lung

transplantation has been reported.

Untreated patient with PAP may have a variable course. Without definitive therapy, about one third of patients progressively deteriorate and die, one third remain stable but symptomatic, and one third spontaneously improve. Most deaths are due to progressive hypoxemia. Recurrence rate of PAP after whole lung lavage is very high, that is 40%, and about 10% fail to respond. Granulocyte colony-stimulating factor, Subcutaneous injections, is a novel treatment option that may prevent progression of disease (only phase II studies, no randomized controlled trial yet). Our patient presented at very young age and her socio-economic conditions were also not good, though she was symptomatic but fortunately stable. Her condition was not worsening and her symptoms were also not progressive, so whole lung lavage was deferred. We are observing her in the hope of spontaneous remission and is stable to date.

We feel that our patient is having the Primary PAP because we did not find any evidence for its association with other conditions. In patient with PAP characteristic imaging findings on HRCT scan chest, followed by lung biopsy will give us sufficient information for an early and correct diagnosis. Plain radiographs should be sufficient for follow up. It should be strongly remembered, that PAP is the only interstitial lung disease where steroids are not used and its use will further complicate the disease severity. As is evident from the discussion, PAP is a less well-understood clinical syndrome, which is in need of more research. Till that time, anecdotal experience remains our guiding light for the management of PAP.

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