A Case Report: Pulmonary Alveolar Proteinosis

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Abstract

Pulmonary alveolar proteinosis (PAP) is a rare disease characterised by diffuse aacumulation of eosinophilic periodic acid-shiff (PAS) positive phospholipid materials within alveoli. The accumulation of this material is due to an increased secretion or a decreased clearance from the alveoli. Whole lung lavage is the most effective and safe method of treatment.

In this report we present a case of a 37 year old male with idiopathic pulmonary alveolar proteinosis The certain diagnosis of PAP was made by transbronchial biopsy (TBB) and bronchoalveolar lavage (BAL). He was treated with whole lung lavage. The procedure was performed three times. Marked clinical and laboratory improvement was achieved besides a minimally radiographic regression.

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Introduction

PAP is an uncommon disorder first described forty-one years ago by Rosen et al (1). Alveolar spaces are progressively filled with a phospholipoproteinaceus material presumably related to a malfunction of the balance between surfactant production by Type II pneumocytes and surfactant removal. The latter is effected primarily by alveolar macrophages (2). The diagnosis is confirmed by typical electron microscopic findings in lung biopsy specimens or bronchoalveolar lavage (3).

Case Report

A 37-year-old male patient who was admitted to our department had a six months' history of cough, sputum production, exertional dyspnea, night sweat, weight loss. He had smoked for 25 years. Six months ago, as his chest X-ray revealed bilateral homogeneous infiltration, the patient was treated with antibiotics. In spite of this treatment, his symptoms became progressive and he was referred to our pulmonary department. On examination, pulse was 108/min;

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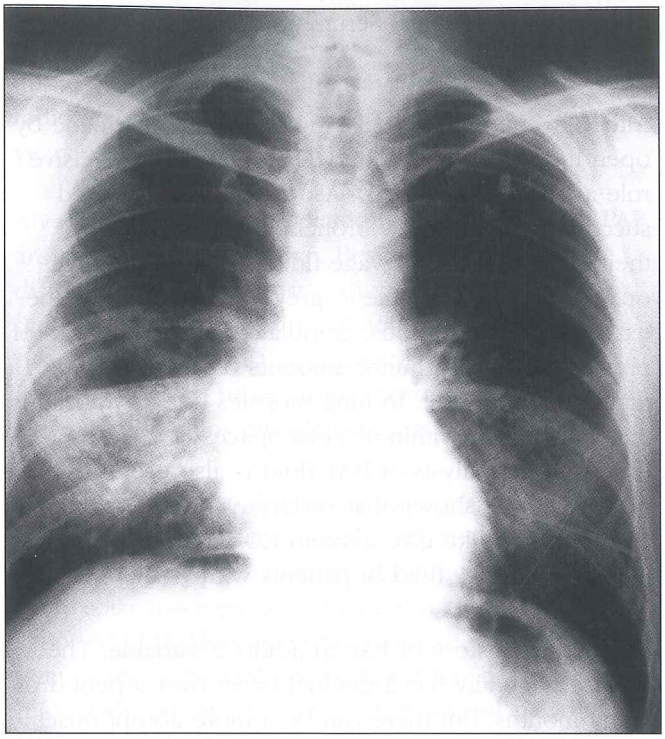

Figure 1. *Chest X-ray at admission showing bilateral infiltrations.*

respiratory rate was 24 per minute. Except for diffuse basillar crackles all his physical examination findings were normal. The white cell count was 5100/mm3, the erythrocyte sedimentation rate was 35 mm/h, and LDH was 600 U/L. The chest X-ray and CT showed alveolar filling pattern in both lungs, more intense on the right lung (Figure 1). Blood gas analysis showed hypoxemia (PaO2: 55 mm/Hg). Shunt fraction was 15%. Pulmonary function tests demonstrated mild restrictive disease with a reduced DLCO (57% predicted). In the bronchoscopic examination, BAL fluid revealed a milky turbid appearance. Pathological examination of BAL and TBB showed eosinophilic lipoproteinaceous material deposition. The LDH level of BAL was high. These findings suggested the diagnosis is alveolar lipoproteinosis. The electron microscopic study confirmed the diagnosis .

Because of severe hypoxemia and high shunt fraction whole lung lavage was performed as described in the literature (4,5,6,7). After full intraoperative monitoring and the proper placement of a double lumen endotracheal tube, its place was checked by fiberoptic bronchoscopy. Then both lungs were ventilated with 100% oxygen for 10 to 15 minutes in order to wash out the nitrogen. To allow the oxygen absorption, the lung to be lavaged was degassed by clamping the channel for 5 minutes. This procedure was carried out in order to avoid development of both airpockets and atelectasis. Warmed saline was suspended 150 cm above the carina. The patient was in the lateral decubitis position. After the lung was filled to FRC, volume required to fill TLC was installed. Then the same volume was allowed to drain. This procedure was repeated until the effluent became completely clear. The total volume used was approximately 32 litres for the right lung. After the last installation, the patient was placed in the Trendelenburg position and as much fluid as possible was drained.

Two days later, the left lung was lavaged with 38 litres. There was no complication related to these interventions. The chest X-ray showed minimal improvement. After a month, the serum LDH level was 455 U/L. PaO2 showed a significant improvement from 55mmHg to 70 mm/Hg, symptomatical relief was also present. As full radiographic improvement was not obtained we repeated the right lung lavage a month after the first lavage. In this procedure we used 50-lt. saline. After this procedure, CT showed marked regression in only the left lung (Figure 2) and DLCO capacity didn't reveal significant improvement. Now the patient is fine and there is no radiological progression.

Discussion

Pulmonary alveolar proteinosis may either be idiopathic (primary) or associated with malignancies, exposure to organic dust or use of certain drugs (8,9) In about 8% of the cases it has been found to be associated with haematological abnormalities. It has been hypothesised that PAP with haematological abnormalities is due to a primary defect in number and/or function of macrophages in the alveoli. The abnormalities associated with PAP include Acute or chronic myelocitic leukemia, Fanconi's anemia, paraproteinemia and dermatomyositis (7). In our case we did not find either a systemic disorder or a causative agent so the patient was diagnosed as an idiopathic PAP.

Pathologically, the alveolar spaces are filled by a granular, eosinophilic and a periodic acid schiff positive material. The alveolar septa are usually normal but type-2 cell hyperplasia is present. (7).

Proposed explanations for the origin of the excessive, intraalveolar accumulation of phospholipids in PAP include overproduction and oversecretion of surfactant, imbalanced production and removal of alveolar phospholipids, defective alveolar macrophage functioning resulting from the excessive

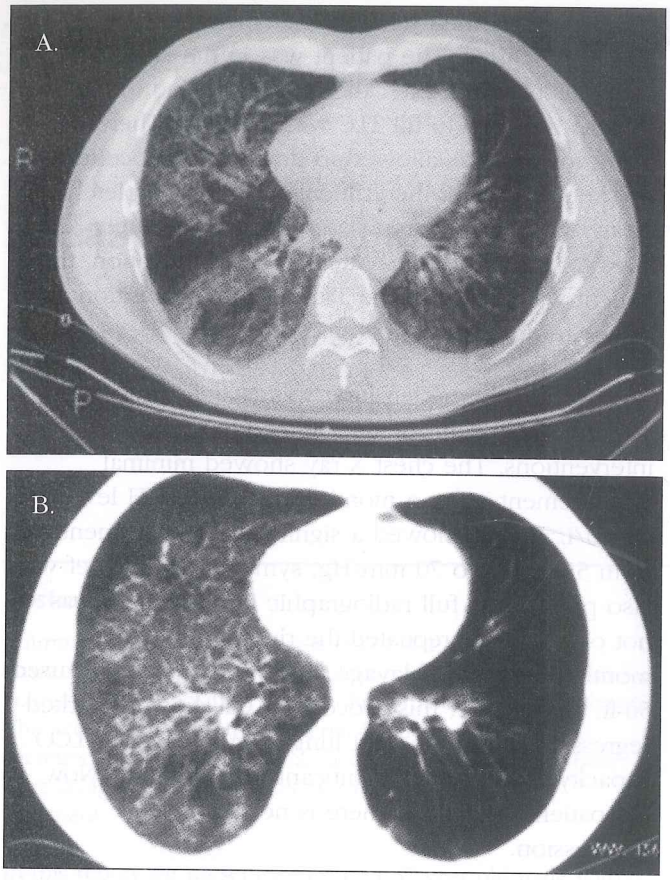

Figure 2 (A) (B). *Computed chest tomography done before (A) and after (B) whole lung lavage.*

intracytoplasmic ingestion of lameller bodies, and/or excessive turnover of type II pneumocytes with resultant accumulation of intra alveolar extracellular substances (8).

In PAP, patients may be asymptomatic with a normal chest roentgenogram or may have cough, dyspnea, fever and pleuretic chest pain (8,10). Weight loss and haemoptysis have been associated (11). In physical examination it is possible to find crackles, cyanosis, clubbing and hepatosplenomegaly (12). The classic radiological appearance of PAP is that of bilaterally, symmetric, perihilar airspace consolidation in a "bat-wing" distribution. Typical CT findings include ground-glass opacity, often associated with reticular interstitial opacities or interlobular septa thickening with a variably diffuse, patchy, central or peripheral distribution (3). Uncommonly, cavitation, asymmetric peripheral infiltrates, mediastinal and hilar lympadenopathy may be present (6). Roentgenographic abnormalities may not correlate with clinical or physiological impairment. Pulmonary function tests show a restrictive defect with diminished lung volumes and decreased DLCO. Hypoxemia occurs in half of the patients. Serum and BAL LDH levels increase (3,5,10,13,14).

Although the definitive diagnosis is generally made by open lung biopsy, BAL and TBB may play a decisive role as in our case (8,15). Asomato et al. reported successful diagnosis by bronchoscopy in 89.7 % of their cases (13). The lavage fluid of PAP is grossly opaque and milky white to grey. Microscopically, the extracellular amorphous, granular debris, composed of phospholipids and minor amounts of protein, is consistently present. In lung biopsies this PAS positive material is seen within alveolar spaces (2). The biochemical analysis of BAL fluid is also useful in the diagnosis. It is shown that surfactant protein-A, LDH and a muscin like glycoprotein KL-6 significantly increased in BAL fluid of patients with PAP (14,16,17).

The natural history of PAP in adults is variable. The disease generally has a gradual onset over a period of many months, but there can be a more abrupt onset with a rapid course. The possibility of spontaneous remission exists but if there is initial severe disease or progressive worsening with significant hypoxemia and shunt fraction, therapy is indicated (1,7,13). None of the treatments previously used like inhaled corticosteroids, heparin, trypsin or pancreatic enzymes have been found successful (18). Treatment with therapeutic whole lung lavage, first described by Ramirez et al in 1965 and slightly modified over years can bring about dramatic improvement in the clinical and physiologic status of patients with this disease (4,14,18). Lavage may reduce lipoproteinaceous debris and helps to recover the macrophage dysfunction. If the definitive diagnosis is established, and if the patient is hypoxemic and shunt fraction is greater than 10%, lavage is required (10,13).

There are two early complications of lavage: leakage into contralateral lung and hydropneumothorax (6). The most severely affected lung is lavaged initially and if there is no complication the other lung is lavaged 3-7 days after the first procedure (3,6). Whole lung lavage usually improves the physiological parameters in 24-48 hours.

In our case, the patient needed 3 lavages and had no complications. He showed marked clinical and physiological improvement but a minimal radiological regression. This finding is supported in other reports. Rogers et al. mentioned that 2 of their 14 patients showed significant clinical and physiologic improvement after therapeutic BAL despite minimal

radiographic improvement (3). Du Bois et al have shown that radiological improvement was less impressive immediately after lavage. In one patient, radiological clearing was observed during the two years after his final lavage (19).

Alveolar macrophages isolated from patients with PAP are shown to be defective. Besides its role in the disease's pathogenesis, it is thought to be related to the high incidence of uncommon infections in these patients like Nocardia, pneumocystis carinii, cytomegalovirus, tuberculosis, histoplasma capsulatum and nontuberculos mycobacteriums (2,8,20,21).

There are recent studies on granulocyte macrophage colony stimulating factor (GM-CSF) therapy in PAP to enhance the activity, increase the function and number of alveolar macrophages. Successful results are reported (22). More recently defective expression of beta chain of the GM-CSF receptor has been shown in mice with PAP like disease and in several patients with PAP. So besides GM-CSF treatment, bone marrow transplantation is also discussed in some reports for the treatment of PAP (23,24,25).

The clinical course is highly variable in PAP. Some patients may have progressive disease with superimposed uncommon infections while others can recover spontaneously. Some patients may need repeated lavages (every 6-24 months). Prognosis is much better with the whole lung lavage therapy (4,10). Our patient hes been stable for 8 months now with no further deterioration.

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