

# Pulmonary alveolar proteinosis

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## Abstract

*Pulmonary alveolar proteinosis (PAP) is a rare lung disease characterized by the accumulation of a lipoproteinaceous substance in the distal air spaces which positively stains with periodic acid-Schiff (PAS). The typical age at presentation is the third or fourth decade. The main symptoms consist of shortness of breath and cough. The physical examination is often normal and inspiratory crackles are the most common abnormality. Pulmonary function tests show a restrictive ventilatory defect and a decreased diffusion capacity. Bilateral air space consolidation is a typical but non-specific feature appearing on chest radiography. High resolution computed tomography scanning (HRCT) reveals ground-glass opacification usually associated with thickened interlobular septa, distinctly visible within the affected lung, referred to as "crazy paving" pattern. The diagnosis of PAP can be made on the basis of HRCT features in conjunction with the typical bronchoalveolar lavage (BAL) findings of milky fluid consisting of basophilic granular extracellular deposits with enlarged foamy macrophages and cellular debris (May-Grünwald Giemsa). If non conclusive, PAP is diagnosed by examination of lung tissue obtained by transbronchial or videoassisted lung biopsy. Most commonly treatment consists of whole lung lavage, but some patients may be successfully treated with daily subcutaneous GM-CSF (granulocyte-macrophage colony-stimulating factor).*

## Keywords

Pulmonary alveolar proteinosis, alveolar phospholipoproteinosis, whole lung lavage, GM-CSF

## Introduction

Pulmonary alveolar proteinosis (PAP), also known as pulmonary alveolar phospholipoproteinosis, was first described by Rosen *et al.* in 1958 (1). It is a rare lung disease characterized by the accumulation of extensive amounts of periodic acid-Schiff (PAS) positive phospholipoproteinaceous material in the distal airspaces. The alveolar architecture is usually

preserved although septal thickening or lymphocyte infiltrates may be observed (1-5).

## Prevalence

The estimated prevalence is about one in a million people. It is a primary acquired disorder in more than 90 percent of cases; 72 percent of the patients have a history of smoking (46). No particular racial predilection has been described.

Although cases in newborns have been observed, the typical age of manifestation is between 20 to 40 years. There is a male/female ratio ranging from 2:1 to 3:1 (6-7).

### **Etiology and pathogenesis**

Most adult patients presenting with PAP have a "primary" or idiopathic form of the disease. More rarely a secondary form occurs in association with malignancies (some hematologic cancers), immune dysfunction (e.g. HIV infection, pharmacological immunosuppression), or certain infections. Exposure to certain environmental dusts, such as silica (silicoproteinosis) and aluminium, titanium oxide and insecticides, cement dust, fibrous insulation material, and nitrogen dioxide have been implicated in some cases of PAP.

Although the specific cellular pathogenesis of PAP is unknown, recent experiments with genetically altered mice have provided some insight in potential mechanisms for PAP. Mice deficient in the gene for granulocyte-macrophage colony stimulating factor (GM-CSF) develop an alveolar proteinosis that is histologically not different from PAP. The disease in mice can be reversed by insertion of the *GM-CSF* gene into respiratory epithelium. Mice deficient in the beta-subunit of the GM-CSF receptor also develop a PAP-like disease, which can be reversed by bone marrow transplantation. These observations are consistent with the assumption that either absolute GM-CSF deficiency or insufficient response of alveolar cells to GM-CSF is the cause of the human form of PAP.

The congenital form of PAP comprises a heterogeneous group of disorders caused by mutations in the genes encoding surfactant protein B or C or the  $\beta_C$  chain of the receptor for granulocyte-macrophage colony-stimulating factor (GM-CSF) (47). The alveoli in PAP are filled with proteinaceous material, which has been analyzed extensively and determined to be normal surfactant composed of lipids and surfactant-associated proteins A, B, C, and D (SP-A, SP-C, SP-D). Evidence exists of a defect in the homeostatic mechanism of either the production of surfactant or the clearance by alveolar macrophages and the mucociliary elevator. A clear relationship has been demonstrated between PAP and impaired macrophage maturation or function, which might account for the high association with malignancies and unusual infections, eg, infection with *Nocardia asteroides*.

The occurrence of at least two different congenital forms, the existence of different animal models and the presence of anti-GM-

CSF antibodies suggest that PAP represents a clinical syndrome rather than a single disease (8-18).

### **Clinical features**

#### ***Clinical presentation***

Almost one third of patients with PAP are asymptomatic. The most common symptom is dyspnea, usually occurring on exertion, but patients with advanced disease may be short of breath already at rest. Another frequent complaint is cough, occasionally accompanied by the expectoration of gelatinous material. Some patients develop low-grade fever, even in the absence of a supervening infection. Generalized symptoms, such as malaise, fatigue, and weight loss, may be associated with PAP.

Physical examination is often normal, but rales may be present in about half of the patients. In some cases finger clubbing can be observed. In patients with advanced disease central cyanosis can be observed.

The severity and natural history of PAP is variable, and spontaneous remissions do occur (19-37).

#### ***Imaging***

The accumulation of phospholipoproteinaceous material in the alveoli results in an unspecific radiographic pattern of airspace consolidation. The most common radiological manifestation consists of bilateral symmetric infiltrates located centrally in the mid and lower lung zones, resulting in a "bat wing" distribution. In some patients the changes are rather extensive despite relatively mild respiratory symptoms. The infiltrates may be also asymmetrical and isolated lobar involvement has been described. Despite the process being alveolar in distribution, air bronchograms are uncommon. In chronic cases areas of fibrosis have been rarely reported.

High resolution computed tomography scanning (HRCT) reveals ground-glass opacification. If thickened intralobular septa in typical polygonal shapes are visible, the pattern is characteristic and referred to as "crazy-paving". However, these findings are not specific and may be observed in other conditions such as lipoid pneumonia or bronchiolo-alveolar cell carcinoma.

#### ***Pulmonary function***

The most common functional abnormality is a restrictive ventilatory defect with a reduction in lung volumes and a decrease of the lungs diffusing capacity for carbon monoxide, which is sometimes an isolated finding. Various degrees of hypoxemia are common and typically worsen with exercise. This is most likely due to a right-

to-left shunt through poorly ventilated areas with a preserved perfusion (22,23).

### **Laboratory abnormalities**

A typical laboratory finding consists of a raised serum level of lactate dehydrogenase (LDH). Elevated serum levels of lung surfactant proteins A and D (SP-A and SP-D) can be found in PAP but are nonspecific, since elevated levels may also be observed in idiopathic pulmonary fibrosis (24,25).

### **Bronchoalveolar lavage**

The most characteristic finding is the recovery of an opaque and milky fluid. Examination of the cytospin reveals a basophilic granular extracellular material with few enlarged foamy macrophages and cellular debris on staining with May-Grünwald Giemsa (BAL).

Various tumor markers (CEA, CA 19-9 etc) have been detected in the BAL fluid of patients with PAP. These findings are however nonspecific, since they are also found in other pulmonary diseases.

Ultrastructural features of BAL fluid consist of abundant laminated structures called lamellar bodies. These bodies are comprised of phospholipids derived from type II alveolar epithelial cells.

### **Histopathology**

Macroscopic pathological findings consist of patchy areas of yellow consolidated lung. By light microscopy the alveoli and terminal bronchioles are filled with a granular lipoproteinaceous material which stains a deep pink with PAS stain. The lungs architecture is usually preserved although septal thickening caused by edema or lymphocytic infiltration may occur. Transmission electron microscopy shows cellular debris and concentrically arranged laminated annular structures, *i.e.* lamellar bodies.

### **Associated infections**

A major and typical complication of PAP is infection with *Nocardia* species, *Mycobacterium* species, *Cryptococcus neoformans*, *Histoplasma capsulatum*, *Pneumocystis carinii* and viruses. This susceptibility to unusual organisms is multifactorial. Impaired macrophage function and impaired host defense due to abnormalities of surfactant proteins may favor the growth of microorganisms.

### **Diagnosis**

The diagnosis of PAP can be made on the basis of a HRCT scan of the lung in conjunction with the typical findings of an alveolar lavage. BAL fluid examination by light microscopy is usual

result from a sampling error due to the patchy distribution of the disease. If the findings are inconclusive, surgical lung biopsy performed by video-assisted thoracoscopy will deliver adequate tissue samples to exclude other diseases and make a firm diagnosis.

### **Treatment**

Drug therapy consisting of corticosteroids, potassium iodide, ambroxol and aerosolised trypsin have been tried in the past. Since none of these treatment modalities was proven to be effective, it should not be used. Particularly corticosteroids have the potential to predispose for opportunistic infections (38-43).

Whole lung lavage (WLL) under anesthesia is the most consistently effective form of treatment of PAP. The restoration of lung function is partially due to the mechanical emptying of airspaces. Although no randomized controlled trials are available, there is good evidence that symptoms, exercise tolerance, gas exchange and lung mechanics improve after this therapeutic procedure. Clearing of the pulmonary infiltrates on imaging is less impressive and occurs more gradually. WLL also improves macrophage function and decreases the incidence of opportunistic infections.

The indication for WLL is limitation of the patients daily activity due to shortness of breath. Functional parameters, such as hypoxemia and particularly the time course of its deterioration, may serve to schedule WLL. The procedure has inherent risks and should only be performed by an experienced anesthetist and a dedicated team. It usually takes several hours and the patient should be closely monitored in a recovery room and eventually in the intensive care unit. The lung to be washed is clamped for 5 minutes to allow oxygen absorption. Then instillation of body temperature normal saline solution to the nonventilated lung is performed with a volume of 800 to 1 200 mL, during each cycle. After passive recovery of the opaque fluid, the next washing cycle is started. Vigorous chest percussion is performed by a physiotherapist during all cycles of instillation and recovery. The procedure is repeated until the fluid recovery is clear. Total volumes of saline required can range from 20 to 40 L.

Most patients have a good response to this invasive treatment procedure. The median duration of clinical benefit from lavage has been reported to be 15 months (46). Some patients require lavage every six months to maintain their functional status and very few patients are nonresponders.

The major risk of WLL is an incorrect placement of the double lumen endotracheal tube with overspill of lavage fluid into the ventilated lung.

Other complications include pneumothorax, hydropneumothorax and nosocomial lung infection.

A novel treatment modality is the subcutaneous application of GM-CSF. After preliminary observations on the effect of GM-CSF by Seymour *et al.* (42), which could be confirmed by our group, a multicenter study with fourteen patients was undertaken. These patients received 5 µg/kg/day GM-CSF for 6 to 12 weeks with serial monitoring of the alveolar-arterial oxygen gradient ([A-a]DO<sub>2</sub>), diffusing capacity of carbon monoxide, computed tomographic scans, and exercise testing. Patients not responding to 5 µg/kg/d GM-CSF underwent stepwise dose escalation, and responding patients were retreated at disease recurrence. According to prospective criteria, five of 14 patients responded to 5 µg/kg/d GM-CSF, and one of four patients responded after dose escalation (20 µg/kg/d). The overall response rate was 43%. The responses lasted a median of 39 wk and were reproducible with re-treatment. GM-CSF was well-tolerated, with no late toxicity seen. The only treatment-related factor predictive of response was GM-CSF-induced eosinophilia. Each of 12 patients tested had GM-CSF-neutralizing autoantibodies present in pretreatment serum. Therefore, GM-CSF has therapeutic activity in idiopathic AP, providing a potential alternative to whole-lung lavage.

### Prognosis

The overall prognosis of patients with PAP is good. There are several reports of spontaneous resolution. Above mentioned infections were responsible for some of the mortality in the past. Since effective treatment of PAP is available such complications are rather exceptional. The development of fibrosis in patients with PAP has been reported in few cases and it remains unclear if this is a causal or coincidental finding (44,45).

**Special Concerns:** In children, PAP may be divided into congenital and childhood forms, each differing from the other and from adult PAP. Generally, PAP in children often is more acute and severe than PAP in adults. Chest radiographic and HRCT findings in childhood forms of PAP are few but are likely similar to their adult counterparts. Miliary-like pattern is encountered more frequently in PAP in children than in adults, and basilar predominant linear and reticular abnormalities may be observed more often on CT in children. HRCT descriptions of childhood PAP suggest that a crazy-paving pattern may be seen in children as it is in adults.

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