Primary pulmonary alveolar proteinosis

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Abstract

Introduction. Pulmonary alveolar proteinosis is an uncommon disease characterized by the accumulation of surfactant proteins and phospholipids within the alveolar spaces. Acquired disease can be idiopathic (primary) and secondary. The prevalence of acquired pulmonary alveolar proteinosis is about 0.37 per 100,000 persons. Common symptoms are dyspnea and cough. Chest X-ray shows bilateral perihilar infiltrates. Open-lung biopsy is the gold standard for the diagnosis. Treatment includes whole-lung lavage, application of granulocyte-macrophage colony-stimulating factor and lung transplantation.

Case report. We reported a 51 year-old man with primary form of the disease. It was the second case of this extremely rare disease in the past 30 years in our clinic. The symptoms were long-lasting dry cough, fever and physical deterioration. Chest X-ray revealed bilateral pulmonary infiltrates; computed tomography showed patchy ground-glass opacification with interlobular thickening. The diagnosis was established by open lung biopsy. Additional tests were performed to exclude secondary form of the disease.

Conclusion. We presented a rare clinical entity with typical clinical features and clinical and radiological course of the disease, in order to improve differential diagnostic approach to patients with bilateral lung infiltrations. In patients with pulmonary alveolar proteinosis timely diagnosis and adequate treatment can improve a prognosis.

Key words: pulmonary alveolar proteinosis; diagnosis, differential; radiography; tomography, x-ray computed; biopsy.

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Acquired PAP can be idiopathic (primary) PAP and secondary PAP. Secondary PAP is associated with hematological malignancies, Pneumocystis carinii pneumonia and inhalation of silica or titanium.
The prevalence of acquired pulmonary alveolar proteinosis has been estimated to be 0.37 per 100,000 persons. It is a primary acquired disorder in more than 90 percent of cases. It is thought that impairment of surfactant clearance by alveolar macrophages, by autoantibody inhibition of the action of granulocyte-macrophage colony-stimulating factor (GM-CSF) may underlie many acquired cases, whereas congenital disease is most commonly attributable to mutations in surfactant protein genes, but may also be caused by GM-CSF receptor defects.

Symptoms are persistent dry cough, progressive dyspnea, fatigue and malaise, weight loss, intermittent low-grade fever and/or night sweats and pleuritic chest pain. Signs are usually non-specific and include: fine end-inspiratory crackles, digital clubbing and cyanosis.

In acquired pulmonary alveolar proteinosis, routine blood counts and the results of routine blood chemical analysis and urine analysis are usually normal.

Pulmonary function tests (PFTs) can be normal, but typically there are restrictive ventilatory defects with slight impairments in the forced vital capacity and total lung capacity and a disproportionate, severe reduction of the carbon monoxide diffusing capacity. Hypoxemia is caused by ventilation-perfusion inequality and intrapulmonary shunting, resulting in a widened alveolar–arteriolar diffusion gradient.

Chest X-ray (CXR) shows bilateral perihilar consolidation. Changes progress into a diffuse reticular pattern. High-resolution computed tomography scan of the chest shows patchy ground-glass opacification with interlobular thickening. Similar appearance can be seen in lipid pneumonia, sarcoidosis and acute respiratory distress syndrome.

In most cases, the diagnosis is confirmed by bronchoalveolar lavage (BAL) and transbronchial biopsy. Macroscopically, BAL fluid shows milky appearance and microscopically characteristic acellular globules. Histopathological finding of lung biopsy shows periodic acid Schiff (PAS)-positive material within the alveoli but contains no organisms or any excessive cellular response. Surgical lung biopsy is rarely necessary.

Treatment includes whole-lung lavage which often produces a dramatic response. Subcutaneous application GM-CSF and lung transplantation are the therapeutic options.

Case report

A 51-year-old male was admitted to the Clinic for Lung Diseases due to fever and radiological changes in the lungs bilaterally (Figure 1). Symptoms were as follows: fever (up to 37.8°C), dry cough, weakness, fatigue, physical decline lasted for several months. The patient denied any possible exposure to occupational hazards or toxic fumes. He had no risk factors for human immunodeficiency virus (HIV) or other infections. He denied any previous medical illnesses and was not taking any medications. He was a smoker for 30 years, smoking 40 cigarettes per day.

On two occasions, he was examined and treated in the hospital, with different antibiotic therapy and low doses of corticosteroids with minimal improvement: he became afebrile, but symptoms and radiographic changes continued to progress.

Physical examination showed a dysphonic patient with mild peripheral cyanosis. Auscultation of the lungs revealed weakened respiratory sound, prolonged expirium bilaterally and diffuse fine end-inspiratory crackles. Other physical examination findings were within normal limits.

Initial laboratory tests revealed erythrocyte sedimentation rate of 40 mm/h and normal complete blood count. Parameters of blood biochemistry, transaminases and tumor markers were in normal ranges except lactate dehydrogenase (LDH) 484 IU/L (normal range 200–378 IU/L).

Virus analyses such as hepatitis B surface antigen (HbsAg), hepatitis C virus (HCV) and HIV antibodies were negative. Sputum and blood cultures were bacteriologically and cytologically negative.

PFTs showed a severe restrictive ventilatory changes (forced vital capacity was 35 percent predicted). The respiratory arterial blood gases analysis at rest showed severe hypoxemia with pO2 6.4 KPa (9.1 is normal for his age), oxygen saturation at 86% (normal > 94 %) and mild hypocapnia with pCO2 4.5 KPa (normal range 4.6–6).

Multislice computed tomography scan of the chest revealed patchy ground-glass opacification with interlobular thickening bilaterally, without fibrotic changes (Figure 2). Bronchoscopic finding was normal. Histological findings of transbronchial biopsy specimen were nonspecific. The examination of bronchial aspirates did not reveal any biological agents. CXR changes continued to progress. The open-lung biopsy was performed because there was no diagnosis. Five days after the intervention, tachypnea, tachycardia and cyanosis occurred with severe impairment of consciousness and a progression of radiographic changes (Figure 3).

Fig. 1 – Frontal chest radiography reveals bilateral air-space opacity without evidence of pleural effusion or mediastinal widening. A faintly reticular pattern is present, representing thickened, interlobular septa

The arterial blood gases were as follows \( pO_2 = 6.0 \text{ KPa} \), \( pCO_2 = 2.44 \text{ KPa} \); \( sO_2 = 82\% \).

Additional tests were performed for suspected pulmonary thromboembolism. Electrocardiography showed sinus tachycardia, with the frequency of 150/min and incomplete right bundle branch block. D-dimer (fibrin degradation fragment) was 747 ng/mL (normal < 500 ng/mL).

Echocardiography revealed normal left ventricle systolic and diastolic function, mild elevation of right ventricle systolic pressure (5 KPa) with normal dimensions of heart cavities.

The patient developed respiratory failure. Mechanical ventilation was applied, but despite the intensive treatment there was a fatal outcome on the same day.

Immediate cause of the patient's death was not determined because the autopsy was not performed.

Histopathological findings from an open lung biopsy, arriving three days after the patient's death, showed PAP (Figures 4, 5, and 6).

**Discussion**

Primary PAP is a rare syndrome that was first described by Rosen et al. in 1958. This disorder is characterized by abnormal intra-alveolar surfactant accumulation with a variable clinical course, ranging from respiratory failure to spontaneous resolution. Three distinct clinical forms of PAP can be distinguished: congenital, secondary, and primary (idiopathic).

This rare lung disorder generally occurs in persons of 30 to 50 years of age. The median age at the time of diag-
nosis is 39 years old. Most patients are men, and 72% have a history of smoking.

Congenital PAP is a heterogeneous group of disorders caused by mutations in surfactant proteins B or C, or the receptor for GM-CSF. Secondary PAP can develop in association with various conditions, such as immunodeficiency states, acute silicosis and other inhalational syndromes, hematologic malignancies and myelodysplastic syndromes. In all of these conditions there is a reduction in the number and/or functional impairment of alveolar macrophages. More than 90% of all cases of PAP occur as the primary (idiopathic) form. Recent studies have led to the current concept that primary PAP is an autoimmune disease, which produces neutralizing immunoglobulin G (IgG) antibodies against GM-CSF. Surfactant is normally cleared by uptake into alveolar macrophages and GM-CSF is critical for this process, as it is a cytokine stimulating the production of alveolar macrophages by the bone marrow. Therefore, all the three forms of PAP share the feature of an impairment in the number and/or activity of alveolar macrophages leading to the alveolar accumulation of surfactant.

The major complication of PAP is an infection with unusual organisms such as Aspergillus species, Nocardia species, Mycobacterium species, Cryptococcus neoformans, Histoplasma capsulatum, Pneumocystis carinii, and viruses.

The serum level of LDH is frequently elevated, but this finding is non-specific. It may be a useful marker of the severity of the disease. Elevations in the serum levels of carcinoembryonic antigen, cytoketarin 19, mucin KL-6, and surfactant proteins A, B, and D are described but with limited significance.

Open-lung biopsy is the gold standard for the diagnosis and reveals alveoli filled with granular, eosinophilic material that is stained with PAS with preservation of the alveolar architecture. This procedure is not always required and can be complicated by false negative results due to sampling error.

Transbronchial biopsy can generally provide a sufficient tissue sample.

In one third of the patients, no appreciable disability develops and the disease remits spontaneously or fails to progress. The natural history depends on the underlying etiology. Estimates of a 5-year mortality rates vary between 10% and 30%.

Successful lung transplantation has been reported in cases of congenital PAP. The whole-lung lavage remains the standard of care for primary PAP, although some patients may respond to subcutaneous application of GM-CSF. In secondary PAP, the treatment depends on the underlying cause.

Our patient had a typical clinical and radiological presentation of PAP. It was a second case of this extremely rare disease in the past 30 years in our clinic.

The results of imaging methods and PFTs supported the diagnosis, which was confirmed by open lung biopsy. Other causes of PAP were not found, and we estimated the existence of a primary form of the disease which had a progressive course, with severe ventilatory changes and manifested partial pulmonary failure.

The surgical procedure additionally impaired the lung function, so there was a lethal outcome of the disease before obtaining the histopathologic confirmation and applying a specific treatment.

Conclusion

We presented a case of a rare clinical entity, primary pulmonary alveolar proteinosis, with typical clinical features and clinical and radiological course of the disease, in order to improve a differential diagnostic approach to patients with bilateral lung infiltrations. In patients with pulmonary alveolar proteinosis, the timely diagnosis and adequate treatment can improve a prognosis.

REFERENCES


