Primary Alveolar Proteinosis and Review of the Literature

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Abstract

Pulmonary alveolar proteinosis is a rare lung disease characterized by the accumulation of lipoproteinaceous material within the alveoli. Analysis of the lipoproteinaceous materials accumulating in the airspaces demonstrates that they represent an abnormal deposition of the normal constituents of surfactant. This deposition is due to an increased secretion or a decreased clearance from the alveoli. We present the diagnosis of primary pulmonary alveolar proteinosis of a 26 year old female. She was admitted to our department with a dry cough and dyspnea with a slowly progressive course. The patient, who was started antituberculous therapy one year ago, had persistent symmetrical airspace consolidation in the chest x-ray. The diagnosis was made by open lung biopsy. Our patient showed radiological and clinical remission during the time she was hospitalized.

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Case Report

The patient is a 26-year-old housewife. She has no history of cigarette smoking. She has had antituberculous treatment because her two sisters had tuberculosis of the lung. Two years ago, the patient was examined because of complaints of chest pain, fever, shortness of breath, weakness and purulent sputum; she was diagnosed as having pneumonia. Antibiotic therapy was given and when the erythrocyte sedimentation rate fell from 110 mm/h to 25 mm/h, the patient was discharged; one month later she was called for radiological examination. A bronchoscopy was carried out to check for tuberculosis, because there was no radiological regression. When a focus of apparent caseous necrosis was identified in the transbronchial biopsy, the patient was started on antituberculous treatment. The patient came to our clinic after 10 months of regular antituberculous treatment with complaints of cyanosis and progressive dyspnea, but without complaints of weight loss, night sweats or hemoptysis.

There were clubbing, cyanosis on physical examination, and fine crackles on pulmonary auscultation. The erythrocyte sedimentation rate was 38 mm/h. No association with particular

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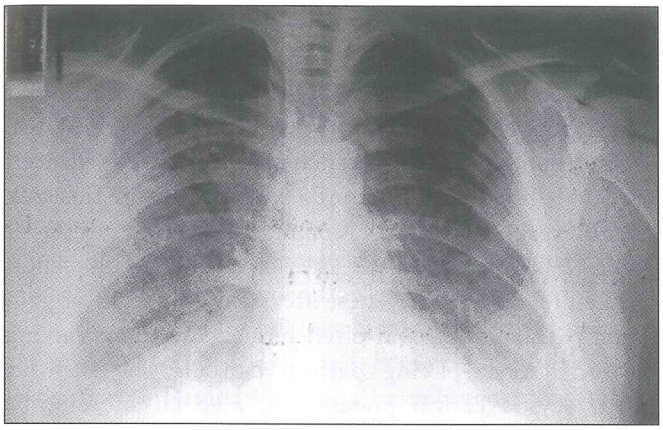

Figure 1. *Chest x-ray showing non-segmental and bilateral reticular shadows in middle and lower lung fields.*

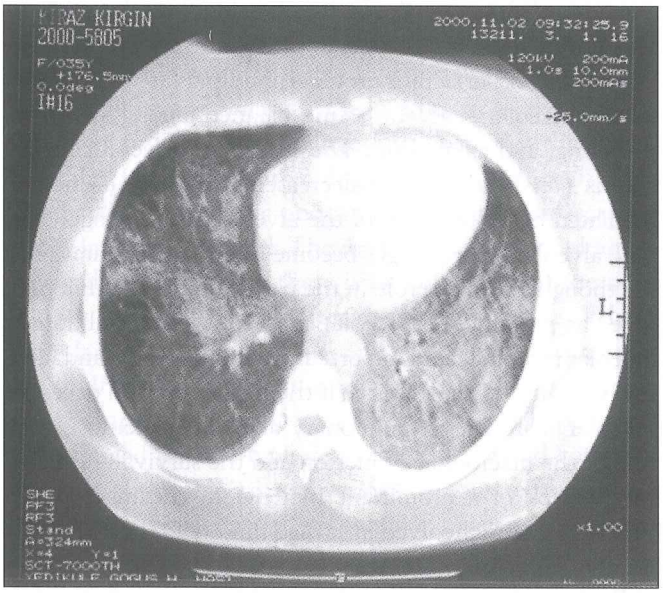

Figure 2. *Chest CT scan revealing diffuse grond glass oacity with well bordered interstitial structures and affect the subpleural areas.*

environmental or occupational exposure was identified. The patient was in hypoxemic respiratory failure at the time that the definitive diagnosis was made (PaO_2: 59.7 mm Hg $PaCO_2$: 27.8 mm Hg). FVC: 79%, FEV_1: 80%, FEV_1/FVC: 88% in pulmonary function tests. An underlying causative organism or agent was not identified. In the chest x-ray, the infiltrates were prominent in the perihilar regions but less so in the periphery, constituting a "bat wing pattern" (Figure 1). In the thorax CT scan, there were abrupt transitious from normal to abnormal lung tissue. Ground glass appearance was present in the abnormal areas and lesions were observed to be characterized by alveolar-filling defect (Figure 2). In the area where the pneumotomy was performed, viscous fluid was observed to be coming from the parenchyma. 3 x 3 cm sized biopsies were taken by wedge resection from the right upper and lower lobes; the histology is illustrated in Figure 3. The specimens obtained from open lung biopsy were diagnostic of pulmonary alveolar proteinosis with amorphous periodic acid-Schiff-positive materials in the alveolar spaces.

Discussion

Pulmonary alveolar proteinosis is a remarkable disease of the lungs resulting from the accumulation in the alveoli of a periodic acid-Schiff-positive lipoproteinaceous material. It consists of three forms known as primary, congenital, and secondary.

Congenital alveolar proteinosis presents with lung dysfunction and respiratory distress in term neonates. Immunohistochemical and genetic studies suggest that congenital alveolar proteinosis may result from abnormalities in one or more of the surfactant proteins. Surfactant is a complex structure primarily of phospholipids but containing essential proteins as well. In some cases, an absence or insufficiency of surfactant apoprotein B has been identified. Congenital alveolar proteinosis due to surfactant protein B deficiency is an inherited disease which results in severe respiratory failure in term infants soon after birth. Surfactant protein B is an essential participant in surfactant homeostasis and required for surfactant uptake by the alveolar type II cells. Experimental studies have demonstrated that exogenous surfactant replacement did not normalize surfactant composition, activity, or pulmonary vascular permeability in these patients. Therefore, it was suggested that endogenous surfactant protein B synthesis is necessary for mature surfactant metabolism and function (1).

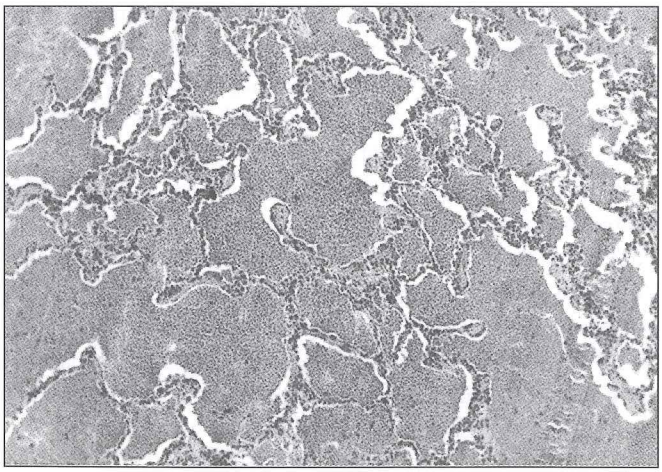

Figure 3. *Light miaoscopy showing airspaces filled with granular lipoproeinaceous material.*

Secondary pulmonary alveolar proteinosis can accompany exposure to titanium (2), water-insoluble nitroaromatic dye (3), dietary 2-methylnaphthalene (4), inhalational quartz (5) (note that the last two study were performed in rodents rather than in humans), cobalt sulphate (6), aluminum dust (7) or fibrous insulation material (8). Therefore, acute silicoproteinosis, first recognized by Beuchner and Ansari in 1969, is observed as a response to inhaled silica (9). There is an increased incidence of secondary pulmonary alveolar proteinosis in hematologic malignancies and a further correlation with myeloid disorder, suggesting a relationship between pulmonary alveolar proteinosis and immune dysfunction (10,11). Another cause of secondary pulmonary alveolar proteinosis is lysinuric protein intolerance. These patients are strongly predisposed to alveolar proteinosis (12). Lysinuric protein intolerance is an autosomal recessive disease characterized by defective transport of cationic amino acids (13). Secondary alveolar proteinosis can accompany renal tubular acidosis, Fanconi disease, glioblastoma multiforme and sometimes atrioventricular septal defect (14). In addition to the examples above, varying degrees of accumulation of the lipoproteinaceous materials in association with Pneumocystis carinii are recognized in acquired immunodeficiency syndrome (12).

Drug-induced pulmonary lipidoses and intraalveolar deposition of IgG-kappa paraproteins in multiple myeloma are considered to be distinct from secondary pulmonary alveolar proteinosis (15). Pulmonary phospholipidosis can be induced by numerous cationic amphiphilic therapeutic agents. They arise as a result of their inhibition of phospholipid catabolism. Inhibition of phospholipases results in the accumulation of phospholipids in the cytoplasm of alveolar macrophages and other cells (7).

Primary pulmonary alveolar proteinosis often occurs between the ages of 20-50 years and is seen four times more often in males. Cyanosis rarely occurs in those who have a moderate dyspnea who generally showing a slow progression. Patients often develop a non-productive cough, sometimes hemoptysis, occasionally pleuritic chest pain, intervals of subfebril pyrexia and loss of weight. Hepatosplenomegaly and clubbing can identified on physical examination and fine crackles can be heard on lung auscultation (16). Asamoto et al. have shown that 1/3 of 68 patients were asymptomatic (17). Laboratory results can show a decrease in diffusion capacity, a restrictive pattern in pulmonary function tests and hypoxemia on arterial blood gas analysis.

Although the distribution of radiographic shadows varies in patients with pulmonary alveolar proteinosis, perihilar or centralized shadows usually predominate. However, subpleural areas of the lung can be affected occasionally (18). The computed tomographic image is characterized by geographically sharply delineated alveolar infiltrates, faint, ground-glass-like parenchymal turbidity, with well bordered interstitial structures and recesses in the subpleural space. The most common pattern consists of ground glass areas with superimposed smooth septal thickening on HRCT. These areas have a patchy or geographic distribution and often termed the "crazy-paving pattern". Crazy-paving pattern can also be seen in Pneumocystis carinii pneumonia, alveolar proteinosis, acute radiation pneumonitis, pulmonary hemorrhage, usual interstitial pneumonia or drug-induced pneumonitis (19).

Pulmonary surfactant lining the alveolus of the lung is critical to postnatal adaptation to air breathing. Precise concentrations of surfactant proteins and lipids are maintained in the alveolar space by a fine balance among synthesis, recycling, and catabolism. The defect in surfactant homeostasis can be caused by decreased surfactant clearance, mediated by dysfunction of the alveolar macrophage (20). The alveolar macrophages become increasingly foamy, and are thought to have a role in the pathogenesis of pulmonary alveolar proteinosis. Alveolar macrophages in pulmonary alveolar proteinosis are reportedly extremely large and have low viability. It is possible that the ingestion of an excess of alveolar materials in pulmonary alveolar proteinosis may impair the macrophage function and the survival, resulting in the lack of a prominent increase in the macrophage number in bronchoalveolar lavage fluid (21). In mice, pulmonary alveolar proteinosis is caused by inactivation of either granulocyte / macrophage colony – stimulating factor (GM-CSF) or granulocyte / macrophage receptor common beta-chain genes, demonstrating a critical role of GM-CSF signaling in surfactant homeostasis (22). Local synthesis of GM-CSF corrects the alveolar proteinosis in the GM-CSF knockout mouse (20). Kitamura et al. have speculated that idiopathic pulmonary alveolar proteinosis is an autoimmune disease with neutralizing antibody of immunoglobulin G isotype against GM-CSF (23). Barraclough and Gillies were reported complete clinical remission in 3 months after starting treatment with GM-CSF in one patient with pulmonary alveolar proteinosis (25).

Bronchoalveolar lavage is an important diagnostic procedure for alveolar proteinosis. Costabel and Guzman advocate the use of bronchoalveolar lavage, stating that the milky white appearance of the recovered fluid, with PAS-positive globules amid cellular debris is diagnostic and negates the need for a biopsy (26). However, the lung

biopsy is almost always necessary for diagnosis. Transbronchial biopsy can generally provide a sufficient tissue sample. More commonly, the diagnoses entertained prior to biopsy suggest to the clinician that a larger biopsy specimen is required to distinguish the possibilities, or the degree of arterial hypoxemia significantly increases the risk of fiberoptic bronchoscopy: therefore an open lung biopsy is obtained. Therapeutic decisions in pulmonary alveolar proteinosis depend on the progression of the illness, the extent of physiological impairment, the presence of coexisting infections, and concurrent illnesses. We have not performed fiberoptic bronchoscopy and related procedures (bronchoalveolar lavage and transbronchial biopsy).

Currently, whole-lung lavage is the only efficient treatment in pulmonary alveolar proteinosis. Corticosteroids, potassium iodide, and streptokinase have all been tried with variable results (25). Treatment with massive bronchial lavage removes the matter from the alveolar space, improves gas exchange and decreases the risk of infection. If the definitive diagnosis is established, and if the patient hypoxemic and shunt fraction is greater than 10%, lavage is required. 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. Whole-lung lavage usually improves the physiological parameters in 24-48 hours (27). Unfortunately this procedure under general anesthesia itself increases the risk of hypoxia due to the need for one-lung ventilation. To avoid complication, it is possible to use veno – venous extracorporeal membrane oxygenation to support oxygenation during whole-lung lavage (24). Leakage into contralateral lung and hydropneumothorax are other early complications (27).

The natural evolution of this disease is poorly understood. In several cases, spontaneous remissions have been observed (24). Asamoto et al. stated that 82% of the 51 cases in which therapeutic bronchial lavage was performed and 94% of the 17 cases which were followed, had symptoms and radiological findings which had gone into remission (17). Our patient showed radiological and clinical remission during the time she was hospitalized. She had no symptom, and no limitations in daily activities due to dyspnea. It was observed regression in her chest X-ray, and no cyanosis on physical examination.

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