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Secondary Pulmonary Alveolar Proteinosis of Occupational Etiology: A Case Report

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Abstract

Pulmonary alveolar proteinosis is a rare disease of alveolar surfactant accumulation. Primary, autoimmune etiology accounts for 90% of cases. This report presents a case of secondary alveolar proteinosis, a metal worker with a pulmonary infection who was subsequently diagnosed with alveolar proteinosis based on the results of bronchoalveolar lavage and lung biopsy. He underwent complete resolution of the alveolar proteinosis after whole lung lavage and change of his workplace. Long term follow-up hasn't shown any sequelae and he has suffered no relapse. This favorable disease course is representative of secondary alveolar proteinosis with a reversible causative agent.

Keywords: Secondary alveolar proteinosis; Metal exposure; Infection; Whole lung lavage

Introduction

Pulmonary alveolar proteinosis (PAP) is a rare disease with an estimated incidence of 0, 36 per million [1]. It is characterized by the abnormal alveolar accumulation of surfactant-derived phospholipids and protein components, caused by their diminished clearance by alveolar macrophages [1]. Based on the etiology, two forms of PAP are currently recognized: the primary form that includes cases of hereditary/congenital and autoimmune origin and the secondary form. Of these, primary PAP is by far the most common, representing 90% of all cases [2]. In this report, we present a case of secondary PAP, due to occupational exposure to mineral dust and the long-term follow-up after treatment with whole lung lavage.

Case Report

In 2000, a 36-year-old male non-smoker without previous history of chronic disease presented at the Department of Infectious diseases of the University Medical Center Ljubljana with a fever of 39 degrees Celsius, chills and productive cough with expectoration of yellow sputum. He was an electronics worker for 13 years and was daily exposed to colophony and mineral dust (zinc, silver, cadmium) and chemical fumes. He had had no previous health issues. He had a raised white blood cell count and C-reactive protein level and was diagnosed as a bilateral pneumonia (Figure 1). However, sputum cultures were negative, probably due to a previous course of antibiotic therapy. He was treated with cefalexin and cefuroxim and his condition improved. He was discharged after 13 days. Despite treatment, he did not feel he had completely recovered and complained of an inability to completely clear his lungs with coughing and had mild dyspnea on exertion. The follow-up chest X-ray one month later showed interstitial changes and he was referred to our Department for Pulmonary diseases and Allergy for evaluation. On examination, his physical status was normal with a pulse rate of 84/min, blood pressure 120/80, respiratory rate of 14/min and oxygen saturation of 96%, without abnormal respiratory phenomena. He had a repeat chest X-ray that showed diffuse reticulonodular opacities, especially in the lower lobes, more on the right side than on the left (Figure 2). Contrast-enhanced computed tomography of the thorax revealed centrolobular ground-glass opacities and interstitial thickening with markedly thickened interlobular septae, most evident in the lower lung lobes (crazy-paving pattern). The process was relatively well demarcated and subpleural parts of the lungs were exempt. Lung function tests showed an abnormality of alveolocapillary diffusion with

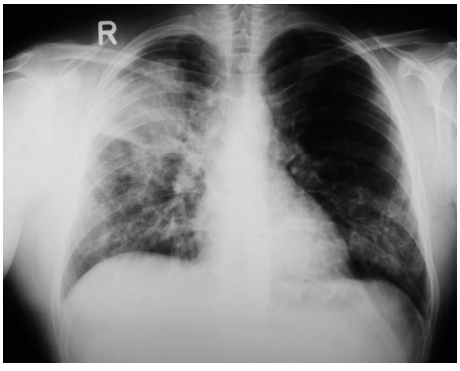

Figure 1: Chest X-ray showing bilateral pneumonia that was worse on the right side.

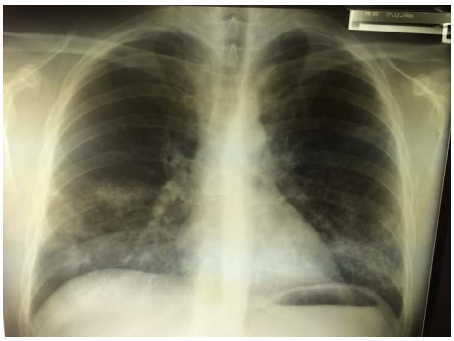

Figure 2: Repeat X- ray showing diffuse reticulonodular opacities, especially in the lower halves of the lungs, more evident on the right side than on the left.

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a DLCO of 70 %, while the lung volumes were normal and the normal ratio of FEV1 to FVC ("Tiffneau index") was maintained (Table 1). We prescribed clarithromycin until the scheduled bronchoscopy.

Bronchoscopy with Bronchoalveolar Lavage (BAL) and transbronchial biopsy was performed in January 2001 (Figure 3). The instilled volume was 200 ml with an output volume of 168ml. The sample was milky in appearance with a cellular concentration of 337/microliter, cell viability of 58%, 23% epithelial cells, 47% macrophages, 40% lymphocytes, 13% neutrophils and globular Periodic-Acid-Schiff (PAS) positive extracellular

	FVC (% of predicted)	FEV1 (% of predicted)	FEV1 to FVC ratio (%)	DLCO (% of predicted)
In 2000	93	93	77	70
2001 before WLL	93	93	69	47
2001 after WLL	98	95	69	81
2014	95	86	71	77

Table 1: Lung function test results.

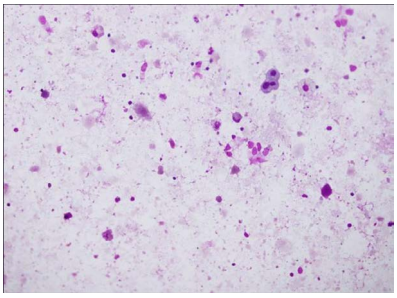

Figure 3: BAL cytology with globular periodic-acid-Schiff (PAS) positive material of extracellular origin.

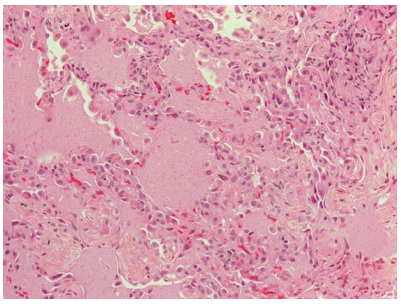

Figure 4: Transbronchial lung biopsy sample showing eosinophilic granular intra-alveolar material and foamy macrophages.

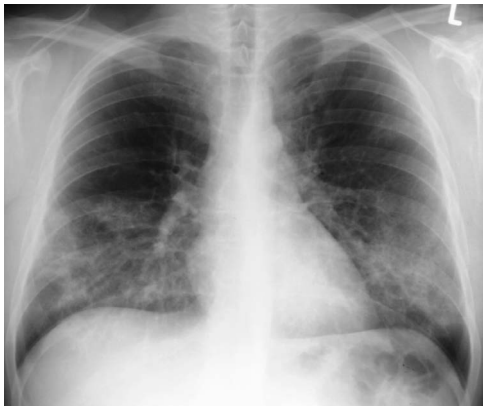

Figure 5: Chest X-ray revealing diffuse bilateral alveolar opacities with a perihilar distribution.

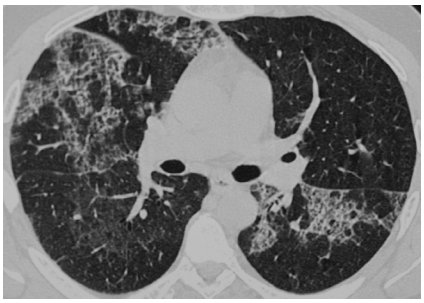

Figure 6: CT scans showing bilateral ground-glass opacities and septal reticulations (crazy pavement pattern).
a: Cross-section of the upper thorax.

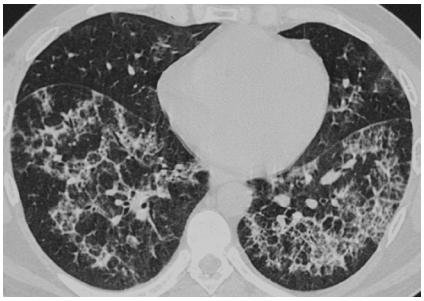

Figure 6 b: Cross-section of the lower thorax showing the more severely affected lower lung lobes.

material. Biopsy samples showed eosinophilic granular intra-alveolar material and foamy macrophages consistent with alveolar proteinosis (Figure 4). It was presumed to be idiopathic, pending more studies. Due to the patients state of good health, whole lung lavage was not attempted at this point, but upon discharge he was instructed to seek immediate medical help if he experienced any difficulty breathing.

He returned later in 2001. He had high fever and an intermittent cough that was worse while exposed to irritants at his workplace. His laboratory tests revealed raised white blood cell count and C-reactive protein levels. In the previous 4 months he had been exposed to more dust than usual. He was admitted to the hospital with bilateral pneumonia and was successfully treated with ciprofloxacin. Two weeks later, his condition worsened, with increased dyspnea and exertional cough. His lips were cyanotic and rales and inspiratory crackles were heard bilaterally over the lower lung lobes. The initial oxygen saturation on room air was 88%. Arterial blood gas analysis showed a pH of 7.469, PCO2 5,4 kPa; PO2 7,9 kPa, HCO3 21.4 mEq/L on 3 L/min supplemental oxygen via nasal cannula. Laboratory tests including blood tests and sputum were normal. Pulmonary function tests showed lung diffusing capacity for carbon monoxide decreased to 47% (Table 1). A chest x-ray revealed bilateral pulmonary infiltrates (Figure 5), while contrast-enhanced chest computed tomography showed ground glass opacities on a reticular background of septal and interstitial thickening resembling a crazy paving pattern (Figure 6a and 6b). Bronchoscopy with Bronchial Alveolar Lavage (BAL) and a transbronchial lung biopsy of the right lower lobe were performed. Bronchoscopy showed proteinaceous secretions in both bronchial trees. The BAL fluid was milky and opaque. Microscopically, the transbronchial lung biopsy showed preserved alveolar architecture with complete filling of the alveoli with periodic-acid-Schiff-positive granular material. The patient was diagnosed with PAP.

Whole-lung lavage was performed under general anesthesia in

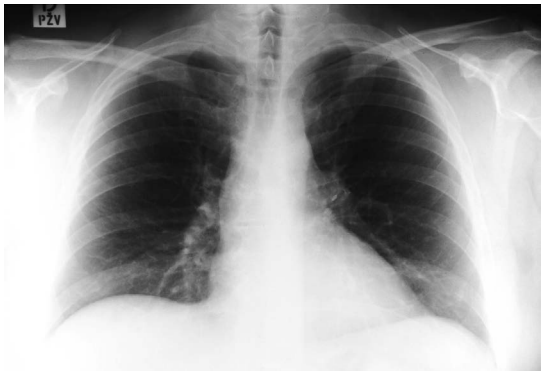

Figure 7: Chest X-ray following whole lung lavage showing improvement of alveolar opacities.

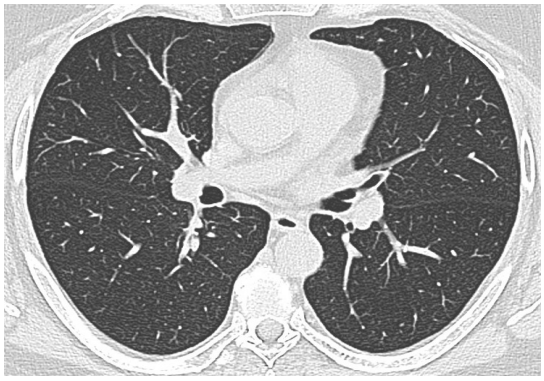

Figure 8: CT scan in 2011 showing complete resolution of alveolar proteinosis.

two separate sessions first on the left, then on the right side of the lungs. On discharge, a chest x-ray showed improved lung haziness bilaterally (Figure 7). His respiratory symptoms improved. Removal from exposure to offending agents was recommended and the patient changed his workplace. Two months later, pulmonary function tests showed that diffusion capacity increased to 81% (Table 1). A follow-up CT in 2011 demonstrated complete resolution of alveolar proteinosis without sequelae (Figure 8). The patient is in good physical condition, pulmonary function tests performed in 2014 have shown no deterioration (Table 1).

Discussion

PAP is a rare diffuse lung disorder that was first described by Rosen et al. [3]. It is characterized by the diffuse intra-alveolar accumulation of amorphous, periodic acid-Schiff (PAS)-positive lipoproteinaceous material, primarily surfactant phospholipids and apoproteins. This accumulation is caused by a disturbance in the balance of either the production of surfactant or its clearance by alveolar macrophages and results in impaired gas transfer between the alveoli and blood [2]. The congenital form is a genetic disease, caused by defective genes for surfactant proteins B or C or granulocyte-macrophage colony stimulating factor (GM-CSF) receptors [2]. The acquired or idiopathic form represents 90% of all PAP cases and is an autoimmune disorder with autoantibodies against the GM-CSF that reduce the number of alveolar macrophages in the lungs [4,5]. Secondary PAP appears when a primary disease reduces either the function or numbers of alveolar macrophages, thereby leading to defective clearance of surfactant. The primary disease is most commonly a hematologic malignancy [6,7] but PAP has been described in the context of immune system dysfunction (AIDS, bone marrow transplantation) or infection (Nocardia, Pneumocysta) [1,2]. Pulmonary alveolar proteinosis has also been connected with the inhalation of mineral dust such as silica, titanium oxide, aluminium oxide and insecticides [8-12]. Cadmium exposure has been found to cause tissue changes similar to pulmonary alveolar proteinosis in animals [13]. Indium-tin oxide is a relatively extensively documented occupational causal agent of PAP [14]. Recent observations have also suggested the possible role of autoimmunity in some, but not all dust-exposure related pulmonary alveolar proteinosis cases. Inhaled agents, such as mineral dusts, could thus be a trigger for autoimmune anti-GM-CSF antibody mediated PAP, blurring the boundaries between disease categories [14-16]. Our patient had a history of 15 years of occupational exposure to mineral and resin dust and fumes in the electronics industry, but as cases of secondary PAP are rare and idiopathic PAP is by far the most common, we could not exclude an autoimmune etiology at the time of diagnosis (anti-GM-CSF antibody tests were not available at the time at our institution). The mineral and resin dusts (with the possible exception of cadmium, due to observations in animals) our patient was exposed to have not been previously implicated in the pathogenesis of PAP in humans, but due to the paucity of cases of secondary etiology, this is not to be wondered at. However, the fact that he underwent complete resolution after WLL and change of workplace and has since suffered no relapse or shown any sequelae on CT exams makes our diagnosis of secondary PAP far more likely.

His environmental exposure to mineral and resin dusts was long-standing, but despite this a chest X-ray performed 5 years before his first hospital admission showed no consequences of exposure. His alveolar proteinosis might have been induced by lung infection in combination with environmental exposure but after his removal from the hazardous workplace subsequent pneumonias failed to induce disease recurrence, showing that these factors might work together in the pathogenesis of PAP in susceptible subjects. Alternately, his pneumonias might have themselves been a consequence of the deranged pulmonary local immunity in the setting of PAP [1].

Patients with secondary alveolar proteinosis are few, but their prognosis in the presence of a known, reversible cause is much more optimistic, whereas up to 66% of patients with primary PAP may require a repeat lavage due to disease relapse [1,17].

Conclusion

Secondary alveolar proteinosis is an extremely rare disease. The diagnosis must be considered when radiologic changes do not comply with the sequelae of lung infection and occupational history reveals exposure. In a susceptible patient, a combination of mineral and resin dust exposure and lung infection presents a high risk for the development of PAP. Whole lung lavage in combination with the timely removal of the offending agent is an efficient treatment option for patients with secondary pulmonary alveolar proteinosis due to work-related dust exposure. It is crucial for the patient to change his work environment. The occupational history of patients with this rare disease is thus an important part of their diagnostic workup.

References

1. Seymour JF, Presneill JJ (2002) Pulmonary alveolar proteinosis: progress in the first 44 years. Am J Respir Crit Care Med 166: 215-235.
2. Trapnell BC, Whitsett JA, Nakata K (2003) Pulmonary alveolar proteinosis. N Engl J Med 349: 2527-2539.
3. Rosen SH, Castleman B, Liebow AA (1958) Pulmonary alveolar proteinosis. N Engl J Med 258: 1123-1142.
4. Kitamura T, Tanaka N, Watanabe J, Uchida, Kanegasaki S, et al. (1999) Idiopathic pulmonary alveolar proteinosis as an autoimmune disease with

neutralizing antibody against granulocyte/macrophage colony-stimulating factor. J Exp Med 190: 875-880.

5. Tanaka N, Watanabe J, Kitamura T, Yamada Y, Kanegasaki S, et al. (1999) Lungs of patients with idiopathic pulmonary alveolar proteinosis express a factor which neutralizes granulocyte-macrophage colony stimulating factor. FEBS Lett 442: 246-250.
6. Chung JH, Pipavath SJ, Myerson DH, Godwin D (2009) Secondary pulmonary alveolar proteinosis: a confusing and potentially serious complication of hematologic malignancy. J Thorac Imaging 24: 115-118.
7. Chaulagain CP, Pilichowska M, Brinckerhoff L, Tabba M, Erban JK5 (2014) Secondary pulmonary alveolar proteinosis in hematologic malignancies. Hematol Oncol Stem Cell Ther 7: 127-135.
8. Miller RR, Churg AM, Hutcheon M, Lom S (1984) Pulmonary alveolar proteinosis and aluminum dust exposure. Am Rev Respir Dis 130: 312-315.
9. Keller CA, Frost A, Cagle PT, Abraham JL (1995) Pulmonary alveolar proteinosis in a painter with elevated pulmonary concentrations of titanium. Chest 108: 277-280.
10. Buechner HA, Ansari A (1969) Acute silico-proteinosis. A new pathologic variant of acute silicosis in sandblasters, characterized by histologic features resembling alveolar proteinosis. Dis Chest 55: 274-278.
11. Miller RR, Churg AM, Hutcheon M, Lom S (1984) Pulmonary alveolar proteinosis and aluminum dust exposure. Am Rev Respir Dis 130: 312-315.
12. Bonella F, Bauer PC, Griese M, Ohshimo S, Guzman J, et al. (2011) Pulmonary alveolar proteinosis: new insights from a single-center cohort of 70 patients. Respir Med 105: 1908-1916.
13. Johansson A, Camner P (1986) Adverse effects of metals on the alveolar part of the lung. Scan Electron Microsc : 631-637.
14. Cummings KJ, Donat WE, Ettensohn DB, Roggli VL, Ingram P, et al. (2010) Pulmonary alveolar proteinosis in workers at an indium processing facility. Am J Respir Crit Care Med 181: 458-464.
15. Inoue Y, Trapnell BC, Tazawa R, Arai T, Takada T, et al. (2008) Characteristics of a large cohort of patients with autoimmune pulmonary alveolar proteinosis in Japan. Am J Respir Crit Care Med 177: 752-762.
16. Costabel U, Nakata K (2010) Pulmonary alveolar proteinosis associated with dust inhalation: not secondary but autoimmune? Am J Respir Crit Care Med 181: 427-428.
17. Gao F, Lu GC, Zhou XY, Yu Z, Wang HM, et al. (2014) Repeated whole-lung lavage for unremitting pulmonary alveolar proteinosis: a eight-year follow-up of a case. Genet Mol Res 13: 6135-6141.