

CASE REPORT

Pulmonary alveolar lipoproteinosis associated with emphysematous areas

MARIANA DEACU¹⁾, DOINA ECATERINA TOFOLEAN²⁾, MĂDĂLINA BOȘOTEANU¹⁾,
MARIANA AŞCHIE¹⁾, I. BULBUC³⁾

¹⁾Department of Pathology

²⁾Department of Internal Medicine

Faculty of Medicine, "Ovidius" University, Constanța

³⁾"Medimar" Imaging Department,
Emergency County Hospital, Constanța

Abstract

Pulmonary alveolar lipoproteinosis, described for the first time in 1958 by Rosen SH, Castleman B and Liebow AA, is a rare pathological condition characterized by alveolar accumulation of lipoproteinaceous material. It is the result of macrophages impairment to rid the alveolar spaces of spent surfactant. This condition involves a restrictive function of pulmonary tissue, reflected in gas exchange impairment and respiratory symptoms of variable severity. Until now, about 410 cases have been reported in the literature. From these cases, 90% were represented by primary type of pulmonary alveolar lipoproteinosis. We present the case of 37-year-old male patient admitted in the Department of Internal Medicine, Emergency County Hospital, Constanța, Romania, with progressive exertional dyspnea, dry cough and perioral cyanosis. The clinical symptoms started three months before hospital admission. Based on clinical findings and imaging features, the primary pulmonary alveolar proteinosis diagnosis has been suspected. Uncharacteristic serous aspect of fluid resulting from bronchoalveolar lavage required open lung biopsy. Pathologic examination of pulmonary slice revealed features consistent with the diagnosis of pulmonary alveolar lipoproteinosis associated with emphysematous foci. The peculiarity of this case lies in the association of two pathological conditions, each of them requiring different pathways.

Keywords: pulmonary alveolar lipoproteinosis, pulmonary emphysema.

□ Introduction

Pulmonary alveolar lipoproteinosis, described for the first time in 1958 by Rosen SH, Castleman B and Liebow AA, is a rare pathological condition characterized by alveolar accumulation of lipoproteinaceous material. It is the results of macrophages impairment to rid the alveolar spaces of spent surfactant [1, 2].

This clinico-pathological syndrome recognizes many causes. The most frequent cause is the development of autoantibodies that neutralize GM-CSF (granulocyte-macrophage colony-stimulating factor) and in this way the macrophages functions are impaired [3, 4]. This pathway induces primary pulmonary alveolar proteinosis. The secondary type of alveolar proteinosis determined by many pathological conditions: heavy dust exposure, various enzyme defects reported in children, autoimmune disorders comprised rheumatoid arthritis, diseases characterized by immunosuppression like leukemia or lymphoma, infection with mycobacteria, *Nocardia* and anaerobes [5–7].

Until now, about 410 cases have been reported in the literature. From these cases, 90% were represented by primary type of pulmonary alveolar lipoproteinosis, less than 10% were secondary form of disease and 2% congenital form. Males are most frequently affected than females, sex ratio M/F 2.65/1. The age of diagnosis ranging from 30 to 50-year-old, with median age of 37±13.3 years. About 72% of patients diagnosed with

primary pulmonary alveolar lipoproteinosis showed history of smoking [8].

Clinical features are non-specific. Most of the time, patients with alveolar proteinosis present with progressive dyspnea of gradual onset, accompanied by fatigue, weight loss, cyanosis and dry cough. Patients with this clinical syndrome have high risk to develop pulmonary infections with opportunistic pathogens like *Nocardia* sp. and *Mycobacterium tuberculosis* [9, 10].

Diagnostic methods include plain chest radiography, high-resolution CT, and also BAL (bronchoalveolar lavage). The open lung biopsy with histopathological exam remains the "gold standard" for final diagnosis of alveolar proteinosis [11, 12].

□ Clinical and imaging findings

We present the case of 37-year-old male (E.G.) patient admitted in the Department of Internal Medicine, Emergency County Hospital, Constanța, with progressive exertional dyspnea, dry cough and perioral cyanosis. Historical data show insidious onset of clinical symptoms three months before hospital admission, except for cyanosis, that occurred two days before admission. At the same time, personal data show 17 years smoking history, about twenty cigarettes daily. Physical exam revealed characteristic signs of respiratory insufficiency: cyanosis, dyspnea, circulation. Crackles have been found on auscultation, too, especially at bases.

On plain chest radiography test, bilateral symmetric confluent alveolar infiltrates with extensive areas of consolidation in perihilar zones were noted. CT scan imaging showed, especially in central zones, bilateral confluent areas of alveolar consolidation with air

bronchograms, and the ground-glass opacifications with interlobular septal thickening – “crazy paving” appearance (Figure 1). The presence of emphysema bubbles with unsystematic disposition was noted, too (Figure 2).

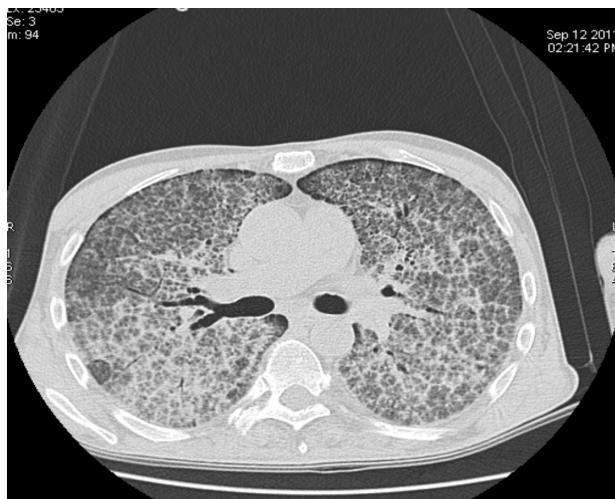


Figure 1 – CT scan imaging showed “crazy paving” appearance and interlobular septal thickening.

Arterial air gas analysis indicated 60% saturation that supports the presence of restrictive pulmonary damage. ELISA test showed the absence of HIV infection. Fluid obtained by bronchoalveolar lavage presented a serous uncharacteristic aspect.

Based on clinical findings and imaging features, the primary pulmonary alveolar proteinosis diagnosis has been suspected. To confirm this diagnosis, open lung biopsy was performed. Patient's evolution was complicated by the infection with opportunistic germ, *Acinetobacter* sp., identified in blood cultures.

Materials and Methods

The macroscopic and histopathologic assessments were performed in the Clinical Service of Pathology, Emergency County Hospital, Constanța, using standard protocols procedures. The surgical sample was macroscopically evaluated and after that, was fixed in 10% formalin. After fixation, specimen was cut into 4–5 mm slice operated with ATP1 Tissue Processor and



Figure 2 – CT scan imaging: emphysema bubbles with unsystematic disposition.

paraffin embedded. The paraffin blocks were serially sectioned at 5 µm, stained with Hematoxylin and Eosin, van Gieson, and PAS.

Results

Macroscopic assessment of the pulmonary tissue slice, measuring 2.2×1.5×0.8 cm, showed thin, transparent pleura on the external surface. On cut surface, we noted a gray-yellowish color, a slight firm consistency, and the presence of multiple small cystic spaces of 0.1 cm in size. After compression, a small amount of opalescent fluid was discharged.

Histopathological examination showed alveolar spaces almost completely filled by an acellular, intense eosinophilic, finely granular fluid (Figure 3). Inside of this, fluid lamellar bodies and cholesterol crystal clefts were identified (Figure 4). A small number of extravasated erythrocytes was observed, too. Alveolar spaces were lined by flattened epithelium.

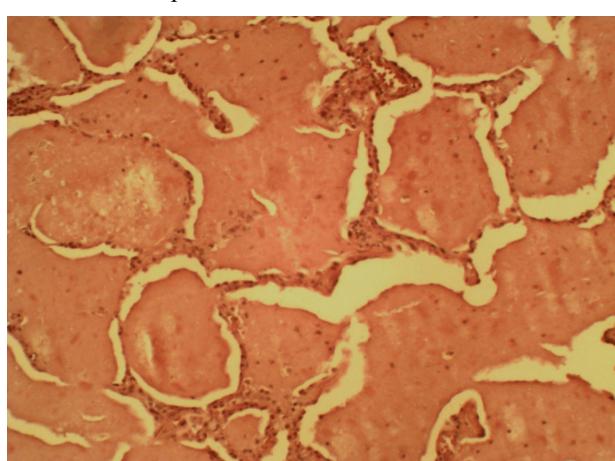


Figure 3 – Alveolar spaces filled by an acellular, intense eosinophilic, finely granular fluid (HE stain,

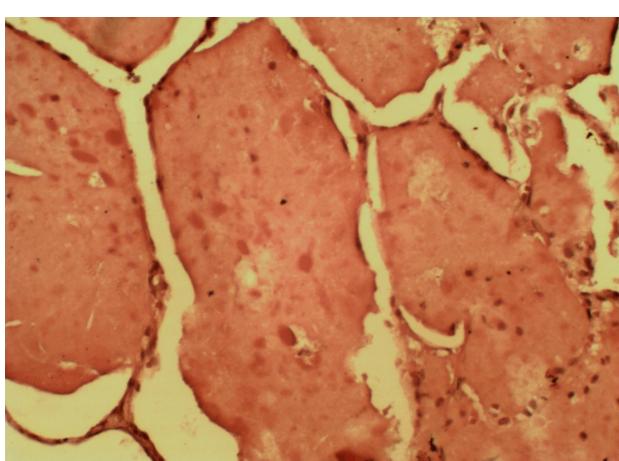


Figure 4 – Lamellar bodies and cholesterol crystal clefts inside eosinophilic fluid (HE stain, ob. ×20).

In the main, microscopic assessment revealed well-preserved alveolar architecture with some exceptions. Thereby, many foamy macrophages inside the alveoli located near pleura were noticed (Figure 5). Alveolar walls were thin, interrupted in places, with emphysematous foci formation (Figure 6). Minimal fibrosis was identified in a small number of septa, too,

especially near emphysematous areas. At the same time, moderate lymphocytic infiltrate of pleura was observed (Figure 7). Applying PAS stain, intra-alveolar fluid was intensely positive (Figure 8).

Based on microscopic findings, the final diagnosis of primary pulmonary alveolar lipoproteinosis associated with emphysematous foci has been confirmed.

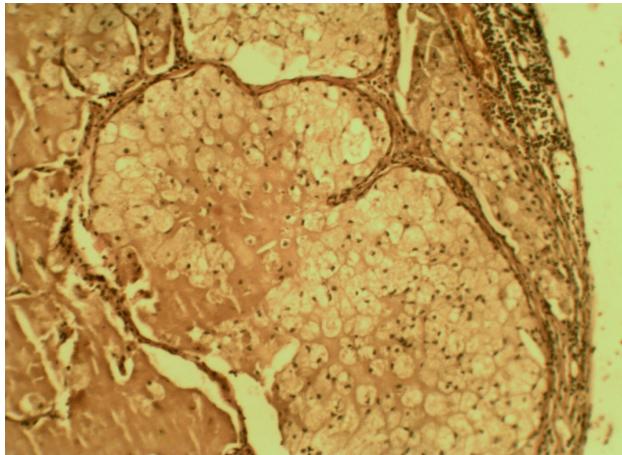


Figure 5 – Alveolar spaces containing foamy macrophages (van Gieson stain, ob. $\times 10$).

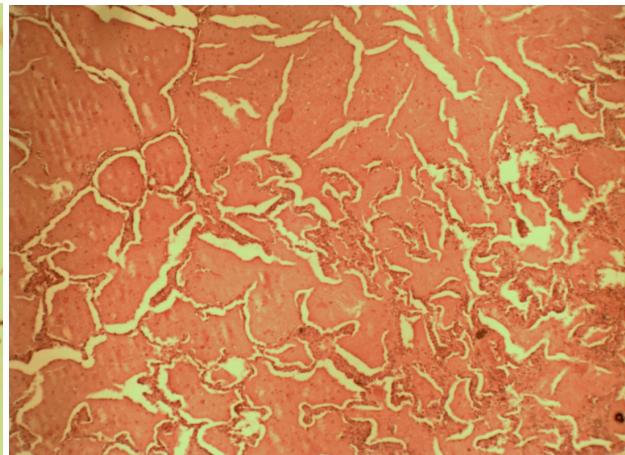


Figure 6 – Interrupted alveolar walls (HE stain, ob. $\times 4$).

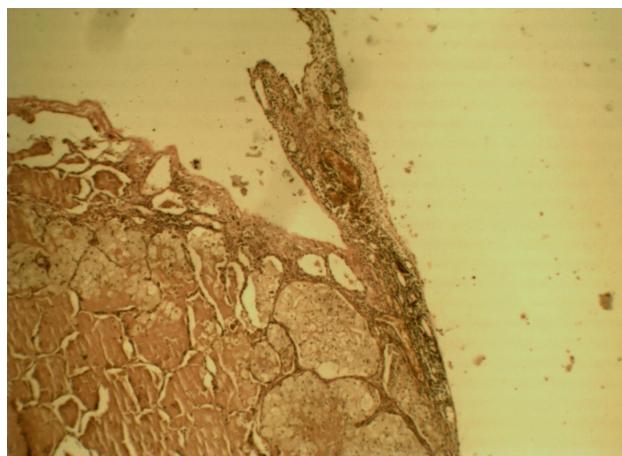


Figure 7 – Lymphocytic infiltrate of pleura and minimal fibrosis (van Gieson stain, ob. $\times 4$).

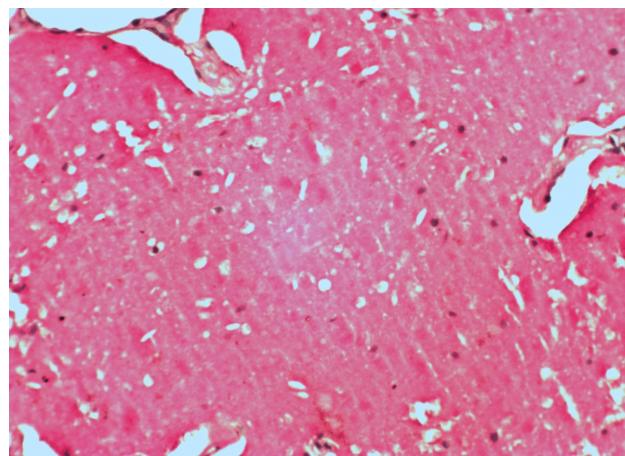


Figure 8 – Intensely positive intra-alveolar fluid (PAS stain, ob. $\times 20$).

Discussion

Pulmonary alveolar lipoproteinosis is a rare clinico-pathological syndrome consisting in abnormal intra-alveolar accumulation of surfactant-derived lipoproteinaceous material of unclear origin [1, 8, 13]. It results in restrictive function of pulmonary tissue, reflected in gas exchange impairment and respiratory symptoms of variable severity.

Clinical course of this disease is variable, ranging from spontaneous resolution to death with pneumonia or respiratory failure. The most effective treatment is whole-lung lavage [2, 8, 14].

Current classification of pulmonary alveolar proteinosis includes three types of disease: primary form with unclear etiology, secondary associated with various pathological conditions, and congenital alveolar proteinosis that involve genetic disorders [2, 8]. Until now, 410 cases have been reported in literature. Primary

pulmonary alveolar lipoproteinosis is the most common form of the disease, consisting in 90% of total cases. Several studies showed that this form is induced by the development of autoantibodies that neutralize GM-CSF. It results in the alveolar macrophages impairment to rid the alveolar spaces of spent surfactant containing large amount of lipids and proteins [1, 2, 15].

In our patient, uncharacteristic serous aspect of fluid resulting from bronchoalveolar lavage, required open lung biopsy. On the other hand, imaging features represented by areas of alveolar consolidation accompanied by aeric bronchogram, ground-glass opacifications and interlobular septa thickening may suggest diagnosis of pulmonary alveolar lipoproteinosis but are still nonspecific.

Histopathological examination using usual and special stains revealed pulmonary tissue changes sustaining diagnosis of alveolar lipoproteinosis. Most of these changes are consistent with the literature [1, 2, 5].

The peculiarity in this case lies in the presence of marked dilation of alveolar spaces accompanied by alveolar walls interruption. Such microscopic changes are consistent with pulmonary emphysema. The consulted literature did not mention an association between pulmonary alveolar lipoproteinosis and pulmonary emphysema. In fact, pathogenesis of pulmonary emphysema involved morphologically alveolar walls destruction accompanied by septal fibrosis and inflammatory infiltrate composed by an increased number of neutrophils, macrophages, lymphocytes and eosinophils [16]. In contrast, alveolar lipoproteinosis involve mild fibrotic degeneration and the absence of inflammatory cells.

Several studies showed that in pulmonary emphysema, interruption of the alveolar walls resulting from elastic fibers damage due to elastolytic enzymes produced by inflammatory cells like neutrophils and macrophages, in addition with MMP-3 (collagenase), MMP-9 (gelatinase), and cathepsins. Besides genetic disorders and inflammatory conditions, an important role in emphysema development is attributed to oxidative stress [16]. In our patient, presence of emphysematous foci could be related with smoking history. Experimental animal models showed that the lung exposure to cigarettes smoke, gradually increases oxidative stress and this might lead to emphysema development. At the same time, prolonged exposure to cigarettes smoke of the lung inhibits fibroblast proliferation that is essential to promote alveolar walls repair [16].

Another aspect observed in our case on microscopic exam was the presence of a large number of foamy macrophages inside alveolar spaces located near pleura. This is a characteristic feature of lipoid pneumonia, an uncommon pathological condition resulting from accumulation of exogenous or endogenous lipidic material inside the alveolar spaces. Several experimental studies showed that clinical course of alveolar lipoproteinosis may be complicated by lipoid pneumonia. Otherwise, the consulted literature mentioned cases with association between these two pathological conditions [5, 17]. In our patient, presence of this feature may be suggestive for a possible evolution of alveolar proteinosis to lipoid pneumonia.

One of the pulmonary lesions we had to exclude on microscopic exam was *Pneumocystis carinii* pneumonia. In pulmonary infection with *Pneumocystis carinii* histopathological exam showed completely filled alveolar spaces by an amorphous, pale-eosinophilic, foamy material. Occasionally, this amorphous material is accompanied by hyaline membranes. In addition, alveolar septa are thickened by an inflammatory infiltrate composed of lymphocytes and plasmocytes [5]. Unlike alveolar lipoproteinosis, PAS stain application in *Pneumocystis carinii* pneumonia revealed only the pathogen inside the alveolar spaces without the presence of the amorphous material.

Regarding *Acinetobacter* sp. infection, this was probably caused by immunosuppression in the absence

of HIV infection. Consulted literature mentioned only one case of alveolar lipoproteinosis that had a secondary infection with *Acinetobacter* sp. [18]. Patients with pulmonary alveolar lipoproteinosis present an increased risk for infection with a wide range of opportunistic pathogens. Otherwise, in cases diagnosed with alveolar lipoproteinosis, more than 20% from deaths are the results of secondary infection. Most frequently, these infections are caused by *Nocardia* sp. and *Mycobacterium tuberculosis* [8–10]. In our case, secondary pulmonary infection required postponing of whole-lung lavage.

Conclusions

This is a rare case of pulmonary alveolar proteinosis associated with areas of pulmonary emphysema. The final diagnosis was established performing the histopathological exam. It may be an example of association of two pathological conditions, each of them requiring different pathways.

References

- [1] Rosen SH, Castleman B, Liebow AA, *Pulmonary alveolar proteinosis*, N Engl J Med, 1958, 258(23):1123–1143.
- [2] Seymour JF, Presneill JJ, *Pulmonary alveolar proteinosis: progress in the first 44 years*, Am J Respir Crit Care Med, 2002, 166(2):215–235.
- [3] Kitamura T, Tanaka N, Watanabe J, Uchida, Kanegasaki S, Yamada Y, Nakata K, *Idiopathic pulmonary alveolar proteinosis as an autoimmune disease with neutralizing antibody against granulocyte/macrophage colony-stimulating factor*, J Exp Med, 1999, 190(6):875–880.
- [4] Bonfield TL, Russell D, Burgess S, Malur A, Kavuru MS, Thomassen MJ, *Autoantibodies against granulocyte macrophage colony-stimulating factor are diagnostic for pulmonary alveolar proteinosis*, Am J Respir Cell Mol Biol, 2002, 27(4):481–486.
- [5] Corrin B, Nicholson AG, Burke M, *Pathology of the lung*, 2nd edition, Churchill Livingstone, 2006, 98–105.
- [6] Miller RR, Churg AM, Hutcheon M, Lom S, *Pulmonary alveolar proteinosis and aluminum dust exposure*, Am Rev Respir Dis, 1984, 130(2):312–315.
- [7] Beers MF, Hamvas A, Moxley MA, Gonzales LW, Guttentag SH, Solarin KO, Longmore WJ, Nogee LM, Ballard PL, *Pulmonary surfactant metabolism in infants lacking surfactant protein B*, Am J Respir Cell Mol Biol, 2000, 22(3):380–391.
- [8] Ioachimescu OC, Kavuru MS, *Pulmonary alveolar proteinosis*, Chron Respir Dis, 2006, 3(3):149–159.
- [9] Witty LA, Tapson VF, Piantadosi CA, *Isolation of mycobacteria in patients with pulmonary alveolar proteinosis*, Medicine (Baltimore), 1994, 73(2):103–109.
- [10] Pascual J, Gómez Aguinaga MA, Vidal R, Maudes A, Sureda A, Gómez Mampaso E, Fogué, *Alveolar proteinosis and nocardiosis: a patient treated by bronchopulmonary lavage*, Postgrad Med J, 1989, 65(767):674–677.
- [11] Goldstein LS, Kavuru MS, Curtis-McCarthy P, Christie HA, Farver C, Stoller JK, *Pulmonary alveolar proteinosis: clinical features and outcomes*, Chest, 1998, 114(5):1357–1362.
- [12] Rubinstein I, Mullen JB, Hoffstein V, *Morphologic diagnosis of idiopathic pulmonary alveolar lipoproteinosis-revisited*, Arch Intern Med, 1988, 148(4):813–816.
- [13] Lee KN, Levin DL, Webb WR, Chen D, Storto ML, Golden JA, *Pulmonary alveolar proteinosis: high-resolution CT, chest radiographic, and functional correlations*, Chest, 1997, 111(4):989–995.
- [14] Cohen E, Eisenkraft JB, *Bronchopulmonary lavage: effects on oxygenation and hemodynamics*, J Cardiothorac Anesth, 1990, 4(5):609–615.

- [15] Cooke KR, Nishinakamura R, Martin TR, Kobzik L, Brewer J, Whitsett JA, Bungard D, Murray R, Ferrara JL, *Persistence of pulmonary pathology and abnormal lung function in IL-3/GM-CSF/IL-5 beta c receptor-deficient mice despite correction of alveolar proteinosis after BMT*, Bone Marrow Transplant, 1997, 20(8):657–662.
- [16] Di Petta A, *Pathogenesis of pulmonary emphysema – cellular and molecular events*, Einstein, 2010, 8(2 Pt 1):248–251.
- [17] Sato K, Takahashi H, Amano H, Uekusa T, Dambara T, Kira S, *Diffuse progressive pulmonary interstitial and intra-alveolar cholesterol granulomas in childhood*, Eur Respir J, 1996, 9(11):2419–2422.
- [18] Gepert EF, *Recurrent pneumonia*, Chest, 1990, 98(3):739–745.

Corresponding author

Mariana Deacu, Lecturer, MD, PhD, Department of Pathology, Faculty of Medicine, “Ovidius” University, C2 Universității Street, 900527 Constanța, Romania; Phone +40741–041 154, e-mail: deacu_mariana@yahoo.com

Received: November 16th, 2011

Accepted: January 25th, 2012