



Bilateral lung disease, extensive and diffuse. Diagnosis of pulmonary alveolar proteinosis by bronchoscopic cryobiopsy

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ABSTRACT

Pulmonary alveolar proteinosis (PAP) is a rare disease characterized by the intra-alveolar accumulation of a proteinaceous phospholipid-laden material called surfactant. Clinically, this disease should be suspected with respiratory failure in association with a crazy paving pattern on high-resolution chest computed tomography. We report a 24-year-old gentleman who was referred to us for a history of respiratory failure, treatment with invasive ventilation and tracheostomy. His blood exams and biochemistry were normal. His infectious and rheumatological panel was negative for a secondary disease. A flexible bronchoscopy with a transbronchial biopsy through a CryoProbe was performed. An anatomopathological analysis was periodic acid-Schiff positive for PAP. A CryoProbe is a recently developed diagnostic tool that improves the diagnostic yield in diffuse lung diseases compared to bronchoscopy with transbronchial biopsy. This method should be considered for patients with diffuse lung disease and PAP.

1. Introduction

Pulmonary alveolar proteinosis (PAP) is a rare disease. It is characterized by the intra-alveolar accumulation of lipoprotein and phospholipid surfactant material. Clinically, it should be suspected in cases of diffuse pulmonary damage with a crazy paving pattern on a thorax CT [1,2]. Its diagnosis requires histological tissue stained by periodic acid-Schiff stain (PAS); positive stains are compatible with PAP [3,4]. As an alternative to surgical biopsy, minimally invasive sampling methods have been developed, such as flexible bronchoscopy with transbronchial biopsy; however, over the past few years, cryobiopsy has been described as a diagnostic alternative that improves the performance of these biopsy techniques [5]. The objective of this work is to present the case of a patient with respiratory failure and severe diffuse pulmonary damage who required invasive mechanical ventilation and was referred to a bronchoscopy for diagnosis. The sample obtained by cryobiopsy was positive for PAP. Finally, the patient was successfully treated with whole lung lavage.

2. Case report

The patient was a 24-year-old obese (BMI 36.6 kg/m²) male; he had been a builder, charcoal bag carrier, and ceramic cutter for 10 years. He had arterial hypertension that was being treated with Enalapril and was a current smoker (16 packs/year). He was diagnosed with community-acquired pneumonia 5 months before intensive care admission for respiratory failure, requiring mechanical ventilation and tracheostomy. At first, he was diagnosed with severe community-acquired pneumonia without isolation of germs.

Thorax CT (Fig. 1a and b) showed extensive bilateral lung involvement, with ground glass infiltrates and a crazy paving pattern.

He received anticoagulation for right arm thrombophlebitis. He was referred to a bronchoscopy service that has cryobiopsy equipment for the hospitalization and ability to perform tracheostomy, which was performed without mechanical ventilation, albeit with supplementary O₂. Upon bronchoscopy service admission, the patient was normotensive and had the following levels: HR: 100/min., FR: 28/min; arterial gases (FiO₂, 0.21): pH: 7.39, CO₂: 36, O₂: 48.5, bicarbonate: 21.4, base

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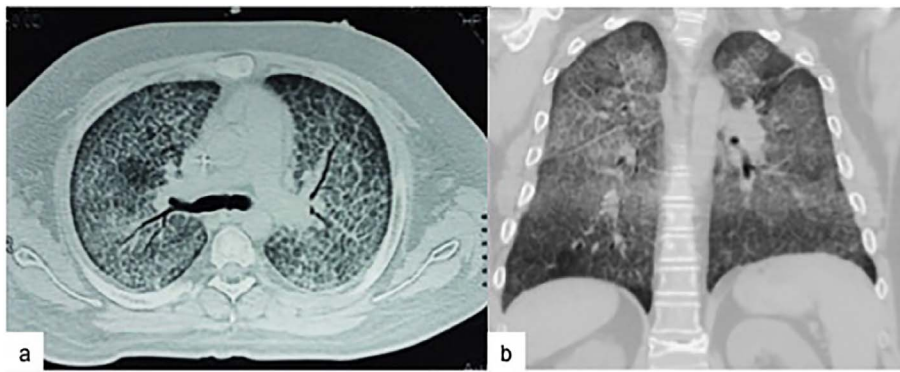


Fig. 1. a and b. Thorax CT showed a bilateral, diffuse infiltrate with a crazy paving distribution.

excess: -2.6 , O_2 saturation: 83.2%. A physical exam showed no digital clubbing and no signs of neurological or cardiovascular deficit; the lung auscultation showed generalized hypoventilation without abnormal noises; the rest of the examination was unremarkable.

Laboratory results: Erythrocyte sedimentation rate: 1 hour 5 mm. Haemoglobin: 16.2 g/dl, Haematocrit: 51%, platelets 443,000/ μ L, WBC: 11.0 (10^9 /lt) (66% neutrophils). Glucose: aminotransferases, creatinine, sodium, potassium and thyroid panel were in normal range values. Serology: human immunodeficiency virus (HIV), hepatitis C virus (HCV), hepatitis B virus (HBV) were negative, and venereal research laboratory (VDRL) was non-reactive. *Cryptococcus neoformans* antigen, IgG and IgM anti cytomegalovirus, IgG and IgM *Epstein Barr* were all negative. IgG toxoplasmosis: positive, IgM: negative. Sputum for Acid-alcohol-resistant bacilli (x3): negative. Tuberculin intradermal reaction (PPD): 0 mm (non-reactive).

Immunologic laboratory latex rheumatoid arthritis, complements levels C3 and C4: normal. Electrophoretic proteinogram: normal. IgA, IgG, and IgM: normal. Antinuclear antibodies (ANA); anti-neutrophil cytoplasm antibodies (ANCA) C and P; anti-mitochondrial antibodies (AMA); anti-microsomal antibodies (AC LKM); anti-parietal cell antibodies (APCA); anti-smooth muscle antibodies (ASMA); anti-glomerular basement membrane antibodies; anti-native DNA antibodies: all negative. Measurement of auto-antibodies against granulocyte-macrophage colony stimulating factor (anti-GM-CSF) antibodies was not available.

The bronchoscopy, with temporary suspension of anticoagulation, did not show pathological findings; the lung lavage yielded negative results for aerobic, mycological germs, mycobacteria, and parasites.

The cryobiopsy was performed using the ERBOKRYO CA system® (ERBE USA Incorporated Surgical Systems), with a 1.9-mm diameter cryoprobe to collect 3 samples. There was not significant bleeding during the study or 24 hours later, after anticoagulation resumption; there were no complications associated with the procedure.

The anatomic pathology report described distended alveolar spaces filled with amorphous, proteinaceous, acidophilic material and PAS+, along with focal microvacuolated cytoplasm macrophages. The inter-alveolar septa present mild interstitial lymphocytic infiltration with small lymphoid aggregates. The overall pathology was compatible with pulmonary alveolar proteinosis (PAP) (Fig. 2).

Two sessions of whole-pulmonary lavage were performed, with temporary suspension of anticoagulation. The sessions were separated by 21 days; the first session included the right lung, and the second session included the left lung, with instillation of the physiological solution at 37 °C in 500 ml aliquots up to 16 L, to determine the moment when the effluent becomes clear (Fig. 3).

The patient was decannulated between both lung lavages; he displays improvement of his infiltrates and no longer requires oxygen. He is currently being monitored in his provenance hospital.

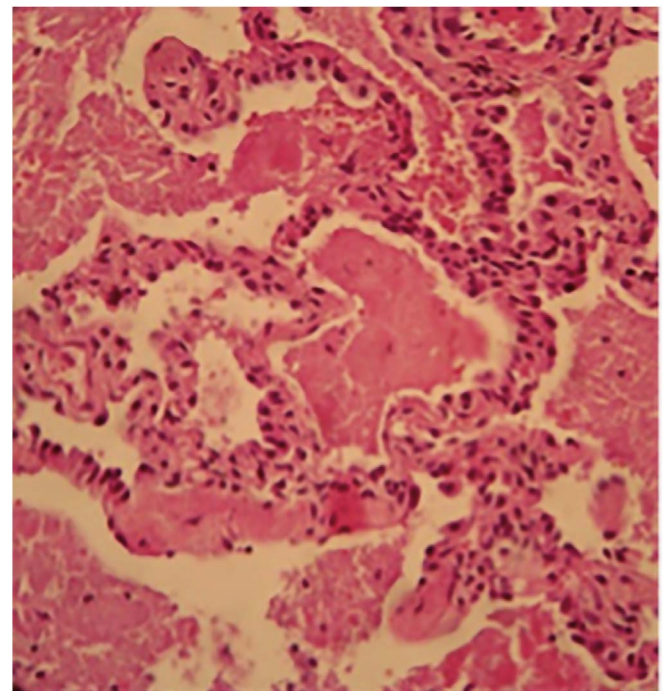


Fig. 2. Histopathological study showed intra alveolar deposit of lipoprotein material wrapped by a thickened wall due to inflammatory cell and type 2 pneumocytes.

3. Discussion

PAP was described by Rosen in 1958 [1]. It is a rare disease, with an estimated prevalence of 0.1 cases per 100,000 persons [6]. It is characterized by the intra-alveolar accumulation of lipoprotein and phospholipid surfactant material; it is periodic acid–Schiff stain (PAS)–positive, which produces gas transfer impairment [3]. There are three forms of PAP: congenital, idiopathic, and acquired. Of the latter, the autoimmune form associated with anti-GM-CSF antibodies, as suspected in this case, comprises almost 90% of PAP cases. The clinical course of PAP is variable, from spontaneous remission to respiratory failure. The onset of symptoms is insidious, and it often delays the diagnosis from months to years [4,7].

The clinical presentation is not specific. Physical examination includes inspiratory crackles (50% of patients), cyanosis (25%), and digital clubbing in a small percentage; *none of these signs were present in our patient*. Thorax CT findings of a crazy paving pattern are highly characteristic of PAP, although broad radiological differential diagnosis includes left heart failure, pneumonia (particularly *Pneumocystis pneumonia*), alveolar haemorrhage, pulmonary adenocarcinoma, carcinomatous lymphangitis, diffuse alveolar damage (adult respiratory distress), radiation or drug-induced pneumonitis, hypersensitivity



Fig. 3. Differential lavage of lung material. Left: initial lavage; right: Final lavage.

pneumonitis, and pulmonary venous-occlusive disease [7–9]. Cryotherapy has been used in bronchoscopy for many years, mainly for endobronchial lesion removal [10]. The upside of transbronchial biopsy with cryoprobe is that bigger tissue samples can be harvested through cryoadhesion [5,11]. In recent years, the usefulness of transbronchial cryobiopsy in diffuse and interstitial lung diseases and in neoplastic disease has been reported in different publications, showing a diagnostic performance superior to forceps for transbronchial use [11,12]. Considering this superior performance, unspecific clinical findings, the advanced state of the lung injury, and the need for a safe diagnosis, a cryobiopsy was performed in our patient for a greater diagnostic chance. At least 2 other studies include 2 patients diagnosed with PAP by cryobiopsy [13,14]. The final treatment consisted of whole-lung lavage with good output; other options, such as plasmapheresis, GM-CSF via inhalation or subcutaneous injection, or rituximab were contemplated in case of relapse [2].

4. Conclusion

PAP is a rare lung disease that can be diagnosed by transbronchial cryobiopsy. This method should also be considered for advanced cases.

Conflict of interest

The authors declare no conflict of interest.

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