OVERLAPPING TUBERCULOSIS IN A PATIENT WITH PULMONARY ALVEOLAR PROTEINOSIS

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ABSTRACT

***Introduction**: Pulmonary alveolar proteinosis (PAP) is a rare disease of unknown origin, characterized by impaired surfactant metabolism that leads to abnormal accumulation of amorphous phospholipoprotein material in the alveoli. The association between PAP and tuberculosis (TB) has been rarely reported.*

***Case presentation**: We present the case of a 33 year-old man diagnosed with PAP and complicated with pulmonary TB. The suspicion of PAP was based on chest computed tomography with "crazy-paving" pattern, and the diagnosis was sustained by eosinophilic PAS (Periodic acid-Schiff) positive lipoproteinaceous material in bronchoalveolar lavage fluid. Two procedures of whole-lung therapeutic lavage were performed with good clinical results. Three years after PAP diagnosis, the patient was diagnosed with TB (bronchial aspirate smears and culture were positive for Mycobacterium tuberculosis).*

***Conclusion**: Pulmonary TB may occur as a complication in an idiopathic PAP due to reduced phagocytic and chemotaxis capacity of alveolar macrophages or as a possible nosocomial Mycobacterium tuberculosis transmission by periodic bronchoscopy exams and washings.*

***Keywords**: Pulmonary alveolar proteinosis, tuberculosis, whole lung lavage.*

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Introduction

Pulmonary alveolar proteinosis (PAP) is a rare disease characterized by progressive accumulation in the alveoli of surfactant, phospholipids and proteins, caused by an imbalance of the mechanisms that control the homeostasis of the surfactant[(1)]. The disease is not associated with inflammation and lung architecture is typically preserved. In more than 90% of all reported cases of PAP, granulocyte macrophage colony stimulating factor (GM-CSF) antibodies are present in serum and bronchoalveolar lavage (BAL), these forms being known as primary or idiopathic PAP[(2)]. Less commonly, PAP is congenital or secondary, when associated with another disorder, such as infection (Pneumocystis jirovecii, Nocardia, Mycobacterium tuberculosis, Mycobacterium avium-intracellulare), hematological malignancies, inhalation of chemical agents (fumes, insecticides) or mineral particles (titanium, aluminium, silica) or various states of immunosuppression (HIV infection)[(3)]. The most frequent infections in patients with PAP are caused by Aspergillus sp.[(4)] and Nocardia sp.[(5)]. Infections involving Mycobacterium tuberculosis (M. tuberculosis) have been rarely reported[(6)]. These infections may be present prior to PAP, acting as a stimulating factor for type II pneumocytes, or may occur as a complication of macrophage impairment secondary to PAP[(7)]. The association between PAP and pulmonary tuberculosis (TB) was reported for

the first time by Ramirez R.J. in 1967[8]. Since then, it has been formulated the hypothesis that the association between these clinical entities is more than coincidental[6]. The overlapping clinical and radiological manifestations of the PAP make the diagnosis of TB more difficult, but it should not be overlooked, especially in countries with high incidence of TB. We report the case of a patient with PAP who was treated with whole lung lavages and who developed tuberculosis.

Case presentation

A 33 year-old male with a 20 pack year history of smoking, exposed to dust as a worker in a reed manufacture, without personal or family history of lung diseases, was admitted in our hospital in May 2009. He had a 3-months history of progressive effort dyspnea estimated on modified Medical Research Council (mMRC) at 2, productive cough with high volume white sputum production (50ml/day) and 3.5kg weight loss. On physical examination the patient was afebrile, had finger clubbing, and fine crackles were heard on auscultation on both lung bases. The oxygen saturation while breathing room air was 93%, blood pressure of 120/70mmHg and heart rate of 70beats/minute. The examination of other systems was normal. Routine biological analyses were normal, with the exception of an increased ESR (62mm/h) and LDH (441 IU/L). Patient was HIV negative. The chest radiography revealed bilateral patchy infiltrates with a "bat-wing" pattern in the mid and lower zones. The computed tomography (CT) scan showed bilateral, patchy, "ground-glass" opacities, with thickening of the interlobular septa, resulting in a "crazy-paving" pattern (Fig. 1).

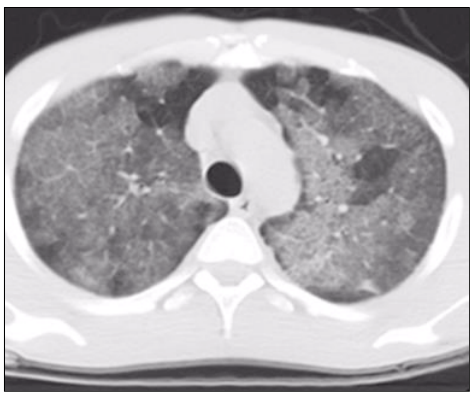

Fig. 1: CT scan: "ground-glass" opacities and thickening of the interlobular septa ("crazy-paving" pattern).

The initial pulmonary function tests revealed distal obstructive syndrome with a maximum expiratory flow after 50% of expired forced vital capacity (MEF50) at 51% predicted, with a moderate decrease of diffusing capacity of the lungs for carbon monoxide (DLCO) at 48.2% predicted. The basal ABG (arterial blood gases analysis) showed a mild hypoxemia with a PaO_2 of 60mmHg, $PaCO_2$ of 32.7mmHg, and pH of 7.44. Tuberculin skin test was positive (patient received Bacillus Calmette-Guérin vaccination in childhood), but sputum examination for acid fast bacilli (AFB) and culture for M. tuberculosis were negative.

Fiberoptic bronchoscopy with BAL was performed on the right middle lobe. Bronchial washing had a white, milky aspect and direct exams and cultures for bacteria, fungi and M. tuberculosis were negative. BAL fluid examination showed amorphous lipoproteinaceous material with characteristic eosinophilic and positive PAS (Periodic acid-Schiff) staining (Fig. 2).

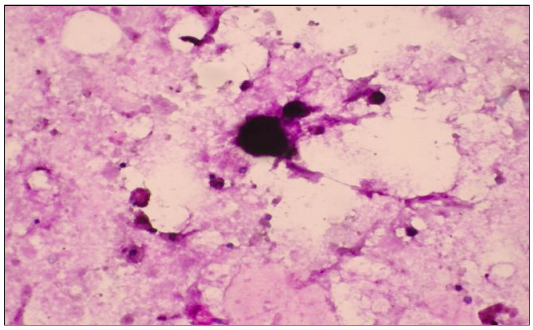

Fig. 2: BAL cytological preparation: alveolar macrophages containing PAS-positive material.

This aspect of eosinophilic proteinaceous material positive PAS staining sustained the diagnosis of PAP. The patient refused lung biopsy. The measurement of serum or BAL anti GM-CSF antibodies was not available. Given the aspect of eosinophilic proteinaceous material and PAS positive the diagnosis of PAP was established. The patient was symptomatic after 3 months of follow-up and had a persistent moderate hypoxemia, therefore two procedures of whole-lung therapeutic lavage were performed, the first one in September 2009 and the second one in August 2011, with a good clinical outcome.

In July 2012, the patient was readmitted in our clinic for fever (37.5C), persistent cough, dyspnea (mMRC 3), night sweats and weight loss (7 kg), symptoms developed in the last month. ABG revealed a PaO_2 of 64mmHg, $PaCO_2$ of 39mmHg, and pH of 7.44. The chest radiography showed patchy areas of alveolar consolidation on bilateral

paracardiac areas. Bronchial aspirate was positive for AFB and Lowenstein-Jensen cultures confirmed the presence of M. tuberculosis. He was, therefore, diagnosed as pulmonary tuberculosis and received 6 months of directly observed antituberculosis treatment with Isoniazid, Rifampicin, Pyrazinamide, and Ethambutol. The treatment was well tolerated and after 6 months the patient was cured. The symptoms of PAP relapsed the next year, requiring two more whole lung lavages, in March and July 2013. After that, his clinical status improved and in September 2015, when the patient came for a routine control, chest radiography showed a dramatic clearing of the shadows, and CT scan revealed only small areas of ground-glass opacities (Fig. 3). AFB smear and cultures for M. tuberculosis from sputum were negative.

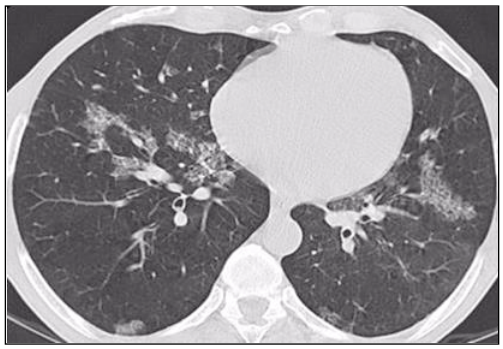

Fig. 3: CT scan: normal structural lung architecture with a few patchy areas of ground-glass opacities (September 2015).

Discussion

PAP is a rare disease of unknown origin, due to an impaired surfactant metabolism, with an estimated prevalence in the general population of 1 case in 2 million people with a male:female ratio of 3:1[9], and a median age at diagnosis of 39 years[10]. Due to low incidence, there are only a few reported cases in the literature. Insidious onset of exertion dyspnea is the most frequent presenting symptom of PAP, although, 30% of cases may be asymptomatic[3]. Approximately 21% of patients present dry cough or with opalescent and viscous sputum[11]. Chest pain, hemoptysis, weight loss, asthenia and fever may rarely occur. Our patient had progressive dyspnea, productive cough, and weight loss. The physical examination is often normal. Auscultation may reveal crackles in the affected areas, and digital clubbing or cyanosis may be present in up to 30% of cases[10, 11], and our patient had all these findings. The most common chest X-ray findings consist of symmetrical, bilateral, alveolar infiltrates, showing a basal and perihilar ("bat-wing") distribution. In rare cases, the opacities are focal and asymmetric[1, 3, 11].

The pattern resembles acute pulmonary edema, but pleural effusion and cardiomegaly are usually absent[11]. The CT scan is a major tool in the diagnosis of PAP. The CT-scan pattern consists of ground-glass opacities and interlobular septa thickening, showing a "crazy paving" pattern, which is highly suggestive of PAP. Alveolar opacities have a typically geographic distribution, being delimited by zones of normal parenchyma[11,12]. Pulmonary function tests usually reveal restrictive dysfunction, with a reduction of lung volumes and DLco[3]. BAL fluid staining is required for the diagnosis of PAP, because it can demonstrate the presence of the characteristic granular, amorphous, PAS-positive lipoproteinaceous material[13].

When BAL is performed in an affected lung area, it has typically a milky aspect, but might appear normal if performed in a healthy zone. Although lung biopsy (transbronchial or surgical lung biopsy) is considered the gold standard, PAP diagnosis can be based on radiological appearance plus BAL fluid analysis, as long as other diseases can be excluded[1, 3]. Whole-lung lavage is the most widely accepted and effective therapy of PAP, although spontaneous resolution was described in variable percentages, between 24%[14] and 50%[15] of cases. This procedure is indicated in symptomatic disease with dyspnea that limits activity and values of PaO_2 under 65 mm Hg, and $P(A\text{-}a)O_2$ over 40 mm Hg[1].

Acquired PAP is the most common type, in which GM-CSF autoantibodies appear to play a causal role[2,7,9]. GM-CSF is a hematopoietic growth factor known to stimulate, in vitro, differentiation, proliferation, and survival of myeloid cells, including monocytes, macrophages, eosinophils, neutrophils, and dendritic cells[16]. In the lungs, the role of GM-CSF is to stimulate the final differentiation of alveolar macrophages (AM), mediated by transcription factor PU.1, and to enhance their capacity for uptake and catabolism the proteins and phospholipids of the surfactant[1,17].

Numerous studies[16-20] showed that in the presence of high-affinity and high specificity neutralizing immunoglobulin G (IgG) GM-CSF antibodies, GM-CSF has an impaired functional activity, with direct consequence of alveolar macrophage dysfunction and surfactant accumulation within the alveoli. Alveolar macrophages play a central role in the host defense and innate immunity of the lung. In PAP, immature AM lose their ability for adhesion, chemo-

taxis, microbicide activity, phagocytosis, and phagolysosome fusion, leading to a decreased capability to defend against different infectious agents[19]. It had been shown that different infections may occur prior to PAP, acting as a stimulating factor for the type II pneumocytes or may occur as a complication of macrophage dysfunction[9].

A few cases of associated PAP and TB are described in the literature[6, 21-23]. The relationship between TB and PAP is not well established. Defective alveolar macrophages showed decreased chemotactic ability and adhesiveness[24]. Washings from a PAP patient proved to be a good support for M. tuberculosis growth in vitro, in the absence of other nutrients[25].

In the present case, we can take into consideration the possibility of an acquired PAP, followed by an infection with M. tuberculosis, given the fact that M. tuberculosis infection is more frequent in a TB burden area, as the South-Eastern region of Romania. The repeated bronchoscopy exams and washings of the lungs performed in this case may also be considered a possible way of nosocomial M. tuberculosis transmission. The possible mechanism of PAP and TB association could be explained by the fact that, in the first stage of infection, the bacilli reach the alveoli and are phagocytized by AM, but in PAP, the macrophages lose this ability, the consequence being the progression of M. tuberculosis infection to active tuberculosis disease. In our patient case, we may also consider a possible secondary PAP due to professional exposure to dust.

Conclusion

Although rare, pulmonary alveolar proteinosis should be taken into account when diagnosing an interstitial lung disease, especially in the presence of the "crazy paving" pattern on CT scan. In confirmed cases, it is essential to look for features suggestive of secondary PAP. The possibility of a secondary PAP to an infection or to professional exposure should be evaluated. Pulmonary TB may occur as a complication in an idiopathic PAP or as a possible nosocomial transmission, due to repeated bronchoscopies and washings of the lungs. The diagnosis of pulmonary tuberculosis in patients with PAP must be considered as well, especially in a region with high incidence of tuberculosis.

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