Bilateral Micronodular Pulmonary Infiltrate: Is It Important to Make a Histological Diagnosis?

Kashif Ali Khan MB MRCPI and JJ Gilmartin MD FRCPI

Pulmonary alveolar microlithiasis is a rare disease characterized by the deposition of calcium phosphate within the alveoli. We report the case of a 20-year-old man with a 6-week history of cough and shortness of breath on exertion. The chest radiograph demonstrated a bilateral symmetrical micronodular pattern. High-resolution computed tomography revealed bilateral diffuse fine nodular shadowing involving the mid zones, with sparing of the apices. The patient underwent a transbronchial lung biopsy, which confirmed the diagnosis of pulmonary alveolar microlithiasis.
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Introduction

Pulmonary alveolar microlithiasis (PAM) is an uncommon chronic disease characterized by the deposition of calcium phosphate within the alveoli. At the initial stage of the disease the imaging findings can be misdiagnosed as sarcoidosis, miliary tuberculosis, or fungal infection. We present the case of a 20-year-old man with a 6-week history of cough and shortness of breath on exertion, whose diagnosis was initially considered sarcoidosis; however, transbronchial lung biopsy confirmed the histological diagnosis of PAM. Our case demonstrates the need for histological confirmation, in particular at early stages of the disease. We have also highlighted the recent discovery of a mutation in the candidate gene SLC34A2 that predispose patients to PAM.

Case Report

A 21-year-old man presented in another hospital with intermittent dry cough and palpitations. He described his symptoms as "cough in the chest," but he had no dyspnea, fever, night sweats, hemoptysis, joint pains, or rash. He had increased use of caffeine (9 cups of coffee) and alcohol. His palpitations were thought to be related to caffeine. Prior to presentation he had used the recreational drugs cannabis, ecstasy, and cocaine. He denied all use of intravenous drugs, and reported one pack-year history of smoking. His chest radiograph showed bilateral fine reticular nodular shadowing, with mid-zone predominance (Fig. 1). The distribution of diffuse pulmonary infiltrate was reported as the possible diagnosis of sarcoidosis, miliary tuberculosis, or hypersensitivity pneumonitis.

A provisional diagnosis of sarcoidosis was made, and initial investigations were directed for sarcoidosis evaluation and to exclude miliary tuberculosis. His full blood count and renal and liver profile tests and 24-hour urinary calcium were entirely within normal limits. His 2 TU Mantoux test was negative. His pulmonary function tests were within normal limits. High-resolution computed tomography (CT) confirmed the chest radiograph findings and reported bilateral diffuse fine nodular shadowing involving the mid zones, with sparing of the apices. There was no evidence of intra- or extra-thoracic lymphadenopathy (Fig. 2). Again, the differential diagnosis of miliary tuberculosis, sarcoidosis, and hypersensitivity pneumonitis was considered.

The patient continued to have intermittent dry cough. A bronchoscopy with bronchoalveolar lavage and transbronchial biopsy was arranged. His bronchoalveolar lavage fluid revealed a CD4:CD8 ratio of 0.7:1, which is not suggestive of sarcoidosis. The bronchoalveolar lavage

The authors are affiliated with the Respiratory Department, Merlin Park Regional Hospital, Galway, Ireland.

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Correspondence: Kashif Ali Khan MB MRCPI, Respiratory Medicine, Merlin Park Regional Hospital, Galway, Ireland. E-mail: drkhan95@hotmail.com.

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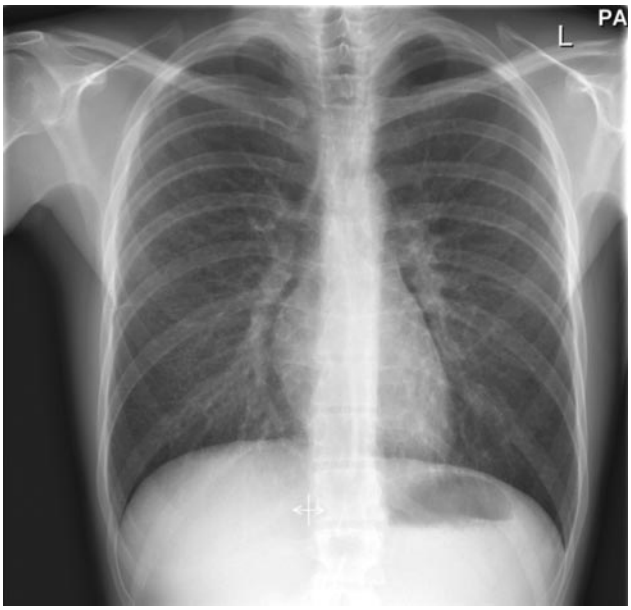

Fig. 1. Chest radiograph shows bilateral fine reticular nodular shadowing in both lungs.

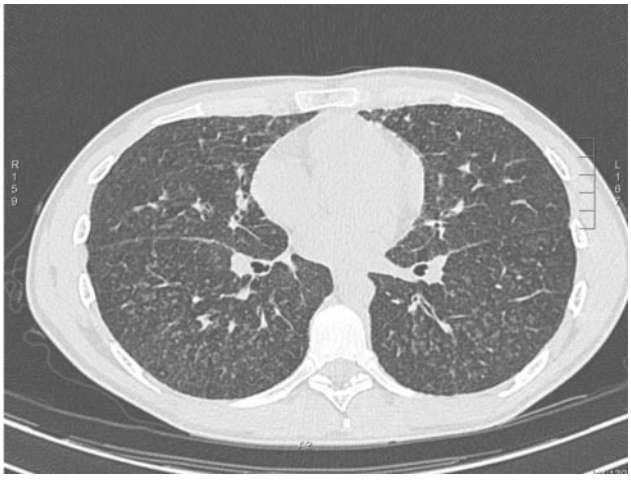

Fig. 2. Computed tomogram of the lungs shows bilateral micronodular infiltrate.

fluid was negative for tuberculosis, malignancy, and microlithiasis. Transbronchial biopsy (Fig. 3) was conclusive of the diagnosis. The histology confirmed the deposit of calcium phosphate at multiple sites in alveolar spaces, consistent with the diagnosis of PAM. The patient was followed up in the out-patient clinic for 6 months, without progression of the disease, and had no treatment for PAM.

Discussion

PAM is a rare disease that is characterized by the formation of innumerable 1–3 mm microliths in the alveolar

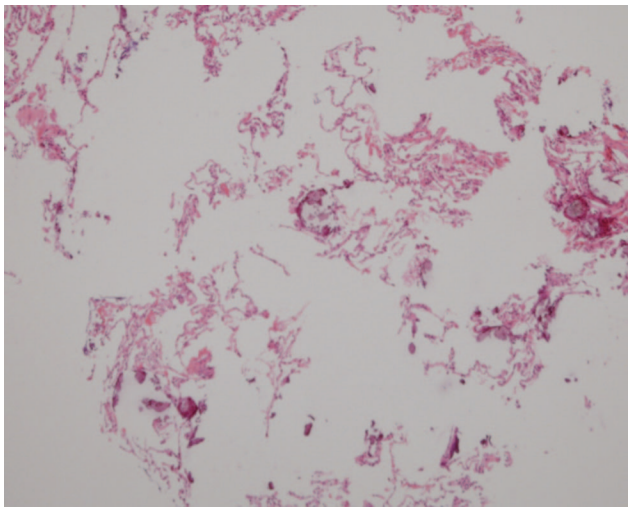

Fig. 3. Histology shows alveolar microliths.

space.[1-3] It was first named by Phur in 1933.[4] To date, less than 600 cases have been reported worldwide.[5-8] The disease has no particular geographical distribution, although most of the cases were reported from Turkey, Japan, and Europe.[6] The disease has been described with slight male predominance in all age groups, and more than 85% of the cases have presented before the age of 50 years.[7]

A familial occurrence has been described in 37–56% of the reported cases,[7] supporting an autosomal inheritance.[9] Recently, mutation in a candidate gene, SLC34A2, which encodes a type IIb sodium phosphate cotransporter specifically in type II alveolar cells, has been identified. It is inherited with an autosomal recessive pattern.[10,11] SLC34A2 is mainly expressed in the lung and mammary glands, and to a lesser extent in the intestine, kidneys, and prostate. This is the only phosphate transporter that is highly expressed in the lung, specifically in type II alveolar cells.[12,13] These cells produce pulmonary surfactant, of which the essential component, phospholipids, is taken up and degraded. Degraded phospholipids release phosphate that should be cleared from the alveolar space. Dysfunctional SLC34A2 may reduce the clearance of phosphate and lead to formation of microliths.

At disease onset the symptoms are limited and often absent; they become serious in advanced stages, when the greater number of alveoli are filled with calcium phosphate deposit. Shortness of breath is the most frequent symptom, followed by cough and chest pain.[4] Pulmonary function testing may be normal initially, as in our case; however, it starts to decline with a restrictive pattern as the disease advances. To a lesser extent, calcification in extra pulmonary sites has been reported, in particular in testicular microlithiasis (0.6–9%), with approximately 1% of male idiopathic infertility, and calcific deposits in the prostate and seminal vesicles.[13,14] The clinical course of the

disease is not chronologically determinable. It may remain static as regards to both symptoms and radiographic findings, while in others it may worsen over time at a different rate, leading to pulmonary fibrosis, respiratory failure, and chronic pulmonary heart disease.

Diagnosis is often made on chest x-ray finding as a surprise, and is confirmed by CT appearance and transbronchial tissue biopsy or video assisted lung biopsy. At the initial stages of the disease, the cases are often misdiagnosed as miliary tuberculosis or sarcoidosis. In the literature, 13.2% of cases have described treating the condition as tuberculosis, and approximately 2% as sarcoidosis.[7] Therefore it is important to confirm the diagnosis histologically, in particular where these diseases are prevalent (eg, Ireland). The chest radiograph shows the infiltrates as fine sand-like calcific micronodules (sandstorm lung) diffusely involving both lungs, usually more marked in the middle and lower zones. CT confirms relatively symmetrical distribution of the disease, predominantly peripheral, mediastinal, and in fissural subpleural regions. Histology proves calcium phosphate microliths in the alveolar space. Positron emission tomography/CT has no definite role in establishing the diagnosis; however, some studies have looked at possible high standard uptake value at calcific sites, suggesting the role of inflammation and justifying anti-inflammatory medicines, without clear therapeutic benefit.[15,16]

Several attempts have been made to treat this disorder, without satisfactory results. Systemic steroids, calcium chelating agent, and repeated bronchoalveolar lavage to remove microliths have been shown to be ineffective, and are used as a palliative measure. Disodium etidronate inhibits microcrystal growth of hydroxyapatite and thus inhibits ectopic calcification. This drug has been used to treat the disease, with little or no benefit.[17] There is no effective treatment for PAM except lung transplantation for end-stage cases.[18] Until 2010, 7 patients had received lung transplantation for this condition.[19] To date, recurrence has not been reported in the transplanted lung, suggesting that, in fact, the PAM is a genetically determined disorder rather than a systemic disease.

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