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Title page:

Bilateral micronudular pulmonary infiltrate – Is it important to make a histological diagnosis?

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Abstract:

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

Introduction:

Pulmonary alveolar microlithiasis (PAM) is an uncommon chronic disease characterized by the deposition of calcium phosphate within the alveoli. At initial stage of the disease, the imaging findings can be misdiagnosed as sarcoidosis, miliary tuberculosis or fungal infection. We present a twenty year-old man with a six weeks 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; which predispose patients to PAM.

Key words: Pulmonary Alveolar Microlithiasis

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Case Report

A twenty one year old gentleman presented in another hospital with intermittent dry cough and palpitations. He described his symptoms as "cough in the chest'' but no dyspnea, fever, night sweats, haemoptysis, 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 recreational drugs cannabis, ecstasy and cocaine. He denied ever any 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 (Figure 1). The distribution of diffuse pulmonary infiltrate was reported as the possible diagnosis of sarcoidosis, military 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, renal and liver profile tests and twenty four hour urinary calcium were entirely within normal limits. His 2TU mantoux test was negative. His pulmonary function tests were within normal limits. The high resolution computerized tomography of thorax was arranged which confirmed the chest radiograph findings and reported bilateral diffuse fine nodular shadowing involving mid zones with sparing of apices. There was no evidence of intra or extra thoracic lymphadenopathy (Figure 2). Again the differential diagnosis of miliary tuberculosis, sarcoidosis, and hypersensitivity pneumonitis were considered.

Patient continued to have intermittent dry cough. A bronchoscopy with bronchoalveolar lavage and transbronchial biopsy was arranged. His bronchoalveolar lavage (BAL) revealed CD4: CD8 ratio of 0.7:1 which is not suggestive of sarcoidosis. The BAL fluid was negative for tuberculosis, malignancy or microlith. Transbronchial biopsy (Figure 3) was conclusive of the diagnosis.

The histology confirms the deposit of calcium phosphate at multiple sites in alveolar spaces consistent with the diagnosis of pulmonary alveolar microlithiasis. Patient was followed up in the outpatient clinic for six months without progression of the disease and had no treatment for PAM.

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Discussion:

Pulmonary alveolar microlithiasis is a rare disease which is characterized by the formation of innumerable, small, 1-3mm microliths in the alveolar space[1-3]. It was first named by Phur.L 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 presented before the age of 50 years.[7] A familial occurrence has been described in varying percentage 37% to 56% [7] of the reported cases, supporting an autosomal inheritance.[9] Recently, mutation in a candidate gene SLC34A2 that encodes a type IIb sodium phosphate cotransporter specifically in type II alveolar cells has been identified. It is inherited as autosomal recessive pattern. [10, 11].SLC34A2 is mainly expressed in lung and mammary gland and to a lesser extent in the intestine, kidney 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 have been reported in particular testicular microlithiasis 0.6-9% with approximately 1% of male idiopathic infertility, calcific deposits in prostate and seminal vesicles[13, 14] The clinical course of the disease is not chronologically determinable. The illness 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 initial stages of the disease the cases are often misdiagnosed as milliary tuberculosis or sarcoidosis. In the literature 13.2% cases have been described to be treated as tuberculosis and approximately 2% as sarcoidosis [7]. Therefore, it is important to confirm the diagnosis histologically, in particular where these diseases are prevalent like 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. Computed tomography of thorax confirms relatively symmetrical distribution of the disease, predominantly peripheral, mediastinal and in fissural subpleural regions. Histology proves calcium phosphate microliths in the alveolar space. PET/CT has no definite role in establishing the diagnosis; however some studies have looked at possible high SUV at calcific site suggesting the role of inflammation and justifying anti-inflammatory medicines without clear therapeutic benefit.[15, 16]

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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 pulmonary alveolar microlithiasis except lung transplantation for end-stage cases[18]. Until 2010, seven patient 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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Figure Legends:

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

Figure. 2. Computed tomogram of the lungs shows bilateral micro nodular infiltrate.

Figure. 3. Histology shows alveolar microliths.

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Figure. 1.

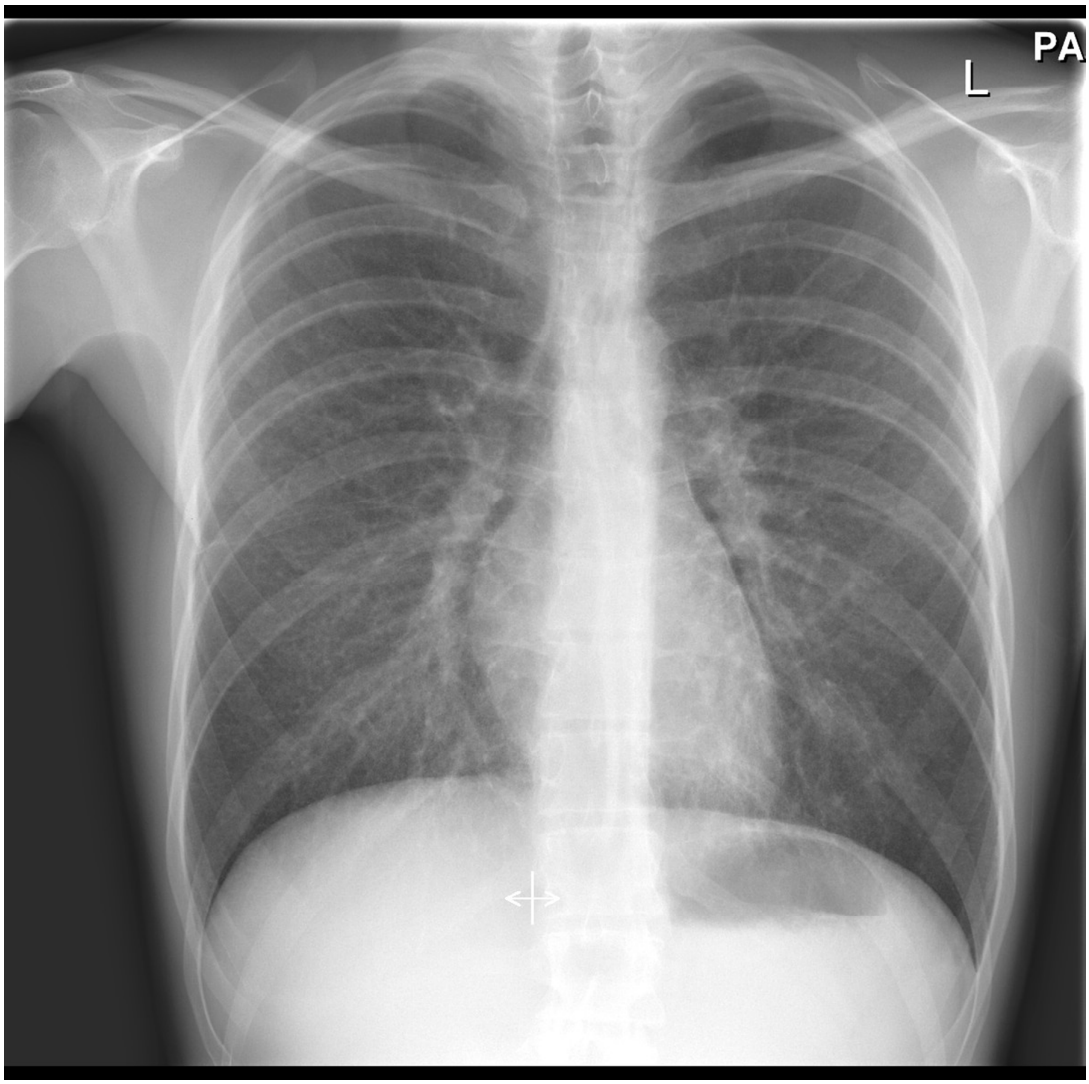

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Figure. 2.

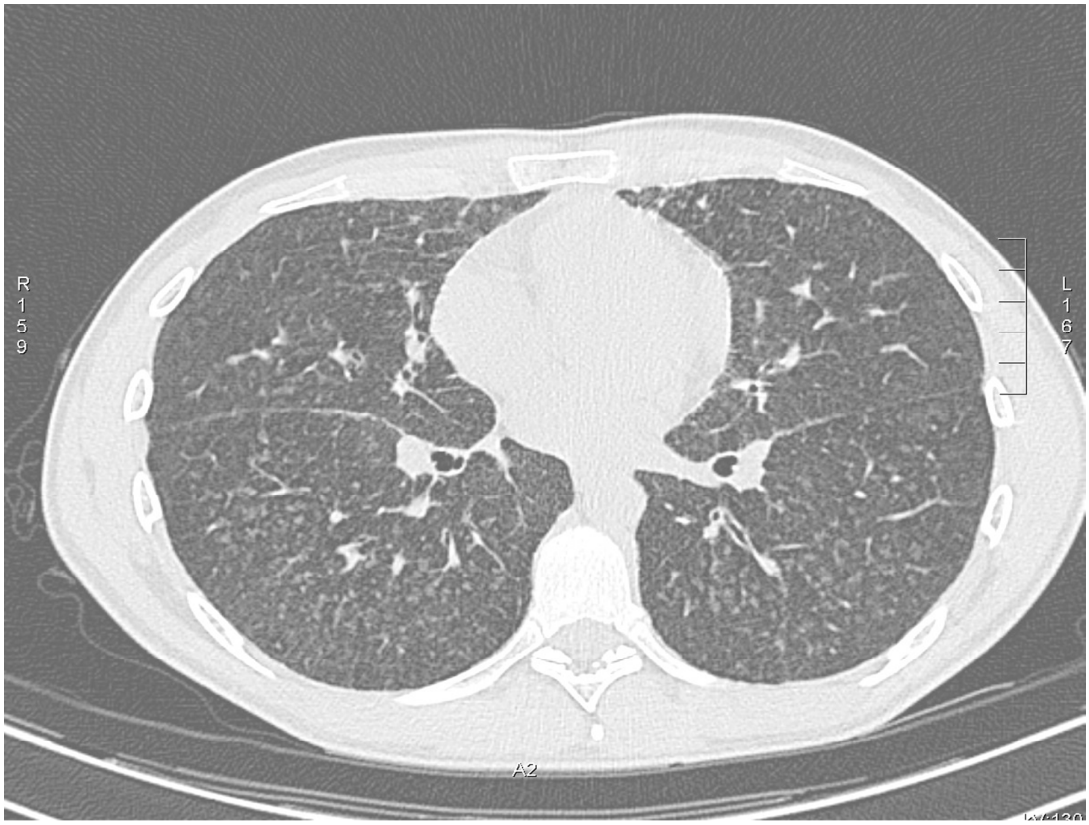

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Figure. 3.