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Pulmonary Alveolar Microlithiasis

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Abstract
Pulmonary alveolar microlithiasis (PAM) is a rare disorder of unknown etiology, characterized by the formation of tiny calcium phosphate calculi in the pulmonary alveoli. About 50% of the cases are familial, mainly in siblings, and the disease is usually diagnosed incidentally by the characteristic chest X-ray findings. We present a report of pulmonary alveolar microlithiasis detected in three siblings.

Keywords: microlithiasis, siblings

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INTRODUCTION

Pulmonary alveolar microlithiasis (PAM) is a rare idiopathic disease characterized by microliths in the alveoli, and was first described by Friedrich in 1856 and then by Harbitz in 1918 [1,2]. In 1957, Sosman emphasized that 50% of the cases were familial [3]. The autosomal recessive inheritance was shown in later reports, with siblings usually being affected [4,5].

As of 2004, 576 PAM cases have been studied, and most have originated from Europe (42.7%) and Asia (40.6%). Symptoms were absent in more than half of the patients; dyspnea, cough and chest pain were reported in the other cases. Pulmonary tuberculosis or sarcoidosis was misdiagnosed in 88 cases of the 576 [6].

The course of the disease was slow and patients usually died as a result of cardio-respiratory failure [3]. In this report, our aim was to emphasize the familial character and the clinical features of the disease.

CASE REPORT

A 27-year-old male was admitted to hospital for routine medical fitness exam. Chest radiograph was taken, which revealed the presence of innumerable, widespread small nodules, diffusely involving both lungs (Figure 1). However, the patient was totally asymptomatic and had no respiratory complaints. The nodular opacities were sharply defined, discrete and showed greater involvement of lower compared to upper zones. Thorax computed tomography (CT) and pulmonary function tests were done. CT of the thorax showed the presence of widespread significant ground-glass appearance, mainly in lower lobes (Figure 2). Pulmonary function tests revealed FVC 79% (3.8 L), FEV1 82% (3.3 L), FEV1/FVC 88%, DLCO 65% (21 ml/mmHg/min), and DLCO/VA 99% (5.1). Systemic examination and routine laboratory tests were unremarkable. There was no known dust or fume exposure. ^{99}Tc-MDP scintigraphy of bone showed diffuse uptake of the tracer throughout both lungs (Figure 3). In fiberoptic bronchoscopy, the endobronchial appearance was normal. Bronchial lavage fluid was examined for tuberculosis and found as negative. The pathology of transbronchial biopsy was reported as alveolar microlithiasis (Figure 4).

In view of the familial association of this disease, two sisters and the brother of our patient (32, 25 and 23 years old, respectively) were invited for chest radiographies. The chest radiography of one sister and the brother revealed multiple, widespread nodular opacities of calcific density.

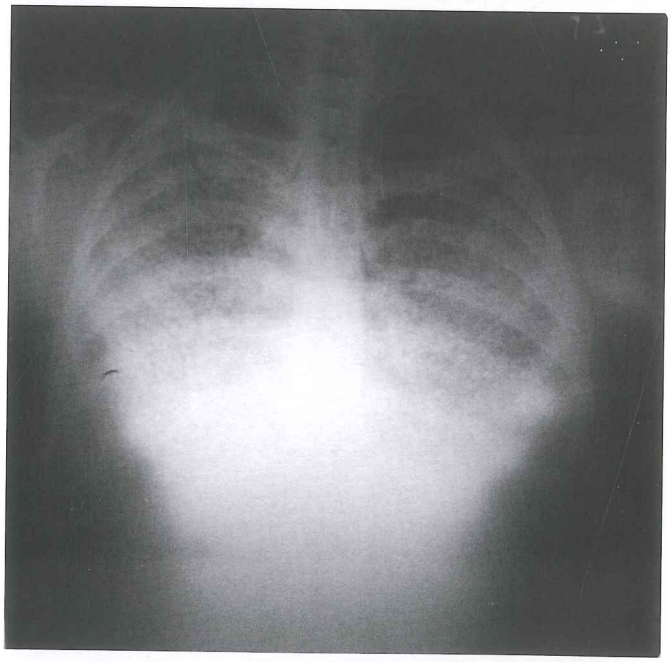

Figure 1. Chest x-ray of index patient with PAM. Note the predominantly perihilar infiltration of fine dense nodules that obliterate the cardıacand medial diafragmatic borders.

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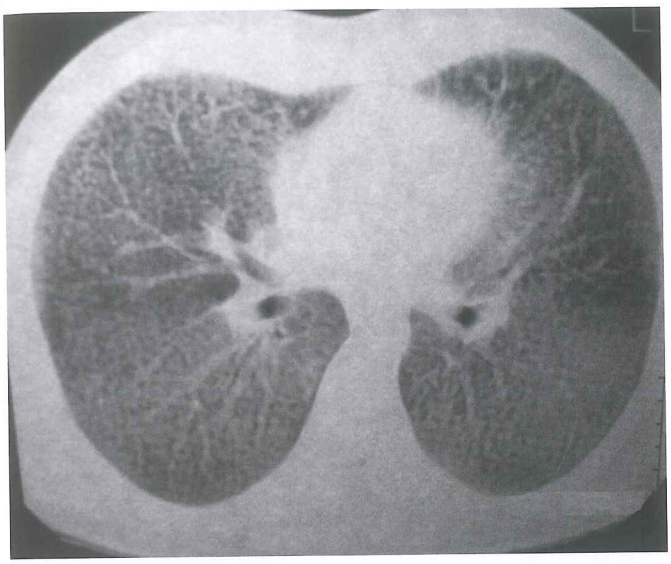

Figure 2. CT scan showing ground glass apperance mainly in lower lobes.

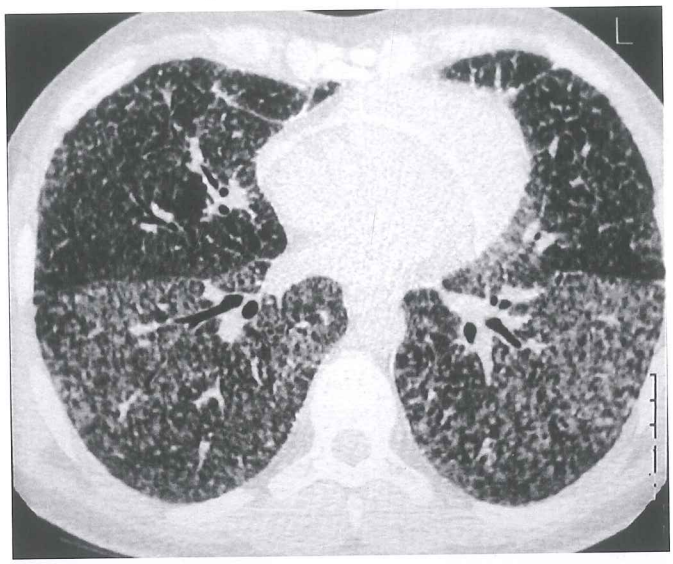

Figure 3. High resolution CT scan showing calcific densities within the lung.

The chest radiograph of the sister revealed obliteration of the mediastinal and diaphragmatic contours due to multiple high density nodules; the other sister's radiograph was normal (Figures 5,6). The siblings were also asymptomatic and refused further examination.

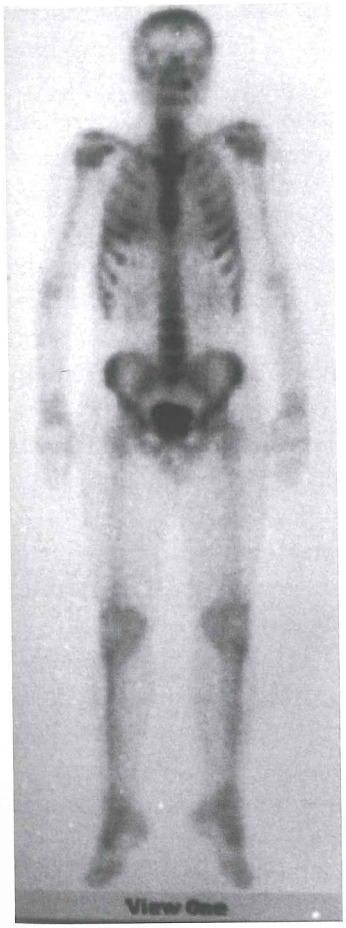

Figure 4. 99Tc-MDP lung scintigram of the propositus,posterior view. Diffuse bilateral intensive uptake is demonstrated in both lower lungs.

DISCUSSION

Pulmonary alveolar microlithiasis is characterized pathologically by the accumulation of numerous, intraalveolar largely calcified bodies. Microliths range from 0.01 to 3 mm in diameter. The chemical analysis and energy dispersion X-ray microanalysis have shown them to be composed of calcium phosphate [3,7].

The etiology and pathogenesis of PAM are unknown. Hypothetical mechanisms that have been proposed include an inborn error of metabolism, an unusual response to an unspecified pulmonary insult, an immune reaction to various irritants, and acquired abnormality of calcium and phosphorus metabolism [8]. Local tissue factors are probably the basis for the development of the microliths in most cases of idiopathic PAM [7,9]. It is speculated

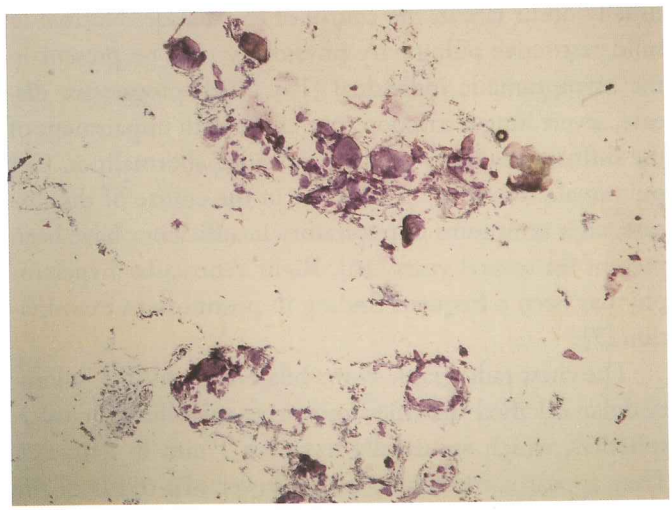

Figure 5. Lung histopathology from the patient with alveolar microlithiasis revealing calcified microliths localized to the intra-alveolar spaces (HE X100)

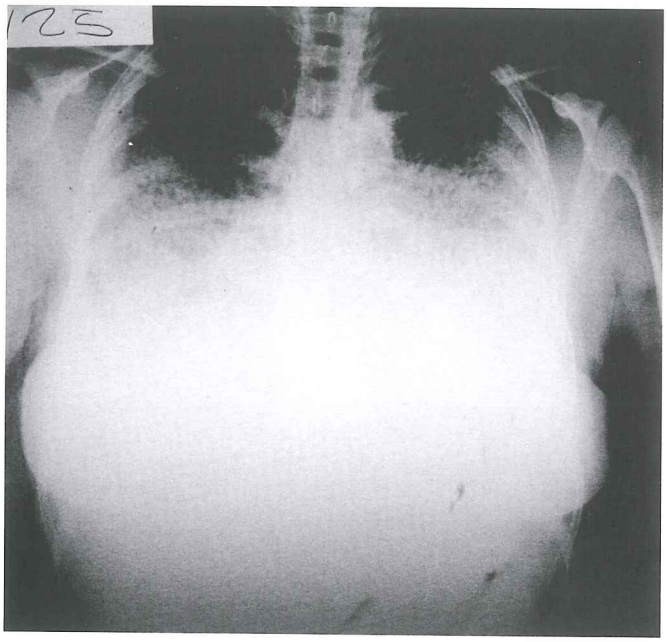

Figure 6. Chest x-ray of index patient's sister

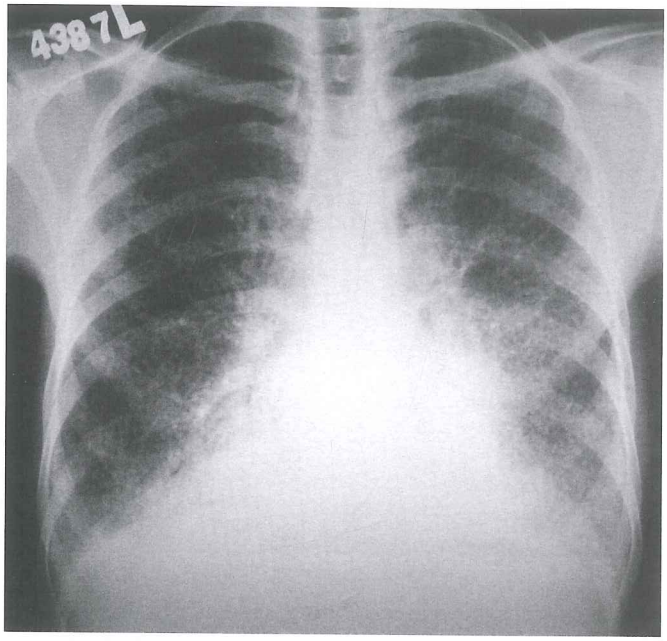

Figure 7. Chest x-ray of index patient's brother

that, due to an unknown stimulus, changes in the alveolar lining membrane or secretions result in greater alkalinity, promoting intra-alveolar precipitation of calcium phosphates and carbonates [10]. Familial occurrence has been noted in more than half of the reported cases. PAM occurs worldwide, though approximately one-fourth of recorded patients are from Turkey [11,12,13]. In the literature about familial PAM cases, horizontal transmission among siblings born to unaffected parents was shown; a high rate of consanguinity was present among the parents of affected individuals [14].

Asymptomatic cases, even with extensive radiographic involvement, are often discovered incidentally. Cough and dyspnea are the most common presenting symptoms and usually occur late in the course of the disease. Normal or mild restrictive pulmonary physiology may be present in the asymptomatic individual [15]. With progressive disease, severe lung restriction may ensue with impairment of the diffusing capacity and gas exchange abormalities. Cor pulmonale frequently occurs late in the course of the disease, after symptoms of respiratory insufficiency have been present for several years [16]. Right ventricular hypertrophy has been a frequent finding in postmortem examination [7].

The chest radiograph shows bilateral, sand-like, micronodular calcified densities known as microliths or calcispherites, which are usually less than 1 mm in diameter. They appear concentrated in the lower two-thirds of the lung, often obliterating the diaphragmatic, mediastinal, and cardiac borders. The greater radiographic density at the lung bases is likely due to the larger lower lobe volumes rather than selective predisposition [3,17]. Other findings that may be seen include bullae in the lung apices, a zone of increased lucency between the lung parenchyma and the ribs (known as a black pleural line), and pleural calcification [18]. CT and the ^{99m}Tc diphosphonate scan have been used to confirm diffuse calcification in PAM. CT scan of the chest reveals a diffuse infiltrative pattern, and the ^{99m}Tc diphosphonate scan reveals increased uptake of the isotope throughout both lungs [19,20,21]. The predominant high resolution (HR)CT finding is the presence of micronodular calcifications primarily located along the bronchovascular bundles and subpleural regions and perilobular distribution [22].

Pulmonary function studies are initially normal. In about 30% of the patients, a mild restrictive defect evolves. The most common findings are decreased vital and total lung capacity, normal residual volume/total lung capacity ratio and decreased diffusing capacity [3,23].

The standard chest radiograph and CT, with results characteristic for PAM, are enough to diagnose the disease, even if microscopic evidence of the microliths in the alveoli was obtained in most cases [24,25]. Microliths in the sputum and bronchoalveolar lavage are not diagnostic because patients with chronic obstructive pulmonary disease and tuberculosis expectorate microliths as well [26]. In histologic examination of open lung or transbronchial biopsies, the lesions of PAM consist of intraalveolar calcispherites, which represent laminated calcium phosphate concretions [10].

There is no known therapy for PAM. Bilateral lung transplantation is a viable option for advanced cases. It has been reported that PAM cases followed after transplantation did not show evidence of recurrence [27,28]. The three siblings in this study who were diagnosed as PAM have been followed for one year and they remain clinically stable.

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