

Familial occurrence of pulmonary alveolar microlithiasis in 3 siblings

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ABSTRACT

Pulmonary alveolar microlithiasis (PAM) is a rare disease of unknown etiology characterized by intra-alveolar calcium deposits. More than 500 cases were reported in the literature. The disorder affects people at every age beginning from the early childhood. It occurs probably as a result of autosomal recessive transmission. Familial occurrence is often found with family history of the disease being present in up to 50% of the reported cases. We report PAM in 3 siblings.

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Pulmonary alveolar microlithiasis (PAM) is a rare disorder characterized by deposition of microliths in the alveolar air spaces. The etiology of the disease is unknown. Most patients are asymptomatic at the time of diagnosis, and the disease is found incidentally. The diagnosis is made on the basis of chest x-ray and high resolution CT scan (HRCT). Unfortunately, there has been no effective therapy. Both familial and sporadic cases have been reported with family history being present in up to 50% of the reported cases. The disease is thought to be transmitted in an autosomal recessive form. We report the disease in 3 brothers, 2 of whom were asymptomatic and were found to have the disease when the family members of our index case were screened using chest radiographs. The aim of this case is to substantiate the heredity nature of the disease and to emphasize the importance of screening of asymptomatic family members for the presence of the disease.

Case Report. A 27-year-old Kuwaiti male patient presented with 2 years history of shortness of breath on exertion associated with history of excessive sputum production. Examination of the patient

revealed finger clubbing. The chest examination showed bilateral basal crackles up to mid chest. A posterior-anterior chest radiograph showed bilateral diffuse, micronodular calcifications (sandlike) in both lung fields predominantly in the middle and lower zones with obliteration of the cardiac borders and both hemi-diaphragms. Laboratory investigations revealed normal hemoglobin, erythrocyte sedimentation rate, blood urea nitrogen and creatinine. Calcium level was normal. Serum angiotensin converting enzyme level was normal. Three sputum specimens were negative for acid fast bacilli. A HRCT scan demonstrated bilateral diffuse calcific, micronodular opacities throughout lung fields more prominent in the lower and middle zones. Ground glass opacities were also seen. A clear thin linear sub-pleural zone (Black subpleural line) was seen (**Figure 1**). Pulmonary function test showed a restrictive pattern with forced expiratory volume (FEV₁) of 66.3% predicted, FVC 57.3% predicted, FEV₁/FVC 98.3%, total lung capacity (TLC) 66% predicted and diffusion capacity of 70.5% predicted. Room air arterial blood gas analysis revealed arterial oxygen tension (PO₂) 62.5 mm Hg, carbon dioxide tension (PCO₂) 34 mm Hg, pH 7.39, and bicarbonate

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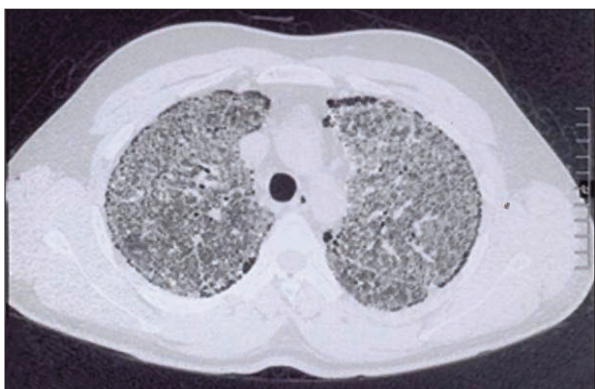


Figure 1 - High resolution CT scan of the index patient showing diffuse bilateral calcific micronodular opacities, ground glass opacities and black subpleural line.

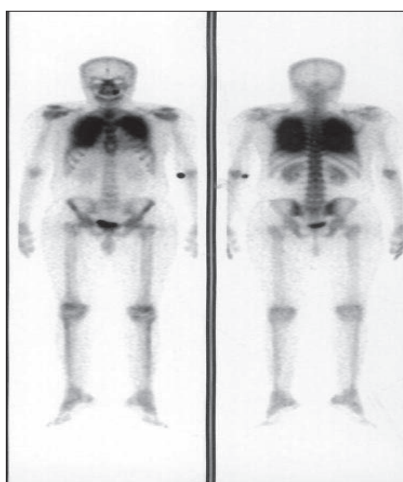


Figure 2 - The ^{99m}Tc bone scintiscan of the index patient showing diffuse uptake in the lungs.

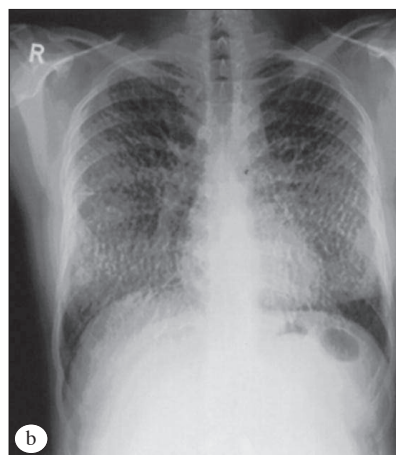
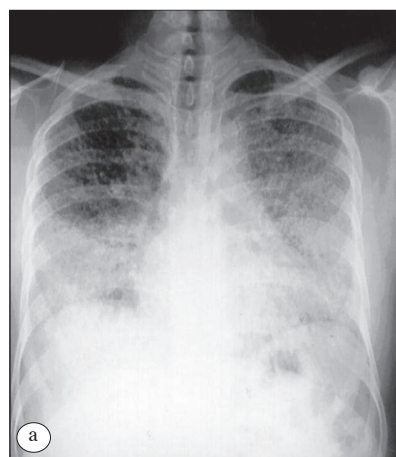


Figure 3 - Chest x-rays of patient's a) sibling no. 1 and b) sibling no. 2. Both shows bilateral diffuse micronodular calcifications.

level of 20.3 mmol/l. The echocardiography was normal with no evidence of mitral valve disease. He was diagnosed to have pulmonary alveolar microlithiasis based on the radiographic appearance. A technetium 99 bone scan showed diffuse uptake in the lungs (**Figure 2**). Sputum examination failed to show microliths, and he declined bronchoscopy and thoracoscopic lung biopsy. Chest radiographs of the patient's siblings showed the disease in 2 of his brothers (**Figures 3a & 3b**) both were asymptomatic. Upon further questioning, he gave history of being admitted to the hospital at age 5 along with the 2 brothers with a diagnosis of tuberculosis.

Discussion. Pulmonary alveolar microlithiasis is a rare disease of unknown etiology. It is characterized by the presence of innumerable tiny calculi, the microliths, within the alveolar air spaces. Mariotta et al¹ recently reviewed 576 cases of PAM published

in the literature, but very little is known regarding the prevalence of the disease as it is likely that some cases have not been reported. The disorder affects people at every age beginning from early childhood.¹⁻³ However, PAM is more frequent in the second decade of life.¹ It occurs equally in men and women.¹ Most of the cases were reported from Europe followed by Asia^{1,3} with the highest number of cases coming from Turkey.¹

The mechanism which may induce microliths to form is unknown. The most accepted hypothesis suggested an inherited metabolic abnormality limited to the alveolar surface involving the enzyme carbonic anhydrase, which promotes alkalinity in the alveoli with consequent precipitation of calcium and the development of calcospherites.^{1,3} The disease occurs in 2 patterns, sporadic and familial.³ Family history of the disease was reported in 181 patients (31.8%) and most of them were siblings.¹ The incidence was

higher in other studies: 36.5%,³ 43.7%,² and 51%.⁴ The most numerous PAM group in a family consisted of 6 patients.⁵ Many observations suggest an autosomal recessive pattern of transmission. In many families, parental consanguinity is present.^{1,3} There is usually a prevalent horizontal sibling incidence. Both findings are supportive of an autosomal recessive transmission. The dissociation between definite x-ray pattern and minimal clinical symptoms is one of the most characteristics of the disease. Most patients are asymptomatic at diagnosis (35.4²-51.8%¹) and the diagnosis of PAM is frequently a chance finding during radiologic examinations performed for different reasons. This was observed in our patients as 2 out of the 3 patients were asymptomatic. The most frequent presenting symptom is dyspnea (24.5¹-67.7%²) followed by cough (13.6¹-32.2%²), chest pain (5.7¹-12.9%²), and asthenia (3.4%).¹ Fever was reported in 9.6% of cases² and sputum in 6.4%.² Physical examinations revealed peripheral cyanosis in 29% of patients² and crackles in 19% of the patients.² Clubbing was reported in few patients.¹

The disease, in many patients, was misdiagnosed as miliary tuberculosis,^{1,2} sarcoidosis,¹ silicosis,² hemosiderosis² and pneumonitis.² Our patients were misdiagnosed as having miliary tuberculosis in childhood. Pulmonary function test in patients with PAM can show a restrictive defect (28.7²-62.2%¹), can be normal (28.7²-34%¹) or might show an obstructive defect (3.8¹-7.1%²). Our patient had a restrictive defect. Chest x-ray shows innumerable sandlike, sharply defined nodules measuring less than one mm in diameter and resulting in a Sandstorm appearance. The overall density is greater over the lower than the upper zones. A zone of increased lucency between the lung parenchyma and the ribs known as black pleural line can be seen. Other findings include apical bullae, and pleural calcification.⁶ High resolution CT manifestations consist of calcific nodules measuring one mm or less in diameter. Calcific interlobular septal thickening is often seen.⁶ Chest x-ray and CT scan are so characteristic that the diagnosis of PAM can be made with confidence from the classic radiographic pattern and the striking radiologic-clinical dissociation.⁶ The ^{99m}Tc diphosphonate scans have been used to verify diffuse calcification in this disorder.^{1,2,7}

Other investigations include the demonstration of microliths in sputum⁸ and the fluid of bronchoalveolar lavage.^{1-3,9} Microliths can also be seen on histological examination of lung biopsies obtained through bronchoscopy, thoracoscopy, open lung biopsy or on autopsy.^{2,5,7} Pulmonary alveolar microlithiasis is not easily described as regards to its clinical course, including the initial phase, evolution and stabilization as the majority of articles published were case reports that highlight some aspect of the disease¹ and few follow up studies. Symptoms are often absent at the

onset of the disease and become serious in advanced stages. No cases with rapid evolution have been described.¹

In general, it appears that PAM has a protracted clinical course. Our patient, most probably, had the disease at age 5 and sought medical advice at age 27 for being symptomatic for 2 years prior to his presentation. The inability to identify clear etiological and pathogenetic elements makes the therapeutic approach difficult. Removal of microliths by bronchoalveolar lavage was attempted with very minor changes in chest x-rays and CT scans.^{1-3,9} Sodium etidronate was tried, but the results were not very encouraging.^{1-3,10} Lung transplantation was performed in 6 patients (5 had bilateral lung transplant and one had a single lung transplant).^{1,3} Three patients had a follow up of 18 months to 7.5 years after transplantation with a very good quality of life.¹ Currently, the only effective therapy is lung transplantation especially when surgery is performed before reaching advanced stages of the disease.

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