Case Report

Spectrum of Clinical Presentation of Pulmonary Alveolar Microlithiasis: Case Series from North India

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Abstract

We describe five cases of pulmonary alveolar microlithiasis (PAM) from North India with characteristic radiological and histopathological features. All patients were symptomatic with variable severity and duration of the symptoms and one patient developed cor-pulmonale during the course of follow-up. Diagnosis of PAM was suspected on the basis of classical sand-storm appearance on radiological examination and confirmed by transbronchial lung biopsy in four of the five cases. Apart from other features, presence of pleural and pericardial calcification in one case makes this discussion valuable. Awareness of this specific entity among the clinicians is essential to avoid unnecessary investigations.

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Key words: Microlithiasis, Sand-storm lung, Pericardial calcification.

Introduction

Pulmonary alveolar microlithiasis (PAM) is an uncommon chronic disease with unknown origin and pathogenesis, characterised by the deposition of calcium phosphate microliths in the alveoli. The entity was first reported by Norwegian Harbitz in 1918[1] and later labelled as PAM by Ludwig Puhr.[2] There are reports from all the continents without any particular geographic or racial distribution; however the maximum numbers of cases belong to Europe, followed by Asia.[3]

Though there are cases of PAM reported from different parts of India; majority of these are in the form of sporadic case reports. This case series of PAM from North India illustrates the spectrum of the clinical presentation and variable progression of the disease.

Case Reports

Mean age of the patients was 29 years (range 18-45 years); there were three males. The spectrum of clinical presentation is described below.

Case 1

An 18-year-old male presented to chest medicine out-patient department with progressive breathlessness on exertion since one year. General physical examination, cardiovascular and respiratory system examination did not reveal any abnormality. Haemogram and biochemical parameters were within normal limits. Mantoux test (5 tuberculin units) was negative and sputum did not reveal acid-fast bacilli (AFB). Pulmonary function testing revealed normal pattern of spirometry. Chest radiograph (Figure 1) showed bilateral diffuse opacities at the lung bases obscuring the cardiac and diaphragmatic Silhouette. Computed tomography (CT) of thorax revealed presence of diffuse intra-alveolar opacities of calcific density, more pronounced in the lower pulmonary regions along with thickening of inter-lobular septa and sub-pleural interstitium (Figure 2).

Transbronchial lung biopsy showed the presence of calcified spherules in the alveolar spaces and presence of mild interstitial fibrosis, thereby confirming the diagnosis of PAM. Chest radiograph of family members did not reveal any abnormality.

Case 2

A 45-year-old female presented with a history of shortness of breath on walking uphill for last four to five years. She was non-smoker, non-alcoholic; she had no history of tuberculosis, diabetes mellitus and hypertension. General physical examination was unremarkable. Respiratory system examination revealed bilateral crackles in infra-clavicular, infra-mammary, infra-axillary regions. Pulmonary function test revealed restrictive ventilatory defect. Diffusion capacity of lung for carbon momoxide (DLCO) was reduced (70.4% of predicted). Chest radiograph showed innumerable small, dense nodules which were diffusely

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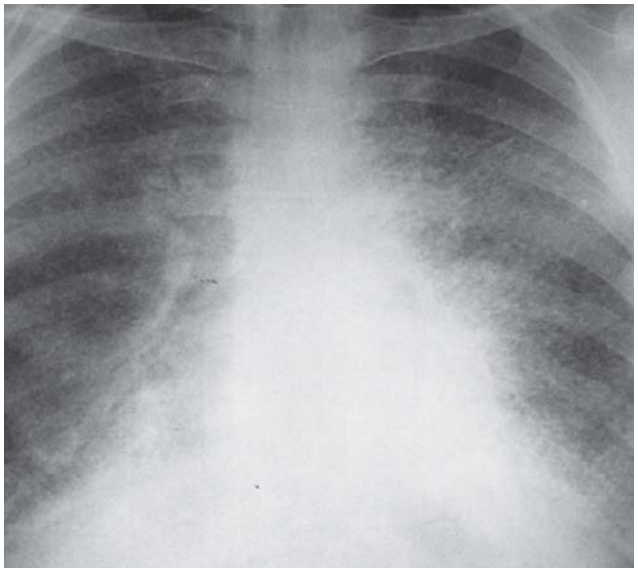

Figure 1. Chest radiograph (postero-anterior view) of first case showing bilateral diffuse opacities at the lung bases obscuring the cardiac Silhouette.

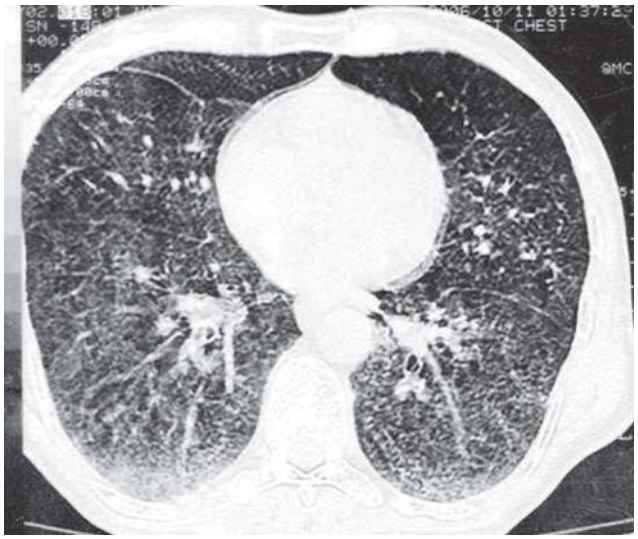

Figure 2. CT thorax (lung window) showing diffuse intra-alveolar opacities of calcific density along with thickening of inter-lobular, peribronchovascular and sub-pleural interstitium.

involving both the lungs. High resolution CT (HRCT) revealed diffusely scattered micronodules along with interlobular septal thickening and few areas of ground-glass opacity.

On the basis of CT findings, diagnosis of PAM was suspected but confirmed on transbronchial lung biopsy. Patient had indolent course of the disease with slow progression and survived almost 20 years before succumbing to respiratory failure.

Case 3

A 22-year-old, male, non-smoker, manual labourer by occupation presented to chest outpatient department with history of breathlessness on exertion for one year. No history of cough, chest pain, anorexia, weight loss was reported. No past history of tuberculosis, alcohol and substance abuse was present. General physical examination and systemic examination did not reveal any abnormality. On laboratory testing, haematological and biochemical parameters were within normal limits. Pulmonary function testing showed mild restrictive ventilatory defect, however diffusion studies were normal. Chest radiograph showed numerous fine, micronodules involving both lungs diffusely which became confluent in some areas (producing ground-glass opacity). Computed tomography demonstrated predominantly symmetric middle and lower zones involvement. The cardiac borders and the diaphragm were obliterated. Diagnosis of PAM was confirmed through histopathological examination of transbronchial lung biopsy. Family screening was negative. Patient is performing well on routine follow-up.

Case 4

A 37-year-old female presented in August 1998 with a history of progressive shortness of breath for the past five years. She was admitted to hospital in June 2002 with Medical Reserch Council (MRC) grade IV dyspnoea along with swelling of feet for one week. She had no previous history of tuberculosis, hypertension and diabetes. Cyanosis was present, jugular venous pulse was raised and pedal oedema was evident. She had features of right heart failure and pulmonary hypertension. Chest examination revealed inspiratory coarse crackles heard on both sides of the chest that were more pronounced at the bases. The plain chest radiograph revealed a diffuse symmetric, dense, micronodular (sand-storm lung) pattern (Figure 3). After few visits, patient was lost to follow-up.

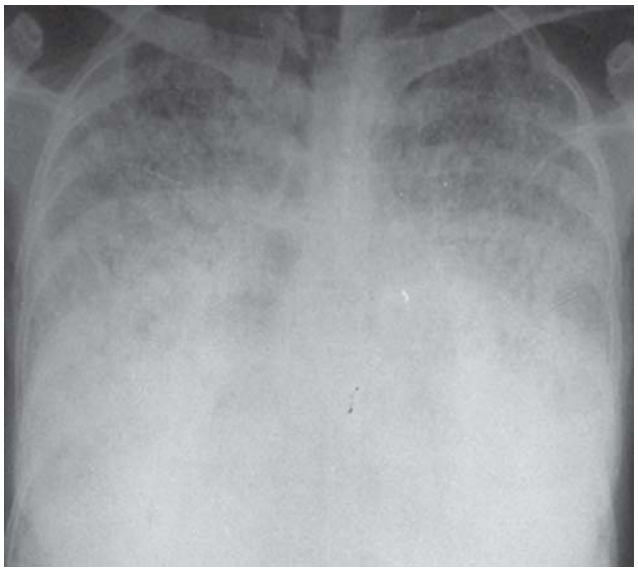

Figure 3. Chest radiograph (postero-anterior view) of fourth case demonstrating a diffuse symmetric, dense, micronodular ('sand-storm') pattern.

Case 5

A 24-year-old male was referred for progressive shortness of breath and dry cough. He had been treated for pulmonary tuberculosis before referral. Chest radiograph showed typical micronodular opacities in bilateral lung fields. Pulmonary function tests revealed a normal spirometric pattern. High resolution CT showed widespread nodular infiltrates. In addition, pericardial and pleural calcification was also noted (Figure 4). Biochemical parameters including serum calcium were within normal limits. Diagnosis was confirmed as PAM by transbronchial lung biopsy which revealed calcific concretions within the alveolar spaces (Figure 5). Family screening was negative.

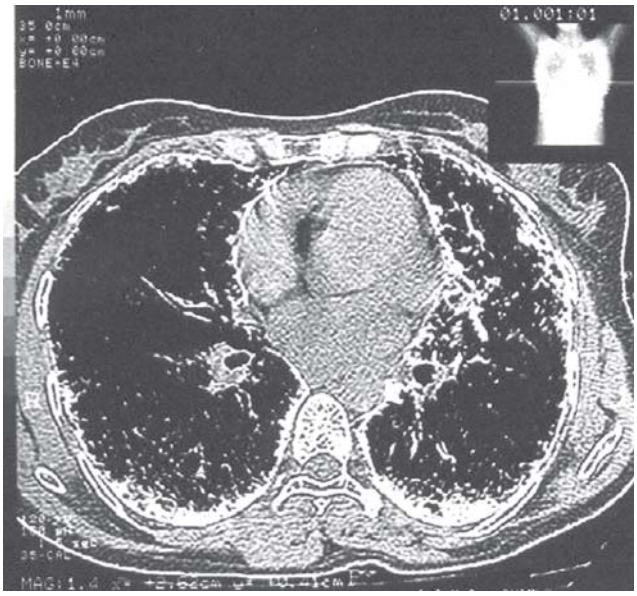

Figure 4. HRCT thorax showing pericardial and pleural calcification in addition to calcific nodules within lung parenchyma.

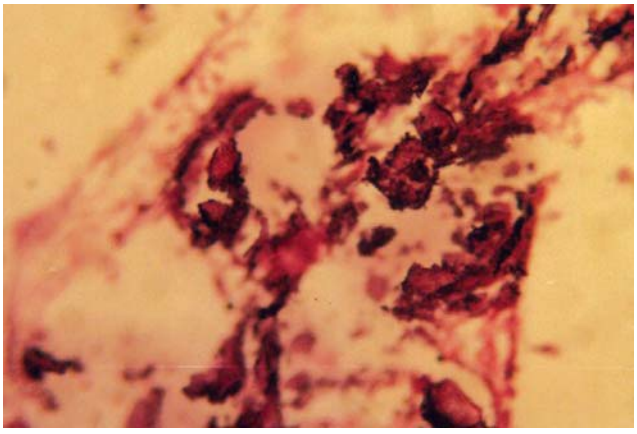

Figure 5. Transbronchial lung biopsy demonstrating the characteristic calcified concretions within the alveoli (Haematoxylin and eosin, × 400).

We managed all the cases symptomatically. We had observed a variable progression of the disease with one patient developing cor-pulmonale early in the course while another had a slow progression over a long period.

Discussion

Pulmonary alveolar microlithiasis is a rare disease with less than 800 cases being documented world-wide.[3] Most of the cases have been reported from Turkey, Japan and Italy. About 30 cases are reported in literature from different regions of India. Pulmonary alveolar microlithiasis was first reported from India by Viswanathan.[4] There are few other sporadic cases reported from different parts of India.[5-10]

The mean age at presentation in the present study was 29 years. Pulmonary alveolar microlithiasis is frequently diagnosed from birth to 40 years of age. Although, reports of disease in premature twins and patients as old as 80 years is available, age of onset of symptoms in most cases is usually the third and fourth decade of life with mean age being 27-30 years.[11,12] Three of the five patients in the present study were men. Pulmonary alveolar microlithiasis has been reported in both genders with a slight male predominance worldwide except in Italy where more frequently PAM cases are reported in females.[13]

Due to lack of knowledge about exact aetiology and pathogenesis of the disease, various hypotheses have been postulated; most accepted theory supporting role of inheritance, involving the enzyme carbonic anhydrase, limited to alveolar surface, due to which alkalinity of the alveolar surface is favoured, thereby leading to precipitation of calcareous salts.[14] According to another hypothesis, abnormal inflammatory response to irritants or infection within the alveoli, leads to formation of exudates which are not easily absorbed and consequently undergo calcification.[15]

Presentation can be either familial or sporadic. Familial occurrence has been observed in approximately 35.6% of cases worldwide[13] with maximum number of cases from Japan (50%).[16] In familial cases, high frequency of horizontal transmission, accumulation of the patients in inbred families and the absence of sex predisposition point towards autosomal recessive mode of inheritance. Genetically, mutation in the solute carrier 34A2 (*SLC34A2*) gene is considered responsible for the development of pulmonary microlithiasis which encodes a type IIb sodium-phosphate co-transporter in type II alveolar cells.[17] Mutations of *SLC34A2* gene may reduce the clearance of phosphate, and thus, may lead to the formation of microliths.[16] All of the cases in this study were sporadic and did not show any familial association despite screening radiography performed in family members.

Four of our patients presented with mild cough and breathlessness and one patient developed cor-pulmonale during the course of the disease. Another patient with longest follow-up, survived for 20 years. All these data hint towards variable clinical course. Rarity of the disease along with scattered case reports, highlighting particular aspects of the disease is a

limiting factor in the understanding of clinical evolution. Typically, patients do not develop any subjective symptoms until middle age and the most common presentation of the disease is the incidental finding of an abnormality on chest radiograph.[18] According to few reports,[19-21] the illness remains static in terms of symptoms and radiographic findings. In other instances,[19-21] the disease progresses over time, ultimately leading to pulmonary fibrosis, respiratory failure and chronic pulmonary heart diseases (cor-pulmonale).

A striking feature of PAM is discordance between clinical and radiographic manifestations and typical presentation is extensive radiological involvement despite minimal symptoms. The characteristic radiographic pattern is described as 'sand-storm lung' with fine calcific micronodules diffusely involving both lungs, though more marked in middle and lower zones with relative sparing of the apices and obliteration of the mediastinal and diaphragmatic contours.[22] These small, nodular, calcific and confluent densities demonstrated with computerised tomography may give rise to areas of ground-glass attenuation and consolidation.[23] These opacities may be numerous to make the lungs appear almost uniformly white. Small apical bullae and black pleural line are the other typical findings which are due to thin-walled sub-pleural cysts, ranging from 5mm to 10mm in diameter. Radiological appearance of stannosis, talc granulomatosis and calcified miliary histoplasmosis may simulate microlithiasis but the lesions in these conditions are larger and have different distribution. Magnetic resonance imaging (MRI) reveals diffuse calcific micronodules, characterised by increased signal intensity on T1-weighted images, predominantly in the posterior lower zones.[24]

In addition to usual pulmonary calcification, we had observed pleural and pericardial calcification in one case which is an uncommon manifestation. There are few reports of PAM calcification affecting extra-pulmonary sites including prostate,[13] sympathetic ganglia, gonads,[25] pericardium, kidney[26] and seminal vesicles.[27] This is probably the first instance where pericardial calcification is being documented in a patient with PAM from India.

One patient was previously treated for pulmonary tuberculosis, though it is not clear whether there was real association with tuberculosis or he was misdiagnosed to have tuberculosis.[13] In review of Turkish rports on PAM[11] though an initial diagnosis of miliary tuberculosis was made in 13 cases; AFB were evident in sputum only in two cases.[11] Other associations are milk alkali syndrome, renal transplant recipient, pericardiac cyst and lymphocytic interstitial pneumonitis.[13]

Confirmation of pulmonary alveolar microlithiasis is usually by bronchoalveolar lavage (BAL), open biopsy or transbronchial lung biopsy, demonstrating the typical microliths within alveoli. The transbronchial lung biopsy is the most acceptable way of diagnosis. Four of our cases were confirmed by transbronchial lung biopsy. No satisfactory treatment is available for PAM. Systemic corticosteroids as well as therapeutic bronchoalveolar lavage have been shown to be ineffective. In PAM, there is deposition of calcium-embedded particles in lung interstitium, which do not get dislodged during BAL.[28] Home oxygen therapy is usually advised for respiratory insufficiency. Disodium etidronate, which inhibits the microcrystal growth of hydroxyapatite, has been proved to be beneficial in the dose of 10mg/kg per day orally with considerable regression of the calcific densities.[29] Some patients have undergone bilateral sequential lung transplantation or unilateral lung transplantation[15,30,31] but effect on long-term survival is yet to be proved.

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