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Identification of Rare Pulmonary Alveolar Microlithiasis in Maharashtra, India

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Authors' contributions

This work was carried out in collaboration between all authors. Author SB wrote the manuscript. Authors RP and TK managed the literature searches, Author KSK provided the radiological images and Author AB provided the clinical data. All authors read and approved the final manuscript.

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Case Study

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ABSTRACT

Pulmonary alveolar microlithiasis (PAM) is a rare diffuse lung disease characterized by intra-alveolar deposition of calcium and phosphate. Clinically, the disease may remain static in some patients while it may progress to pulmonary fibrosis, marked hypoxemia and cor pulmonale in others. We report a case of a 44-year-old male, tailor by occupation, nonsmoker, presented with shortness of breath on exertion for three years. His chest radiograph showed bilateral diffuse calcifications and high-resolution computerized tomography (HRCT) scan showed "crazy paving pattern" involving diffuse bilateral lung parenchyma. Histopathology of lung biopsy with use of special stains confirmed the diagnosis of pulmonary alveolar microlithiasis. Patient refused any further intervention or lung transplant and lost to follow up after a year.

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1. INTRODUCTION

Pulmonary alveolar microlithiasis (PAM), first described by Puhr is a rare progressive pulmonary disease characterized by the formation and accumulation of tiny, roundish spherules called “microliths” within the alveoli. There are over 800 cases reported in medical literature so far. It has been misdiagnosed in the past and still continues to be misdiagnosed as miliary tuberculosis and sarcoidosis [1]. PAM is usually presents between 20 to 40 years of age and the diagnosis of PAM is considered after unexpected abnormal chest x ray findings and histopathology of lung tissue is required to confirm the diagnosis [2]. Currently, lung transplantation seems to be the only effective treatment in selected cases.

2. AIMS

Our aim is to emphasize that PAM needs to be considered as an alternative diagnosis in suspected miliary tuberculosis and occupational lung diseases as more and more cases of PAM are being reported in recent past in various literature of which significant number of cases are misdiagnosed as tuberculosis, sarcoidosis or occupational lung disease.

3. PRESENTATION OF CASE

A 44-year-old male, a tailor by occupation, and a known epileptic presented in our hospital with dry cough and mild breathlessness on exertion since 3 years. The patient had exposure to dust for more than 20 years of his work in construction industry in the past.

Physical examination revealed bilateral fine late inspiratory crepitations. Pulmonary function test showed restrictive type of ventilatory defect. His haematological investigations were within normal limits. A sputum examination was negative for tubercle bacilli. His serum calcium and phosphorus levels were normal. Chest radiograph showed diffuse dense bilateral lung calcifications, mainly in the basal zones (Fig. 1). High-resolution computed tomography (HRCT) revealed diffuse widespread tiny micro calcifications and dense calcifications scattered throughout the lungs resulting in a “crazy-paving pattern” which is described as a classic appearance of PAM. The lesions were distributed in sub-pleural and peribronchial areas. There was interlobular septal thickening predominantly in basal segments; bilaterally. (Fig. 2). These radiological features were strongly suggestive of PAM. Transbronchial lung biopsy was done and histology revealed numerous round, concentrically laminated microliths in the alveoli, which stained positively for periodic acid-Schiff (PAS) and Von Kossa stains conforming to the diagnosis of PAM (Figs . 3,4).

4. STAINING METHOD

In Von- kossa stain method for calcium salts, tissue sections are treated with silver nitrate (AgNO3) solution. In this, silver ions from aqueous AgNO3 displace calcium from deposits of calcium carbonate or phosphate and form insoluble silver carbonate or phosphate (precipitation reaction), which is quickly decomposed by the action of light to form black colloidal silver (photochemical reaction) which is visualised microscopically as presence of calcium deposits (microliths). As with any method for calcium, acid fixatives should be avoided, buffered neutral formalin being recommended.

4.1 Solutions

2% aqueous silver nitrate.

Van Gieson’s stain or 1% aqueous neutral red.

4.2 Technique

1. Sections were washed in two or three changes of distilled water.
2. Sections were then placed on a slide rack and section covered with the 2% aqueous silver nitrate solution and exposed to sunlight, checking microscopically.
3. Sections are washed in several changes of distilled water followed by washing in tap water.
4. Counterstaining was done using Van Gieson’s stain for 5 min.
5. Sections were dehydrated through alcohols, cleared in xylene and mounted in DPX [3].

The alveolar microliths showed prominent concentric laminations (Fig. 5) and mild collagenous thickening of alveolar septae. The patient refused any further intervention or lung transplant and his one year follow-up was uneventful.

5. DISCUSSION

PAM is a rare diffuse pulmonary disease which is chronic and irreversible; it characterized by intra-alveolar accumulation of microliths consisting of calcium phosphate. Some studies have shown mutation of SCL34A2 gene in the alveolar type II cells, which encodes a sodium phosphate co-transporter, causing pulmonary microlith deposits [4]. The abnormal co-transporter cannot remove phosphorus ions from the alveolar spaces, leading to phosphate chelating calcium in the extracellular fluid and microlith formation [5]. PAM pathogenesis is characterized by early onset and very slow progression of the disease process. Although full penetrance of genetic defect with autosomal recessive pattern has been noticed in the development of PAM, however, non-genetic environmental factors seem to contribute significantly in its progression [6]. Our patient also had environmental exposure to dust and cement for over 20 years of his occupation in construction industry in the past.

PAM is found worldwide but it is predominantly found in Turkey, Italy, and in the USA [1]. The disease is usually diagnosed between 20 and 40 years of age both in men and women. An autosomal recessive mode of inheritance is common. The hallmark of the disease is asymptomatic patients with clinical-radiological dissociation, inspite of extensive radiographic changes. Patients may remain without symptoms for long duration and usually start having dyspnoea on exertion or cough between third and fourth decades when greater number of alveoli are filled with calcium phosphate deposit. The disease may progress gradually leading to severe cardio-respiratory failure [2,4].

PAM can mimic both clinically and radiologically other conditions like pulmonary tuberculosis, sarcoidosis and occupational lung diseases, but histopathological examination of lung biopsy shows characteristic lamellated calcium phosphate microliths [4].

In literature, approximately 13.2% and 2% of cases have been misdiagnosed and treated as tuberculosis and sarcoidosis respectively [7]. Hence histological confirmation of PAM is essential in the management of such cases. Chest radiograph usually shows bilateral fine sand-like calcific spherules throughout the lung fields predominantly involving middle and lower lobes, producing a “sand-storm” appearance [8]. CT scan usually shows characteristic ground glass opacity (“crazy-paving pattern”) in basal segments on HRCT. Similar CT scan pattern can also be seen in other conditions like pulmonary alveolar proteinosis (PAP), pneumocystis carinii pneumonia, adult respiratory distress syndrome, pulmonary haemorrhage, acute radiation pneumonitis, interstitial pneumonia and sarcoidosis [7,8].

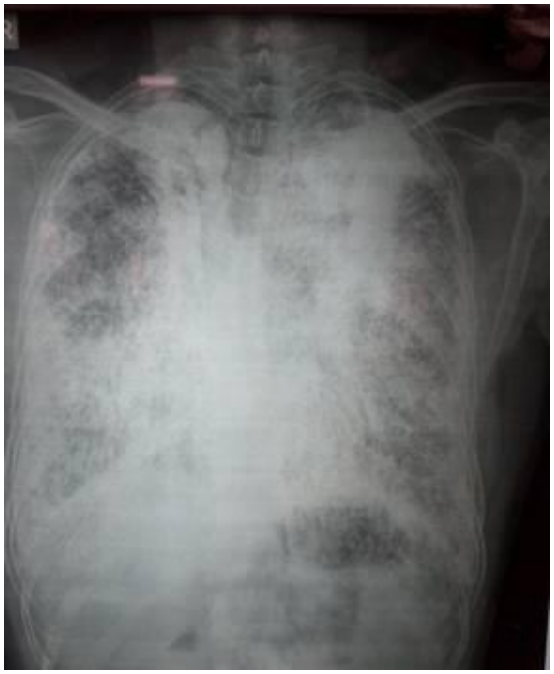

Fig. 1. The plain chest X-ray posterior-anterior view showing diffuse dense calcifications in both lung fields mainly in the basal zones

In PAM, histological examination of lung tissue shows characteristic intra-alveolar lamellated calcified sphelules of varying sizes ranging from 0.01 to 0.5 mm. These spherules are not embedded in the fibrous tissue; therefore tend to fall out of lung tissue easily. Histologically, they have concentric layers with fine radial striations and are birefringent under polarized light. They stain positively with PAS and calcium stains like Von-kossa [9]. Increasing numbers of bodies are associated with fibrosis and chronic inflammation [10].

Differential diagnosis of PAM for a pathologist include pulmonary calcification, blue bodies, corpora amylacea and metastatic calcifications which can be differentiated from PAM by clinical history, biochemical investigations, their

characteristic appearance, size and by special stains like PAS and Von-Kossa [11].

With increasing evidence of possible autosomal recessive mode of inheritance and radio-clinical dissociation, family members of the patient need to be screened for PAM [2]. Lung transplantation is reported as the only possible treatment for end-stage cases. Disodium edidronate, a calcium chelating agent, has been advocated to treat PAM in past with no significant improvement. PAM when diagnosed early in childhood is known to retard the progression of the disease following long term treatment with disodium etidronate [8].

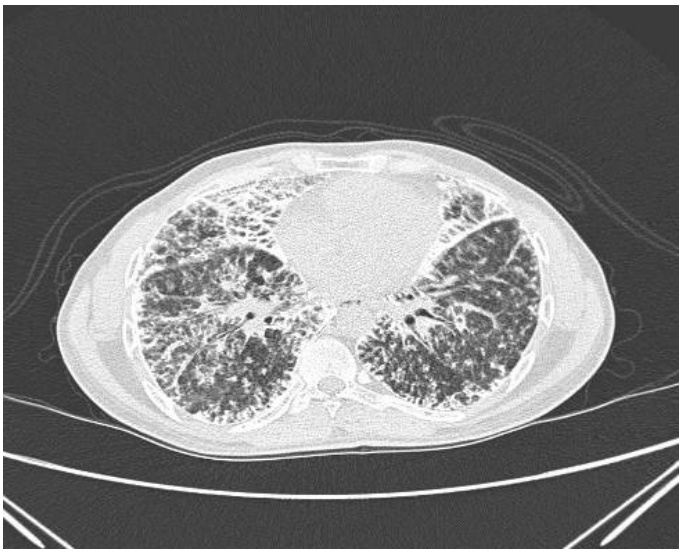

Fig. 2. The HRCT scan of the chest, axial image showing diffuse widespread calcifications with crazy-paving reticular pattern with subpleural and peribronchial distributions and interlobular septal thickening predominantly in basal segments

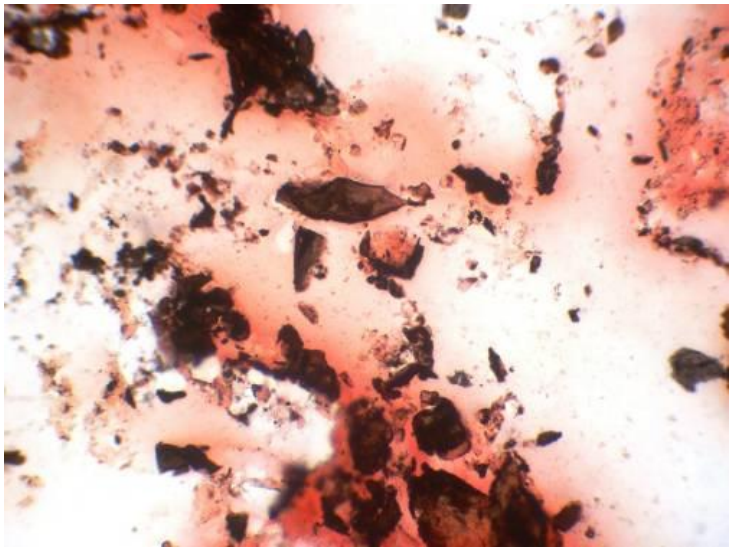

Fig. 3. Histopathology examination revealed multiple microliths within the alveoli of lung parenchyma, Von Kossa stain, x100

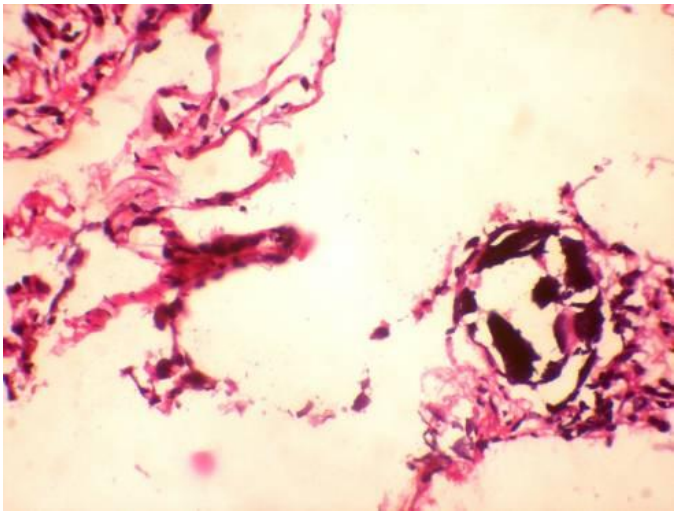

Fig. 4. Lung section showing calcified microlith localised in the intra-alveolar spaces. H & E stain, x100

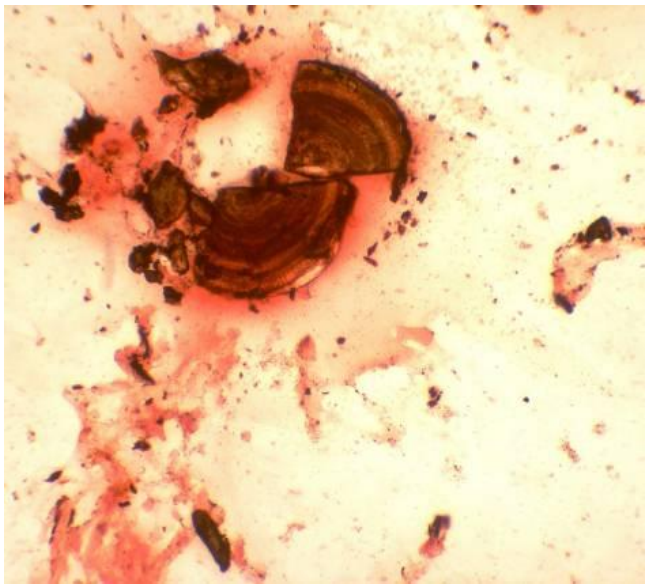

Fig. 5. An alveolar microlith showing laminations, Von Kossa stain, x400

5. CONCLUSION

Pulmonary alveolar microlithiasis is a rare diffuse chronic lung disease with an autosomal recessive mode of inheritance following mutation of the SCL34A2 gene. The condition although rare, must be kept in mind by clinicians in view of its close resemblance to other pulmonary diseases. A characteristic radiological finding along with histopathological examination of lung biopsy is necessary to confirm the diagnosis. Although there is no specific treatment for PAM; patients are known to improve in respiratory function following lung transplantation. Early and accurate diagnosis in suspected individuals can help to slow the disease progression. Identification of the abnormal gene has enabled prospects for future targeted therapy for this chronic debilitating condition.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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