

CASE REPORT

FAMILIAL PULMONARY ALVEOLAR MICROLITHIASIS

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INTRODUCTION: Pulmonary Alveolar Microlithiasis is rare diffuse lung disease of unknown Cause in which diffuse accumulation of numerous calcospherites in the alveolar space with or without thickened interstitium.¹ Pulmonary Alveolar Microlithiasis was described first by FRIEDREICK² in 1856, later by Harbitz³ in 1918. LUDWIG PUHR⁴ named this condition as Microlithiasis alveolaris pulmonum in 1933. The first Indian case was reported by Viswanadhan⁵ in 1962 from V. P. Chest institute. SOSMAN⁵ emphasized that 50% cases were familial, and this suggestive of autosomal recessive hereditary factor. The radiographic appearance is pathognomic of pulmonary alveolar Microlithiasis, although not usually required, Bronchoalveolar Lavage fluid⁶ or Biopsy can confirm the diagnosis.

Plain chest radiograph shows a white lung or sandstorm lung consisting of diffuse, fine sand like Microcalcifications. Heart borders and the diaphragm are usually obliterated and there is presence of black pleural lines which represents thin walled subpleural cysts.

EPIDEMIOLOGY: Around 600 cases have been reported worldwide in medical literature. Most cases have been reported from Turkey, Japan and Italy. Not more than 30 cases are reported in literature from different regions of India till to date.⁷ Pulmonary alveolar Microlithiasis occurs equally in both sexes⁸ and in all age groups from new born to 80yrs, majority of them are diagnosed between 30-50 yrs.

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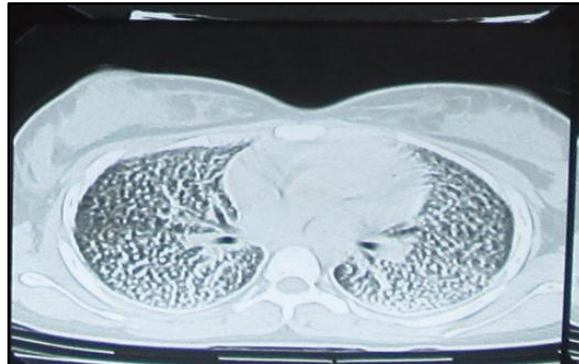
CASE ONE: A 15 years old girl presented to Pulmonology OP department with chief complaint of progressive Breathlessness from age of 10yrs and aggravated Breathlessness from last 2 years. One episode of Haemoptysis occurred in January 2015. There was no history of cough, fever and chest pain. No history of Pulmonary Tuberculosis in the family. On physical examination patient had no clubbing, no cyanosis, no lymphadenopathy and no peripheral oedema. Cardiac auscultation was normal. Auscultation of lungs was nothing to contribute. Pulmonary function test revealed normal spirometry. Routine lab investigation was normal. Serum calcium levels were normal. Chest x-ray showed bilateral finely granular calcified strands predominantly in the middle and lower zones.

HRCT chest showed calcified nodules and reticular pattern involving predominantly in mid and lower zones. Sputum for calcium bodies was negative. Fiber optic Bronchoscopy was performed and Bronchoalveolar lavage fluid was positive for calcium bodies by stained Microscopic examination. Three General physicians saw her and prescribed anti tuberculous drugs 8 months ago but no response.

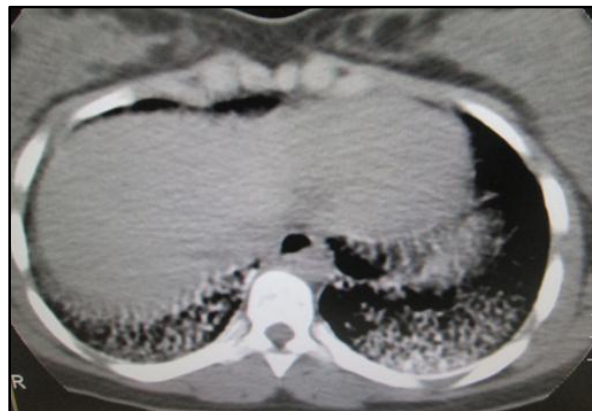
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C X Ray showing B/L fine granular calcified strands predominantly in the lower & mid zones

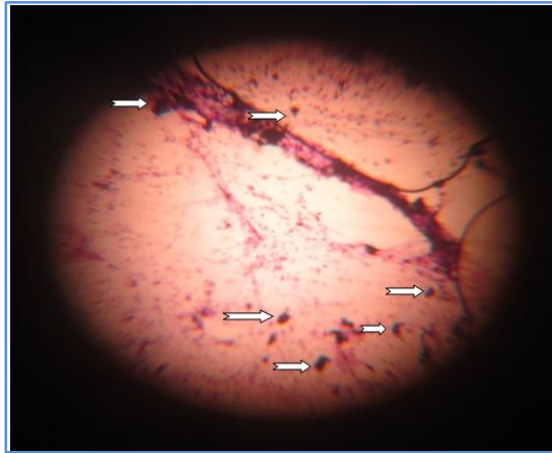


Lung window showing B/L diffuse calcified micronodular opacities with reticular pattern and thickening of the interlobular septae



Mediastinal window showing diffuse B/L calcified fine nodular and reticular pattern

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Arrows in the microscopic field showing black granules which constitute calcospherites

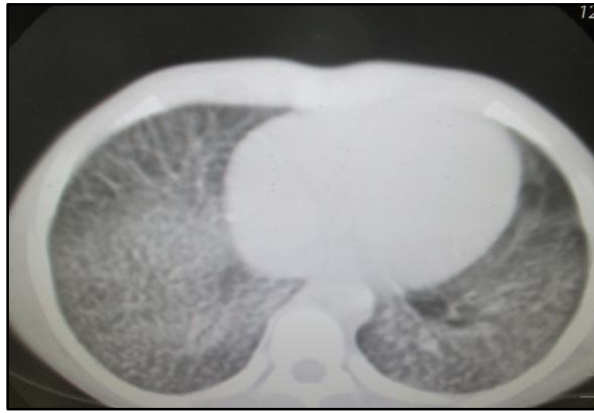
CASE 2: As PAM is familial disease, we screened girl's mother, 32yrs and younger brother 11 yrs. Father was not available as he left the family long ago. Her mother's chest x-ray was normal.

Her brother was 11yrs old boy and his chest x-ray is similar to her showing Bilateral finely granular calcified strands predominantly in mid and lower zones. HRCT chest shows calcified nodules and reticular pattern but less intensity when compared with his sister. Boy was completely asymptomatic and his PFT showed normal spirometry. Sputum of calcium bodies was negative. The boy was not cooperative to undergo Bronchoscopy and not willing to undergo further investigations. BAL or Biopsy is not necessary for him to confirm diagnosis as his sister's BAL fluid was positive for calcium bodies.



Chest x-ray showing B/L fine granular calcified strands predominantly in the lower and mid zones

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Lung window showing B/L diffuse calcified fine micronodular ground glass opacities and reticular pattern

DISCUSSION: Although aetiology of PAM remains unclear, mutations of the solute carrier family 34 (Sodium phosphate) member 2 gene (SLC 34 A2 GENE) which encodes a type II b sodium dependent phosphate co-transporter (NaPi-II b) are considered to be the cause of the disease. SLC 34 A2 is primarily expressed in alveolar type II cells of lung. Loss of function of this gene due to mutations may lead to decreased cellular uptake of phosphate, leading to its accumulation in alveoli. As phosphate chelates calcium in extracellular fluid, microliths (calcospherites) will be formed in the alveolar space. In 1957, SOSMAM showed a high incidence of familial links. The study of familial cases indicates the characteristic of an autosomal recessive disease. Familial occurrence has been observed in 30-50% of cases. A high rate of consanguineous marriages has been observed in the families affected, like in our cases.

The composition of the calcifications is calcium and phosphate in a ratio of 2:1. The microliths are rounded, oval, and lobular with a concentric laminated appearance. Grossly, the lungs are firm to hard in consistency. The size of the calcospherites ranges from 0.01 to 3 mm within the alveoli. In the early stage, alveolar walls are normal, but with the progression of the disease and at a later stage, fibrosis, interstitial thickening, and giant cells are noticed. Apical blebs and bullae may cause recurrent pneumothorax in these cases.

A striking feature of this disease is the lack of significant symptoms despite extensive radiographic changes. In some patients, the disease remains static as regards to both symptoms and radiographic findings, while in some patients it has worsened over time in different rates, leading to pulmonary fibrosis, respiratory failure, and chronic right heart failure (cor pulmonale). Dyspnea on exertion occurs as the disease progresses, and late symptoms of cor pulmonale appear in the terminal stage of the disease. Cough may occur at any stage of disease, and even expectoration of microliths has been reported. Haemoptysis can occur in some patients.

Elevated serum concentrations of surfactant protein SP-A and SP-D have been seen in PAM, like other interstitial lung diseases (ILDs), with a tendency of increasing levels as the disease progresses. So SP-A and SP-D are useful as serum markers for monitoring the disease activity and progression.

On radiographs, PAM is characterized by diffuse fine calcific micronodules that involve both lungs, classically described as sandstorm-like. Increased calcific densities are often more pronounced

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in the lower zones, a fact that has been attributed to the larger surface area and greater thickness of the lower zones of the lungs. A vertical linear radiolucency between the ribs and lung parenchyma is also common finding secondary to sub pleural cystic changes. HRCT chest findings noted that extensive microliths involving both lungs with predisposition for posterior segments of lower lobes and anterior segments of upper lobes. Additionally medial aspect of lung appears to be more heavily involved than lateral aspect. Confluent areas of calcifications may be identified often in the upper lobe. Microliths with diameter of <1mm produce a groundglass appearance. Extra Pulmonary involvement is usually in testes and lumbar sympathetic chain.

Differential diagnosis includes miliary tuberculosis, lymphocytic interstitial pneumonia, pulmonary hemosiderosis, amyloidosis, tumour metastasis, sarcoidosis, healed calcified lesions of histoplasmosis and Pneumoconiosis like silicosis, beriliosis, talcosis, silicosis.

Bone scintigraphy shows diffuse uptake of Tc 99 in PAM and may be useful as a diagnostic adjunct. spirometry may be normal or restrictive pattern in late stage of disease. Impairment of gas transfer with V/Q mismatch has been reported in late stage of disease. On Bronchoscopic examination Tracheobronchial tree is usually normal.

At present, effective medical treatment is not available either to treat or even to halt the progression of the PAM. Treatment with corticosteroids is not useful. Observational studies have found therapeutic BAL is not effective unlike in pulmonary alveolar proteinosis. Disodium etidronate⁹ which regress the formation of microliths at a dose of 10 mg/kg/day orally for a period of 1yr is useful in some patients. Nasal CPAP has been improved oxygenation in hypoxic state in some patients who developed corpulmonale or Respiratory failure. End stage lung disease due PAM may require Bilateral Sequential lung transplantation¹⁰ was reported to be successful in some selected patients. Infective exacerbations of PAM should be treated like any other ILDs.

Long term survival in PAM is still uncertain. Only few reports with long term follow-up data are available. Survival period is variable after diagnosis and it is about 10 to 49 yrs is reported till to date.

CONCLUSION: PAM is a rare parenchymal lung disease often diagnosed incidentally during taking chest X-ray for other reasons. Chest X-ray and HRCT with either BAL positive for calcium bodies or Biopsy for HPE will confirm the diagnosis. Effective medical therapy is not available till to date. The usual course of the disease to death is either due to respiratory failure or corpulmonale. Bilateral sequential lung transplantation is definitive surgical treatment at some stage of progression of the disease.

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