

Pulmonary Alveolar Microlithiasis: An Indolent Disease with Astounding Radiological Findings

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Abstract

Pulmonary Alveolar Microlithiasis is a disorder in which calcospherites composed of calcium and phosphorous accumulate in the alveoli throughout the lung parenchyma leading to a progressive infiltrative lung disease. It can present completely asymptotically in early childhood, only to end with cor pulmonale in later life. We report two cases- the first, a six-year-old boy who had a strong familial history of lung diseases and presented with a history of chronic cough. No further symptoms were elicited, although two elder familial members had passed away of cor pulmonale in their mid-30s. The other is an eight-year-old boy referred to as a case of "non-responsive pulmonary tuberculosis, diagnosed sans microbiological evidence. Respiratory examination, and growth were normal in both children. Chest X-ray had a typical 'Stone Lung' appearance. The clinical findings were in contrast to the radiological picture and hence a CT scan (Chest) was done. On further suspicion, lung biopsy and genetic analysis established the diagnosis of Pulmonary Alveolar Microlithiasis. The patients were given supportive treatment and started on oral Etidronate. With an indolent clinical course, Pulmonary Alveolar Microlithiasis poises itself to remain a "missed diagnosis" with eventual poor outcome, unless the paediatrician is vary about the astounding radiological findings, which should immediately prompt towards further workup for the disease.

Keywords: Stone Lung, calcospherites, Harbitz' syndrome, snowstorm lung

Introduction

Pulmonary Alveolar Microlithiasis (PAM) is a rare chronic autosomal recessive lung disease characterised by intra-alveolar deposition of calcospherites. Mutation in SLC34A2 gene, encoding sodium-dependent phosphate transporter in alveolar type II cells, causes microliths rich in calcium and phosphate to be deposited in alveoli. [1] Most affected individuals are asymptomatic for several years or only complain of intermittent mild cough or slowly progressive dyspnea, only to eventually lead to cor pulmonale in later life. Inclined that a patient may have relative paucity of symptoms, the hallmark of PAM is the striking dissociation between the radiological appearance and clinical presentation, which clues into clinching the diagnosis. In this report, we present two cases with such an indolent course, and posing a diagnostic dilemma. The cases are presented due to their rarity and also to highlight the approach a clinician should use in diagnosing this disease.

Clinical description

Case 1: A six-year boy, born of consanguineous union, was referred to our respiratory clinic for chronic complaints of cough and for further evaluation of his abnormal chest X-Ray. The parents noted no other symptoms, and our child was well-grown for his age. On probing, we elicited a history of his maternal uncle and aunt having expired at the young age of 36 years and 34 years, respectively, of cor-pulmonale. Their X-rays were available for reference (fig: 1 & fig 2). On examination, our child had a normal respiratory rate with no evidence of cyanosis or any clubbing, and respiratory system examination revealed no abnormalities.

Case 2: An eight-year-old boy, born out of non-consanguineous union, was referred to our center for management of “non-responsive” pulmonary tuberculosis. The diagnosis of Tuberculosis was made based on an abnormal chest X-ray without any microbiological evidence to confirm the same. He only had a history of chronic cough for the past 2 months, with no other symptoms. There was no history of Koch’s contact. He was well-grown for age, and general examination was within normal limits. Respiratory examination revealed no abnormality.

Management and outcome: In the first case, the Chest X-ray showed bilateral symmetrical diffuse dense micronodular opacities, widespread across the lung parenchyma giving it a “sand storm” appearance (fig: 3). The child’s hemogram, calcium profile and renal parameters were within normal limits. But, as the clinical and biochemical profile of the child was in complete contrast to the radiological picture, a CT scan of the Chest was ordered which was suggestive of calcification of interlobular septa and pleural thickening (fig:4). 2-D Echo and Pulmonary Function Tests were normal. The clinical diagnosis of pulmonary alveolar microlithiasis was made based on clinico-radiological dissociation, characteristic X- ray findings and positive family history. A lung biopsy was conducted which showed multiple intra-alveolar concentric lamellar calcification which further strengthened the diagnosis of PAM. Genomic sequencing was suggestive of homozygous nonsense mutation (c.675G>A, p.Trp225Ter) in exon of the SLC34A2 gene. The child was started on etidronate and is on regular follow-up. Genetic counselling was done for the family.

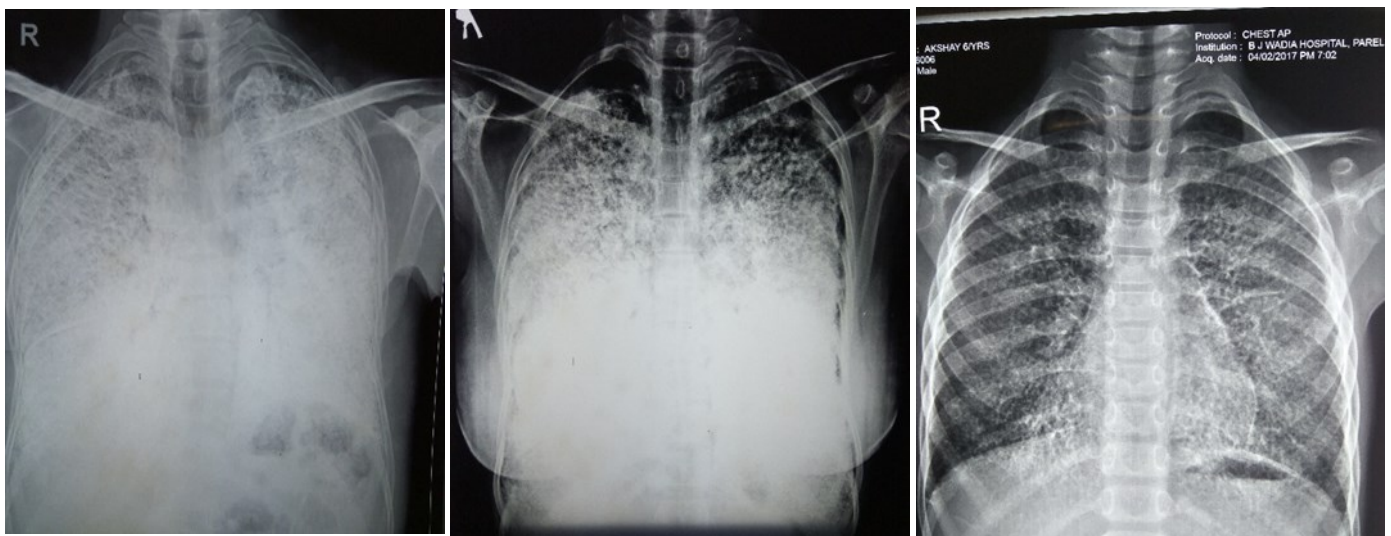


Figure 1: Chest Xray of maternal uncle who was suspected to be a case of PAM, x ray represents an extensive involvement of lung parenchyma commonly seen in late adulthood.

Figure 2: Maternal aunt's chest Xray who died of cor pulmonale showing typical sandstorm appearance.

Figure 3: Chest Xray of case 1 showing widespread deposition of micronodular opacities across the lung fields suggestive of PAM.

In the second case, the chest X-ray was suggestive of a sand-like micronodular pattern distributed throughout the lung with more basal concentration (fig: 5). CT Chest was done which was suggestive of microcalcifications throughout the lung with septal thickening (fig:6). 2D-Echo was normal, but Pulmonary Function Test was suggestive of mild restriction. There was a strong suspicion of PAM, hence a lung biopsy was done. The lung biopsy showed that alveolar air spaces were filled with calcospherites and genomic sequencing showed a nonsense homozygous mutation (c.675G>A, p.Trp225Ter) in exon of the SLC34A2 gene. This confirmed the diagnosis of pulmonary alveolar microlithiasis. The child was started on sodium etidronate and was asymptomatic on subsequent follow-up.

The further plan of management for both cases is a biannual chest X-ray and pulmonary function test to see for improvement on Disodium etidronate therapy, and an annual 2D- Echo to check for pulmonary arterial hypertension.

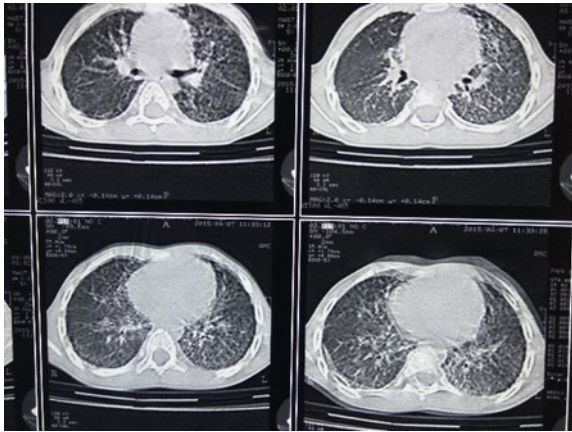


Figure 4: Chest CT of case 1 showing calcification of interlobular septa and pleural thickening.

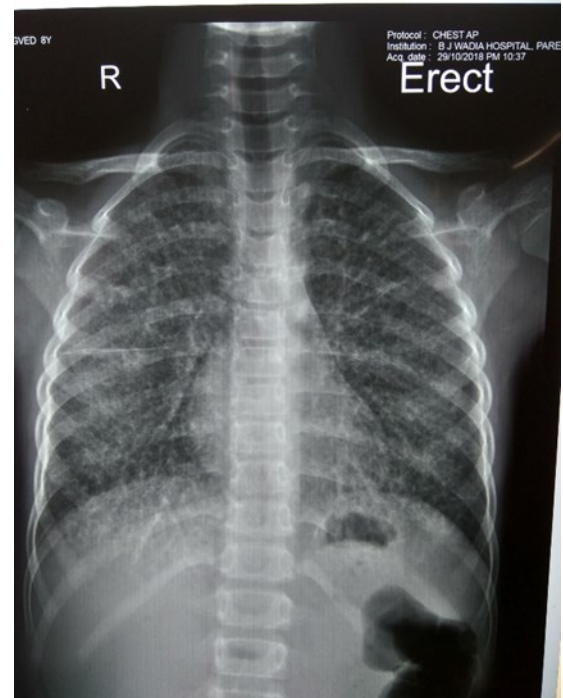


Figure 5: Chest Xray of case 2 showing micronodular appearance throughout the lung parenchyma more in the basal areas.

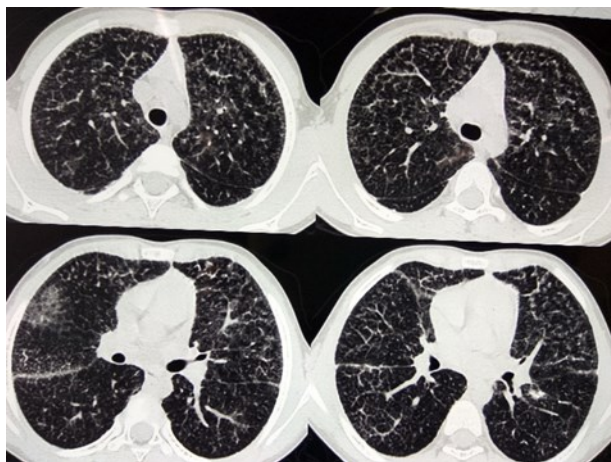


Figure 6: Chest CT of case 2 showing microcalcifications across bilateral lung fields with septal thickening.

Discussion

Pulmonary Alveolar Microlithiasis is a rare lung disease that transmits horizontally and is associated with consanguinity. Marcello Malpighi first described PAM in the year 1868. [3,4] Since the discovery of PAM 150 years ago, worldwide, about 1000 cases are described in literature.

The clinical presentation of PAM in the pediatric population is mild to asymptomatic. The most common presentation is a chronic cough. The pulmonary function tests in the early course of the disease are usually within normal limits. As the disease progresses, there is a widespread accumulation of calcospherites in the lung parenchyma, leading to a restrictive type of pulmonary dysfunction.[7] This dysfunction eventually results in hypoxia and an increase in CO₂ arterial levels which leads to respiratory failure.

The inheritance pattern seen in familial cases is autosomal recessive with high penetrance, as seen with our Case 1. In children due to varied stage of disease progression uncommonly a radiological picture can be differing. Hence, histopathological evidence remains the gold standard to establish the diagnosis of PAM.

Microliths containing calcium are widespread across the lung parenchyma which appears radiopaque such that it gives an appearance as if sand is sprinkled across the lung fields. The most common findings on HRCT are ground glass opacities which are due to small calculi in the air space. Subpleural calcifications on HRCT are microliths in the periphery of secondary pulmonary lobules which demarcate the pleural surface and appear as pseudo pleural calcifications. [4]

The radiological differential diagnosis of PAM are miliary tuberculosis, sarcoidosis, pneumoconiosis, pulmonary alveolar proteinosis, pulmonary amyloidosis, metastatic, and dystrophic pulmonary calcification. [7] In our second case, the patient was misdiagnosed with miliary tuberculosis.

On histopathology, lung biopsy shows intra-alveolar concentric lamellar calcifications situated loosely within the alveolar lumen with no fibrosis. Genetic testing for SLC34A2 gene mutation in suspected cases of PAM further establishes the genotype and can be used as a screening test for the family members of the affected patient and act as a guiding tool in the genetic counselling of the family.

Treatment in most cases remains supportive with supplemental oxygen therapy. The only treatment option for end-stage lung disease is a lung transplant. Drugs such as calcium chelators and corticosteroids have not shown efficiency in arresting the disease progression and are considered to have more of a palliative role. Therapeutic BAL also has proven to be of no benefit to these patients. [8] There are few cases reports in the literature which show the efficacy of disodium etidronate therapy. [8,9] Disodium etidronate acts by inhibiting the formation of hydroxyapatite crystals and their amorphous precursors by chemisorption to calcium phosphate surfaces. [8,10] Whether this drug has direct implications in preventing the formation of calcospherites in the alveoli is yet to be proven. Both our cases are on disodium etidronate and are on regular follow-up.

Conclusion

In the early phase of the disease, where symptoms are not predominant, the typical radiological picture should prompt further evaluation and PAM should be kept a close differential. In the Indian subcontinent where Tuberculosis is endemic, diagnosis of PAM may get missed and hence it warrants a high index of suspicion. Early diagnosis with a CT scan and a Lung Biopsy, prompt treatment, regular lung function monitoring, pulmonary rehabilitation and genetic counseling will be of much benefit to these children.

Conflict of Interest

The authors declare no conflict of interest.

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