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IP Indian Journal of Immunology and Respiratory Medicine

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Case Report

Sandstorm lung: A rare case report of pulmonary alveolar microlithiasis

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Abstract

Pulmonary alveolar microlithiasis (PAM) is considered as one of the rarest diseases of respiratory system with chronicity in order. Its development is usually attributed to a genetic defect in phosphate transport mechanism, however comprehensible pathogenesis is not known, leading to accretion of calcium and phosphate units in the alveoli. These calcium-phosphate units resemble calculi, hence, called microliths. Concurrently, the name of the disease. The most common mutation associated with PAM found till date is the mutation of SLC34A2. In alveolar type II cells, the SLC34A2 gene, which codes for a sodium-phosphate co-transporter, causing microliths to accumulate and develop (owing to defective clearance). The clinical presentation of the disease has a variable spectrum. Radiology imaging remains the cornerstone of diagnosis for this disease. . A big lacuna is present in the field of research when it comes to this disease, ergo no standardized or definitive treatment at hand even today except lung transplantation.

Keywords: PAM, Microlithiasis, Phosphate transport, Alendronate

Received: 08-08-2025; **Accepted:** 16-09-2025; **Available Online**: 30-09-2025

1. Introduction

Pulmonary alveolar microlithiasis (PAM) is a rare pulmonary disease that is associated with the cumulation of hydroxyapatite microliths (calcium-phosphate concretions) within the lumen of the alveolar spaces.[1] The rarity of the disease is remarkable as less than 2000 cases have been reported globally so far.[2] Out of which, incidence for India is 0.06 per million persons.[3] It's a disease of heriditary origin, related to impairment of phosphate transport. Corut A et al in 2006 confirmed that SLC34A2 gene mutations are responsible for the defective sodium-dependent phosphate transport in the lungs, hence leading to accumulation of microliths, rich in calcium phosphate as a consequence.[4] 27 types of these gene mutations have been identified related to the phenotype this disease.[5] The clinical course of this disease exhibits a variable spectrum, manifesting diversity in signs and symptoms. A myriad of patients are discovered due to incidental findings on chest radiograph with disparate complaints to the hilt. Chest imaging (radiography and high resolution computed tomography) with genetic testing remain the bedrock for the diagnosis of PAM.[6] Some serological tests can also be used as an adjunct to better diagnosis like serum levels of Surfactant protein (SP)-D.[7] Sputum analysis is also considered critical as microliths can be anticipated, but it's not a definitive finding.[8] In addition to that transbronchial forceps biopsy, transbronchial cryobiopsy and surgical lung biopsy, have been obtained in some cases showing granular and nodular pleural surface with fibrous and calcified areas, with relevance to Von-Kossa stain.[9] There's an absence of specific treatment options for PAM due to limited trials assesing efficacy of pharmacological therapies in it. Though from the available data, empirical therapies like bisphosphonates, oral steroids, inhaled steroids and sodium thiosulphate have been used. Supportive management by low-phosphate diet[10] and whole lung lavage[11] have a very limited role. Lung transplantation is the only proven resort for advanced PAM.[12-16]

2. Case Report

A 23-year-old lactating mother, a homemaker by occupation, with no underlying comorbidities presented to the out-patient department with complaints of intermittent, dull-aching, non-radiating type of chest pain over bilateral infraclavicular and

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http://doi.org/10.18231/j.ijirm.12789.1959320591

interscapular areas with dyspnoea on exertion which progressed from mMRC grade 0 to grade 2 over the course of one month. She had no history of cough, haemoptysis, fever, wheezing, syncope-like features, paroxysmal nocturnal dyspnoea, orthopnoea and palpitations. She had no constitutional symptoms of weight loss or decreased appetite. She had a significant history of acid reflux since two years for which she had been taking over-the-counter antacids. On asking, no significant past or family history was noted. Clinical examination revealed pulse rate of 102/min, respiratory rate of 22/min, blood pressure of 130/100 mm Hg with SpO_2 at room air of 92%. On examination of the respiratory system, auscultation revealed vesicular breath sounds of decreased intensity with end inspiratory fine crackles predominantly in bilateral supraclavicular, infraclavicular, axillary, infraaxillary and infrascapular areas. Cardiovascular system examination was unremarkable.

On investigation, complete blood count and biochemical profile came to be normal. Sputum analysis came negative for microliths and acid-fast bacilli. Serum rapid testing for human immunodeficiency virus was negative. The chest radiograph revealed diffuse reticular opacities of high density with a symmetrical and bilateral micronodular pattern (**Figure 1**). These findings were confirmed by a high resolution computed tomography (HRCT) scan of chest (**Figure 2a**), which revealed diffuse calcification along the interlobar septa and subpleural regions in the lower pulmonary regions, with ground-glass attenuation and septal thickening in between resembling a 'sandstorm appearance' (**Figure 2b**). Multiple cysts along the subpleural line were identified as causing a fade black pleural line sign. Spirometry showed moderate restriction.

The patient underwent a bronchoscopy with bronchoalveolar lavage and transbronchial lung biopsy. The branches of the bronchial tree were all patent. BAL showed alveolar macrophages with giant cells with no microliths. The histology findings revealed scattered calcific foci (**Figure 3**) in lung parenchyma with lymhocytic infiltrates in the background, on H&E staining.

The electrocardiogram and echocardiography were unremarkable. Pulmonary function tests were not performed due to history of Lower segment caesarean section (LSCS) 3 weeks back. 6 minute walk distance was 450 metres with no desaturation.

A DNA sequencing analysis of whole coding regions of *SLC34A2* was performed pro bono showing a genotype with a homozygous c.1402-1404delACC mutation in exon 12 of the *SLC34A2* gene. Its association with PAM is not well-established but given the structure of the mutation it was considered very likely that this mutation plays a role in the disease of the patient.

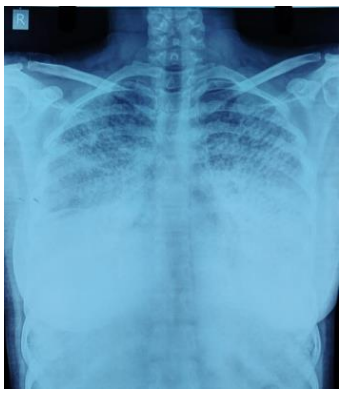

Figure 1: Chest radiography (postero-anterior view) showing diffuse reticular opacities of high density with a symmetrical and bilateral micronodular pattern.

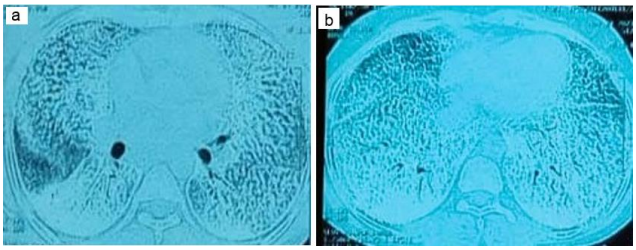

Figure 2: a: HRCT chest findings (middle lobes); **b:** Typical "Sandstorm appearance" on HRCT with interlobular septa thickening with diffuse calcification in nodular pattern (lower lobes).

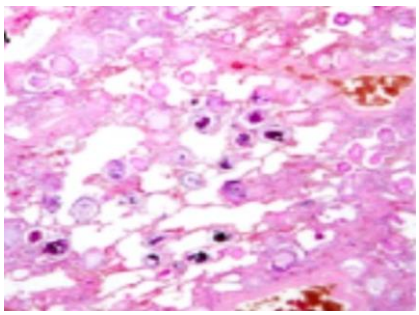

Figure 3: Histological findings showing basophilic calcific foci

Based on all the findings, a diagnosis of Pulmonary alveolar microlithiasis was made and the patient was started on Oral Alendronate (70 mg/week) with some dietary restrictions (low-phosphate diet). Follow-up was done after six months and the patient was doing symptomatically better. The patient was walking uphill with no dyspnoea, though still experienced mild dyspnoea on strenuous exercise (mMRC grade 0). There was no development of any new symptom. The patient looked good overall clinically. On examination, the intensity of breath sounds had improved with persistence of end inspiratory fine crackles predominantly in bilateral supraclavicular, infraclavicular, axillary, infraaxillary and infrascapular areas. A High-resolution computed tomography (HRCT) scan was done at the follow-up, showing no changes when compared to the first HRCT done at the presentation, implying that there was no progression of disease over the

course of time after alendronate was started. Lung transplantation was advised along with family counselling.

3. Discussion

Pulmonary Alveolar Microlithiasis is a very out of the common, chronic disease of variable clinical spectrum described as accumulation of calcium-phosphate microliths, of around 1-2 microns, in the alveoli attributing to a defective phosphate transport mechansism, though very unconvincing evidences of the etiopathogenesis.[17]

The rarity of the disease in evident globally as less that thousand cases were reported till June 2018 , out of which only 0.06% were from India (2). The most repeated gene mutations associated were s SLC34A2 (solute carrier family 34 member A2) gene mutations, with no age or gender paramountcy.[18]

With lack of homogeneity in the clinical presentation, the diagnosis for PAM is strenuous. In addition to that, a gradiational diagnosis scheme is absent for this disease leading to an obscure approach in management of PAM. Association of clinical finding with radiological confirmations stay as the main track way for its diagnosis. Due to recent advances, genetic sequencing has helped in more convalescent approach but it still stays inaccessible to majority, especially in India.

Hence, radiological appearances like micronodular calcifications, reticular opacities, sandstorm appearance (HRCT), interlobular septal thickening (HRCT), etc give a very satisfactory evidences for PAM,[19] like in this case of ours. Lung biopsy or BAL analysis can help as a supplement in diagnosing a case of PAM effectively.

There is a big lacuna in the research field when it comes to PAM. Consequently, there is lack of definitive treatment but there are substantiates exhibiting use of empirical therapies but not very proficient.[20] The role of bisphosphonates in management of PAM is uncertain as usually steroids are used as an adjunct with them but, in this case monotherapy proved to be helpful for the patient as after two month follow-up, the patient was symptomatically better. Even so, lung transplantation being the only terminus.[21]

4. Conclusion

Pulmonary alveolar microlithiasis is a rare disease with no definitive treatment yet. Chest imaging remains key to diagnosis. Genetic counselling and affordable DNA analysis need to be principal, as finer awareness of aetiology and genotype–phenotype correlation may help to develop specific treatment consequentially. There is a void in the research which can be filled by trials evaluating the clinical spectrum in PAM and assessing efficacy of different pharmacological therapies. Strengthening the scaffolding of research considering PAM, especially for meticulous diagnosis and management, is crucial as there are various challenges when it comes to its pinpoint diagnosis like the late presentation of the disease, inconsistent clinical spectrum of symptoms, unavailability of affordable diagnostic tests, lack of knowledge about the genetics of the disease and awareness about course of PAM even among medical fraternity. There are very few diseases in today's day and age that lack specificity when it comes to stewardship and PAM is one of them. Eclectic treatment plans are used like shots in the dark with exiguous results. Hence, a substantial system needs to be developed for the diagnosis and treatment of Pulmonary Alveolar Microlithiasis.

5. Contributors

SM was responsible for conception of article, reporting, acquisition of data or analysis, interpretation of data and presentation of data. BS was responsible for guiding through the process of case management. VH and MMV were responsible for planning and conduct.

6. Patient Consent for Publication

Obtained.

7. Source of Funding

The authors have no funding for this specific report from any funding agency in the public, commercial or not-for-profit sectors.

8. Conflict of Interest

None declared.

9. Acknowledgment

None.

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Cite this article: Malik S, Shivalingaiah B, Hemraj V, Vadakkan MM. Sandstorm lung: A rare case report of pulmonary alveolar microlithiasis. *IP Indian J Immunol Respir Med*. 2025;10(3):158-161.