

Original Research Article

## **Pulmonary Alveolar Microlithiasis: A Retrospective study**

Narendra Kumar Narahari<sup>1</sup>, Sudhir Kumar Vuhini<sup>2</sup>

<sup>1</sup>Assistant Professor, Department of Respiratory Medicine, Nizam's Institute of Medical Sciences, Hyderabad, India

<sup>2</sup>Associate Professor, Department of Transfusion Medicine, Nizam's Institute of Medical Sciences, Hyderabad, India

### **\*Corresponding author**

Sudhir Kumar

Email: [vujhini07@yahoo.com](mailto:vujhini07@yahoo.com)

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**Abstract:** Pulmonary alveolar microlithiasis (PAM) is a rare disorder of uncertain etiology which is present world-wide with both sporadic and familial occurrence. The clinical diagnosis of PAM remains challenging because of its rarity worldwide. It is often diagnosed incidentally following a chest radiograph and confirmed by transbronchial lung biopsy or open lung biopsy. PAM is an orphan disease and should always be considered in the differential diagnosis of lung conditions which cause striking clinico-radiological dissociation. The present study is a retrospective study done in our institute over a period of three years, with an aim of understanding the clinical, radiological, diagnostic and therapeutic aspects of this uncommon disease. We discuss all the cases with a review of literature.

**Keywords:** Pulmonary alveolar microlithiasis, calcispherites, sand storm appearance, crazy paving pattern, lung transplantation

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### **INTRODUCTION:**

Pulmonary alveolar microlithiasis (PAM) is a rare disorder characterized by widespread laminated calcispherites in the alveolar spaces in the absence of any known disorder of calcium metabolism [1]. It is an autosomal recessive disease with a high penetrance caused by mutation of the SLC34A2 gene encoding the type IIb sodium phosphate co-transporter in alveolar type II cells [2]. This inherited metabolic abnormality leads to defective phosphate homeostasis in the alveoli. The inability to clear phosphate from the alveolar spaces leads to formation of calcium containing bodies also referred as calcispherites or microliths [3].

A total of 1022 cases were reported in the literature till December 2014, with highest number of cases originating from Asia followed by Europe. Turkey has the highest number of reported cases of PAM followed by China and Japan. [3] A total of 80 cases are reported in literature from different regions of India, as of December 2014. [3] PAM may affect people of any age, however affected individuals usually become symptomatic in the third or fourth decade of life. The disease is both sporadic and familial in occurrence [1].

The clinical diagnosis of PAM remains challenging because of its rarity worldwide. It is often diagnosed incidentally following a chest radiograph and confirmed by transbronchial lung biopsy or open lung biopsy. This is a retrospective study done in our institute over a period of three years, with an aim of understanding the clinical, radiological, diagnostic and therapeutic aspects of this uncommon disease.

### **METHODS:**

We retrospectively reviewed the medical records of all patients admitted in the respiratory unit of our hospital and diagnosed as Pulmonary alveolar microlithiasis (PAM) over a period of 3 years from 2012-2015.

### **RESULTS:**

The demographic data, clinical presentation, radiological features, mode of diagnosis, hospital course and management of patients presenting with PAM are summarized in Table 1. A total of three patients (females) were diagnosed with PAM during the study period.

**Table 1: Summary of the patients presented with pulmonary alveolar microlithiasis over a period of three years**

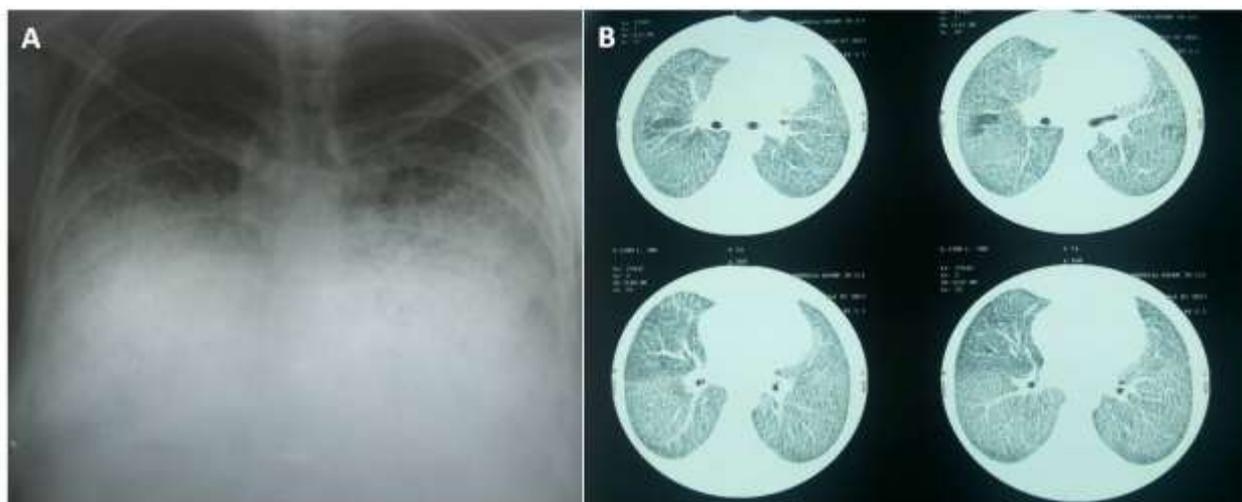
Sno	Age/sex	Clinical history	Imaging features	Mode of diagnosis	Treatment and follow up
Case 1	20 years/F	SOB, dry cough of 6 months duration ABG:hypoxic respiratory failure	Chest x ray: bilateral, diffuse sand storm pattern more at bases HRCT chest: extensive crazy paving pattern	TBLB	Long term oxygen therapy. On regular follow up
Case 2	14 years/F	SOB, dry cough of 2 years duration	Chest x ray: bilateral, diffuse micro nodular opacities more at bases HRCT chest: crazy paving pattern and ill-defined nodules within the ground glassing	TBLB	Symptomatically stable. On regular follow up
Case 3	40 years/F	SOB, dry cough of one year duration. ABG: hypoxic respiratory failure	Chest x ray: bilateral diffuse and symmetric nodular opacities HRCT chest: diffuse calcific nodular densities	TBLB	Advised long term oxygen therapy Lost to follow up.

F: Female, SOB: Shortness of breath, TBLB: Transbronchial lung biopsy, HRCT: High resolution chest tomogram, ABG: Arterial blood gas analysis

**Case 1:**

A 20 year old female presented to our institute with complaints of dry cough and progressive shortness of breath of six months duration. Her general physical and systemic examination was unremarkable. Her vitals revealed mild tachypnea with oxygen saturation of 86% on room air. Her chest radiograph revealed bilateral diffuse and symmetrical reticulo-nodular opacities

which were dense over the bases resembling sand storm pattern. (Figure 1A) HRCT of the chest revealed bilateral extensive crazy paving pattern with subpleural sparing. (Figure 1B) Histopathological examination of transbronchial lung biopsy specimen revealed lamellated calcified concretions within the alveolar spaces, consistent with diagnosis of pulmonary alveolar microlithiasis.



**Fig 1: (A) Bilateral diffuse and symmetrical reticulo-nodular opacities which were dense over the bases resembling sand storm pattern. (B) Bilateral extensive crazy paving pattern with sub pleural sparing.**

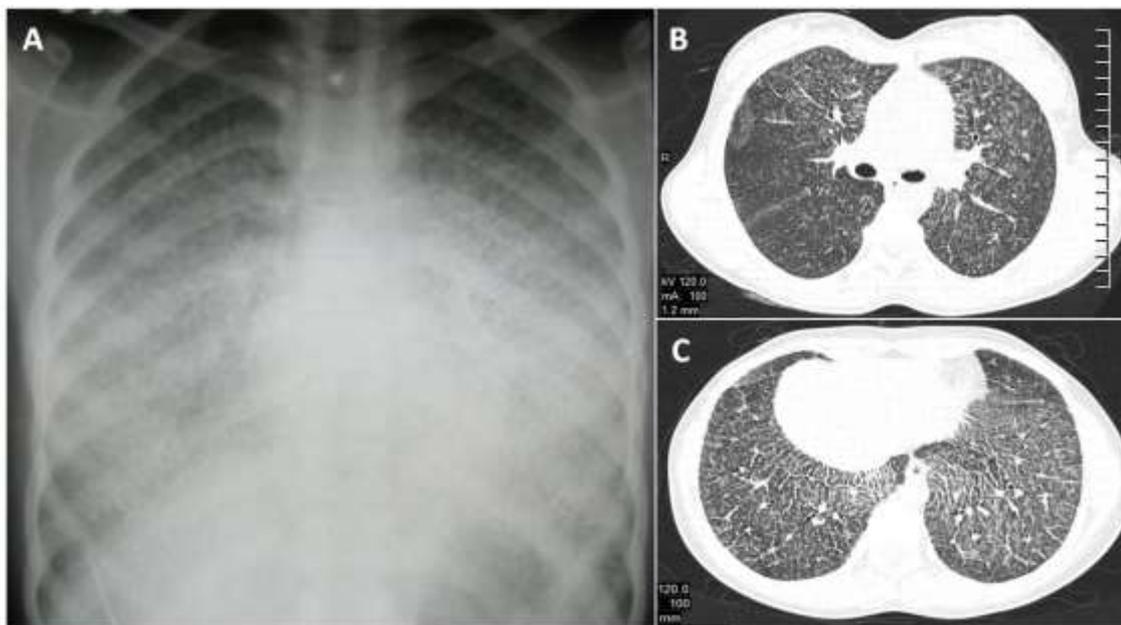
**Case 2:**

A 14 year-old female presented with shortness of breath on exertion, which was gradually progressive and dry cough of 2 year duration. She was diagnosed as sputum negative pulmonary tuberculosis and was given six months of anti-tubercular therapy (ATT) by a local medical practitioner. She was referred to our institute in

view of persistent symptoms and radiological worsening. She was thin built and ill nourished. Auscultation of the lungs revealed bilateral basal crackles. Chest radiograph (Figure 2A) showed bilateral diffuse micro nodular opacities distributed all over the lung fields, predominantly over the bases and obliterating diaphragm and cardiac borders.

Her sputum was negative for acid fast bacilli (AFB) and fungal stains. Arterial blood gas (ABG) analysis was within normal limits. High resolution computed tomogram (HRCT) of the chest revealed bilateral diffuse ground glassing along with smooth interlobular septal thickening suggestive of crazy

paving pattern. HRCT also showed ill defined nodules within the ground glassing. (Figure 2B&C) Bronchoscopy was done and bronchial washings were negative for AFB and fungal cytopathology. Transbronchial lung biopsy revealed the diagnosis of pulmonary alveolar microlithiasis.



**Fig 2:(A) Bilateral diffuse micro nodular opacities distributed all over the lung fields, predominantly over the bases and obliterating diaphragm and cardiac borders. (B&C) Bilateral diffuse ground glassing along with smooth interlobular septal thickening suggestive of crazy paving pattern. HRCT also showed ill-defined nodules within the ground glassing.**

**Case 3:**

A 40 year old female was referred to our institute with complaints of progressive breathlessness of one year duration. Her general physical and systemic examination was unremarkable except for mild tachypnea and SpO<sub>2</sub> of 88% on room air. She had a history of ATT for a period of six months earlier and was referred to us in view of persistent symptoms.

Pulmonary function test (PFT) showed restrictive pattern. Chest radiograph (Figure 3) showed bilateral diffuse and symmetric nodular opacities. HRCT of the chest revealed diffuse calcific nodular densities. A transbronchial biopsy of the lung parenchyma demonstrated calcispherites within the alveolar spaces which confirmed the diagnosis of pulmonary alveolar microlithiasis.



**Fig 3:Bilateral diffuse and symmetric nodular opacities**

## DISCUSSION:

Pulmonary alveolar microlithiasis (PAM) is a rare disorder of uncertain etiology which is present world-wide with both sporadic and familial occurrence [4]. The clinical course of PAM is highly variable ranging from totally asymptomatic to respiratory failure [5]. The first symptom to develop is shortness of breath on exertion followed by dry cough. Occasionally patient may expectorate microliths in sputum [6]. As the disease progresses, respiratory insufficiency may develop along with cyanosis and cor pulmonale may be seen. Death may occur as a result of cardio-respiratory failure [7]. The disease may remain static, while in some it progresses to pulmonary fibrosis, respiratory failure and cor pulmonale requiring lung transplantation [8, 9]. All the three patients in our study presented with dyspnea on exertion and dry cough. The disease remained static in case 2, but the other two cases it was progressive with hypoxic respiratory failure but none had cor pulmonale.

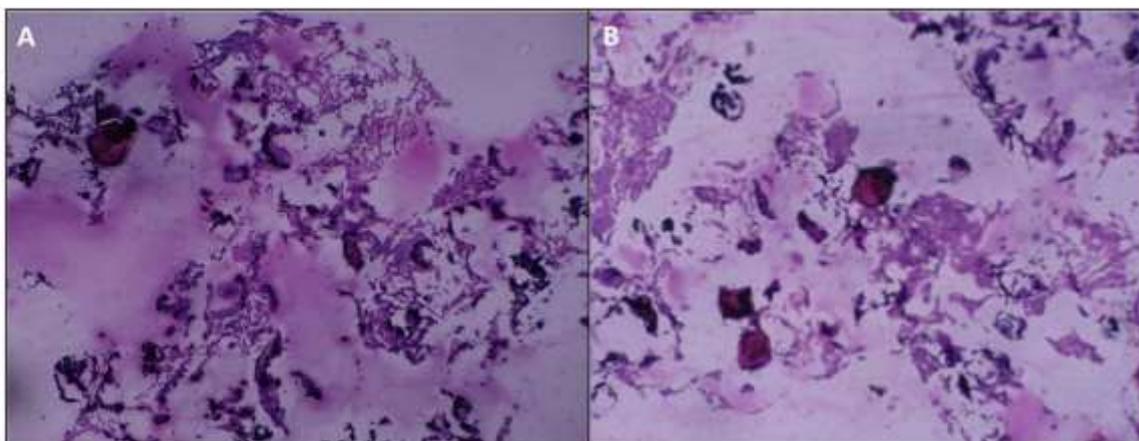
Chest radiographs usually reveal diffuse, scattered, bilateral areas of micro nodular calcifications ("sand storm") that predominate in the middle and lower lung areas [10]. The hall mark of PAM is clinico radiological dissociation; with most of the patients remaining asymptomatic despite wide spread sand storm appearance in the chest radiograph [11]. The heart borders and diaphragm are usually obliterated in advanced stages due to extensive microliths. Black pleura sign is classical of PAM, which is demonstrated as an area of increased translucence between the lung parenchyma and the ribs [10]. The typical HRCT findings in PAM are so characteristic that, when present, can rule out the need for lung biopsy [12]. HRCT of the chest usually reveals diffuse ground-glass opacities throughout both lungs, associated with confluent and diffuse calcified nodules [13]. The most frequent findings reported in literature include diffuse ground glass attenuation and subpleural linear calcifications. Other findings include: small parenchymal nodules; calcifications along interlobular septa, sometimes determining the crazy paving pattern; small subpleural nodules, nodular fissures, subpleural cysts and dense consolidations [12, 14]. Ground-glass attenuation in the HRCT can be explained by filling of the alveolar air spaces by tiny microliths. Septal thickening is due to deposition of calcific nodules along the interlobular septa and within the peripheral lobular parenchyma adjacent to the septa [12]. Two of our cases had crazy paving pattern in HRCT of the lungs as

suggested by EL Gasparetto *et al.*; PAM should be considered in the differential diagnosis of lung lesions that present with a crazy-paving pattern on HRCT [13].

Radiologically, it is often difficult to define the calcium density in the nodules, due to their small dimensions. However, when the microliths converge to form parenchymal consolidation, the calcium density can be better characterized, and is higher than soft tissues [10, 14]. Calcium deposition in the alveoli generally starts in the lower lobes owing to the greater thickness of tissue in these areas and also due to relative higher blood supply and takes the entire lung over a period of years, with involvement to the middle thirds and then to the upper portions of the lungs [7,12].

In the early stages of PAM, gas exchange is usually normal as the interlobular septae remain intact. However as the disease progresses, microliths gradually fill the alveolar spaces and impairs gas exchange [11]. As the disease progresses, the number and size of the calcific deposits grown even more, and there is intense calcification of the interstitium and sometimes the pleural serosa, which makes the lungs appear almost entirely opaque also referred as white lungs. The extent and severity of PAM generally depend on the patient's age and the speed of progression of the disease [11]. Pulmonary function tests (PFT) are near normal, however with progression of the disease restrictive pattern develops with impairment of gas exchanges [11]. PFT of the three cases showed moderate restrictive pattern. Demonstration of microliths in broncho-alveolar lavage [7] can be seen in some cases. The calcific nature of the lesions can be confirmed by bone scintigraphy which shows diffuse uptake of technetium-99 in the lungs [15].

The definitive diagnosis of PAM is by transbronchial lung biopsy or open lung biopsy [5, 7]. Numerous large intra-alveolar calcific bodies (microliths) which are 0.01 to 3 mm in diameter are revealed in the histopathological examination. These microliths have concentric lamellated appearance suggesting that they grow by addition of successive layers [16]. All the three cases in our study are diagnosed by transbronchial lung biopsy (Figure 4&5). Differential diagnosis includes many conditions like miliary tuberculosis, metastatic pulmonary calcifications, pulmonary alveolar proteinosis, histoplasmosis, pneumoconiosis, varicella pneumonia, sarcoidosis, metastases from thyroid neoplasm [3, 11].



**Fig 4:(A)**This shows a low power view of lung tissue with basophilic calcified material. (H and E x100).  
**(B)**Higher magnification of the same with numerous foci of calcifications. (H and E x 200)



**Fig 5:Calcispherite under higher magnificationshowing lamellated appearance of the calcified bodies**

Given the striking dissociation between the radiological appearance and clinical presentation of PAM, the diagnosis is often delayed and misunderstood as miliary tuberculosis in the endemic areas. Physicians tend to suspect tuberculosis more readily, due to the lack of knowledge and awareness of PAM with the similar imaging features, despite different clinical manifestations [3]. PAM was wrongly diagnosed as miliary tuberculosis and ATT was administered in more than 72 cases as reported by castenella *et al.*; [3]. Similar associations were also reported by Ucan *et al.*; where PAM is initially misdiagnosed as miliary tuberculosis [17]. Two of the cases in our study were earlier diagnosed as pulmonary tuberculosis and started anti tubercular therapy (ATT). They were later referred to us as these patients did not respond to ATT and there was worsening of radiological pattern. So, histopathological examination of the lung tissue remains gold standard in the definitive diagnosis. Lack of awareness about the disease and lack of diagnostic facilities like bronchoscopy in every centre and expertise in the bronchoscopic technique are main diagnostic challenges. However characteristic

radiological pattern in the correct clinical context can rule out the need for biopsy in familial cases of PAM during screening procedures [12]. Because characteristic chest CT findings correlate well with specific pathological findings, the diagnosis of PAM can be confidentially made on the basis of the typical radiological pattern [11].

Currently there is no effective therapy for PAM. Corticosteroids, chelating agents, and bronchoalveolar lavage are ineffective and have demonstrated no benefit, and the role for the use of bisphosphonates remains to be proven [3,11]. End stage lung disease due to PAM may require bilateral lung transplantation and was reported to be successful in few cases with good post-operative results [9, 18]. Lung transplantation has been beneficial in patients with severe respiratory failure and right heart failure who require supplemental oxygen therapy [11]. All the three patients in the study were offered symptomatic and supportive treatment. One of the patients was lost to follow up. The other two were in regular follow up with long term oxygen therapy.

## CONCLUSIONS:

PAM is an orphan disease and should always be considered in the differential diagnosis of lung conditions which cause striking clinico-radiological dissociation. The progression of the disease is highly variable and may take years to manifest clinically and succumb to fatal respiratory failure and corpulmonale. As PAM carries a very poor long term prognosis, further research of its etiology and pathogenesis are required along with long term follow up studies to improve outcomes. This may help in near future to avoid errors in diagnosis and to plan an effective management strategy to arrest the progression of the disease in the early stage. Recent genetic study showed that remedies that target phosphate metabolism rather than calcium metabolism may be beneficial for the treatment of PAM [2].

## LIMITATIONS:

This is a single departmental study with retrospective analysis of a small group of patients. Therefore the data presented here may not be representative of the larger population group.

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