Pulmonary alveolar microlithiasis: A report of two unique cases

Haneen Al-Maghrabi a, Ghadeer Mokhtar a,b, Jaudah Al-Maghrabi a,b, Abdelrazak Meliti a,b,*

a Department of Pathology, King Faisal Specialist Hospital and Research Centre, Jeddah, Saudi Arabia
b Department of Pathology, Faculty of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia

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ABSTRACT
Pulmonary alveolar microlithiasis (PAM) is an inherited autosomal recessive disease. PAM is classically characterized by calcium phosphate deposition within alveolar airspaces due to SLC34A2 (solute carrier family 34 member 2) gene mutation located on chromosome 4p15.2. Such cellular genetic mutation would lead to a defect in the sodium-phosphate cotransporter channel located in alveolar epithelial cells type-II. Ultimately, it would result in a malfunction of alveolar epithelial cells and the failure of these cells to clear-up the released phosphorous particles in the cellular surfactant recycling. PAM is usually diagnosed in adulthood, frequently notable in the third and fourth decades of life, occasionally can be associated with more severe clinical presentation and radiological findings.

Nevertheless, the disease could manifest itself in the pediatric age group, which either shows non-specific signs and symptoms or be exclusively asymptomatic. Histopathological examination is the gold standard for the PAM diagnosis. Genetic counseling and testing might benefit the patient’s family members. Herein, we present 2 cases of PAM in the pediatric age group, along with their clinical history, presentation, radiological studies, and histopathological findings, as well as a brief literature review.

1. Introduction

Pulmonary alveolar microlithiasis (PAM) is caused by calcium phosphate microliths (calciospherites) deposition in pulmonary alveolar spaces [1]. PAM is an autosomal recessive disease caused by a genetic mutation in solute carrier family 34 members 2 (SLC34A2) located on chromosome 4p15.2, which is responsible for encoding sodium-phosphate cotransporter type IIb located in type II alveolar pneumocytes. SLC34A2 plays an essential role in phosphate ions transport from pulmonary alveoli into alveolar type II pneumocytes. SLC34A2 mutation will cause alveolar type II dysfunction that would lead to cellular phosphate accumulation and microliths deposition in pulmonary alveolar spaces [2,3]. PAM show a slight female predominance, commonly diagnosed in Asian and European population. Patients with PAM may initially be asymptomatic and are discovered incidentally after careful radiological examination for another medical purposes. The typical radiographic findings on chest X-ray include scattered micronodular pattern giving “sandstorm-like” appearance and calcification widely distributed throughout the lung parenchyma. Furthermore, loss of sharp borders between heart, diaphragm, and pulmonary vascular tree as a result of the dense calcifications. Middle and lower lung zones are more likely to be involved.

Interestingly, the severity of the disease radiologically may not conform to the clinical presentation. Patients may present with shortness of breath, dry cough, chest pain, and asthenia. As PAM progressed, the patient can present with hemoptysis and pneumothorax [4]. Cyanosis and clubbing of fingers have been reported. A chest computed tomography (CT) scan is a preferred testing modality, which demonstrates the sand-like appearance of calcifications in the lung parenchyma as well as subpleural and peri-bronchial zones. Ground glass appearance is commonly seen in pediatric patients [5]. The definite diagnosis can be confidently reached through a combination of clinical findings, radiological features, and histopathology tissue examinations. In this study, we present two cases of PAM in the pediatric age group.

2. Case presentation

2.1. Case 1

A 3-year-old female patient with a known clinical history of
recurrent chest infections. The patient admitted to the emergency department complaining of recurrent, continuous, progressive dry cough. No other associated signs and symptoms, no evidence of fever. Her chest X-ray PA (posteroanterior) and lateral views revealed widespread nodular shadowing of both lung fields. They were rather dense, most likely representing tiny calcification within the alveoli. The appearance was compatible with pulmonary alveolar microlithiasis. High-resolution CT scan was performed for the patient for further evaluation utilizing standard technique at 1 mm slice thickness without IV (intravenous) contrast administration in lung and soft tissue window, which demonstrated bilateral innumerable dense centrilobular opacities involving the upper and lower lobes of the lung associated with an interlobular interstitial thickening. These densities were of uniform size with no evidence of macronodules or masses (Fig. 1A and B). No definite pleural and pericardial effusion. The CT scan findings concluded that changes were consistent with alveolar microlithiasis with no CT evidence suggestive of pulmonary consolidation. A small lung wedge resection was received at the histopathology lab, measured 3.2 × 1.2 × 0.7 cm. Histopathologic examination confirmed the presence of numerous lamellated calcified structures within alveolar spaces consistent with pulmonary microlithiasis (Fig. 1C and D). Background of mild non-specific interstitial inflammation was seen. The patient lost her hospital follow up appointments and did not show up after then.

2.2. Case 2

A 9-year-old boy known case of bronchial asthma with frequent hospital admissions for pulmonary support and management of pulmonary hypertension. His condition was medically controlled on Lasix and Sildenafil for one month. He stopped Sildenafil for two weeks and continued on Lasix. He was transferred from an outside hospital as a case of pulmonary hypertension with suspicion of pulmonary veno-occlusive disease (PVOD). On admission, he was conscious, alert, and vitally stable. No pallor, cyanosis, fingers clubbing, or jaundice. Lymph nodes were impalpable, and the rest of his general physical examination was unremarkable. Chest X-ray performed and revealed diffuse bilateral interstitial markings. No consolidation, pleural effusion, or pneumothorax were seen. Cardiomegaly and silhouette was within normal limits. The osseous structures appeared unremarkable. Non-enhanced CT scan of the chest was performed with no prior study for comparison. The main tracheobronchial tree was patent. Both lungs demonstrated patchy areas of ground-glass opacification, primarily involving the upper lobes and right middle lobe with associated interlobular septal thickening and scattered centrilobular nodules seen bilaterally (Fig. 2A). There was peribronchial interstitial thickening. A tiny suspicious white opacity located at the middle lobe of the right lung, not continuous with the air spaces and their branches (Fig. 2B). No pleural or pericardial effusion could be detected. No bony lesions were seen. The final CT impression was ground-glass and interlobular septal thickening with associated centrilobular nodules suspicious of pulmonary veno-occlusive disease. The patient referred to pediatric surgery for an open lung biopsy. Histopathologic examination revealed extensive widespread intra-alveolar accumulation of minute calcified lamellated structures (Fig. 2C and D). The final diagnosis was pulmonary alveolar microlithiasis. At the time of patient discharge, he was healthy, vitally stable, scheduled to follow up regularly with a pediatric pulmonologist.

3. Discussion

PAM is considered a unique, rarely diagnosed inherited genetic lung disease, which is characterized by intra-alveolar calciphosphates deposits made up of calcium and phosphorus. PAM shows no significant gender predilection. Although some studies reported a slight female predominance. More than 1.000 reported cases globally of PAM, mostly from
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Asia, particularly Turkey, China, Japan, and India, followed by Italy and the USA [3,6]. PAM patients are typically present during their third to fourth decades; nevertheless, PAM has been reported in the pediatric age group [7]. One-third of PAM cases are familial, primarily autosomal recessive inheritance pattern. Studies reported 35–50% of inherited PAM cases were found in Turkey, Japan, and Italy [2]. PAM occurs due to an inactivating genetic mutation in the SLC34A2 gene located on chromosome 4p15 exon 13. SLC34A2 gene is expressed predominantly in type II alveolar cells, mammary glands, ovaries, epithelial cells of small bowel, pancreas, kidney, liver, testes, prostate, and placenta [7]. SLC34A2 gene is considered crucial in the lungs, as it purely acts as a sodium-particles dependent-phosphate transporter. Its physiological function is considered imperatively attributable to its role in phosphate clearing from alveolar spaces through phosphates ions transportation into type II pulmonary alveolar cells. Typically, the wild-type gene controls the transport phosphate into pulmonary type II cells with the presence of sodium ion (Na+) ratio 3Na+ :1HPO4−2. Unlike the mutated SLC34A2 gene, it ultimately leads to a deficiency in alveolar type II cellular phosphate uptake [8] and gradual accumulation of intra-alveolar calcium microliths. SLC34A2 gene mutation has been found on multiple exons. Studies have shown that PAM patients from Turkey exhibit variable exons involvement, patients from China demonstrate mutated exon 8, while patients from Japan found to have mutated exons 7 and 8 [2]. Some studies reported PAM occurrence among families in horizontal patterns affecting cousins and siblings, more frequently than vertical patterns affecting parents and children [1]. (Lungs affected with PAM will be enlarged, heavy and dusky on gross examination). Serial sectioning of the affected lung tissue will reveal diffuse fine granular cut surface, calcification with gritty sensation [3]. Microscopic examination is the gold standard for diagnosis; it demonstrates classical intra-alveolar lamellated calcified microliths, composed of Ca3 (admixed with other minerals) others such as Fe, Zn, Mg, CaCO3, Al, and SiO2 in small amounts [9]. PAM is considered an indolent irreversible disease with long progression and late clinical presentation. Microliths usually progress over a long period of time. The pulmonary function tests in the early stages of the disease are usually within normal limits. However, restrictive pulmonary dysfunction develops when microliths occupied a large volume of functional lung parenchyma. Eventually results in hypoxic changes, increase CO2 arterial level, pulmonary fibrosis, and respiratory failure. Serum phosphate and calcium levels are usually within normal limits. Some PAM patients may have elevated levels of serum monocyte chemotactic protein-1, surfactant protein (SP)-A, and SP-D, which can be used for patients’ follow up and to monitor the level of progression [10]. Patients with PAM may have extra-pulmonary calcium deposition, particularly in testes, which can result in testicular atrophy, azoospermia, or tumorigenesis. Other extra-pulmonary sites of involvement, such as kidney, gall bladder, lumbar sympathetic chain, and cardiac involvement, had been reported. Studies suggested that the likelihood of extra-pulmonary manifestation depends on the percentage of mutated SLC34A2 gene involvement [11]. Accurate diagnosis of PAM can be established by a thorough chest radiological examination and histopathologic tissue confirmation. Genetic testing for SLC34A2 gene mutation can be used as a screening test for the family members of affected patients. Treatment in most cases remains supportive, including supplemental oxygen therapy. For patients with end-stage disease, lung transplantation is available as a last resort [12].

There are few case reports in the literature describing the efficacy of Disodium Etidronate (DE) therapy. A larger cohort and long term follow up are required to assess the beneficiary effect of (DE) [13]. Both of our cases did not receive DE therapy as one was lost during follow up and the other patient is scheduled to see a pediatric pulmonologist to explore his treatment options including DE.

Radiological differential diagnosis includes military (tuberculosis), sarcoidosis, pneumoconiosis, pulmonary alveolar proteinosis, pulmonary amyloidosis, metastatic, and dystrophic pulmonary calcifications.

Fig. 2. (A): CT scan without contrast shows diffuse ground-glass opacification primarily involving the upper lobes (bilateral) and right middle lobe with an associated interlobular septal thickening. (B): Soft tissue window of lung-CT scan reveals suspicious white opacity located at the middle lobe of the right lung, not continuous with the air spaces branches (yellow arrow). (C): (H & E; 4x) and (D): (H & E; 10x) numerous lamellated calcified structures within alveolar spaces consistent with pulmonary microlithosis.
The diagnosis of the latter can be easily attained as the patient’s clinical history would be positive for chronic renal failure. Microscopically, PAM microliths and corpora amylacea can look alike. PAM microlithiasis is more extensive as opposed to corpora amylacea. The latter may contain rings, but with no calcifications. Congo-red special stain will highlight the polarized material maltese cross pattern in corpora amylacea. Whereas, periodic acid-Schiff (PAS) stain positively in a concentric lamellated pattern around the centrally located nucleus with an amorphous or granular background.

4. Conclusion

We present two cases of pulmonary alveolar microlithiasis in the pediatric age group, a rare inherited disease due to mutation in the SLC34A2 gene. PAM diagnosis should be made on the clinical, radiological, and histopathologic confirmation. Patients with PAM may present with non-specific signs and symptoms, or be clinically asymptomatic. Severe progressive disease stages may lead to respiratory failure. Management options for PAM depend on the severity of the disease, which would include supplemental therapy, use of Disodium Etidronate (DE), and lung transplantation as a last option.

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Informed consent

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Appendix A. Supplementary data

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