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Case Report

Pulmonary alveolar microlithiasis: A case report and brief review of literature

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Abstract

Background: Pulmonary alveolar microlithiasis (PAM), a rare autosomal recessive pulmonary disease, is mainly characterized by extensive calcium phosphate microliths deposition in the alveoli. The major mutation, causing the characteristic of this disease, occurs in solute carrier family 34 members 2 (SLC34A2), which is placed on chromosome 4p15.2. SLC34A2 encodes sodium-phosphate cotransporter type IIb, NPT2b, which plays a critical role in the transportation of phosphate ions from pulmonary alveoli into type II pneumocytes.

Case Presentation: Herein, we have reported a 50-year-old male presented with recent sore throat, fever, and sweating. Radiological findings revealed bilateral micronodular pattern with diffuse ground glass attenuation in lower regions. Subsequent histologic examination of lung biopsy confirmed intra-alveolar accumulation of calculi and the diagnosis of PAM. In addition, we reviewed the literature narratively to clarify different aspects of PAM.

Conclusion: In this paper, we presented a sporadic case of PAM which was suspected with chest x-ray and confirmed by HRCT and trans-bronchial lung biopsy. We hope that it can help clinicians to be more aware of this condition and make proper diagnosis.

Keywords: Pulmonary alveolar microlithiasis, SLC34A2, Diagnostic radiology.

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Pulmonary alveolar microlithiasis (PAM), a rare autosomal recessive pulmonary disease, is mainly characterized by extensive calcium phosphate microliths deposition in the alveoli (1). The major mutation, causing the characteristic of this disease, occurs in solute carrier family 34 members 2 (SLC34A2), which is placed on chromosome 4p15.2. SLC34A2 encodes sodium-phosphate cotransporter type IIb, NPT2b, which plays a critical role in the transportation of phosphate ions from pulmonary alveoli into type II pneumocytes. The phosphate reabsorption blockage, caused by SLC34A2 mutation, will result in excessively increased concentration of alveolar phosphate which will form calcium phosphate crystals through binding with calcium (2-4). Herein we have reported a sporadic case of PAM which was suspected with chest x-ray and confirmed by high resolution computed tomography (HRCT) and histopathologic exam on trans-bronchial lung biopsy. In addition, we reviewed the literature narratively to clarify different aspects of PAM.

Case Presentation

A 50-year-old building painter, who complained of a sore throat and several episodes of fever and sweating 3 days ago, referred to Ayatollah Rouhani Hospital in Babol, Mazandaran. He had no complaints of nausea and vomiting, and his bowel movements were normal. He had no cough or sputum. He had a history of hypertension for 8 years, which had been controlled with losartan (25 mg twice a day).

There was also a family history of hypertension in his father. The patient had a social habit of smoking (20 packs/year). The vital signs of the patient on admission day were as follows: blood pressure, 100/60 mmHg; pulse rate, 84 beats per min; respiratory rate, 18 breaths per min; temperature, 36.8 °C; oxygen saturation, 95%; and fraction of inspired oxygen (FiO2), 21%. On physical examination, heart and lung auscultation was normal and no cyanosis or peripheral edema was observed. Arterial blood gas analysis, echocardiography and pulmonary function tests (PFT) showed no important abnormalities. The laboratory data on admission are demonstrated in table 1.

Table 1. Laboratory data on admission

Variables	Value	Variables	Value
WBC (per µL)	10400	**Lipase (U/L)**	25
Neutrophil (%)	85	**Procalcitonin (ng/mL)**	0.33
Lymphocyte (%)	15	**NT-proBNP (pg/mL)**	13
Hb (mg/dL)	11.8	**BUN (mg/dL)**	15
MCV (fL)	86.6	**Creatinine (mg/dL)**	1
PLT (per µL)	156000	**PT (sec)**	15.3
D-dimer (ng/mL)	847	**PTT (sec)**	27
Amylase (U/L)	56	**INR**	1.4

WBC: White Blood Cells, Hb: Hemoglobin, MCV: Mean Corpuscular Volume, PLT: Platelets, BUN: Blood Urea Nitrogen, PT: Prothrombin Time, PTT: Partial Thromboplastin Time, INR: International Normalized Ratio.

He was tested for COVID-19 and influenza with RT-PCR method which was negative for both of these infections. The chest plain films revealed a diffuse symmetric dense bilateral micronodular pattern along with interstitial reticular opacity and basal consolidation (figure 1). Based on this finding, HRCT scan was conducted, revealing diffuse ground glass attenuation and septal thickening, more pronounced in lower pulmonary regions, with high attenuation lesions due to calcifications along the interlobar septa and subpleural regions.

The HRCT also demonstrated thickening and calcification of interlobular septa and dense consolidation (figure 2). The patient underwent a fiberoptic bronchoscopy with bronchoalveolar lavage and transbronchial lung biopsy. Microscopic examination of the lavage fluid showed few multinucleated giant cells and was negative for tuberculosis or fungi, but histologic examination of lung biopsy revealed diffuse intra-alveolar accumulation of calculi consistent with the diagnosis of PAM (figure 3).

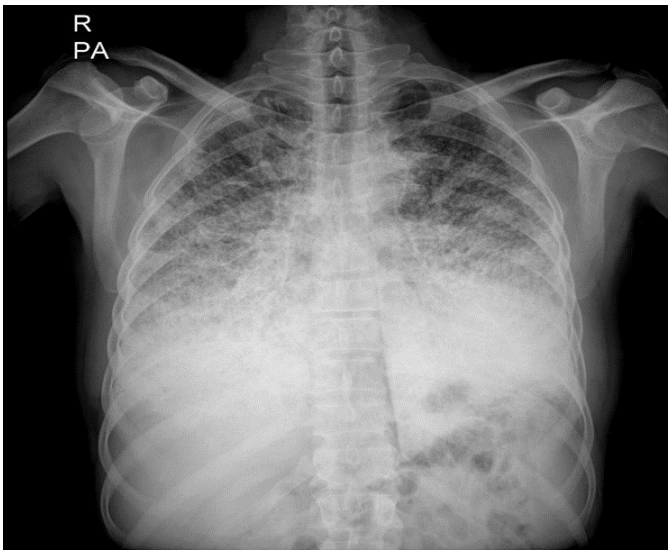

Figure 1. Chest x-ray image showed a diffuse symmetric dense bilateral micronodular pattern along with interstitial reticular opacity and basal consolidation

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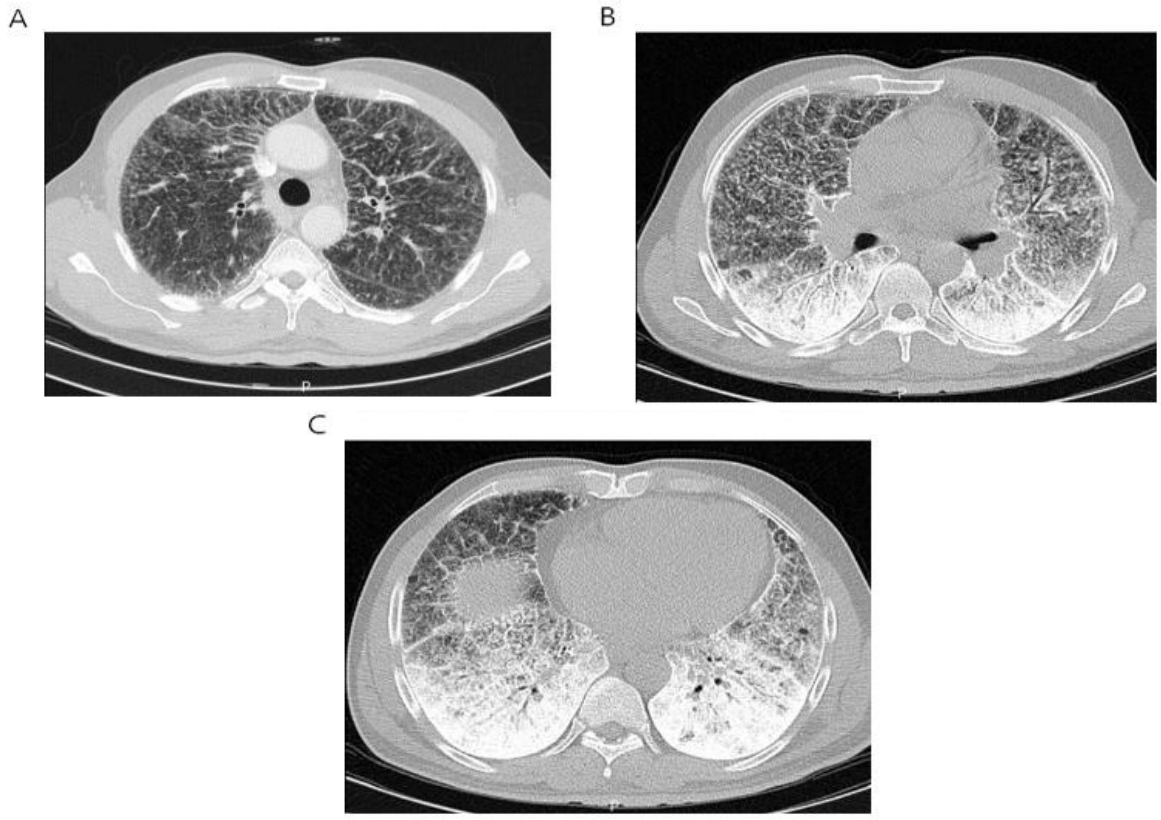

Figure 2. A, B, and C are high-resolution CT scan images showing different lung levels. They demonstrate thickening and calcification of interlobular septa and dense consolidation

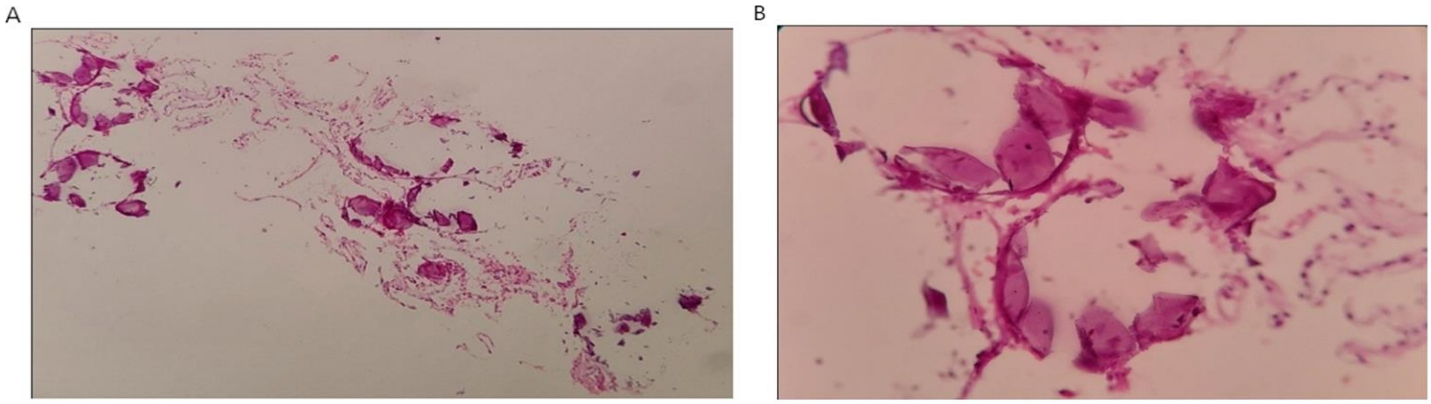

Figure 3. H&E slides of lung biopsy shows intra-alveolar accumulation of calculi called microliths; original magnifications 40x (A), 400x (B).

Discussion

As mentioned before, PAM is a rare autosomal recessive pulmonary disease, which is mainly characterized by extensive calcium phosphate microliths deposition in the alveoli. Asia (56.3%) and Europe (27.8%) have reported most of the cases. Its incidence varies from approximately 1.85 (per million) in Turkey to 0.06 (per million) in India. Nearly half of the cases are males, while females are responsible for 41%. Although PAM has been reported at any age, most of the patients are diagnosed in the second to fourth decade of their life (5). Although PAM is classified as an autosomal recessive lung disease, approximately two-thirds of patients have sporadic mutations. In their study, Castellana et al. demonstrated that in nearly all familial cases, there was a horizontal transmission, which is a support for the existence of autosomal recessive pattern, and appealingly, when more than three siblings were affected, they were generally females (3). Inactivation of the SLC34A2 gene, located on chromosome 4p15, is considered to be the main genetic disorder in PAM. Twelve

exons of this gene encode NPT2b, or also known as NaPi-IIb or NPTIIb (2, 5), which plays a critical role in the transportation of phosphate ions from pulmonary alveoli into type 2 pneumocytes. In fact, NPT2b is the only identified sodium-phosphate cotransporter expressed in the lungs. This transporter exerts its phospholipid-clearing role by the transportation of phosphate ions, produced by the catabolism of surfactant phospholipids by alveolar macrophages, into type II pneumocytes (5, 6). Insufficient or impaired function of NPT2b caused by SLC34A2 mutations results in reduced phosphate uptake by type 2 pneumocytes, which can generate intra-alveolar microliths (7). The location of SLC34A2 mutations varies in different countries. For instance, they usually congregate in exons 7 and 8 in Japanese patients or in exon 8 in Chinese cases. However, in Turkish patients the mutations have been detected on various exons (2). Unfortunately, there is no study that identifies the location of SLC34A2 mutations congregation in Iranian patients.

Given the fact that the expression of the SLC34A2 gene also occurs in another tissues like prostate, pancreas, kidneys, seminal vesicles, and liver, PAM patients could present calcifications in extrapulmonary tissues such as seminal vesicles, nephrolithiasis, and medullary nephrocalcinosis (3, 8, 9). For instance, Qublan et al. reported periurethral and epididymal calcifications of seminal vesicles which led to azoospermia (10). The patient, presented in our study, did not experience extrapulmonary disorders. In early stages of PAM, patients are usually asymptomatic or may suffer from mild symptoms like dyspnea or non-productive cough. Nevertheless, the progression of PAM varies after the diagnosis. Most of the patients experience a slowly progressive course, which finally leads to pulmonary fibrosis, corpulmonale, and respiratory failure. However, few patients remain stable and will not experience poor prognosis (11-13).

Regarding auscultation of lungs, fine crackles on both sides, basal decreased lung sounds, or normal auscultation can all be discovered in PAM patients (14). The identification of typical findings in radiology and histopathology usually establishes the diagnosis of PAM. However, radiological features depend on the severity of the disease. PAM patients usually represent bilateral, sand-like micronodules with calcific density, on chest radiography. These micronodules have a sandstorm appearance and are usually located in the lower and middle zones of lungs. Subtler features can be seen on HRCT, such as bilateral non-calcified micronodules in the early stages of an asymptomatic pediatric case of PAM. Nonetheless, these lesions can slowly progress to numerous micronodules with calcific density, as the disease progresses. They continue to grow in size and density and gather together to form ground-glass opacities, which is often associated with a crazy paving appearance. bilateral subpleural cystic alterations and apical bullae are other typical findings on HRCT or chest radiography (13). To confirm the diagnosis, lung biopsy or bronchoalveolar lavage could be applied, which could show microliths that are often periodic Acid-Schiff positive and constructed of a central nucleus which is surrounded by centric calcareous lamellae (13). Conditions like sarcoidosis, pulmonary alveolar proteinosis, miliary tuberculosis, post-varicella pneumonia, infectious pneumonias, amyloidosis, hemosiderosis, pulmonary silicosis, metastatic pulmonary calcifications, and dendriform ossification include in the differential diagnosis of PAM (15). Dendriform pulmonary ossification (DPO) usually affects men. It has a chronic, progressive process which results in metaplastic ossification. This disorder can be due to an idiopathic process or associated with some pre-existing conditions including organizing pneumonia, chronic obstructive pulmonary disease (COPD), acute respiratory distress syndrome (ARDS), asbestosis, exposure to heavy metals, and idiopathic pulmonary fibrosis (16). In chest CT scan, DPO displays interstitial calcifications with a branching, linear form with width of 1–4 mm (17).

It can be useful to distinguish between PAM and infectious pneumonia because PAM typically has a sluggish onset while infectious pneumonias manifest symptoms more quickly. PAM and pulmonary tuberculosis could share several radiographic features. Moreover, they could have overlapping epidemiologic traits (3). It is possible to rule out pulmonary tuberculosis by analyzing sputum or BAL fluid using an acid fast bacilli (AFB) stain, an AFB culture, or nucleic acid amplification testing (18). The amount of infiltrates visible in the mediastinal windows of the chest CT can help to distinguish PAM from pulmonary alveolar proteinosis (2). More frequent and extensive thoracic lymphadenopathy than PAM is frequently seen in patients with pulmonary sarcoidosis (19). The rest of the differential diagnoses of PAM are listed in table 2.

Although, till now, there is no curative treatment for PAM, calcium chelating agent, corticosteroids and bronchoalveolar lavage could be utilized to manage or lessen the speed of progression. Etidronate, a bisphosphonate, reduces bone loss by preventing osteoclast viability and activity. Following the competition between etidronate and phosphate, this drug incorporates into hydroxyapatite and prevents the formation of calcium phosphate crystals. Nevertheless, the results reported about the effectiveness of this drug are conflicting and some

studies have shown its effectiveness and some have not reported the effectiveness of etidronate (24-27). It has also been suggested that sodium thiosulfate, a calcium-chelating agent, be used to treat PAM as well as disorders involving calcium deposition like ectopic calcification and calciphylaxis (28). Unfortunately, none of these medications have been reported to be efficacious. Eventually, in poor prognosis patients, lung transplant is considered as the only effective treatment with no reported recurrence after surgery (13, 29). PAM is a rare autosomal recessive pulmonary disease, which is mainly characterized by extensive calcium phosphate microliths deposition in the alveoli. The major mutation, causing the characteristic of this disease, occurs in solute carrier family 34 members 2 (SLC34A2), which is placed on chromosome 4p15.2 and encodes NPT2b, which plays a critical role in the transportation of phosphate ions from pulmonary alveoli into type II pneumocytes. In this paper, we presented a sporadic case of PAM which was suspected with chest x-ray and confirmed by HRCT and trans-bronchial lung biopsy. We hope that it can help clinicians to be more aware of this condition and make proper diagnosis.

Table 2. The other differential diagnoses of PAM

Disorder	Pathology	Clinical features	Radiographic or CT findings	Treatment	References
Pulmonary amyloidosis	Extracellular deposition of proteins of abnormal folding	Depending on the organs involved and how much they are involved, there are different clinical presentations.	Extremely variable, with solitary to diffuse nodules that can be smooth or spiculated, as well as diffuse septal thickening, pleural thickening, and pleural effusions.	As first-line therapy: daratumumab, bortezomib, cyclophosphamide, and dexamethasone	(20, 21)
Post-varicella pneumonia	Diffuse alveolar damage by VZV	Pneumonia before the traditional varicella rash	Diffuse nodular calcifications	Acyclovir (200 mg five times a day for 7 days)	(22)
Metastatic pulmonary calcification	The alveolar epithelial basement membranes are the primary locations where calcium salts are deposited during this interstitial process.	Multiple myeloma, hyperparathyroidism, or end-stage renal disease are frequently associated with increased serum calcium and phosphate levels.	Multiple diffuse calcified nodules • Diffuse or patchy areas of ground-glass opacity • confluent high-attenuation parenchymal consolidation	• Bisphosphonate (in hypercalcemic patients), • Phosphate binders (in isolated hyperphosphatemia and tertiary hyperparathyroidism) • Parathyroidectomy (in unresponsive patients)	(23)
Dendriform pulmonary ossification	Chronic, progressive process of metaplastic ossification	Idiopathic or associated with organizing pneumonia, COPD, ARDS, asbestosis, heavy metals, and idiopathic pulmonary fibrosis	Interstitial calcifications with a branching, linear form with width of 1–4 mm	No specific treatment; however, symptomatic management and imaging follow-up may be helpful.	(16)

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Conflict of interest: We declare no conflict of interest.

Author contributions: ATP: gathering the patient's medical history, writing the article, and revising the content

of manuscript. MGA and SAH: gathering the patient's medical history and helped with manuscript writing and revision. SB: reporting and assessing histopathologic changes on trans-bronchial lung biopsy and helped with manuscript writing. RMA: the patient's physician, gathering the medical history, helped with manuscript writing and revising the content of manuscript.

Data availability statement: The data supporting the findings of this study are available upon request from the corresponding author and with permission from Babol University of Medical Sciences, Babol, Iran.

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