Alveolar Microlithiasis with Mild Clinical Symptoms But Severe Imaging Findings: A Case Report

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Clinical Medicine Insights: Case Reports
Volume 17: 1–4

DOI: 10.1177/11795476241236350

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ABSTRACT: Pulmonary alveolar microlithiasis (PAM) is a rare genetic disorder that causes calcium phosphate microliths to form in the alveoli. Symptoms usually appear in a person's third or fourth decade of life. A definitive diagnosis does not always demand a lung biopsy but can be achieved in families with more than one member with PAM and compatible chest imaging. We present the case of a 47-year-old woman referred to us for shortness of breath. Chest imaging revealed bilateral diffuse ground-glass opacities, interlobar fissure calcification, and subpleural linear calcifications, leading to a diagnosis of PAM. Although there is no specific treatment for this condition, early diagnosis can help prevent it from progressing rapidly by avoiding exposure to risk factors.

KEYWORDS: Alveolar microlithiasis, calcium phosphate microliths, SLC34A2, genetic lung disease

RECEIVED: December 15, 2023. **ACCEPTED:** February 12, 2024.

TYPE: Case Report

FUNDING: The author(s) received no financial support for the research, authorship, and/or publication of this article.

DECLARATION OF CONFLICTING INTERESTS: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Introduction

Pulmonary alveolar microlithiasis (PAM) is an autosomal recessive lung disease seen more often in consanguineous marriages. In this disease, calcium phosphate microliths, called chalcospheritis, accumulate in the alveolar spaces.[1,2] Mutations in the solute carrier family 34 member 2 (SLC34A2) gene, which encodes the second type of sodium-phosphate transporter in type II alveolar cells, are responsible for the pathogenesis of PAM.[3] A high proportion of cases of PAM has been published in Asia, with a rate of 56.3%. In Turkey, the incidence of this disease is 1.85 per one million people, while in Italy, it is 1.08, in Japan 0.92, in the United States 0.15, in China 0.10, and in India 0.06.[4]

Most patients with PAM are asymptomatic at the time of diagnosis and are usually diagnosed with random chest imaging.[3] The appearance of a sandstorm figure is usually seen in these patients' chest radiography; as the name suggests, it is usually apparent and severe. Still, despite the intensity of radiologic findings, the patients show minor or no signs and symptoms.[5] In symptomatic patients, shortness of breath is the most common symptom, followed by dry cough, chest pain, diffuse hemoptysis, and asthenia.[1] In diagnosing this disease, radiographic features, the absence of clinical symptoms, and family history of PAM are essential.[6,7] However, there is currently no definitive treatment to prevent the progression of PAM.[6,8]

Case Presentation

The reported patient is a 47-year-old woman who came to the hospital's emergency department complaining of shortness of breath. Her shortness of breath began 2 months ago at the intensity level of modified medical research council (mMRC) I and escalated to mMRC II 2 week before her visit, and it was not accompanied by cough and sputum. In the physical examination, her blood pressure was 120/80 mmHg, pulse rate was 88 beats/min, respiratory rate was 18 min, body temperature was 36.8°C, and oxygen saturation was 96%. Auscultation of the lungs was clear. She did not mention the history of other diseases or smoking. In the family history, her parents were not related, and she also mentioned the history of the same respiratory symptoms in her siblings. Out of 2 brothers and one sister, 2 of her brothers were diagnosed with PAM in their forties. One exhibited respiratory symptoms and radiologic findings, while the other only showed radiographic evidence. Her mother had no respiratory symptoms or radiologic findings, but her father died young in a car accident, and no lung evaluation was done on him. The patient was admitted for additional medical examination. Laboratory tests were normal, including calcium and phosphorus serum concentration, liver and parathyroid function, and arterial blood gas (ABG) measurement. Additionally, the tuberculin skin test was normal. High-resolution computed tomography (HRCT) showed multiple bilateral diffuse ground-glass opacities, interlobar fissure calcification, and subpleural linear calcifications with greater intensity in the lower regions of the lungs. Also, blurred borders of the heart and diaphragm were evident (Figure 1).

Also, there were no pathologic findings in the patient's echocardiography. Based on the appearance of HRCT and mild clinical symptoms, the patient was diagnosed with PAM. She was treated with Dexamethasone ampule 4 mg stat, Fluticasone inhaler 250 mg 2 puff twice a day, and other conservative treatments. After spending 2 days in the hospital, her respiratory symptoms improved to some extent, and she was

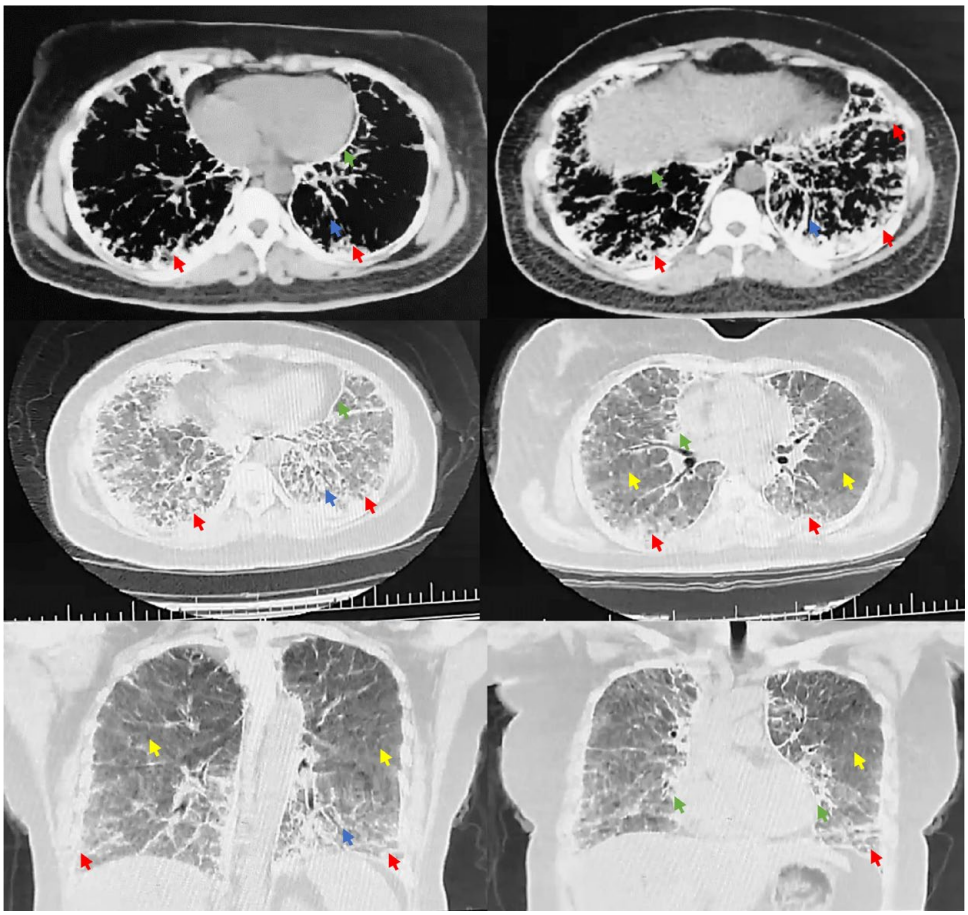

Figure 1. The imaging indicates the presence of multiple bilateral diffuse ground-glass opacities (yellow arrow) in the lungs, along with interlobar fissure calcification (blue arrow) and subpleural linear calcifications (red arrow), with more intense calcification found in the lower regions of the lungs. Additionally, the borders of the heart and diaphragm were found to be blurred (green arrow).

allowed to go home with a prescription for Fluticasone inhaler, 250 mg, 2 puffs, twice a day. She also received instructions to follow a low phosphate diet and was informed about the disease and its possible complications. She was advised to visit the pulmonology clinic every 3 months for follow-up and to seek medical attention immediately in case of severe complications. Her 2 daughters also underwent chest radiography screening for early diagnosis of PAM, but the results were normal.

Discussion

PAM is a rare genetic lung disease characterized by extensive sand-like intraalveolar calcifications (chalcospherites) composed of calcium and phosphorus. Inconsistency of clinical and radiological findings is characteristic of this disease.[3,9] To date, about 1000 cases of PAM have been reported worldwide, but most of the cases were reported from Asia and Europe.[5] The prevalence of this disease is the same in both genders, and patients are usually diagnosed in their third or fourth decades.[5] It is worth noting that only a few reports have documented the occurrence of this disease in infants.[10]

It is found that inactivating mutations in the SLC34A2 gene, mainly expressed in type II alveolar cells, cause the appearance of PAM.[11] This gene is also expressed in other epithelial tissues, including mammary glands, small intestine, kidneys, pancreas, ovaries, liver, testes, placenta, and prostate.[1] SLC34A2 is the only known sodium-dependent phosphate transporter and plays a key role in the clearance of phospholipids from alveolar spaces by transferring phosphate ions to type II alveolar cells, and dysfunction or deficiency of sodium-dependent phosphate transporter due to SLC34A2 gene mutations leads to reduction of phosphate absorption from type II alveolar cells and formation of the PAM.[5] This, in turn, may lead to the formation of intra-alveolar microliths in the extracellular fluid. PAM has been reported to occur among siblings and cousins in a horizontal pattern and less often between parents and children in a vertical pattern.[12] In this report, the patient's siblings had similar clinical findings, but they have not undergone imaging for further diagnosis.

PAM has a relatively slow progression, and there is often a long interval until clinical symptoms appear. As PAM progresses, patients usually experience shortness of breath during activity; other symptoms such as cough, chest pain, hemoptysis, asthenia, and pneumothorax have also been reported. Cyanosis and clubbing of the fingers may also be seen in the advanced stages. In our report, our patient's only complaint was shortness of breath while doing activity, which started 2 months ago and

worsened recently, and no symptoms related to long-term PAM were observed in this patient. During the initial stages of PAM, pulmonary function tests (PFT) are often normal. Still, the progression of the disease is accompanied by impaired ventilation and leads to a decrease in diffusion capacity over time. This also leads to hypoxemia, increased arterial CO2 levels, pulmonary fibrosis, respiratory failure, and cor pulmonal.[1,12,13] PFT was not performed for our patient, and the echocardiography showed no sign of right heart failure secondary to lung involvement with PAM.

Routine blood tests are usually normal in these patients. Serum monocyte chemotactic protein-1, surfactant protein (SP)-A, and SP-D are increased in certain patients. These proteins may serve as diagnostic biomarkers or indicate PAM activity and progression.[12] Typical features of PAM on chest radiographs are a fine, diffuse ground-glass pattern that produces a "sandstorm" appearance. Diffuse involvement of both lungs is generally more apparent in the middle and lower regions.[14,15] High-resolution computed tomography (HRCT) findings can be classified into four stages based on the degree of radiological intensity. The first stage is referred to as pre-calcification because of the small number and size of calcifications. In the second stage, scattered calcified micronodules (less than 1 mm in diameter) are visible, and a "sandstorm" appearance can be observed.[11] The third stage of the disease shows a more significant number and volume of opacities. This may lead to blurring the outlines of the heart and diaphragm. As the number and size of calcific deposits sharply increase, severe calcification of the interstitial space and pleural serosis may occur. In the fourth stage, as seen in our patient, it creates the characteristic appearance of "white lungs." The first stage is usually observed in children, the second in adolescence, and the last two in the last years of life.[11]

Based on the diagnostic features of this disease and the National Institute for Health and Care Excellence (NICE) guidelines, it is recommended to conduct lung radiography for patients with respiratory symptoms lasting more than 3 weeks.[16] When radiologic images show micronodular and dense vitreous opacities, differential diagnoses for PAM include miliary tuberculosis, sarcoidosis, pneumoconiosis, pulmonary alveolar proteinosis, pulmonary hemosiderosis, and amyloidosis. In areas where tuberculosis is highly prevalent and consanguineous marriage is common, PAM is often misdiagnosed as tuberculosis.[6] The bacterium Mycobacterium tuberculosis causes miliary tuberculosis and is a condition that arises in patients with weakened immune systems, where tuberculosis disseminates hematogenously and presents itself through the formation of miliary lung nodules and multi-organ involvement.[17] In patients with sarcoidosis, imaging typically reveals symmetric adenopathy in the hilar and mediastinal regions and pulmonary micronodules distributed in a perilymphatic fashion. Additionally, this disease can lead to irreversible pulmonary fibrosis.[18] Our patient exhibited no signs of immune-compromised diseases and showed no evidence of unilateral or bilateral hilar adenopathy. Additionally, the patient had a negative tuberculin test. Given that the patient's siblings were also diagnosed with PAM, other diagnoses are highly unlikely.

Previous studies have shown that systemic steroids and bronchopulmonary lavage are ineffective treatments. In our patient, despite the absence of evidence showing positive intervention of systemic steroids, they were prescribed to control the symptoms due to a lack of other treatment options. Inhalant steroids have been proven to effectively alleviate symptoms without affecting imaging progress.[4,5] Therefore, our patients were prescribed the steroid inhalant for the same purpose. Although some studies suggest that disodium etidronate improves lung function and radiographic appearance, its efficacy remains uncertain.[1] Additionally, it is recommended that PAM patients maintain a low phosphate diet.[4,19] Currently, there are no specific treatments available for PAM. However, the risk factors that contribute to PAM, such as smoking, snuff inhalation, repetitive lung infections, and cold weather, can be prevented. Additionally, supporting therapies such as oxygen, vaccination, smoking cessation, rehabilitation, and lung transplantation can be used.[2,20,21] In the later stages of PAM, a lung transplant is the only option for improving right ventricular function. Lung transplantation has been shown to increase survival rates, and there have been no reported cases of PAM recurrence after the procedure.[20]

Conclusion

Identifying patients with PAM and managing potential risk factors in the early stages is essential, even though it may not alter the course of treatment. Early detection could play a significant role in slowing down the progression of the disease.

Acknowledgements

Not applicable.

Author Contributions

SH visited the patient in the hospital daily, checking and revising the manuscript. MS, RJ, and AS helped gather patient data and draft the manuscript. MN drafted and revised the manuscript.

Consent to Participate

Written informed consent was obtained from the patient for his participation in this case report. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Consent for Publication

Written informed consent was obtained from the patient to publish this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

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