



Case Series *Diagnostic Radiology*

Losing vigilance in diagnosing pulmonary alveolar microlithiasis: A report on four cases

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ABSTRACT

Pulmonary alveolar microlithiasis (PAM) is a rare chronic lung disease characterized by calcium and phosphate deposition in the alveolar lumen throughout the parenchyma of both lungs, with predominance in the middle and lower lung fields. It is caused by mutations in the recessive gene, *SLC34A2*, on the autosomal chromosome. In this article, we characterize four cases of PAM and analyze the loss of diagnostic vigilance in two of them. Patients came to medical facilities with clinical manifestations such as cough, shortness of breath, chest pain, and fatigue. The initial diagnosis was unclear in two cases because the X-ray film's quality was not good enough and the medical staff had little experience in clinical and chest X-ray interpretations for PAM. The definitive diagnosis was based on a combination of high-resolution computed tomography (CT) and bronchoalveolar lavage fluid testing. In addition, chest X-ray and high-resolution CT enable the assessment of the stage, progression, and severity of the disease. There is currently no specific treatment for PAM other than lung transplantation.

Keywords: Alveolar, Calcification, Microlithiasis, Pulmonary, Pulmonary alveolar microlithiasis

INTRODUCTION

Pulmonary alveolar microlithiasis (PAM) is a rare hereditary lung disease caused by mutations in the recessive gene, *SLC34A2*, on the autosomal chromosome, which encodes a phosphate transporter in alveolar epithelial cells, leading to the accumulation and formation of calcium phosphate-rich granules in the alveoli.^[1-3]

The disease was first described by Malpighi (Italy) in 1686.^[1] Later on, many other authors, such as Harbitz (Norway, 1918), Schildknecht (Germany, 1932), Puhr (Hungary, 1933), Mariani (Italy, 1947), and Mikhailov (Bulgaria, 1954) began to refer to this disease. Since then, there have also been several reports on this pathology.^[1-3] The disease is usually diagnosed before the age of 40 years, with non-specific clinical manifestations such as persistent cough, shortness of breath (especially on exertion), and chest pain when coughing, sneezing, or taking deep breaths.^[2-4] The X-ray findings of PAM are highly specific, so if they are detected, it is the most important initial diagnostic hint.^[4-6] Specifically, in the early stages of the disease, the appearance of small calcium stones (diameter: 0.01–0.03 mm) in the alveolar lumen is seen. In the advanced stage, the diameter of the stone can be up to 2–4 mm; in the late stage, stones can accumulate in clusters or plaques, leading to complete coverage of the mediastinum and diaphragm, creating an image of a “disappearing heart.”^[2]

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In this article, we characterize four cases of PAM and analyze the loss of diagnostic vigilance in two of them.

CASE SERIES

Our patients were three adults and one child, who were all examined and treated at the National Lung Hospital in Hanoi, Vietnam. They all had unremarkable personal and family histories, their clinical manifestations were almost non-specific, mainly cough and dyspnea on exertion, and none of them had symptoms severe enough to cause respiratory failure or cardiovascular complications. All patients had slow clinical progress and effective medical treatment from the beginning. In the case of a 4-year-old male patient [Figure 1], 4 months after his birth, the child had pneumonia. Although it was adequately treated, the patient often had a cough and difficulty breathing afterward, and he was diagnosed with bronchitis and treated many times. About 2 months before this hospital admission, the child had more cough, for which the family took him to Hanoi City Lung Hospital in Hanoi, Vietnam. Here, the patient underwent chest conventional X-rays and did some tests, including blood and urine tests, respiratory function tests, bacteriological tests, and sputum tests. The fresh sputum

smear tested negative thrice for tuberculosis (TB), and the GeneXpert test of gastric juice and bronchial lavage was also negative. Bacterial culture results were not available; however, the clinical manifestations were prolonged cough, high fever, and body fatigue. Therefore, by experience and X-ray images, doctors diagnosed pulmonary TB and prescribed in-hospital TB treatment. However, even after 2 months of treatment, the disease did not improve, and the patient still had a fever (temperature of approximately 38.5°C) and a severe cough; thus, he was transferred to the National Lung Hospital.

The remaining three patients were adults, including a 35-year-old male patient [Figure 2] who works as a mason and often uses coal for cooking. He sometimes has a cough, chest pain, and mild shortness of breath. The patient was admitted to a general hospital (not a lung specialist hospital) due to a road traffic accident that resulted in a fracture of the left collarbone. The chest radiography revealed many small lesions such as millet kernels, concentrated in the lung's base, suggesting pneumoconiosis caused by long-term coal dust inhalation; however, the symptomatic treatment did not result in any improvement. The patients in the remaining two cases [Figures 3 and 4] had cough, shortness of breath, chest

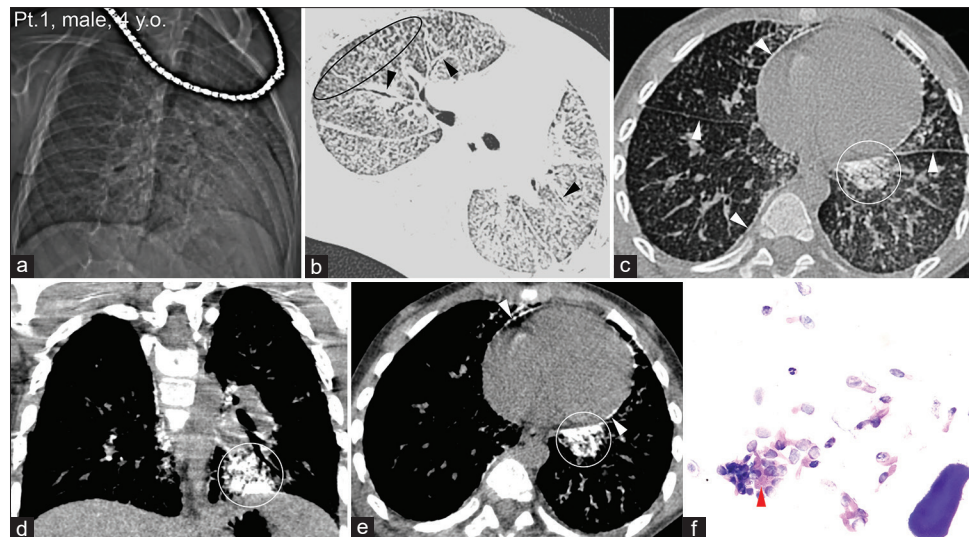


Figure 1: Chest X-ray, computed tomography, and a microscopic image of bronchoalveolar lavage (BAL) fluid in a 4-year-old male patient diagnosed with pulmonary alveolar microlithiasis. (a) The chest X-ray image shows many small opacities measuring approximately 1 mm in diameter that spread throughout both lung fields. The X-ray intensity of the tube must be increased 3 times the normal value to clearly visualize. (b-e) The chest high-resolution computed tomography images on the lung and mediastinum windows revealed many small opacities measuring approximately 1–2 mm in diameter, with the density of calcification being 120 HU, clustering in the lower parts, creating the “sandstorm” sign or concentrating to create the “stone lung” sign (white circle); wall thickening and narrowing of the bronchial branches, including both lobar and segmental bronchi (black arrowheads); reticular interstitial thickening around the bronchioles in both lungs (black oval), calcification of the pericardium, interlobar fissures, and the pleura close to the diaphragm (white arrowheads). (f) A microscopic image of the BAL fluid shows a pink microcalcified particle (red arrowhead) interspersed with bronchial mucosal cells (purple).

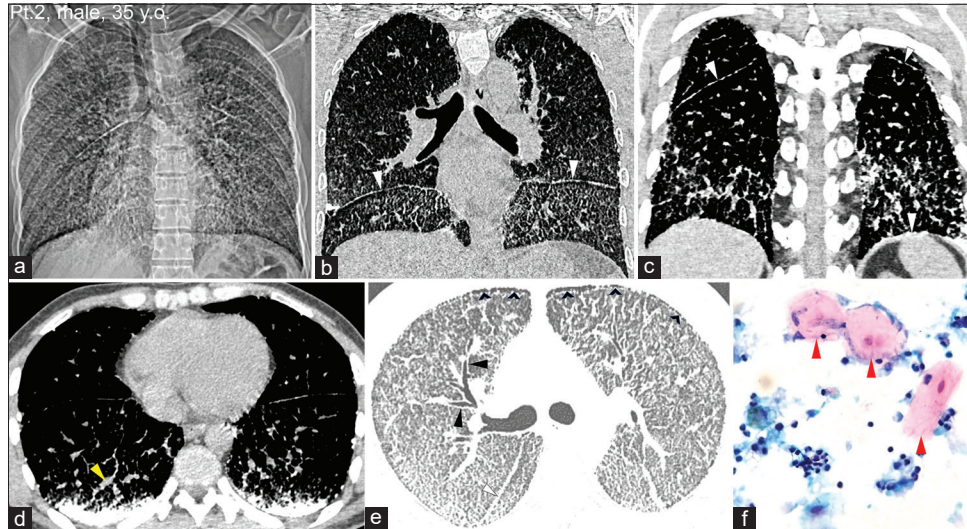


Figure 2: Chest X-ray, computed tomography (CT), and microscopic images of the bronchoalveolar lavage (BAL) fluid of a 35-year-old male patient who was diagnosed with pulmonary alveolar microlithiasis (PAM). (a-e) The chest X-ray and CT images show many small opacities measuring 1–2 mm in diameter, with diffused interstitial thickening throughout both lung fields, predominately in the lower and posterior regions, forming a “sandstorm” image; calcifications along the blood vessels (a yellow arrowhead) and peripheral regions with air spaces just below the pleura (subpleural sparing) (black ^ shapes). Calcification of the interlobular fissure and pleura adjacent to the diaphragm (white arrowheads) produced sharp contours. (f) A microscopic image of BAL fluid showing pink microcalcified particles (red arrowheads) intermingled with bronchial mucosal cells (dark blue), confirming PAM.

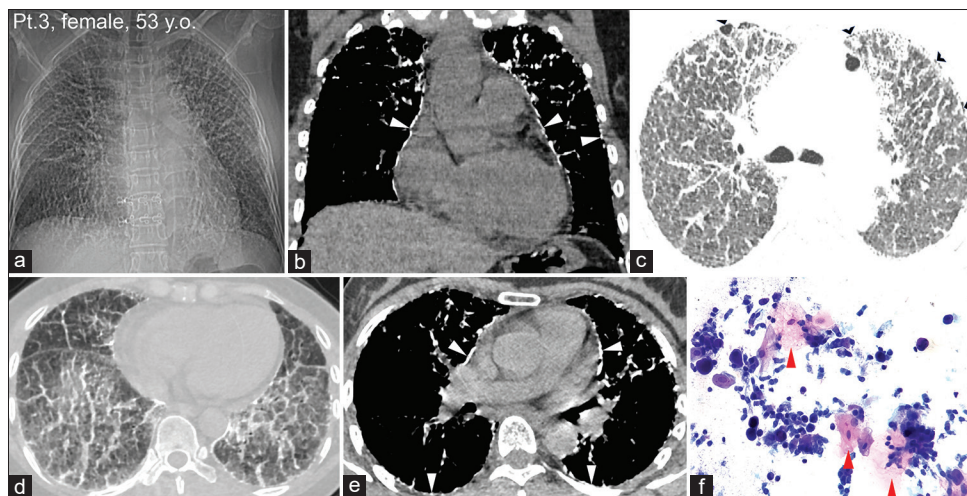


Figure 3: Chest X-ray, computed tomography (CT), and microscopic images of bronchoalveolar lavage (BAL) fluid on a 53-year-old female patient diagnosed with pulmonary alveolar microlithiasis (PAM). (a-e) The chest X-ray and CT images show many large calcified opacities (1–3 mm), spreading throughout both lung fields, predominantly in the periphery (pleura and mediastinum) forming a line with a clear border; reticular interstitial thickening with air spaces just below the pleura and small-balloon alveolar dilatation near the periphery of the lung (black ^ shapes). There is no “sandstorm” sign. (f) A microscopic image of the BAL fluid showing pink microcalcified particles (red arrowheads) intermingled with bronchial mucosal cells (purple), confirming PAM.

pain, fatigue, and slight weight loss at the time of admission (approximately 1 kg/month). For all three adult patients, microbiological tests for TB, non-tuberculous bacteria, fungi,

and parasites were negative. Biochemistry, hematology, and urine tests yielded unremarkable results. Moreover, abdominal ultrasonography revealed no abnormality.

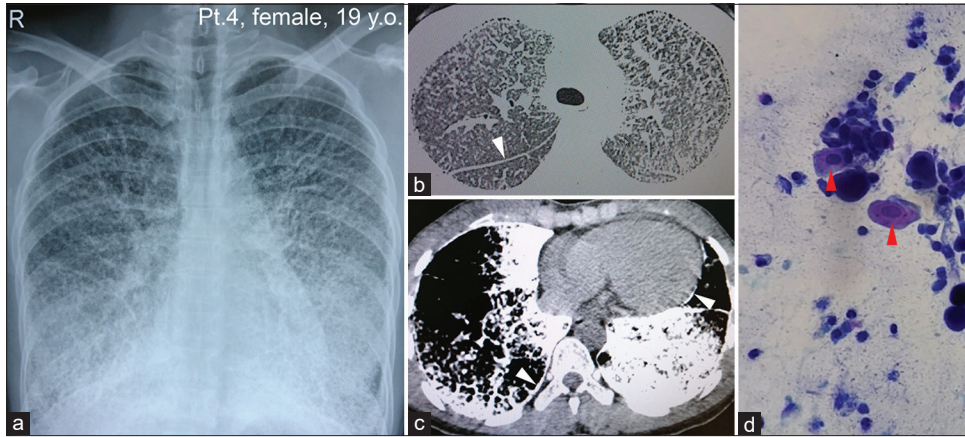


Figure 4: Chest X-ray, computed tomography (CT), and microscopic images of bronchoalveolar lavage (BAL) fluid in a 19-year-old female patient diagnosed with pulmonary alveolar microlithiasis (PAM). (a-c) The chest X-ray and CT images show many densely calcified nodules, clustering in the periphery and lower part, sticking together to create the “stone lung” image, accompanied by severe pleural calcification adjacent to the diaphragm and the interlobular fissure and pericardial calcification (white arrowheads), looking like an eggshell enclosing the lung parenchyma. (d) A microscopic image of the BAL fluid showing pink microcalcified particles (red arrowheads) intermingled with bronchial mucosal cells (purple), confirming PAM.

Respiratory function tests performed in the three adult patients yielded results that were within normal limits; the bronchodilator test revealed decreased airflow in the small bronchi, and the bronchial recovery test was negative.

Especially for the male patient with long-term coal exposure, the 6-min walk test was performed, and the rate of carbon dioxide diffusion across the alveolar-capillary membrane (DLCO) was measured. As the results show, in 6 min, the patient walked 645 m, scoring 57.29%; the patient’s DLCO was within normal limits. In the child, the impulse oscillometry test showed decreased respiratory function due to peripheral airway obstruction and decreased airway responsiveness to bronchodilators; the cerebrospinal fluid (CSF) test showed <3 cells/mm³, adenosine deaminase – 2.32 U/L, chlorine – 114 mmol/L, glucose – 4.1 mmol/L, protein – 0.22 g/L, and Pandy negative CSF count. Echocardiography in all four patients was normal, with no pulmonary hypertension.

Computed tomography (CT) scanning in the National Lung Hospital for all four patients showed that there were many small opacities measuring 1–3 mm in diameter, with the density of calcification being ≥ 120 HU, which were millet-shaped and spread throughout the parenchyma of both lungs. There was irregular thickening of interstitial tissues and calcification in the interlobular and interloblastic fissures, predominantly in the periphery and lower parts, which was consistent with the typical image of PAM [Figures 1-4]. In addition, in the 4-year-old male patient [Figure 1], wall thickening and narrowing of the bronchial branches (including both lobar and segmental bronchi) were found,

and diffuse reticular thickening around the bronchioles was observed in both lungs. Microcalcified opacities in the two lung fields were clustered in the lower parts, creating the “sandstorm” sign, or concentrated to create the “stone lung” sign. In the 35-year-old male patient [Figure 2], in addition to the abovementioned CT findings, calcification of the interlobular fissure and pleura adjacent to the diaphragm produced sharp contours with air spaces just below the pleura (subpleural sparing); calcifications along the blood vessels and peripheral regions were also seen; there was a “sandstorm” image in the posterior basal segment on both sides.

In the 53-year-old female patient [Figure 3], reticular interstitial thickening was shown to be accompanied by large calcified nodules (1–3 mm), with air spaces just below the pleura and small-balloon alveolar dilatation near the periphery of the lung. There was no “sandstorm” sign. In the 19-year-old female patient [Figure 4], densely calcified nodules were found, clustering in the periphery and lower part, sticking together to create the “stone lungs” image, accompanied by severe pleural calcification, which looked like an eggshell enclosing the lung parenchyma.

The patients then underwent bronchoscopy, bronchial mucosal biopsy, and bronchoalveolar lavage (BAL). Bronchoscopy revealed bilateral bronchial hypersecretory inflammation. Endoscopic bronchial mucosal biopsies revealed areas of metaplasia, stromal fibrosis, the infiltration of lymphocytes, neutrophils, and macrophages, and the absence of malignant cells. Periodic acid-Schiff staining

revealed positive results for benign bronchial epithelial cells. The BAL fluid test revealed that there were some components such as calcium granules, inflammatory cells, and macrophages. The combined results confirmed these as PAMs. All four patients received symptomatic treatment such as oxygen, corticosteroids, and physical enhancement. At present, the symptoms are well controlled, and the patient continues to be monitored and treated as an outpatient.

DISCUSSION

PAM is a rare disease.^[1,3,6] To date, at least 27 genetic mutations have been found to be associated with this disease whose main cause is the presence of mutations in the recessive gene, *SLC34A2*, on the autosomal chromosome.^[2,7] This gene is the genetic code used to make a protein, a type IIb sodium-phosphate cotransporter, which regulates phosphate levels (phosphate homeostasis). This protein can be found in many tissues and organs of the body; however, it occurs mainly in the lungs, especially in type II alveolar cells. These cells produce and recycle surfactant, a mixture of certain phospholipids with proteins that make up the lung parenchyma that helps us to breathe. Surfactant recycling releases phosphate into the alveolar lumen. Researchers have shown that a sodium-phosphate cotransporter of type IIb helps to remove this kind of phosphate.^[2,3] Reduced activity of the sodium-phosphate cotransporter leads to the accumulation of calcium phosphate granules in the alveolar lumen throughout the lung parenchyma.^[3] This deposition is evident on X-ray and CT images.

According to Prakash *et al.*, the age of onset of PAM ranged from 0 to 80 years, with the average age at diagnosis being 35 years. There was no sex pre-disposition, and there was a contributive family history in approximately 50% of cases.^[8]

PAM can either be asymptomatic or symptomatic; however, its symptoms are often non-specific and occur only when there is extensive alveolar damage combined with damage to surrounding tissues, causing respiratory abnormalities.^[1,3] Usually, radiological abnormalities are detected before clinical manifestations appear.^[2] In people with PAM, calcium phosphate deposits may also be seen in other tissues and organs in the body, such as the kidneys, gall bladder, testes, and heart valves (common in the aortic valve).^[2,3,9] In some rare cases, the complications of aortic stenosis may be associated with the accumulation of these deposits, which impede blood flow.^[3] All four of our patients had atypical clinical symptoms such as cough, chest pain, and dyspnea on exertion. There were no real ventilation disorders and no cardiovascular disorders. There were no microcalcifications in other organs in all four cases.

PAM is a good example of clinico-radiological dissociation.^[2,3] The characteristic radiographic image of

PAM is the infiltration of fine calcified particles resembling sand; thus, it is also known as a “pulmonary sandstorm.” In this condition, there is extensive involvement of both lungs, mostly in the middle and lower regions, predominantly anteriorly and posteriorly, often causing blurring of the mediastinal margin and diaphragm.^[3] In advanced forms of the disease, microparticles can be distributed in the pericellular interstitium. On chest radiography, it can be seen that the cardiac and diaphragmatic margins are completely erased, and the pleura is calcified, creating dense, sharp white lines that run along the pleural surface and mediastinum margins.^[2] The chest CT image in advanced stages is characterized by thickening of the interlobular septum, thickening of the peribronchial and subpleural interstitial tissue, and their calcifications.^[2,3] These abnormalities on pulmonary CT are usually symmetrical, and the calcifications are well-defined. Calcifications are most predominant in the periphery, mediastinum, and subpleural regions, looking like each lobe is surrounded by a thick border. The opacity of the lungs often also varies widely, and the organs can be so dense that they appear almost homogeneously white, giving the impression of “stone lungs.” Many small subpleural air cysts can be seen due to long-term gas retention.^[3]

Routine blood biochemistry tests show that serum calcium and the functions of the liver, kidney, and parathyroid may be normal.^[3,10,11] Elevated levels of surfactant proteins A and D in patient serum may be an indicator of disease activity and progression.^[3]

Lung biopsy (transthoracic or open) and histopathological examination revealed characteristic microparticles in the alveoli to confirm the diagnosis. In addition, these microparticles can be seen in the BAL fluid. Lung biopsy is the first-choice modality for the definitive diagnosis of PAM. Open lung biopsy is not feasible in most cases; therefore, transbronchial biopsy to obtain lung parenchymal specimens remains the most widely accepted technique.^[3,7,9] Four of our cases were confirmed by radiography, chest CT, bronchial mucosal biopsy through a flexible bronchoscope, and BAL fluid testing.

Two of the four patients in our case series were misdiagnosed with TB and pneumonitis. The alleged causes of the missed diagnoses were as follows: (a) The patients were hospitalized in medical facilities with low levels of specialization, one was the Lung City Hospital and the other was a general hospital, whereas PAM is a rare disease that has never been taught and announced in Vietnam. Thus, the medical staff has little knowledge of the clinical, radiographic, and high-resolution CT interpretations of PAM. At first, when they saw the pulmonary X-ray of PAM, they easily associated it with TB or pneumoconiosis, which are common diseases in developing countries like Vietnam. Meanwhile, the remaining two patients who came to the National Lung Hospital at the

beginning were immediately diagnosed with PAM; (b) when patients with PAM arrived at the hospital and underwent routine X-ray examinations, the typical calcifications of PAM were not obvious because the X-ray intensity of the tube was not strong enough, which made it easy for less experienced doctors to mistake PAM for other diseases such as TB and pneumonitis.

In the literature, there is little published information on the clinical course of the disease, its onset, progression, and stable phases.^[2,3] Most of the literature only deals with certain aspects of the disease. The point at which the disease worsens is often the time it is studied. In some cases, the disease remains static in terms of clinical manifestations and radiographic findings.^[2] There are patients who were followed up for more than 15 years and their disease either remained stable or progressed slowly. Extrapulmonary manifestations and complications are uncommon.^[2,3,5]

In rare cases, the disease rapidly worsens to varying degrees, either leading to pulmonary fibrosis, respiratory failure, or chronic cardiopulmonary disease (cor pulmonale). Dyspnea on exertion (which occurs as the disease progresses) and cardiac arrhythmias are the hallmarks of end-stage disease. Cough can appear at any stage of the disease. Often, the disease progression will eventually lead to heart failure, respiratory failure, and death. Pulmonary fibrosis, cardiac arrhythmias, and respiratory failure exacerbate the condition.^[2,3] The diagnosis can be established early, before the patient develops clinical manifestations, by screening the family members of patients with PAM through chest radiography.^[3] In our patients, the disease progressed slowly, there were no cardiovascular manifestations, and treatment with oxygen therapy and corticosteroids yielded a good response.

The discovery of genes as the cause of the disease and its pathogenesis has so far been confirmed. Counseling the patient's family about the genetic nature of the disease is critical for the early detection of the disease and its timely management.^[3,5]

Regarding the differential diagnosis, on chest radiography, PAM can be mistaken for other lung diseases such as TB, pulmonary fungus, sarcoidosis, pneumoconiosis, and amyloidosis.^[2,4,9] In all of the above diseases, diffuse pulmonary nodules may appear; however, in PAM, the lesions are usually larger and distributed in a completely different manner. In addition, PAM has milder clinical manifestations than these diseases. Moreover, due to the strong calcification process in PAM, when taking a chest radiograph, the X-ray intensity needs to be 3–5 times stronger than normal to get a good quality film, fully demonstrating the expressions of this disease.^[3] According to a study by Giuseppe *et al.*, PAM is common in countries

such as Turkey, China, India, and Vietnam where TB is common.^[3] Because this is a rare disease, most physicians have inadequate knowledge of PAM and the characteristic imaging features on film; thus, they tend to easily suspect TB, despite the significant difference that exists in the clinical presentations of PAM and TB. Therefore, there were 72 cases of PAM misdiagnosed as miliary TB leading to useless treatment.^[3] In contrast, there were also cases where PAM was diagnosed but later found to be sarcoidosis.^[2,3] In the four cases that we reported, there was one case that was initially misdiagnosed as miliary TB and treated with anti-TB drugs for 2 months without any improvement. The patient was transferred to the National Lung Hospital. CT scanning and BAL fluid testing confirmed the diagnosis as PAM in this study.

Regarding treatment, there is currently no specific treatment for PAM and the only effective treatment is lung transplantation. However, when the cause of the genetic mutation that causes PAM was found, people began to study a new treatment modality (hormone replacement therapy), hoping that this therapy would reduce the amount of phosphate ions in the interalveolar space, leading to a delay in the formation of microparticles as well as the progression of interstitial diseases. If the patient has respiratory failure, oxygen therapy is necessary. Systemic corticosteroids and BAL have been shown to be ineffective.^[2,3] Disodium etidronate administered at a dose of 10 mg/kg body weight/day orally for 1-year inhibited the progression of hydroxyapatite microparticles, resulting in a significant decrease in calcium density. BAL has no therapeutic effect on PAM because, in PAM, calcium particles are also deposited in the interstitial tissue of the lung so that they are not removed during BAL.^[2] So far, some patients have received unilateral or sequential lung transplantation; however, to date, the long-term survival of these patients has not been evaluated.^[2,3,12] Therefore, longitudinal follow-up and outcome assessment over time are essential to determine patient survival and the risk of PAM recurrence after lung transplantation.^[2,3]

CONCLUSION

PAM is a rare disease that easily catches medical staff off guard due to a lack of knowledge and experience in diagnosis. The disease is related to mutations in the recessive gene, *SLC34A2*, on the autosomal chromosome. Characteristic chest radiography and CT findings, combined with BAL fluid test results, help confirm the diagnosis. Lung biopsy is the gold standard diagnostic modality; however, it is not always feasible. In general, the disease progresses slowly and lasts for a long time. The long-term prognosis is poor, and respiratory failure is a possible cause of death. At present, there is no specific treatment, and the disease can only be completely cured by lung transplantation.

Ethical approval

The authors declare that they have taken the ethical approval from IRB/IEC.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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