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A Case Report of Pulmonary Alveolar Microlithiasis: Focus on Radiologic Findings

Authors' Contribution:
Study Design A
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Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Patient: Male, 57-year-old
Final Diagnosis: Pulmonary alveolar microlithiasis
Symptoms: Shortness of breath on exertion • dyspnea • cough
Medication: —
Clinical Procedure: CT scan
Specialty: Pulmonology • Radiology

Objective: Rare disease

Background: Pulmonary alveolar microlithiasis (PAM) is an uncommon pulmonary disease characterized by deposition of microliths in the alveoli. In this report, we describe the first ever documented case from the Indonesian population of an adult patient who was diagnosed with PAM based on clinical and pathognomonic radiological findings.

Case Report: A 57-year-old man with a 12-year history of progressive shortness of breath on exertion was admitted to our center. When the lungs were listened to, there were coarse crackles and wheezing during inspiration, and the vesicular sound was lower in all thoracic regions. Cardiac auscultation was unremarkable, with fingers having a clubbed drumstick appearance. Bronchoscopy revealed all patent branches of the bronchial tree. Unfortunately, the microliths were absent, and the histology findings from bronchoalveolar lavage and transbronchial lung biopsy were inconclusive. Radiologic features of a chest radiograph show the characteristic finding of multiple diffuse micronodules with a high density in both lungs. A high-resolution computed tomography (HRCT) scan corroborated the typical findings of extensive intraparenchymal calcified micronodules with diffuse ground-glass attenuation areas. Black pleural line signs were also seen.

Conclusions: PAM is a rare disease with a chronic clinical course and varying manifestations according to phase, but progressive deterioration may result in a poor prognosis. It is particularly important for clinicians to be able to narrow down the differential diagnosis of multiple diffuse micronodules of the lungs. When a non-invasive method of diagnosis is preferred, chest X-rays and, even better, HRCT should be used to find the characteristic features of alveolar microlithiasis.

Keywords: Pulmonary Alveolar Microlithiasis • Radiography • Tomography, X-Ray Computed

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/938456

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Background

Pulmonary alveolar microlithiasis (PAM) is a rare pulmonary diagnostic entity characterized by chronic deposition of multiple microscopic calculi within the alveoli. It is widely believed that the condition is inherited autosomal recessive [1]. Clinically, there may be an absence of symptoms despite extensive imaging findings. In most cases, symptoms begin at between 20 and 40 years of age [2]. In this report, we describe an adult patient with progressive dyspnea on exercise who was diagnosed with PAM. The patient was identified based on clinical and pathognomonic radiological findings. This is the first ever documented case from the Indonesian population.

Case Report

A 57-year-old man of Javanese ethnicity, Indonesia, with a 12-year history of progressive shortness of breath on exertion was admitted to our center. Auscultation of the lungs indicated inspiratory coarse crackles and occasional wheezing with diminished vesicular sound across all thoracic areas, particularly in the bilateral base of the lungs. Egophony and pectoriloquy were absent. Cardiac auscultation was unremarkable, with observable clubbed drumstick appearance of the fingers, without cyanosis or peripheral edema. He had a long history of heavy smoking, with around 40 pack-years. There was also a previous history of completed treatment of pulmonary tuberculosis in 2018.

A laboratory examination in our center revealed a negative result on sputum testing for acid-fast bacillus. Serum rapid testing for human immunodeficiency virus was negative. The chest radiograph revealed a diffuse opacity of high density with a symmetrical and bilateral micronodular pattern. A peripheral hyperlucency of both lung fields or a black pleural line was seen (**Figure 1**). The finding was confirmed by an HRCT scan, which revealed diffuse calcification along the interlobar septa and subpleural regions in the lower pulmonary regions, with ground-glass attenuation and septal thickening in between. Multiple cysts along the subpleural line were identified as causing the black pleural line signs (**Figure 2**).

The patient underwent a bronchoscopy with bronchoalveolar lavage and transbronchial lung biopsy. The branches of the bronchial tree were all patent. Unfortunately, the microliths were absent and the histology findings were inconclusive.

The electrocardiogram revealed sinus rhythm with right atrioventricular chambers enlargement. The echocardiography confirming the finding by demonstrating that right and left chambers were dilated, resulting in mitral and tricuspid valve

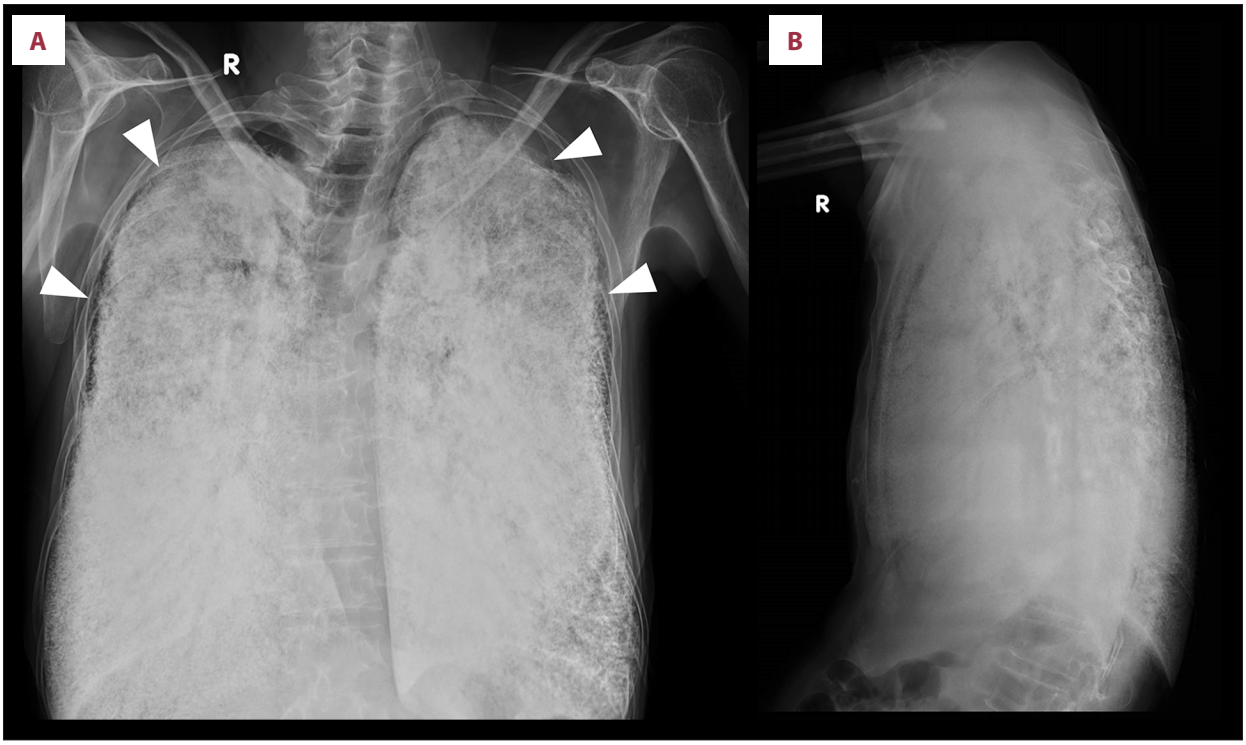

Figure 1. (**A, B**) Chest X-ray. Chest X-ray with posteroanterior and lateral view shows a pattern of diffuse opacity of high density with symmetrical and bilateral micronodular patterns. Notice the subpleural lucency in keeping with the black pleural line (arrow head).

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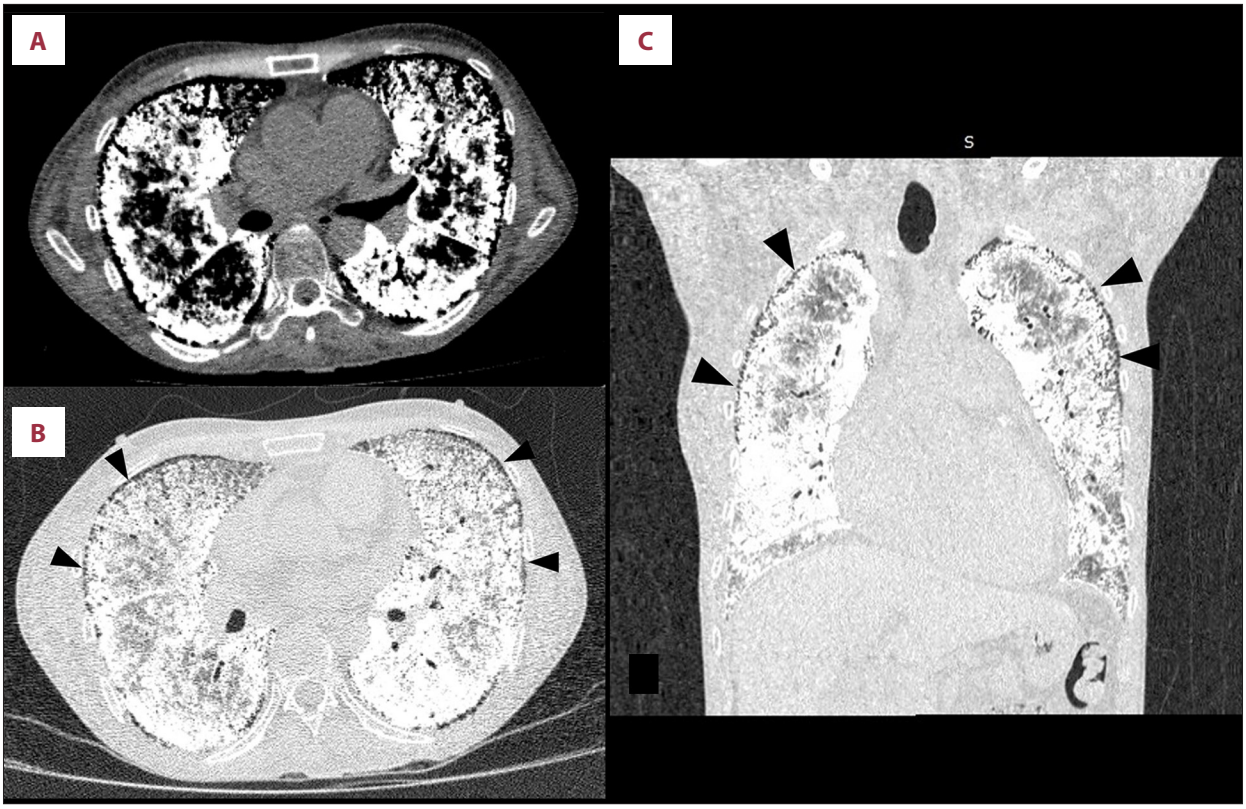

Figure 2. Chest HRCT. Reconstructed plane of axial and coronal with mediastinal (**A**) and lung (**B, C**) window of HRCT revealed diffuse micronodular calcification along the interlobar septa and subpleural regions in the lower pulmonary regions, with ground-glass attenuation and septal thickening in between. Multiple cysts were also noticed along the subpleural line (arrow head).

regurgitation. Left ventricle contractility decreased with an ejection fraction of 22% and right ventricle contractility decreased with a tricuspid annular plane systolic excursion of 1.4 cm. Pulmonary function tests were not performed due to clinical deterioration of progressive dyspnea during inpatient hospital observation. Hematologic tests on blood cell counts and chemistry panels were unremarkable. Arterial blood gas analysis showed metabolic alkalosis with respiratory compensation. The patient, however, refused to be treated in the high care unit and decided to stop the treatment.

Discussion

There have been over a thousand recorded cases of PAM across the world. Asia had the highest burden of cases, whereas Turkey and Italy had the highest number of reported cases per population [1,4]. Despite a modest male predominance, the majority of reports revealed no sex preference [4]. The fact that the disease runs in families suggests that it is passed on through autosomal recessive inheritance [5].

This condition develops chronically with an initially poorly defined etiopathogenesis. However, recent investigations have revealed that genetic mutations of the SLC34A2 gene cause the disease. The SLC34A2 gene encodes a type of pH-sensitive sodium-dependent phosphate transporter, i.e., sodium-dependent phosphate transport protein 2b or NaPi-IIb. This protein plays a pivotal role in phosphate homeostasis in several organs and tissues in the body. However, its main location is in the alveoli of the lungs, specifically in alveolar type II cells [1]. These cells create surfactant from phospholipids and are also responsible for recycling and decomposing old surfactant. The problem with SCLC34A2 is that it is likely to make it harder to get rid of the waste product phosphate, which leads to calcium-phosphate buildup in the alveoli [5,6].

Several publications have proved the utility of monitoring the blood concentration of surfactant protein-A (SP-A) and surfactant protein-D (SP-D) in PAM patients. In the lungs, type II alveolar cells and Clara cells produce these 2 proteins. Due to PAM-induced widespread parenchymal fibrosis, permeability increases, leading to a rise in the blood levels of these 2 proteins. Consequently, SP-A and SP-D measurements may be a viable option for monitoring the course and activity of the disease [7,8]. However, due to limited resources, these assays were not performed in our center.

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Different clinical manifestations are possible. Intriguingly, people can be asymptomatic for many years before developing symptoms in their third or fourth decades of life [2]. Upon initial presentation, patients often have restrictive lung disease [9]. Pulmonary function of adult patients frequently deteriorates over time, and respiratory failure caused by cor pulmonale chronicum is the leading cause of death in middle age [1].

Radiological diagnosis is used as the main diagnosis of PAM, especially in the setting of limited diagnostic resources. The typical chest radiograph findings, as featured in our patient, are bilateral diffuse areas of micronodular "sand storm" calcifications that predominate in the middle and basal lung areas, which obliterate the margin of the heart and the diaphragm [3,4,10]. A hyperlucency area between the lung parenchyma and the ribs, known as the black pleural line, is usually demonstrated [3,10]. The chest radiographs in our patient corroborated the characteristic pattern described in the literature.

It is imperative to confirm the chest radiograph findings with HRCT, which can corroborate the finding of 'black pleural line' signs, observed on chest radiographs as small subpleural cysts with thin walls. It was reported that the predominant deposition of calcipheriths along the interlobular septa, often associated with ground-glass opacities, is virtually pathognomonic of PAM [11]. The considerable variation of the HRCT findings in patients with PAM depends on the stage of the disease, which is classified into 4 phases based on HRCT findings [1]. The initial phase, termed as pre-calcific, indicates the earliest stage of the illness without the characteristic PAM features. The second phase of "snowstorm"-like lungs begins to exhibit the characteristic radiological appearance of a diffuse distribution of calcific nodules. Although a predilection for the basal and middle zones of the lung has been documented, they tend to be diffusely dispersed across the lungs. Most calcific nodules are less than 1 mm, although larger 2-4 mm nodules are observable. The third phase is characterized by the increase in the number and size of opacifications, as well as a little interstitial thickening, which obliterate the contour of the heart and diaphragm. The fourth phase, or what is known as "white lung" appearance, is characterized by a rise in the quantity and size of calcific deposits, which results in a significant calcification of the interstitial and pleural line [11,12]. This terminal phase is the typical appearance, as was present in our patient.

Clinicians should be aware that some PAM findings, such as nodular calcifications pattern, can also be observed in other disorders. Other pathologies, such as miliary tuberculosis, metastatic pulmonary calcification, sarcoidosis, pneumoconiosis, and dystrophic calcification due to infectious or occupational etiologies, can have the relatively similar features. It is particularly important in Indonesia, as it is one of the countries with the highest burdens of tuberculosis. Miliary tuberculosis, while accounting for just 1% to 2% of tuberculosis cases [13], is nonetheless more prevalent than PAM and is more likely to be at the top of the list of differential diagnoses when a miliary nodular pattern is encountered on chest radiography.

Certain features may help to differentiate the micronodular pattern of pulmonary diseases. The micronodules of miliary tuberculosis are not calcified but are instead diffuse and uniformly distributed in a random pattern [10]. Enlarged mediastinal and hilar lymph nodes may be present and show necrosis. Another cause of randomly distributed micronodules is hematogenous pulmonary metastasis, which can occur in thyroid cancer, melanoma, renal cancer, and breast cancer [14]. In certain conditions, pulmonary metastasis can have calcification, which occurs most often in association with conditions that directly or indirectly result in hypercalcemia, for example, hyperparathyroidism and chronic renal failure [15]. Sarcoidosis and pneumoconiosis share similar features, with perilymphatic and paraseptal nodules in distribution and an upper-lobe predominance. Patchy consolidation may also accompany it [14]. Dystrophic calcifications are the most common cause of multiple diffuse pulmonary calcifications of greater than 5 mm in size. Lymph node enlargement or calcification and pleural calcification with thickening or plaques are often present [15].

In this regard, radiology results, especially HRCT, and clinical characteristics should always be correlated, as various illnesses appear and progress differently. Chest radiography could be vague and potentially misdiagnosed. Therefore, HRCT has better sensitivity to reveal characteristic features of PAM than lung biopsy, reserving lung biopsy only for atypical and inconclusive cases.

A lung biopsy, needle biopsy, or transbronchial biopsy is required for histopathological diagnosis of PAM. Open lung biopsy remains the most definitive method for diagnosing PAM. Alternatively, a transbronchial biopsy may be done [4]. A transbronchial biopsy that reveals microliths within the alveolar lumen is more compelling, but its yield is prone to sampling error depending on the amount of microlith deposition, and is associated with the risks of hemorrhage and pneumothorax [3]. Most of the pathological characteristics are invariably intra-alveolar microlith deposition. Lamellar calcified microliths within alveolar luminal spaces with fibrosis and thickening of alveolar walls constitute the characteristic microscopic pattern [3,4].

Various treatments have been attempted. Other approaches such as calcium chelators, serial bronchopulmonary lavage, and corticosteroids have not been shown to be effective as definitive treatment. Bisphosphonates, specifically disodium etidronate, have been considered as treatment, yet no solid evidence for the efficacy was found [12]. At present, lung

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transplantation remains the only viable treatment option, although there are no prognostic data to determine the optimal time to refer a patient for lung transplantation. Right ventricular function serves as the parameter to prescribe this approach. Referring the patient with well-preserved ventricular function before the onset of severe right ventricular dysfunction is expected to gain the optimal benefit of this curative treatment [16].

Conclusions

In conclusion, PAM is a rare disease with a chronic clinical course that starts at an early age. Its manifestation varies according to phase, but progressive deterioration may result in poor prognosis. Clinicians should have a high index of suspicion in the case of miliary pattern diseases. When a non-invasive diagnostic approach is preferred, chest radiography and, preferably, HRCT should be used to identify the characteristic features of alveolar microlithiasis.

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Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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