

Pulmonary alveolar microlithiasis with finger clubbing: A case report and literature review

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Abstract. Pulmonary alveolar microlithiasis (PAM) is a rare autosomal recessive and slowly progressive disease. Mutations of the solute carrier family 34, member 2 gene are considered to be the cause of the disease. The present study reported the case of a 35-year-old female patient who was diagnosed with PAM. The parents of the patient were reported to be blood-related (cousins). The clinical manifestations and radiological and pathological characteristics of the patient are reported. A pulmonary function examination detected restrictive ventilatory and diffusion defects, and a high-resolution computed tomography scan showed multiple bilateral diffuse ground-glass opacifications and subpleural linear calcifications. A bronchoalveolar lavage fluid (BALF) examination detected a calcified body in the lavage fluid and a transbronchial biopsy showed numerous calcified bodies, concentrically laminated with an onion skin-like appearance in the alveolar spaces. Based on the aforementioned observations, the patient was diagnosed with PAM. Following administration of inhaled corticosteroid treatment, the symptoms were improved and the patient was discharged. After 1 year, the patient was lost to follow-up. The present study presents and reviews the typical radiological appearance, clinical presentation, pathological characteristics and treatments of PAM, and suggests that, often, the parents of the patients are blood-related and typically cousins. In addition, the present study proposes that a BALF examination may be considered an alternative method for the pathological diagnosis of PAM.

Introduction

Pulmonary alveolar microlithiasis (PAM) is a rare genetic diffuse lung disease characterized by calcifications within the alveolar airspaces. It is caused by inactivating mutations in the solute carrier family 34, member 2 (SLC34A2) gene, which encodes the type IIb sodium phosphate cotransporter in alveolar type II cells (1-3). SLC34A2 is primarily expressed in alveolar type II cells, where it is responsible for the transport of phosphate ions from the alveolar space into the alveolar type II cells (4). Therefore, the inability of the alveolar type II cells to remove phosphorus ions from the alveolar space as a result of inactivating mutations in SLC34A2, leads to microlith formation in the alveolar space (2,4).

PAM has been reported in all continents, with no particular geographic or racial distribution. However, a review of 1,022 published cases showed that PAM was more prevalent in Asia, followed by Europe, North America, South America and Africa, with the majority of cases reported in Turkey, followed by China, Japan, India, Italy and the USA (1). Furthermore, the ratio between the number of cases per 1 million people was 1.85 for Turkey, 1.08 for Italy, 0.92 for Japan, 0.15 for the USA, 0.1 for China and 0.06 for India (1). PAM may affect people of any age, ranging from premature infants to the elderly; the youngest reported case was of premature twins (5), and the eldest patient to be diagnosed with PAM was an 84-year-old female (6). Familial occurrence has been observed in 50% of Japanese, 48% of Turkish and 43.7% of Italian patients (7). A recent review analyzing 1,022 patients worldwide showed that 37.2% (381 of 1022 patients, belonging to 163 families) of PAM cases have familial presentation (1). Furthermore, in 36 of 163 families, the parents were cousins (1).

The hallmark of PAM is the striking dissociation between the radiological appearance and clinical presentation, meaning that a patient may present with a paucity of symptoms in contrast to image findings (2). Frequently, patients may have no clinical symptoms, such that diagnosis is often fortuitous (8). In symptomatic patients, dyspnoea is the most frequently encountered symptom, followed by a cough, chest pain and asthenia (8). The radiological appearance on high resolution computed tomography (HRCT) scans include ground-glass opacities, small parenchymal nodules, small subpleural nodules, subpleural cysts and subpleural linear calcifications (9). Given the striking dissociation between the

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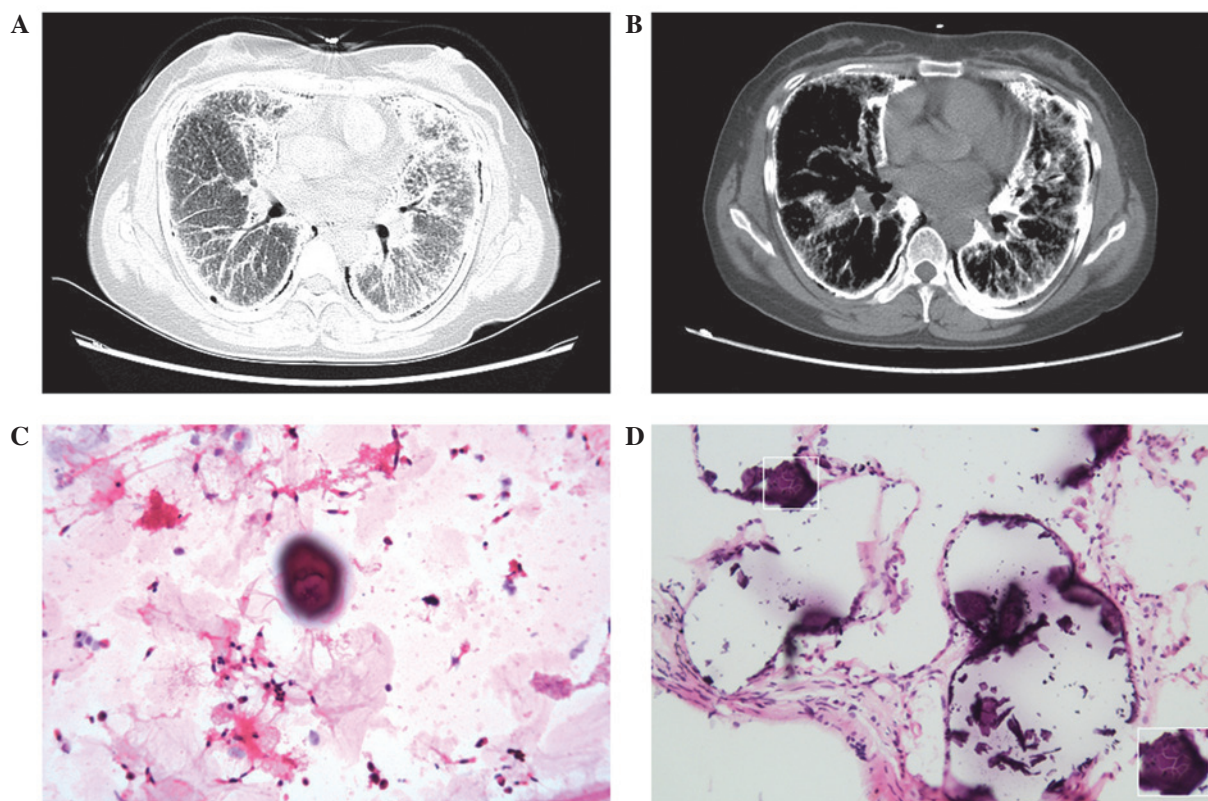


Figure 1. Typical computed tomography images of a 35-year-old female with pulmonary alveolar microlithiasis. (A) Lung window. The black pleura sign was presented between the ribs and calcified parenchyma. (B) Mediastinal window. Hyperdense consolidations were observed in both lungs. (C) Bronchoalveolar lavage fluid examination showed a calcified body in the lavage fluid (magnification, x200; HE stain). (D) Transbronchial biopsy demonstrated characteristic intra-alveolar lamellar microliths (magnification, x200; HE stain). The highlighted section corresponds to lamellar microliths. HE, hematoxylin and eosin stain.

radiological appearance and clinical presentation of PAM, the diagnosis may be based on typical radiological findings, particularly in family members of a patient previously diagnosed with PAM (2).

At present, no definitive treatment is available to reduce the disease progression. Systemic corticosteroids, calcium-chelating agents and serial bronchopulmonary lavage have been shown to be ineffective and are used as palliative treatments (1). Disodium etidronate (DE) has been proposed as an effective medicine to reduce calcium phosphate precipitation in PAM (10-12).

In the present study, a case of PAM in a 35-year-old female patient with severe typical imaging findings, mild clinical manifestation and characteristic histopathology is reported. In addition, the present study reviewed the typical radiological appearance, clinical presentation, pathological characteristics and novel treatments for PAM, and supported that often the parents of the patients are cousins. Furthermore, the present study proposes that a bronchoalveolar lavage fluid (BALF) examination may be considered an alternative method for the pathological diagnosis of the PAM.

Case report

A 35-year-old female patient presented at the Taihe Hospital (Shiyan, China) in October 2013 with a 4-year history of a persistent dry cough. The parents of the patient were reported to be blood-related (cousins). A physical examination

revealed striking bibasilar inspiratory crackles (velcro rales), and finger clubbing was observed. An arterial blood gas test revealed that the oxygen saturation was 96% (normal, $\geq 95\%$) and the oxygen partial pressure was 84 mmHg (normal, ≥ 80 mmHg) on ambient air. A pulmonary function examination showed typical features of a restrictive ventilatory defect with a reduced vital capacity of 55% and a diffusion defect with a reduced lung transfer factor for carbon monoxide of 47% of the predicted values (normal, $\geq 80\%$ predicted value). The results of a 6-min walk distance test indicated a reduced exercise capacity [distance walked, 331 m; normal for women = $(2.11 \times \text{height in cm}) - (2.29 \times \text{weight in kg}) - (5.78 \times \text{age}) + 667$ m] (13). In addition, a HRCT scan showed multiple bilateral diffuse ground-glass opacifications and subpleural linear calcifications. A number of small subpleural air cysts were observed between the bony rib cage and the calcified pulmonary infiltrate (also termed the black pleural line). Subpleural linear calcification and interlobar fissure calcification were also evident (Fig. 1A and B).

A BALF examination detected a calcified body in the BALF and a transbronchial biopsy was subsequently performed. The lung tissue specimens were fixed in 10% neutral-buffered formalin (Jiangxi Liansheng Experiment Technic Assembly Co., Ltd., Nanchang, China) over night, dehydrated through a graded alcohol series, cleaned with dimethylbenzene and embedded in paraffin (both Sinopharm Chemical Reagent Co., Ltd., Shanghai, China). Subsequently, the paraffin-embedded tissue specimens were cut into 5- μ m sections, stained with

hematoxylin (Shanghai Chemical Reagent Co., Ltd., Shanghai, China) and eosin (Tianjin Bodi Chemical Co., Ltd., Tianjin, China) and then visualized and photographed under a microscope (BX51; Olympus Corporation, Tokyo, Japan). Numerous calcified bodies, concentrically laminated with an onion skin-like appearance in the alveolar spaces, were observed under the microscope (Fig. 1C and D; hematoxylin and eosin stain).

Based on the aforementioned observations, the patient was diagnosed with PAM. Following inhalation of budesonide suspension (1 mg; AstraZeneca, London, UK), the symptoms were improved and the patient was discharged. After 1 year, the patient was lost to follow-up. The present study was conducted with approval from the ethics committee of Shiyuan Taihe Hospital (Shiyuan, China), and with written informed consent from the patient.

Discussion

PAM is characterized by calcifications within the alveolar spaces, and clinical-radiological dissociation is the hallmark of this disorder (2). Numerous PAM patients do not present any clinical symptoms; however, the typical presentations in symptomatic patients include dyspnea, a nonproductive cough, sporadic hemoptysis, chest pain and asthenia (8,14). Due to the chronic hypoxia, finger clubbing is observed in a small portion of patients in the advanced stages of the disease (1). Plain chest radiography, HRCT, magnetic resonance imaging, ^{99m}Tc -methylene diphosphonate, ^{18}F -fluorodeoxyglucose-positron emission tomography/CT and pulmonary function tests have been commonly used to provide diagnostic evidence for PAM (2). However, the diagnosis of PAM can be established on the basis of the typical radiological characteristics of the disease, which includes interlobular septal thickening, ground-glass opacities, calcified micronodules, pleural and subpleural calcification and cysts (2). In the present case, HRCT detected multiple bilateral diffuse ground-glass attenuation and subpleural linear calcifications, which was consistent with a previous study (9). In addition, a lung biopsy (transbronchial or open) and BALF examination was performed to confirm the diagnosis of PAM. Histologically, typical findings within the alveolar spaces include numerous calcified bodies, which are concentrically laminated with an onion skin-like appearance (14-16). This appearance is distinct from metastatic and dystrophic calcifications, which are located in the interstitial or vascular compartments (2,17). In the early stages of PAM, the lung involvement is limited, the interlobular septa are intact and gas exchange and the pulmonary function tests are normal (2,8). However, as the disease progresses, the microliths gradually grow in size and occupy a large number of alveolar spaces (2,8,15). In doing so, they make contact with the walls, exerting pressure and causing damage that leads to the replacement of the walls with fibrous tissue, which in turn results in the deterioration of ventilatory and perfusion disorders (2,8,15). In addition, the pulmonary function tests reveal typical features of a restrictive defect with reduced forced vital capacity (2,8). In the present case, the pulmonary function tests suggested that the patient had both restrictive and diffusion defects.

In previous studies, a family history of PAM was reported in 31.8 to 37.2% of cases (1,8), and often the parents of

patients were cousins, which was indicative of a genetic aetiology with a pattern of autosomal recessive inheritance (1,8). First cousins are third-degree relatives, sharing 1/8 of their genes, and with a 1/16 chance of homozygosity by descent (1). Consistent with this, the parents of the present patient were cousins. A mutation in the SLC34A2 gene, which encodes the type IIb sodium-dependent phosphate co-transporter, is considered to be responsible for familial PAM (3). This mutation leads to the reduced ability of the alveolar type II cells to clean-up the phosphorus ions from the alveolar space, which subsequently results in calcium phosphate chelation and microlith formation in the alveolar air spaces (2,3).

To date, no effective treatment has been established for the prevention of PAM progression. DE, which is a member of the bisphosphonate family, has been considered a candidate drug for the treatment of patients with PAM due to its inhibitory effect on the precipitation of hydroxyapatite microcrystals (10). Although the effect of DE treatment on PAM is controversial, a previous study by Ozcelik *et al* (11) reported two cases of PAM that were treated with DE (200 mg/day) for a duration of 9 and 11 years; an evident improvement of the progression-free survival was observed during the treatment. In addition, in one of the cases, pulmonary calcifications gradually disappeared and no new calcifications were formed during the 11-year treatment (11). Furthermore, Cakir *et al* (12) reported the case of three siblings (an 11-year-old boy and 4-year-old twin girls) who were treated with DE (200 mg/day) for a 1-year period; two of the siblings exhibited radiological improvements, whereas one did not. Based on these results, DE may be considered a treatment option for PAM, although further studies are required. Lung transplantation remains the only possible treatment for end-stage cases of PAM, although the long-term survival of such patients is uncertain (18,19). An alternative treatment may include a low-phosphate diet; in a previous study of a mouse model, a low-phosphate diet prevented microlith formation in young mice and reduced lung injury (20). Furthermore, the burden of pulmonary calcium deposits in established PAM was diminished within 4 weeks of a low-phosphate diet (20). Despite these treatment options, the long-term prognosis of patients with PAM is poor, with advanced pulmonary fibrosis, respiratory failure, cor pulmonale and mortality observed in end-stage PAM patients (2).

In conclusion, the present study reported a typical case of PAM; the parents of the patient were cousins, the predominant symptom was a dry cough and the physical examination revealed finger clubbing. The HRCT scan showed the typical PAM radiological appearance, including multiple bilateral diffuse ground-glass attenuations and subpleural linear calcifications. The mild clinical presentation was markedly dissociated from the severe radiological appearances. A pulmonary function test suggested that the patient had both restrictive and diffusion defects, a BALF examination detected a calcified body in the BALF and a transbronchial biopsy demonstrated the characteristic intra-alveolar lamellar microliths.

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