



Available online at www.sciencedirect.com

SciVerse ScienceDirect

journal homepage: www.elsevier.com/locate/rmed



REVIEW

Pulmonary alveolar microlithiasis. State-of-the-art review



Flávia Angélica Ferreira Francisco ^{a,c}, Jorge Luiz Pereira e Silva ^{b,d},
Bruno Hochhegger ^{a,e}, Gláucia Zanetti ^{a,f}, Edson Marchiori ^{a,*}

^a Department of Radiology, Federal University of Rio de Janeiro, Rio de Janeiro, Brazil

^b Department of Internal Medicine and Diagnostic Support, Federal University of Bahia, Salvador, Brazil

Received 23 June 2012; accepted 27 October 2012

Available online 23 November 2012

KEYWORDS

Pulmonary alveolar microlithiasis;
Pulmonary diseases;
Congenital diseases;
Computed tomography

Summary

Pulmonary alveolar microlithiasis (PAM) is a rare genetic lung disease characterized by calcifications within the alveoli. Mutations in the SLC34A2 gene, which encodes a type IIb sodium-phosphate cotransporter, are responsible for this disease, leading to intra-alveolar accumulation of phosphate that favors the formation of microliths. The hallmark of this disorder is clinical-radiological dissociation, with typical imaging findings that correlate well with specific pathological findings. The long-term prognosis is poor and no treatment has been discovered to date. The aim of this review is to describe the main pathological, clinical, and imaging aspects of PAM, ranging from its genetic basis to treatment.

© 2012 Elsevier Ltd. All rights reserved.

Contents

Introduction	2
Epidemiology	2
Genetic aspects	2

* Corresponding author. Rua Thomaz Cameron 438, Valparaíso, CEP 25685-120, Petrópolis, Rio de Janeiro, Brazil. Tel.: +55 24 22492777; fax: +55 21 26299017.

E-mail addresses: flaviangel@gmail.com (F.A. Ferreira Francisco), cpc-ba@svn.com.br (J.L. Pereira e Silva), brunohochhegger@gmail.com (B. Hochhegger), glauciazanetti@gmail.com (G. Zanetti), edmarchiori@gmail.com (E. Marchiori).

^c Rua Cristóvão Xavier Lopes, 131/306, Coelho Neto, CEP: 21530120, Rio de Janeiro, Brazil. Tel.: +55 21 71566944.

^d Rua Conselheiro Correia de Menezes n° 91, Horto Florestal, CEP 40.295-030, Salvador, Bahia, Brazil. Tel.: +55 71 3334 7547.

^e Rua João Alfredo, 558/301, CEP 90050-230, Porto Alegre, Brazil. Tel.: +55 51 32864230.

^f Rua Coronel Veiga, 733/504, Centro, CEP 25655-504, Petrópolis, Rio de Janeiro, Brazil. Tel.: +55 24 22429156.

Pathogenesis	3
Pathology	3
Clinical manifestations	4
Extrapulmonary manifestations	4
Imaging findings	4
Chest radiography	4
High-resolution computed tomography	5
Magnetic resonance imaging	5
Nuclear medicine	6
Pulmonary function tests	6
Clinical course	6
Diagnosis	7
Treatment	7
Conclusion	7
Conflict of interest statement	7
References	7

Introduction

Pulmonary alveolar microlithiasis (PAM) is a rare autosomal-recessive disorder characterized by intra-alveolar accumulation of spherical calcified concretions (called calci-ferites, calcospherites, or microliths), in the absence of any known calcium metabolism disorder. Most patients are asymptomatic at the time of diagnosis and the disease is usually detected incidentally during routine examinations, although the diagnosis can be made during the investigation of family history in an individual with alveolar microlithiasis.^{1,2}

PAM may affect people of any age, ranging from early childhood to advanced age. However, affected individuals usually become symptomatic in the third or fourth decade of life. The occurrence may be sporadic or familial; about one-third of cases are hereditary, with autosomal-recessive inheritance.^{1,2}

A "sandstorm" appearance is the typical radiographic presentation of this disease.³ Given the striking dissociation between the radiological appearance and clinical presentation of PAM, the diagnosis is sometimes based on radiological findings, particularly when the disease has affected another member of the patient's family.²

PAM has been diagnosed in patients in various stages of life, and the disease has a long and progressive course resulting in the deterioration of lung function.¹ The pathology of PAM has been attributed to a mutation in the type IIb sodium-phosphate cotransporter (SLC34A2) gene, which is involved in phosphate homeostasis in various organs, including the lungs, that induces excessive phosphate accumulation that may later act as a nidus for microlith formation.⁴ This review describes the main clinical, pathological, and imaging aspects of PAM.

Epidemiology

PAM has been found on all continents, with no particular geographic or racial distribution. It is more prevalent in

Europe, followed by Asia, notably Asia Minor, with most cases found in countries such as Turkey and Italy.²

The age of PAM onset is difficult to establish because the disease is generally diagnosed incidentally on a chest radiograph requested for other reasons. Although PAM has been described in all age groups, including one case report in an 8-month-old infant,⁵ the mean age at diagnosis is 35 years among cases reported in the literature. No significant gender predominance has been observed.^{1,2,6,7}

Genetic aspects

Familial cases of PAM occur at reported frequencies ranging from 36% to 61%, indicating the importance of genetic factors in the genesis of the disease.² PAM has been reported to occur among siblings and cousins in a horizontal pattern,^{6,8,9} and less frequently between parents and children in a vertical pattern of familial inheritance.^{10,11}

Several authors independently identified the gene responsible for PAM. These studies found that homozygous mutations in the gene of solute carrier family 34 (sodium-phosphate), member 2 (SLC34A2) are significantly related to PAM, as this gene encodes a type IIb sodium-dependent phosphate transporter (NaPi-IIb).^{4,8,12–15} In a genetic analysis of a family with consanguineous marriage, Dogan et al¹⁶ noted that three children diagnosed with PAM had a homozygous mutation in the SLC34A2 gene and that their parents, who were carriers of the disease, had a heterozygous mutation in the same gene. These findings suggest that impaired activity of the SLC34A2 gene may be responsible for familial PAM. Thus, evidence supports the hypothesis that this disease is hereditary and related to the pattern of autosomal-recessive inheritance with a high penetrance.¹² These mutations occur very rarely; the frequency of a chromosome with a mutant gene in the general population is less than 0.008.¹

The SLC34A2 gene is located on the short arm of chromosome 4 (4p15). It has 13 exons, the first one noncoding, and encodes a 2280-nt mRNA and a 690-amino acid protein. The homozygous mutations described may occur in

different ways, such as by frameshifts, chain terminations, and amino acid substitutions, among others.¹³ These mutations can determine the production of a defective protein or abolish gene expression,^{4,17} resulting in the loss of function of the encoding protein.^{4,13}

The SLC34A2 gene encodes a membrane protein that is expressed primarily in the apical portions of alveolar type II cells¹⁸ and is the most common phosphate carrier in the lungs.¹² It has eight predicted transmembrane domains; proteins lacking five of these domains are likely to lose normal function.⁴

Pathogenesis

Trans epithelial transport of a variety of solutes across the alveolar epithelium maintains the composition of alveolar fluid. Type II alveolar cells have many important functions in the lung, including the regulation of surfactant metabolism, ion transport, and alveolar repair. Several types of epithelial transport occur in type II cells, including carriage as sodium-dependent glucose and the transport of amino acids, protons, and sodium along epithelial sodium channels. These and other means of trans epithelial transport may provide the substrate required for the synthesis of pulmonary surfactant in type II cells.¹²

Type II cells produce pulmonary surfactant, of which phospholipids are essential constituents. Outdated surfactant is taken up by type II cells for recycling and degradation and by alveolar macrophages for degradation. Degraded phospholipids release phosphate that should be cleared from the alveolar space.¹⁹ The wild-type IIb sodium-phosphate cotransporter transports phosphate in the presence of sodium, whereas mutants do not. These proteins cotransport sodium and phosphate into the cells with a stoichiometry of $3\text{Na}^{+}:1\text{HPO}_4^{2-}$, forming NaH_2PO_4 and thus producing inward current. The wild-type IIb sodium-phosphate cotransporter elicited inward current with the addition of NaH_2PO_4 , whereas mutants did not.⁴ Therefore, the inability of type II alveolar cells to clean phosphorus ions from the alveolar space may lead to microlith formation in the extracellular fluid.^{12,19}

The type IIb sodium-phosphate cotransporter is a protein expressed primarily in the lungs and mammary glands, and less frequently in various other tissues of epithelial origin, such as the small intestine, kidney, pancreas, ovaries, liver, testes, placenta, and prostate. In most cases, the lungs are the only affected organs.²⁰ Calcium deposits have been found in other organs in patients with PAM, including the pleura, kidneys,²¹ seminal vesicles,²² urethra and gallbladder.²³ Aortic valve calcification and arteriosclerosis have also been described.²⁴

Three sodium-phosphate cotransporters have been identified in mammals (types I–III). Types I and II are expressed primarily in the kidneys, liver, and small intestine, whereas type III is distributed ubiquitously, including in the lungs. The type II NaPi cotransporter can be subdivided into types IIa and IIb. The first is expressed mainly in proximal tubules, and no evidence has been found for its expression in the lungs. PAM is characterized by a loss of type IIb sodium-phosphate cotransporter function.²⁵

A low dietary phosphate intake increases the expression of type IIa NaPi cotransporter in the kidney and small intestine, but results in no change in the amount of IIb protein in the lungs. This finding suggests that type IIb is not regulated directly or indirectly by dietary phosphate content *via* 1,25 dihydroxyvitamin D3.¹⁸

Pathology

The pathological findings of the PAM may be confined to certain areas or show diffuse distribution through the lungs.²⁶ Lung biopsy and autopsy specimens demonstrate characteristic intra-alveolar lamellar microliths.^{26,27} Calcium deposits in the alveoli begin in the lower lobes and spread over a period of years throughout the lungs, progressing to the middle thirds and then to the upper portions.¹

Microliths associated with PAM are ovoid or round and have diameters of 0.01–2.8 mm.¹ X-ray energy-dispersive spectroscopy of the microliths yielded a phosphorus:calcium ratio of 1:2, consistent with calcium phosphate and calcium hydroxyapatite or carboxyapatite.²⁷ Deposits of iron, zinc, aluminum, silica, and magnesium are also encountered frequently.¹

Histologically, the microliths are periodic acid-Schiff—positive²⁶ and consist of calcareous concentric lamellae around a central nucleus with an amorphous or granular aspect (Fig. 1). This appearance is distinct from those of metastatic and dystrophic calcifications, which are located in the interstitial or vascular compartments.²⁸

In the early stages of PAM, the interlobular septa are intact and the gas exchange is normal. When the concretions are small, spaces may exist between the alveolar walls and microliths. These microliths gradually grow within the alveoli to fill the entire alveolar space and contact the walls, exerting pressure and causing damage that leads to the replacement of the walls by fibrous tissue.^{1,27}

On macroscopic examination, lungs affected by PAM show reduced elasticity and can weigh up to 5 kg in cases of

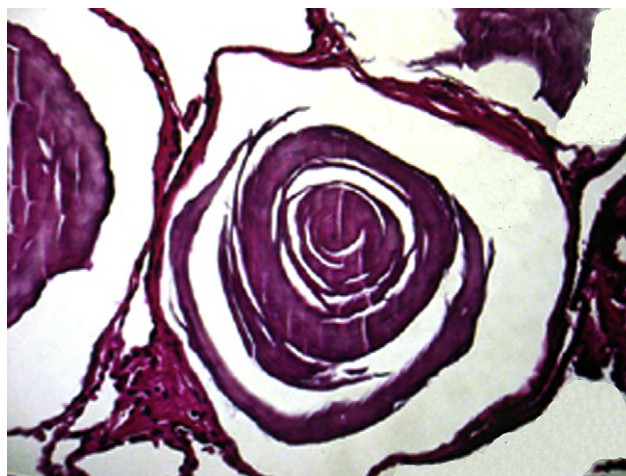


Figure 1 Photomicrograph of a section of resected lung tissue showing a concentrically laminated microlith filling the alveolar space (original magnification, $\times 100$; hematoxylin and eosin stain).

diffuse distribution. The outer surfaces of the lungs are granular and irregular due to protrusions of microliths by visceral pleura. Greatly increased parenchymal resistance is also apparent.¹ On gross examination, apical blebs and bullae may be present in the anterior portions and lung apices.²⁶

Clinical manifestations

The hallmark of this disorder is clinical-radiological dissociation, meaning that clinicians will find a paucity of symptoms in contrast to imaging findings.²⁹ At diagnosis, most patients are asymptomatic and changes in the lung parenchyma are found incidentally. In more serious cases, cyanosis and clubbing are the first detected signs. The most common symptom is dyspnea, followed by dry cough, chest pain, sporadic hemoptysis, and asthenia.^{1,2,12,26} Pneumothoraces have also been reported.³ Direct stimulation by microliths is believed to induce unmyelinated C fibers, which are found in the bronchial tree and lung parenchyma, to release tachykinins, which have potent inflammatory effects and activate other receptors, thereby causing cough.^{1,30}

In the general clinical course of PAM, microliths probably begin forming early in childhood, but clinical symptoms arise much later.¹³ In the early stages of the disease, when lung involvement is limited, pulmonary function tests are normal. In later stages, as the disease progresses, the microliths occupy a large number of alveoli and the lungs become hardened, causing deterioration of mechanical ventilatory disorders as well as perfusion and ultimately resulting in hypoxemia, increased arterial carbon dioxide levels, pulmonary hypertension, and *cor pulmonale*.^{1,2,12,15,31}

Routine blood test findings, including serum calcium concentration and hepatic, renal, and parathyroid functions, remain normal in patients with PAM. Marked elevations in the serum concentrations of surfactant proteins A and D have been recently reported; these proteins are also elevated in patients with pulmonary alveolar proteinosis and pulmonary fibrosis. These increases in serum levels may be explained by the histological characteristics of PAM, one of which is diffuse fibrosis in the parenchyma that increases permeability, leading to elevated levels of these two proteins in the blood. These levels increase further with the deterioration of pulmonary function. They may therefore serve as markers to monitor disease activity and progression.³²

Extrapulmonary manifestations

Extrapulmonary calcifications related to mutations in the SLC34A2 gene include medullary nephrocalcinosis, nephrolithiasis,²¹ cholelithiasis,²³ calcification of the lumbar sympathetic chain, and testicular involvement.³³ Calcifications in the seminal vesicles²² and epididymal and periurethral calcifications causing obstructive azoospermia have also been described.³⁴ Cardiac complications, such as aortic and mitral valve²⁴ and pericardiac calcifications, have been reported.^{35,36}

Comorbidities associated with PAM include pectus excavatum,³⁷ hypertrophic pulmonary osteoarthropathy,³⁸



Figure 2 Chest radiograph of a 25-year-old male patient with pulmonary alveolar microlithiasis, showing diffuse opacification in both lungs with a dense micronodular ("sandstorm") appearance.

milk-alkali syndrome,³⁹ diaphyseal aclasia,⁴⁰ autosomal-recessive Waardenburg anophthalmia syndrome,⁴¹ and lymphocytic interstitial pneumonitis.⁴² A case of PAM after varicella zoster infection has been reported in a patient with antiphospholipid syndrome and discoid lupus erythematosus.⁴³ Extrapulmonary calcifications may vary according to the penetrance of the mutation.¹²

Imaging findings

Chest radiography

Plain chest radiographs of patients with PAM usually reveal diffuse, scattered, bilateral areas of micronodular calcifications, producing a "sandstorm" appearance (Fig. 2) that first involves the inferior portions and then the middle and upper portions of the lungs.¹ The distribution of calcified nodules can also be explained by the increased blood supply to these areas.⁴⁴ The lung bases show increased density due to thicker lung tissue and increased surface densities.⁷ The calcifications may be so dense that may obliterate the cardiac borders, diaphragm, and costophrenic or cardiophrenic sinuses.^{6,45}

Other radiographic findings include small apical bullae and a black pleural line, which appears as an area of linear hyperlucency caused by small, thin-walled subpleural cysts.^{3,7} This line, which some authors have described as the "black pleura" sign, is visible on chest radiographs between the calcified parenchyma and the ribs or

mediastinum.^{3,7} Radiographs of most patients with PAM do not show the black pleural line, and subpleural cysts can be detected more clearly by high-resolution computed tomography (HRCT), as described below.⁴⁵

High-resolution computed tomography

On HRCT, the most common findings are diffuse ground-glass attenuation and subpleural linear calcifications. Tomographic alterations are predominant in the inferior and posterior portions of the lungs.^{6,7,41,45–47} Additionally, the medial aspects of the lungs appear to be more heavily involved than the lateral aspects.⁴⁵ Ground-glass opacities, probably due to small calculi in the air space,⁶ are the most common finding in children and in patients with early-stage PAM.⁴¹ Subpleural linear calcifications due to the accumulation of intra-alveolar calculi in the peripheries of secondary pulmonary lobules demarcate the pleural surface and appear as pseudo-pleural calcifications.^{7,46}

Other alterations found on HRCT images are small parenchymal nodules, nodular fissures, subpleural nodules, calcifications along the interlobular septa that sometimes show a crazy-paving pattern, dense consolidations, and subpleural cysts. HRCT can also highlight areas of bullous emphysema in the apices. The crazy-paving pattern is defined as areas of ground-glass opacity with thickening of interposed interlobular septa, which occurs due to the accumulation of calculi in the peripheries of secondary pulmonary lobules. This pattern can also be observed in mediastinal window images because calcification is present along the interlobular septa. The literature contains no report of any other disease with a similar tomographic manifestation; these HRCT findings are thus considered to be very specific and even pathognomonic of PAM.^{6,47}

The small nodules seen on HRCT images correspond to the typical “sandstorm” appearance of dense micronodules (<1 mm) on plain chest radiographs and are very thin, well defined, and diffusely spread throughout the parenchyma, making the lungs homogeneously hypotransparent. The calcium density of the nodules is often impossible to define on HRCT images, probably due to their small dimensions. When they converge to form parenchymal consolidation, density can be better characterized and is often greater than that of the soft tissues.^{3,6} These consolidations predominantly occur along the heart borders in the lower posterior regions of the lungs and tend to be symmetrical (Fig. 3). Dense consolidations containing interposed air bronchograms can be present, especially in the lower posterior regions.^{6,7,45,48}

Studies of PAM using HRCT imaging have frequently mentioned the presence of subpleural cysts with diameters of 5–10 mm that may represent early lung fibrosis.⁴⁵ These cysts correspond to the “black pleura” sign described in the radiography section above. Using HRCT, Hoshino et al⁴⁶ suggested that this radiographic sign corresponded to the fat-dense layer between the ribs and calcified parenchyma. However, other authors were not able to detect fat density in any of the corresponding sites and the structure of these black pleural lines remains unclear because they are too thin to clearly visualize.⁴⁵



Figure 3 High-resolution computed tomographic images of a 31-year-old female patient with pulmonary alveolar microlithiasis. Images obtained at the levels of the superior (A) and inferior (B) lobes with an intermediary window show hyperdense consolidations in both lungs caused by the confluence of calcified nodules.

Areas of bullous emphysema may also be found on the anterior margins and apices of the lungs, and an associated pneumothorax may be seen.⁴⁹

The findings of PAM on plain chest radiography and CT are so characteristic that more diagnostic investigations are usually unnecessary, especially in patients whose families contain another member with PAM.²

Magnetic resonance imaging

On magnetic resonance imaging (MRI), the calcific lesions usually show hypointensity or a signal void on T1- and T2-weighted images. Hoshino et al⁴⁶ described a case in which MRI showed numerous, likely diffuse, microliths in the lower zones of the lungs as an increased signal intensity on T1-weighted images. Henkelman et al⁵⁰ found that particulate calcium with a microscopically visible high crystal surface area can reduce T1 relaxation times, producing a predominant T1 effect. Thus, the surface area of these small calcific nodules may be very large, leading to increased signal intensity on T1-weighted images.

Interstitial fibrosis and thickened alveolar walls are often seen in advanced stages of PAM, but these changes show higher signal intensity on T2- than on T1-weighted images.^{46,50}

Nuclear medicine

In patients with PAM, bone scintigraphy scanning agents, such as technetium (Tc)-99m methylene diphosphonate, should be taken up in the lungs due to chemisorption on the surfaces of calcium salts, the principal components of microliths.⁵¹ Tc-99m-labeled diphosphonate compounds have a natural affinity for calcification foci at the soft-tissue level and may detect early pulmonary calcification in PAM.²⁸

In a case report, Günay et al⁵² observed low ¹⁸F-fluorodeoxyglucose (FDG) uptake in the calcifications of PAM and lower FDG accumulation in the lung parenchyma without micronodular opacities. They thus suggested that combined positron emission tomography/computed tomography using ¹⁸F-FDG (¹⁸F-FDG-PET/CT) revealed low maximal standardized uptake values in patients with PAM due to the normal levels of inflammatory markers. Ito et al⁵³ reported a case in which high FDG uptake was observed in lung lesions showing sparing calcifications on CT, with no evidence of severe inflammation, whereas low uptake was observed in radiodense areas. Given the death of this patient within 1 month of the examination producing these findings, they postulated that high FDG uptake may be

a poor prognosis predictor for PAM. Therefore, FDG accumulation observed on PET/CT is not helpful for differential diagnosis, but may be useful for the evaluation of inflammation or the prediction of a patient's prognosis.^{52,53}

Pulmonary function tests

Pulmonary function tests, arterial blood gases, ventilation perfusion relationships, and O₂ diffusing capacity are normal in the initial stages of PAM. As the disease progresses, pulmonary function tests reveal typical features of a restrictive defect with reduced forced vital capacity (FVC) and elevated forced expiratory volume in 1 s/FVC. Reduced total lung capacity and tidal volume (V_T) have also been described (Table 1).^{12,26,46,54,55}

Arterial blood gas studies over a period of years can show resting hypoxemia that worsens with exercise, variable PaCO₂ values, and reduced O₂ diffusing capacity. The alveolar arterial O₂ gradient, venous admixture-like effect, and ratio of physiological dead space to V_T can be greater than normal in patients with PAM (Table 1). These findings suggest the presence of alveoli that are hypoventilated in relation to pulmonary capillary blood flow, leading to reduced O₂ tension in the mixed arterial blood.^{12,26,46,54,55} The paucity of studies investigating lung function in patients with PAM and the lack of disease staging and padronization limit its characterization.

The anatomic basis for these disturbances in lung function is likely multifactorial, including septal fibrosis and thickening and the physical presence of space-occupying microliths that may adhere to the alveolar membrane, resulting in the uneven distribution of inspired gas.⁵⁵

Table 1 Pulmonary function parameters in patients with pulmonary alveolar microlithiasis.

Respiratory function tests	
FVC (L)	Normal or low
FEV ₁ (L)	Normal
FEV ₁ /FVC (%)	Normal or high
TLC (L)	Low
RV (L)	Normal
RV/TLC (%)	Normal
DLCO (mL CO/min/mmHg)	Normal or low
V _T (L)	Normal or low
V _E (L/min)	Normal
VO ₂ (mL/kg/min)	Normal
Q _{VA} /Q _T (%)	Normal or high
V _D /V _T (%)	High
Arterial blood gases	
pH	Normal or high
PaO ₂ (mmHg)	Normal or low
PaCO ₂ (mmHg)	Normal or low
SaO ₂ (%)	Normal or low
(A-a) PO ₂ (mmHg)	High

FVC, forced vital capacity; FEV₁, forced expiratory volume in 1 s; TLC, total lung capacity; RV, residual volume; DLCO, lung diffusing capacity; V_T, tidal volume; V_E, minute ventilation volume; VO₂, O₂ consumption; Q_{VA}/Q_T, venous admixture-like effect; V_D, physiological dead space; pH, hydrogenionic potential; PAO₂, alveolar O₂ tension; PaCO₂, arterial CO₂ tension; SaO₂, arterial O₂ saturation; A-a, alveolar arterial gradient.

Clinical course

PAM has been described in different age groups ranging from children to seniors, but it is usually diagnosed around the age of 40 years.² Although the disease course is often protracted, patients may be asymptomatic for years before respiratory insufficiency becomes manifest,^{1,12} usually in the third or fourth decade of life.

The slow and progressive evolution of the disease may be responsible for the heterogeneity of symptoms. In some cases, the disease remains static; in others, it progresses over time to lung fibrosis, respiratory failure, and *cor pulmonale* accompanied by dyspnea and deterioration in pulmonary function test results demonstrating progressive worsening of the restrictive pattern and gas exchange.^{2,56}

Increased turnover of alveolar epithelial cells due to inflammation or smoking may accelerate the onset and development of symptoms in patients with reduced SLC34A2 gene activity. Thus, smokers have more severe clinical phenotypes than non-smokers.¹³

Long-term survival in patients with PAM remains uncertain, likely due to variability in the clinical course; diagnostic parameters may not reflect the onset of the disease. PAM normally progresses within 10–20 years,¹ and most cases have been followed for up to 10 years after initial diagnosis; however follow-up periods of >40 years have been reported in a few cases.^{2,57} Death typically occurs 10–15 years after diagnosis,²⁶ at a mean age within the fifth

decade of life, from respiratory failure due to pulmonary hypertension and *cor pulmonale*.¹² Chronic irritation of alveolar walls by microliths has been speculated to cause pulmonary fibrosis and destruction of alveolar wall capillaries. Thus, decreased pulmonary capillary beds associated with pulmonary fibrosis are responsible for marked pulmonary hypertension and *cor pulmonale*. PAM thus causes slow and progressive impairment of lung architecture, resulting in hypoxemia and a restrictive pattern.^{56,57} Thus, the pathologic process involves parenchymal and vascular tissues.⁵⁵ For these reasons, the long-term prognosis is poor in patients with PAM, even in those first diagnosed during the asymptomatic phase in childhood.

Diagnosis

PAM is usually diagnosed on the basis of a typical radiological pattern, namely a very fine, sand-like micronodulation of calcific density diffusely involving both lungs, with basal predominance. Many authors argue that this pattern precludes the need for a lung biopsy in most cases.^{1,6,51} However, histological examination shows intra-alveolar microliths in the alveolar spaces and can reveal an increase in chronic inflammatory cells that may induce interstitial fibrosis. Microliths may also be seen in the interstitium.³¹ They are purple-brown with concentric layering and resemble psammoma bodies. A pericentral crescentic halo is frequently apparent. Single and multiple intracellular microliths can be engulfed by uninuclear or multinuclear alveolar macrophages.⁵⁸ Microliths can sometimes be found in sputum or bronchoalveolar lavage, which can contain alveolar macrophages with or without carbon particles.⁵⁸

Calcifications within the lung can result from a number of systemic and pulmonary conditions, and the differential diagnosis is complex, including sarcoidosis, pneumoconiosis, pulmonary hemosiderosis, amyloidosis, miliary tuberculosis, histoplasmosis, calcifications after viral pneumonia, and metastatic pulmonary calcifications associated with chronic renal failure.^{45,59,60}

After PAM is diagnosed in a given patient, family members should be screened by chest radiography, and parents should be counseled that future children are also at risk of developing the disease.⁴⁴

Treatment

To date, no treatment has been proven to effectively prevent the progression of PAM. The disease may progress with chronic alveolar calcification causing interstitial inflammation, and fibrosis leading to decreased lung volumes and, eventually, right heart failure.⁵⁸

Systemic steroids and bronchoalveolar lavage are ineffective for the treatment of PAM.¹² Currently, the only effective therapy is lung transplantation, especially when it is performed before the disease progresses to an advanced stage.⁶¹

Disodium etidronate, a diphosphonate, has been used to treat PAM with mixed results. It acts by inhibiting the formation of new pulmonary calcium-phosphate crystallization and resolving previously formed calcifications, as

observed in other diseases.⁶² Some reports have shown little or no benefit of this therapy,^{63,64} whereas other studies have demonstrated an improvement in lung functions and radiological changes.^{62,65}

Lung transplantation has been beneficial in patients with severe respiratory failure and right heart failure who require supplemental oxygen therapy.⁶¹ To maximize the chances of a successful outcome, such patients should be referred before the development of severe right ventricular dysfunction. Patients who undergone lung transplantation have shown an increase in right ventricular ejection fraction and regression of right ventricular hypertrophy.⁴⁹ However, few published cases have reported lung transplantation in patients with PAM, and most transplantations have been bilateral. Survival after lung transplant and the risk of PAM recurrence are unknown. To date, the longest survival for a patient with PAM treated with lung transplantation is 15 years without recurrence. As PAM requires years to become clinically manifest, further follow-up studies are required to understand the rates of survival and risk of recurrence.⁶⁶

Conclusion

PAM is a genetic lung disease with an autosomal-recessive trait caused by mutations of the SLC34A2 gene. Microlith formation is the result of phosphate-chelating calcium in the extracellular fluid. The disease shows an important clinical-radiological dissociation. Most patients are asymptomatic and changes in the lung parenchyma are incidental findings, but other cases exhibit more severe symptoms at diagnosis.

Because characteristic chest CT findings correlate well with specific pathological findings, the diagnosis of PAM can be made on the basis of the typical radiological pattern. The long-term prognosis is poor due to progressive deteriorations in pulmonary function, respiratory failure and, *cor pulmonale*. No effective treatment has been established; thus, lung transplantation is currently the only effective therapy.

Conflict of interest statement

All authors inform that there are none conflicts of interest.

References

1. Mariotta S, Ricci A, Papale M, De Clementi F, Sposato B, Guidi L, et al. Pulmonary alveolar microlithiasis: report on 576 cases published in the literature. *Sarcoidosis Vasc Diffuse Lung Dis* 2004;**21**(3):173–81.
2. Castellana G, Lamorgese V. Pulmonary alveolar microlithiasis. World cases and review of the literature. *Respiration* 2003;**70**(5):549–55.
3. Korn MA, Schurawitzki H, Klepetko W, Burghuber OC. Pulmonary alveolar microlithiasis: findings on high-resolution CT. *AJR Am J Roentgenol* 1992;**158**(5):981–2.
4. Huqun Izumi S, Miyazawa H, Ishii K, Uchiyama B, Ishida T, et al. Mutations in the SLC34A2 gene are associated with pulmonary alveolar microlithiasis. *Am J Respir Crit Care Med* 2007;**175**(3):263–8.
5. Dahabreh M, Najada A. Pulmonary alveolar microlithiasis in an 8-month-old infant. *Ann Trop Paediatr* 2009;**29**(1):55–9.

6. Marchiori E, Gonçalves CM, Escuissato DL, Teixeira KI, Rodrigues R, Barreto MM, et al. Pulmonary alveolar microlithiasis: high-resolution computed tomography findings in 10 patients. *J Bras Pneumol* 2007;**33**(5):552–7.
7. Cluzel P, Grenier P, Bernadac P, Laurent F, Picard JD. Pulmonary alveolar microlithiasis: CT findings. *J Comput Assist Tomogr* 1991;**15**(6):938–42.
8. Senyigit A, Yaramiş A, Gürkan F, Kirbaş G, Büyükbayram H, Nazaroğlu H, et al. Pulmonary alveolar microlithiasis: a rare familial inheritance with report of six cases in a family. Contribution of six new cases to the number of case reports in Turkey. *Respiration* 2001;**68**(2):204–9.
9. Biary MS, Abdullah MA, Assaf HM, Wazzan A. Pulmonary alveolar microlithiasis in a Saudi child and two cousins. *Ann Trop Paediatr* 1993;**13**(4):409–13.
10. Mikhailov V. Pulmonary alveolar microlithiasis and interstitial diffusion. *KlinMed (Mosk)* 1954;**32**(3):31–6.
11. Perosa L, Ramunni M. La microlitiasi endoalveolare del polmone. *Rec Progr Med* 1959;**26**:353–429.
12. Tachibana T, Hagiwara K, Johkoh T. Pulmonary alveolar microlithiasis: review and management. *Curr Opin Pulm Med* 2009;**15**(5):486–90.
13. Corut A, Senyigit A, Ugur SA, Altin S, Ozcelik U, Calisir H, et al. Mutations in SLC34A2 cause pulmonary alveolar microlithiasis and are possibly associated with testicular microlithiasis. *Am J Hum Genet* 2006;**79**(4):650–6.
14. Huqun Izumi S, Miyazawa H, Ishii K, Uchiyama B, Ishida T, et al. The autozygous segments predicted by a genome-wide SNP typing revealed mutations in the type IIb sodium phosphate cotransporter (SLC34A2) causing pulmonary alveolar microlithiasis. *Proc Am Thorac Soc* 2006;**3**:A102.
15. Hagiwara K, Johkoh T, Tachibana T. Pulmonary alveolar microlithiasis. In: Panos R, Trapnell B, McCormack F, editors. *Molecular basis of lung disease, insight from rare lung disorders*. New Jersey: Humana Press; 2009.
16. Dogan OT, Ozsahin SL, Gul E, Arslan S, Koksall B, Berk S, et al. A frame-shift mutation in the SLC34A2 gene in three patients with pulmonary alveolar microlithiasis in an inbred family. *InternMed* 2010;**49**(1):45–9.
17. Ishihara Y, Hagiwara K, Zen K, Huqun Hosokawa Y, Natsuhara A. A case of pulmonary alveolar microlithiasis with an intragenetic deletion in SLC34A2 detected by a genome-wide SNP study. *Thorax* 2009;**64**(4):365–7.
18. Traebert M, Hattenhauer O, Murer H, Kaissling B, Biber J. Expression of type II Na-P(i) cotransporter in alveolar type II cells. *Am J Physiol* 1999;**277**(5 Pt 1):L868–73.
19. Poelma DL, Ju MR, Bakker SC, Zimmermann LJ, Lachmann BF, van Iwaarden JF. A common pathway for the uptake of surfactant lipids by alveolar cells. *Am J Respir Cell Mol Biol* 2004;**30**(5):751–8.
20. Xu H, Bai L, Collins JF, Ghishan FK. Molecular cloning, functional characterization, tissue distribution, and chromosomal localization of a human, small intestinal sodium-phosphate (Na⁺-Pi) transporter (SLC34A2). *Genomics* 1999;**62**(2):281–4.
21. Pant K, Shah A, Mathur RK, Chhabra SK, Jain SK. Pulmonary alveolar microlithiasis with pleural calcification and nephrolithiasis. *Chest* 1990;**98**(1):245–6.
22. Arslan A, Yalin T, Akan H, Belet U. Pulmonary alveolar microlithiasis associated with calcifications in the seminal vesicles. *J Belge Radiol* 1996;**79**(3):118–9.
23. Piesiak P, Kasibowska-Kuźniar K, Jankowska R. Pulmonary alveolar microlithiasis in a patient with urolithiasis and cholelithiasis. *Pneumonol Alergol Pol* 2001;**69**(5–6):285–9.
24. Jönsson ÅL, Hilberg O, Bendstrup EM, Mogensen S, Simonsen U. SLC34A2 gene mutation may explain comorbidity of pulmonary alveolar microlithiasis and aortic valve sclerosis. *Am J Respir Crit Care Med* 2012;**185**(4):464.
25. Werner A, Dehmelt L, Nalbant P. Na⁺-dependent phosphate cotransporters: the NaPi protein families. *J Exp Biol* 1998;**201**(Pt 23):3135–42.
26. Lauta VM. Pulmonary alveolar microlithiasis: an overview of clinical and pathological features together with possible therapies. *Respir Med* 2003;**97**(10):1081–5.
27. Barnard NJ, Crocker PR, Blainey AD, Davies RJ, Ell SR, Levison DA. Pulmonary alveolar microlithiasis. A new analytical approach. *Histopathology* 1987;**11**(6):639–45.
28. Chan ED, Morales DV, Welsh CH, McDermott MT, Schwarz MI. Calcium deposition with or without bone formation in the lung. *Am J Respir Crit Care Med* 2002;**165**(12):1654–69.
29. Shah M, Joshi JM. Bone scintigraphy in pulmonary alveolar microlithiasis. *Indian J Chest Dis Allied Sci* 2011;**53**(4):221–3.
30. Millqvist E, Bende M. Capsaicin cough sensitivity is decreased in smokers. *Respir Med* 2001;**95**(1):19–21.
31. Wallis C, Whitehead B, Malone M, Dinwiddie R. Pulmonary alveolar microlithiasis in childhood: diagnosis by transbronchial biopsy. *Pediatr Pulmonol* 1996;**21**(1):62–4.
32. Takahashi H, Chiba H, Shiratori M, Tachibana T, Abe S. Elevated serum surfactant protein A and D in pulmonary alveolar microlithiasis. *Respirology* 2006;**11**(3):330–3.
33. Coetzee T. Pulmonary alveolar microlithiasis with involvement of the sympathetic nervous system and gonads. *Thorax* 1970;**25**(5):637–42.
34. Kanat F, Teke T, Imecik O. Pulmonary alveolar microlithiasis with epididymal and periurethral calcifications causing obstructive azospermia. *Int J Tuberc Lung Dis* 2004;**8**(10):1275.
35. Richardson J, Slovis B, Miller G, Dummer S. Development of pulmonary alveolar microlithiasis in a renal transplant recipient. *Transplantation* 1995;**59**(7):1056–7.
36. Kiatboonsri S, Charoenpan P, Vathesatogkit P, Boonpucknavig V. Pulmonary alveolar microlithiasis: report of five cases and literature review. *J Med Assoc Thai* 1985;**68**(12):672–7.
37. Hasan S, Cevat O, Sami C, Yen, Terz, Mehmet, et al. Pulmonary alveolar microlithiasis with pectus excavatum. Case report. *Indian J Med Sci* 1994;**48**(9):199–200.
38. Emri S, Cöplü L, Selçuk ZT, Sahin AA, Baris YI. Hypertrophic pulmonary osteoarthropathy in a patient with pulmonary alveolar microlithiasis. *Thorax* 1991;**46**:145–6.
39. Portnoy LM, Amadeo B, Hennigar GR. Pulmonary alveolar microlithiasis. an unusual case (associated with milk-alkali syndrome). *Am J ClinPathol* 1964;**41**:194–201.
40. Ritchie DA, O'Connor SA, McGivern D. An unusual presentation of pulmonary alveolar microlithiasis and diaphyseal aclasia. *Br J Radiol* 1992;**65**(770):178–81.
41. Schmidt H, Lörcher U, Kitz R, Zielen S, Ahrens P, König R. Pulmonary alveolar microlithiasis in children. *Pediatr Radiol* 1996;**26**(1):33–6.
42. Ratjen FA, Schoenfeld B, Wiesemann HG. Pulmonary alveolar microlithiasis and lymphocytic interstitial pneumonitis in a ten year old girl. *Eur Respir J* 1992;**5**(10):1283–5.
43. Yilmaz MI, Koc B, Kantarcioğlu M, Akinci SB, Ayta H, Bulucu F, et al. Pulmonary alveolar microlithiasis after Varicella zoster infection in a patient presenting with antiphospholipid syndrome and discoid lupus. *Rheumatol Int* 2002;**22**(5):213–5.
44. Helbich TH, Wojnarovsky C, Wunderbaldinger P, Heinz-Peer G, Eichler I, Herold CJ. Pulmonary alveolar microlithiasis in children: radiographic and high-resolution CT findings. *AJR Am J Roentgenol* 1997;**168**(1):63–5.
45. Deniz O, Ors F, Tozkoparan E, Ozcan A, Gumus S, Bozlar U, et al. High resolution computed tomographic features of pulmonary alveolar microlithiasis. *Eur J Radiol* 2005;**55**(3):452–60.
46. Hoshino H, Koba H, Inomata S, Kurokawa K, Morita Y, Yoshida K, et al. Pulmonary alveolar microlithiasis: high-resolution CT and MR findings. *J Comput Assist Tomogr* 1998;**22**(2):245–8.

47. Gasparetto EL, Tazoniero P, Escuissato DL, Marchiori E, Frare E, Silva RL, Sakamoto D. Pulmonary alveolar microlithiasis presenting with crazy-paving pattern on high resolution CT. *Br J Radiol* 2004;**77**(923):974–6.
48. Marchiori E, Franquet T, Gasparetto TD, Gonçalves LP, Escuissato DL. Consolidation with diffuse or focal high attenuation: computed tomography findings. *J Thorac Imaging* 2008;**23**(4):298–304.
49. Samano MN, Waisberg DR, Canzian M, Campos SV, Pêgo-Fernandes PM, Jatene FB. Lung transplantation for pulmonary alveolar microlithiasis: a case report. *Clinics (São Paulo)* 2010;**65**(2):233–6.
50. Henkelman RM, Watts JF, Kucharczyk W. High signal intensity in MR images of calcified brain tissue. *Radiology* 1991;**179**(1):199–206.
51. Sahin U, Yildiz M, Bircan HA, Akkaya A, Candir O. Absence of pulmonary uptake of Tc-99m methylenediphosphonate in alveolar microlithiasis. *Ann Nucl Med* 2004;**18**(8):695–8.
52. Günay E, Ozcan A, Günay S, Tatci E, Keyf AI, Simsek C. Pulmonary alveolar microlithiasis with low fluorodeoxyglucose accumulation in PET/computed tomography. *Ann Thorac Med* 2011;**6**(4):237–40.
53. Ito K, Kubota K, Yukihiko M, Izumi S, Miyano S, Kudo K, et al. FDG-PET/CT finding of high uptake in pulmonary alveolar microlithiasis. *Ann Nucl Med* 2007;**21**(7):415–8.
54. Fuleihan FJ, Abboud RT, Balikian JP, Nucho CK. Pulmonary alveolar microlithiasis: lung function in five cases. *Thorax* 1969;**24**(1):84–90.
55. Brown J, Leon W, Felton C. Hemodynamic and pulmonary studies in pulmonary alveolar microlithiasis. *Am J Med* 1984;**77**(1):176–8.
56. Terada T. Pulmonary alveolar microlithiasis with cor pulmonale: an autopsy case demonstrating a marked decrease in pulmonary vascular beds. *Respir Med* 2009;**103**(11):1768–71.
57. Jönsson ÅL, Simonsen U, Hilberg O, Bendstrup E. Pulmonary alveolar microlithiasis: two case reports and review of the literature. *Eur Respir Rev* 2012;**21**(125):249–56.
58. Monabati A, Ghayumi MA, Kumar PV. Familial pulmonary alveolar microlithiasis diagnosed by bronchoalveolar lavage. A case report. *Acta Cytol* 2007;**51**(1):80–2.
59. Weinstein DS. Pulmonary sarcoidosis: calcified micronodular pattern simulating pulmonary alveolar microlithiasis. *J Thorac Imaging* 1999;**14**(3):218–20.
60. Saputo V, Zocchi M, Mancosu M, Bonaldi U, Croce P. Pulmonary alveolar microlithiasis: a case report with a discussion of differential diagnosis. *Helv Paediatr Acta* 1979;**34**(3):245–55.
61. Stamatis G, Zerkowski HR, Doetsch N, Greschuchna D, Konietzko N, Reidemeister JC. Sequential bilateral lung transplantation for pulmonary alveolar microlithiasis. *Ann Thorac Surg* 1993;**56**(4):972–5.
62. Ozelik U, Yalcin E, Ariyurek M, Ersoz DD, Cinel G, Gulhan B, et al. Long-term results of disodium etidronate treatment in pulmonary alveolar microlithiasis. *Pediatr Pulmonol* 2010;**45**(5):514–7.
63. Mariotta S, Guidi L, Mattia P, Torrelli L, Pallone G, Pedicelli G, et al. Pulmonary microlithiasis. Report of two cases. *Respiration* 1997;**64**(2):165–9.
64. Jankovic S, Pavlov N, Ivkovic A, Erceg I, Glavina-Durdov M, Tocilj J, et al. Pulmonary alveolar microlithiasis in childhood: clinical and radiological follow-up. *Pediatr Pulmonol* 2002;**34**(5):384–7.
65. Ozelik U, Gülsün M, Göçmen A, Ariyürek M, Kiper N, Anadol D, et al. Treatment and follow-up of pulmonary alveolar microlithiasis with disodium editronate: radiological demonstration. *Pediatr Radiol* 2002;**32**(5):380–3.
66. Moon E, Tsuang W, Bonnette P, Jackson K, Lien D, Blumenthal N, et al. Lung transplantation outcomes for pulmonary alveolar microlithiasis: a limited case series. *Am J Respir Crit Care Med* 2009;**179**:A4602.