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# Pulmonary Alveolar Microlithiasis

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### Keywords

Pulmonary alveolar microlithiasis; congenital disease; SLC34A2; Type ll b sodium-phosphate co-transporter (NPT2B); Phosphate homeostasis

## Introduction

Pulmonary alveolar microlithiasis (PAM) is a rare hereditary lung disease in which calcium phosphate deposits (calcospherites) accumulate in the distal airspaces. PAM was first described by an Italian scientist, Marcello Malpighi, in 1868 and the histopathology was first carefully detailed by Harbitz in 1918 [1]. The disease was named “Microlithiasis Alveolaris Pulmonum” by the Hungarian pathologist Puhr in 1933 [2]. Since the first description of the disease almost 150 years ago, over 1200 cases have been reported in the world literature [3]. PAM is often discovered on chest radiographs obtained for other purposes during early adulthood. Patients typically remain asymptomatic until middle age, when pulmonary fibrosis, pulmonary hypertension, and chronic respiratory failure ensue. Chest radiographs reveal diffuse, hyperdense, micronodular shadows producing a characteristic ‘snow storm’ appearance [4]. The diagnosis can often be established based on radiographic appearance alone, especially in patients with a family history. The recent discovery in PAM patients of genetic mutations in the SLC34A2 gene, which encodes the sodium-phosphate co-transporter Npt2b (*SLC34A2*, NPT2b, NaPi-2b), has opened a window into PAM disease pathogenesis [5,6]. An animal model has been developed that can serve as a preclinical model for testing candidate therapies, and a worldwide network of Rare Lung Disease Clinics has identified potential PAM subjects for trials. Here we review the etiology, epidemiology, pathology, clinical features and potential future treatment strategies for PAM.

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## Epidemiology

PAM has long been considered to be autosomal recessive disorder, since it transmits horizontally and is associated with consanguinity. Most patients with PAM have at least one sibling who is also affected by the disease. Mariotta et al reported that 35.8% of PAM patients were diagnosed before 20 age and 88.2% before 50 years of age [7]. PAM has also been reported in newborns and toddlers, including twins who died within 12 hours of birth [8], and in octagenarians [9,10]. Familial incidence has been reported in 35–50% of cases reported from Japan [11], Turkey [12], and Italy [13], and other sources [14]. The frequency of PAM mutations in the Japanese population was determined to be less than .008 [6]. There is no clear gender predilection for PAM.

## Pathology

### Molecular Pathogenesis

In 2006 and 2007, SLC34A2 mutations were identified in patients with PAM by homozygosity mapping [5,6]. The SLC34A2 gene is located on 4p15 and comprises 13 exons. It encodes a 2,280-nt mRNA and a 690 amino acid sodium-phosphate co-transporter called Npt2b. A total of more than 15 different mutations have been described in 30 patients to date (Fig. 1) [3]. Mutations have been found on multiple exons in patients from Turkey, but mutations appear to cluster in exon 8 in cases from China, and in exons 7 and 8 in Japan [15]. The heterogeneity in mutations found is inconsistent with a founder effect, at least in the Turkish and Japanese populations, which have the largest populations studied. Most DNA aberrations found to date are missense mutations that result in protein truncation, but three damaging substitutions (G106R, T192K, Y455H) and a nonsense mutation that introduces a premature stop codon have been described [5,15,16]. In the few family studies that have been completed, the disease has demonstrated 100% penetrance in that all those with homozygous mutations are affected [5]. There does not appear to be any genotype/phenotype correlation, based on variation in the age of disease onset in large family cohorts [5]. Genetic heterogeneity (i.e-more than one gene involved) is not likely since mutations in SLC34A2 have been identified in almost all patients studied. Almost all mutations identified to date have been homozygous, suggestive of identity by descent.

Npt2b is abundantly expressed in lung, primarily on the surface of alveolar type II cells, where it is thought to function as an exporter of phosphate generated by the metabolism of surfactant phospholipids [17,18]. In the absence of Npt2b activity, phosphate levels likely rise in the alveolar lining fluid and form complexes with calcium, resulting in the formation of lamellated microliths [19]. Alveolar pH, calcium concentrations and nucleating proteins, lipids or other molecules likely play an important role in microlith formation, but little is known about the conditions that favor stone initiation and growth. Npt2b is also expressed in the gut, where it functions as the major transporter for the uptake of dietary phosphorus, as well as in the breast, liver, testes, prostate, kidney, pancreas and ovary [20,21].

Other sodium phosphate co-transporters include SLC34 family members Npt2a, Npt2c, which are predominantly expressed in the kidney, and SLC20 family members Pit1 and Pit2, which are ubiquitously expressed. The pulmonary expression of SLC20, Npt2a and Npt2c

transporters has not been well characterized in humans. Recently Saito reported expression of Pit1 and Pit2 but not Npt2a or Npt2c in mouse lung [19]. The three SLC34 isoforms (NaPi-IIa,b,c) transport a divalent Pi ($HPO_4^{2-}$) upon binding of two or three sodium ions, and use the inwardly directed Na+ electrochemical gradient to catalyze uphill movement of Pi [22]. The crystal structure has not been solved for any of the sodium dependent phosphate co-transporters, and the bacterial dicarboxylate transporter has been used as a model for sodium dependent anion transport [23]. The 3D structures of the wild-type Npt2b and two naturally occurring mutants were predicted by protein folding recognition with 3D-pssm (Phyre Version0.2), and molecular dynamics simulations [15].

Epithelial deletion of Npt2b in mice resulted in a progressive pulmonary process characterized by diffuse alveolar microlith accumulation, radiographic opacification, restrictive physiology, inflammation and fibrosis that closely mimic PAM [19]. Expression of Npt2b on the luminal surface of alveolar type II cells was apparent in the wild type mice and lost in the knockout (KO) mouse (Fig. 2A). The concentrations of calcium and phosphorus in alveolar lavage fluids were increased by roughly ten fold in the Npt2b deficient animals compared to wild type mice, while serum concentrations of the ions were unchanged in the two groups. The microliths that were isolated were demonstrated to contain calcium phosphate. The KO animals developed an unexpected alveolar phospholipidosis, which has not been reported in humans to our knowledge, and may be related to altered surfactant catabolism due to dysfunction of alveolar macrophages. Filling of alveolar spaces with abundant eosinophilic material has been reported in identical twins with PAM who died within 12 hours of birth, however, which could be consistent with phospholipidosis [8], as could serum surfactant protein elevations [24] and Oil red O positive alveolar macrophages that have been reported in patients with PAM [25]. Cytokine and surfactant protein elevations in the alveolar lavage and serum of PAM mice and confirmed in serum from PAM patients validated serum MCP-1 (monocyte chemotactic protein 1) and SP-D (surfactant protein D) as potential biomarkers (Fig. 2B). Microliths introduced by adoptive transfer into the lungs of wild-type mice produced marked macrophage rich inflammation and elevation of serum MCP-1 that peaked at 1 week and resolved at 1 month, concomitant with clearance of stones. Microliths isolated by bronchoalveolar lavage readily dissolved in EDTA, and therapeutic EDTA lavage reduced the burden of stones in the lungs. A low-phosphate diet prevented microlith formation in young animals and reduced serum SP-D, a potential biomarker of lung injury (Fig. 2C). The burden of pulmonary calcium deposits in established PAM was also diminished within 4 weeks by a low-phosphate diet challenge. The rapid reversal of an established PAM lesion in the lungs of mice suggests an active transport process that removes calcium, phosphate or both, in a process that may be triggered by vitamin D, FGF23 or serum levels of calcium or phosphate. These data support a causative role for Npt2b in the pathogenesis of PAM and the use of the PAM mouse model as a preclinical platform for the development of biomarkers and therapeutic strategies.

## Histology

At autopsy, the lungs from patients with PAM are enlarged, heavy, and non-bouyant [26]. The pleural surface has a studded, fine granular appearance. Sectioning of the lung reveals a diffusely calcified and gritty surface. Stones isolated from the lung range from 50 to 5,000

μm in diameter [27–31], and have a lamellated, 'onion-skin' appearance under the microscope. The microliths are primarily composed of calcium phosphate, and small amounts of calcium carbonate, magnesium and iron [32]. Under the microscope, the pulmonary architecture is diffusely altered due to filling of alveoli with multiple microliths [33]. Patchy inflammation is frequently present, especially in patients with a longer duration of illness. Variable degrees of pulmonary fibrosis are often found in the pulmonary interstitium [27]. Evidence of pulmonary hypertension, with increased intimal and medial thickening, is also apparent in advanced cases [34]. Morphometric analysis of CD34 immunostained sections in an autopsy case revealed a significant reduction in the pulmonary capillary beds as a potential mechanism for pulmonary hypertension [35].

The pathologic changes in PAM are primarily confined to lungs but occasional reports of extra-pulmonary calcifications, in the pleura [36], diaphragm [37] , lumbar sympathetic chain and testicles [5] have appeared in the literature.

## Clinical Features

### Symptoms and Signs

In early stages, patients with PAM are asymptomatic. Cases of early disease onset or rapid progression are rare. As the disease progresses, symptoms such as dyspnea on exertion and dry cough may develop. Asthenia, chest pain, cyanosis, hemoptysis and pneumothorax have been all been reported. Physical examination may reveal rales and finger clubbing. Subjective complaints are often less severe than radiological findings suggest, a scenario that has been termed clinical-radiological dissociation. There is some evidence that smoking and infection may accelerate disease progression [5].

### Clinical testing

Pulmonary function testing is usually normal in early stages. Reduction in diffusing capacity (DLco) for carbon monoxide and a restrictive ventilatory impairment develop over time. Echocardiography may reveal evidence of pulmonary hypertension and right heart strain [38]. Serum phosphate and calcium are typically normal in patients with PAM [39], as are other hematological and biochemical parameters. In two patients, surfactant protein D (SP-D) was found to be elevated in the serum, which could reflect higher alveolar SP-D levels or compromised barrier integrity or both [24]. Serum MCP-1 was found to be elevated in patients with PAM [19]. These reports suggest the possibility that SP-D and MCP-1 may be useful as diagnostic biomarkers or indicators of disease activity or progression.

### Radiology

The routine chest radiograph in patients with PAM typically reveals a fine, sandlike micronodular pattern that is more pronounced in the bases than in the apices (Fig. 3A). The vascular tree and the borders of the heart and diaphragm are often obscured (vanishing heart phenomenon) and air bronchograms coursing through areas of consolidation may be apparent.

The HRCT also reveals widespread, tiny microcalcifications throughout the lungs. Ground-glass opacities and airspace consolidation may occupy a large fraction of the lung fields (Fig. 3B) [40,41]. Microliths are typically diffusely distributed but may be preferentially deposited in the posterior segments of the lower lobes. The profusion of microliths may be increased in the upper lobes of smokers. Interlobular septal thickening is often apparent, and may produce a 'crazy paving' appearance. A linear radiolucency at the pleural boundaries abutting the heart, diaphragm and pleura is a characteristic radiological feature of PAM, and is likely secondary to the subpleural cystic changes that are often seen at cross sectional imaging and pathological evaluations [42]. These cystic changes appear to be due to dilation of alveolar ducts [41]. Small apical bullae are another typical feature.

In a radiological study of 13 PAM cases in Brazil, CT findings in decreasing order of prevalence included ground glass opacities, small parenchymal nodules, and small subpleural nodules in over 90%; subpleural cysts in 85%; and subpleural linear calcifications, crazy paving pattern, nodular fissure, calcification along interlobular septa, and dense consolidations in 46–70%[43]. Intermingled air bronchograms were identified in 6 cases. The lower third of the lungs was predominantly affected but there was no predominant distribution along the axial or anteroposterior axes.

### Extrapulmonary disease

Deposition of microliths in the external male genitalia has been described in patients with PAM, including deposition in testicles and seminal vesicles associated with hematuria, testicular atrophy, obstructive azoospermia and infertility [44–49]. Testicular microlithiasis occurs in .6–9% of the male population and it is associated with the majority of primary testicular malignancies and in about 1% of cases of male infertility [50–52]. Corut tested 15 patients with testicular microlithiasis for Npt2b mutations and found 2 mutations that were not conclusively damaging [5]. It is not clear whether Npt2b plays a role in the pathogenesis of testicular microlithiasis.

### Associated diseases

Other diseases that have been reported in patients with PAM include pericardial cyst, lymphocytic interstitial pneumonitis, non-Hodgkin lymphoma, antiphospholipid syndrome, discoid lupus, rheumatoid arthritis, psoriasis, osteopetrosis, Sjogren's syndrome, hypertrophic pulmonary osteoarthropathy, and pectus excavatum. It is unclear if there is any association between these disorders and PAM, or whether these were chance occurrences. Other heritable diseases that have been reported in patients with PAM may be coincidental, due to cotransmission in families with consanguineous relationships, and include diaphyseal aclasia and autosomal recessive Waardenburg-anophthalmia syndrome.

## Diagnosis

The diagnosis of PAM can usually be established radiographically. Bronchoalveolar lavage demonstrating microliths with the typical lamellar structure has been helpful in cases where doubt exists. In some cases, microliths have been recovered in expectorated sputum [53]. Transbronchial biopsy appears to have a reasonable yield and safety profile, but is not

usually required when the radiographic presentation is typical. In the literature, the diagnosis has been determined by lung biopsy in about 46.9% of cases[7], likely because the disease is unfamiliar to many physicians. In general, lung biopsy should be reserved for cases where uncertainty persists despite more conservative diagnostic methods. Genotyping for SLC34A2 gene mutations is commercially available and may be useful for screening family members, with appropriate genetic counseling, but is currently not otherwise clinically informative or necessary for diagnosis.

## Differential Diagnosis

When the chest radiograph demonstrating dense micronodular and ground glass opacities in an asymptomatic patient is first obtained, diagnostic considerations may include miliary tuberculosis, pulmonary alveolar proteinosis, sarcoidosis, healed varicella or variola pneumonia, metastatic calcification, pneumoconioses including silicosis, pulmonary hemosiderosis, or amyloidosis. PAM is perhaps most frequently confused with pulmonary tuberculosis, in part because regions where consanguinous marriage is common and Tb is highly prevalent frequently overlap. There have been at least 5 cases of concomitant Tb in patients with PAM[3]. The crazy paving pattern that has been described in PAM was once felt to be pathognomonic for pulmonary alveolar proteinosis, and can lead to diagnostic confusion [3,54]. However, discrete calcifications visualized within mediastinal window settings distinguish PAM from PAP. In patients who are demonstrated to have diffuse pulmonary calcifications on CT or chest radiograph, the differential includes the many causes of both metastatic and dystrophic pulmonary calcification, which occur in formerly normal lung tissue and damaged lung tissue, respectively [55]. Pulmonary metastatic calcification is most frequently due to chronic renal failure, but may also be seen in patients with hyperparathyroidism, mild alkali syndrome, talcosis, amiodarone toxicity, iodinated oil embolism, and aspirated or extravasated contrast material. Dystrophic calcification may occur as a sequela of viral infection due to varicella or variola, granulomatous disease due to tuberculosis, histoplasmosis, coccidioidomycosis or sarcoidosis.

## Prognosis

The prognosis of PAM is unclear. In a study of 53 Japanese patients, 34.1–42.9% died within 10–49 years of diagnosis, at a mean age of 46.2 years. The most common cause of death was respiratory failure. These results suggest a poor long-term prognosis for patients with PAM, including patients discovered to have asymptomatic disease in childhood [39].

## Pharmacologic Treatment Options

### Etidronate

Etidronate is a unique bisphosphonate that not only inhibits osteoclast driven bone resorption, as do many other members of the class, but also inhibits crystal formation and bone mineralization. Etidronate is FDA-approved for the treatment of Paget’s disease and heterotopic calcification [56]. In a handful of case studies, etidronate has been reported to improve lung function and reduce radiographic opacification of the lung in patients with

PAM [13,57–60]. In other reports, etidronate has been been ineffective [13,61]. Further studies will be required to determine if etidronate has a role in the treatment of PAM.

### Steroid hormones

In general, steroid hormone therapy appears to be ineffective for PAM, though a few authors have reported subjective improvement in some patients [62,63].

### Bronchoalveolar lavage

Repeated lavage is often used for pulmonary alveolar proteinosis, and is a plausible treatment strategy for PAM since the microliths are exclusively localized to the alveolar lumen. Unfortunately, there is no evidence that this approach has been effective [64].

### Oxygen Therapy and Vaccinations

Supplemental oxygen therapy is prudent for patients who are hypoxemic with rest, exercise or sleep. PAM patients should receive pneumococcal and influenza vaccinations.

## Surgical Treatment Options

### Lung Transplantation

As of 2015, unilateral and bilateral lung transplantation had been reported in 17 patients with PAM [65–69], without any documented recurrence in the grafts [33] Comparison of outcomes of transplant in PAM patients with those of patients with other lung diseases has not been completed.

## Summary

PAM is a genetic lung disorder that is characterized by the accumulation of calcium phosphate deposits in the alveolar spaces of the lung. Mutations in the type ll sodium phosphate co transporter, Npt2b, have been reported in patients with PAM. Patients typically present without symptoms at a young age, with dense ground infiltrates noted on chest radiographs obtained for another purpose, as well as dyspnea on exertion, a restrictive ventilator defect and decreased diffusion capacity. Dissociation between radiological findings and clinical symptoms is a clinical feature of PAM. PAM progresses gradually, often producing incremental dyspnea on exertion and desaturation in young adulthood and, ultimately, respiratory insufficiency by late middle age. Extrapulmonary disease is uncommon. Treatment remains supportive, including supplemental oxygen therapy. For patients with end stage disease, lung transplantation is available as a last resort. Patients are so rare and geographically dispersed that trials are difficult. The recent development of laboratory animal model has revealed several promising treatment approaches for future trials.

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**Key Points**

- PAM is a genetic lung disorder that is characterized by the accumulation of calcium phosphate deposits in the alveolar spaces of the lung
- Mutations in the type ll sodium phosphate co transporter, Npt2b, have been reported in patients with PAM
- Patients typically present without symptoms at a young age, with dense ground infiltrates noted on chest radiographs obtained for another purpose
- PAM progresses gradually, often producing incremental dyspnea on exertion and desaturation in young adulthood and, ultimately, respiratory insufficiency by late middle age.
- Treatment remains supportive. For patients with end stage disease, lung transplantation is an option

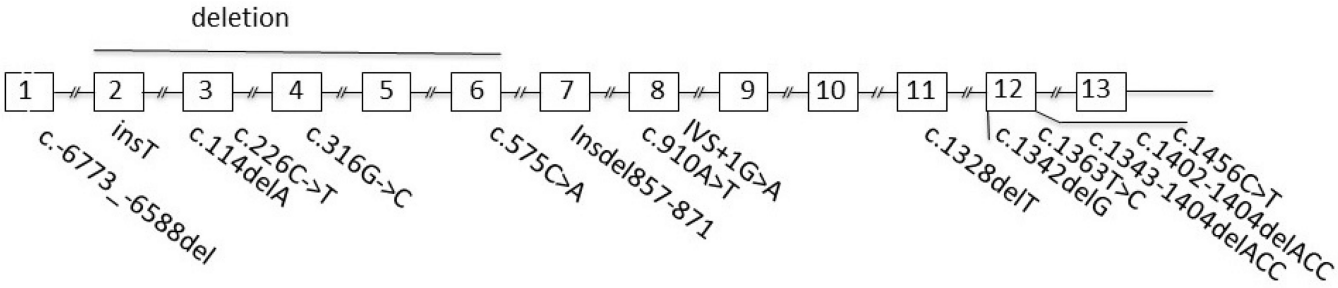


**Fig. 1.**
SLC34A2 mutations gleaned from the recent 1022 PAM cases based on Castellana 2015 [3].

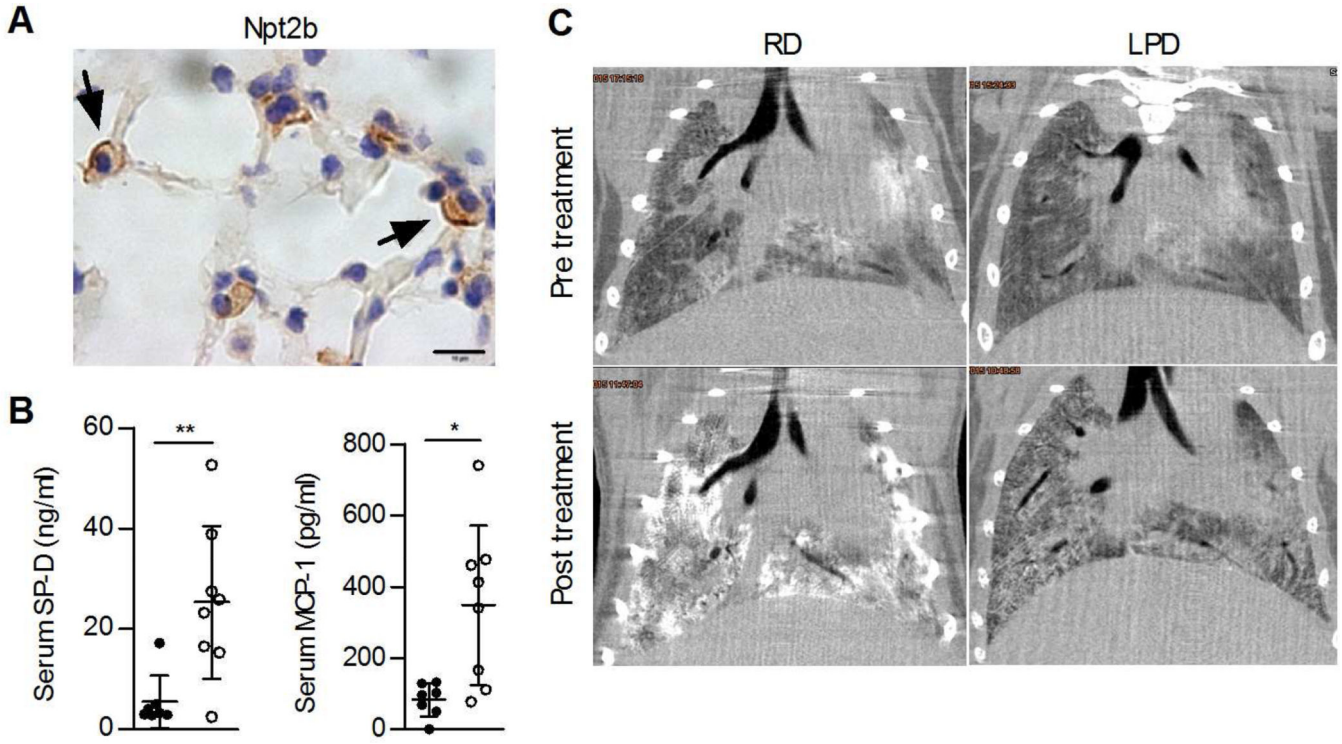


**Fig. 2.**

(A) Arrows demonstrate enhanced Npt2b staining in the apical membrane of AECII of wild type mice. (B) The elevation of human SP-D and MCP-1 in the serum from PAM patients (opened circle) compare to healthy volunteers (closed circle). (C) Low phosphate diet (LPD) prevents microlith accumulation in mice. RD, Regular diet.

From Saito, A., Nikolaidis, N.M., Amlal, H., *et al.* Modeling pulmonary alveolar microlithiasis by epithelial deletion of the Npt2b sodium phosphate cotransporter reveals putative biomarkers and strategies for treatment. Sci Transl Med 2015;7(313):313ra181; with permission.

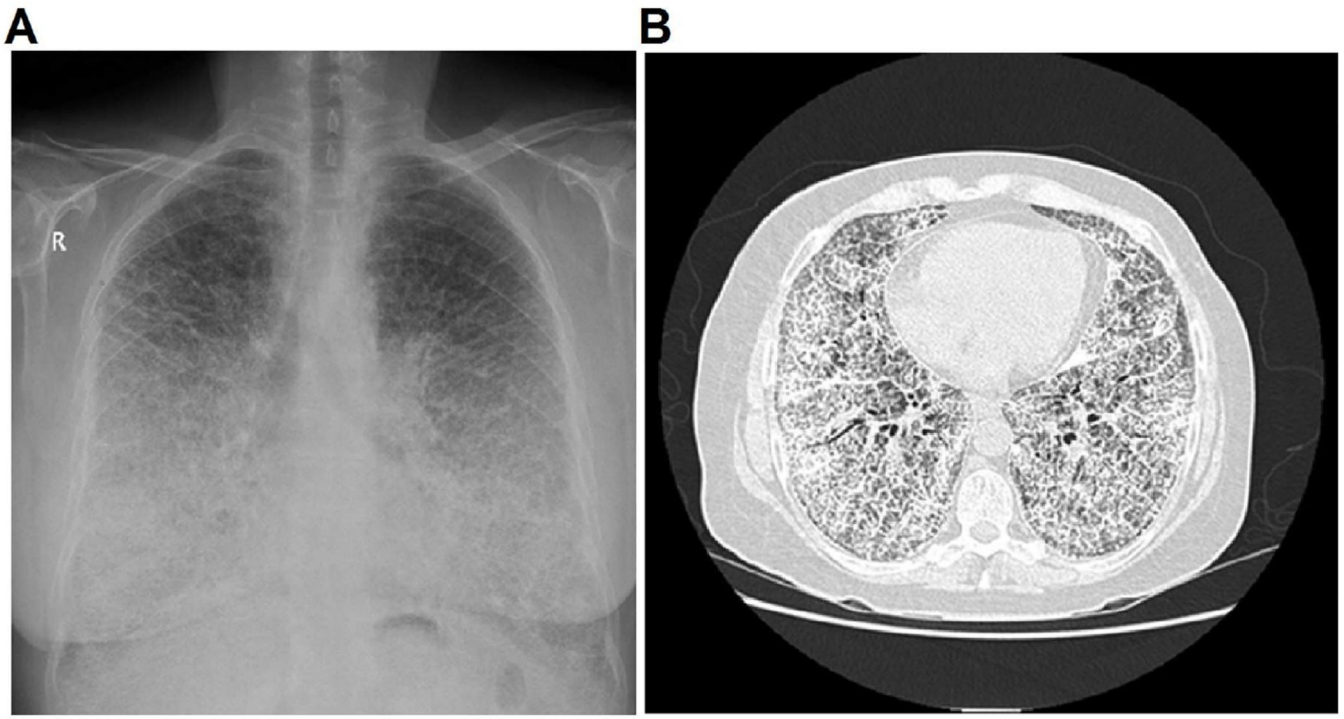


**Fig. 3.**

Chest radiograph (A) and High-resolution computed tomography findings (B) of a 59-year-old Middle Eastern female with a history of pulmonary alveolar microlithiasis, showing diffuse opacification in both lung with hyper dense micronodular, called "sand-storm appearance" From Gupta, N. & McCormack, F.X. Pulmonary alveolar microlithiasis. Am J Respir Crit Care Med 2013;188(7):e11–12; with permission.