JETIR.ORG ISSN: 2349-5162 | ESTD Year : 2014 | Monthly Issue
JOURNAL OF EMERGING TECHNOLOGIES AND INNOVATIVE RESEARCH (JETIR)
An International Scholarly Open Access, Peer-reviewed, Refereed Journal

PULMONARY ALVEOLAR MICROLITHIASIS: A REVIEW

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ABSTRACT

Pulmonary alveolar microlithiasis (PAM) is a rare fascinating lung disease characterized by intra-alveolar calcium deposits or the accumulation of hydroxyapatite microliths inside the lumen of the alveolar areas. PAM is discovered incidentally on radiographs carried out for other purposes on patients and the typical disease course is characterized by slowly modern respiratory insufficiency over a decade. The etiology of the ailment is still idiopathic and many authors have supposed that an inherited neighborhood enzymatic defect is responsible for calcium deposition. A recent discovery in PAM patients revealed the deficiency of the sodium -phosphate co-transporter Npt2b (SLC34A2, NPY2b, NaPi-2b), is the cause of PAM and has opened a window into the pathogenesis. Powerful animal models are developed which can serve as preclinical models that inform our approach to the management of disease and treatment. Here we review the epidemiology, etiology, radiographic and pathologic features,and clinical management strategies for PAM.

KEYWORDS

Pulmonary alveolar microlithiasis, sodium phosphate co-transporter NPT2b.

INTRODUCTION

Pulmonary alveolar microlithiasis (PAM) is a rare hereditary lung disease characterized with the aid of the presence of calcium salt deposits in the distal airspaces of alveoli, named microliths or calcospherites[1]. PAM was first detailed by an Italian scientist, Marcello Malpighi, in 1868 , and histopathology was first carefully described by Harbitz in 1918. The disease was named "Microlithiasis Alveolaris Pulmonum" by Puhr a Hungarian pathologist in 1933 [2]. Over 1200 cases have been reported, Since the first description of the disease almost 150 years ago. PAM is often found on chest radiographs that reveal diffuse, hyperdense, micronodular shadows producing a characteristic 'snowstorm' appearance which is obtained for other purposes during early adulthood. Patients typically remain asymptomatic until the completion of young age, when pulmonary fibrosis, pulmonary hypertension, and chronic respiratory failure take place[7]. A recent discovery in PAM patients revealed the deficiency of the sodium-phosphate co-transporter Npt2b (SLC34A2, NPY2b, NaPi-2b), is the cause of PAM and has opened a window into the pathogenesis. Powerful animal models are developed which can serve as preclinical models that inform our approach to the management of disease and treatment. Here we review the epidemiology, etiology, radiographic and pathologic features, and clinical management strategies for PAM.

EPIDEMIOLOGY

PAM has been reported in almost every part of the world. The most of cases in the literature have been from Asia (56.3%) and Europe (27.8%) [3]. The incidence per million persons is about 1.85 for Turkey, 1.08 for Italy, 0.92 for Japan, 0.15 for the USA, 0.10 for China, and 0.06 for India. In the literature, about 50% of patients are male and 41% are female, with sex being unspecified in 9% of cases. There is no clear gender specification for PAM. Mariotta et al reported that 35% of PAM patients were diagnosed before 20 age and 88.2% before 50 years of age 7. The diagnosis is most commonly reported in persons of all ages from newborns and toddlers, including twins who died within 12 hours of birth 8, and in octagenarians [8,9]. In almost all PAM cases, the transmission was horizontal and considered to be an autosomal recessive pattern of inheritance. Occasionally, PAM was described in association with other diseases such as mitral stenosis or kidney stones, or calcifications in the seminal vesicles or other organs [10,15].

PATHOPHYSIOLOGY

In six individuals from five families, a Japanese research team used genome-wide high-density single-nucleotide polymorphism-based homozygosity mapping to find the SLC34A2 gene in a DNA region on chromosome 4p15 harboring the sodium phosphate co-transporter [8]. It was discovered that PAM patients had homozygous mutations in this gene that caused loss of function. Through linkage analysis of a sizable sample, a different independent group also connected chromosome 4p15 to three members of a consanguineous family are impacted [9]. There are 13 exons in the SLC34A2 gene. NPT 2b, also known as NPT IIb or 12 encodes the type II sodium-dependent co-transporter, is Na Pi-IIb).

However, the gene is also expressed in the thyroid, salivary gland, mammary gland, uterus, and testes. NPT2b is most frequently expressed in the lung and small intestine, with the highest levels of expression in the alveolar epithelium and ileal epithelium, respectively. Noting that NPT2b expression is present in the kidney. The expression seems to be most prevalent in alveolar type II cells in the lung, where it is believed to be necessary for the export of phosphate produced by the catabolism of the phospholipid surfactants. NPT2b works to absorb dietary phosphate in the gut [10]. not being due to compensating renal processes, intestine NPT2b expression does not result in hypophosphatemia.

As shown in Table 1 [8, 9, 15–26], 27 mutations have so far been found to be associated with the phenotypic evolution of PAM. Homozygous mutations in SLC34A2 have been found in the majority of PAM patients who have undergone genotyping. Few cases with unrelated parents and compound heterozygous mutations have been reported [19, 23]. According to family pedigrees, the disease will almost always be manifested in people who have both SLC34A2 genes affected, supporting complete penetrance [21,22].

A mouse model for PAM was created by SAITO et al. [11] by removing NPT2b from the epithelium of the lung and stomach. These animals experience reticular and micronodular calcific opacities, high-density consolidation with air bronchograms, and widespread, hyperdense opacification with ground-glass infiltrates as age-dependent radiographic symptoms. When compared to Npt2b+/+ mice, the surfactant protein (SP)-D and monocyte chemoattractant protein (MCP)-1 levels in the serum of the Npt2b/ animals are higher and rise with the progression of the microlith load. Histological examinations showed that microliths from Npt2b/ mice were dispersed throughout the lung on day 1, collected into macrophage-rich aggregates by day 7, and were removed without lingering inflammation or fibrosis at one month. The blood level of MCP-1 in Npt2b+/+ mice following a microlith challenge took the same temporal course, peaking on day 7 and reverting to baseline by day 28, suggesting possible use as a biomarker of stone burden and clearance. Collectively, these findings point to genetic modification of NPT2b expression in airway epithelial cells as a potential future strategy for lowering microlith load in PAM. Other treatment options investigated on this pre-clinical platform included therapeutic alveolar lavage with calcium chelators ethylenediaminetetraacetic acid or egtazic acid, which decreased stone burden in a human PAM lung explant and NPT2b/ mice, and low-phosphate diet treatment for 8 weeks, which successfully prevented and reversed microlith accumulation.

SIGNS AND SYMPTOMS

There is a lot of variation in the symptoms and course of the disease.

In the early stages, patients are asymptomatic. Early disease onset or rapid progression is rare. As the disease progresses, dyspnoea is the most frequent symptom followed by cough, chest pain, and asthenia. Cyanosis, hemoptysis, and pneumothorax have been reported. Patients exhibit dyspnoea on exertion and dry cough as the disease worsens. Physical examination may exhibit rales and finger clubbing.

. It is assumed that coughing could be related to the stimulation of the C fibers or receptors directly by the microliths. Sometimes cyanosis or finger clubbing is the first sign.

PULMONARY FUNCTION TESTS

Although pulmonary function tests (PFTs) are often ordinary in early disease, a restrictive defect with a reduction in diffusion capacity for carbon monoxide is most normal [37]. There are reports of children with normal initial PFTs who develop a restrictive defect.

Diagnostics

Microliths can be seen in sputum, bronchial wash, and the fluid of bronchoalveolar lavage [23, 104-109]. PAM can be diagnosed by using a lung biopsy through a thoracotomy, through the transbronchial or trans parietal route, and through necropsy [5-8].

The accumulation of numerous calculi in the alveoli causes a characteristic radiologic feature which, at first, involves the lower lobes and then the middle and upper areas of the lungs creating a “sandstorm-like” picture (Fig. 4) [5-9, 20, 51]

Serological testing

There are several blood tests appear to be normal in patients with PAM. Although MCP-1 and SP-D will not have diagnostic utility as they can be elevated in other pulmonary diseases, they may help in assessing disease severity in patients with PAM.

Genetic testing

Test on DNA taken from peripheral blood myeloid cells illustrates the damaging mutations in SLC34A2 which is highly specific for PAM, with at least 27 known mutations reported to date

Radiology

Chest radiography Often the first study suggests PAM is abnormal chest radiographs. The microlith deposition on the chest radiograph may eventually become dense enough to produce a fine, sand-like pattern, which is often more prominent in the bases than in the apices as displayed. This can be seen in figure 1a

a) b)

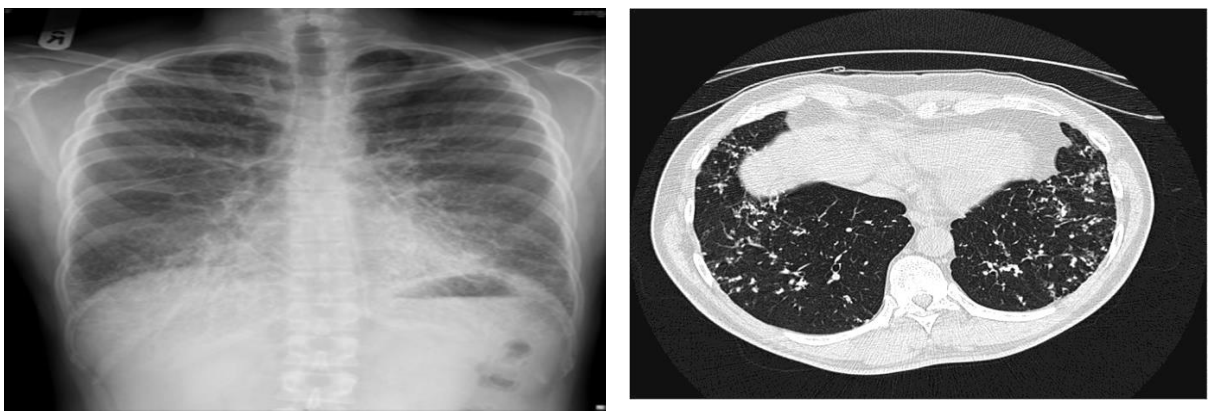

Figure 1 Radiographic findings in pulmonary alveolar microlithiasis. a) Chest radiograph depicting a fine, sand-like micronodular pattern with basilar predominance. b High-resolution computed tomography with micronodules, interlobular septal thickening, subpleural emphysema with predominance of small cysts.

High-resolution computed tomography of the chest

Computed tomography of the chest is the most useful radiologic modality for the prognosis of PAM displayed in figure 1b. Images normally reveal diffuse hyperdense micronodular airspace opacities that are most extensive in the posterior segments of the lower lobes and anterior segments of the upper lobes [41]. Aggregates of microliths might also appear as calcific deposits >3mm in diameter. The ground-glass opacities may be caused by an inflammatory reaction to the microliths. Subpleural reticular change and the traction bronchiectasis of the peripheral airways are examples of features associated with interstitial lung disease [7, 41, 42]. Figures 1b and c show many of these characteristics in action. Even though the fact that on mediastinal windows the calcifications can be seen tracing septal lines, this process can be distinguished from PAP and the radiographic pattern of interlobular septal thickening known as "crazy-paving" may be detected in PAM [43]. Figure 1d illustrates this. Pleural calcification may result from progressive subpleural interstitial thickening, albeit this condition is uncommon on initial diagnostic imaging [41]. Small cysts may appear in areas of low attenuation close to the pleural surface as a symptom of paraseptal and subpleural.

Four steps of a radiographical evolution have been proposed [44]. A small number of imperfectly calcified microliths and diffuse ground-glass opacity are present in the first (pre-calcific) phase. The occurrence of this presentation in adults has not been established; it has only been recorded in asymptomatic youngsters. The radiograph appears "sandy" in the second phase, with scattered 2–4 mm-diameter calcified micronodules and maintained cardiac and diaphragmatic boundaries. The interstitium thickens, the interstitium gradually becomes opaque, and the heart and diaphragm become obscured. The lung appears "white out" in the fourth and final stage, which is characterized by strong calcification of the interstices with varied pleural serosa involvement, sometimes with apical sparing.

FELSON [46] was the first to describe a black pleural line between the rib cage and calcified pulmonary infiltration on chest radiography. It can be detected on HRCT as a layer of delicate cystic alterations in the subpleural ventral region or as a fat-density layer between the ribs and calcified parenchyma in the lower and middle lung fields [47, 48]. To monitor disease development, quantitative computed tomography may be used to measure changes in mean lung density based on Hounsfield units [49].

Positron emission tomography scan

An adult case underwent fluorodeoxyglucose positron emission tomography, which showed a maximum standardized uptake value of 7.3 in areas without calcification and a lower standardized uptake value of 2.6 in areas with dense calcification [50]. This pattern points to the existence of inflammation, particularly in lung tissue that hasn't entirely calcified.

Bone scan

For diagnostic purposes, early investigations frequently used bone scintigraphy (technetium 99m-methylene diphosphonate bone scan) to show that lung opacities on chest radiographs were receptive to the tracer and consistent with bone [51–54]. In the majority of PAM instances, HRCT has eliminated the necessity for bone scintigraphy as a diagnostic tool.

Ultrasonography

Chest ultrasonography can detect echogenic foci on the order of millimeteres without acoustic shadowing in the subpleural region, as well as pleural thickness and abnormalities [47, 55]. The complicated pleural interface with enlarged pleura, subpleural microcysts, and thickened interstitium is blamed for the lack of expected acoustic shadow artifact, commonly known as the "comet tail" phenomenon, which may have reduced the depth to which ultrasound waves may penetrate.

DIAGNOSIS

Radiographic analysis can typically be used to confirm the PAM diagnosis. In situations when there is uncertainty, bronchoalveolar lavage exhibiting microliths with the usual lamellar structure has proven beneficial. Microliths have occasionally been found in expectorated sputum 53. Transbronchial biopsy is not typically necessary when the radiographic presentation is typical because it seems to have a reasonable yield and safety profile. Lung

biopsies have been used to make the diagnosis in the literature in about 46.9% of cases7, perhaps because few doctors are familiar with the condition. Lung biopsy should generally only be used in situations where doubt remains despite more cautious diagnostic techniques. Commercially available SLC34A2 gene genotyping could be used to test family members with the help of genetic counseling, but currently not necessary for diagnosis.

DIFFERENTIAL DIAGNOSIS

Diagnostic possibilities include miliary tuberculosis, pulmonary alveolar proteinosis, sarcoidosis, healed varicella or variola pneumonia, metastatic calcification, pneumoconioses including silicosis, pulmonary hemosiderosis, or amyloidosis when a chest radiograph with dense micronodular and ground glass opacities in an asymptomatic patient is first obtained. Due in part to the fact that areas where consanguinous marriage is prominent and Tb is extremely prevalent commonly overlap, PAM and pulmonary tuberculosis are likely to be confused the most. There have been at least five instances of concurrent Tb in PAM individuals[28]. PAM describes a bizarre paving pattern that was once felt to be pathognomonic for pulmonary alveolar proteinosis and may cause confusion in the diagnosis [28,29]. PAM and PAP can be distinguished from one another by separate calcifications that can be seen in mediastinal window settings. The differential encompasses the various causes of both metastatic and dystrophic pulmonary calcification, which happen in once normal lung tissue and damaged lung tissue, respectively, in individuals who are shown to have diffuse pulmonary calcifications on CT or chest radiographs 55. The most common cause of pulmonary metastatic calcification is chronic renal failure, but it can also occur in cases of hyperparathyroidism, mild alkali syndrome, talcosis, amiodarone toxicity, iodinated oil embolism, aspirated contrast material, and extravasated or aspirated blood. Varicella or variola virus infections, granulomatous diseases caused by tuberculosis, histoplasmosis, coccidioidomycosis, or sarcoidosis can all lead to dystrophic calcification as a complication.

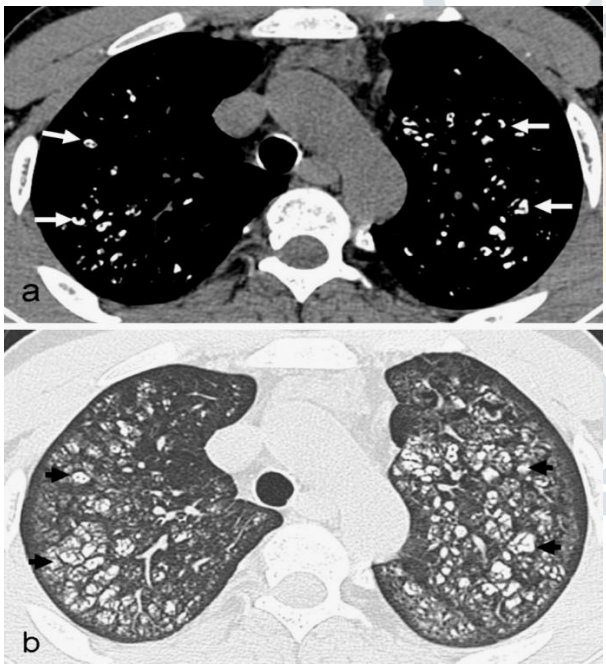

FIGURE 2 Other examples of diffuse lung calcification. Computed tomography depicting examples of a) amyloidosis with calcified masses, lymphadenopathy and rare cysts, b) silicosis with peri-lymphatic calcified nodules, eggshell lymph node calcifications and conglomerate fibrosis.

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 30.

PHARMACOLOGICAL TREATMENT OPTIONS

Etidronate is a special type of bisphosphonate that slows bone mineralization and crystal growth in addition to osteoclast-driven bone resorption, as do many other drugs in its class. The FDA has given etidronate approval to

treat Paget's disease and heterotopic calcification [31]. Etidronate has been shown in a small number of case studies to enhance lung function and lessen lung radiographic opacification in individuals with PAM 13,57-60.

Children with PAM have reportedly benefited from etidronate therapy. After taking daily oral disodium etidronate for 36 months, a 3.5-year-old girl with PAM, failure to thrive, and a nonproductive cough showed radiographic and symptomatic improvement [33]. She continued using disodium etidronate for a total of 9 years, after which she was prudently managed without assistance for an additional 11 years [34]. After the conclusion of the observation period, PFTs showed modest advancement of septal thickness and calcifications on HRCT compared to her baseline and a nonsignificant decline in spirometric indices. Similar to this, after receiving oral disodium etidronate medication for 12 months, a 9-year-old girl with failure to thrive who was discovered to have radiographs compatible with PAM showed radiographic improvement in HRCT [35]. She was given disodium etidronate on a different schedule after experiencing rickets as a side effect of treatment. She kept receiving disodium etidronate medication in 15-day cycles every four months for a total of 11 years of therapy, with spirometry showing improvement [34]. Finally, disodium etidronate was administered to an 11-year-old boy and his identical 4-year-old sisters who both had the homozygous SLC34A2 gene mutation. After 12 months of treatment with disodium etidronate, the youngster and one of his female siblings showed improvement in radiographic chest radiography and HRCT results [36], while the other twin did not. These findings suggest that treatment outcomes can vary greatly across patients, even those who have the same genetic abnormality.

Etidronate is ineffective in additional studies [32]. Etidronate may be used to treat PAM, however, more research is needed to confirm this.

INHALED CORTICOSTEROIDS

Radiographical features of PAM do not appear to be improved by inhaled corticosteroid therapy. There is little evidence to support the routine use of inhaled corticosteroids in PAM patients, but it has been used successfully to treat symptoms and abnormal lung function in PAM patients who present with accompanying conditions like lymphocytic interstitial pneumonitis, discoid lupus erythematosus, spirometrically proven obstructive lung disease suggestive of asthma, among others [37–39].

SYSTEMIC CORTICOSTEROIDS

Systemic corticosteroids have been tried as a PAM therapy by a few doctors. A PAM patient had steroid treatment from BADGER et al. [40] for 48 days without any improvement. In one study, prednisone was administered to two patients; the first was a 66-year-old who was lost to follow-up, and the second, was an adult who received treatment for two months without any results [41]. A 47-year-old man who received prednisone treatment was reported to have made some progress before transplantation, albeit it is unclear how this was determined [42].

SODIUM THIOSULFATE

A calcium-chelating and solubilizing drug called sodium thiosulfate (STS) have been used to treat conditions like calciphylaxis in end-stage renal illness that are linked to heterotopic ossification [43]. Since there are currently no trials, treatment is still empirical and is effective with systemic medication and direct intra-lesional injection [44]. A less intense monthly intravenous infusion was tried by TAILLE et al. [46] for 9 months, but there was no change in symptoms, PFTs, or microlith load as determined by HRCT examination. Instead, they noticed a pronounced rise in lung density and a fall in diffusion, and they hypothesized that the STS dose or interval might not have been sufficient to stop the disease from progressing. It's also conceivable that the STS therapy sped up the course of the illness.

SUPPORTIVE MANAGEMENT

OXYGEN THERAPY AND VACCINATIONS

Patients who become hypoxemic during rest, activity, or sleep may consider receiving additional oxygen therapy. PAM sufferers should have their influenza and pneumococcal immunizations.

PROCEDURAL/SURGICAL TREATMENT OPTIONS

Whole Lung Lavage

Several researchers have tried whole lung lavage to see if microliths could be manually removed. Even though the fact that numerous spherules of less than 1 mm were found in the serial lavages of a single patient, there was no appreciable improvement in the radiographic abnormalities [105]. In another instance, 14.5 g of solid debris was successfully removed by lavage using 22 L of buffered saline, but neither the radiological findings nor the clinical symptoms improved [32]. The researchers hypothesized that entire lung lavage could not effectively remove microliths whose diameter exceeded that of the respiratory bronchioles or the alveolar orifice.

LUNG TRANSPLANTATION

Lung transplantation is the only proven treatment for advanced PAM. Both single lung and double lung transplantation have been successful in PAM despite many procedural difficulties, such as calcified lung parenchyma limiting intra-operative deflation and access to the hilum, more dense pleural adhesions, and a higher risk of intra-operative and post-operative bleeding. [47, 48]. Initial worries that pulmonary shunting would negatively affect the results of single lung transplantation have been disproved. In patients with lung transplants, there have not yet been any recorded recurrences of intra-alveolar microliths.

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