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Review Article

Alveolar Concretions (Microlithiasis): A Review Article on Lung Involvement

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Abstract

Alveolar concretions or also known as pulmonary alveolar microlithiasis (PAM), a disease with variable inheritance. This disease is very rare and this article represents work on PAM till end of the December 2023 by means of a full reviewing the total articles and case reports from available literature. A total of more than 1100 cases of PAM have been reported worldwide. Turkey, Chinese, Japanese, Indian, Italian populations accounting approximately 52.4% of total cases worldwide. Clinical features of PAM family history, clinical course, genetic association, prognosis and recent advancement in diagnosis and treatment have all been analyzed from all case reports and available review articles.

Keywords: Pulmonary alveolar microlithiasis, SLC34A2, Sandstrom appearance, Stony lung, Rare lung disease.

Introduction

This is a review article on alveolar concretions or PAM. It is one of the rare depositional disorders related to all organs but pulmonary involvement is discussed here. This study is about knowing the epidemiological, clinical, genetic, radiological, prognostic and management of PAM. We have searched all the related articles and case report from the beginning to till today. The first concise and detailed macroscopic description was given by an Italian scientist, Marco Malpighi [1] in the late 17th century around 1686: "In vesiculitis pulmonum innumeri lapilli sunt". Norwegian Harbitz was the first scientist who gave most accurate description of PAM autoptic and radiological. The term pulmonary alveolar microlithiasis was given by a Hungarian pathologist Puhr[2] in 1933.

Pathophysiology

It is an autosomal recessive disorder that occurs due to SLC34A2 (expanded term solute carrier family 34 member 2) gene mutation at 4p15.2. It encodes for a co-transporter NPT2b (sodium phosphate transporter).[3] This transporter helps in clearing phosphate from alveoli into pulmonary macrophage cells (Type 2) at the ratio of $3Na^{+1}$:$1HPO_4^{-2}$.[4] If this protein is dysfunctional, then homeostasis of phosphate is affected because type 2 alveolar cells are unable to clear phosphate. Phosphate clearance is impaired, leading to the accumulation of phosphate in the alveoli. Over time, excess phosphate forms precipitate with calcium, which we now call microliths. These microliths accumulate in the alveoli, causing characteristic radiological findings and eventually impairing lung function as the name microlith suggests the formation of calcified concretions deposited in alveoli. In this disorder, there is no abnormality of calcium metabolism in spite of phosphate elimination being defective, which leads to excess accumulation of phosphate. Other organs apart from the lung also express this transporter, but usually, these microliths are not formed because of alternative mechanisms present in these organs for clearing phosphate; hence, it leads to minimal extrapulmonary features of PAM.[5] This transporter is present in high amounts in the lungs and gut. Thyroid, salivary gland, mammary gland, uterus and testes also expressed some amount of transporter.

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Geographic Distribution

PAM is found worldwide. The highest number of cases are from Turkey (159 cases), China (68), Japan (63), India (43), and Italy (40). Distribution is not uniform. The majority of cases are from Asia, 576 (56.3%) and 285 (27.8%) cases in Europe. Turkey, China, Japan, India and Italy account for 52.4% of total world cases.

Genetics

Autosomal recessive disease and often associated with consanguinity, but about two third cases had sporadic mutations in PAM. Independent peoples from Turkey and Japan identified gene SLC34A2 in 2006, which leads to us thinking of a genetic cause for PAM. Over 34 SLC34A2 different alleles have been identified.[6] Both homozygosity and heterozygosity are found in these 34 alleles but the majority are homozygous. Frameshift or nonsense mutation of these alleles (more than 50%) occurs, leading to mRNA terminating prematurely or decaying early.[7] Nutritional phosphate is absorbed in the gut by this transporter. Despite of defect in the transporter (NPT2b), hypophosphatemia did not occur because of a strong compensatory renal mechanism that maintains normal phosphate homeostasis with adequate dietary intake. However, mouse models suggest that when dietary phosphate is limited, NPT2b protects the host from hypophosphatemia. Apart from the above gene, there are other genes that can affect phosphate transport are SLC34A1 (NPT2a), SLC34A3 (NPT2c), SLC20A1 (PIT1) and SLC20A2 (PIT2).[8-10] This gene consists of 13 exons, and mutations lead to the disease by preventing proper phosphate clearance in alveolar epithelial cells. Corut[11] et al. found six mutations (homozygous) among 6 patients and one family. Since then, 18 patients and five families have been studied, revealing 16 different mutations, primarily in exons 8 and 12.

Clinical Presentation

PAM has an indolent course in nature. Despite dramatic imaging findings on radiographs (clinical-radiological dissociation), most patients are asymptomatic initially at the time of suspicion of PAM. PAM is often found incidentally on imaging studies performed for another reason. Symptoms usually develop during the third or fourth decade of life. Presentation at an extreme age is also possible. In these patients' presentation will be more acute and aggressive, which can lead to acute respiratory failure. Common symptoms in descending order are shortness of breath (24%), dry cough (14%), chest discomfort/pain (6%) and frailty (3%). Less frequent symptoms were sputum production, hemoptysis, and fatigue.

A literature review from a large series identifies that 1/3rd cases are familial.[12] Familial clustering was particularly seen in Turkey and Italy. In the report by Castellan,[13] identified that PAM is familial in around 37% of total patients. The autosomal recessive pattern of inheritance was supported by horizontal transmission of PAM. Although 17% had vertical transmission also, that was explained by the presence of consanguinity among them. Females are commonly affected especially when more siblings are affected. Extrapulmonary microliths have been found in the male genitalia in several cases, potentially causing infertility.

Pulmonary Alveolar Microlithiasis (PAM) and Comorbidities

Tuberculosis is the most common comorbidity found with PAM. Apart from tuberculosis, many diseases can mimic PAM. These are achalasia of the diaphysis, milk-alkali syndrome, pericardial cyst, lymphocytic interstitial pneumonitis (LIP), Waardenburg syndrome, hypertrophic pulmonary osteoarthropathy (HOPA). Less common are cobbler's chest, connective tissue disorders and malignancies like non-Hodgkin lymphoma were also noted in patients with PAM.

Diagnosis

Laboratory investigations are usually normal hence, radiological imaging is first clue for suspicion of PAM but as from recent advances genetic testing is now key to diagnosis apart from histopathological examination.

Blood investigation: - Usually, all serum investigations are normal, including measuring mineral levels.

Pulmonary function testing- Initially, it can be normal and requires repeated follow-up. In the advanced stage restrictive pattern is seen. Exercise limitation is also seen as disease progression occurs.

Chest X-ray

Abnormal X-rays is the first clue in thinking of PAM, especially in asymptomatic patients. On x-ray, small diffuse scattered innumerable micronodule predilection to bases compared to apices. Typically called as "sandstorm appearance" (usually size <1 mm but can be up to 2–4 mm) as shown in Fig. 1. It is also observed that in children (the youngest patient reported being diagnosed at 8 months[14]) ground glass opacities are not infrequent as compared to calcification and are restricted to lower zones.[15] The vanishing heart phenomenon[16] is a radiological feature that occurs in more advanced diseases, as we cannot identify heart borders clearly. This phenomenon is non-specific as it can present in any cause of respiratory distress syndrome (ARDS).

Computed Tomography (high-resolution CT)

It is the most diagnostic imaging modality available. It shows bilateral, symmetric involvement with mid and lower lung involvement occurs. Diffuse calcified pulmonary nodules, sup-pleural cyst, diffuse ground glass opacity, inter-septal septal thickening, consolidation, crazy-paving pattern and emphysema are commonly seen on HRCT scans. Pulmonary calcified nodules are the most important finding which can be present along with fissures, subpleural (peripheral). Castellan[13] called as "stony lung," while Bendstrup[6] called as "white-out lung," as shown in Fig. 2. Predominant CT

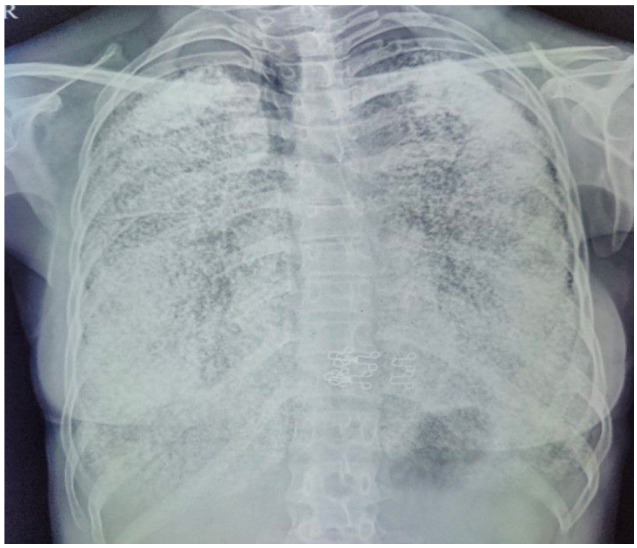

Fig. 1: Chest x-ray of female showing sandstorm appearance typical for PAM

findings that are present in almost all cases of PAM are parenchymal nodules (small size) and ground glass opacities.[17] The "Black pleura" sign also presents in some patients and is characterize by cysts are subpleural in location. In PAM, "crazy-paving" with calcification that seen as tracing septal lines is seen. This can help distinguish PAM from pulmonary alveolar proteinosis.[18]

Evolutionary Phases and Radiological Classification

- ***Phase 1: Pre-calcific***

Early stage with minimal and less calcified microliths. Rarely reported and often not recognized, typically observed in asymptomatic children. The radiological pattern is not yet typical.

- ***Phase 2: Calcific/Classical "sandstorm-like" appearance***

Typical "sandy" appearance with diffuse, scattered calcific micronodules (<1 mm). Microliths are bright, uniformly sized, and distributed, more concentrated in medial and inferior lung regions. Heart and diaphragm outlines remain visible. Larger micronodules (2-4 mm) can resemble berries. Usually seen in childhood or adolescence.

- ***Phase 3: Granular***

Increase in number and volume of opacifications. Granular and nodular pattern is due to initial interstitial thickening. Medial and inferior fields' opacifications obscure heart and diaphragm outlines. Commonly observed in young adults.

- ***Phase 4: Advanced***

Intense calcification and "white lungs" appearance due to extensive calcific deposits. Apical regions may be partially spared. Associated with para-septal emphysema, large air cysts, pneumothorax, and ossification are typically seen in older adults or advanced cases.[19-20]

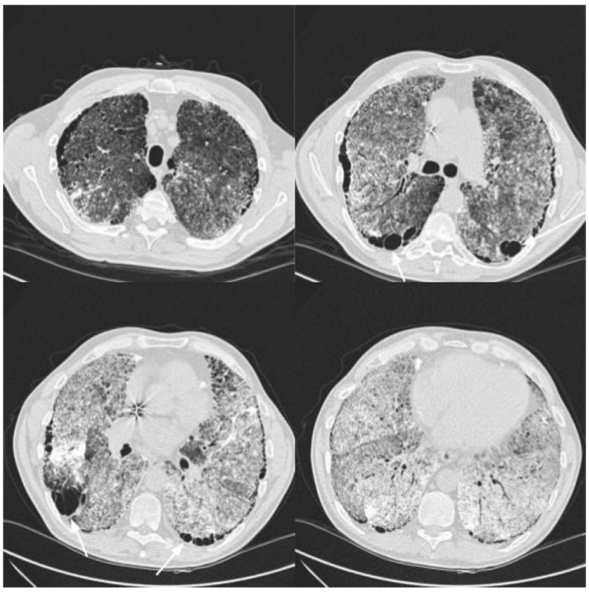

Figure 2. HRCT scan showing diffuse microcalcifications. The apical to basal gradient common in PAM is here clearly visible. Arrows indicate subpleural cysts ie, the "black pleura sign."

PET Scan

This scan provides some information about calcified and those who are going to be calcified later on. Solely based on standard uptake. Uptake remains high (7.3) in areas without calcification and lower (2.6) in areas with dense calcification. The above observation tells us about ongoing inflammation in areas of the lung that have not developed calcification.[21]

Flexible Bronchoscopy

By this procedure one can obtain bronchoalveolar lavage (BAL) and transbronchial biopsy. Concentric lamellar concretion (microliths) can be present.

Genetic Testing

Other investigations can be adjunctive for diagnosis. After knowing the genetic basis of PAM, identifying mutated genes will confirm a diagnosis. It is now a standard test for diagnosis of PAM if available. Online sources for genetic testing are available at https://www.fulgentgenetics.com/Pulmonary-Alveolar-Microlithiasis.

Differential Diagnosis

- Pulmonary ossification- large size of pulmonary nodules with underlying disease process for example, metastatic pulmonary ossification.
- Sarcoidosis – histopathological epithelioid granulomas present.
- Tuberculosis
- Hemosiderosis
- Pneumoconiosis
- Nodular amyloidosis

Misdiagnosis with tuberculosis is common, especially in regions where tuberculosis is prevalent (Turkey, China, India), leading to incorrect treatments.

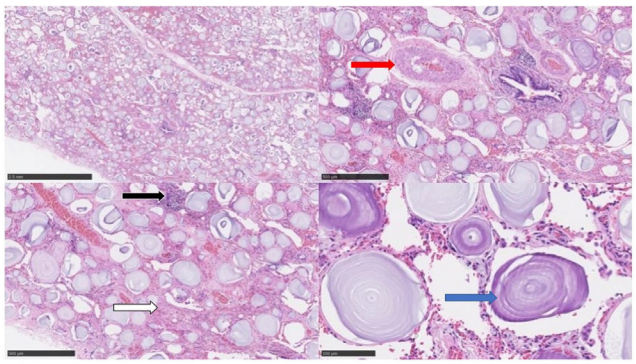

Figure 3. Lung section from a patient with PAM showing calcified microliths in intraalveolar space. The blue arrow indicates the lamellar appearance of microliths, the red arrow vasculopathy, and the black arrow a lymphoplasmacytic infiltrate. Haematoxylin and eosin staining. Scale bars in figure.

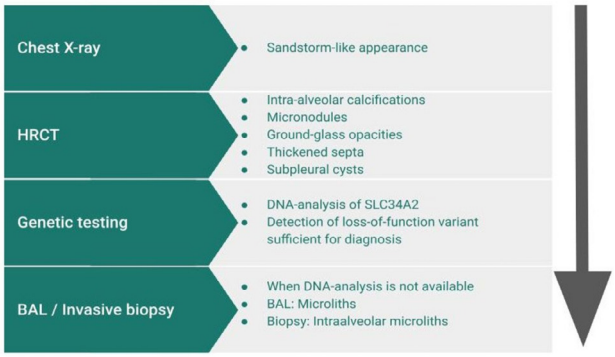

Figure 4. Suggested diagnostic approach to confirm PAM diagnosis. In cases with familial history, the classic radiological findings may be sufficient to make the diagnosis.

Lung Biopsy

In cases where imaging was inconclusive, lung biopsy was helpful in making a diagnosis. This shows the presence of concentric lamellar arranged concretions (microliths) in the biopsy sample, as shown in Figure 3.

Treatment

Current treatments

No effective medical or gene therapy currently exists for PAM. Available treatments that are tried in PAM but did not show any effect or lead to cure are inhaler therapy, either steroids or bronchodilators or oral steroids, chelating agents with serial lavage. Bisphosphonates have been proposed to reduce calcium phosphate precipitation, but their effectiveness is controversial due to limited reports. Bisphosphonates like disodium etidronate have been explored with varying success in reducing progression, especially in children, but the evidence is not convincing.[22]

Lung transplantation

Lung transplantation remains the only definitive modality and it is reserved for life-threatening or last stage of PAM. Transplantation can significantly improve the quality of life and survival in patients with late disease.[23] Post-transplant outcomes were generally favorable, although data was limited due to the rarity of the condition. The longest-living transplanted patient is a 63-year-old female, with the longest survival post-transplantation reported at 15 years without recurrence.[24]

Course and prognosis

PAM generally has a slow but progressive course. Pulmonary function tests often remained normal till the disease became advanced. The advanced disease could result in severe respiratory insufficiency and right heart failure. Despite slow progression, the prognosis in advanced cases was poor, with significant morbidity and mortality due to respiratory failure. There is no curative treatment for PAM; management focuses on symptom relief and supportive care. Lung transplantation may be considered for severe cases. The prognosis in PAM is variable. Some patients remain asymptomatic or mildly symptomatic for many years, while others progress to severe respiratory and cardiac complications. Long-term survival varies, with an average lifespan post-diagnosis ranging from 10 to 20 years, although rare cases of long-term survival have been reported.[25]

Conclusion

PAM is a rare disease with a global distribution and characteristic radiological features. Despite its typically slow progression, PAM can lead to severe respiratory impairment in advanced stages. There are no effective medical therapies. Hence, management remains supportive. Lung transplantation offers hope for patients with end-stage disease. Advances in genetic testing and imaging techniques have improved diagnostic accuracy. Future research into the underlying pathophysiological mechanisms may offer new insights and potential therapeutic targets to improve outcomes for individuals affected by this rare disease.

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