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REVIEW

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Pulmonary Alveolar Microlithiasis – A Review

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Pulmonary Alveolar Microlithiasis (PAM) is a rare genetic disorder causing widespread deposition of calcium-phosphate crystals in the alveolar space. A hallmark of the disease is the discrepancy between perceived symptoms upon diagnosis compared with the extensive, sandstorm-like appearance of the microliths on chest X-ray or HRCT. Caused by a defective sodium-dependent phosphate transport protein due to loss-of-function variants of the *SLC34A2* gene, PAM is an autosomal recessive transmitted disorder, and as such has a high correlation to consanguinity. The most common variants of the *SLC34A2* gene are single nucleotide biallelic changes, but larger deletions are described. Initial suspicion of PAM on radiological examination should be followed by genetic testing to verify the diagnosis and identify the disease-causing variant. When not available, the diagnosis can be made by means of invasive techniques, such as transbronchial forceps or cryobiopsy, or a surgical lung biopsy. In families with a history of PAM, genetic counseling should be offered, as well as preimplantation/prenatal testing if necessary. As of writing this review, no definitive treatment exists, and PAM may in some cases progress to severe pulmonary disease with respiratory failure and potential death. Patients with PAM should be offered preventative and symptomatic treatments such as vaccinations and oxygen therapy when needed. In some cases, lung transplantation may be required.

INTRODUCTION

Pulmonary Alveolar Microlithiasis (PAM) is an autosomal recessive genetic disorder caused by a loss-of-function of the *SLC34A2* gene, causing deposition of miniscule calcium crystals, the so-called microliths [1].

PAM is a rare disorder with around 1100 cases having been reported worldwide [2]. PAM was first described in 1686 by the Italian physician Malpighi in his work "In vesciculis pulmonum innumeri lapilli sunt." Here he describes lungs that "were heavy and compact with patches of black countless small stones." A Norwegian physician by the name of Harbitz later categorized the disease with a description of the radiological signs and objective findings on autopsies related to the disease. Following his description, the disease was known as Harbitz's syndrome until the Hungarian pathologist Puhr renamed it as its current name, PAM, in 1933 [3].

PAM is characterized by the presence of microliths in the alveoli of the lung. The microliths are made up of calcium phosphate and are formed due to dysfunction of the *SLC34A2* gene encoding the sodium-dependent phosphate transport protein 2B, NaPi-2b [4]. A hallmark of the disease is the surprising discrepancy between the extensive radiological findings on conventional chest

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Abbreviations: PAM, Pulmonary Alveolar Microlithiasis; DLCO, diffusion capacity for carbon monoxide; FVC, forced vital capacity; TLC, total lung capacity; CT, Computerized tomography; HRCT, high-resolution CT; LUS, Lung ultrasound.

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X-rays and CT-scans and the perceived symptoms of the patients. PAM presents a wide spectrum from patients being asymptomatic for many decades, to patients suffering from progressive respiratory failure and death.

EPIDEMIOLOGY

PAM is seen all over the world with no particular affinity for geographical location or ethnicity. Turkey, Italy, and the US have reported the largest number of cases.

Previously, there seemed to be a slight male predominance but with the increasing number of cases published, the gender distribution is now the same between males and females [3,5,6].

PATHOPHYSIOLOGY

Prior to the breakthroughs in genetic testing, there was already a prevailing theory in the medical community that PAM was caused by autosomal recessive transmission, as inheritance was horizontal, and there seemed to be a higher incidence among children of consanguineous parents [1].

The lack of re-absorption of phosphate from the alveolar space is caused by a loss-of-function due to variants in the *SLC34A2*-gene. The most common type of variant is a single nucleotide biallelic change, but larger deletions do occur. The variants are present in a homozygous state, or more rarely in a compound heterozygous form [1].

SLC34A2 consists of 13 exons located on the short arm of chromosome 4 (4p15.2), encoding a sodium-phosphate carrier protein, NaPi-2b. This carrier protein is expressed in multiple organs, including the lungs, intestines, mammary glands, salivary glands, and testes [4]. The primary organ affected by the illness is the lungs, probably because of the lack of other pathways for phosphate-clearance present in other organs [7].

In the lungs, the phosphate-transporter is mainly expressed in type II alveolar cells. These cells produce and excrete surfactant into the alveolar space. An important component of surfactant is phosphorus in the form of phospholipids, and the human body has salvage systems in place to reabsorb the broken-down surfactant for reuse. In patients with *SLC34A2* variants, this re-absorption is compromised, thus leading to a build-up of phosphate in the alveolar space which may facilitate the formation of calcified microliths [8,9].

SYMPTOMS

Some patients remain asymptomatic for several decades, but most patients with PAM present with a dry cough and breathlessness on exertion. The cough is rarely productive and expectoration of the small microliths has seldom been reported [10]. Other common symptoms are fatigue and chest pains [11,12].

The disease most often becomes symptomatic in the fourth to fifth decade of life, but can present at all ages, including childhood and infancy. In children, the symptoms can be severe and similar to adults with breathlessness and cough but can also present as failure to thrive and recurrent lower respiratory infections [13].

Often, PAM is an incidental finding, resulting in patients being referred to further examination after the discovery of classic radiological findings or as part of family investigations.

The symptoms can be stable for many years, and the progression rate is mostly slow. PAM will, however in many patients, progress to respiratory and cardiac failure and eventually death [14]. Over time, patients can begin to show symptoms similar to those of interstitial pulmonary disease and can experience type I hypoxic respiratory failure [5,6].

CLINICAL FINDINGS

Many patients appear normal without findings on clinical examination but as the disease progresses, the patients may show signs of digital clubbing, as well as peripheral or central cyanosis. However, as with all the following findings (except radiological examinations), patients can exhibit all, some, or none of these findings.

Patients with PAM can be found to have bilateral, fine crackles [5,6,8], basal diminished lung sounds [13], or normal auscultation.

Patients will often show some level of type I hypoxemia on room air with a reduced saturation or desaturation on exertion. Tachypnea and tachycardia are seen upon worsening of the disease.

BIOCHEMISTRY

PAM is defined by the concretion of concentric calcium-phosphate crystals in the alveoli of the lungs, but patients generally have serum values of both calcium and phosphate within normal parameters [15].

PULMONARY FUNCTION

Many patients with PAM will show varying levels of restrictive pattern on a pulmonary function test, as well as reduced, sometimes severely impaired diffusion capacity for carbon monoxide (DLCO) [5]. As with many other clinical parameters, the pulmonary function of patients with PAM can show a wide spectrum ranging from normal values, to a more restrictive pattern. The patients can present with a reduced forced vital capacity (FVC), as well as reduced total lung capacity (TLC), and DLCO.

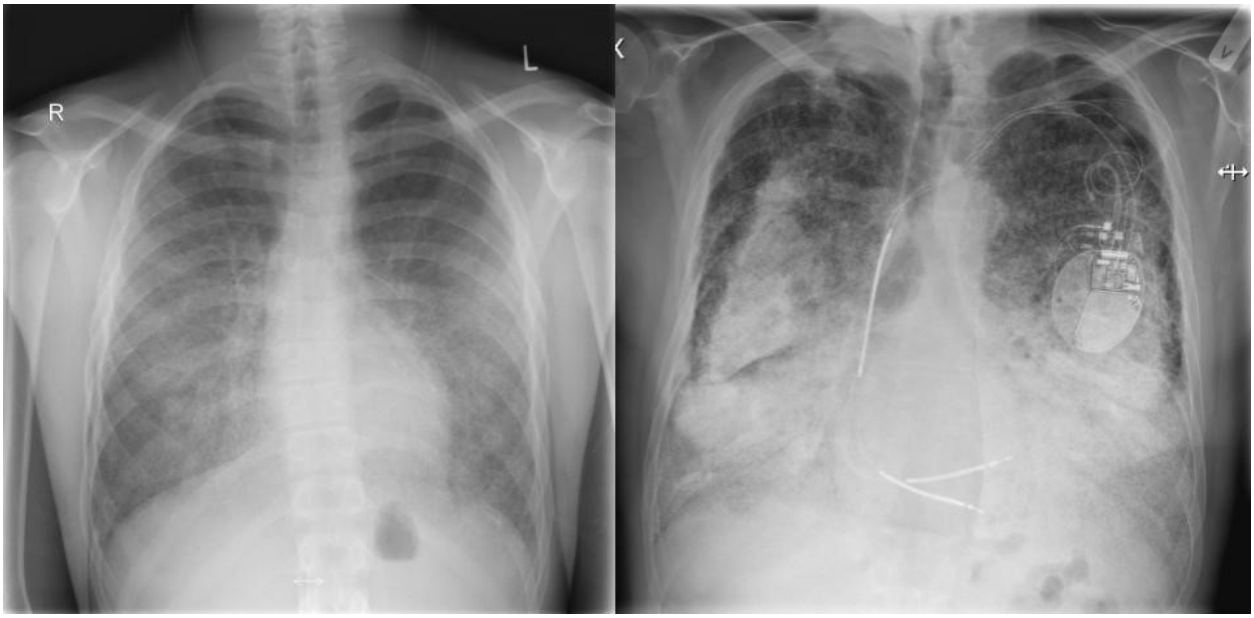

Figure 1. **Conventional chest X-ray of the same patient 18 years apart showing the characteristic "sandstorm like" infiltrations bilaterally**. The pacemaker visible in the image is unrelated to the patients PAM diagnosis.

These findings will often progress with disease and become more affected over time [15]. Six-minute walk tests will similar show reduced distance and desaturation as the disease worsens.

RADIOLOGY

A conventional chest X-ray is often the first sign of a possible PAM diagnosis. The lungs appear with a classic image of bilateral diffuse micronodular calcified infiltrations, mainly in the middle and lower segments of the lungs. The infiltrations have a fine, sand-like appearance on the chest X-ray, which leads to it being referred to as "sandstorm like" infiltrations (Figure 1) [14]. The noticeable findings on routine chest X-ray examinations can be in stark contrast to the clinical appearance of the patients who may be completely asymptomatic.

Computerized tomography (CT), and in particular high-resolution CT (HRCT), can show the same "sandstorm like" appearance as seen on the conventional chest X-ray. The micronodules observed on CT can be up to 3 mm in size. Also, thickening and calcification of the pleura and interlobular septae are often seen together with subpleural cysts, the so-called "black pleura sign." "Ground-glass opacity" as well as "crazy paving" has also been described (Figure 2) [16,17].

A technetium bone scintigraphy with TcMDP will show massive uptake of radio-tracer in the lungs [18]. However, scintigraphy are rarely necessary as it does not provide further information beyond that of HRCT.

Lung ultrasound (LUS) may be able to visualize the pleural thickening and irregularities associated with PAM as well as the microliths, which will show as hyperechogenic foci without acoustic shadowing [19].

Echocardiography can show the secondary effects on the circulatory system, in particular pulmonary hypertension and associated findings, such as an enlarged right ventricle. Left ventricular function is often intact [5,20].

STAGING

In recent years, it has been suggested that PAM can be categorized into four stages, based on the findings on HRCT:

Stage I: Sometimes described as the "pre-calcific stage," due to the low amount of microliths and grade of calcifications. This is rarely seen, as most cases have more wide-spread microliths by time of diagnosis, but it can be observed in asymptomatic children.

Stage II: The classical "sandstorm like" appearance is now visible. Microliths can be seen throughout the lungs, with a predominance for the basal and mid-lung segments. Most of the microliths are less than 1 mm in diameter, but larger (up to 2-4 mm) calcified nodules can be observed. It is still possible to make out the boundaries of the diaphragm and heart. This presentation is mainly seen in younger patients.

Stage III: The microliths are more widespread, and the boundaries of the heart and diaphragm become obliterated. Interstitial thickening begins to set in. Stage III is often found in younger adults with the disease.

Stage IV: "White lungs." The most severe presenta-

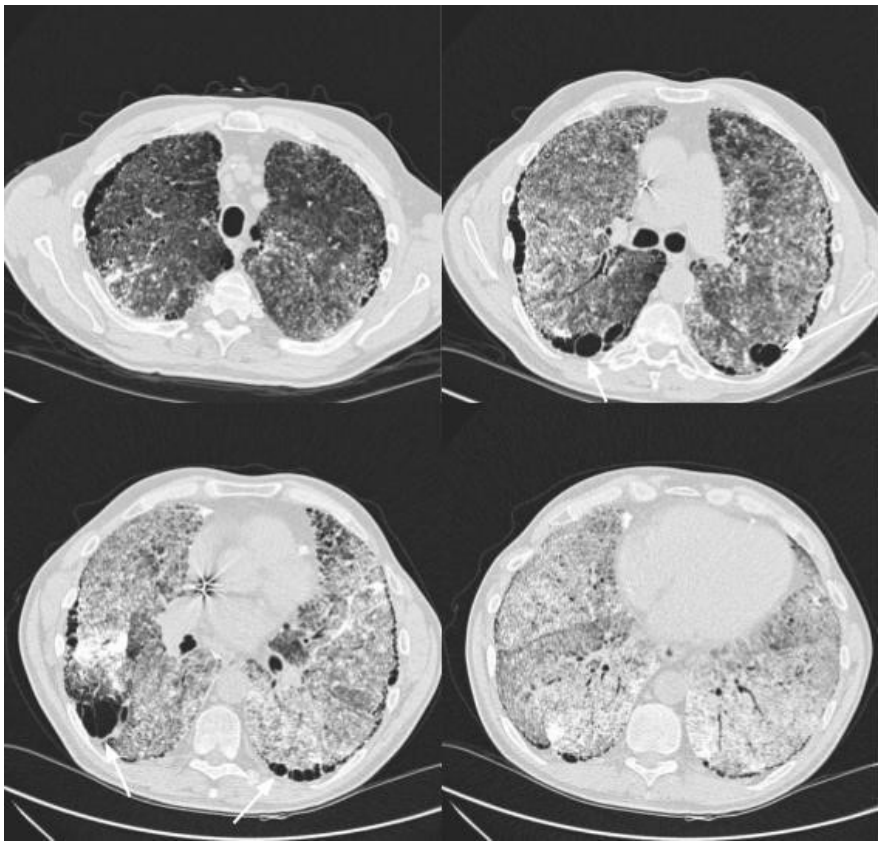

Figure 2. **HRCT scan showing diffuse microcalcifications.** The apical to basal gradient common in PAM is here clearly visible. Arrows indicate subpleural cysts ie, the "black pleura sign."

tion, characterized by extensive interstitial calcification, with involvement of the pleura. At this stage it is not uncommon to see interstitial fibrosis, microcysts, and beginning ossification. Pneumothorax is also described in this stage. The presentation of stage IV is so characteristic for PAM, that it in some cases can be sufficient to make the diagnosis (Figure 2) [1,21].

GENETIC TESTING

PAM is an autosomal recessive disease with a high penetrance and is caused by biallelic variants of the *SLC34A2*-gene. As of today, we are aware of at least 30 allelic variants associated with PAM [1,6,21].

SLC34A2 variants have been found in affected families, but can also be found in individuals with no prior family history of PAM [22].

The identification of pathogenic variants on both alleles of the *SLC34A2*-gene is sufficient for the diagnosis of PAM in patients with relevant radiology and medical history.

With the knowledge of the genetics of PAM it is now possible to offer genetic counseling to patients and their families, which includes the possibility of prenatal or preimplantation genetic diagnostic testing.

INVASIVE INVESTIGATIONS

When genetic testing is not available in the context of a suspected case of PAM, or if the family history is not convincing, it is often of value to continue with an invasive diagnostic approach.

Biopsies can provide evidence of the pathognomonic calcium-phosphate microliths. When choosing which modality to use, it is encouraged to start with the least invasive procedure available. If a patient is seen in a hospital that does not routinely carry out such diagnostic procedures, the patient should be consulted by a facility with the required expertise.

Lung biopsies, either by transbronchial forceps or cryobiopsies, are preferred over surgical biopsies, as these methods are associated with a lower risk of complications [23].

If microliths are found by means of bronchoalveolar lavage, under the right clinical context, this is also considered sufficient to diagnose the condition.

PATHOLOGY

Histopathological samples acquired through biopsy will show concentric, laminated calcified concretions,

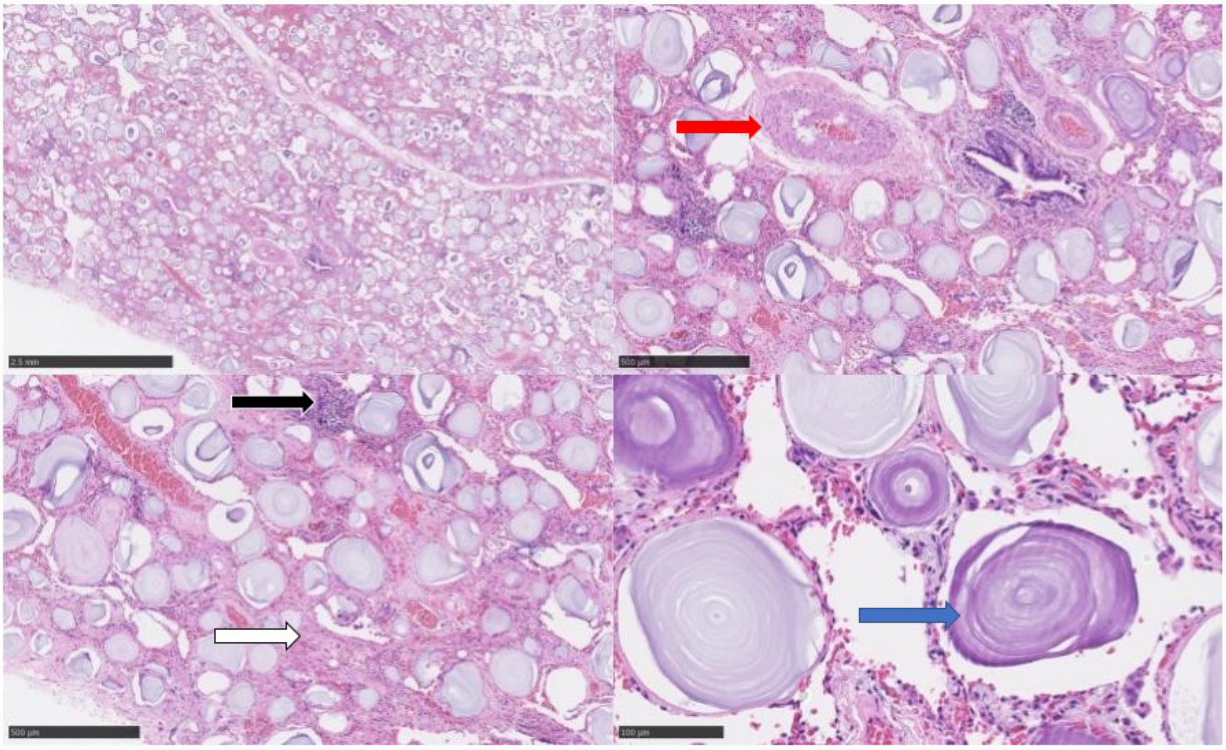

Figure 3. **Lung section from a patient with PAM showing calcified microliths in intraalveolar space**. The blue arrow indicates the lamellar appearance of microliths, the red arrow vasculopathy, and the black arrow a lymphoplasmacytic infiltrate. Haematoxylin and eosin staining. Scale bars in figure.

the microliths. These will appear basophilic on a haematoxylin and eosin stain and will be found in the alveolar space [17,24]. Surrounding tissue can show signs of inflammation in form of lymphomononuclear infiltration [5] (Figure 3).

Additionally, the histopathological findings related to PAM may show fibrosis as well as calcification of the lung parenchyma and pleura.

DIAGNOSIS

The classic presentation on chest X-ray and CT-scan is considered pathognomonic, and the diagnosis of PAM can in some cases be made solely on this basis. This is particularly in families with a known history of PAM. A patient with relevant family history and radiology consistent with PAM, can thus be diagnosed without the need of further invasive examination. However, in families with an unknown genetic background, genetic investigations are recommended to identify possible variants of the *SLC34A2*-gene. In the case of suspected PAM with no prior family history, it is encouraged to perform a genetic analysis in order to test for genetic variants. If the genetic test is unavailable, the final diagnosis is best based on the presentation of microliths in invasive procedures, either through biopsy or BAL. It should be noted, that the presence of microliths in BAL without other classic findings related to PAM should not be considered diagnostic, as other diseases, such as metastatic calcification in kidney failure [20], can show pulmonary crystallizations (Figure 4).

DIFFERENTIAL DIAGNOSTICS

PAM shares symptomatology and radiological findings with a number of other pulmonary disorders, primarily tuberculosis, sarcoidosis, amyloidosis, and metastatic microcalcification [5]. PAM is sometimes first considered a diagnostic option after treatment of these disorders fail to result in the usual treatment response.

TREATMENT

There is no present cure for PAM and several different treatments have been tried with varying degrees of efficacy.

As the disease is related to the deposit of calcium-phosphate crystals in the lung, attempts to mitigate the symptoms and progression of the disease with bisphosphonates such as disodium etidronate [5,13,20] or alendronate [5], has been used with varying results. As of 2020, 12 cases have been reported, wherein bisphos-

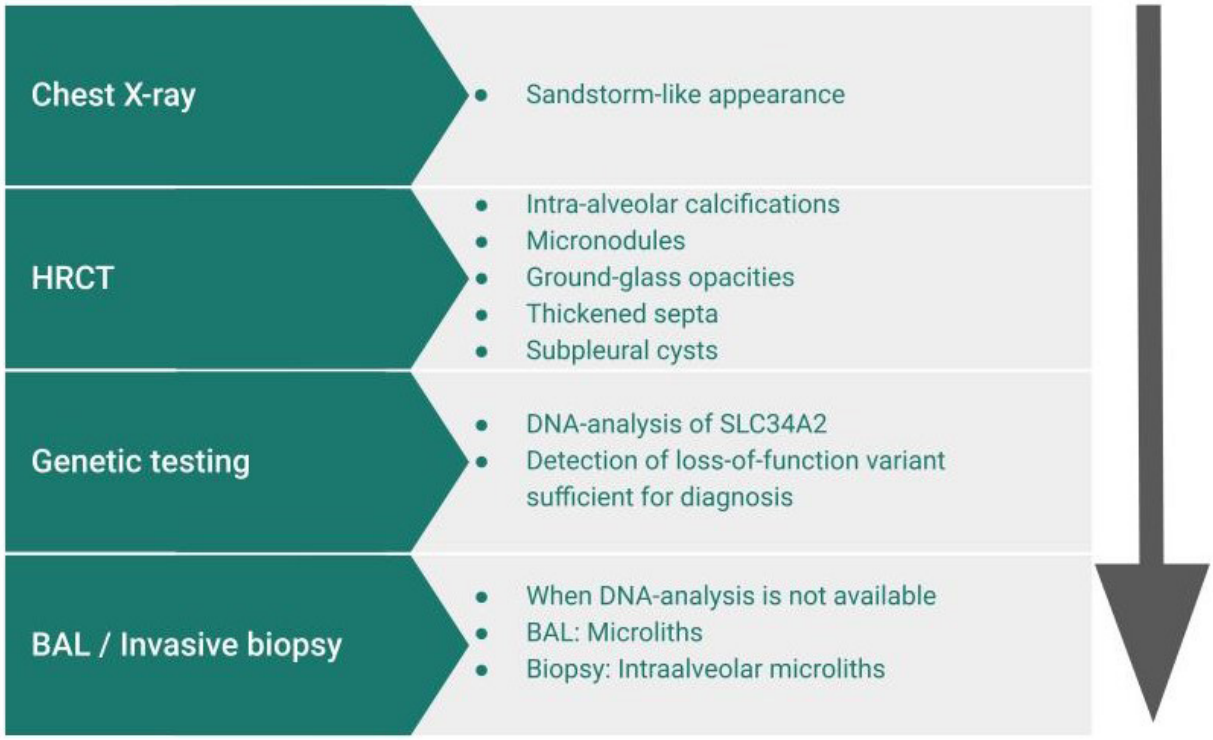

Figure 4. **Suggested diagnostic approach to confirm PAM diagnosis**. In cases with familial history, the classic radiological findings may be sufficient to make the diagnosis.

phonates, primarily disodium etidronate, were used. The stage of disease, the dosage, and the treatment periods varied greatly, and no solid evidence for the efficacy of bisphosphonates were found [1].

Treatment with corticosteroids is generally considered ineffective and any benefits are ascribed to treatment of a secondary interstitial inflammatory disease [25].

The only treatment broadly agreed upon for PAM is transplantation of one or both lungs [20,26]. One study found that out of a population of 18 patients who received one or more lung transplants, 12 were alive after a mean follow-up of 2.77 years. Those who died, did so from complications such as bronchiolitis obliterans or organ failure. Seven patients had no complications following the procedure [20].

Although no definitive treatment exists, there are a number of common supportive care approaches that can alleviate some symptoms as well as related complications. In case of hypoxemia, patients should be prescribed domiciliary oxygen to prevent manifest desaturation [6,20]. Furthermore, all patients with PAM should be advised against smoking, as this may exacerbate disease progression [15].

It is also recommended to administer vaccinations for influenza and pneumococcus, and COVID-19 [5,20].

A low phosphate-diet has been shown to have a favorable effect in a mouse model and in a patient where serum phosphate levels were shown to decrease [2,27]. The effect on symptoms and disease progression remains to be seen [2].

Overall the slow and varied disease progression has been hypothesized to play a part in the different outcomes, with some patients remaining relatively asymptomatic for years after diagnosis, with other progressing to respiratory failure in spite of treatment [15].

FOLLOW-UP

Follow-up of patients with PAM should include monitoring of symptoms, pulmonary function, and when appropriate, 6-minute walk test and imaging. The interval should be individualized according to the progression rate of the disease.

PROGNOSIS

Although disease progression in PAM is slow, and most patients are asymptomatic or showing very mild symptoms upon diagnosis, the prognosis is generally considered severe. Most patients will eventually start to experience increasing shortness of breath upon exertion and later show signs of hypoxemia on room air

and progress to respiratory failure. Many patients also experience secondary cardiac involvement, often due to complicating pulmonary hypertension, which can lead to cor pulmonale [5,13,20].

On average, patients tend to live 10-20 years after diagnosis [18]. However, long term survivors have been reported, the longest continued follow-up of a patient with PAM is 58 years [21].

CONCLUSIONS AND OUTLOOK

PAM is a rare autosomal recessive disorder that usually worsens over time and may lead to death.

The recommended diagnostic approach is to do a chest X-ray followed by the criterion standard of HRCT and genetic testing. In cases where genetic evaluation is not available lung biopsy is suggested for a definitive diagnosis.

Genetic testing is always recommended in order to provide genetic counseling to the patients and their families.

Although no successful treatment is available, all patients should be advised to stop smoking and receive relevant vaccinations, and oxygen therapy in case of hypoxemia. Some patients may require lung transplantations.

As we increase our knowledge of the genetic background and pathophysiology of PAM, we may be able in the future to improve the lives of the patients and hopefully develop more specific treatment options.

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