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# Pulmonary Hypertension and Polycythemia Secondary to Pulmonary Alveolar Microlithiasis Treated with Sequential Bilateral Lung Transplant: A Case Study and Literature Review

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Conflict of interest: None declared

**Patient:** Male, 49
**Final Diagnosis:** Pulmonary alveolar microlithiasis
**Symptoms:** Coughing • shortness of breath
**Medication:** —
**Clinical Procedure:** —
**Specialty:** Surgery

**Objective:** Rare disease

**Background:** Pulmonary alveolar microlithiasis is an autosomal recessive disease in which a mutation in the SLC34A2 gene that codes for a sodium phosphate type IIb transporter protein (expressed in human epithelial tissues and functions in the clearance of phosphate ions) leads to the formation of extensive pulmonary intra-alveolar microliths. The subsequent characteristic clinical features of dyspnea and hypoxia are a manifestation of these microliths. There have been fewer than 1000 cases of pulmonary alveolar microlithiasis reported worldwide, and there have been 19 reported lung-transplanted patients.

**Case Report:** A 49-year-old Saudi male patient presented with longstanding history of easy fatigability and tiredness on exertion since he was 16 years old. Throughout his follow-up in different hospitals (1986–1989), tuberculosis and pulmonary fibrosis were suspected. The patient was lost to follow-up between 1989 and 2001. In 2002, he presented to the emergency room with coughing, shortness of breath on exertion, abdominal swelling, and pedal edema. An investigation with chest x-rays, CT scan, electrocardiogram, and an echocardiogram was conducted. After referral to a tertiary care center, the patient was diagnosed with pulmonary alveolar microlithiasis. He subsequently developed pulmonary hypertension and polycythemia and therefore received a bilateral lung transplant in 2016. Following the lung transplant, he developed a mild reperfusion injury and tonic-clonic seizures, requiring ICU admission. After a successful extubatation with stable vitals and good recovery, he was discharged home in stable condition with planned follow-up.

**Conclusions:** We report a case of pulmonary alveolar microlithiasis successfully treated with a bilateral lung transplant. Although pulmonary alveolar microlithiasis is a rare entity, healthcare providers should consider it in the differential diagnoses of parenchymal lung diseases and differentiate it from tuberculosis and pulmonary fibrosis.

**MeSH Keywords:** Hypertension, Pulmonary • Lung Transplantation • Polycythemia • Pulmonary Alveoli

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## Background

Pulmonary alveolar microlithiasis (PAM) was first diagnosed by Harbitz in 1918 in Norway as an autosomal recessive disease consisting of extensive pulmonary intra-alveolar microliths (minute calculi) on autopic and radiological findings, with characteristic clinical features of dyspnea, and hypoxia [1]. Hence, it was previously named Harbtiz syndrome. It has since been renamed PAM in 1933 by Ludwig Puhr of Hungry [2]. Since the first case presentation, the disease has been rarely reported, with only 1000 cases reported worldwide. Asia reports the highest prevalence of PAM, and the highest number of cases is seen in people of Turkish and Italian descent. PAM presents most commonly in the second and third decade of life [1].

Patients with PAM have tested positive for a mutation in the SLC34A2 gene that codes for a sodium phosphate type IIb transporter protein, which is expressed in human epithelial tissues and functions in the clearance of phosphate ions [1]. With the mutation, there is a loss of function of the transporter protein and accumulation of phosphate within the lung alveoli in particular, leading to the classical appearance of microliths [3]. PAM can sometimes be confused with other lung conditions such as tuberculosis, sarcoidosis, and amyloidosis [4–6], but these produce more severe clinical traits compared to PAM. The clinical characteristics in PAM are heterogeneous and the disease progression is unpredictable, ranging from asymptomatic to heart failure and respiratory failure. PAM exhibits clinical-radiological dissociation [6]. Extra-pulmonary calcifications such as medullary nephrolithiasis, calcifications in the lumbar sympathetic chain, tesicles, punctuate calcifications in seminal vesicles, and periurethral and epididymal calcifications can also cause symptoms in PAM patients [1,6].

There is currently no established medical approach to successfully treat PAM. Many therapies have failed to prove effective in treating the disease. The only proven definitive treatments for PAM are unilateral lung transplant or bilateral sequential lung transplantation [4,5]. Herein, we report a case of PAM in a patient with a longstanding history, who subsequently developed secondary pulmonary hypertension and polycythemia, and then received a bilateral lung transplant (Figure 1). While there are over 1000 cases of PAM reported in the literature [6], there have been only 19 lung-transplanted patients reported. We reviewed these 19 cases, and their characteristics and outcomes are summarized in this paper.

## Case Report

A 49-year-old male Saudi patient had been previously assessed at age 16 at a local hospital for easy fatigability and tiredness on exertion. At that time, he was investigated for possible tuberculosis, which he did not have. For 3 years, the patient had the same complaints without seeking medical attention. At age 19, before beginning university studies, he had a medical examination, in which he again reported easy fatigability and tiredness on exertion. A chest X-ray was performed, which showed abnormal findings. The patient was then referred to another medical complex in Riyadh, Saudi Arabia for further investigation. The work-up at the medical complex included a transbronchail excisional biopsy of the lung, which, according to the patient, was reported to be pulmonary fibrosis. During that time, the patient was advised to cease smoking but did not, however, until 2 years later. At 31 years old (in 2002), the patient visited the emergency room in King Khalid University Hospital (KKUH) with complaints of coughing,

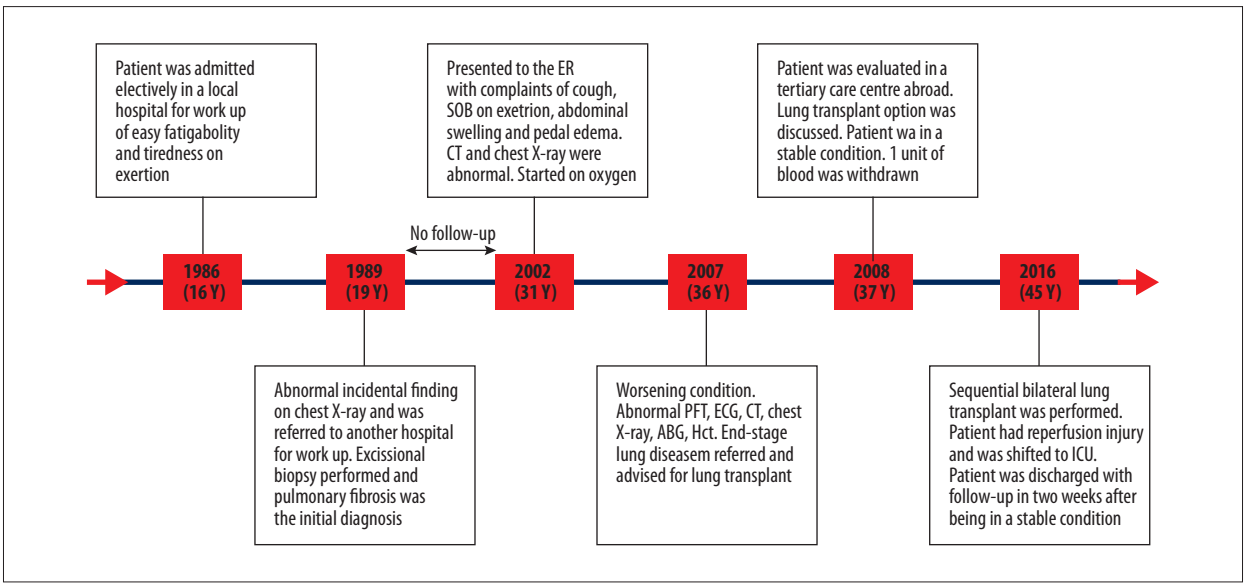


**Figure 1.** Summarizes the patient's history from 1986 to 2016.



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**Table 1.** Patient's functional parameters.

| Year | PAP (mmHg) | RVF | Hct (%) | FEV1 (%) | Home O2 (L/m) | O2 Saturation (%) |
|---|---|---|---|---|---|---|
| 2002 | 45/25 | Normal, no enlargement | 52.3 | 45 | 2 | 90 |
| 2007 | 55/30 | Normal, borderline enlargement | 57.8 | 39.7 | 2.5 | 91 |
| 2008 | 57/30 | Normal, borderline enlargement | 59 | 35 | 3 | 91 |
| 2015 | 71/35 | Severely dilated, mild hypertrophy, mildly reduced systolic function | 62.6 | 18 | 3.5 | 90 |

PAP – pulmonary arterial pressure; RVF – right ventricle function; Hct – hematocrits; FEV1 – forced expiratory volume in one second.

shortness of breath on exertion, abdominal swelling, and pedal edema. The patient had an unremarkable review of systems, social history, and family history. He reported no use of medications at that time. His arterial blood gas (ABG) results in 2001 were: Ph=7.4, $PO_2$=29.2 mmHg, $PCO_2$=44.5 mmHg, and $HCO_3$=27.2 mEq/L on room air. At 36 years old (in 2007), he was admitted to KKUH and was investigated with chest x-rays, a CT scan, an electrocardiogram (ECG), and an echocardiogram. X-rays revealed bilateral reticular nodular shadowing involving both lungs. The CT scan showed diffuse fine nodular densities scattered in both lungs. Also, the patient was revealed to have mild cardiomegaly. He was advised to use home oxygen at a flow of 2 liters. His ECG showed a sinus rhythm with right axis deviation and right ventricular hypertrophy with voltage criteria and P-pulmonale in lead II. The echocardiogram showed good left ventricular systolic function, no regional wall motion abnormalities, and normal function of the right ventricle with minimal enlargement (Table 1). The patient was put on 2.5 liters oxygen, vitamin E (400 IU per oral once daily), colchicine (0.5 mg per oral twice daily), and Sildenafil (25 mg per oral 3 times daily). He was then referred to a tertiary care center with a lung transplant service outside the Kingdom of Saudi Arabia. The patient was admitted to the Mayo Clinic in 2008 for evaluation, with no significantly different findings from before (Table 1). His radiographic work-up was consistent with the diagnosis of PAM. The possibility of lung transplant was discussed with the patient and the staff at the Mayo Clinic lung transplant service explained the restrictions of lung transplant to a non-US citizen as being available to 1 in every 10 patients. As the patient was in a relatively stable condition, the hospital explained that he was not a candidate for lung transplant at the time. One unit of blood was withdrawn from the patient to relieve the viscosity of blood, as he had a hematocrit of 57.8%. He was advised to return home on long-term oxygen therapy, since his condition was clinically stable. In 2015, the patient presented to our care at King Faisal Specialist Hospital and Research Center (KFSH&RC), and was placed on the lung transplant list pending availability of a donor. A chest X-ray upon admission showed diffuse dense opacification of both lungs, comparable to pulmonary calcinosis (Figure 2A). A CT scan showed diffuse opacification of both lungs, with calcific densities involving the entire lungs, and enlarged pulmonary trunk comparable to pulmonary hypertension. Also, the calcification was denser than the bones in the thorax (Figure 2B, 2C).

The patient was admitted in February 2016 to KFSH, as a suitable lung transplant donor had become available. His crossmatch was negative for T cells and B cells. The induction therapy was started with methylprednisolone 500 mg for each lung, CellCept, and broad-spectrum antibiotics meropenem, colistin, and vancomycin as per lung transplant protocol. The intraoperative course was smooth and was done on ECMO without any major intraoperative complications. The ischemia time for the right lung was 6 h, and 6.5 h for the left lung.

After transplant, there was a mild reperfusion injury, causing the patient to be shifted to the ICU, and he was intubated with minimal inotropic requirements. He was successfully weaned off inotropes and extubated the next day, with stable vitals and good recovery. The patient was successfully extubated within the next 2 days and was shifted to the general ward. His respiratory cultures were negative except for Legionella, for which he was treated. The transbronchial biopsy showed no evidence of any cellular rejection. He was discharged home in stable condition with a follow-up clinic visit in 1 week, with repeat lab imaging and spirometry.

## Discussion

Pulmonary alveolar microlithiasis (PAM) is a rare autosomal recessive lung disease in which calcium phosphate deposits (calcospherites) accumulate in the distal airspaces known as alveoli [7]. The distinguishing feature of this disease is the clinical-radiological dissociation [8]. PAM is associated with consanguinity and most patients with PAM have at least 1 sibling who is also affected by the disease [9]. Despite the autosomal recessive inheritance pattern, environmental factors, such as



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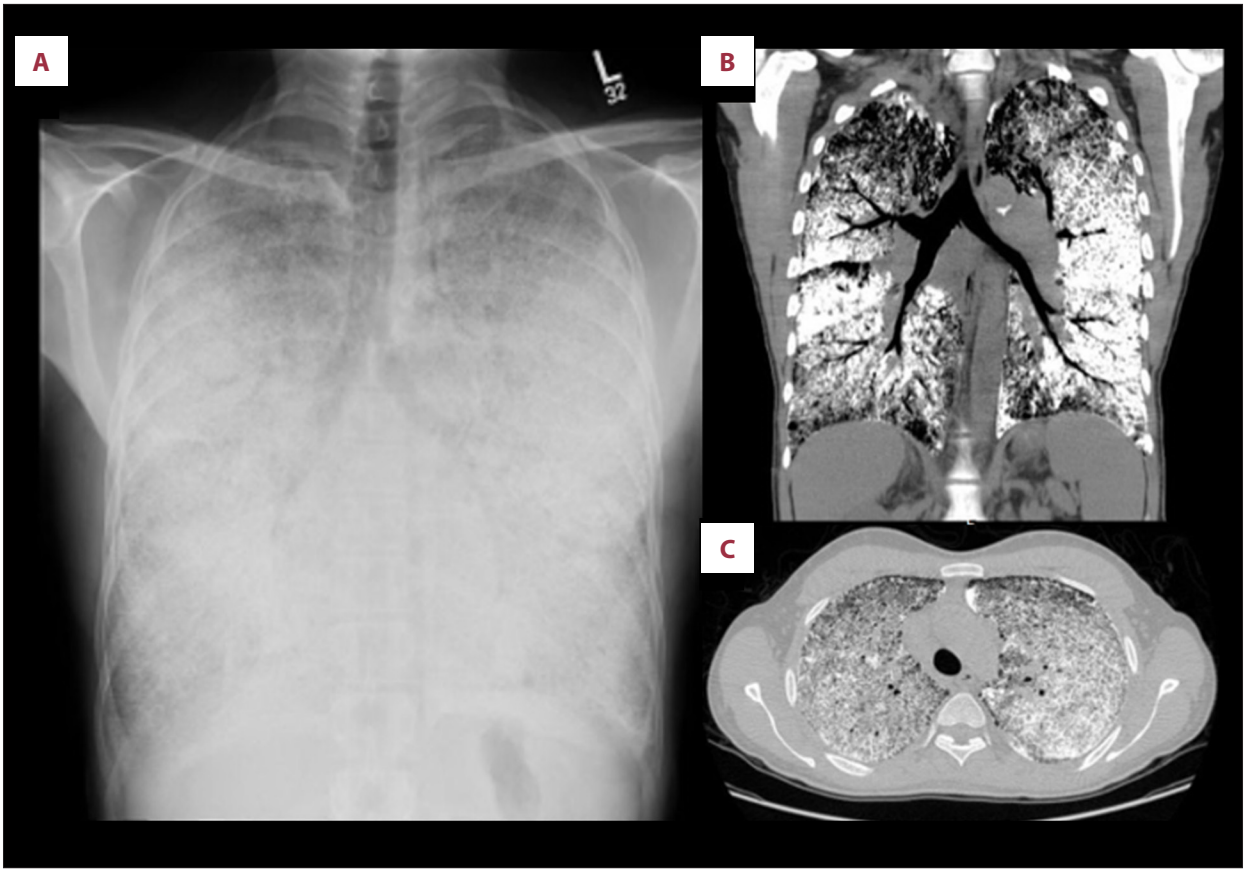


**Figure 2.** Shows diffuse opacification on chest, which appears dense; the appearance is compatible with pulmonary calcinosis. The visualized bony thorax appears grossly unremarkable on X-ray (**A**). CT scan shows diffused opacification of both lungs, with calcific densities involving the entire lungs. The calcific densities predominantly involve the middle lobe and lingula more extensively. The tracheobronchial tree appears grossly unremarkable. There is enlargemt in the pulmonary trunk, compatible with pulmonary hypertension (**B, C**).

heavy smoking and infection, play a role in accelerating the progression of this disease [9].

It has been reported that 35.8% of PAM patients were diagnosed before age 20 and 88.2% before 50 years of age [7]. There is no clear sex predilection for PAM [7–9]. The countries with the highest number of reported cases include Turkey, China, Japan, India, and Italy [9].

Our literature search revealed a total of 19 published cases with PAM who underwent lung transplant. The average follow-up period for this group of patients was 2.77 years. The majority of the patients were female (12/19). The mean age of diagnosis was 22 years and the average number of years for symptom manifestation was 15. Most of the patients (n=10) were diagnosed via radiological modalities, 6 by open lung biopsy, and 1 through genetic analysis. The mean age at transplant for all patients was approximately 47 years, with 14 out of 19 receiving a double transplant, and 5 out of 19 receiving a single transplant. In terms of outcomes, 12 of the 18 patients are still alive. The cause of death among the deceased patients included bronchiolitis obliterans (n=2), sepsis (n=2), hemodynamic instability (n=1), and multiorgan failure (n=1). Six patients exhibited no post-operative complications such as major bleeding, acute rejection, infection, atrial fibrillation, sepsis, anastomotic stenosis, and reperfusion syndrome (Table 2) [6,10–21].

The hereditary nature of PAM is due to inactivating mutations within the SLC34A2 gene (located on chromosome 4p15) identified in patients [8]. SLC34A2, the only known sodium-dependent phosphate transporter expressed in the lungs, is chiefly expressed in alveolar type II cells, but it is also expressed in other epithelial tissues, including mammary glands, the small intestine, kidneys, pancreas, ovaries, liver, testes, placenta, and prostate [8]. The function of the transporter is to clear phospholipids from alveolar spaces by transporting phosphate ions into alveolar type II cells [8]. Mutations in the SLC34A2 result in impaired function or deficiency in the transporter, decreased alveolar cell phosphate uptake, and the formation of intra-alveolar microliths as a result of phosphate-chelating calcium in the extracellular fluid [8].



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**Table 2.** Characteristics and outcomes of 19 patients who received lung transplant for the management of pulmonary alveolar microlithic [10–21].

| **Patients' Characteristics and outcomes** | |
|---|---|
| **Gender** | |
| Male (7/19) | |
| Female (12/19) | |
| **Mean age at diagnosis (22 yrs.)** | |
| **Mean time of symptoms (15 yrs.)** | |
| **Diagnostic modality** | |
| Radiology (10 pts.) | |
| Genetic (1pt.) | |
| Open lung biopsy (6 pts.) | |
| **Mean age at transplant (46.93 yrs.)** | |
| **Type of transplant** | |
| Single (5/19) | |
| Double (14/19) | |
| **Average follow-up duration (2.77 yrs.)** | |
| **Outcome** | |
| No complications (7 pts.) | Alive (12/18 pts.) |
| Post-operative complications (8) | Deceased (6/18) |
| *Major bleeding (2)* | *Bronchiolitis obliterans (2)* |
| *Acute rejection (1)* | *Hemodynamic instability (1)* |
| *Infection (1)* | *Multiorgan failure (1)* |
| *Atrial fibrillation (1)* | *Sepsis (2 pts.)* |
| *Anastomotic stenosis (1)* | |
| *Reperfusion syndrome (2)* | |

Although PAM is often discovered incidentally on chest radiographs in asymptomatic patients, the presence of intra-alveolar microliths can eventually lead to cyanosis, clubbing, dyspnea followed by dry cough, chest pain, hemoptysis, weight loss, and weakness [7,6,9]. The disease eventually progresses to fatal respiratory or cardiac failure [6,9].

PAM is diagnosed based on genetic testing for SCL34A2 gene mutation, radiographic findings, and a broncho-alveolar lavage (BAL) with transbronchial biopsy. Radiographic imaging illustrating a 'sandstorm' appearance with a mixture of ground-glass opacities is characteristic for PAM. On high-resolution CT scans, PAM will demonstrate thickened interlobular septa. Lastly, BAL, including a transbronchial biopsy for definite diagnosis, will show intra-alveolar concretion, and this is best seen with trichrome staining. Other aspects of diagnosis such as clinical features and pulmonary function tests (PFTs) will most often present as normal, and thus do not determine diagnosis [3]. The described radiological and clinical findings can easily be confused with diseases such as pulmonary alveolar proteinosis, silicosis, sarcoidosis, amyloidosis, pulmonary hemosiderosis, and metastatic calcification in chronic renal failure [4]; therefore, it is important to differentiate PAM from other similar disease presentations for accurate treatment.

## Conclusions

Therapies such as steroid hormone therapy and therapeutic BAL have been reported [7]. There is evidence that disodium etidronate (10 mg/kg per day) causes extensive regression of calcific densities in patients after 1-year treatment [2]. Although there is no evidence to support it, repeated broncho-alveolar lavage is often used for the treatment of pulmonary alveolar proteinosis [6,7]. All PAM patients who are hypoxemic with rest, exercise, or sleep should receive supplemental oxygen therapy. Pneumococcal and influenza vaccinations should be received by all PAM patients [7]. However, the only proven definitive treatments for PAM are unilateral lung transplant and bilateral sequential lung transplantation [5].

**Conflict of interest.**

None.

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