Bilateral Sequential Lung Transplantation for Pulmonary Alveolar Microlithiasis*

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Pulmonary alveolar microlithiasis (PAM) is characterized by deposition of calcium phosphate within the alveolar airspaces. There is currently no effective medical therapy and affected individuals may
progress to end-stage lung disease requiring transplantation. Two patients with PAM underwent bilateral sequential lung transplantation. This study reviews the clinical manifestations of PAM and discusses the particular difficulties that may be encountered in the use of lung transplantation as treatment for this uncommon disease. Also addressed is the question of recurrence in the allograft. (CHEST 1997; 112:1140-44)

Key words: lung transplantation; pleural disease; pulmonary alveolar microlithiasis

Abbreviations: PAM = pulmonary alveolar microlithiasis

Pulmonary alveolar microlithiasis (PAM) is a rare idiopathic disorder leading to alveolar filling with calcium phosphate concretions. Though clinical progression occurs at a slow pace, patients can ultimately develop advanced lung disease with hypoxemia and cor pulmonale. Two patients with PAM have undergone bilateral sequential lung transplantation at the University of Pennsylvania Medical Center. One patient was successfully treated and continues to do well, while the other patient died of complications in the perioperative period. To date, there is only one previous report of successful lung transplantation involving a patient with PAM. The additional cases included in this study both confirm the potential of this intervention to dramatically reverse the course of this disease and serve to highlight particular difficulties encountered in this unusual patient population.

REPORT OF PATIENTS

PATIENT 1

A 56-year-old man was referred for lung transplantation evaluation in July 1993. PAM had been diagnosed by open-lung biopsy in 1978 after a spontaneous pneumothorax. He had several subsequent spontaneous instances of pneumothorax and had developed progressive cor pulmonale. He required several hospitalizations for treatment of ascites and anasarca. At the time of his evaluation, he reported dyspnea with minimal activity despite continuous administration of nasal oxygen at 6 L/min and noted marked decline in his exercise tolerance over the previous 4 months. He had smoked 1 to 1.5 packs of cigarettes per day for 30 years and discontinued smoking in 1985. There was no known family history of PAM. Physical examination revealed a thin, chronically ill appearing male with a respiratory rate of 25 breaths per minute. Prominent inspiratory crackles were noted bilaterally, and the pulmonic component of the second heart sound was increased. Hepatomegaly and bilateral lower extremity edema were present. Chest radiographs revealed near complete opacification of both lung fields (Fig 1, top). Pretransplantation physiologic and functional studies are summarized in Table 1.

The patient underwent bilateral sequential lung transplantation via a bilateral thoracosternotomy incision in February 1994. He was unable to tolerate single-lung ventilation and was therefore placed on cardiopulmonary bypass. Significant blood flow through the bronchial circulation as well as marked mediastinal and pleural adhesions with increased vascularity led to difficulties

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**Figure 1.** Posteroanterior chest radiograph of patients 1 (top) and 2 (bottom) prior to transplantation demonstrating widespread bilateral micronodular infiltrates characteristic of PAM.
in removing the native lungs and maintaining hemostasis. Total bypass time was 6 h. His postoperative course was notable for persistent blood loss, hemodynamic instability, and progressive hypoxemia. The patient died on the 5th postoperative day.

**Patient 2**

A 35-year-old woman was referred for lung transplantation evaluation in January 1993. PAM had been diagnosed by open-lung biopsy at age 11 years. After three instances of spontaneous pneumothorax of the left side, pleurectomy and stapling of apical blebs was performed in 1988. The patient had been maintained on continuous oxygen therapy since 1991. She reported a chronic nonproductive cough and dyspnea with minimal activity while on supplemental oxygen. She had smoked 1 to 1.5 packs of cigarettes per day for 17 years and discontinued smoking in 1992. She was adopted and her family history was unknown. She had two children aged 7 and 9 years who were in good health. On physical examination, her lungs were clear to auscultation. An accentuated pulmonic component of the second heart sound was noted though a right ventricular heave was not present. Marked digital clubbing was noted. Her chest radiograph is shown in Figure 1, **bottom**. Pretransplantation physiologic and functional studies are summarized in Table 1.

In May 1994, the patient underwent bilateral sequential lung transplantation via a bilateral thoracotomy incision without the use of cardiopulmonary bypass. Her postoperative course was uneventful. Transbronchial biopsies performed 3 months after transplantation did not show evidence of recurrence of PAM. She has continued to do well as of follow up at 32 months after transplantation with resumption of a normal active lifestyle. A chest radiograph obtained at 32 months and a high-resolution CT scan at 24 months posttransplantation have shown no abnormalities. Posttransplant functional data are summarized in Table 1.

**Discussion**

PAM was first described by Harbitz in 1918 and named by Puhr in 1933. The disease is characterized by formation of lamellar concretions of calcium phosphate within the alveoli. The cause of this process remains unclear. One hypothesis is that an abnormal inflammatory response to irritants or infection leads to formation of an exudate that is not easily absorbed and ultimately undergoes calcification. It is also possible that inborn errors in metabolism at the alveolar interface leading to increased alkalinity or that mucopolysaccharide deposition may promote the local accumulation of calcium salts. As extrapulmonary calcifications are unusual and studies of calcium metabolism in affected patients have been normal, it is unlikely that PAM is due to a systemic derangement of calcium metabolism.

The mean age at diagnosis is 35 years though the disease has been reported in neonates and octogenarians. Males and females are affected with equal frequency. There appears to be a familial association in approximately half of the reported cases. Most commonly, the affected relative is a sibling.

A striking feature of this disease is the frequent discordance between the clinical and radiographic manifestations. Many patients display only minor symptoms despite impressive radiographic features. Those patients who are symptomatically typical complain of dyspnea and nonproductive cough, and the disease may develop slowly and progressively culminating in cor pulmonale. Instances of spontaneous pneumothorax occur, as in the patients, herein reported, and are attributed to the formation of subpleural blebs. Pleural adhesions and calcifications, as well as dense pleural thickening and fibrosis also have been reported. Though pulmonary function testing frequently yields normal results, more severely affected patients demonstrate a restrictive pattern along with impaired diffusing capacity.

**Table 1—Physiologic Assessment of Patients**

<table>
<thead>
<tr>
<th>Tests and Values</th>
<th>Patient 1 Pretransplantation</th>
<th>Patient 2 Pretransplantation</th>
<th>24 mo Posttransplantation</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFTS: (% predicted)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV₁, L</td>
<td>0.99 (34%)</td>
<td>2.15 (67%)</td>
<td>3.02 (106%)</td>
</tr>
<tr>
<td>FVC, L</td>
<td>1.11 (30%)</td>
<td>2.72 (72%)</td>
<td>3.49 (97%)</td>
</tr>
<tr>
<td>FEV₁/FVC ratio</td>
<td>89%</td>
<td>79%</td>
<td>92%</td>
</tr>
<tr>
<td>TLC, L</td>
<td>Unable to obtain</td>
<td>3.99 (77%)</td>
<td>5.50 (103%)</td>
</tr>
<tr>
<td>DCO, mL/min/mm Hg</td>
<td>Unable to obtain</td>
<td>4.15 (14%)</td>
<td>16 (64%)</td>
</tr>
<tr>
<td>6-min walk</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximum oxygen requirement</td>
<td>100% O₂ via face mask</td>
<td>6 L transtracheal</td>
<td>Room air</td>
</tr>
<tr>
<td>Distance walked</td>
<td>652 ft</td>
<td>770 ft</td>
<td>1,682 ft</td>
</tr>
<tr>
<td>Lowest O₂ saturation</td>
<td>87%</td>
<td>80%</td>
<td>98%</td>
</tr>
<tr>
<td>Exercise testing</td>
<td></td>
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<tr>
<td>VO₂ max, mL/min</td>
<td></td>
<td></td>
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<tr>
<td>Breathing reserve</td>
<td></td>
<td></td>
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<tr>
<td>O₂ sat at VO₂ max</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Echocardiogram</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RV size</td>
<td>Severely dilated</td>
<td>Dilated</td>
<td>Normal</td>
</tr>
<tr>
<td>RV function</td>
<td>Markedly reduced</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Estimated PA systolic pressure</td>
<td>112 mm Hg</td>
<td>78 mm Hg</td>
<td>36 mm Hg</td>
</tr>
<tr>
<td>Room air PO₂</td>
<td>31 mm Hg</td>
<td>47 mm Hg</td>
<td>73 mm Hg</td>
</tr>
</tbody>
</table>

*Abbreviations used are as follows: PFTS=pulmonary function tests; TLC=total lung capacity; DCO=diffusion of CO; VO₂ max=maximum oxygen consumption; RV=right ventricular; PA=pulmonary artery
The typical finding on chest radiography of bilateral infiltrates with a fine sandlike micronodular appearance and greater density in the lower and middle lung fields is considered to be diagnostic.

CT scans demonstrate diffuse distribution of micronodular calcific densities which are usually most prominent in the middle and lower lung zones with greatest concentration in the subpleural parenchyma and along the bronchovascular bundles. A high-resolution CT scan demonstrates thickening of the lobular septae with distribution of microliths along the septae and around centrilobular distal bronchioles. Diffuse pulmonary uptake of technetium 99m diphosphonate also has been reported.

On gross examination, the lungs have been described as heavy, with a gritty texture, and appear to remain inflated. Apical blebs and bullae may be present. Concentrically laminated concretions, 1 to 3 mm in diameter are seen within the alveoli (Fig 2). The alveoli themselves often are normal, though in more severe cases diffuse interstitial fibrosis may be seen.

At present, no medical therapy has been shown to definitively alter the progression of this disease. Therapeutic modalities including systemic corticosteroids, calcium-chelating agents, and bronchopulmonary lavage have been shown to be ineffective. A single case report discusses the use of etidronate disodium to treat one pediatric patient.

Lung transplantation has been successfully applied to the treatment of advanced lung disease resulting from a wide variety of disorders. As a disease restricted to the lungs, PAM would appear to be well-suited to transplantation. PAM leads to filling of the alveolar spaces and the consequent creation of large areas of intrapulmonary shunt. Bilateral lung transplantation would thus appear to be the procedure of choice as replacement of only one lung might result in persistent shunting of blood through the native lung.

The insidious nature of PAM and the lack of well-defined prognostic indices make decisions regarding the timing of transplantation somewhat problematic. Indeed, patient 1 was referred after having manifested clinically overt signs of cor pulmonale for several years while patient 2 was referred much earlier with hypoxia, significant exercise limitation, and echocardiographic evidence of pulmonary hypertension in the absence of overt failure of the right side of the heart. Not surprisingly, patient 1 could not tolerate single-lung ventilation or clamping of the pulmonary artery and required prolonged cardiopulmonary bypass during surgery, increasing the risk of perioperative bleeding. Furthermore, the hemodynamic instability which characterized the immediate postoperative period was likely related in part to the severe degree of preexistent right ventricular dysfunction. The uneventful course followed by patient 2 was facilitated by her more favorable presurgical hemodynamic status.

The pleural manifestations of PAM also pose particular problems in the performance of transplantation. Instances of recurrent pneumothorax, experienced by both of our patients, are common to individuals with PAM and may require chemical or surgical pleurodesis, resulting in the formation of pleural adhesions. Two recent studies have addressed lung transplantation in patients who have had previous intrapulmonary procedures. In one study, trends toward longer operating time, longer ICU stay, increased blood loss, and greater chest tube time and drainage were noted though overall outcome did not differ from that of control patients. In the second study, trends toward longer intubation and hospital stay and a statistically significant increase in transfusion requirements were observed. Extensive pleural adhesions also may be a manifestation of PAM itself as was likely the case in patient 1. This patient had far-advanced pleural involvement characterized by dense pleural fibrosis, which, in combination with increased vascularity and the use of cardiopulmonary bypass, resulted in the severe and uncontrollable hemorrhagic complications that led to the patient’s death. Although it is important to be able to anticipate this problem prior to surgery, CT scanning is likely to be of limited utility in distinguishing pleural disease from dense subpleural deposition of radiopaque microliths.

Finally, it is not known if PAM recurs after transplantation. If the disease results from a genetically determined error in alveolar metabolism or local inflammatory response, recurrence would be unlikely. If the pulmonary disease is a manifestation of a systemic disorder, as in sarcoidosis and lymphangioleiomyomatosis, recurrence in the allograft is a possibility. The lack of radiographically apparent disease in our surviving patient 32 months following surgery and in the previously reported patient at 18 months is reassuring. Given that the disease often takes many years to come to clinical attention, more extended follow-up will be required to address this concern adequately.

In summary, we have demonstrated that bilateral sequential lung transplantation can be successfully employed in properly selected patients with end-stage PAM. In order to maximize the chances for a successful outcome, we recommend that patients be referred before the development of severe right ventricular dysfunction. In suitable candidates, the timing of transplantation should...

FIGURE 2. Histologic specimen from the explanted lung of patient 2 demonstrating the characteristic lamellar appearance of microliths within the alveoli as well as prominent interstitial fibrosis (hematoxylin-eosin, original ×40).
be based predominantly upon functional status and quality of life given the indolent course of this disease and the lack of prognostic indices.

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Automatic Internal Cardioverter-Defibrillator Patch Erosion Into the Upper Airway Presenting as a Cavity Lesion*

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Erosion of an automatic internal cardioverter-defibrillator (AICD) patch into the lingular bronchus occurred 4 years after implantation; the erosion presented as a cavitary mass associated with hemoptysis and weight loss. On bronchoscopy to evaluate for suspected carcinoma, a cavity was entered through a bronchial defect and the AICD patch clearly identified. The complication was successfully treated with patch removal and fistula closure.

(CHEST 1997; 112:1144-46)

Key words: automatic internal cardioverter-defibrillator; complications; upper airway

Abbreviations: AICD = automatic internal cardioverter-defibrillator

Since the introduction of transvenous automatic internal cardioverter-defibrillator (AICD) leads, epicardial and pericardial patches have rarely been used. Before transvenous leads were available, many patients had these patches placed, often prophylactically, at the time of coronary artery bypass. One may expect to see late complications from these patches. When AICD leads were placed in patients with coronary artery bypass grafts, it was common practice to place the patches, especially on the left side, extrapericardially to avoid contact with the grafts. Erosion into adjacent structures has rarely occurred, and only one case of erosion into the lung, which presented with hemoptysis, has been reported.1 A case of airway erosion, which clinically mimicked a cavitary lung carcinoma is reported herein.

CASE REPORT

This 82-year-old man presented with several months of hemoptysis, a 30-lb weight loss, and coughing when supine. Four years earlier, he had presented with ventricular fibrillation, was found to have significant coronary artery disease, and underwent coronary artery bypass grafting to the diagonal, obtuse marginal, posterior descending, and posterior lateral vessels, and extrapericardial AICD patch placement, with the left patch just anterior to the lung hilum. Electrophysiologic studies after revascularization did not show a high risk for life-threatening dysrhythmias, so no AICD generator was placed. He remained well until his current illness.

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