Management of pulmonary alveolar proteinosis by repeated bronchoalveolar lavage

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Pulmonary alveolar proteinosis is a rare disease of the lung in which excessive thick granular phospholipoproteinaceous material accumulates within the air spaces. Many patients with this disease suffer from progressive dyspnea and cough that at times is accompanied by worsening hypoxia. At present, the only effective treatment is bronchoalveolar lavage, first described by Ramirez in 1963 (1). Presumably, this therapy is effective because it washes the proteinaceous debris from the airways and alveolar spaces. This case report describes the management of pulmonary alveolar proteinosis in 1 patient, who has undergone multiple, alternating, single-lung lavages over the past 10 years, with dramatic improvements in her symptoms following each therapy. We believe this to be the longest reported treatment of pulmonary alveolar proteinosis with repetitive bronchoalveolar lavage.

CASE REPORT

A 31-year-old woman presented with dyspnea and worsening cough producing thick, tenacious clear sputum. She also noted vague bilateral chest discomfort but denied hemoptysis, orthopnea, or constitutional symptoms. Her symptoms had persisted despite several courses of antibiotics. There was no significant family or occupational history, but she admitted to a 20-pack-a-year history of smoking. On examination, she was a well-developed woman, breathing comfortably with a room air oxygen saturation of 95%. Her chest was clear to auscultation, and there was no cyanosis, digital clubbing, or edema. Spirometry demonstrated a forced vital capacity and a 1-second forced expiratory volume that were within normal limits. A chest radiograph revealed confluent bilateral infiltrates with a mixed interstitial and ground-glass appearance (Figure 1). A computed tomography (CT) scan confirmed the mosaic distributions of mixed interstitial and ground-glass infiltrates consistent with pulmonary alveolar proteinosis.

Bronchoscopy was performed, and transbronchial biopsies were obtained but found to be nondiagnostic. Therefore, an open-lung biopsy was undertaken, which demonstrated the accumulation of eosinophilic granular lipoproteinaceous material within the alveoli and hyperplasia of type 2 pneumocytes. No inflammatory changes were seen, and the alveolar architecture was grossly preserved. These findings confirmed the diagnosis.

Because of the patient's worsening symptoms, single-lung bronchoalveolar lavage was performed. Alternating single-lung lavage has now been carried out on 8 occasions over the past 10

Figure 1. A chest radiograph reveals confluent bilateral infiltrates with a mixed interstitial and ground-glass appearance.

years. Each time, the patient experienced a marked improvement in her symptoms and chest radiographic findings (Figure 2).

BRONCHOPULMONARY LAVAGE PROCEDURE

Under general anesthesia using propofol, remifentanyl, and vecuronium intravenously, lung separation was achieved by placing a 35F left double-lumen endobronchial tube into the left mainstem bronchus. Radial arterial and central venous catheters were inserted to maintain continuous hemodynamic monitoring. The lavage process consisted of slowly instilling 1-liter aliquots of warmed, balanced electrolyte solution into the isolated lung. The limiting factor to instillation of fluid was a reduction in blood pressure and elevation of the central venous pressure due to mechanical compression of the heart by the fluid-filled lung. Once the fluid had been instilled, the chest was vigorously

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Figure 2. Chest radiograph after right lung lavage shows marked improvement. Left lung still shows severe disease process.

percussed and the operating table tilted to enhance the distribution of the lavage solution. The fluid was then gravitationally drained. This process was repeated 20 times for a total lavage volume of 20 liters. The initial effluent was thick with chalky white sediment that cleared with successive lavages (Figure 3).

The patient was placed on mechanical ventilation in the postanesthesia care unit until the excess fluid in the lungs had been absorbed or suctioned. The trachea was then extubated and aggressive pulmonary toilet performed. She required further supplemental oxygen and chest physiotherapy, but within a few hours, she noted an improvement in her breathing compared with her preoperative condition.

DISCUSSION

Pulmonary alveolar proteinosis is a rare disease of unknown etiology and variable natural history that results in the accumulation of proteinaceous surfactant-like material within the alveoli. Since its initial description by Rosen in 1958 (2), fewer than 350 cases have been reported in the literature (3).

Typically, the onset of this condition occurs between 20 and 50 years of age. Most patients are male (70%), and the majority have a significant smoking history. Presenting symptoms are usually dyspnea with a productive cough; hemoptysis and chest pain may occur, though less frequently (3). Both primary and secondary forms of this condition exist. In the primary form, no inciting event can be identified. In the secondary presentation, there are various associated conditions, including previous pulmonary infection with *Pneumocystis carinii* or mycobacteria; a history of inhalational exposure to a variety of substances, including silicates, beryllium, aluminum, and insecticides; or hematological malignancy and other immunosuppressed states (3–5). In the primary, or idiopathic, form, mortality is low (<10%), and spontaneous remission may occur. Most remaining patients will experience a chronic course punctuated by exacerbations and remissions and will eventually develop end-stage lung disease with pulmonary fibrosis. Approximately 50% of this patient group will require bronchoalveolar lavage. Prognosis depends

Figure 3. Twenty liters of progressively clearing lavage fluid were drained from the right lung.

upon the underlying condition and the occurrence of opportunistic infections such as *Nocardia asteroides*.

When pulmonary function tests are performed, spirometry is typically normal or mildly restrictive, and there is frequently a decrement in diffusing capacity for carbon monoxide. Chest radiographs show bilateral infiltrates in alveolar and, less commonly, interstitial distributions. CT is useful in defining the extent of the disease. Diagnosis is made by tissue pathological examination, either from transbronchial or open-lung biopsies. The histological appearance demonstrates alveolar spaces filled with periodic acid–Schiff–positive material, while the architecture of the airways and interstitial spaces is relatively well preserved (3, 5).

Recent evidence suggests that this proteinaceous accumulation occurs as a result of defective macrophage clearance (6). An animal model has been designed to study this disease process (7–9). Mice genetically engineered to be deficient in the gene producing granulocyte-macrophage colony-stimulating factor (GM-CSF) develop a pulmonary abnormality similar to pulmonary alveolar proteinosis. Providing these mice with an exogenous GM-CSF gene appears to reverse the condition, but this has not yet been attempted in humans. Because of the rarity of this condition, establishing a nationwide database and conducting a multicenter prospective treatment trial will be important steps in advancing our knowledge of this disease. In the meantime, until genetic therapy is established, the only therapeutic modality available is bronchoalveolar lavage.

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