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Pulmonary Alveolar Proteinosis Treated with Oral Ambroxol Hydrochloride and Bronchoalveolar Lavage

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A 59-year-old man visited our hospital in June 1997 because of cough and dyspnea at rest. He was diagnosed as pulmonary alveolar proteinosis (PAP) by bronchoalveolar lavage (BAL) and transbronchial lung biopsy. The alveoli were distended with pink homogeneous material that showed staining with the periodic acid Schiff method. The concentration of surfactant protein A in BAL fluid was significantly increased. We treated the patient with oral ambroxol hydrochloride and therapeutic BAL. We believe that this combination of therapies is the first choice for the treatment of PAP.

Key words: ambroxol hydrochloride; bronchoalveolar lavage; flexible bronchofiberscope; pulmonary alveolar proteinosis; surfactant protein A

Pulmonary alveolar proteinosis (PAP) is characterized by the presence of copious eosinophilic, periodic acid Schiff (PAS)-positive material in the alveoli and by an excess of surfactant components (both lipids and proteins) in lung lavage. It may be present during the neonatal period or later in life. PAP is the consequence of a genetic defect involving the lungs, such as a mutation of the surfactant protein B (SP-B) gene, or it can represent an aspect of a different genetic disease, such as lysinuric protein intolerance. PAP may also be associated with infections, malignancies, exposure to dusts, or the use of certain drugs. In most cases, however, it occurs as an isolated entity with no apparent cause, and is known as idiopathic alveolar proteinosis (Antonella et al., 1996). The cause is likely related to either overstimulation of type II pneumocytes or an impairment of the mechanism for removal of alveolar phospholipids (Cesar et al., 1995). In the alveoli of patients with PAP, the alveolar clearance of proteinaceous materials is impaired. Many investigators have reported biochemical studies of bronchoalveolar lavage (BAL) fluid in the patients with PAP, including analyses of proteins

and phospholipids (Sahu et al., 1976; Akino et al., 1978; Onodera et al., 1983; Honda et al., 1989). Amounts of protein and phospholipid were found to be significantly increased relative to those in contrast to normal subjects. Surfactant protein A (SP-A) is the predominant phospholipid-associated glycoprotein in pulmonary surfactant and is specific to the lung. The contents of SP-A in BAL fluid can be measured to diagnose PAP (Honda et al., 1993). We report a case of PAP diagnosed by an increase of SP-A in BAL fluid, and treated by oral ambroxol hydrochloride and BAL.

Patient report

A 59-year-old Japanese man who lives in Tottori Prefecture, Japan was admitted to our hospital in June 1997 because of cough and dyspnea at rest. His past medical history included 2 admissions for pneumonia in 1994 and 1995. He had smoked 20 cigarettes per day for over 30 years and had been employed as a garbage man of a building for over 18 years.

Abbreviations: BAL, bronchoalveolar lavage; PAS, periodic acid Schiff; PAP, pulmonary alveolar proteinosis; SP-A, surfactant protein A; SP-B, surfactant protein B; WLL, whole lung lavage



Fig. 1a. Computed tomogram of the chest on admission.

Although physical examination on admission showed respiratory distress, he complained only of mild dyspnea. He had a non-productive cough. Auscultation of the lung showed coarse inspiratory crackles in both lung fields. There was mild clubbing of the nail beds. The laboratory findings showed high levels of lactic acid dehydrogenase (421 IU/L), C-reactive protein (1.27 mg/dL) and carcinoembryonic antigen (7.3 ng/mL). Sputum cultures for bacteria, fungi and tuberculosis were negative. His chest radiograph showed diffuse bilateral interstitial reticular and alveolar densities of both lung fields. Computed tomography of the chest showed diffuse, non-segmental densities of various degrees, with a peripheral clear zone, primarily in the mid-lung field, and honeycombing shadows in the lower lung field (Fig. 1a). Analysis of arterial blood gases showed hypoxia (arterial oxygen pressure, 54.1 mm Hg). On the 3rd day after admission, the patient developed respiratory failure. BAL was performed on the right B⁴ seg-

ment and a transbronchial lung biopsy was performed on the right B⁴ and B⁸ segments. The specimens were stained with hematoxylin and eosin. Light microscopy of the transbronchial lung biopsy showed distended alveoli with a pink homogeneous material that was PAS-positive, and slight thickening of the alveolar walls with minimal infiltration of lymphocytes (Fig. 2a). Immunostaining for SP-A of lung biopsy specimens resulted in positive staining (Fig. 2b). No atypical lymphocytes were detected in the infiltrating cells.

The BAL fluid contained phospholipid and was sent to Sapporo Medical College, Sapporo, Japan to measure SP-A. The concentration of SP-A in the BAL fluid was significantly increased at 482.2 µg/mL (normal range, 1.3 to 5.2 µg/mL). Also the ratio of SP-A to phospholipid was 3.58 µg/nmol (normal range, 0.05 to 0.11 µg/nmol) (Honda et al., 1993). Therefore, we made a diagnosis of PAP, and treated the patient with oral ambroxol hydrochloride



Fig. 1b. Computed tomogram of the chest obtained after oral administration of ambroxol hydrochloride and therapeutic bronchoalveolar lavage (BAL).

(45 mg/day) and therapeutic BAL. BAL was performed weekly with 100 to 150 mL of saline instilled through a fiberoptic bronchoscope into a segmental bronchus under local anesthesia. The recovered lavage fluid was initially milky, and the lavage was repeated until the fluid became clear. After 3 series of therapeutic lavages, his radiographic infiltrates have cleared significantly (Fig. 1b). He is now living and well 2 years following our treatment with no evidence of recurrence of the disease.

Discussion

PAP is characterized by the deposition of proteinaceous material in air spaces, originally described in 1958 (Roen et al., 1958). Associated conditions include immunocompromised states, which suggests that malfunction of alveolar macrophages allow for the accumulation of abnormal intra-alveolar material. This material

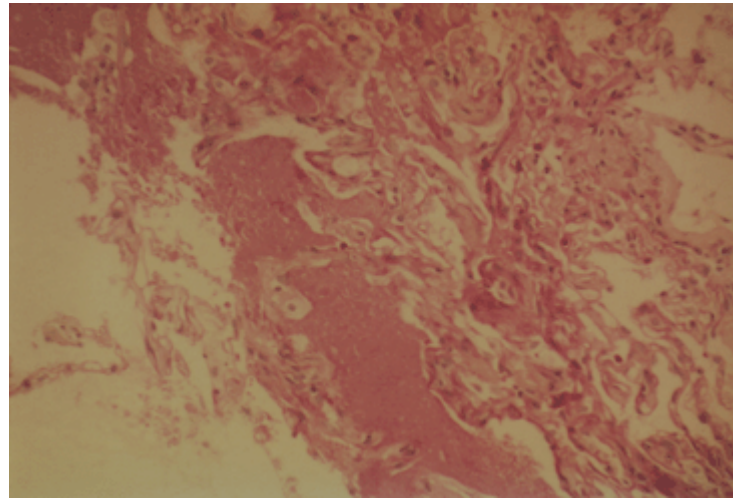


Fig. 2a. Photomicrograph of lung biopsy. Alveolar spaces are filled with dense, periodic acid Schiff (PAS)-positive and proteinaceous material. Alveolar septa are thin throughout the section. PAS stain, $\times 400$.

consists of lipid bilayer membranes separated by amorphous proteinaceous material containing phospholipids and proteins similar to surfactant or one of its components. The lung surfactant system is a mixture of phospholipids and protein synthesized and secreted in the alveolar spaces primarily by type II pneumocytes. Its main function is the reduction of surface tension to insure stability of alveolar units. Surfactant is also thought to be involved in mucus transport and to interact with the pulmonary

defense system (Luisetti et al., 1987). SP-A is a major hydrophilic (28 to 36 kDa) glycoprotein of pulmonary surfactant and is specific for pulmonary surfactant, synthesized by type II cells and secreted into the alveolar space. An immunohistochemical study using a polyclonal antibody to surfactant-specific apoprotein has demonstrated that SP-A is a useful immunohistochemical marker for the diagnosis of PAP (Honda et al., 1993). In our case, the concentration of SP-A in

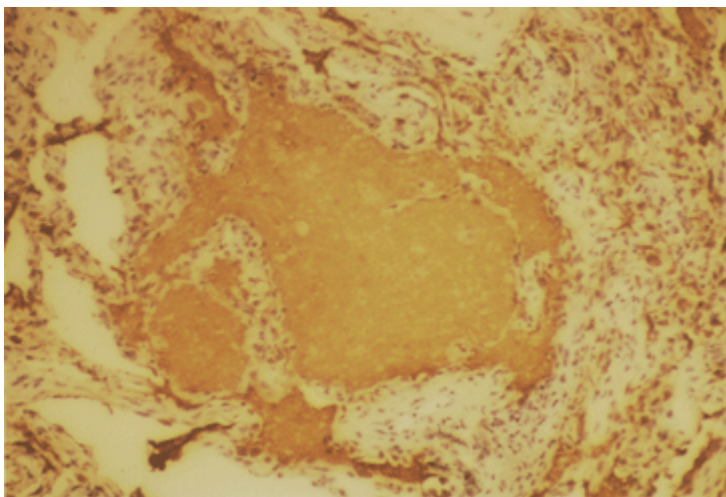


Fig. 2b. Immunostaining for surfactant protein A (SP-A) of lung biopsy specimens shows positivity, $\times 100$.

BAL fluid was significantly higher, confirming the diagnosis of PAP.

The established treatment of choice for PAP is therapeutic whole lung lavage (WLL), performed under general anesthesia, although this method may be associated with severe hypoxia. After such WLL, migration of alveolar macrophages increases to supernormal levels, and subsequent clinical relapse is associated with a decreased level of migration. These results support the conclusion of a previous study that the abnormal alveolar macrophage function in PAP is an acquired defect (Robert et al., 1989).

Problems with WLL include hypoxia, flooding of the contralateral lung, ipsilateral hydrothorax, airway trauma, hypothermia and electrolyte disequilibrium, and thus WLL requires a trained and experienced staff of physicians and nurses (Rodi et al., 1995). So this technique must be reserved for clinically progressive forms of the disease and for experienced hands (Diaz et al., 1984). In our patient, after treatment with oral ambroxol hydrochloride and therapeutic BAL the radiographic infiltrates have cleared.

The main pharmacodynamic effects of ambroxol hydrochloride are surfactant stimulation, mucokinetic activity and some secretagogue activity (Karl, 1987). The lung surfactant system is a mixture of phospholipids and protein synthesized and secreted in the alveolar spaces primarily by type II pneumocytes. So type II pneumocyte stimulation with ambroxol hydrochloride can lead to chemico-physical and functional changes in alveolar macrophages, probably through an increase in surfactant secretion and uptake (Luisetti et al., 1987).

Thus, we propose that oral ambroxol hydrochloride and therapeutic BAL should be the first choice in treating PAP.

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