Development of Treatment for Pulmonary Alveolar Proteinosis

Key words: pulmonary surfactant, ambroxol, lung lavage, granulocyte-macrophage colony-stimulating factor (GM-CSF)

Pulmonary alveolar proteinosis (PAP) was first reported as an independent disease in 1958 by Rosen and colleagues (1). They described the histological appearance of slight interstitial inflammation and the marked periodic acid Schiff (PAS)-positive proteinaceous alveolar deposits, which were confirmed as alveolar accumulation of the components of pulmonary surfactant morphologically, immunologically, and biochemically (2–5). In addition, serum levels of surfactant protein (SP)-A and -D, components of the accumulated surfactant, are quite high possibly because of their leakage from alveolar spaces to bloodstream (5, 6). Clinical courses of PAP were variable ranging from spontaneous resolution to death with respiratory failure or uncontrolled infection. According to Seymour and Presneill, 24 of 303 cases in collected reports (7.9%) were described as cases of spontaneous improvement (7).

In the past, treatment for PAP has included antibiotics, corticosteroids, potassium iodide, and trypsin with variable effects (8–10). A single case was reported outside Japan in which ambroxol improved PAP (11). In addition, recently several reports in Japan stated that ambroxol was effective for PAP (12–14). Although the mechanisms responsible for the effectiveness of ambroxol for PAP are still not understood, Suyama and colleagues suggested that alveolar type II cells stimulated with ambroxol could effect the surfactant metabolism of alveolar macrophages (13). It was reported that ambroxol stimulates surfactant secretion from alveolar type II cells, therefore, ambroxol could be effective for replacement of the degenerated surfactant to the intact form. In this issue, Hashizume reports a case of PAP in which ambroxol was effective, with a discussion of the current concepts on pathogenesis and diagnosis (14).

See also p 1175.

Now, the prognosis of this disease is improved by removal of accumulating surfactant with whole lung lavage method and the survival rate at 5 years of cases with therapeutic lavage is 94% compared to 85% in those without therapeutic lavage (7). Whole lung lavage is generally done with up to 3 *l* of saline via a double lumen endotracheal tube under general anesthesia. Recently, some modifications for whole lung lavage have been carried out (15–17). Although some complications including hypoxemia due to a shunt created by filled alveoli and hemodynamic changes due to single lung ventilation may occur, invasive monitoring is unnecessary in most cases and only one patient died related to this procedure (7).

Recently, there has been a discovery in understanding the pathogenesis of PAP in gene-targeted mice lacking granulocyte-macrophage colony-stimulating factor (GM-CSF) (18, 19). In addition, Tanaka et al (20) and Kitamura et al (21) identified an autoantibody against GM-CSF in the serum and bronchoalveolar lavage fluid of patients with idiopathic PAP but not with congenital or secondary PAP. Seymour and colleagues reported that the response rate to the treatment of idiopathic PAP with GM-CSF was 43% (22). GM-CSF administration, therefore, may be a possible potential treatment for idiopathic PAP in future.

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