Pulmonary Alveolar Proteinosis Successfully Treated with Ambroxol

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Abstract

A 79-year-old woman was admitted to hospital due to a four-month history of a cough and dyspnea on exertion. Chest CT scans revealed ground glass opacity with thickened interlobular septa in both lungs. Bronchoalveolar lavage fluid (BALF) had milky appearance and revealed large acellular eosinophilic amorphous bodies positively stained with periodic acid-Schiff (PAS). Autoantibodies against granulocyte-macrophage colony-stimulating factor (GM-CSF) were present in sera and BALF from the patient. Ambroxol was started in a daily dose of 45 mg orally. Her oxygen saturation improved and abnormal shadows in CT scan disappeared 6 months after beginning the therapy.

(Key words: bronchoalveolar lavage, granulocyte-macrophage colony-stimulating factor (GM-CSF)

Introduction

Pulmonary alveolar proteinosis (PAP) is a rare disease of unknown etiology, which is characterized by excessive surfactant accumulation within alveoli (1, 2). Standard therapy for PAP is whole-lung lavage, but it requires special techniques and is associated with potential morbidity. Ambroxol, a surfactant activator, has been reported to be effective in some patients with PAP (3–6). Here, a case of PAP successfully treated with oral ambroxol is presented.

Case Report

A 79-year-old woman was admitted to our hospital in September 1999, with a four-month history of a progressive cough and dyspnea on exertion. She was under medication for hypertension from the age of 75 years. Her body temperature was 36.5°C, heart rate 65/min, and blood pressure 119/72 mmHg. Physical examination revealed fine crackles on the bilateral chest. A chest radiograph showed bilateral ground glass shadows (Fig. 1). Chest CT scan showed the combination of a geographic distribution of areas of ground glass opacity with thickened interlobular septa, resulting in a “crazy-paving” appearance (Fig. 2). Laboratory studies revealed a leukocyte count of 4,300/µl with normal differentials, hemoglobin 13.9 g/dl, platelet count 193,000/µl, LDH 485 IU/l (normal, 180–460), and CRP <0.20 mg/dl. Serum titer of antinuclear antibody was elevated at 1:80, homogeneous and speckled type, but no other specific autoantibodies were detected. Serum KL-6 level was 3,910 U/ml (normal, <500) and SP-D level was 395 ng/ml (normal, <110). Serum CEA level was 25.9 ng/ml (normal, <5.0) and CA19-9 level was 22 U/ml (normal, <37). Arterial blood gases showed pH 7.425, PaCO2 36.1 Torr, PaO2 61.3 Torr, and bicarbonate 23.7 mM. Spirogram showed a restrictive impairment: %VC 73.6% and FEV1% 81.7%.

She was suspected to have a type of interstitial pneumonia, thus bronchofiberscopy was performed to make a diagnosis. The bronchoalveolar lavage fluid (BALF) obtained from the middle lobe had a milky appearance, and revealed 675x104 cells/ml, 44% lymphocytes, 55% macrophages, 1% neutrophils, and CD4/8 ratio 2.01. Transbronchial biopsy specimen showed many macrophages accumulating in alveolar spaces, but no periodic acid-Schiff (PAS)–positive eosinophilic materials. The smear of BALF showed amorphous lipoproteinaceous materials that were characteristically eosinophilic, granular, and brightly positive with a PAS stain. Autoantibodies against granulocyte-macrophage colony-stimulating factor (GM-CSF) was detected in the patient’s serum and BALF, at 60.49 µg/ml and 2.1 µg/ml respectively. This case was diagnosed as idiopathic pulmonary alveolar proteinosis.

The initial treatment was a segmental lavage using bronchofiberscope. After performing lung lavage twice, ground–glass shadows remained unchanged in a chest radiograph (Fig. 3) and hypoxemia persisted in arterial blood gas analysis: pH 7.428, PaCO2 36.3 Torr, PaO2 56.3 Torr, and bicarbonate 23.9 mM. As the patient refused further lavage an oral dose of 45
mg/day of ambroxol was started in November 1999. Dyspnea was gradually alleviated and the oxygen saturation (SpO₂) level was elevated to 97% in February 2000. In March 2000, chest radiograph findings became normalized and the serum markers were decreased: LDH 428 IU/l, CEA 2.8 ng/ml, KL-6 725 U/ml, and SP-D 254 ng/ml. Chest CT taken in May 2000 showed disappearance of abnormal shadows (Fig. 4). She is now treated with oral ambroxol and maintains remission.
Pulmonary Alveolar Proteinosis

Discussion

The only clearly beneficial therapy for pulmonary alveolar proteinosis (PAP) is the periodic physical removal of accumulated surfactant through total lung lavage (1, 2). But it requires special techniques and is associated with potential morbidity. More effective and less invasive therapies are expected. Diaz et al reported the first case of PAP which responded favourably to treatment with the surfactant activator ambroxol in 1984 (3). Subsequently, several cases of PAP in which treatment with ambroxol seemed to be effective have been reported in Japan (4–6). In the present case, the lung lavage did not provide an improvement. This might be due to an incomplete lavage, because segmental lavage was performed only in the middle lobe and the right upper lobe. In PAP patients in Japan, the response rate of lung lavage is about 80% (7). In about 20% of them the disease remained unchanged or progressed despite undergoing lung lavage. After beginning oral administration of ambroxol, the oxygen saturation of my patient gradually improved and ground glass shadows disappeared. But the effectiveness of ambroxol for PAP is not universal; it is controversial because spontaneous resolution without treatment has been reported to occur in 20 to 30% of patients with PAP (8). A controlled study will be needed to confirm the effectiveness of ambroxol for PAP.

There are some presumed reasons why treatment with ambroxol seemed to be effective in the present patient. First, as noted in a review by Asamoto et al (7), the mild type of PAP tended to resolve spontaneously and none of the patients with a PaO₂ of less than 60 Torr had spontaneous improvement. In the present case, PaO₂ was 61.3 Torr and alveolar-arterial gas tension difference (A-aDO₂) was 43, indicating that this case was a moderate to severe type of PAP. Thus, treatment with ambroxol might have been beneficial for this patient, because PAP resolved without lung lavage despite it being the severe type. In a recent literature review, only 24 instances of spontaneous resolution among 303 published cases with follow-up information (8%) have been identified (9). Spontaneous resolution of PAP thus appears to be infrequent. Second, abnormal shadows and symptoms progressively worsened before admission and diminished soon after the initiation of therapy with oral administration of ambroxol. The present patient has been in remission for more than 2 years under treatment with oral ambroxol.

The alveolar macrophages (AM) are vital to normal lung surfactant metabolism, to which they contribute by catabolism of both surfactant lipids and surfactant proteins (10). They are predominantly derived from circulating blood monocytes which enter the lung and other tissues and differentiate into morphologically, histochemically, and functionally distinct tissue macrophage populations (11). A critical role for granulocyte macrophage colony-stimulating factor (GM-CSF) in lung homeostasis was revealed by ablation of murine loci for GM-CSF (GM-CSF knockout mice), which resulted in PAP and abnormalities of AM function (12). AM abnormalities in GM-CSF knockout mice include decreased surfactant catabolism, phagocytosis, and bacterial killing. A recent study has revealed that GM-CSF stimulates terminal differentiation/maturation of AM in the lung through an ets-family transcription factor PU.1 (13). GM-CSF interacts with macrophage precursors in the lung, stimulating PU.1 protein levels. PU.1 is required for terminal differentiation/maturation of AMs, resulting in stimulation of multiple, diverse, and complex functions that enable mature AMs to play critical roles in the maintenance of lung homeostasis and innate immune defense. Recently, it has been shown that autoantibodies against GM-CSF are specifically present in sera and BALF from patients with idiopathic PAP (14). Consistently, they were detected in sera and BALF in the present case. The autoantibody against GM-CSF is considered to be a causative agent for idiopathic PAP, because dysfunction of AM due to neutralization of endogenous GM-CSF bioactivity by the autoantibody should result in impairment of surfactant clearance.

Although treatment with ambroxol seems to be effective in some of the patients with PAP, it is unknown how ambroxol causes an improvement. The action of ambroxol on AM has not been clearly elucidated. It is interesting whether or how ambroxol acts on AM made incapable of clearing surfactants by lack of GM-CSF. It is also unknown how to identify the patient with PAP in whom treatment with ambroxol is beneficial. Recent studies suggests therapeutic efficacy of GM-CSF in PAP (9, 15). GM-CSF therapy may provide an alternative approach for treating patients with idiopathic PAP.

Acknowledgements: I thank Dr. Koh Nakata (Department of Pulmonary Disease, Research Institute, International Medical Center of Japan, Tokyo) for assaysing the serum and BALF of the present patient for the presence of autoantibodies against GM-CSF.

References

Abstract in English).


