CASE REPORT

Pulmonary Alveolar Proteinosis with Bilateral Ground-glass Opacities Localized in Subpleural Areas

Keiji Mohri1; Naoyuki Miyashita1; Yasushi Obasa1; Minoru Fukuda1; Yoshihiro Ohue1; Shiro Ueno1; Shin-ichi Yagi1; Koichiro Yoshida1; Yoshihiro Kobashi1; Hiroshi Soda2; Mikio Oka1

ABSTRACT — Background: Pulmonary alveolar proteinosis (PAP) located only in subpleural areas is quite rare. Case. A 32-year-old asymptomatic nonsmoker woman was found to have bilateral ground-glass opacities in subpleural areas from basal to apical segments. The bronchoalveolar lavage fluid had a light-milky appearance and contained large eosinophilic bodies stained with periodic acid-Schiff. Anti-GM-CSF antibody in the serum and the lavage fluid was markedly elevated to 632 μg/ml and 1.4 μg/ml, respectively. These findings were consistent with acquired PAP. The opacities partly improved spontaneously during 15 months. Conclusion. Ground-glass opacities localized in subpleural areas are rare in alveolar proteinosis, however, detailed analysis of lavage fluid should be actively done for diagnosis. (JSRE. 2007;29:275-278)
KEY WORDS — Chest computed tomography, Bronchoalveolar lavage, GM-CSF, Anti-GM-CSF antibody, Spontaneous improvement

INTRODUCTION

Pulmonary alveolar proteinosis (PAP) is a rare disease characterized by abnormal surfactant accumulation within alveoli,1,2 and it is clinically classified into 3 types: congenital, secondary, and acquired (idiopathic) type.1,2 Most PAP cases are the acquired type,1,2 in which anti-granulocyte-macrophage colony stimulating factor (GM-CSF) antibody is specifically detected in serum and bronchoalveolar lavage fluid (BALF).3 The autoantibody indirectly inhibits differentiation and function of alveolar macrophages, resulting in surfactant accumulation.1,3

Patients with PAP have various symptoms such as cough, sputum, chest pain, hemoptysis, dyspnea, or sometimes none,1,2,3,5 which are also common in other respiratory diseases. Alternatively, findings on chest computed tomography (CT) are often suggestive of PAP.4,6 Additionally, BALF characteristically has a milky appearance, large eosinophilic bodies stained with periodic acid-Schiff (PAS), and large and foamy alveolar macrophages.1,2 The CT findings are air-space ground-glass, interlobular, and intralobular opacities and consolidation, or a combination of those, which show geographic or patchy pattern from central to peripheral zone.1,2,4,6,8 However, PAP localized in subpleural areas only is quite rare.

Here, we present an acquired PAP localized in subpleural areas, with a tendency of spontaneous improvement.

CASE REPORT

A 32-year-old asymptomatic nonsmoker woman was referred to our hospital for further examination of bilateral ground-glass opacities (GGOs) on chest CT, in June 2004. She had no symptoms, underlying disease, or history of exposure to dusts or toxins. The GGOs had been found on an annual screening chest radiograph in August 2003, and were determined by chest CT to show only interstitial pneumonia not requiring treatment.

Received December 7, 2006; accepted April 9, 2007.
© 2007 The Japan Society for Respiratory Endoscopy

Pulmonary Alveolar Proteinosis Localized in Subpleural Area—Mohri et al

Physical examination, blood cell counts, urine, and biochemical analysis all showed normal results. The serum carcinoembryonic antigen, cytokeratin 19, mucin KL-6, and immunoglobulin levels were all within normal limits, but only surfactant protein D (SP-D) was moderately elevated, 148 ng/ml (normal limit < 110 ng/ml). Serologically, autoantibodies related to collagen diseases were not detected. Blood gas analysis and pulmonary function tests were all normal. On chest radiographs, GGOs in the poststernal area were visible on the left lateral view only. On chest CT, bilateral GGOs localized in subpleural areas were seen from basal to apical segments (Figure 1).

Bronchoalveolar lavage (BAL) was performed in the lateral segment of the right middle lobe, followed by transbronchial lung biopsy (TBLB) in the anterior basal segment of the right lower lobe. The biopsy specimens showed no specific or diagnostic findings. The BALF had a light-milky appearance and contained large eosinophilic bodies strongly staining with PAS. The BALF contained increased numbers of total cells (15.7 × 10⁵/ml) and lymphocytes (25.6% of total cells), and the ratio of CD4+/CD8+ lymphocyte was 2.23. The percentage of macrophages and neutrophils was 68.6% and 3.4%, respectively. Anti-GM-CSF antibody levels in serum and BALF were 632 pg/ml (normal limit < 3 pg/ml) and 1.4 µg/ml (normal limit < 0.1 µg/ml), respectively. These findings were consistent with acquired PAP, and no treatment was given because of the absence of symptoms and localized small lesions on chest CT. Fifteen months later, the GGOs partly improved spontaneously with a decrease of SP-D to 96.5 ng/ml (Figure 2).

**DISCUSSION**

Usually, chest CT findings are most helpful to detect...
Pulmonary Alveolar Proteinosis Localized in Subpleural Area—Mohri et al

Figure 2. Chest CT images (1-mm sections) in March 2006, at the levels corresponding to those in Figure 1. Bilateral ground-glass opacities partly improve, and some of them still remain.

PAP, and the findings include air-space GGOs and/or consolidation, and interlobular septal thickening with map-like or patchy patterns from the central to peripheral zones.4,6,8 The extent of these radiologic findings closely reflects disease severity.7 A typical PAP feature combined with these CT findings is the “crazy-paving” appearance,1 which is often seen in other respiratory diseases.9 Our PAP patient showed bilateral GGOs extremely localized in subpleural areas from basal to apical segments, which is rare in PAP patients. Inui et al. reported a PAP case which showed patchy peripheral GGOs localized subpleural areas.10 The diagnosis of that case was made by video-assisted thoracic surgery (VATS)-biopsy because BALF and TBLB specimens showed no specific diagnostic findings. TBLB specimens of our case also did not show any specific findings, including PAP. Thus, we believe that the GGOs observed our case indicate PAP since the radiographic findings of our case were identical to those of PAP case of Inui et al. However, the difference in radiographic features between typical PAP cases and the present case is unclear. It is possible to speculate that the present patient had localized small GGOs without symptoms, indicating that these may be early chest CT findings of PAP. If the GGOs are early PAP features, in the near future, there is a possibility that the GGOs could extend to the central zone from the peripheral zone and develop into air-space consolidation with respiratory symptoms. The present patient is of great interest in terms of going insight into radiologic sequence and natural history of acquired PAP.

The gross appearance and cytologic findings of our BALF were helpful to diagnose PAP, as reported previously.1,4 In addition to the above findings, anti-GM-CSF autoantibody in BALF and serum was remarkably elevated, which was quite diagnostic for acquired PAP. Usually, BALF in PAP is reported to contain a few cells, with or without a high proportion of lymphocytes.1 In our patient, both total cells and lymphocytes with a normal CD4+/CD8+ ratio were increased.
strongly suggesting the presence of an active cellular response to unknown antigens in the lung. Considered together with the small GGOs in our patient, the cellular response might be that of those in the early stage of PAP. Sequential immunologic analysis in the lung is needed to explore the etiology and natural process of PAP.

Our PAP patient showed a spontaneous improvement for 15 months. A retrospective study reported that 24 (7.9%) of 303 patients spontaneously improved, and the 5-year survival rate of 343 patients was approximately 75% overall. Since the critical roles of GM-CSF were elucidated in the pathogenesis of acquired PAP, during the past 10 years, GM-CSF therapy by subcutaneous injection or inhalation was found to be effective for the acquired type. In the present patient, no treatment was given, because she had no symptoms and all lesions were extremely localized in subpleural areas, and spontaneous improvement resulted. Although the early clinical features of acquired PAP remain unknown, our patient might have been in the early stage of PAP. From this point of view, the future clinical course of our patient is of a great interest.

ACKNOWLEDGMENT

The authors wish to thank Koh Nakata, Bioscience Medical Research Center, Niigata University Medical and Dental Hospital, Niigata, for his technical assistance and advice.

REFERENCES