

Secondary pulmonary alveolar proteinosis in a patient with chronic myeloid leukemia in the accelerated phase

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Pulmonary alveolar proteinosis (PAP) is a rare respiratory disease the character of which is accumulation of protein consisting of surfactant in alveolar spaces. PAP sometimes complicates with hematological malignancies, especially myeloid leukemia. As one of the cause of PAP, impairment of alveolar macrophage is considered. We experienced a case of PAP with chronic myeloid leukemia (CML). 41 years old woman having CML for nine years developed PAP, and was treated by bronchoalveolar lavage and imatinib. She died of respiratory failure in the end, but BAL fluid had been becoming gradually crystalline after induction of imatinib. We consider that we should try to treat to improve respiratory status not only PAP but also hematological disease.

Key words: pulmonary alveolar proteinosis, pulmonary hemorrhage, chronic myeloid leukemia, imatinib

INTRODUCTION

Pulmonary alveolar proteinosis (PAP) is a rare respiratory disease characterized by the accumulation of protein consisting of surfactant in the alveolar spaces. It is classified as congenital, acquired, or secondary, and the causes of secondary PAP are regarded as hematologic malignancies, pharmacologic immunosuppression, inhalation of inorganic dust or toxic fumes, and infections¹. Here, we report a case of secondary PAP and chronic myeloid leukemia (CML) that showed potential reversibility of PAP as a result of treatment of the hematological disease.

CASE REPORT

A 41-year-old woman was diagnosed with CML and treatment with hydroxyurea and interferon alpha was initiated. Interferon alpha treatment was subsequently stopped because of toxicoderma, and her white blood cell count was controlled using only hydroxyurea. Treatment with imatinib (400 mg per day) was initiated three years after diagnosis, but hematological toxicities and skin rash necessitated the dose to be reduced to 100-200 mg per day. Six years after diagnosis, the patient complained of dry cough, and interstitial changes were noted on chest X-ray. Interstitial pneumonia caused by imatinib was suggested, but imatinib was continued because the patient was able to tolerate the cough using antitussive drugs and prednisone.

Eight years after diagnosis, the patient's CML began to progress at an accelerated phase, and her dyspnea gradually worsened. She was admitted to our hospital for treatment of respiratory failure nine years after

diagnosis. On admission, laboratory studies revealed the following: white blood cell count, $11.9 \times 10^6/L$ with 73% neutrophils, 4% lymphocytes, 12.5% eosinophils, 8.5% basophils, and 0.5% blasts; Hb, 7.9 g/dL; and platelet count, $1628 \times 10^9/L$. Lactate dehydrogenase level was 324 IU/L, C-reactive protein level was 6.80mg/dL, and sialylated carbohydrate antigen KL-6 was remarkably increased to 3702 U/L. Arterial blood gas analysis of the room air showed the following: pH, 7.420; pCO₂, 36.0 mmHg; pO₂, 79.5 mmHg; base excess, -0.9 mmol/L; and HCO₃⁻, 22.9 mEq/L. Chest X-ray and CT scan showed bilateral alveolar infiltrates (Figure 1).

Figure 2 indicates the clinical course. Because imatinib-mediated progression of interstitial pneumonia was suspected based on the X-ray and CT scan findings, imatinib was stopped and steroid pulse therapy was initiated. The patient's dyspnea temporally improved in response to the steroid pulse therapy, but the level of sialylated carbohydrate antigen KL-6 increased to 4486 U/L. Bronchoscopy with transbronchial lung biopsy was performed on the 45th hospital day, and a section of the lung tissue was obtained, which revealed fresh hemorrhage with fibrin deposits in the alveolar space, mild infiltration of neutrophils, and no evidence of interstitial pneumonia. Although the dose of prednisone was adjusted for pulmonary hemorrhage, the patient's dyspnea was exacerbated, and sialylated carbohydrate antigen KL-6 increased to 6182 U/L. A second bronchoscopy with transbronchial lung biopsy was performed on the 61st hospital day. The bronchoalveolar lavage (BAL) fluid (BALF) was cloudy with minute white granules and on pathologic

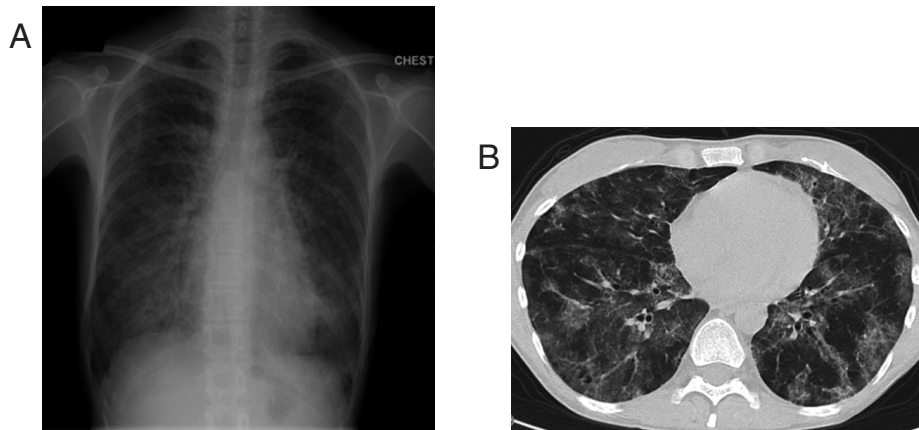


Fig. 1. A: Chest X-ray showed dense alveolar infiltrates in the lower lung field bilaterally. B: Thoracic CT scan showed patchy, ground-glass like consolidation..

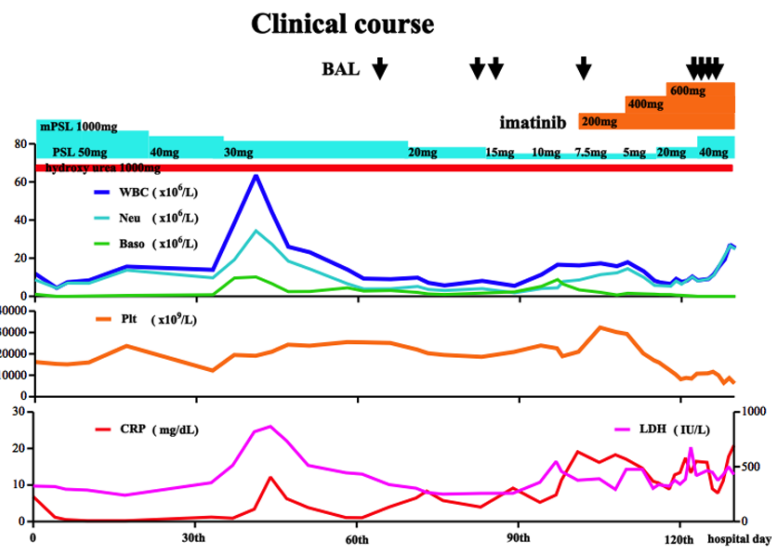


Fig. 2. Clinical course

evaluation, the eosinophilic material with cholesterol clefts was positive for PAS staining, with surfactant apoprotein in the alveolar spaces (Figure 3).

Based on these findings, the patient was diagnosed as having PAP. Although we could not identify the cell fraction in the BALF because of the number of cells destroyed, it was suggested that the alveolar macrophages were derived from the CML clone based on the detection of bcr/abl in the BALF. We measured the levels of granulocyte/macrophage factors (GM-CSF) and macrophage colony-stimulating factors (M-CSF) and anti-GM-CSF antibody in the serum and BALF. The level of GM-CSF in serum was less than 8 pg/mL, and that of M-CSF was 3470 pg/mL. The level of GM-CSF in BALF was 173 pg/mL, and that of M-CSF was more than 10,000 pg/mL. Anti-GM-CSF antibody was negative for both. These findings suggested that the function of both monocytes and alveolar macrophages was impaired, and that PAP was secondary to CML.

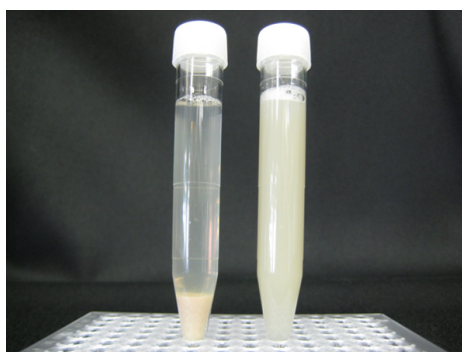
Although therapeutic BAL was performed repeatedly, the patient's respiratory status gradually worsened. We judged that the improved functioning of the alveolar macrophages depended on the control of CML, which was in an accelerated phase, and we re-

started imatinib administration at 600 mg per day on the 97th hospital day. After re-induction of imatinib, the white blood cell and platelet counts decreased to approximately $4\text{--}6 \times 10^9/L$ with normal fraction and $6000 \times 10^6/L$, respectively. The patient's respiratory status showed weak improvement regardless of hematological improvement, and she remained on mechanical ventilation on the 114th hospital day. Over the course of repeated BAL procedures, BALF gradually became clear, but the patient developed *Pseudomonas aeruginosa* pneumonia and continuous pulmonary hemorrhage. Despite administration of anti-pseudomonal drugs and steroid pulse therapy, she died of respiratory failure on the 135th hospital day.

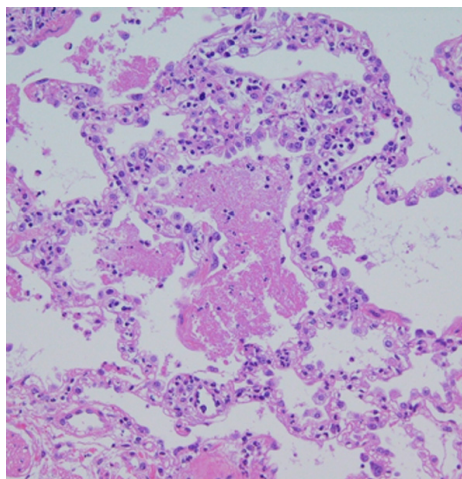
DISCUSSION

PAP sometimes complicates hematological malignancies, especially myeloid leukemia. The incidence of secondary PAP is estimated to be 5.3% among patients with hematological malignancies². The frequency of PAP seems to be quite high among leukemia patients.

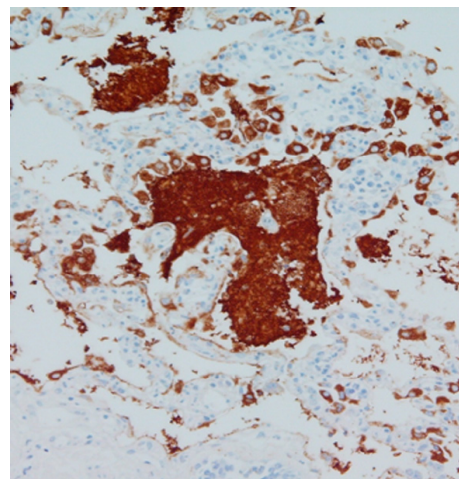
When the chest X-ray showed interstitial changes, we initially considered the respiratory symptoms in our patient to be a drug-induced pneumonia caused by



A



B



C

Fig. 3. A : BALF was cloudy with minute white granules (right side). A day after left quietly, significant precipitate was noted (left side).

B : Section of the lung tissue showed eosinophilic material with cholesterin clefts in the alveolar spaces. Alveolar wall fibrosis was focal and mildly noted (Hematoxylin-Eosin stain; left side).

C : The intra-alveolar material was immunohistochemically positive for surfactant apoprotein (right side).

imatinib. Such cases have been reported previously³, and she had a medical history of adverse effects in response to several drugs, including imatinib. Moreover, use of prednisone made her symptoms tolerable. In PAP caused by impairment of alveolar macrophages, prednisone may worsen PAP by depressing the function of monocytes. However, our patient's symptoms were improved by induction of steroid pulse therapy. The first biopsy specimen showed that the pulmonary changes were caused not by interstitial pneumonia, but by pulmonary hemorrhage; this explained why the steroid pulse therapy was effective. It remained unclear when the patient had developed PAP, and whether a relationship exists among pulmonary hemorrhage, imatinib, and PAP. The mechanism of drug-induced pneumonia is considered to have either a cytotoxic or a non-cytotoxic pattern. In the cases of interstitial pneumonia caused by imatinib, the mechanism of pneumonitis is a non-cytotoxic pattern, and the pathological findings are heterogeneous^{4, 5}. Because our patient developed pulmonary hemorrhage two times during imatinib treatment, there was a possibility that imatinib was involved.

Impairment of alveolar clearance due to dysfunction of alveolar macrophages was considered as one of the causes of PAP⁶. Dranoff *et al* reported that GM-CSF deficient mice developed progressive accumulation of surfactant lipids and proteins in the alveolar space; thus, GM-CSF is thought to play a critical role in pulmonary homeostasis⁷. In patients with primary PAP, anti GM-CSF antibody is elevated⁸. It neutralizes

GM-CSF, resulting in the impairment of alveolar macrophages. Bonfield⁹ reported that the level of GM-CSF is not elevated in PAP patients because anti-GM-CSF antibody neutralizes circulating GM-CSF. In secondary PAP, however, the level of anti-GM-CSF antibody is not elevated⁸. Some reports indicate that GM-CSF in BALF is consequently elevated¹⁰⁻¹² because of this lack of neutralizing activity. The elevation of M-CSF has also been reported, not only in the GM-CSF knockout mouse¹³ but also in PAP patients^{12, 14}. This may be a compensatory mechanism due to a deficiency in biologically active GM-CSF⁹.

In our patient, M-CSF was remarkably elevated in both serum and BALF, and GM-CSF was slightly elevated only in BALF but not in serum. Both serum and BALF were negative for anti-GM-CSF antibody. Elevation of M-CSF and GM-CSF in BALF might reflect the impairment of alveolar macrophages, but it was not clear why a decrease was seen only in the level of GM-CSF in serum. On admission, although the patient's lymphocyte count decreased to less than $100 \times 10^9/L$, it was speculated that the function of T-lymphocyte-generating cytokines was maintained at a sufficient level because the M-CSF level was high. We could not find any other factor accounting for the decreased level of GM-CSF in our study.

Treating secondary PAP is difficult. Many reports have described poor outcomes, but Cordonnier *et al* reported that improvement of hematological status resulted in potential reversibility of PAP². We re-initiated imatinib (600 mg per day) in our patient in

expectation of improving her hematological status, namely, by inducing recovery of macrophage function. She ultimately died of respiratory failure, but over the course of treatment, the BALF had gradually become crystalline. We conclude that the treatment of patients with hematological malignancies should focus on improving the respiratory status not only in PAP but also in hematological diseases.

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