Clinical features of secondary pulmonary alveolar proteinosis associated with myelodysplastic syndrome

Two case reports

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1. Introduction

Pulmonary alveolar proteinosis (PAP) is a rare lung disorder characterized by the abnormal accumulation of alveolar surfactant protein in alveolar spaces. Secondary PAP can result from myelodysplastic syndrome (MDS). When PAP accompanies other nonrespiratory diseases, it is generally categorized as secondary PAP. The most frequent underlying disorder for secondary PAP is hematologic malignancies. Here we retrospectively assessed the clinical features of 2 patients with secondary PAP associated with MDS.

2. Case report

Written informed consent was obtained from both patients for the publication of this manuscript and accompanying images.

2.1. Case 1

A 65-year-old female Chinese woman who had no significant past medical history or any congenital disease manifested a developing recurrent cough and shortness of breath in July 2015. She initially received methylprednisolone pulse therapy...
(500 mg/d) and then with prednisolone at a dose of 1 mg/kg bodyweight before being sent to our hospital. She had no history of known exposure to carcinogenic or mutagenic agents. Hematological examination showed white blood cells count was $4.3 \times 10^3$ L$^{-1}$, hemoglobin was 10 g/dL, and platelet count was $2.65 \times 10^9$ L$^{-1}$. Arterial blood gas analysis showed PO$_2$ of 40 mm Hg and PCO$_2$ of 38.4 mm Hg. Computed tomography scan disclosed GGOs with interlobular septal thickening in bilateral lungs (Fig. 2). BAL revealed 98% macrophages and 2% neutrophils. The specimens from BAL were compatible with the pathologic findings of PAP with amorphous PAS-positive materials in the alveolar spaces (Fig. 3). The patient was diagnosed with PAP. A bone marrow biopsy was taken showing a hypocellular marrow with trilineage myelodysplasia. Dysplasia was also seen in megakaryocytes, as well as myelocytic and monocytic lineages. A diagnosis of MDS was made. Sputum studies for pneumocystis carinii, acid-fast bacilli (AFB), and influenza were negative, as were blood and urine cultures. Although antibiotics and corticosteroids were administered, the patient’s symptoms became worse. Because the patient became febrile, WLL was not used in this case. In this patient, treatment with granulocyte-macrophage colony stimulating factor (GM-CSF) was not effective, her general condition continued to deteriorate, and she died from respiratory failure.

3. Discussion

PAP was first reported by Rosen et al in 1958. It is characterized by accumulation of intra-alveolar proteinaceous material which is rich in lipid and positive on periodic acid-Schiff stain. Three types of PAP have been described: idiopathic, secondary, and congenital. Secondary PAP arises in association with hematologic malignancies, inhaled dust exposure, fumes or gases, infectious or pharmacologic immunosuppression, or lysinuric protein intolerance. Secondary PAP in MDS, however, has been rarely reported. Prior to our report, review of the literature showed that there are 21 cases from 13 articles written in English.

PAP occurs in all age groups, but is most common in adults between 20 and 50 years of age. The most common presenting symptoms are dyspnea and nonproductive cough. Pleuritic chest pain, malaise, and low-grade fever may also be present. Secondary PAP usually occurs after MDS. In this report, we present 1 female patient who developed secondary PAP at the same time as MDS, and a male patient who developed secondary PAP during the course of MDS. The physical examination is typically nonspecific: crackles, clubbing, and cyanosis all have been reported, but rarely.

The classic high-resolution CT (HRCT) findings in idiopathic PAP have been termed crazy paving, representing diffuse GGO combined with interlobular septal thickening. Other typical HRCT scan findings for idiopathic PAP patients were subpleural sparing and predominance in the lower lung field. Ishii H demonstrated that GGOs typically showed a diffuse pattern in a secondary PAP group. The so-called crazy-paving appearance and subpleural sparing were less frequently seen in the secondary
PAP group. The 2 patients in our cases showed diffuse homogenous patterns in the distribution of GGO, which is characteristic for secondary PAP.

PAP secondary to MDS results in worsening of prognosis. Autoantibodies against GM-CSF may cause idiopathic PAP, now referred to as autoimmune PAP. Although the functional impairment of the alveolar macrophages has been shown to play a pivotal role in PAP pathogenesis, GM-CSF autoantibodies are not found in secondary PAP. In our patient, treatment with GM-CSF was not effective. The therapy for secondary PAP mainly depends on the treatment used for the underlying disease. When PAP is associated with MDS, successful bone marrow transplantation could correct the associated pulmonary disorder. WLL has been used to ameliorate symptoms; however, this method was not used in this case because the patient's general condition was poor. Ishii H et al reveal that steroid-treated patients had worse prognosis than did patients without steroid therapy.

The pathogenesis of secondary PAP associated with MDS remains obscure. In idiopathic PAP, lipids and proteins accumulate within the alveoli because alveolar macrophages cannot catabolize surfactants. Alveolar macrophages require GM-CSF to perform this function. Autoantibodies against GM-CSF may cause idiopathic PAP. The mechanism underlying secondary PAP is unclear. It is thought that secondary PAP is caused by a reduction in either the functional capacity or absolute numbers of alveolar macrophages, but data supporting this hypothesis are limited. In secondary PAP associated with hematological diseases, the alveolar macrophages may be defective because it derives from the malignant clone itself and has a defective GM-CSF transduction pathway. This suggestion is supported by the alleviation of the pulmonary process following the recovery of hematopoietic function. Iriguchi et al studied wild-type and transgenic mice heterozygous or homozygous for a human CD2-T-bet transgene. The results identified a novel mechanism by which increased expression of T-bet, exclusively in T lymphocytes, spontaneously drives the pathogenesis of both MDS and secondary PAP in a dose-dependent manner. In this report, 1 case developed secondary PAP happened at the same time as MDS, and the other occurs after MDS. We speculate that the functional impairment of mononuclear phagocytes in the lung associated with aberrant hematopoiesis of myeloid cells might account for the development of secondary PAP in our patients. Future studies are required to determine the pathogenic mechanism of MDS and secondary PAP. Infection often coexists with secondary PAP. Impaired macrophage function, dysfunction of surfactant, or retention of proteinaceous materials may increase the risk of an opportunistic infection, such as pulmonary aspergillosis. Fungal pulmonary infections, especially aspergillosis, are likely to develop secondary PAP. In our series the male patient became continuous febrile, the sputum smear examination showed the sputum contained fungal spores. Superimposed infection accounts for a significant degree of morbidity and mortality in patients with secondary PAP.

In conclusion, the 2 cases can raise physicians' awareness of the disease. When they encounter a case of unexplained pulmonary infiltrates in a patient with some hematologic or infectious disease who shows diffuse bilateral GGO on an HRCT scan, pulmonary physicians should suspect the possibility of secondary PAP.

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[11] Tabata S, Shimoji S, Murase K, et al. Defective expression of GM-CSF to perform this function. Autoantibodies against GM-CSF may cause idiopathic PAP. The mechanism underlying secondary PAP is unclear. It is thought that secondary PAP is caused by a reduction in either the functional capacity or absolute numbers of alveolar macrophages, but data supporting this hypothesis are limited. In secondary PAP associated with hematological diseases, the alveolar macrophages may be defective because it derives from the malignant clone itself and has a defective GM-CSF transduction pathway. This suggestion is supported by the alleviation of the pulmonary process following the recovery of hematopoietic function. Iriguchi et al studied wild-type and transgenic mice heterozygous or homozygous for a human CD2-T-bet transgene. The results identified a novel mechanism by which increased expression of T-bet, exclusively in T lymphocytes, spontaneously drives the pathogenesis of both MDS and secondary PAP in a dose-dependent manner. In this report, 1 case developed secondary PAP happened at the same time as MDS, and the other occurs after MDS. We speculate that the functional impairment of mononuclear phagocytes in the lung associated with aberrant hematopoiesis of myeloid cells might account for the development of secondary PAP in our patients. Future studies are required to determine the pathogenic mechanism of MDS and secondary PAP. Infection often coexists with secondary PAP. Impaired macrophage function, dysfunction of surfactant, or retention of proteinaceous materials may increase the risk of an opportunistic infection, such as pulmonary aspergillosis. Fungal pulmonary infections, especially aspergillosis, are likely to develop secondary PAP. In our series the male patient became continuous febrile, the sputum smear examination showed the sputum contained fungal spores. Superimposed infection accounts for a significant degree of morbidity and mortality in patients with secondary PAP.

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