Clinical Case Report

Medicine®

OPEN

Clinical features of secondary pulmonary alveolar proteinosis associated with myelodysplastic syndrome

Two case reports

Yin Liu, MD, Lu Lu Chen, MD, Yu Ying Qiu, MD, Yong Long Xiao, MD, Hou Rong Cai, MD*

Abstract

Rationale: 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).

Patient concerns: But most reports described a single case; here we reported 2 cases of PAP secondary to MDS. One case developed secondary PAP at the same time as MDS, and the other developed during the course of MDS.

Diagnoses: The diagnosis of PAP was made by bronchoalveolar lavage and based on the identification of periodic acid-Schiff-positive proteinaceous material. Chest high resolution CT (HRCT) scans showed variable distribution of ground glass opacities, but crazy-paving appearance was not seen in our 2 cases.

Interventions: Because the patients' general conditions were poor, whole lung lavage was not used in the 2 cases.

Outcomes: And the 2 cases' prognoses were poor.

Lessons: In conclusion, pulmonary physicians should suspect the possibility of secondary PAP when they encounter unexplained pulmonary infiltrates with some hematologic or infectious disease that shows diffuse bilateral GGO on an HRCT scan.

Abbreviations: AFB = acid-fast bacilli, BAL = bronchoalveolar lavage, GGOs = ground glass opacities, GM-CSF = granulocyte-macrophage colony stimulating factor, HRCT = high resolution CT, MDS = myelodysplastic syndrome, PAP = pulmonary alveolar proteinosis, TBLB = transbronchial lung biopsy, WLL = whole lung lavage.

Keywords: ground glass opacity, myelodysplastic syndrome, secondary pulmonary alveolar proteinosis

1. Introduction

Pulmonary alveolar proteinosis (PAP) is a rare lung disorder characterized by excessive accumulation of periodic acid-Schiff (PAS) stain-positive materials in the pulmonary alveolar space.[1] When PAP accompanies other nonrespiratory diseases, it is generally categorized as secondary PAP. The most frequent underlying disorder for secondary PAP is hematologic malignancies.[2] 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.

Editor: Anser Azim.

The authors report no conflicts of interest.

Department of Respiratory, Drum Tower Hospital, Nanjing University Medical School, Nanjing, Jiangsu, China.

** Correspondence: Hou Rong Cai, Department of Respiratory, Drum Tower Hospital, Nanjing University Medical School, 321 Zhongshan Road, Nanjing, Jiangsu 210008, China (e-mail: caihourong2013@163.com).*

Medicine (2017) 96:44(e8481)

Received: 15 July 2016 / Received in final form: 23 September 2017 / Accepted: 6 October 2017

http://dx.doi.org/10.1097/MD.0000000000008481

2.1. Case 1

A 39-year-old Chinese man was diagnosed with MDS in June 2011. In May 2012, he presented to our hospital due to high fever, recurrent cough and progressive shortness of breath. A diagnosis of pulmonary fungus was made based on a sputum smear examination and he was treated with fluconazole. His complete blood count tests showed a white blood cell count of 5.4×10^9 L^{-1} with neutrophils of 85.8%, hemoglobin concentration of 5.2 g/dL and platelet count of 25×10^9 L^{-1}. Serum C-reactive protein and erythrocyte sedimentation rate were elevated. Arterial blood gas analysis under room air revealed hypoxemia. Chest x-ray revealed bilateral ground glass opacities (GGOs) (Fig. 1). Computed tomography scan disclosed GGOs with interlobular septal thickening. Bronchoalveolar lavage (BAL) was performed. The lavage fluid was opaque and contained amorphous debris and cholesterol crystals. Lipid analysis of the BAL fluid revealed that the fluid was rich in phosphatidylcholine. The amorphous material was PAS positive. Transbronchial lung biopsy (TBLB) was aborted due to massive bleeding. A diagnosis of secondary PAP was made. Because the patient's general condition was poor, whole lung lavage (WLL) was not used in this case. The patient died from respiratory failure.

2.2. Case 2

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

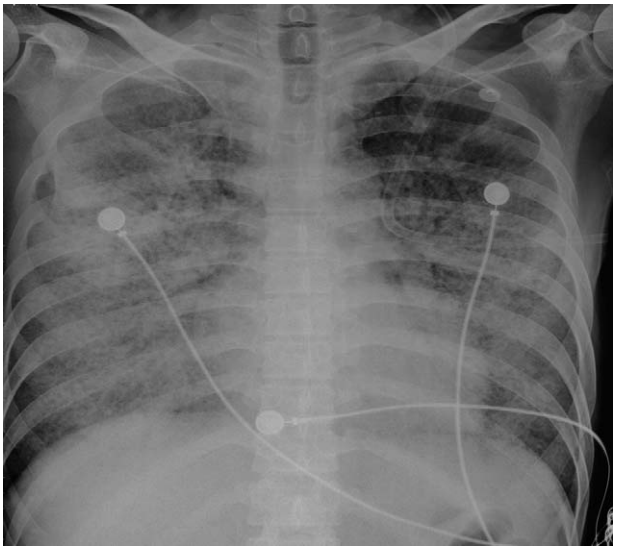

Figure 1. Chest radiograph showing bilateral GGOs. GGO = ground glass opacity.

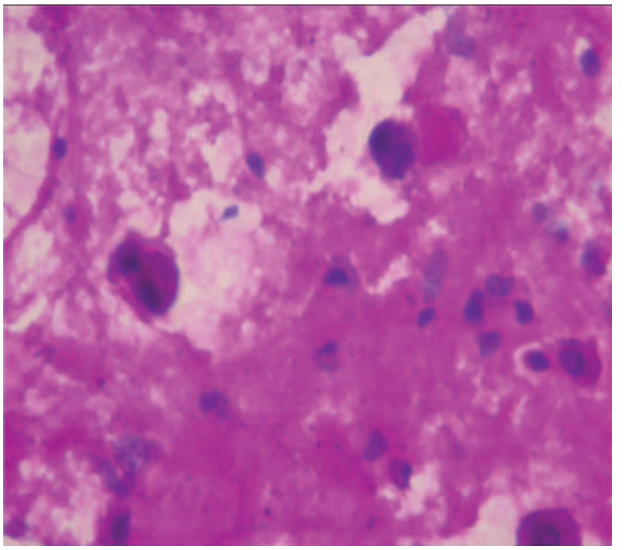

Figure 3. Characteristic proteinaceous material filling the alveoli of PAP (periodic acid-Schiff staining for the specimen, magnification ×200).

(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 4.3×10^9 L^{-1}, hemoglobin was 10 g/dL, and platelet count was 265×10^9 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.

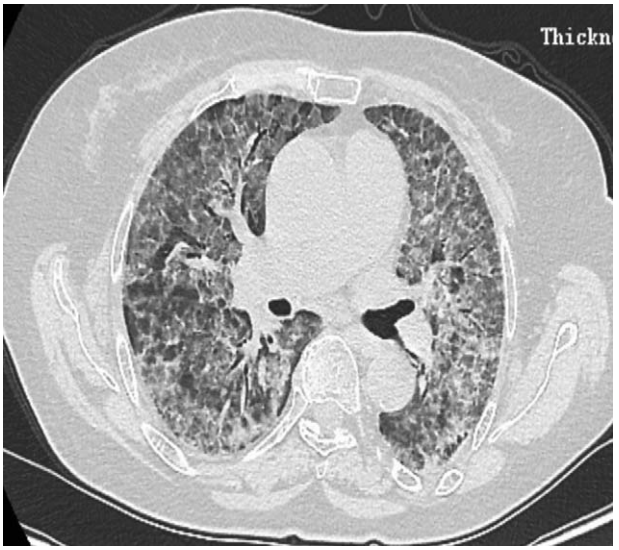

Figure 2. The high-resolution computed tomography of the chest showing bilateral interlobular septal thickening on a background of GGOs.

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.[1] Secondary PAP arises in association with hematologic malignancies, inhaled dust exposure, fumes or gases, infectious or pharmacologic immunosuppression, or lysinuric protein intolerance.[2] 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.[3–15]

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.[16] 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.[2] 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.[17] 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.[18]

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.[19] 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.[20] 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.[18]

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.

References

[1] Seymour JF, Presneill JJ. Pulmonary alveolar proteinosis: progress in the first 44 years. Am J Respir Crit Care Med 2002;166:215–35.

[2] Ishii H, Trapnell BC, Tazawa R, et al. Comparative study of high-resolution CT findings between autoimmune and secondary pulmonary alveolar proteinosis. Chest 2009;136:1348–55.

[3] Kajiume T, Yoshimi S, Nagita A, et al. A case of myelodysplastic syndrome complicated by pulmonary alveolar proteinosis with a high serum KL-6 level. Pediatr Hematol Oncol 1999;16:367–71.

[4] Shoji N, Ito Y, Kimura Y, et al. Pulmonary alveolar proteinosis as a terminal complication in myelodysplastic syndromes: a report of four cases detected on autopsy. Leuk Res 2002;26:591–5.

[5] Ando J, Tamayose K, Sugimoto K, et al. Late appearance of t(1;19)(q11; q11) in myelodysplastic syndrome associated with dysplastic eosinophilia and pulmonary alveolar proteinosis. Cancer Genet Cytogenet 2002; 139:14–7.

[6] Yoshioka Y, Ohwada A, Harada N, et al. Increased circulating CD16+ CD14dim monocytes in a patient with pulmonary alveolar proteinosis. Respirology 2002;7:273–9.

[7] Ohnishi T, Yamada G, Shijubo N, et al. Secondary pulmonary alveolar proteinosis associated with myelodysplastic syndrome. Intern Med 2003;42:187–90.

[8] Fukuno K, Tomonari A, Tsukada N, et al. Successful cord blood transplantation for myelodysplastic syndrome resulting in resolution of pulmonary alveolar proteinosis. Bone Marrow Transplant 2006;38: 581–2.

[9] Pollack SM, Gutierrez G, Ascensao J. Pulmonary alveolar proteinosis with myeloproliferative syndrome with myelodysplasia: bronchoalveolar lavage reduces white blood cell count. Am J Hematol 2006;81:634–8.

[10] Xie LX, Zhao TM, Wang QY, et al. Secondary pulmonary alveolar proteinosis associated with myelodysplastic syndrome. Chin Med J (Engl) 2007;120:1114–6.

[11] Tabata S, Shimoji S, Murase K, et al. Successful allogeneic bone marrow transplantation for myelodysplastic syndrome complicated by severe pulmonary alveolar proteinosis. Int J Hematol 2009;90:407–12.

[12] Chung JH, Pipavath SJ, Myerson DH, et al. Secondary pulmonary alveolar proteinosis: a confusing and potentially serious complication of hematologic malignancy. J Thorac Imaging 2009;24:115–8.

[13] Xue Y, Han Y, Li T, et al. Pulmonary alveolar proteinosis as a terminal complication in a case of myelodysplastic syndrome with idic(20q). Acta Haematol 2010;123:55–8.

[14] Nishida A, Miyamoto A, Yamamaoto H, et al. Possible association of trisomy 8 with secondary pulmonary alveolar proteinosis in myelodysplastic syndrome. Am J Respir Crit Care Med 2011;184:279–80.

[15] Zhao Y, Xiong W, Wu X. A case of secondary pulmonary alveolar proteinosis, but prior to myelodysplastic syndrome. Respirol Case Rep 2013;1:58–61.

[16] Trapnell BC, Whitsett JA, Nakata K. Pulmonary alveolar proteinosis. N Engl J Med 2003;349:2527–39.

[17] Trapnell BC. A lymphocyte-mediated cause of secondary PAP. Blood 2015;125:215–6.

[18] Ishii H, Seymour JF, Tazawa R, et al. Secondary pulmonary alveolar proteinosis complicating myelodysplastic syndrome results in worsening of prognosis: a retrospective cohort study in Japan. BMC Pulm Med 2014;14:37.

[19] Dirksen U, Hattenhorst U, Schneider P, et al. Defective expression of granulocyte-macrophage colony-stimulating factor/interleukin-3/interleukin-5 receptor common beta chain in children with acute myeloid leukemia associated with respiratory failure. Blood 1998;92:1097–103.

[20] Iriguchi S, Kikuchi N, Kaneko S, et al. T-cell-restricted T-bet overexpression induces aberrant hematopoiesis of myeloid cells and impairs function of macrophages in the lung. Blood 2015;125:370–82.