A Case of Autoimmune Pulmonary Alveolar Proteinosis with Pulmonary Fibrosis and Asbestosis-Like Features

MASAYUKI NAKAMURA, MASAKI OKAMOTO, KIMINORI FUJIMOTO *, SHIGEKI SHIMIZU **, MASAKI TOMINAGA, SHINGO TSUNEYOSHI, YOSHIKA ZAIZEN, TAKASHI NOUO, SATOSHI SAKAMOTO, TOMOTAKA KAWAYAMA AND TOMOAKI HOSHINO

Division of Respirology, Neurology and Rheumatology, Department of Internal Medicine, * Department of Radiology and Center for Diagnostic Imaging, Kurume University School of Medicine, Kurume 830-0011, ** Department of Pathology, Kindai University Faculty of Medicine, Osakasayama 589-8511, Japan

Received 2 August 2018, accepted 15 January 2019
J-STAGE advance publication 24 April 2020
Edited by MASAHIRO MITSUOKA

Summary: A 78-year-old man who had worked in the building industry visited our hospital because of ground-glass opacity with smoothly thickened, intralobular interstitial lines and interlobular septal lines on chest high-resolution computed tomography (HRCT). HRCT image also showed a focal area of reticulation and pleural thickening. Lung specimens obtained by surgical lung biopsy showed accumulations of intra-alveolar periodic acid-Schiff-positive materials, usual interstitial pneumonia (UIP)-like subpleural lung fibrosis and asbestosis bodies (1 body/cm2 in high-power field, ×400). Serum granulocyte-macrophage colony stimulating factor autoantibody was positive. The patient was diagnosed as having autoimmune pulmonary alveolar proteinosis (PAP) and needed differential diagnosis from secondary PAP caused from pulmonary asbestosis and UIP. Careful observation of the manifestations of pulmonary asbestosis and the progression of fibrosis using HRCT will be necessary in this patient.

Key words autoimmune pulmonary alveolar proteinosis, usual interstitial pneumonia, anti-granulocyte-macrophage colony-stimulating factor antibody

INTRODUCTION

Pulmonary alveolar proteinosis (PAP) is a lung disease characterized by accumulation of lipid-rich proteinaceous materials that stain positive with periodic acid-Schiff (PAS) in the pulmonary alveolar space [1,2]. Although autoimmune PAP, pulmonary asbestosis, and idiopathic pulmonary fibrosis/usual interstitial pneumonia (IPF/UIP) are independent pulmonary disorders, cases of secondary PAP caused by asbestosis or PAP-leading pulmonary fibrosis may occur occasionally. Differential diagnosis among these diseases is important but difficult.

Here we report a case of autoimmune PAP with pulmonary asbestosis-like features including asbestosis bodies in the lung tissue and pleural thickening on high-resolution computed tomography (HRCT), and a histologically possible UIP pattern.

CASE REPORT

A 78-year-old man visited a local hospital in May 2016 because of persistent productive cough and ground-glass opacities (GGOs) were observed on a chest radiograph and HRCT at a nearby hospital in May 2016. The productive cough eventually resolved, but the chest radiograph and HRCT showed expansion...
of GGOs. In February 2017, he visited our hospital. He had an occupational history of working in the building industry from 20 to 58 years of age, during which time he might have been exposed to asbestos and other materials. He had no additional history of environmental exposure. He was an ex-smoker with a 5-year smoking history of 0.75 pack/years. Before presentation, he had also been treated for hypertension and benign prostatic hyperplasia. Vital signs on admission were as follows: respiratory rate, 22/min; heart rate, 66/min; blood pressure, 124/76 mmHg; body temperature, 36.1°C. No fine crackles were auscultated, and there were no clubbed fingers, or other abnormal physical findings. Blood hematological and biochemical examinations revealed no abnormal findings. Arterial blood gas analysis indicated mild hypoxemia (PaO₂ 75.9 torr) and widening of the A-aDO₂ (21.0 torr). There were no physical or hematological findings suggesting any complication with connective tissue diseases or hematologic diseases including myelodysplastic syndrome (MDS) and multiple myeloma. Chest radiograph showed bilateral GGOs with a patchy distribution predominantly in the right perihilar region (figure 1). Areas of GGO with smoothly thickened, intralobular interstitial lines and interlobular septal lines on HRCT were expanded at the first visit to our hospital compared with the findings 6 months earlier (figure 2A, B). HRCT images also demonstrated a focal area of reticulation with small air cysts in subpleural lung parenchyma of the right basal segments, and pleural plaque with calcification (figure 2C, D, E). No typical radiological features of pulmonary asbestosis including a subpleural dotlike opacity, subpleural curvilinear line, or parenchymal band were evident on HRCT images. Pulmonary function tests demonstrated no restrictive ventilatory impairment or reduction of diffusion capacity (forced vital capacity 89.5%, predicted; diffusing capacity of the lungs for carbon monoxide 123.6%, predicted). A six-minute walking test yielded a distance of 276.3 m and a minimum SpO₂ of 94%. Analysis of bronchoalveolar lavage fluid showed no sign of milky appearance, bacterial or fast-acid bacillus bodies or atypical cells. Transbronchial lung biopsy revealed no specific findings of lung disease. In May 2017, we performed a surgical lung biopsy (SLB) using video-assisted thoracoscopy from the anterior segment of right upper lobe (S3) and the lateral segment of right middle lobe (S4) to establish a diagnosis. Histological examination revealed accumulations of intra-alveolar lightly eosinophilic finely granular material that stained positive with PAS, slightly foamy intra-alveolar macrophages and mild infiltration of the alveolar septa. There was also a histologically possible UIP pattern including lung fibrosis with a predominantly subpleural distribution and fibroblastic foci. Asbestos bodies (1 body/cm² in high-power field, ×400) were found in a lung specimen obtained from right S4 (figure 3). A high serum level of granulocyte-macrophage colony-stimulating factor (GM-CSF) autoantibody at 56.4 μg/mL (cut-off level 1.0 μg/mL) was found after SLB examination. On the basis of these findings, we diagnosed this patient as having autoimmune PAP with pulmonary fibrosis. The subtype of PAP in this case was considered to be idiopathic PAP on the basis of the clinical features. We are now observing carefully the progression of fibrosis and the manifestation of the clinical features of pulmonary asbestosis by HRCT. The patient’s disease is currently stable.

DISCUSSION

PAP is a rare pulmonary disorder, with a minimum incidence and prevalence of 0.49 and 6.2 per million, respectively. [3] Rosen et al. first reported 27 patients with PAP in 1958. [1] Three types of PAP have been described: idiopathic, secondary, and congenital. [4,5] The causes of secondary PAP include hematologic diseases such as MDS and multiple myeloma, inhalation exposure to dust, and infectious disease. [6] Congenital PAP is caused by gene mutations of SP-B or C or the GM-CSF receptor [2]. Idiopathic PAP is considered to be an autoimmune disorder caused by dysfunc-

Fig. 1. Chest radiograph at the first visit to our hospital showed ground-glass opacities with a patchy distribution predominantly in right perihilar region.
Fig. 2. Chest high-resolution computed tomography images at the first visit to our hospital (B, C, D) and 6 months before (A). Images at the first visit showed areas of ground-glass opacity (GGO) with thickened, intralobular interstitial lines and interlobular septal lines with a patchy distribution predominantly in right perihilar region and inner lung zone (B, white arrowheads), focal area of reticulation with small air-cysts in the right lower lobe (C, D, black arrowheads), and a pleural plaque with calcification (E, white arrow) in the right lower lung zone. Note progression of extent areas of GGO on image B compared with those on image A.
tion of surfactant catabolism due to neutralization of GM-CSF by autoantibodies. [7,8]

The present patient was diagnosed as having autoimmune PAP with pulmonary fibrosis because of the presence of anti-GM-CSF autoantibody in serum and the features revealed by HRCT. The present case should be distinguished from pulmonary asbestosis. A previous study has revealed that rats developed PAP after inhalation of quartz dust. [9] The mechanism of PAP development in patients with asbestos exposure is unclear. Some previous reports suggested that the pathogenesis of secondary PAP caused from dust exposure may be attributed to impaired alveolar surfactant disposal by macrophages. [10-11] Beuchner et al. reported 4 patients with acute silicosis who were all diagnosed as having PAP. [12] Moreover, previous studies suggested that an exposure to material can lead to the production of anti-GM-CSF autoantibody [13-14]. The percentage of autoimmune PAP patients who also had inhalational exposure varies between 26% and 54% in studies [3,15-18]. Although the present case had asbestosis-like findings including asbestos bodies and pleural thickening on HRCT, no typical radiological findings such as a subpleural dotlike opacity, subpleural curvilinear line, or parenchymal band were observed. [19] In this patient, there was not enough evidence to determine that his pulmonary fibrosis has been caused by asbestosis. Asbestos-like findings may suggest a simple asbestos exposure.

The present case demonstrated a focal subpleural area of reticulation with small air cysts on HRCT and possible UIP pattern on SLB histological specimens. The typical feature of PAP is accumulation of proteinaceous materials within the air spaces, without thickening and fibrosis of the alveolar septa. [2] On the other hand, Rosen et al. in their first report of PAP stated that 2 of their 27 patients showed development of mild alveolar fibrosis. [1] Interstitial fibrosis that rarely develops secondary to PAP had been described in several previous reports. [3,20-27] The present case may show a natural course of PAP, distinct from IPF/UIP and asbestosis-related pulmonary fibrosis.

In the present case, a differential diagnosis was needed to distinguish idiopathic PAP from secondary PAP caused by pulmonary asbestosis and IPF/UIP. It is necessary to monitor disease behavior to establish a

---

**Fig. 3.** Histological findings in the lung specimen obtained by surgical lung biopsy shows accumulations of intra-alveolar lightly eosinophilic finely granular materials (A; hematoxylin and eosin (HE) stain, right S3, original, ×400). Asbestos bodies (1 body/cm² in high-power field, white arrow) were found (B; HE stain, right S4, original, ×400). Histological UIP pattern including lung fibrosis in a predominantly subpleural distribution and fibroblastic foci (arrow head) were shown (C; HE stain, D; Elastica van Gieson stain, right S4, original, ×100).
diagnosis in this type of case.

The standard therapy for PAP is whole lung lavage. GM-CSF inhalation is a new non-invasive treatment for autoimmune PAP. However, the patient did not receive such treatment because he was asymptomatic and had only mild hypoxemia with no abnormal pulmonary function. We are carefully observing the progression of respiratory symptoms and fibrosis by HRCT and are watching for any decline of pulmonary function in this patient.

In summary, autoimmune PAP with asbestososis-like features and UIP-like pulmonary fibrosis is a rare disease combination. Accumulation of similar case reports and studies of the pathogenesis are important.

ACKNOWLEDGEMENT: We are grateful to all the members who contributed to medical care in this case.

CONFLICT OF INTEREST: The authors of this manuscript have no conflicts of interest to declare.

REFERENCES

1. Rosen SH, Castiman B, and Liebow AA. Pulmonary alveolar proteinosis. New Engl J Med 1958; 258(23):1123-1142.
2. Trapnell BC, Whitsett JA, and Nakata K. Pulmonary alveolar proteinosis. N Engl J Med 2003; 349(26):2527-2539.
3. Inoue Y, Trapnell BC, Tazawa R, Arai T, Takada T et al. Characteristics of a large cohort of patients with autoimmune pulmonary alveolar proteinosis in Japan. Am J Respir Crit Care Med 2008; 177(7):752-762.
4. Luisetti M, Bruno P, Kadija Z, Suzuki T, Raffa S et al. Relationship between diffuse pulmonary fibrosis, alveolar proteinosis, and granulocyte-macrophage colony stimulating factor autoantibodies. Respir Care 2011; 56(10):1608-1610.
5. Seymour JF and Presnell JJ. Pulmonary alveolar proteinosis: progress in the first 44 years. Am J Respir Crit Care Med 2002; 166(2):215-235.
6. Ishii H, Trapnell BC, Tazawa R, Inoue Y, Akira M et al. Comparative study of high-resolution CT findings between autoimmune and secondary pulmonary alveolar proteinosis. Chest 2009; 136(5):1348-1355.
7. Sakagami T, Uchida K, Suzuki T, Carey BC, Wood RE et al. Human GM-CSF autoantibodies and reproduction of pulmonary alveolar proteinosis. N Engl J Med 2009; 361(27):2679-2681.
8. Trapnell BC, Carey BC, Uchida K, and Suzuki T. Pulmonary alveolar proteinosis, a primary immunodeficiency of impaired GM-CSF stimulation of macrophages. Curr Opin Immunol 2009; 21(5):514-521.
9. Gross P and DeTreville RT. Alveolar proteinosis. Its experimental production in rodents. Arch Pathol 1969; 86(3):255-261.
10. Miller RR, Churg AM, Hutcheon M, and Lom S. Pulmonary alveolar proteinosis and aluminium dust exposure. Am Rev Respir Dis 1984; 130(2):312-315.
11. Keller CA, Frost A, Cagle PT, and Abraham JL. Pulmonary alveolar proteinosis in a painter with elevated pulmonary concentrations of titanium. Chest 1995; 108(1):277-280.
12. Buechner HA and Ansari A. Acute silico-proteinosis. A new pathologic variant of acute silicosis in sandblasters, characterized by histologic features resembling alveolar proteinosis. Dis Chest 1969; 55(4):274-284.
13. Costabel U and Nakata K. Pulmonary alveolar proteinosis associated with dust inhalation: not secondary but autoimmune? Am J RespirCrit Care Med 2010; 181(5):427-428.
14. Cummings KJ, Donat WE, Ettenson DB, Roggli VL, Ingram P et al. Pulmonary alveolar proteinosis in workers at an indium processing facility. Am J Respir Crit Care Med 2010; 181(5):458-464.
15. Hwang JA, Song JH, Kim JH, Chung MP, Kim DS et al. Clinical significance of cigarette smoking and dust exposure in pulmonary alveolar proteinosis: a Korean national survey. BMC Pulm Med 2017; 17(1):147.
16. Xiao YL, Xu KF, Li Y, Li Y, Li H et al. Occupational inhalational exposure and serum GM-CSF autoantibody in pulmonary alveolar proteinosis. Occup Environ Med 2015; 72(7):504-512.
17. Bonella F, Bauer PC, Griese M, Ohshima S, Guzman J et al. Pulmonary alveolar proteinosis: new insights from a single-center cohort of 70 patients. Respir Med 2011; 105(12):1908-1916.
18. Li M, Alowami S, Schell M, Davis C, and Naqvi A. Pulmonary Alveolar Proteinosis in Setting of Inhaled Toxin Exposure and Chronic Substance Abuse. Case Rep Pulmonol 2018; 2018:5202173.
19. Akira M, Yamamoto S, Inoue Y, and Sakatani M. High-resolution CT of asbestosis and idiopathic pulmonary fibrosis. Am J Roentgenol 2003; 181(1):163-169.
20. Agarwal PP, Seely JM, Perkins DG, Matzinger FR, and Alikhan Q. Pulmonary alveolar proteinosis and end-stage pulmonary fibrosis: a rare association. J Thorac Imaging 2005; 20(3):242-244.
21. Arbiser ZK, Guidot DM, Pine JR, Giltman LI, and Gal AA. Pulmonary alveolar proteinosis mimicking idiopathic pulmonary fibrosis. Ann Diagn Pathol 2003; 7(2):82-86.
22. Holbert JM, Costello P, Li W, Hoffman RM, and Rogers RM. CT features of pulmonary alveolar proteinosis. Am J Roentgenol 2001; 176(5):1287-1294.
23. Clague HW, Wallace AC, and Morgan WK. Pulmonary interstitial fibrosis associated with alveolar proteinosis. Thorax 1983; 38(1):865-866.
24. Miller PA, Ravin CE, Smith GJ, and Osborne DR. Pulmonary alveolar proteinosis with interstitial involvement. Am J Roentgenol 1981; 137(5):1069-1071.
25. Hudson AR, Halpin G, Miller JA, and Kilburn KH. Pulmonary interstitial fibrosis following alveolar proteinosis. Chest 1974; 65(7):700-702.
26. Fraimow W, Cathcart RT, Kirshner JJ, and Taylor RC. Pulmonary alveolar proteinosis: A correlation of pathological and physiological findings in a patient followed up with serial biopsies of the lung. Am. J. Med 1960; 28:458-467.
27. Akira M, Inoue Y, Arai T, Sugimoto C, Tokura S et al. Pulmonary Fibrosis on High-Resolution CT of Patients With Pulmonary Alveolar Proteinosis. Am J Roentgenol 2016; 207(3):544-551.