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Case report

Autoimmune pulmonary alveolar proteinosis with features similar to nonspecific interstitial pneumonia

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ABSTRACT

A 58-year-old woman with cough and dyspnea who was suspected of having idiopathic interstitial pneumonia had been treated with corticosteroids and cyclosporine, but the symptoms had worsened. There were no findings to suspect pulmonary alveolar proteinosis (PAP) in the bronchoalveolar lavage fluid, 17 months after the start of treatment. The transbronchial lung biopsy specimens showed eosinophilic bodies that strongly stained with periodic acid-Schiff staining. Anti-granulocyte macrophage colony-stimulating factor (anti-GM-CSF) antibodies were detected in her serum. We diagnosed the patient with autoimmune PAP. Thus, we present a rare case of PAP presenting atypical radiological images and bronchoalveolar lavage fluid findings.

1. Introduction

Pulmonary alveolar proteinosis (PAP) is a rare disease characterized by an abnormal accumulation of surfactants in the alveoli. Radiological images often show the abnormalities distributed predominantly in the perihilar regions [1]. Bronchoalveolar lavage fluid (BALF) from patients with PAP often has an opaque and milky appearance, which can confirm the diagnosis in approximately 75% of suspected cases [2]. Here we present a rare case of autoimmune PAP (APAP) with atypical radiological abnormalities and BALF findings.

2. Case report

As part of her physical examination 17 months ago, a 58-year-old woman underwent chest computed tomography (CT), which showed no abnormalities. Six months ago, she began to experience a persistent cough and dyspnea, for which she was prescribed 20 mg of prednisolone, but there was no response. Then, she was prescribed concomitant cyclosporine, but her condition worsened. The patient was admitted to our hospital for examination. She had no past medical history or family history of PAP, and she did not smoke, but she was taking estradiol and raloxifene to prevent menopausal disorders.

The patient's physical examination revealed the following: height 155 cm, weight 44.3 kg, temperature 36.6 °C, blood pressure 150/101 mmHg, radial pulse 100 bpm, respiratory rate 14 bpm. Fine crackles were heard in both lungs. Lactate dehydrogenase (250 IU/L), Krebs von den Lungen-6 (KL-6 1329 U/mL), and lung surfactant protein D (211.5 ng/mL) levels were elevated. Arterial blood gas analysis in room air showed no hypoxemia (partial pressure of oxygen, 91.1 torr), and respiratory function tests revealed no

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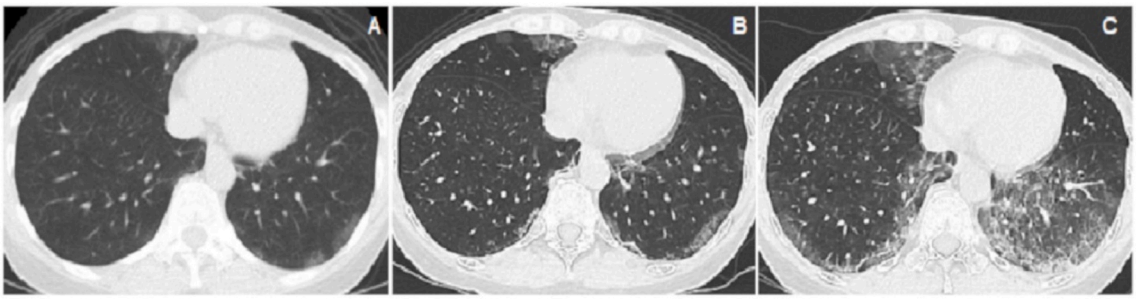

Fig. 1. Computed tomography images
(A) During the first visit, we observed bilateral ground-glass opacities with significant distribution in the peripheral regions. (B) Nine months after the first visit, the abnormal shadows had expanded to neighboring regions. (C) Seventeen months after the first visit, the abnormal shadows had spread in the center.

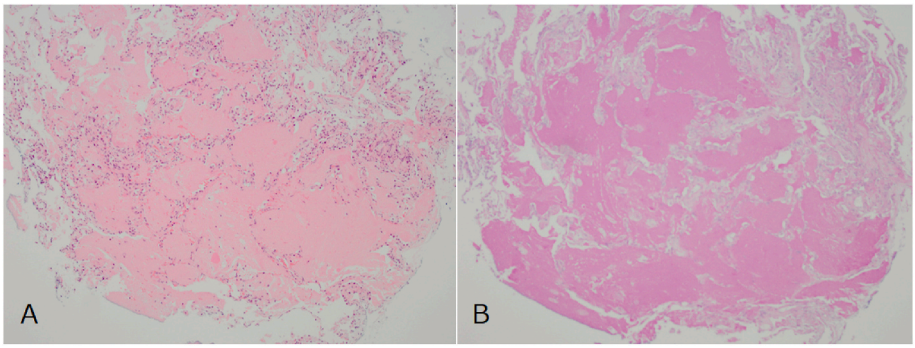

Fig. 2. Transbronchial lung biopsy specimens stained with (A) hematoxylin and eosin and (B) periodic acid-Schiff staining. The biopsy specimens contained eosinophilic bodies that stained strongly with periodic acid-Schiff staining.

Table 1
Cases of pulmonary alveolar proteinosis (PAP) with a significant distribution of abnormal shadows in the peripheral regions.

Case	Age	Sex	Smoking	Symptoms	BALF	Diagnosis	Author	Year
1	39	F	never	no	transparent	BAL, TBLB, SLB	Inui	1999
2	38	F	unknown	no	white	BAL, TBLB	Mita	2003
3	55	F	never	no	white	BAL, TBLB	Sugimoto	2006
4	32	F	never	no	white	BAL, TBLB	Mohri	2007
5	58	F	never	no	none	SLB	Taniguchi	2008
6	56	F	never	no	transparent	BAL, TBLB, SLB	Yamazaki	2008
7	45	M	never	no	transparent	BAL, TBLB, SLB	Toyama	2008
8	65	F	never	no	White	BAL, TBLB	Haga	2009
9	57	M	never	no	None	SLB	Sunadome	2010
10	55	F	never	dyspnea	White	BAL,TBLB	Satoh	2012
11	41	M	never	no	unknown	BAL,TBLB	Sugino	2019

abnormalities. Chest CT showed bilateral ground-glass opacities and reticular shadows, mainly distributed in the lower lobes. The abnormal shadows tended to enlarge over time after the initial examination (Fig. 1).

Neither findings nor history were suggestive of hypersensitivity pneumonia, drug-induced pneumonia, eosinophilic pneumonia, or collagen vascular disease. Idiopathic interstitial pneumonia, including nonspecific interstitial pneumonia (NSIP), was suspected. Bronchoalveolar lavage was performed in the superior lingular segment of the left lobe, followed by a transbronchial lung biopsy (TBLB) of the left lower lobe. The BALF was transparent and did not have a milky appearance. The BALF cell count was unremarkable. The biopsy specimens contained eosinophilic bodies that strongly stained with periodic acid-Schiff (PAS) staining (Fig. 2).

The serum level of anti-granulocyte macrophage colony-stimulating factor (anti-GM-CSF) antibody was high at 74.0 U/mL (normal level <1.7). Based on these findings, the diagnosis of APAP was confirmed.

3. Discussion

We came across a rare symptomatic APAP case with NSIP-like radiological findings without a milky appearance of the BALF. PAP, first reported by Rosen et al., is a rare disorder where lipoproteins accumulate in the alveoli [3]. Clinically, PAP can be classified into

three types: congenital, secondary, and autoimmune. Most cases of PAP are categorized into the autoimmune type, in which anti-GM-CSF antibodies are specifically detected [4]. In the diagnosis, BALF typically has a milky appearance. TBLB and surgical lung biopsies show eosinophilic bodies that stain strongly with PAS staining or surfactant protein A. Chest radiographs of patients with PAP generally show more pronounced abnormalities in the perihilar regions. Chest CT scans show air-space filling with a variable patchy distribution [1].

Our patient's chest CT showed bilateral ground-glass opacities and reticular shadows, mainly distributed in the lower lobes. Only 11 cases with a significant distribution in the peripheral regions have so far been reported in Japan (Table 1) [5–15].

All cases, except for the case reported by Satoh [14], were asymptomatic. The case reported by Satoh was similar to our case in that the patient had symptoms that worsened with steroid and cyclosporine treatment.

Although our case did not show the typical milky appearance of BALF, we diagnosed APAP by TBLB and by measuring the serum anti-GM-CSF antibody levels. In previous reports, bronchoalveolar lavage was performed in nine patients, and three out of nine patients (33.3%) showed no milky appearance in the BALF, as in our case. All three of these patients underwent invasive surgical lung biopsy (SLB) [5,10,11]. The measurement of anti-GM-CSF antibody levels at the early stage of this case would have been less invasive and useful for diagnosing PAP. In this case, we were able to shift from immune suppressant therapy to disease-specific therapy (such as total lung lavage) at an early stage when the lung function had not declined. Further investigation is necessary to elucidate the importance of anti-GM-CSF antibody measurements in cases with interstitial pneumonia.

We reported a case of APAP with features similar to NSIP. Therefore, it is important to include PAP in the differential diagnosis, even in atypical cases.

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Authors' contributions

Koki Fujii wrote the manuscript. Hideyuki Takeshima, Taku Nishimura, Toshio Sakatani, and Kazuhiro Usui reviewed and edited the manuscript. Yoshio Masuda and Teppei Morikawa contributed to the pathological diagnosis.

Declaration of competing interest

The authors declare that they have no competing interests.

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