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【 CASE REPORT 】

Rheumatoid Arthritis Accompanying Diffuse Panbronchiolitis

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Abstract:
A 58-year-old woman with rheumatoid arthritis (RA) visited our hospital complaining of a persistent cough and sputum for the past year. She had a high cold hemagglutinin titer and chronic sinusitis. Chest computed tomography revealed bilateral diffuse centrilobular nodules, bronchiectasis, and bronchial wall thickening. A surgical lung biopsy was performed that confirmed diffuse panbronchiolitis (DPB) because of the lymphocytic and plasmacytic infiltrates in the respiratory bronchioles. Her condition improved after the administration of clarithromycin. Several cases of RA complicating DPB have previously been reported, but only in Japan. We need to consider DPB as a bronchiolitis types accompanying RA among Japanese patients.

Key words: diffuse panbronchiolitis, rheumatoid arthritis, surgical lung biopsy, Japanese

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Introduction

Bronchiolitis is an inflammation of the bronchioles, and this inflammatory reaction is a response to injury, reflecting the interplay between inflammatory cells and mesenchymal tissue (including fibrosis) (1). Classifications of bronchiolitis include asthma, chronic obstructive pulmonary disease, cellular bronchiolitis (CB) [including follicular bronchiolitis (FB) and diffuse panbronchiolitis (DPB)], respiratory bronchiolitis, respiratory bronchiolitis-associated interstitial lung disease, bronchiolitis obliterans (BO), dust-related small airway fibrosis, and post-inflammatory bronchiolar scarring and peribronchiolar fibrosis (1). DPB is a chronic airway disease mainly seen in East Asian people, such as the Japanese (2). Before macrolide treatment was introduced, the 5-year survival rate was 63%; since its introduction, the rate has improved to 91% (2, 3).

Bronchiolitis types directly associated with rheumatoid arthritis (RA) usually include FB and BO. Several patients with RA accompanied by DPB have been reported, but few have been analyzed pathologically. We herein report a woman with RA who underwent a surgical lung biopsy (SLB) and was pathologically diagnosed with DPB.

Case Report

A 58-year-old woman visited our hospital complaining of a persistent cough and sputum for the past year. She had been diagnosed with RA at 46 years old and was being treated with methotrexate 12 mg/week and tacrolimus 2 mg/day. Her RA had remained in remission with treatment. She had no history of sinusitis, smoking, or dust exposure. She did not have shortness of breath on exertion, nasal discharge, nasal obstruction, or posterior rhinorrhea.

Her vital signs on the first visit included a heart rate of 83 beats/min, blood pressure of 126/74 mmHg, and body temperature of 36.4℃. Chest auscultation revealed bilateral coarse crackles. Deformity of the metacarpophalangeal joint of the right first finger was also observed.

An arterial blood gas analysis under ambient air showed a pH of 7.434, partial pressure of carbon dioxide of 41.1 Torr, and partial pressure of oxygen (PaO_2) of 85.1 Torr. Laboratory findings were as follows: white blood cell count, 9,200/mm^3; neutrophils, 5,900/mm^3; eosinophils, 400/mm^3; basophils, 100/mm^3; monocytes, 400/mm^3; lymphocytes, 2,400/

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mm^3; hemoglobin, 12.5 g/dL; platelet count, 28.0×10^4/mm^3; serum total protein, 7.2 g/dL; albumin, 3.8 g/dL; normal liver transaminase; lactate dehydrogenase, 211 IU/L; creatinine, 0.63 mg/dL; C-reactive protein, 0.28 mg/dL; IgG, 1,262 mg/dL; erythrocyte sedimentation rate, 46 mm/h; and brain natriuretic peptide, 42.9 pg/mL. Rheumatoid factor was 24 U/mL (normal: <15 U/mL), and the cold hemagglutinin titer was ×256 (normal: <×64). Matrix metalloprotease 3, anti-cyclic citrullinated peptide antibody, anti-nucleolar antibody, and anti-neutrophil antibodies were all negative. Beta-D glucan, *Aspergillus* antigen, *Aspergillus* antibody, *Mycobacterium avium* complex antibody, and interferon

Table 1. Pulmonary Function Test Results.

Parameter	Value
VC	2.71 L
VC, %predicted	93.1 %
FVC	2.79 L
FVC, %predicted	95.9 %
FEV_1	1.98 L
FEV_1, %predicted	99.5 %
FEV_1/FVC	71 %
FEV_1 (after inhaling bronchodilator)	1.98 L
FeNO	37 ppb
TLC	4.44 L
RV	1.44 L
RV, %predicted	120 %
RV/TLC	32.43 %
DL_{CO}	13.4 mL/min/mmHg
DL_{CO}, %predicted	78.9 %
DL_{CO}/VA	3.25 mL/min/mmHg/L
DL_{CO}/VA, %predicted	68.3 %

DL_{CO}: diffusing capacity of the lungs for carbon monoxide, FeNO: fractional exhaled nitric oxide, FEV_1: forced expiratory volume in 1 second, FVC: forced vital capacity, RV: residual volume, TLC: total lung capacity, VA: alveolar gas volume, VC: vital capacity

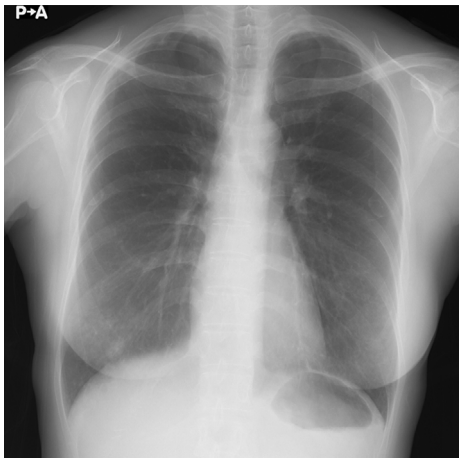

Figure 1. Chest radiography revealed diffuse small nodular shadows and tram lines in both lower lungs at the initial visit.

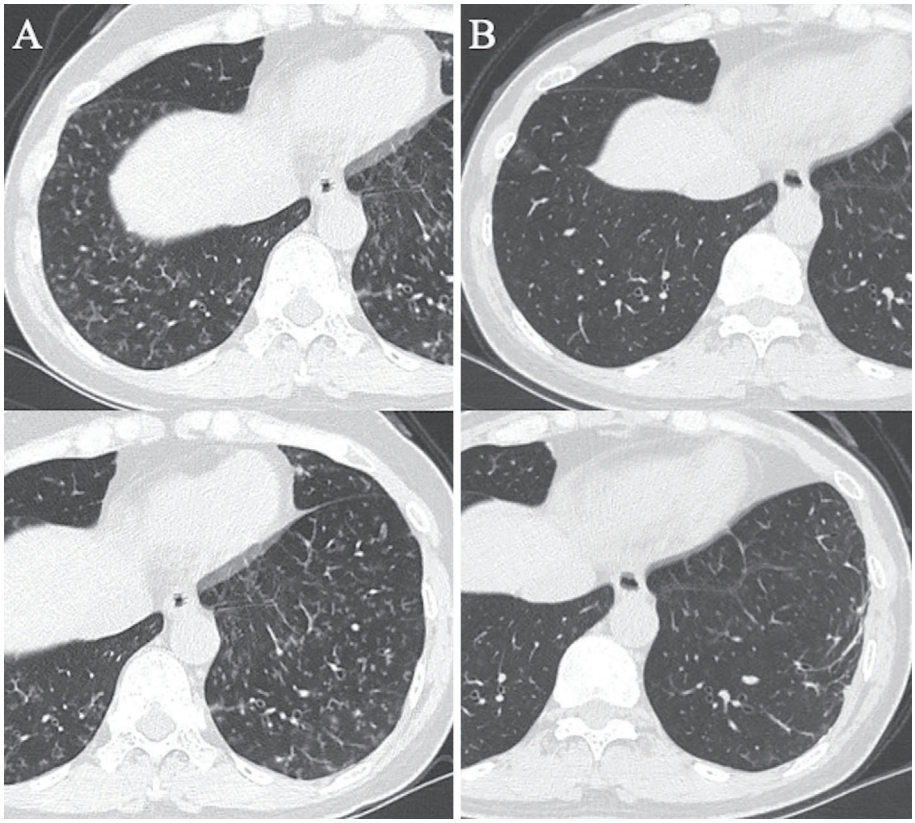

Figure 2. Chest high-resolution computed tomography at the initial visit (A) revealed bilateral diffuse centrilobular nodules, tree-in-bud appearance, bronchial wall thickening, and bronchiectasis that had almost resolved two months after starting the clarithromycin (B).

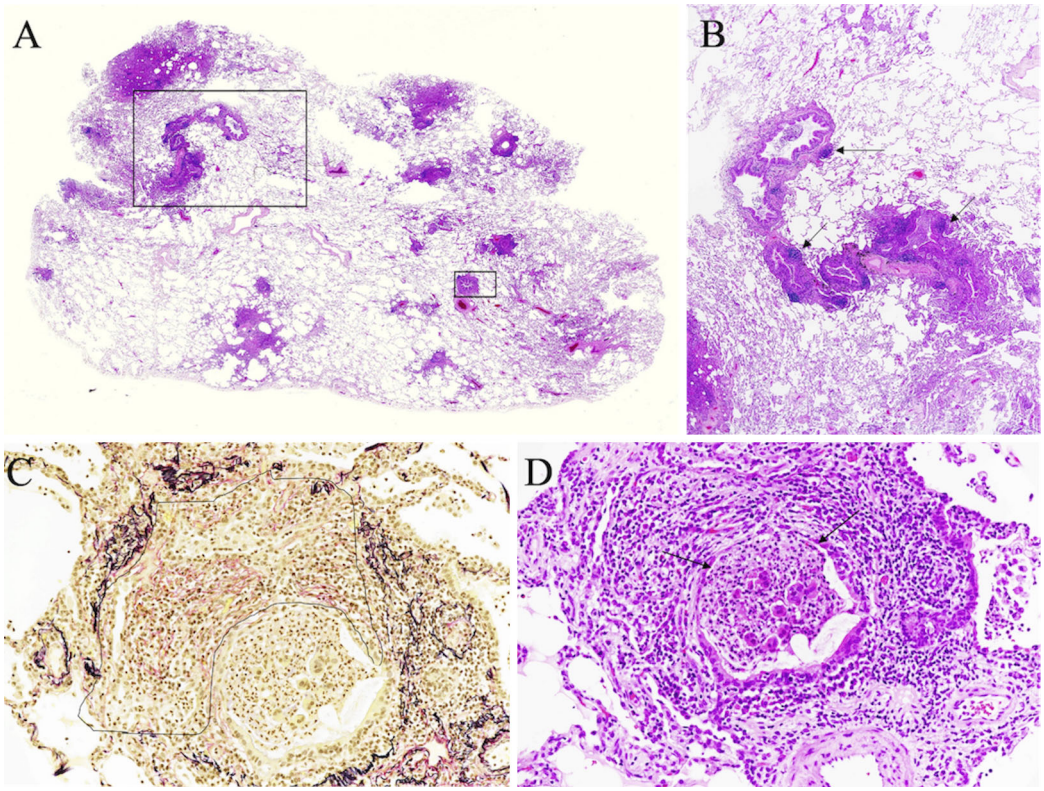

Figure 3. **Pathological findings of the surgical lung biopsy. (A) Scattered airway-centric lesions [Hematoxylin and Eosin (H&E) staining; panoramic view]. (B) The upper left enclosed area of (A). Membranous to respiratory bronchioles were seen. Exudates were present in the lumen. Lymphatic follicles and inflammatory cell infiltrates were present in the wall (arrows) (H&E staining; magnification, ×20). (C) Elastica van Gieson staining and (D) H&E staining of the lower right enclosed area of (A) (magnification, ×200). (C) The respiratory bronchiole was narrowed because organizing and inflammatory cell infiltrates were present in the lumen (enclosed area). (D) In the respiratory bronchiole, neutrophil exudation was present in the narrowed lumen (arrows). Many lymphocytic and plasmacytic infiltrates were present in the wall.**

gamma release assay (QuantiFERON®) were also all negative.

Pulmonary function testing showed a decreased diffusing capacity of the lungs for carbon monoxide (Table 1). Chest radiography showed diffuse small nodular shadows and tram lines in both lower lungs (Fig. 1). Chest high-resolution computed tomography (HRCT) showed bilateral diffuse centrilobular nodules, tree-in-bud appearance, bronchial wall thickening, and bronchiectasis (Fig. 2A). Bronchoalveolar lavage fluid (BALF) obtained from the right B^{8} (19 of 150 mL recovered) showed a total cell count of 6.3×10^{5} cells/mL (macrophages, 19.6%; lymphocytes, 6.6%; neutrophils, 73.8%; and eosinophils, 0.0%). The CD4/CD8 lymphocyte ratio was 9.4. No significant pathogens were cultured from the BALF. Transbronchial lung biopsy specimens of the right B^{8a} showed infiltration of lymphoid cells into the membranous bronchioles. We suspected her of having bronchiolitis associated with RA because of her history of RA and the absence of sinusitis symptoms.

An SLB of the left lung base was performed to obtain a definitive diagnosis. The specimen showed scattered airway-centric lesions, neutrophil infiltrates and organization in the lumen of the respiratory bronchioles, and lymphocytic and plasmacytic infiltrates in the wall of the respiratory bronchioles (Fig. 3). Based on the diffuse respiratory bronchiolar involvement and the lack of hyperplasia of lymphoid follicles around the bronchioles as seen in FB or narrowing of the membranous bronchioles as seen in BO, we made a diagnosis of DPB.

After the SLB, paranasal CT was performed that showed paranasal sinusitis in the frontal, maxillary, and ethmoid sinuses (Fig. 4), and chronic sinusitis was confirmed by an otolaryngologist. After initiating treatment with clarithromycin 200 mg per day, her respiratory symptoms improved. Two months after starting the clarithromycin, her PaO_2 had increased to 98.4 Torr, and chest HRCT showed improvement of the centrilobular shadows (Fig. 2B).

Discussion

We experienced a case of DPB that developed in a patient under treatment for RA. Initially, we suspected her of having bronchitis associated with RA, such as FB or BO, but the pathological findings led to the diagnosis of DPB.

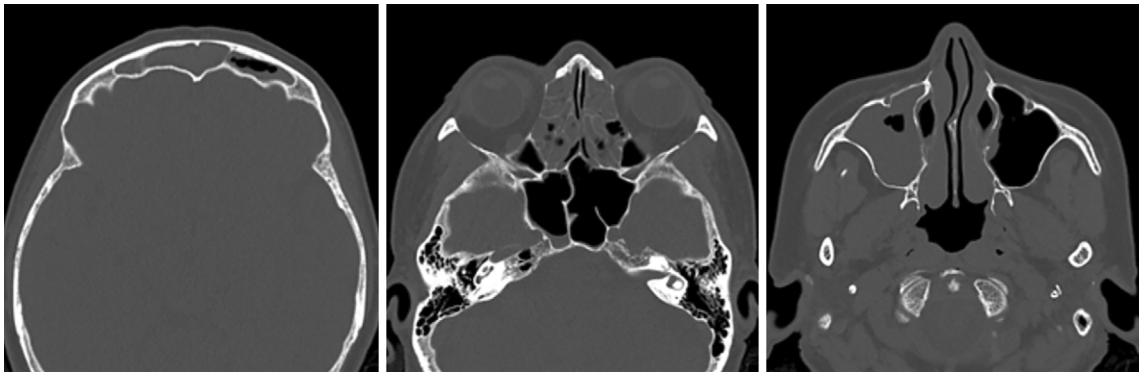

Figure 4. **Paranasal computed tomography showed paranasal sinusitis in the frontal, maxillary, and ethmoid sinuses.**

Table 2. **Previously Reported Cases and the Present Case of RA Complicating DPB.**

Case	Age/Sex	Method of histopathological diagnosis	Treatment of RA	BALF Mφ/Lym/Neu/Eos (%)	Treatment of DPB	Outcome	Prognosis	HLA B54	HLA DR4
1 (13)	61/Female	Autopsy	Corticosteroid, gold	NA	-	Worsened	30 years dead (respiratory failure)	NA	NA
2 (13)	61/Male	Autopsy	Corticosteroid, penicillamine	NA	-	Worsened	4 years dead (respiratory failure)	NA	NA
3 (14)	47/Female	NA	MTX	NA	CAM	Improved	4 months alive	+	+
4 (14)	52/Female	NA	NSAIDs	1.6/2.1/96.3/NA	CAM	Improved	NA	+	NA
5 (14)	66/Female	NA	Bucillamine	NA	EM	Improved	1 year dead (respiratory failure)	NA	NA
6 (15)	67/Female	Autopsy	NSAIDs, corticosteroid, penicillamine, gold	NA	-	Worsened	5 years dead (respiratory failure)	NA	NA
7 (12)	47/Female	NA	NSAIDs, bucillamine	NA	EM	Improved	NA	+	+
8 (12)	58/Female	NA	NSAIDs, auranofin	NA	NA	NA	NA	+	+
Present case	58/Female	SLB	MTX, tacrolimus	19.6/6.6/73.8/0.0	CAM	Improved	1 year alive	NA	NA

CAM: clarithromycin, BALF: bronchoalveolar lavage fluid, DPB: diffuse panbronchiolitis, EM: erythromycin, Eos: eosinophil, HLA: human leukocyte antigen, Lym: lymphocyte, MTX: methotrexate, Mφ: macrophage, NA: not available, Neu: neutrophil, NSAIDs: non-steroidal anti-inflammatory drugs, RA: rheumatoid arthritis, SLB: surgical lung biopsy

Patients with RA frequently have complications of bronchiolar lesions, such as FB or BO. Tanaka et al. analyzed the chest CT findings of 63 patients with RA and reported that 11 patients (17.5%) had bronchiolitis (4). FB is characterized by hyperplasia of the lymphoid tissue of the bronchioles (5). FB responds to corticosteroids and immunosuppressants, and most patients have a good prognosis (6). In contrast, BO is characterized by stenosis or obstruction of the membranous bronchioles (7). Despite the use of immunosuppressants or macrolides, BO tends to be refractory to treatment and has a poor prognosis (8). Because of their different prognoses, the differentiation of bronchiolitis associated with RA is important.

DPB is characterized by chronic cough, purulent sputum, chronic paranasal sinusitis, elevated cold hemagglutinin titer, and pathologically chronic inflammation in the respiratory bronchioles (2). More than 80% of such patients have a history of chronic paranasal sinusitis. Even if patients are asymptomatic, most have chronic sinusitis on imaging (9). Human leukocyte antigen (HLA)-B54 is associated with DPB in Japanese (10). Conversely, HLA-DR4 is associated with RA in various races, including Japanese (11, 12). Because HLA-B54 and HLA-DR4 constitute a haplotype among Japanese, these diseases are considered to occur together (13). However, as HLA testing for DPB is not covered by insurance in Japan, it was not performed in the present case.

Similar to the present case, eight other patients with RA

complicating DPB have been reported (Table 2) (13-16), and all were from Japan. Only four patients including the present patient were pathologically diagnosed with DPB; the others were diagnosed clinically. The present case is the first, to our knowledge, in which an SLB was performed to obtain a pathological diagnosis while the patient was alive. The patients in eight of the nine reported cases (including the present case) were women. BALF was obtained in Case 4 and showed an increased neutrophil rate. Five patients were treated with macrolides, and their symptoms improved. Three patients were autopsied prior to the introduction of macrolide treatment and found to have died of respiratory failure. The patient in Case 5 was not pathologically diagnosed with DPB. She was treated with erythromycin (EM), and her symptoms initially improved, but she ultimately died of respiratory failure one year later. All three patients in whom both HLA-B54 and HLA-DR4 were measured were positive for both.

It is important to differentiate DPB from FB or BO associated with RA, but this is often difficult in practice. Hayakawa et al. studied 15 RA patients with biopsy-proven bronchiolar disease (8 with FB and 7 with BO) and showed that 11 (73%) had chronic sinusitis, and 11 who received EM therapy experienced a significant improvement in symptoms (17). Homma et al. reported three RA patients clinically diagnosed with DPB. The cold hemagglutinin titer in all three patients was elevated over 512-fold. All three patients were autopsied, and two were pathologically diagnosed with DPB, while the other was deemed to have BO (14).

In conclusion, we encountered a case of DPB in a patient with RA. Among Japanese RA patients, we need to consider DPB as a type of bronchiolitis that can accompany RA. However, it is difficult to differentiate DPB from other types of bronchitis associated with RA based on the radiographic findings, presence of sinusitis, cold hemagglutinin titer, and response to macrolide therapy.

The authors state that they have no Conflict of Interest (COI).

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