Rheumatoid Arthritis Associated with Diffuse Panbronchiolitis

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Diffuse panbronchiolitis (DPB) is a distinct clinicopathologic entity, which is characterized by chronic recurrent sinopulmonary infection and inflammation. We describe 3 patients with rheumatoid arthritis (RA) associated with DPB and consider that DPB is one of the bronchopulmonary manifestations associated with RA.

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Key words: human leukocyte antigen (HLA), high-resolution computed tomography, bronchopulmonary manifestation

Introduction

Diffuse panbronchiolitis (DPB) is a distinct clinicopathologic entity, which is characterized by 1) symptoms: chronic cough with sputum and dyspnea on exertion; 2) physical signs: rales and rhonchi; 3) chest X-ray film: diffusely disseminated fine nodular shadows; 4) pulmonary function test and arterial blood gas analysis: forced expiratory volume % in one second (FEV1,0%) <70%, partial pressure of oxygen (PaO2) <80 mmHg; 5) cold hemagglutinin (CHA) titer elevation; 6) association with or past history of chronic paranasal sinusitis; 7) pathological findings: respiratory bronchiolitis and peribronchiolitis. Over 1,000 cases of definite or probable DPB have been reported exclusively in Japan, and the reason for such a high incidence compared with Western countries is considered to be the strong correlation between DPB and human leukocyte antigen (HLA) B54, which exists only in Japanese, Chinese and Korean populations (3). We describe 3 patients with rheumatoid arthritis (RA) who developed DPB and discuss the clinical characteristics of DPB in these patients.

Case Reports

Case 1

A 47-year-old woman with a 5-year history of RA complained of a progressively worsening cough and sputum production in April 1996. Since adolescence she had suffered from chronic paranasal sinusitis, for which she underwent surgical treatment when she was 16 years old. She developed respiratory symptoms about 6 months after the onset of RA. Due to severe RA disease activity, she took methotrexate (MTX) orally (5-6.25 mg/week) since April 1995, with slight improvement in her arthralgia, but her C-reactive protein (CRP) level remained high at 6-7 mg/dl. She had no history of smoking, and her late father had also suffered from RA with a productive cough.

Physical examination revealed inspiratory crackles audible on auscultation. There were no symptoms suggesting the presence of vasculitis, such as mononeuritis multiplex, skin ulcer, serositis, and scleritis. Laboratory blood tests revealed an erythrocyte sedimentation rate (ESR) of 95 mm/h, a CRP level of 7.6 mg/dl, a white blood cell (WBC) count of 6,000/µl and a hemoglobin (Hb) level of 11.8 mg/dl. The rheumatoid factor (RF, 272.6 IU/ml, normal: <6.0), immunoglobulin (Ig)G (2,780 mg/dl, normal: 1,048-1,646), IgA (868 mg/dl, normal: 146-340), IgM (296 mg/dl, normal: 131-283) and CHA titer (1:1,024, normal: <1:64) levels were high. Chest roentgenography showed diffuse fine nodular shadows in both lower lungs and a mild degree of pulmonary hyperinflation (Fig. 1A) and chest high-resolution computed tomography (HRCT) showed centrilobular small rounded and linear opacities (Fig. 1B). Pulmonary function tests revealed a vital capacity (VC) of 2,210 ml (79.5% of predicted value), FEV1.0 of 1,840 ml (76.3% of the forced vital capacity) and residual volume (RV) of 1,870 ml (142.7% of the predicted value). Arterial blood gas analysis while breathing room air revealed a PaO2 of 72.6 mmHg, partial pressure of carbon dioxide (PaCO2) of 38.1 mmHg and pH of 7.43. HLA typing of class I and class II HLA DR antigens showed she had the A2/3-B54-Cw1/3-DR4/6 phenotype.

As a diagnosis of DPB was made, oral clarithromycin (400 mg/day) was administered. Four months later, her CHA titer had decreased to 1:128, VC, FEV1.0 and PaO2 had increased to...
2,660 ml (95.7% of the predicted value), 1,910 ml and 76.6 mmHg, respectively. The productive cough and nasal discharge both decreased markedly, whereas the arthralgia severity was unchanged. The patient refused to undergo bronchoalveolar lavage (BAL), transbronchial lung biopsy (TBLB) or open lung biopsy.

**Case 2**

A 52-year-old woman with RA was admitted to our hospital in June 1996, complaining of exertional cough with sputum production. RA was diagnosed in 1985 and she had taken nonsteroidal antiinflammatory drugs (NSAIDs) since then and she took bucillamine from 1992 until 1994. She had suffered from parainfluenza since 13 years of age; she underwent surgery for breast cancer (Stage I) in October 1995, and received radiation therapy in November 1995. As chest roentgenography revealed a ground glass opacity of the right upper lung field in the radiation area during radiation therapy and she developed a cough, oral prednisolone (PSL, 40 mg/day) was started for suspected radiation pneumonitis. The abnormal shadow disap-

![Figure 1](image1.png)

**Figure 1.** A) Chest roentgenogram showing diffuse fine nodular shadows in both lower lungs and a mild degree of pulmonary hyperinflation (case 1). B) Chest HRCT demonstrating centrilobular small rounded and linear opacities (case 1).

![Figure 2](image2.png)

**Figure 2.** A) Chest roentgenogram showing diffuse fine nodular shadows throughout the middle and lower lung fields (case 2). B) Chest HRCT demonstrating centrilobular small rounded and linear opacities and bronchiectasis (case 2).
peared soon after and PSL was gradually tapered to 12.5 mg/day. However, fine nodular shadows were observed throughout her middle and lower lung fields in April 1996 (Fig. 2A). She had no history of smoking and no family history of RA.

Physical examination revealed inspiratory crackles audible on auscultation, mild arthralgia and swelling of the bilateral proximal interphalangeal joints, and the absence of skin ulcers and scleritis. Laboratory blood tests revealed an ESR of 50 mm/h, a CRP level of 1.4 mg/dl, a WBC count of 9,000/μl and a Hb level of 12.3 mg/dl. The RF (58.3 IU/ml), IgG (2,040 mg/dl), IgA (426 mg/dl) and CHA titer (1:1,024) levels were high. Chest HRCT showed centrilobular small rounded and linear opacities and bronchiectasis (Fig. 2B). Pulmonary function tests revealed a VC of 2,620 ml (94.6% of the predicted value), a FEV\(_1\) of 1,640 ml (66.7% of the predicted value) and RV of 2,070 ml (147.9% of the predicted value). Arterial blood gas analysis while breathing room air revealed a PaO\(_2\) of 77.2 mmHg, PaCO\(_2\) of 37.4 mmHg and pH of 7.44. Classification of BAL cells revealed 1.6% macrophages, 2.1% lymphocytes and 96.3% neutrophils, compatible with bronchopulmonary infection related to DPB. A TBLB specimen of the left lower lobe showed non-specific, mild, chronic inflammation with interstitial fibrosis in the bronchiolar subepithelium. The HLA type of the class I antigen was Al l/2-B54/35-Cwl. As a diagnosis of DPB was made, oral clarithromycin (400 mg/day) was administered and her respiratory symptoms improved.

**Case 3**

A 66-year-old woman with RA was admitted to our hospital in November 1988, complaining of a worsening productive cough and exertional dyspnea. RA was diagnosed in 1978 and she had taken D-penicillamine (200 mg/day) from 1979 until 1987, when its effect had decreased, followed by administration of bucillamine. She had suffered from parasinusitis since she was 40 years old and received surgical treatment for it when she was 54 and 62 years old. She developed respiratory symptoms when she was 61 years old and had no history of smoking.

Physical examination revealed inspiratory crackles and some rhonchi audible on auscultation, and mild arthralgia of the bilateral knee joints. There were no abnormal findings in the eyes, skin, abdomen, or upon neurological examination. Laboratory blood tests revealed an ESR of 110 mm/h, a CRP level of 1.7 mg/dl, a WBC count of 8,900/μl and a Hb level of 11.6 mg/dl. The RF (435.2 IU/ml) and CHA titer (1:1,024) levels were high. Chest roentgenography showed diffuse fine nodular shadows in both lungs, particularly in the lower fields. Chest CT showed small nodular shadows and bronchiectasis. Pulmonary function tests revealed a VC of 1,550 ml (63.6% of the predicted value) and a FEV\(_1\) of 820 ml (52.9% of the forced vital capacity). Arterial blood gas analysis while breathing room air revealed a PaO\(_2\) of 61.7 mmHg, PaCO\(_2\) of 38.4 mmHg and pH of 7.47. HLA typing was not done and she refused to undergo BAL, TBLB or open lung biopsy. Exacerbation of DPB was suspected, and intravenous cefpimizole sodium (2 g/day) and erythromycin (600 mg/day) was administered. Her respiratory symptoms gradually improved and she was discharged in December 1988. Although she had been prescribed erythromycin (400–600 mg/day) after discharge, she often suffered from bacterial pneumonia and died in 1989 of respiratory failure. Autopsy could not be performed.

**Discussion**

Clinically, all of the present 3 RA patients were considered to have DPB, according to the diagnostic criteria (1, 2). That is, they presented with appropriate clinical symptoms, including chronic cough with sputum production and dyspnea with crackles on auscultation, diffuse fine nodular shadows in both lungs, marked CHA titer elevation, hypoxia and the presence of chronic paranasal sinusitis (Table 1). Bronchiolitis obliterans (BO) and bronchiolitis obliterans organizing pneumonia (BOOP) have also been reported as bronchiolar lesions of RA (4, 5). BO presents as rapid onset of dyspnea, a normal or hyperinflated chest X-ray picture, and obstructive impairment of pulmonary function. The incidence of BO associated with RA seems to be very low in comparison with that of DPB-like pulmonary manifestations (6). On the other hand, BOOP is a relatively common complication of RA characterized by wandering,

| Table 1. Characteristics of 3 Patients with RA Associated with Diffuse Panbronchiolitis |
|-----------------|-----------------|-----------------|
| Age/Sex | Case 1 | Case 2 | Case 3 |
| Chest X-ray | 47/F | 52/F | 66/F |
| Chronic paranasal sinusitis | Diffuse fine nodular shadows | Diffuse fine nodular shadows | Diffuse fine nodular shadows |
| Positive | Positive | Positive |
| Cold hemagglutinin titer | 1:1,024 | 1:1,024 | 1:1,024 |
| VC (%) | 79.5 | 94.6 | 63.6 |
| FEV\(_1\) (%) | 76.3 | 66.7 | 52.9 |
| PaO\(_2\) (mmHg) | 72.6 | 77.2 | 61.7 |
| HLA class I-B54 | Positive | Positive | ND |
| class II-DR4 | Positive | ND | ND |
| F: female, VC: vital capacity, FEV\(_1\): forced expiratory volume in one second, ND: not done. | | | |
patients (n=3) and others (n=3) with RA and DPB reported to complications of RA for the following reasons: First, all of our patients, causing differences in bronchopulmonary manifestations between typical DPB and RA-associated DPB. Thus, DPB is likely to be one of the bronchopulmonary complications of RA for the following reasons: First, all of our patients (n=3) and others (n=3) with RA and DPB reported to date (10, 11) developed DPB after the onset of RA. Second, to our knowledge, there have been no reports of DPB associated with connective tissue diseases other than RA, such as progressive systemic sclerosis and polymyositis/dermatomyositis. Third, an association with HLA should be considered (10). Since HLA-DR4, whose incidence is significantly higher in RA patients (12), creates a linkage disequilibrium in Japanese with HLA-B54 (13), which is strongly associated with DPB (3), it may be possible that RA and DPB are closely associated in Japanese patients. To date few cases of RA associated with DPB have been reported, which might be due to the milder manifestations of DPB in these patients, and we propose the possibility that RA patients associated with DPB may be more common than expected in Japan.

References