Diffuse Panbronchiolitis and Rheumatoid Arthritis: A Possible Correlation with HLA-B54

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We analyzed the HLA antigens in two patients with rheumatoid arthritis accompanied by diffuse panbronchiolitis in whom HLA typing could be done and found the presence of B54 and DR4 alleles. We previously reported that the frequency of HLA-B54 is significantly increased in patients with diffuse panbronchiolitis. This allele demonstrates a linkage disequilibrium with DR4 (or DR4.1) in Japanese individuals. The association of rheumatoid arthritis with HLA-DR4 is well established in various ethnic groups including Japanese people. Since both diseases show the same pattern of HLA correlation, more Japanese patients with these two diseases are likely to be encountered.

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Introduction

Diffuse panbronchiolitis is a clinicopathologic entity found primarily in Japan (1). The characteristic features of this disorder are chronic recurrent or continuous sinopulmonary infection and inflammation, and its histologic features include diffuse respiratory bronchiolitis and peribronchiolitis with predominance in the lower lung fields (1, 2).

In patients with diffuse panbronchiolitis, the frequency of the HLA haplotype, A24/11-B54-Cw1-DR4 (4.1), is significantly increased (2). On the other hand, rheumatoid arthritis is also known to be significantly correlated with HLA-DR4 and B54 in Japanese patients (3). We have identified 56 patients with diffuse panbronchiolitis, 4 of whom showed concomitant rheumatoid arthritis. Since both diffuse panbronchiolitis and rheumatoid arthritis show the same pattern of HLA correlation in Japan, it is likely that these two diseases may accompany each other. We therefore analyzed the HLA antigens in two patients with both rheumatoid arthritis and diffuse panbronchiolitis and found B54 and DR4 in both.

Case Reports

Patient 1

A 47-year-old non-smoking Japanese housewife with a 3-year history of rheumatoid arthritis complained of progressive cough, yellow sputum, wheezing and breathlessness which had continued for one year. She had no other occupational or environmental exposure. She had had chronic sinusitis since the age of 10 years. Three years previously, she had complained of swelling and arthralgia of the bilateral 3rd finger PIP joint. Subsequently, symmetrical involvement of the shoulders, elbows, and ankle MTP joints appeared. She had morning stiffness but no dryness of the eyes and mouth. The laboratory data at that time included: white blood cell count, 9,500/mm³; erythrocyte sedimentation rate, 61 mm/h; C-reactive protein, 2.02 mg/dl (normal: <0.06); rheumatoid factor, positive; and RAHA/RAPH x320 (normal: <x40). She was diagnosed as having rheumatoid arthritis according to the new American Rheumatism Association criteria (4), and had been treated during the intervening period with a nonsteroidal anti-inflammatory drug and bucillamine.

In November 1992, she visited our department because of continuous productive cough with a history of about one year. At that time, laboratory results included: WBC count, 13,300/mm³; ESR, 35 mm/h; C-reactive protein, 0.512 mg/dl; and cold hemagglutinin titer, >512 (normal: <x128). Anti-human T-cell leukemia virus type I antibody was negative. Examination of the chest disclosed bilateral inspiratory and expiratory crackles. Pulmonary function tests revealed an obstructive pattern with FVC, 2.34 L (92% of predicted); FEV1.0, 1.45 L (66% of predicted); FEV1.0/FVC, 62%; RV, 1.77 L (138% of...
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predicted); RV/TLC, 44% (175% of predicted). Diffusing capacity (Dco) was normal. Haemophilus influenzae was cultured from her sputum. Chest roentgenogram revealed small nodular shadows with an unclear margin diffusely scattered in both lower lung fields (Fig. 1). Computer tomography also revealed many small nodular shadows located in the centrilobular area (Fig. 2). Diffuse panbronchiolitis was diagnosed on the basis of her history, chest X-ray findings, and laboratory data. Low-dose long-term erythromycin treatment was started, and after three months considerable regression of both subjective complaints and radiological findings was noted. The response to erythromycin therapy in this patient was not inconsistent with that in diffuse panbronchiolitis (5).

HLA typing
Typing for HLA-A, B, C, DR and DQ was performed by the NIH standard method as described previously (6). The specificities of selected antisera obtained locally and from foreign laboratories were defined according to the standards established by the International Histocompatibility Workshop. We defined DR4.1 by a positive reaction to all three alloantisera, AOH 600, AOH 602 and TD 511, which are the key sera for determining the serologic “split” of the DR4 antigen (7), and the serologically determined DR4.1 specificity includes the cytologically determined Dw14, Dw15, and Dw4 specificities (8). The patient’s HLA type was A24, A6–B61, B54–Cw1, Cw10 – DR4.1, DR9 – DR53 – DQ3, DQ4.

Patient 2
A 58-year-old non-smoking Japanese housewife had been diagnosed as having rheumatoid arthritis in 1980 and had been treated with nonsteroidal anti-inflammatory drugs and auranofin. She had no inhalation exposure history. In 1982, she complained of gradually progressive cough and yellow sputum discharge. She had had chronic sinusitis since her childhood. Her chest roentgenogram, pulmonary function tests and laboratory data revealed that the pulmonary disorder presented features consistent with diffuse panbronchiolitis.

Her HLA typing was A11, A24 – B7, B54 – Cw1 – DR1, DR4 – DR53 – DQ1, DQ4. At the time that this HLA typing was conducted, we could not determine the DR4.1 status, and it is unclear whether the DR4 was DR4.1.

Discussion
Diffuse panbronchiolitis is characterized by chronic recurrent or continuous sinopulmonary infection and respiratory bronchiolitis with an unknown etiology. Familial occurrence of diffuse panbronchiolitis has been recognized in Japan. We have performed HLA analysis in such patients (2). Our results
revealed a significantly increased frequency of B54 (63.2%, compared with control; 11.4%; RR = 13.30) among HLA class I and class II antigens in the patients with diffuse panbronchiolitis. This antigen, B54, is known to form part of the characteristic Japanese haplotype A24/A11-B54-Cw1-DR4 (9). Consequently, the frequency of DR4 was also increased in the patients in our study (60.0% compared with the control; 37.9%) (2), and the frequency of HLA-DR4 was suggested to be increased due to linkage disequilibrium with the HLA-B54. On the other hand, the association of rheumatoid arthritis with HLA-DR4 is well established in various ethnic groups including Japanese (3, 10, 11). It has also been reported that the frequencies of HLA-B54, B59 and DR4 are increased in Japanese patients with rheumatoid arthritis (12). Takeuchi et al also reported the existence of a putative susceptibility haplotype, B54 or B59-C4B5-DR4.1, in Japanese patients with rheumatoid arthritis (12).

Recently, DR4 has been divided into DR4.1 and 4.2, the former of which is associated with rheumatoid arthritis (13). The DR4 in the present Patient 1 was typed as DR4.1. In rheumatoid arthritis, the lungs are frequently involved and various pleuropulmonary manifestations, including interstitial lung disease, pleural disease, bronchiolitis obliterans, and bronchiolitis obliterans organizing pneumonia (BOOP), have been reported (14). Multiple necrobiotic pulmonary nodules are usually present in patients with rheumatoid arthritis, but the average diameter is 1 to 2 cm (15). On the other hand, the average diameter of the nodular lesions in diffuse panbronchiolitis is 1 to 2 mm (2).

The features in the present patients could easily be distinguished from these manifestations accompanying rheumatoid arthritis on the basis of the clinical manifestations, chest roentgenography findings, and laboratory data. Our patients presented with chronic sinusitis, chronic productive cough, obstructive impairment demonstrated on pulmonary function test, diffuse nodular shadows which showed a characteristic distribution, and elevation of cold hemo-agglutinin titer. It was also noted that both patients demonstrated a favorable response to low-dose, long-term erythromycin therapy. These features suggested that the entity in these patients was diffuse panbronchiolitis rather than pulmonary involvement of rheumatoid arthritis.

At present, we have collected data regarding 56 cases of diffuse panbronchiolitis; among them, four cases including one autopsied case were complicated by rheumatoid arthritis. Three of the patients had had chronic sinusitis from childhood, and had manifested the symptoms and signs of diffuse panbronchiolitis after the onset of rheumatoid arthritis. Because the frequency of HLA-B54 is significantly increased among patients with diffuse panbronchiolitis and since B54 is correlated with DR4 as the extended haplotype, both diffuse panbronchiolitis and rheumatoid arthritis have the same HLA haplotype correlation including B54 and DR4. Therefore, it is likely that more Japanese patients with diffuse panbronchiolitis accompanied by chance with rheumatoid arthritis will be encountered in the future.

Concerning the relationship of rheumatoid arthritis with other pulmonary diseases, accompanying silicosis has been reported (16). South African gold miners with rheumatoid arthritis are more likely to develop silicosis when exposed to silica than are miners without rheumatoid arthritis (16). Furthermore, it has been reported that the frequency of HLA-B54 is also increased in Japanese patients with silicosis (17).

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References