

[CASE REPORT]

Interstitial Pneumonia with HLA-B54 Antigen that Responded Well to Erythromycin

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Abstract:

A 65-year-old Japanese man with interstitial pneumonia demonstrated honeycomb lung with thickened walls on chest high-resolution computed tomography (HRCT) and predominance of neutrophils in the cell fraction of the bronchoalveolar lavage fluid. Although there were no centrilobular nodular or branching shadows on chest HRCT suggestive of diffuse panbronchiolitis, he exhibited sinusitis and had the human leukocyte antigen (HLA)-B54 antigen. With long-term macrolide therapy, the cough and sputum production markedly improved, wall thickening of the honeycomb lung on chest HRCT decreased, and the forced vital capacity increased. Confirming the presence of HLA-B54 antigen may help determine the indication for long-term macrolide therapy in interstitial pneumonia patients.

Key words: interstitial pneumonia, HLA-B54 antigen, diffuse panbronchiolitis, macrolide, erythromycin

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Introduction

Idiopathic pulmonary fibrosis (IPF) has a poor prognosis, with a median survival of 35 months (1). Acute exacerbations and chronic respiratory failure are the causes of death in two-thirds of all cases (1). Pneumonia also increases the risk of mortality during hospitalization for IPF; therefore, prevention of pneumonia is important (2).

Analyses of the microbiota of the lower respiratory tract in IPF have shown that an increased bacterial burden is a poor prognostic factor in IPF (3). Although the antimicrobial effect of trimethoprim-sulfamethoxazole has been verified, it has not been confirmed to improve the prognosis of IPF (4). In addition, a retrospective analysis suggested that macrolide antimicrobial agents may improve the prognosis of IPF, but this has not been fully verified yet (5).

HLA-B54 antigen, which is often carried by East Asians, including the Japanese, has been associated with diffuse panbronchiolitis (DPB) in Japan (6, 7). We have shown previously that HLA-B54 antigen may be a risk factor for the development of pneumonia and is associated with a poor

prognosis in patients with interstitial pneumonia (8). If the presence of the HLA-B54 antigen is a predisposing factor for lower respiratory tract infection, namely DPB, macrolide antimicrobial agents may be useful for patients with interstitial pneumonia carrying the HLA-B54 antigen.

To our knowledge, there are no detailed reports of macrolides improving symptoms, respiratory function tests, or radiographic findings in patients with interstitial pneumonia carrying the HLA-B54 antigen. We herein deliver the first detailed description of this condition through a report of a characteristic case included in a previously published cohort study (8).

Case Report

A 65-year-old Japanese man presented with a chief complaint of chronic cough with sputum that had persisted for approximately 10 years. He had a history of pneumonia in childhood and tuberculous pleurisy at the age of 40 years old and had smoked for 60 pack-years until he was 55 years old. There was no history of occupational dust exposure, use of feather bedding, or bird breeding.

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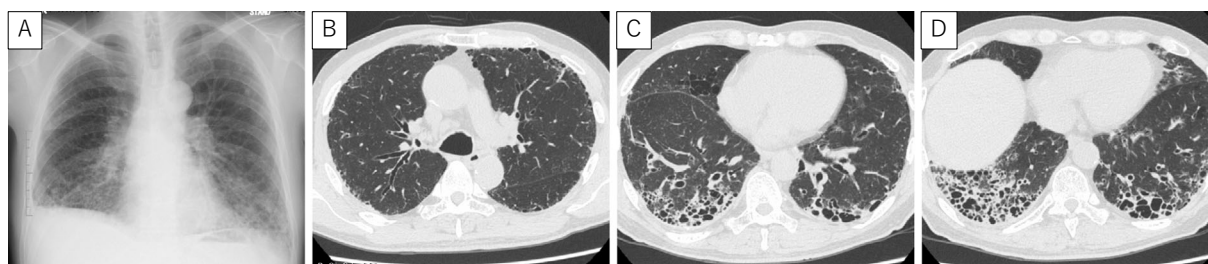


Figure 1. Chest X-ray and high-resolution computed tomography (HRCT) findings at the diagnosis. The chest radiograph shows elevation of the right diaphragm with granular reticular shadows in the bilateral lower lung fields, especially on the left, obscuring the diaphragm and cardiac shadowing (A). Emphysematous changes can be seen just below the pleura in the upper lobe. There are no centrilobar nodular shadows (B). On the dorsal side of the lower lobe, honeycomb lung with thickening of the wall is visible. In some lesions, there is also consolidation around the honeycomb lung. Thickening of the bronchial wall can also be seen (C, D).

A physical examination revealed a body temperature of 36.7°C, pulse rate of 74/min, blood pressure of 126/67 mmHg, and oxygen saturation of 97% on room air. On chest auscultation, fine crackles were heard in both lungs. There were no physical findings suggestive of connective tissue disease (CTD), such as swollen joints or a skin rash. Blood tests showed a mildly elevated inflammatory response with leukocytes of $8,900 \times 10^3/\mu\text{L}$ and C-reactive protein (CRP) of 0.30 mg/dL, but other blood biochemical tests showed no abnormalities. There was an increase in the levels of interstitial pneumonia markers of Krebs von den Lungen-6 (650 U/mL), surfactant protein (SP)-D (337 ng/mL), and SP-A (62.7 ng/mL). Antinuclear antibodies of the speckled type were 80-fold increased, and rheumatoid factor was as high as 262.4 IU/mL, although other autoantibodies suggestive of CTD or vasculitis were negative.

Plain chest radiography showed dulling of the right costophrenic angle and elevation of the right diaphragm. In the lung fields, granular reticular shadows were observed in the bilateral middle and lower lung fields (Fig. 1A). Chest high-resolution computed tomography (HRCT) demonstrated a honeycomb lung centered on the dorsal aspect of the bilateral lower lobes, with thickening of the wall and partial consolidations around it (Fig. 1C, D). In the upper lobes, emphysematous changes were also observed, although there were no granular or branched shadows throughout the lung fields (Fig. 1B). In addition, sinusitis was confirmed by computed tomography.

Respiratory function tests showed no restrictive or obstructive impairment: vital capacity (VC) 3.03 L, %VC 86.1%, forced vital capacity (FVC) 3.00 L, %FVC 85.2%, forced expiratory volume 1 (FEV1) 2.53 L, FEV1% 84.3%, and percentage diffusing capacity of the lungs for carbon monoxide 93.0%. Bronchoscopy revealed abundant sputum in the bilateral lower lobe branches. The recovery rate of bronchoalveolar lavage (BAL) performed at right B8 was 28%. The cell concentration was $19.3 \times 10^5/\text{mL}$, and the fractional distribution of the cells was as follows: macrophages, 28%; lymphocytes, 10%; neutrophils, 59%; eosinophils, 3%;

and CD4/CD8 ratio of 1.4. Culture of the sputum and lavage fluid did not show significant growth.

The imaging findings suggested a usual interstitial pneumonia (UIP) pattern as the base condition; however, considering the consolidation and wall thickening around the honeycomb lung and the endoscopic findings, we considered the coexistence of a chronic lower respiratory tract infection. Rheumatoid arthritis, Sjögren's syndrome, vasculitis, and human T-lymphotropic virus type 1-associated bronchioloalveolar disorder were considered, but all were ruled out. Given the complication of DPB, HLA serotyping was performed, and the patient was found to carry the HLA-B54 antigen. Although the patient had concomitant chronic sinusitis, the diagnosis of DPB could not be made because there were no centrilobular nodular lesions on chest HRCT. A surgical lung biopsy was not performed, and the final diagnosis was unclassifiable idiopathic interstitial pneumonia combined with sinobronchial syndrome.

Since cough and sputum were the main complaints, erythromycin 400 mg/day was started for sinobronchial syndrome. Cough and sputum improved markedly, chest HRCT showed a reduction in the wall thickening of the honeycomb lung (Fig. 2B), and respiratory function test findings improved. However, FVC, which had improved after the start of erythromycin, tended to worsen again. It was judged that the fibrosis of the lung was becoming apparent, and the concomitant administration of nintedanib was initiated (Fig. 2). During the clinical course of 4 years, there was no occurrence of pneumonia.

Discussion

The use of antifibrotic agents has improved the survival rate of IPF patients (9). However, the effect of antifibrotic agents is limited to preventing disease progression; therefore, not all problems associated with IPF treatment have been resolved. Multifaceted treatment approaches aimed at improving the clinical condition of IPF patients are needed. Increased bacterial burden according to an analysis of mi-

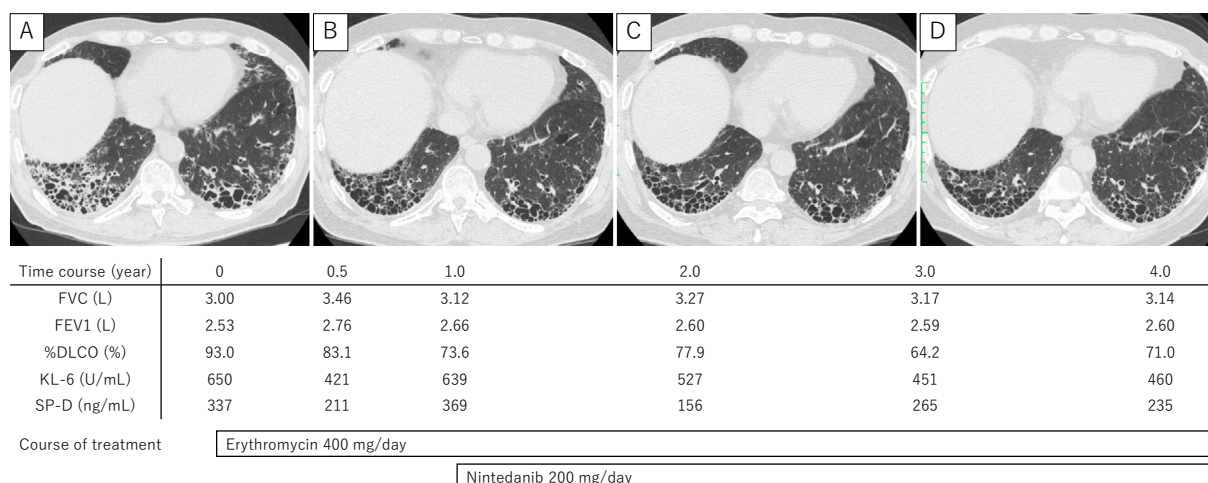


Figure 2. High-resolution chest computed tomography (HRCT) and clinical course. Chest HRCT at the time of the diagnosis shows thickening of the walls of the honeycomb lung and consolidation (A). After erythromycin was started, the wall thickening of the honeycomb lung was reduced on chest HRCT. Chest HRCT images obtained one year (B), two years (C), and four years (D) after the diagnosis are shown. After the initiation of erythromycin, respiratory function test findings and markers of interstitial pneumonia showed improvement; however, they deteriorated again, and nintedanib was initiated one year after the diagnosis.

crobiota in the BAL as well as increased neutrophils in the BAL are considered to be poor prognostic factors in IPF (3, 10). Approaches to reducing the bacterial burden of the lower respiratory tract and neutrophilic airway inflammation in IPF may thus be key to improving the management of IPF patients.

In DPB, a chronic lower respiratory tract infection, low-dose macrolides that have no antibacterial activity against *Pseudomonas aeruginosa* are effective, even in cases with persistent *P. aeruginosa* infection (11). HLA-B54 inheritance has been associated with the occurrence of DPB in Japanese individuals (6, 7). Confirmation of the presence of HLA-B54 not only identifies a DPB predisposition but can also be a factor for determining the indication of macrolide therapy for treatment of interstitial pneumonia. In our study of HLA antigens in Japanese patients with interstitial pneumonia, the prevalence of HLA-B54 was 19.4% (8). The usefulness of macrolide therapy for IPF may be validated by appropriate case selection.

Wall thickening and surrounding consolidation of the honeycomb lung on chest HRCT may indicate an increase in the inflammatory cells in the local area. Such images are commonly associated with concomitant infections, such as aspergillosis and nontuberculous mycobacteria, but they also occur in myeloperoxidase-antineutrophil cytoplasmic antibody (MPO-ANCA)-positive IPF and have been shown to be effectively treated with immunosuppressive therapy (12). In the presence of wall thickening and surrounding consolidation of the honeycomb lung, it is important to perform sputum culture and bronchoscopy to identify local infection. Furthermore, it is important to evaluate CTD- and vasculitis-associated autoantibodies, including MPO-ANCA. It may also be worth considering the possibility of a predilection

for sinobronchial syndrome, such as the coexistence of sinusitis or presence of HLA-B54.

Although the patient described in this report did not meet the diagnostic criteria for DPB, he responded well to macrolide therapy. While bacterial cultures from sputum and bronchoalveolar lavage fluid showed negative results, bronchoalveolar lavage fluid showed neutrophilic inflammation. Macrolide antibiotics, including erythromycin, reportedly have anti-inflammatory effects (13). In addition, the administration of azithromycin to adult patients with cystic fibrosis does not appear to cause obvious changes in the microbiota in sputum (14). These findings suggest that erythromycin did not work through an antibacterial effect but rather through the control of neutrophilic airway inflammation in the present case. A temporary improvement in FVC was also achieved following the initiation of macrolides; however, in the long term, fibrosis of the lungs progressed in stages despite the use of a combination of anti-fibrotic agents. Nevertheless, cough, sputum, and wasting demonstrated continuous improvement, and there was no occurrence of pneumonia in this patient. Provided there is proper selection of cases, macrolide therapy for interstitial pneumonia may be beneficial.

While the relationship between lung microbiota and HLA is unclear at present and remains a topic for future research, confirmation of the presence of the HLA-B54 antigen may be a useful way to determine the indication for macrolide therapy in patients with interstitial pneumonia.

We have received written consent from the patient for the publication of this report.

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

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