Diffuse Panbronchiolitis and Rheumatoid Arthritis-Associated Bronchiolar Disease: Similarities and Differences


There is a considerable overlap between diffuse panbronchiolitis (DPB) and bronchiolar disease associated with rheumatoid arthritis (RA). The present study assessed how these conditions could be differentiated. The subjects included 25 DPB patients and 15 RA patients with bronchiolar disease (RA-BD). Patients with either condition had chronic cough, purulent sputum, dyspnea and coarse crackles. Most patients with either DPB or RA-BD had a history of sinusitis as well as elevated cold hemagglutinin titers and decreased levels in partial pressure of oxygen (PaO2), forced expiratory volume in one second (FEV1.0) and V 25/Ht. On histological examination, both conditions also shared various histological patterns although panbronchiolitis lesions were more common in DPB than RA-BD (68% vs 20%) and bronchiolar obliteration appeared to occur at more proximal sites in RA-BD than DPB. However, there were important differences: long-term treatment with erythromycin had less effect in RA-BD than DPB, and the frequency of HLA B54 tended to be higher in DPB than RA-BD (50.0% vs 22.2%), suggesting that they are distinct conditions.

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Key words: bronchiolitis, erythromycin

Introduction

Diffuse panbronchiolitis (DPB) was first described by Yamanaka et al in 1969 (1), and was established as a distinct clinicopathological entity through a nationwide study in Japan (2). Patients with DPB have purulent sputum, cough, and dyspnea (3). The pathological features of this disease include chronic inflammation and accumulation of foamy cells in the walls of the respiratory bronchioles and the adjacent alveolar regions [known as panbronchiolitis lesions (PB lesions)] (3). DPB used to be a fatal disease due to progressive impairment of pulmonary function, with 5-year and 10-year survival rates in 1983 of 62.1% and 33.2%, respectively (4). However, long-term erythromycin (EM) treatment was found to be so effective (5) that the 10-year survival rate is now higher than 90% (6). DPB has been largely restricted to Japan and shows a strong association with HLA B54, which is limited to some Asian people such as the Japanese, Chinese, and Koreans (7). However, DPB is now occurring in areas other than Japan, such as North America, Europe, China and Korea (3, 8).

Bronchiolar diseases such as cellular bronchiolitis, follicular bronchiolitis (FB), and bronchiolitis obliterans (BO) are known to be associated with rheumatoid arthritis (RA) (9). Our recent study demonstrated that most RA patients with bronchiolar disease show a chronic clinical course with a productive cough, impaired respiratory function, and diffuse shadows on chest radiographs (10), suggesting that there is a considerable overlap between DPB and RA-associated bronchiolar disease (RA-BD) although no previous reports have indicated such marked similarity.

Therefore, we investigated the similarities and differences of DPB and RA-BD based on the long-term follow-up of patients who were diagnosed from histological and clinical findings. We determined that DPB and RA-BD share many pathological and clinical features, but EM treatment had a greater effect on DPB than RA-BD.
Patients and Methods

The subjects were 40 Japanese patients, including 25 with DPB and 15 with RA plus bronchiolar disease. The study was approved by the Human Studies Committee of the institutes. DPB was diagnosed clinicopathologically according to the guideline (3). RA was defined by the American Rheumatism Association criteria, and the presence of Sjögren’s syndrome was carefully excluded. RA was staged as described previously (11). None of DPB patients received EM at the time of the study. In contrast, 9 of 15 RA-BD patients had disease-modifying

Figure 1. Histological pattern of bronchiolar lesions. A) Cellular bronchiolitis in the lung from a DPB patient. Infiltration of small mononuclear cells is seen in the respiratory bronchiole (HE, ×25). B) FB in the lung from a DPB patient. Hyperplasia of lymph follicles is seen around the bronchiole (HE, ×20). C) BO (respiratory type) in the lung from a DPB patient (arrow) (EVG, ×20). D) BO (non-respiratory type) in the lung from a patient with RA. Lumens of non-respiratory bronchioles are occupied by granulation tissues (arrows) (EVG, ×20). E) PB lesion in the lung from a DPB patient. There is an accumulation of foamy macrophages in the walls of respiratory bronchioles (arrow) (HE, ×25).
antirheumatic drugs. All patients underwent open lung biopsy or thoracoscopic lung biopsy to determine the cause of chronic respiratory symptoms such as productive cough and dyspnea and/or abnormal chest X-ray findings.

Lung biopsy specimens were obtained from multiple lobes, fixed in 10% formaldehyde using an inflation apparatus, and stained with hematoxylin-eosin (HE) and elstica van Gieson (EVG) stains. Histologic sections were reviewed by at least two observers, who were blinded to the clinical data of the patients. The bronchiolar lesions were observed in all cases and classified as follows (9): 1) cellular bronchiolitis (Fig. 1A), 2) FB (Fig. 1B), 3) BO (only obliteration by intraluminal polypoid tissue was included and constrictive BO was excluded due to significant differences in the evaluations of the two observers, and BO was classified as "respiratory" or "non-respiratory" depending on whether the lesions were mainly localized in the respiratory bronchioles or more proximal bronchioles) (Figs. 1C, D), and 4) PB lesions (Fig. 1E).

A chest X-ray film was obtained before lung biopsy and was assessed by two observers who were blinded to the clinical and pathological data. The following radiographic features were assessed: 1) overinflation, 2) small nodular shadows, and 3) bronchial wall thickening.

For follow-up, chest X-ray and lung function tests were repeated at least every 6 months.

**Statistical analysis**

Data were analyzed by Student's unpaired t-test and differences were considered significant at p<0.05.

**Results**

**Clinical and laboratory findings**

The clinical and laboratory features of DPB and RA-BD are summarized in Table 1. Four DPB patients (16%) and 5 RA-BD patients (33%) were current smokers and none of the other patients had a smoking history. The mean age at presentation was significantly lower in DPB than RA-BD. Patients with DPB or RA-BD had chronic respiratory symptoms, including, cough, purulent sputum, and less frequently dyspnea. Coarse crackles were audible in all patients with either disease. Associated sinusitis was common in both conditions. Sputum culture revealed bacteria such as *Hemophilus influenzae* and *Pseudomonas aeruginosa* in 70% and 60% of DPB and RA-BD patients, respectively. Both conditions were associated with elevated cold hemagglutin titer. HLA typing was performed in 9 RA-BD patients and 16 DPB patients, revealing that the frequency of B54 tended to be higher in DPB than RA-BD (50.0% vs 22.2%), although the difference was not statistically significant.

**Histological findings**

Table 2 summarizes histological findings. PB lesions were significantly more common in DPB (68%) than in RA-BD (20%), whereas non-respiratory BO was more frequently observed in RA-BD than in DPB (16% vs 47%). However, there was no specific histological pattern for either DPB or RA-BD. In fact, several histological patterns coexisted in a single patient.

We also investigated whether B54 positivity was associated with appearance of the DPB-related findings including PB lesions and respiratory BO in RA-BD patients. The results indicated that there was no such association.

**Lung function tests**

Although there was considerable variation in severity, decreased levels of forced expiratory volume in one second (FEV₁0%) V₂5/Ht and partial pressure of oxygen (PaO₂) were common in both conditions (Table 3). When these parameters at the first visit were compared, PaO₂ level was significantly lower in DPB than RA-BD. Patients with DPB or RA-BD had chronic respiratory symptoms, including, cough, purulent sputum, and less frequently dyspnea. Coarse crackles were audible in all patients with either disease. Associated sinusitis was common in both conditions. Sputum culture revealed bacteria such as *Hemophilus influenzae* and *Pseudomonas aeruginosa* in 70% and 60% of DPB and RA-BD patients, respectively. Both conditions were associated with elevated cold hemagglutin titer. HLA typing was performed in 9 RA-BD patients and 16 DPB patients, revealing that the frequency of B54 tended to be higher in DPB than RA-BD (50.0% vs 22.2%), although the difference was not statistically significant.

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DPB and RA-Associated Bronchiolar Disease

Table 2. Histological Findings

<table>
<thead>
<tr>
<th>Findings</th>
<th>DPB (n=25)</th>
<th>RA-BD (n=15)</th>
<th>Statistical analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cellular bronchiolitis</td>
<td>100</td>
<td>100</td>
<td>N.S.</td>
</tr>
<tr>
<td>FB</td>
<td>48</td>
<td>73</td>
<td>N.S.</td>
</tr>
<tr>
<td>BO (Total)</td>
<td>32</td>
<td>47</td>
<td>N.S.</td>
</tr>
<tr>
<td>Respiratory</td>
<td>16</td>
<td>7</td>
<td>N.S.</td>
</tr>
<tr>
<td>Non-respiratory</td>
<td>16</td>
<td>47</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>PB</td>
<td>68</td>
<td>20</td>
<td>p&lt;0.01</td>
</tr>
</tbody>
</table>

N.S.: Not significant.

Table 3. Lung Function Tests

<table>
<thead>
<tr>
<th></th>
<th>DPB</th>
<th>RA-BD</th>
<th>Statistical analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>%VC (%)</td>
<td>76.7±16.5</td>
<td>83.1±15.6</td>
<td>N.S.</td>
</tr>
<tr>
<td>FEV1,0% (%)</td>
<td>65.7±11.3</td>
<td>71.6±11.2</td>
<td>N.S.</td>
</tr>
<tr>
<td>V25/Ht (l/s/m)</td>
<td>0.24±0.18</td>
<td>0.37±0.34</td>
<td>N.S.</td>
</tr>
<tr>
<td>PaO2 (Torr)</td>
<td>69.7±10.0</td>
<td>77.8±8.3</td>
<td>p&lt;0.05</td>
</tr>
</tbody>
</table>

Results are expressed as the mean ± SD.

lower in DPB than in RA-BD (p<0.05).

With special attention to the possible correlation between the appearance of a certain histological pattern and mode of impairment in lung function, we carried out further clinicopathological studies. However, no specific relationship was found.

Chest X-ray findings

The frequency of small nodules was significantly higher in DPB (100%) than RA-BD (67%). In contrast, the frequency of overinflation and bronchial wall thickening was similar in the two conditions (Table 4).

Treatment and prognosis

Two DPB patients and 3 RA-BD patients were lost to follow-up, so 23 and 12 patients were evaluated, respectively. Twenty-three DPB patients and 9 RA-BD patients were treated with EM at 600 mg/day for a mean of 37.1 and 33.1 months, respectively. Three patients with RA-BD did not receive specific treatment because of their mild symptoms. EM treatment produced improvement of chronic productive cough in all patients, except for 1 with DPB. However, the efficacy rate was significantly higher in DPB than RA-BD (p<0.01) when the effect was evaluated from the improvement of FEV1,0. Therapy was defined as “effective” when the FEV1,0 was increased by more than 15% after treatment (Fig. 2).

Table 4. Chest X-ray Findings

<table>
<thead>
<tr>
<th>Findings</th>
<th>DPB (n=25)</th>
<th>RA-BD (n=15)</th>
<th>Statistical analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overinflation</td>
<td>42</td>
<td>60</td>
<td>N.S.</td>
</tr>
<tr>
<td>Small nodule</td>
<td>100</td>
<td>67</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td>Bronchial wall thickening</td>
<td>42</td>
<td>53</td>
<td>N.S.</td>
</tr>
</tbody>
</table>

N.S.: Not significant.

Figure 2. Changes of the FEV1,0 after treatment with EM. The result was evaluated as “effective” when the FEV1,0 increased by more than 15% after treatment. *: p<0.05.

Discussion

Comparison of the clinical findings indicated that the frequency of dyspnea and sinusitis was lower in RA-BD than DPB. It was also found that the mean PaO2 level at the initial visit was lower in DPB than RA-BD, whereas the frequency of small nodule was significantly higher in DPB than RA-BD. However, these differences did not seem to be fundamental, and rather our data indicated that the two conditions largely share clinical, laboratory, and radiological features, except for the presence of joint lesions in RA-BD.

We have previously reported that RA-BD is basically a chronic disease (10), while BO associated with RA has been characterized by acute or subacute progressive dyspnea with a fatal outcome in other previous studies (12–18). Although further investigation is needed to explain this discrepancy, it is
possible that the number of patients with chronic RA-BD was underestimated and the uncommon acute or subacute cases were overemphasized due to their poor prognosis (19).

Histological examination showed that PB lesions, which are reported to be the most distinctive feature of DPB (3), were more frequent in DPB than RA-BD (68% vs 20%), while bronchiolar obliteration appeared to occur at more proximal sites in RA-BD than DPB. However, it should be noted that the same histological patterns were seen in both conditions, indicating that the pathological features also showed overlap.

Long-term treatment with low-dose EM produced less improvement of FEV$_1$0 in RA-BD than in DPB. EM has been shown to improve the prognosis of DPB (5). Macrolides such as EM and roxithromycin are reported to induce the suppression of neutrophil chemotactic activity in the lungs (20, 21), as well as inhibiting cytokine production by neutrophils (IL-8) (21), macrophages (IL-1) (22), lymphocytes (IL-2) (22), and bronchial epithelial cells (IL-6) (23), suggesting that the suppression of inflammation is at least partly responsible for the clinical effect of these drugs. However, the exact mechanism involved needs further study, and DPB should be carefully distinguished from other conditions until it is clarified how EM induces a good effect in the disease.

Although the present study failed to show a significant difference in the frequency of HLA B54 between DPB and RA-BD (probably due to the limited number of patients), DPB tends to have a high association with B54, whereas RA-BD does not. B54 was identified in 50% of our DPB patients, and this percentage is comparable to that found in a previous study on DPB (63.2%) (7). In contrast, the frequency of B54 in RA-BD (22.2%) was close to that reported in a normal Japanese population (11.4%) (7).

We conclude that DPB and RA-BD are distinct entities based on the differing response to EM and the possible difference in association with HLA B54. Better understanding of the etiology of RA and DPB would be helpful for distinguishing these two conditions.

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References