Centrilobular Nodules Correlate With Air Trapping in Diffuse Panbronchiolitis During Erythromycin Therapy*

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Background: Low-dose erythromycin therapy improves airflow limitation and airway inflammation in patients with diffuse panbronchiolitis (DPB). However, to our knowledge there has been no study to determine whether physiologic improvement during erythromycin therapy correlates with radiologic findings.

Study objective: To clarify whether improvement in pulmonary function correlates with specific changes on chest CT.

Design: The relationship between five CT findings and five pulmonary function parameters was evaluated before and 3 months after low-dose erythromycin therapy in 24 patients with DPB retrospectively.

Results: After erythromycin therapy, the predicted percentage of vital capacity (%VC; 87.0 ± 3.07% vs 98.9 ± 3.39%; p = 0.00006) and 50% of the maximum midexpiratory flow rate of FVC (1.41 ± 0.26 L/s vs 1.61 ± 0.27 L/s; p = 0.03) significantly increased, and the residual volume/total lung capacity ratio (RV/TLC%; 44.5 ± 1.93% vs 40.7 ± 1.83%; p = 0.0019) significantly decreased, but the FEV1 to FVC ratio and 25% of the maximum expiratory flow rate of FVC did not. In five CT findings, centrilobular nodules (3.7 ± 0.4 vs 1.5 ± 0.3; p = 0.0001), peripheral bronchiolar wall thickness (3.8 ± 0.3 vs 2.6 ± 0.4; p = 0.0007), and peripheral bronchiolectasis (2.8 ± 0.3 vs 2.2 ± 0.4; p = 0.0058) had significantly improved, whereas low attenuation area and central bronchiectasis had not. There were positive correlations of improved scores of centrilobular nodules with improved %VC (r = 0.58, p = 0.0062) and RV/TLC% (r = 0.64, p = 0.0022).

Conclusions: Decreased air trapping in DPB correlates with an improvement of centrilobular nodules, which reflects the obstructive lesions of bronchioles during the erythromycin therapy. (CHEST 2001; 120:198–202)

Key words: air trapping; centrilobular nodules; CT; diffuse panbronchiolitis; pulmonary function test

Abbreviations: DPB = diffuse panbronchiolitis; FEV1/FVC% = FEV1 to FVC ratio; RV/TLC% = residual volume to total lung capacity ratio; V25 = 25% of the maximum midexpiratory flow rate of FVC; V50 = 50% of the maximum midexpiratory flow rate of FVC; %VC = predicted percentage of vital capacity

Diffuse panbronchiolitis (DPB) is a progressive disease characterized by chronic recurrent bronchiolitis and peribronchiolitis, affecting the respiratory bronchiole. The characteristic pathologic features of DPB are thickening of the respiratory bronchiolar wall with infiltration of lymphocytes and plasma cells, consequently causing obstruction or stenosis of respiratory bronchioles.1,2 Chest radiography demonstrates mild-to-moderate overinflation in the initial stage of the disease. With progression, small nodular shadows and tramlines in the lower lung fields appear; in the advanced stage, diffuse bronchiectasis occurs.3

DPB is common in East Asia, and human leukocyte antigen B54 is a frequent haplotype (63.2%), appearing in 11.4% of Japanese patients.4 In the past, the prognosis of this disease was poor and most patients suffered from continuous infection and died of chronic respiratory failure in spite of combined antibiotic administration. In 1987, it was first reported that low-dose (400 to 600 mg/d), long-term (at least 4 weeks) administration of erythromycin was
effective for DPB.\textsuperscript{5} Since then, erythromycin therapy has been used in the treatment of patients with DPB,\textsuperscript{6–8} and it has been confirmed that erythromycin raised the survival rate markedly.\textsuperscript{2}

Although erythromycin therapy improves physiologic and radiographic findings,\textsuperscript{5–7} it is unknown whether radiologic improvement reflects pulmonary function in patients with DPB following erythromycin therapy. In order to address this problem, we evaluated the radiologic images on CT by using a scoring method and investigated the relationship between CT findings and pulmonary function tests before and 3 months after erythromycin therapy.

\textbf{Materials and Methods}

\textbf{Patients}

All patients were recruited from Kushiro City General Hospital, Sapporo Medical University Hospital, and Minami Ichijo Hospital during the period from 1991 through 1997, and radiologic findings and clinical information were evaluated retrospectively. Thirty-three patients received a diagnosis of DPB during this period. The clinical diagnostic criteria for DPB\textsuperscript{1,2} were as follows: (1) symptoms of chronic cough, sputum, and dyspnea on exertion; (2) physical signs consisting of coarse crackles, rhonchi, or wheezes on auscultation of the chest; (3) bilateral fine nodular shadows, mainly in the lower lung fields often with hyperinflation of the lungs on chest radiograph; (4) FEV\textsubscript{1}, 70% of predicted on pulmonary function tests, and PaO\textsubscript{2}, 80 mm Hg on blood gas analysis; (5) elevated cold hemagglutinin titers 64 times; (6) history or coexistence of chronic paranasal sinusitis; and (7) transbronchial lung biopsy specimens, if obtained, showing thickness of the wall of respiratory bronchiole with infiltration of lymphocytes, plasma cells, and foamy histiocytes expanding into the peribronchiolar area.

Of the 33 patients, 24 patients (13 men and 11 women; age range, 30 to 84 years; mean ± SE age, 60 ± 3 years) underwent complete pulmonary function tests and CT scans both before and 3 months after erythromycin therapy.

\textbf{Scoring Method of CT Findings}

Chest CT scans were obtained on an SCT5000TH scanner (Shimazu; Kyoto, Japan) or a TCT scanner (model 60A; Toshiba; Tokyo, Japan) using 5-mm collimation at 10-mm intervals from the sternal notch to below the diaphragm during breath-holding after deep inspiration. The lungs were imaged at the window width of 1,500 Hounsfield units and the window level of –700 Hounsfield units.

All CT images were independently reviewed and scored by three qualified chest radiologists. Each CT score of the airway was based on five findings: (1) low attenuation areas in the outer zone of the lungs; (2) small nodules with a centrilobular distribution in both lower lungs; (3) peripheral bronchiolar wall thickness; (4) peripheral bronchiectasis; and (5) central bronchiectasis. For each CT finding, scores of 0 to 2 were given on the basis of the following grades: 0 = absent, 1 = sparsely or slightly existent, and 2 = dense or clearly apparent (Fig 1). The observers reviewed every CT image of all patients before and 3 months after erythromycin therapy. The CT score of each finding was determined by the sum of the scores obtained from the three observers; therefore, the highest possible value was 6 and the lowest was 0. We calculated the CT score difference between before and after treatment by the following formula:

\[ \Delta \text{CT scores} = \text{scores of before} - \text{scores of after} \]

\textbf{Pulmonary Function Tests}

CT scans and pulmonary function tests using a spirometer (Chestac 25; Chest; Tokyo, Japan) were performed on the same
day. The predicted percentage of vital capacity (%VC), the FEV$_1$ to FVC ratio (FEV$_1$/FVC%), the residual volume to total lung capacity ratio (RV/TLC%), 50% of the maximum midexpiratory flow rate of FVC (V50) and 25% of the maximum midexpiratory flow rate of FVC (V25), and the ratio of V50 to V25 were assessed. The changes of %VC and RV/TLC% before and 3 months after erythromycin therapy were calculated by the following formulas:

\[
\Delta%VC = \text{values of after} - \text{values of before} \\
\DeltaRV/TLC\% = \text{values of after} - \text{values of before}
\]

**Statistical Analysis**

All results were expressed as mean ± SE. Differences in each CT score both before and 3 months after erythromycin therapy were compared using the Wilcoxon signed-rank test. Differences in the pulmonary function tests before and after erythromycin therapy were compared using Student’s paired t test. Spearman’s rank correlation test was used to assess the relationship between the score difference in CT findings and the pulmonary function test parameters. Differences and correlation were considered statistically significant at p < 0.05.

**RESULTS**

**Changes of the CT Score**

Three months of erythromycin therapy improved CT images in 22 of 24 patients with DPB, but not in the other 2 patients. No adverse effects of erythromycin therapy appeared during this study. Every CT score both before and after erythromycin therapy was assessed. The changes of %VC and RV/TLC% before and 3 months after erythromycin therapy were compared using Student’s paired t test. Spearman’s rank correlation test was used to assess the relationship between the score difference in CT findings and the pulmonary function test parameters. Differences and correlation were considered statistically significant at p < 0.05.

**Pulmonary Function Tests**

The results of the pulmonary function tests are demonstrated in Table 1. %VC increased significantly from 87.0 ± 3.07% to 98.9 ± 3.39%, and RV/TLC% decreased significantly from 44.5 ± 1.93% to 40.7 ± 1.83%, whereas V50 increased significantly from 1.41 ± 0.26 to 1.61 ± 0.27 L/min. However, there were no significant differences in FEV$_1$/FVC% and V25.

**Relationship Between CT Scores and Pulmonary Function Tests**

A moderately positive correlation between the decrease in centrilobular nodules and the Δ%VC (r = 0.58, p = 0.0062) was found (Fig 2). Moreover, a positive correlation between the decrease in centrilobular nodules and the ΔRV/TLC% (r = 0.64, p = 0.0022) was disclosed (Fig 3). No significant correlations were obtained between other CT scores and pulmonary function tests.

**DISCUSSION**

Erythromycin therapy has been established as a standard treatment for DPB. More than 80% of patients with DPB show good radiologic and physiologic responses to this therapy. In our study, 22 of 24 patients responded to erythromycin therapy, and this result was consistent with previous reports. However, the remaining two subjects were poor responders. Their clinical symptoms and obstructive changes in pulmonary functions before erythromycin therapy were more severe. Moreover, these two patients had more severe airway lesions; their peripheral bronchiolar wall thickness scores were 6 and

### Table 1—Comparison of CT Scores and Pulmonary Function Tests Before and After Erythromycin Therapy

<table>
<thead>
<tr>
<th>Variables</th>
<th>Before</th>
<th>After</th>
<th>p Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT score†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low attenuation areas</td>
<td>0.8 ± 0.2</td>
<td>0.5 ± 0.2</td>
<td>NS</td>
</tr>
<tr>
<td>Centrilobular nodules</td>
<td>3.7 ± 0.4</td>
<td>1.5 ± 0.3</td>
<td>0.0001</td>
</tr>
<tr>
<td>Peripheral bronchiolar wall thickness</td>
<td>3.8 ± 0.3</td>
<td>2.6 ± 0.4</td>
<td>0.0007</td>
</tr>
<tr>
<td>Peripheral bronchiolectasis</td>
<td>2.8 ± 0.3</td>
<td>2.2 ± 0.4</td>
<td>0.0058</td>
</tr>
<tr>
<td>Central bronchiolectasis</td>
<td>2.1 ± 0.4</td>
<td>1.6 ± 0.4</td>
<td>NS</td>
</tr>
<tr>
<td>Pulmonary function tests‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>%VC</td>
<td>87.0 ± 3.07</td>
<td>98.9 ± 3.39</td>
<td>0.00006</td>
</tr>
<tr>
<td>FEV$_1$/FVC%</td>
<td>63.2 ± 2.95</td>
<td>64.6 ± 2.39</td>
<td>NS</td>
</tr>
<tr>
<td>RV/TLC%</td>
<td>44.5 ± 1.93</td>
<td>40.7 ± 1.83</td>
<td>0.0019</td>
</tr>
<tr>
<td>V50, L/s</td>
<td>1.41 ± 0.26</td>
<td>1.61 ± 0.27</td>
<td>0.03</td>
</tr>
<tr>
<td>V25, L/s</td>
<td>0.39 ± 0.08</td>
<td>0.40 ± 0.08</td>
<td>NS</td>
</tr>
</tbody>
</table>

*All data are expressed as mean ± SE. NS = not significant.
†Differences are considered statistically significant at p < 0.05.
‡Compared using Wilcoxon sign-rank test.
§Compared using Student’s paired t test.
Peripheral bronchiolectasis scores were 6 and 5, and central bronchiectasis scores were 6 and 5, respectively. Moreover, the centrilobular nodule scores also increased during erythromycin therapy. These high CT scores before erythromycin therapy represented an irreversible stage of the disease. Kudoh et al2 reported that the prognosis of patients with advanced DPB was poor in spite of erythromycin therapy.

In our study, significant improvements were found in centrilobular nodules, peripheral bronchiolar wall thickness, and peripheral bronchiolectasis. Ichikawa et al9 demonstrated the reversibility of airway lesions on CT in response to erythromycin therapy. They reported a significant reduction in the extent of centrilobular nodules, the periairway thickening, and the extent of mucus plugging in conjunction with an improvement of the pulmonary function tests. These results concur with those of our study. However, they did not investigate the correlation between each CT finding and each pulmonary function test.

We found a significant relationship between a decrease in centrilobular nodules and an increase in both Δ%VC and ΔRV/TLC%. These findings mean that there is an increase in the %VC but a decrease in the RV/TLC%. Centrilobular nodules are pathologically correlated with respiratory bronchiolitis and with peribronchiolar inflammatory cell infiltration.3,9,10 These nodules represent obstructive or stenotic changes in the respiratory bronchioles in patients with DPB (Fig 4). It is reasonable to suppose that erythromycin therapy improves these abnormalities around respiratory bronchioles, which may cause air trapping through a check valve mechanism.

The limitation of our study was that we evaluated only radiologic and physiologic findings. The improvements in the radiologic abnormalities were not documented because lung biopsy specimens were not obtained before or after erythromycin therapy. Therefore, our interpretation of the radiologic pathologic correlation depends on previously reported results.10 We conclude that CT images of centrilobular nodules in patients with DPB reflect

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air trapping and that they may be a useful radiologic marker to assess the effect of low-dose erythromycin therapy.

REFERENCES