Diffuse panbronchiolitis (DPB) is a disease in which chronic inflammation manifests mainly in the region of the respiratory bronchiole between the terminal bronchiole and the pulmonary parenchyma (1).

Its clinical onset usually occurs after the age of 40 or 50, and men are more commonly affected than women. Patients often have a past history of chronic paranasal sinusitis. Insidious and chronic expectoration of purulent sputum is found in the early stages of the disease, and progressive exertional dyspnea appears later. In the late stages, large amounts of purulent sputum and severe bronchiolar dilatation are present. Finally, patients succumb to respiratory failure (2).

Effectiveness of Low-Dose Erythromycin Therapy in Diffuse Panbronchiolitis: Assessment with Serial Changes on High-Resolution CT and Pulmonary Function Test

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Purpose: To determine evaluate the clinical effectiveness of low-dose erythromycin (EM) therapy in patients with diffuse panbronchiolitis (DPB), and to correlate the pulmonary function testing (PFT) changes seen at serial high-resolution CT (HRCT) with the results of post-treatment.

Materials and Methods: We retrospectively evaluated 13 DPB patients [seven men and six women aged 23 - 68 (mean, 46.2) years] who had undergone PFT, HRCT, and transbronchial or open lung biopsy prior to long-term, low-dose EM therapy (250 mg twice daily for more than six months). The interval between initial and follow-up study ranged from 7 to 32 (mean, 16.6 ± 8.0) months, and we compared the changes in HRCT findings and PFT parameters before and after treatment.

Results: At HRCT after EM therapy, the extent of centrilobular nodules \( p = 0.006 \), peripherial bronchiolar wall thickening \( p = 0.02 \), and areas of low attenuation \( p = 0.011 \) decreased significantly, while FVC and FEV1 showed significant increases: FVC, from 2.47 ± 0.83 to 2.74 ± 0.95 \( p = 0.028 \); and FEV1, from 1.66 ± 0.75 to 1.95 ± 0.87 \( p = 0.02 \). As the extent of peripherial bronchiolar wall thickening \( r = - 0.609, p = 0.047 \) and areas of low attenuation \( r = - 0.687, p = 0.041 \) decreased at serial HRCT, FVC and FEV1 increased significantly.

Conclusion: Long-term follow-up HRCT findings showed that for DPB patients, low-dose EM provides effective treatment. In addition, HRCT appears to be valuable for the objective evaluation of responses to EM therapy.

Index words: Bronchiolitis
Lung, CT
Lung, diseases
The HRCT findings of DPB include the presence of centrilobular nodules, branching linear opacity, dilated peripheral airways with thick walls, and decreased lung attenuation in peripheral areas due to air trapping caused by bronchiolar obstruction (2-4).

Until the development of erythromycin (EM) treatment, DPB had an extremely poor prognosis. Kudoh et al. (5, 6), however, reported that long-term EM therapy is effective in such patients. Ichikawa et al. (7, 8) found that DPB involves neutrophil-mediated inflammation, and it provides effective treatment because EM inhibits the excessive accumulation of neutrophils in the small airways. The accurate evaluation of HRCT findings in DPB is therefore very important. HRCT scans after EM therapy in DPB patients demonstrated that centrilobular and branching linear areas of high attenuation decrease in number and size, though airway dilatation and decreased lung attenuation in peripheral areas remain unchanged or increase slightly (4, 9, 10).

Though it is known that in DPB patients the physiologic/ radiologic findings after EM therapy reflect improvements in their condition, including improved pulmonary function (10), it has not been shown whether improvements demonstrated radiologically are reflected by the results of PFT after low-dose, long-term EM therapy. The objectives of this study were to evaluate the clinical effectiveness of low-dose long-term EM therapy in DPB patients by identifying changes in serial HRCT findings, and to correlate these with the results of PFT.

Materials and Methods

Patients

Thirteen DPB patients, seven men and six women aged 23-68 (mean, 46.2) years, were enrolled in our study. In all 13, clinical diagnostic criteria of DPB were satisfied after reviewing the histological specimens obtained by means of transbronchial (n=8) or open lung biopsy (n=5). If the pathologic findings were inadequate (n=6), diagnosis was supported by the clinical findings, as follows: symptoms of chronic cough, sputum, and dyspnea on exertion, and physical signs which included rales and rhonchi. Chest radiography revealed diffuse, disseminated, fine nodular shadows, mainly in the lower lung, and lung hyperinflation, while lung function studies revealed at least three of the following abnormalities: FEV1/FVC <70%; vital capacity <80%; residual volume >150%, or ratio of residual volume to total lung capacity >45%; PaO2 <80 mm Hg. All five patients who underwent open lung biopsy had lesions typical of panbronchiolitis, namely aggregates of foamy lymphoid cells within the walls of the respiratory bronchioles and adjacent alveolar ducts. Microbiologic studies such as bronchoalveolar lavage (BAL), were also performed, and in which all patients showed marked neutrophilia, and radiological examination of the sinuses revealed chronic paranasal sinusitis in all patients. All underwent HRCT and PFT prior to treatment involving therapy lasting 6-28 (mean, 13.8±7.3) months with low-dose EM (250 mg twice daily, Dae Woong, Seoul, Korea). The interval between initial and follow up study ranged from seven to 32 (mean, 16.6±8.0) months, while that between initial CT scanning and PFT was 1-28 (mean, 15) days and that between follow-up CT and PFT was 1-7 (mean, 3.5) days. Follow-up CT and PFT was both performed within the seven days of ending EM therapy.

Scoring Method for CT findings

Initial HRCT scans were obtained at the time of diagnosis, before the initiation of therapy. For all HRCT, whether initial or follow-up, a Somatom Plus-4 scanner (Siemens, Erlangen, Germany) was used, with 1.0-mm collimation at 2.0-cm intervals from the apex to the base of the lung during breath-holding after full inspiration. Expiratory scans were obtained at six evenly divided levels of the whole lung. A high -spatial-frequency algorithm was used for image reconstruction, and high-resolution images were displayed at window levels appropriate for pulmonary parenchyma [window width: -750 HU, 1500 HU] and the mediastinum [window width: 35 HU, 350 HU]. In all patients, HRCT scans obtained at similar but not exactly the same levels were available for anatomic comparison. Changes in the depiction of each abnormality were evaluated at follow-up HRCT.

All HRCT images were independently reviewed and scored by two radiologists, being assessed for the presence and extent of (1) small centrilobular nodules in both lower lobes, (2) peripheral bronchiolar wall thickening, (3) peripheral bronchiolar dilatation, (4) a peripheral low attenuation area, and (5) central bronchiectasis before and after EM therapy. A centrilobular nodule less than 1cm in diameter and appearing as an opaque area centered within the lobule was considered 'small', bronchiolar wall thickening was subjectively assessed by comparing the bronchiolar wall of normal lung with that of areas of abnormal opacity, while bronchiolar di-
lation was regarded as present when the diameters of the bronchi were greater than those of accompanying pulmonary arteries. Bronchiectasis is defined as irreversible bronchial dilatation, with thickening of the bronchial wall, and was categorized as predominantly central if located in the inner third of the lung, or peripheral if located in the outer third. An area of low attenuation was considered present if expiratory scans failed to demonstrate normal increases in lung attenuation in more than five isolated or more than three contiguous secondary pulmonary lobules. For each CT finding, scores of 0 to 2 were assigned on the basis of the following criteria: 0 = absent; 1 = sparsely or slightly evident; and 2 = dense or clearly apparent. The CT score for each finding was determined by the sum of the scores assigned by each of the two observers; thus, the highest possible value was 4 and the lowest was 0. The \( \kappa \) test demonstrated fair to good agreement between the two assessments (\( \kappa = 0.83 \)), differences in each CT score before and after erythromycin therapy were compared using Wilcoxon’s signed rank test. Differences and correlation were considered statistically significant at \( p < 0.05 \).

### Pulmonary Function Tests

Before and after EM therapy, all patients underwent pulmonary function testing using a 2200 spirometer (Sensor Medics Co, Model number 2200, U.S.A.) and following the American Thoracic Society (ATS) guidelines. After three expiratory efforts, the best result was chosen for analysis and compared with predicted values. The PFT result [predicted percentage of forced vital capacity [%FVC] and forced expiratory volume in one second [FEV1]] was available for all patients; FEV1 was obtained by referring to maximal expiratory flow volume curves. Differences in PFT parameters before and after treatment were compared using Student’s paired t test, and differences and correlation were considered statistically significant at \( p < 0.05 \). Changes in the CT findings and those of PFT were correlated using Spearman’s rank correlation coefficient.

### Results

CT scores before and after EM therapy are shown in Tables 1 and 2. In all 13 patients (100%), initial HRCT revealed the presence of centrilobular nodules and areas of low attenuation. In 11 (84.6%), there was peripheral bronchiolar wall thickening; in 12 (92.3%), peripheral

<table>
<thead>
<tr>
<th>Table 1. Comparison of HRCT and Pulmonary Function Tests of Patients with DPB before and after Erythromycin Therapy</th>
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<td><strong>Variable</strong></td>
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</tr>
<tr>
<td>CT score</td>
</tr>
<tr>
<td>Centrilobular nodule</td>
</tr>
<tr>
<td>Peripheral bronchiolar wall thickening</td>
</tr>
<tr>
<td>Peripheral bronchiolar dilatation</td>
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<tr>
<td>Low attenuation areas</td>
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<tr>
<td>Central bronchiectasis</td>
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*All data are expressed as mean± SD, NS = not significant
+Differences are considered statistically significant at \( p < 0.05 \)
+ Compared using Wilcoxon’s signed rank test.
bronchiolar dilatation was noted; in two (15.4%), central bronchiectasis was present. HRCT after EM therapy demonstrated the following improvement: in centrilobular nodules in 11 patients (84.6%), in peripheral bronchiolar wall thickening in eight (61.5%), and air trapping in six (46.2%), in peripheral bronchiolar dilatation in two (15.4%). For centrilobular nodules ($p=0.006$) and peripheral bronchiolar wall thickening ($p=0.02$), areas of low attenuation areas ($p=0.011$), the improvement was significant (Fig. 1).

The results of the pulmonary function testing are shown in Table 3. FVC and FEV₁ increased significantly after low-dose EM therapy: FVC, from 2.47±0.83 to 2.74±0.95 ($p=0.028$); FEV₁, from 1.66±0.75 to 1.95±0.87 ($p=0.02$); FEV₁/FVC, from 65±11.35 to 68.9±8.41 ($p=0.101$).

The greater the reduction in peripheral bronchiolar wall thickening follow-up HRCT and the greater the decrease in areas of low attenuation, the greater the significant increase in FVC and FEV₁ [respectively, $r = 0.609$, $p=0.047$] (Fig. 2). The more peripheral bronchiolar wall thickenings decreased on follow-up HRCT, the more FEV₁ significantly increased (Fig. 3).
The clinical effectiveness of EM therapy, through its unique pharmacologic mechanisms, has been established in patients with DPB [8-12], and its effects might include immuno-modulating effects other than antibacterial activity. Akira et al. [9] reported a high success rate with EM therapy, noting that in the treated group, centrilobular and branched linear areas were fewer and smaller after low-dose EM therapy (200 mg three times daily). For our patients, treatment was different (250 mg twice daily), but equally effective clinically. Furthermore, reductions in number of centrilobular nodules, peripheral bronchiolar wall thickening and areas of low attenuation were significantly reduced. Ichikawa et al. [4] has described the differences in HRCT findings before and after EM therapy after short-term follow-up, noting that the extent of the small nodular opacities was significantly reduced. Lesions such as these, as well as mucus plugging and thickening around airways, suggested the presence of reversible airway lesions, and the extent of airway ectasia suggested irreversible airway lesions. Our results are similar. Small centrilobular nodules, peripheral bronchiolar wall thickening of dilated airways, and areas of low attenuation were significantly reduced after EM therapy. However, in three patients who showed no improvement, centrilobular nodules as well as peripheral bronchiolar wall thickening and bronchioloectasis were still apparent in both lower lobes. In addition, centrilobular nodules were superseded by airway dilatation as the disease progressed. These three underwent more long-term EM therapy than other patients and showed initial HRCT findings of severe peripheral bronchioloectasis and central bronchiectasis, suggesting that these did not respond to EM therapy and that treatment became ineffective as DPB progressed.

Successful treatment of chronic infections of the lower respiratory tract is clinically important because persistent infection can lead to progressive pulmonary dysfunction and respiratory failure. Pseudomonas aeruginosa often occurs in patients with DPB, and Pseudomonas superinfection has been found to be a major reason for the poor prognosis. Ichikawa et al. [6] demonstrated the utility of bronchioloalveolar lavage (BAL) for DPB in adult patients, reporting a significant difference in cell populations recovered by BAL between DPB and chronic bronchitis. Analysis of BAL fluid culture demonstrated the existence of marked neutrophilia in DPB patients, suggesting that this played an important role in the development of DPB. There was, though, no evidence of bacterial, fungal, mycobacterial or mycoplasmal infection. In our study, all DPB patients showed marked

### Table 3. Comparison of Pulmonary Function Tests Before and After Erythromycin Therapy

<table>
<thead>
<tr>
<th>Pulmonary function test*</th>
<th>Before</th>
<th>After</th>
<th>p Value*</th>
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<tbody>
<tr>
<td>FVC</td>
<td>2.47±0.83</td>
<td>2.76±0.94</td>
<td>0.028</td>
</tr>
<tr>
<td>FEV1</td>
<td>1.66±0.75</td>
<td>1.95±0.87</td>
<td>0.02</td>
</tr>
<tr>
<td>FEV1/FVC</td>
<td>65±11.35</td>
<td>68.9±8.41</td>
<td>0.101</td>
</tr>
</tbody>
</table>

*Compared using Student’s paired t-test

Differences are considered statistically significant at p < 0.05

and \( p = 0.047 \) (Fig. 2); \( r = 0.687 \), and \( p = 0.041 \) (Fig. 3).

### Discussion

DPB is a chronic inflammatory lung disease of unknown causes. Histologically, chronic inflammatory airway diseases diffusely involve both the right and left lungs, being characterized by the interstitial accumulation of foamy cells with lymphoid cells in the walls of a respiratory bronchioles and adjacent alveolar ducts with alveoli, and extension of these inflammatory changes toward the peribronchial tissues. In the advanced stage, narrowing and constriction of respiratory bronchioles and secondary ectasia of proximal terminal bronchioles occur [1].

The usefulness of HRCT in the evaluation of both the location and severity of airway lesions is well documented in patients with DPB. Akira et al. [2,8] stated that their HRCT findings closely reflected the clinical stages and pathologic process of DPB. In earlier stages, only small nodules are seen at HRCT, but as the disease progresses, these decrease in number as ductal opacity increases. In the final stage, bronchiectasis with bronchiolectasis occurs, and in some patients, the centrilobular nodule initially observed progresses to dilatation of the proximal airway. In our study, initial HRCT revealed mainly centrilobular nodules, tree-in-bud, and branching linear areas. Initial PFT showed reduced FEV1 values. After EM treatment, HRCT demonstrated marked reductions in the size of centrilobular nodules, in peripheral wall thickening and in areas of low attenuation. FEV1 also showed marked improvement.

According to this result, centrilobular nodules, peripheral bronchiolar wall thickening and areas of low attenuation show a reversible response after low-dose EM therapy and are possible predictors of FEV1 improvement. Thus, we know that in DPB patients, the HRCT findings closely reflected the clinical stages.

The clinical effectiveness of EM therapy, through its
neutrophilia at BAL, and in ten who had been temporarily treated with antimicrobial agents including ceftazidime (Fortum, Glaxo Wellcome, Italy), on the basis of the findings of sputum and BAL fluid Gram stain and cultures, analysis of BAL fluid culture demonstrated Pseudomonas infection.

We found that PFT parameters such as the FVC and FEV\textsubscript{1} increased significantly after EM treatment. Ichikawa et al. [4] and Yamada et al. [10] reported that conditions such as bronchiolar inflammation, mucus plugging, and thickening around airways might be important causes of pulmonary dysfunction. After EM therapy, significantly increased vital capacity and 50% of the maximum mid-expiratory flow rate of FVC correlated with improvement in centrilobular nodules. We thought that in our cases, the changes in the HRCT findings after EM therapy might correlate with the improved PFT parameters. Therefore, however, in our cases, no significant correlation between centrilobular nodules and PFT, even though the nodules improved after EM therapy. The peripheral bronchiolar wall thickening and areas of low attenuation observed at CT significantly correlated with the changes seen at PFT, however. This difference between our findings and these previously reported might be due to differences in the interval between initial HRCT and initial PFT. In the study by Yamada et al. [10] CT scanning and PFT were performed on the same day, but, in our cases, the interval between initial CT scanning and PFT ranged from one to 28 days. For this reason, although follow-up PFT findings did not change on follow-up in some patients, the extent of centrilobular nodules decreased markedly at follow-up HRCT.

In conclusion, long-term follow up CT after EM therapy showed that the extent of centrilobular nodules, peripheral bronchiolar wall thickening and areas of low attenuation decreased significantly. Pulmonary function also showed marked improvement. Long-term, low-dose EM therapy is, therefore, effective in the treatment of DPB patients. HRCT appears to be valuable for the objective evaluation of clinical response to EM therapy, and the observed changes in HRCT findings correlate closely with those of PFT.

References

1. 1, 3-아미노-글로신을 이용한 레르타민(erythromycin)을 250mg, 3회/일로 6일간 투여하였다.
2. 13예 중 7예(54.6%)에 흐트러움이 발생하였으며, 6예의 병력은 23예의 HRCT와 일치하였다.
3. 32예의 70.1±8.0(평균±표준편차)에서 FVC, FEV1, FOR,أمر, 13, 32에서 2.47±0.83 to 2.74±0.95 (p=0.028), FEV1, from 1.66±0.75 to 1.95±0.87(p=0.02).