Diffuse panbronchiolitis—The response and recurrence after erythromycin therapy

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Background/purpose: Diffuse panbronchiolitis (DPB) is a rare clinicopathological entity. To date, no cohort study of DPB has been conducted in Taiwan. Erythromycin treatment improves the clinical outcome of DPB; however, whether relapse will occur or not is unclear. Herein, we report the first retrospective cohort of DPB patients in one medical center in Taiwan, including their clinical presentation and outcomes of erythromycin treatment.

Methods: The study comprised a retrospective cohort analysis of 27 patients with a confirmed diagnosis of DPB. Clinical, radiological, and laboratory parameters were analyzed, and the course and outcome of erythromycin treatment were examined.

Results: The mean age at symptom onset was 56.6 ± 18.5 years, and the time between symptom onset and a correct diagnosis was 4.3 ± 4.2 years. The percentages of patients with centrilobular micronodules on chest computed tomography, obstructive ventilator impairment with hypoxemia, and an elevated cold agglutinin titer were 72%, 37%, and 78%, respectively. After erythromycin treatment, 22 of the 27 (81.5%) patients showed clinical improvement, of whom six suffered a relapse. Four of these six patients clinically improved after a second course of erythromycin treatment.

Conclusion: Erythromycin therapy was suitable for DPB in our experience. In this study cohort, 27% experienced a relapse, of which two-thirds of the patients improved after a second course of erythromycin treatment.

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Introduction

Diffuse panbronchiolitis (DPB) is a chronic inflammatory disease of unknown etiology that affects the distal airways, and predominantly the transition zone between the respiratory bronchioles and alveoli. If left untreated, it can progress to bronchiectasis, respiratory failure, and death. The prognosis of DPB is poor, and the reported 10-year survival rate was only 33.2% in 1983. Since long-term treatment with erythromycin was introduced in 1984, the 10-year survival rate has improved to 90%. However, the incidence of relapse after completing a course of erythromycin treatment and the response rate to a second course of treatment remain unclear. Nevertheless, an early and correct diagnosis followed by immediate erythromycin treatment is most important for DPB patients.

DPB was first described by Yamanaka et al in 1969 in Japan as a suppurative and obstructive airway disease that coexists with sinusitis. DPB was subsequently recognized in other parts of Asia, including Korea and China; however, the clinical presentations appear to be slightly different between these areas. To date, only a few cases of DPB have been reported in Western countries. The first case of DPB in Taiwan was reported in 1991, and to the best of our knowledge, only seven case reports and one article including a total of 11 patients with findings on plain chest film and high-resolution computed tomography (HRCT) have been published in Taiwan. The scarcity of published data raises the concern that most clinicians may be unfamiliar with DPB, and that it could be underdiagnosed in Taiwan.

It is unknown whether the clinical presentations and response to erythromycin treatment in Taiwanese patients are similar to those observed in Japanese patients. Hence, the aim of this study was to investigate the clinical profiles and responses to erythromycin treatment in 27 Taiwanese DPB patients, including the relapse rate and the response to a second course of erythromycin treatment.

Methods

Patients

This retrospective study was approved by the local Institutional Review Board (IRB) of Chang Gung Memorial Hospital (IRB approval number 103-3795C).

From January 1, 2002, to January 1, 2014, 645 patients who received the serum cold hemagglutinin (CHA) test were screened retrospectively. We sequentially excluded patients who were younger than 18 years and those who received the CHA test for a reason other than suspected DPB (Figure 1). We further excluded patients who did not meet the following diagnostic criteria of DPB:

1. Persistent cough, sputum, and exertional dyspnea
2. History or current symptoms of chronic sinusitis
3. Bilateral, diffuse, small nodular shadows on a plain chest radiograph or centrilobular micronodules on chest computed tomography (CT) images
4. Coarse crackles

The ratio of forced expiratory volume in 1 second (FEV1) to forced vital capacity (FVC) (FEV1/FVC) < 70% and partial pressure of oxygen (PaO2) < 80 mmHg (10.64 kPa)

CHA titer of ≥ 64

These criteria were proposed by a working group of the Ministry of Health and Welfare of Japan. All patients enrolled for final analysis should fulfill the first three criteria and at least two of the remaining criteria. Two of our patients were also diagnosed to have DPB by histopathological examination.

The medical records and radiological reports were evaluated by two pulmonologists to confirm the accuracy of the extracted information, which included demographic data, arterial blood gas analysis, blood CHA test, pulmonary function test, radiological findings, and pathological findings.

The duration of erythromycin treatment was calculated according to the medical records. The patient’s response to erythromycin treatment (failure, clinical improvement, or radiological improvement) and the recurrence of DPB (worsening of clinical symptoms and the need for a second course of erythromycin treatment, as judged by the physician) were also documented according to the medical records.

Statistical analysis

Data were analyzed using Predictive Analytics SoftWare Statistics 18 (SPSS Inc., Chicago, IL, USA). Continuous data were presented as mean ± standard deviation, and categorical data were presented as number and percentage. The paired t test was used to compare pulmonary test results before and after erythromycin treatment. All tests were two tailed, and a p value < 0.05 was considered to be statistically significant.

Results

Demographic data

Twenty-seven patients were enrolled in the final analysis, with a male-to-female ratio of 1.08. The mean age at symptom onset was 56.6 ± 18.5 years, and the mean age at diagnosis of DPB was 60.5 ± 17.1 years (Table 1). The
interval between the first clinic visit and the correct diagnosis was 4.3 ± 4.2 years. Surprisingly, only 22% of the patients had a history of smoking, however, 37% were diagnosed and treated for chronic obstructive pulmonary disease. In addition, 44% of the patients were diagnosed and treated for asthma.

Clinical manifestations

All of the patients presented with chronic sinusitis, chronic cough, and copious sputum production. Other common presentations included hemoptysis (30%), exertional dyspnea (30%), and body weight loss (15%). On physical examination, all of the patients were found to have end-inspiratory crackles, and 59% also had wheezing.

Laboratory findings

Arterial blood gas analysis on room air was available for 19 of the 27 (70%) patients. The PaO2 and partial pressure of carbon dioxide (PaCO2) values are shown in Table 1. Mild hypercapnia without hypoxemia was noted in our cohort.

All of the patients received a serum CHA test. According to the definition of our laboratory, 90% of our patients had a positive result (CHA titer ≥ 16). However, only 78% of our patients met the diagnostic criteria of DPB (CHA titer ≥ 64; Table 2).

Pulmonary function

Pulmonary function tests were available for 25 of the 27 (93%) patients. The FEV1/FVC, FEV1, FVC, and forced expiratory flow 25–75% (FEF25–75%) values are presented in Table 1. Although the mean FEV1/FVC was < 70%, nine of the 25 (36%) patients demonstrated pure restrictive ventilatory impairment. In addition, only 22 of the 25 (88%) patients had narrowing of the small airway as defined by FEF25–75% < 65% of predicted values.

Radiological manifestations

Twenty-six of the 27 (96%) patients had a bilateral, diffuse, small nodule pattern on plain chest film. Twenty-five of the 27 (93%) patients underwent chest CT around the time of their diagnosis, and they were scanned in the supine position (scan thickness 1 mm and slice interval 10 mm) at the end of inspiration. Only 72% of these patients had small nodules distributed in a centrilobular fashion and connected to small linear opacities, the so-called tree-in-bud pattern, which was described previously as CT classification type II by Odaka et al.19 Peripheral air trapping, emphysema, interstitial change, and bronchiectasis were also observed in some of the patients.
Pathological findings

To further confirm the diagnosis, two of our patients underwent open lung biopsy. Both of them showed the typical pathological changes of DPB including diffuse, bilateral chronic airway inflammation with some centrilobular chronic interstitial inflammation; the classic feature of foamy cells in the walls of respiratory bronchioles, alveolar ducts, and alveoli; intraluminal acute inflammation; follicular bronchiolitis; bronchiectasis; organizing pneumonia; and postobstructive lipoid pneumonia.

Diagnostic criteria

The percentages of the patients fulfilling each diagnostic criterion are summarized in Table 2. As mentioned, all patients had typical symptoms, a history of chronic paranasal sinusitis, crackling sounds while breathing, and typical imaging findings. However, only 30% of the patients complained of exertional dyspnea (Table 1). Surprisingly, eight patients had bilateral, diffuse, small nodular shadows on plain chest radiography but did not have typical centrilobular micronodules on chest CT. Only 37% of the patients had both FEV1/FVC < 70% and PaO2 < 80 mmHg, and 78% of the patients had a CHA titer of ≥ 64%.

Outcome of erythromycin treatment

According to current guidelines, all patients were treated with erythromycin (400–600 mg/d orally) since their DPB diagnosis. Table 3 presents the outcomes of erythromycin treatment in our DPB patients. After treatment, 22 of the 27 patients (82%) showed improvement clinically; however, only 56% of the patients demonstrated improvements in radiological findings. Of the five patients who did not respond to erythromycin treatment, four progressed and needed long-term oxygen therapy during the observation period, and two of these patients eventually became ventilator dependent. Two of the 27 patients died during the follow-up period: one due to a head injury and the other due to pneumonia-related respiratory failure.

Sixteen of the 27 (59%) patients received pulmonary function tests after completing erythromycin treatment. Figure 2 shows the comparisons of pulmonary function tests before and after treatment. After erythromycin treatment, significant improvements in FEV1 (before vs. after, 40.3 ± 15.8% of predicted vs. 50.1 ± 23.8% of predicted; p < 0.05) and FVC (before vs. after, 45.2 ± 15.2% of predicted vs. 57.6 ± 21.7% of predicted; p < 0.05) were noted. However, the improvement in FEF25–75% was not statistically significant (before vs. after, 31.9 ± 19.5% of predicted vs. 37.1 ± 25.7% of predicted; p = 0.341). Overall, 75%, 75%, and 56% of the patients had improvements in FVC, FEV1, and FEF25–75%, respectively.

Six of the 22 patients (27%) experienced recurrence of clinical symptoms after completing erythromycin treatment. The treatment duration of these patients was 7.5 ± 8.6 months, and the symptom-free interval was 19.9 ± 12.7 months. The second treatment course of erythromycin had a duration of 7.4 ± 7.4 months. Four of the six (67%) patients achieved clinical improvement again. One patient was lost to follow up after receiving 1 month of treatment, and one patient failed to respond to the second course of erythromycin treatment and became ventilator dependent (Table 4).

Discussion

Only a few studies about DPB in Taiwan have been published (Table 5), and this study is the first and largest retrospective cohort study in Taiwan to date. We investigated the clinical presentations and response to erythromycin treatment, and found that 27% of the DPB patients experienced recurrence of symptoms 20 months after treatment, two-thirds of whom clinically improved after the second course of erythromycin treatment. To the best of our knowledge, this is the first study to report on the management of recurrence of DPB.

Most epidemiological studies on DPB have come from Japan. In Japan, patients with DPB are predominantly men (approximately 58–67%) and nonsmokers (approximately 66%). Similarly, in this study, 52% of the patients were men and 78% were nonsmokers. The clinical presentations including age, chronic sinusitis history, chronic productive cough, and crackling sounds while breathing were also similar between Taiwanese and Japanese patients. A few case reports have mentioned hemoptysis or body weight loss. In our cohort, 30% of the patients reported hemoptysis and 19% had unexplained body weight loss. A delayed diagnosis and misdiagnosis of DPB are common. In one case series from Hong Kong, the time from onset of symptoms to diagnosis ranged from 1 year to 4 years. Another case series from China reported that 95.6% of their patients had been misdiagnosed with other diseases such as chronic bronchitis (44%), pulmonary tuberculosis (28%), and asthma (5%). In our cohort, the interval between onset of symptoms and diagnosis was 4.3 ± 4.2 years, and 81% of the patients were misdiagnosed and initially treated for chronic obstructive pulmonary disease or asthma. The high misdiagnosis rate and delayed diagnosis suggest that most clinical physicians are not familiar with DPB and highlight the importance of testing for DPB in patients with chronic productive cough and chronic sinusitis and with a poor response to chronic obstructive pulmonary disease or asthma therapy.

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Outcomes of diffuse panbronchiolitis patients after erythromycin treatment (n = 27).</th>
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</thead>
<tbody>
<tr>
<td>Value</td>
<td></td>
</tr>
<tr>
<td>Follow-up period (mo)</td>
<td>27.7 ± 16.4</td>
</tr>
<tr>
<td>Treatment duration (mo)</td>
<td>7.9 ± 7.7</td>
</tr>
<tr>
<td>Clinical improvement</td>
<td>22 (82)</td>
</tr>
<tr>
<td>Radiological improvement</td>
<td>15 (56)</td>
</tr>
<tr>
<td>Both clinical and radiological improvement</td>
<td>13 (48)</td>
</tr>
<tr>
<td>Recurrence</td>
<td>6 (22)</td>
</tr>
<tr>
<td>Long-term oxygen use</td>
<td>4 (15)</td>
</tr>
<tr>
<td>Ventilator dependent</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Mortality</td>
<td>2 (7)</td>
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</tbody>
</table>

Values given as mean ± standard deviation or n (%).
Current guidelines include six criteria to diagnose DPB, and definite cases should fulfill the first three criteria and at least two of the remaining criteria. Our study is the first to report the percentages of patients fulfilling each criterion (Table 2). Although all of the patients had bilateral, diffuse, small nodular shadows in radiological images, only 72% of the patients had centrilobular micronodules on chest CT, and only 30% of the patients showed an obstructive pattern in pulmonary function tests and $\text{PaO}_2 < 80 \text{ mmHg}$. An increased CHA titer has been reported in most Japanese patients, whereas it has been reported to be almost negative in Chinese patients. In our cohort, 78% of the patients had a CHA titer of $\geq 64$. The percentages of patients who fulfilled the criteria of typical chest CT findings, hypoxemia, and positive CHA seemed to be lower in Taiwanese patients than in Japanese patients, possibly due to ethnic differences.

DPB affects the small airways, and FEF$_{25-75\%}$ in spirometry is thought to be sensitive in detecting small airway obstruction. In this study, 64% of the patients had FEV$_1$/FVC $< 70\%$ and 88% had FEF$_{25-75\%} < 65\%$ of the predicted value. FEF$_{25-75\%}$ therefore seems to be more sensitive than FEV$_1$/FVC in diagnosing DPB. However, a significant improvement in FEV$_1$/FVC was found after erythromycin treatment with no significant improvement in FEF$_{25-75\%}$ in this study. Further studies are needed to evaluate the value of FEF$_{25-75\%}$ in patients with DPB.

Based on clinical experience, erythromycin is identified as the drug of choice for the treatment of DPB. Many studies from Japan have established the efficacy of erythromycin therapy in improving symptoms, lung function, CT scan changes, and survival rate. In this study, 81.5% of the patients experienced symptom relief following erythromycin treatment; however, only 55.6% of the patients achieved radiological improvement after erythromycin treatment. A review article by Azuma and Kudoh in 2006 demonstrated a significant improvement in vital capacity (before vs. after, 63.4 $\pm$ 18.1% of predicted vs. 82.3 $\pm$ 19.4% of predicted) and FEV$_1$ (before vs. after, 60.5 $\pm$ 11.6% of predicted vs. 65.7 $\pm$ 12.0% of predicted) after erythromycin treatment, which is consistent with our findings (Figure 2).

Table 4 Clinical courses of diffuse panbronchiolitis patients who experienced recurrence after erythromycin treatment ($n = 6$).

<table>
<thead>
<tr>
<th>Value</th>
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<tbody>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Duration of first erythromycin</td>
</tr>
<tr>
<td>treatment course (mo)</td>
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<tr>
<td>Disease-free interval (mo)</td>
</tr>
<tr>
<td>Duration of second erythromycin</td>
</tr>
<tr>
<td>treatment course (mo)</td>
</tr>
<tr>
<td>Clinical improvement after second</td>
</tr>
<tr>
<td>course of erythromycin treatment</td>
</tr>
</tbody>
</table>

Values given as mean $\pm$ standard deviation or $n$ (%).

Figure 2 Changes in lung function in the diffuse panbronchiolitis patients after erythromycin treatment. FVC and FEV$_1$ were significantly improved whereas there were no significant differences in changes of FEV$_1$/FVC and FEF$_{25-75\%}$ after erythromycin treatment. FEF$_{25-75\%}$ = forced inspiratory flow at 25–75% of the pulmonary volume; FEF = forced expiratory flow; FEV$_1$ = forced expiratory volume in 1 second; FVC = forced vital capacity.
these results together make BALF neutrophil and IL-8 potential makers to evaluate the efficacy of erythromycin and treatment duration. Further research is warranted to confirm this hypothesis.

According to current guidelines, the treatment duration should range from 6 months to 2 years, however, the precise duration of treatment remains unclear. A reasonable point at which therapy can be terminated is after the resolution of the symptoms and the disappearance of centrilobular nodules on HRCT scans. Once treatment has finished, the patient must be followed up for relapse of symptoms and HRCT, as recurrence has been documented even after lung transplantation.

Of note, six of our patients experienced recurrence of symptoms after stopping erythromycin treatment, and the mean treatment duration was 7.5 ± 8.6 months. Four of these patients took erythromycin for < 6 months and their average disease-free interval was 23.2 months. The remaining two patients took erythromycin for > 1 year and their average disease-free interval was 13.3 months. Further investigations are necessary to clarify the relationship between treatment duration and recurrence rate. Moreover, five males (83%) experienced recurrence, which implies that male gender could be a risk factor for recurrence. However, a larger sample size is necessary to prove this hypothesis. Although DPB has been widely studied for over 50 years, few studies have focused on recurrence. We hope that the current case can elicit interest and prompt further research on this issue.

There are several limitations to this study. First, we assumed that all of the DPB patients in our hospital received a CHA test, and thus we defined DPB patients as those who had received a CHA test. This assumption may have caused underestimation of the case number because not every physician considers CHA titer as a diagnostic tool for DPB. Considering that DPB is a rare disease and that there is no International Classification of Diseases, Ninth Revision, Clinical Modification code for DPB, our method may be the most practical way of enrolling patients retrospectively. In addition, this was a retrospective study using existing data that were recorded for reasons other than research. Some documentation was incomplete, and this may have affected the statistical analysis. However, this study is the first and largest cohort study of DPB in Taiwan, and it may serve as a pilot study for future perspective studies.

We reported the clinical presentation and treatment outcomes of Taiwanese DPB patients. Compared with Japanese patients, fewer patients in this study had an elevated CHA titer, obstructive ventilator impairment, and hypoxemia. Overall, 27% of our DPB patients experienced a relapse after completing the first course of erythromycin treatment, most of whom were male. Two thirds of the patients who relapsed had a good response to a second course of erythromycin treatment. Further studies are needed to investigate the risk factors of recurrent DPB, such as the duration of erythromycin treatment and gender.

References