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Diffuse panbronchiolitis—The response and recurrence after erythromycin therapy

Min-Chun Chuang [a,b], Yu-Ting Chou [a], Yu-Ching Lin [a], Meng-Jer Hsieh [a], Ying-Huang Tsai [a,*]

[a] Department of Pulmonary and Critical Care Medicine, Chiayi Chang-Gung Memorial Hospital, Taiwan
[b] Graduate Institute of Clinical Medical Sciences, College of Medicine, Chang Gung University, Taiwan

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.

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.[1] If left untreated, it can progress to bronchiectasis, respiratory failure, and death.[2] 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%.[3,4] 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[2] 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 [5,6]; 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.[7,8] The first case of DPB in Taiwan was reported in 1991,[9] 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.[10-17] 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
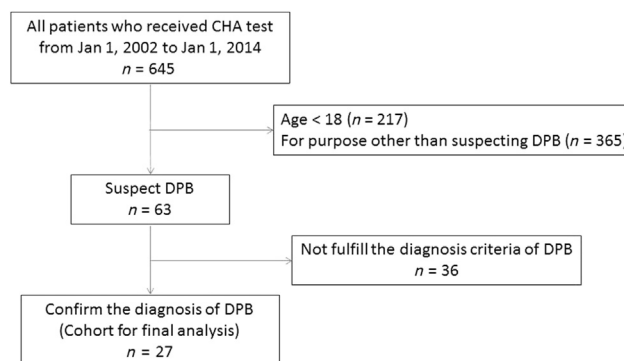
Figure 1 Flowchart for selecting the cohort of DPB patients. CHA = cold agglutinin; DPB = diffuse panbronchiolitis.

(5) The ratio of forced expiratory volume in 1 second (FEV1) to forced vital capacity (FVC) (FEV1/FVC) < 70% and partial pressure of oxygen (PaO$_2$) < 80 mmHg (10.64 kPa)
(6) CHA titer of $\geq$ 64

These criteria were proposed by a working group of the Ministry of Health and Welfare of Japan.[18] 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 $\pm$ 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 $\pm$ 18.5 years, and the mean age at diagnosis of DPB was 60.5 $\pm$ 17.1 years (Table 1). The