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Persistent impairment on spirometry in chronic eosinophilic pneumonia: a longitudinal observation study (Shizuoka-CEP study)

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ABSTRACT

Background: Chronic eosinophilic pneumonia (CEP) is characterized by the accumulation of eosinophils in the lung with unknown etiology. Although systemic corticosteroid administration leads to dramatic improvement, nearly half the patients with CEP experience relapse and some develop persistent impairment of pulmonary function. However, predictive factors for this persistent impairment have not been determined.
Objective: To investigate the occurrence of persistent impairment of pulmonary function in CEP and determine its predictive factors.
Methods: This observational study consisted of 133 consecutive patients with CEP who were followed for longer than 1 year. Spirometry was performed at the time of diagnosis and at follow-up.
Results: During the observational period (6.1 ± 4.1 years), relapse occurred in 75 patients (56.4%). Remarkably, 42 patients (31.6%) had a persistent pulmonary function defect (27 obstructive, 10 restrictive, and 4 obstructive and restrictive cases) at the last evaluation. Logistic analyses showed that the relapse was associated with neither persistent obstructive nor restrictive defects. Persistent obstructive defect was significantly associated with the comorbidity of asthma and obstructive defect at the initial CEP diagnosis, whereas persistent restrictive defect was significantly related to reticulation at high-resolution computer tomography and restrictive defect at diagnosis.
Conclusion: Persistent impairment of pulmonary function is common in CEP. Concurrent asthma and obstructive defects at diagnosis were predictors for persistent obstructive impairments, whereas reticulation at high-resolution computer tomography and restrictive defect at diagnosis predicted persistent restrictive impairment. Attention should be paid to these persistent impairments in the management of CEP.

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Introduction

Chronic eosinophilic pneumonia (CEP) is an idiopathic disorder characterized by marked eosinophil infiltration in the lung.[1–3] Although severe hypoxia or respiratory failure is sometimes found, administration of systemic corticosteroid therapy rapidly alleviates clinical symptoms and radiologic abnormalities.[4–8] Moreover, symptomatic and radiographic "relapses" are common in the course of this disease. More than 50% of patients with CEP have been reported to have relapse during the tapering off or after cessation of steroid treatment.[4–8] Although readministration or resumption of corticosteroid therapy also rapidly leads to resolution, some patients with CEP receive oral corticosteroid therapy indefinitely.

Asthma is the most common complication of CEP and is concurrent with CEP in more than 50% of patients.[4–8] The severity of concurrent asthma has been reported to increase after the onset of CEP.[6] In patients with asthma, airway remodeling attributed to underlying persistent eosinophilic inflammation results in decreased pulmonary function.[9–11] In addition, CEP occasionally leads to physiologically important and irreversible fibrosis.[12] Thus, onset of CEP, repeated relapse, and concurrent asthma could synergistically prolong lung function impairment.

Because mortality from CEP is extremely unusual, the management goal of CEP has been to control the disease with the smallest cumulative dose of corticosteroid to minimize a potential relapse and decrease corticosteroid-related adverse effects. In this context, we recently conducted a randomized, open-label, parallel-group study to compare relapse rates between short-term (3-month) and long-term (6-month) corticosteroid treatments.[4] This study showed no significant difference in the cumulative rate of relapse between the 2 regimens, suggesting that the short-term regimen is a potential option for treatment of CEP in terms of relapse rate. Although pulmonary function at the last evaluation was not routinely assessed in our previous study, some patients underwent spirometry at that time. Surprisingly, we found that approximately 30% of them had persistent impairment of pulmonary function. This suggests that, in addition to relapse, persistent impairment of pulmonary function should be included in the management of CEP. However, few studies have examined persistent impairment of pulmonary function in CEP. Thus, the present study was conducted to investigate the occurrence of persistent impairment of pulmonary function in patients with CEP and elucidate its predictive factors.

Methods

Subjects

This multicenter study was conducted in 11 referral hospitals covering 3.5 million people in Shizuoka, Japan. From January 2000 to March 2016, patients with CEP who had follow-ups lasting longer than 12 months were enrolled in this study. CEP was diagnosed according to the following criteria: (1) clinical symptoms suggestive of CEP (eg, fever, cough, or dyspnea on exertion) lasting longer than 2 weeks; (2) infiltrative shadows on chest radiographs; (3) eosinophilia in bronchoalveolar lavage (BAL) fluid and/or evident eosinophilic infiltration in lung biopsy specimens; and (4) exclusions of infection (ex eosinophilia in BAL >15% and/or eosinophils >5 high-power fields).[4] Asthma was defined according to the Global Initiative for Asthma (GINA).[13]

According to our previous study,[4] relapse was defined as at least 2 of the following: (1) recurrence of subjective symptoms; (2) increase in infiltrative shadows on chest radiographs and/or high-resolution computer tomography (HRCT) images; and (3) recurrence of blood or BAL eosinophilia. In relapse cases, infections were excluded if there was no clinical (eg, grossly purulent sputum was absent and patients were resistant to antibiotic therapy) or microbiological evidence for infection.

The study protocol was approved by the ethical committee of the Hamamatsu University School of Medicine (Hamamatsu, Japan) and other institutes (approval number E15-166) and registered in the University Hospital Medical Information Network in Japan (UMIN000019092). This study was conducted according to the Declaration of Helsinki, involved a review of clinical records, and the information was posted on the web (http://hamamatsu-lung.com/study.html). The need for patient approval and/or informed consent was waived, because the study consisted of reviews of the patients' records and images. Our institutional review board determined that ethical approval was not necessary and did not require the patients' approval or informed consent.

Pulmonary Function Test

Spirometry was performed according to the guidelines of the American Thoracic Society, the European Respiratory Society, and the Japanese Respiratory Society.[14–17] Predicted values of forced vital capacity (FVC) and forced expiratory volume in 1.0 second ($FEV_{1.0}$) were referenced from the Japanese Respiratory Society.[18,19] Normal values were defined as FVC at least 80% of predicted and $FEV_{1.0}$ at least 80% of predicted. Restrictive ventilatory defect was defined as VC less than 80%. Obstructive defect was defined as $FEV_{1.0}$/FVC less than 70% according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria.[20] Obstructive or restrictive defect was defined as VC less than 80% of predicted and $FEV_{1.0}$/FVC less than 70%.

Review of Radiographic Findings

The HRCT images taken at the initial CEP diagnosis were reviewed by 2 radiologists independently. These images, composed of 1- to 2.5-mm collimation sections at 10-mm intervals, were reconstructed by a high spatial frequency algorithm and were displayed at window settings appropriate for viewing the lung parenchyma (window level −600 to −800 Hounsfield units; window width 1,200−2,000 Hounsfield units). Images were randomized and reviewed independently by 2 expert chest radiologists. The HRCT findings were interpreted according to current Fleischner criteria.[21] The HRCT patterns were classified as CEP, acute eosinophilic pneumonia, or patchy based on modifications of our previous study.[22] The CEP pattern was defined as the occurrence of patchy unilateral or bilateral airway space consolidation, predominantly peripheral distribution, areas of ground-glass attenuation predominantly in the middle and upper lung zones, and band-like subpleural attenuation. The acute eosinophilic pneumonia pattern was defined as the occurrence of ground-glass attenuation, diffuse areas of ground-glass attenuation, defined nodules, smooth interlobular septal thickening, and pleural effusion. The patchy pattern was defined as the occurrence of patchy unilateral or bilateral centrilobular opacities with or without consolidation or ground-glass attenuation (eFigure 1). Patients whose condition could not be classified according to these criteria were categorized collectively as unclassifiable CT patterns. Disagreements regarding HRCT interpretation were resolved by consensus agreement.

Statistical Analysis

Discrete variables are expressed as count (percentage) and continuous variables are described as mean ± SD, unless otherwise specified. The Mann-Whitney test was used for continuous variables. Categorical data were compared between groups using Pearson and Fisher exact tests for independence. Univariate and multivariate analyses were performed by logistic regression analysis. Statistical analyses were performed using GraphPad Prism 6 (GraphPad Software, San Diego, California) and SPSS Statistics (IBM