



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

Yuzo Suzuki, MD, PhD^{*}; Yoshiyuki Oyama, MD^{*}; Hironao Hozumi, MD, PhD^{*}; Shiro Imokawa, MD, PhD[†]; Mikio Toyoshima, MD, PhD[‡]; Koshi Yokomura, MD, PhD[§]; Hidenori Nakamura, MD, PhD^{||}; Shigeki Kuroishi, MD, PhD[¶]; Masato Karayama, MD, PhD^{*}; Kazuki Furuhashi, MD, PhD^{*}; Noriyuki Enomoto, MD, PhD^{*}; Tomoyuki Fujisawa, MD, PhD^{*}; Yutaro Nakamura, MD, PhD^{*}; Naoki Inui, MD, PhD^{*}; Naoki Koshimizu, MD[#]; Takashi Yamada, MD, PhD^{**}; Kazutaka Mori, MD, PhD^{††}; Masafumi Masuda, MD, PhD^{‡‡}; Toshihiro Shirai, MD, PhD^{§§}; Hiroshi Hayakawa, MD, PhD^{§§}; Mitsuhiro Sumikawa, MD, PhD^{|||}; Takeshi Johkoh, MD, PhD^{¶¶}; Takafumi Suda, MD, PhD^{*}

^{*} Second Division, Department of Internal Medicine, Hamamatsu University School of Medicine, Hamamatsu, Japan

[†] Respiratory Medicine, Iwata City Hospital, Iwata, Japan

[‡] Respiratory Medicine, Hamamatsu Rosai Hospital, Hamamatsu, Japan

[§] Respiratory Medicine, Seirei-Mikatahara General Hospital, Hamamatsu, Japan

^{||} Respiratory Medicine, Seirei-Hamamatsu General Hospital, Hamamatsu, Japan

[¶] Respiratory Medicine, Enshu Hospital, Hamamatsu, Japan

[#] Respiratory Medicine, Fujieda City Hospital, Fujieda, Japan

^{**} Respiratory Medicine, Shizuoka City Shizuoka Hospital, Shizuoka, Japan

^{††} Respiratory Medicine, Shizuoka City Shimizu Hospital, Shizuoka, Japan

^{‡‡} Respiratory Medicine, Shizuoka General Hospital, Shizuoka, Japan

^{§§} Respiratory Medicine, Tenryu Hospital, National Hospital Organization, Hamamatsu, Japan

^{|||} Department of Diagnostic Radiology, Osaka International Cancer Institute, Osaka, Japan

^{¶¶} Department of Radiology, Kinki Central Hospital, Itami, Japan

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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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Reprints: Yuzo Suzuki, MD, PhD, 1-20-1 Handayama Higashi-ku, Hamamatsu, Shizuoka 431-3192 Japan; E-mail: yuzosuzu@hama-med.ac.jp.

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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 $\pm$ 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

Table 1
Clinical Characteristics of 133 Patients With Chronic Eosinophilic Pneumonia

Women, n (%)	84 (63.2)
Age (y), mean $\pm$ SD; median (range)	58.3 $\pm$ 14.2; 58 (21–84)
Observation period (y), mean $\pm$ SD; median (range)	6.1 $\pm$ 4.1; 5.9 (1.1–15.0)
Never smoker, n (%)	87 (65.4)
Prior asthma, n (%)	67 (50.4)
Allergic rhinitis, n (%)	35 (26.3)
Symptoms, n (%)	
Cough	86 (64.7)
Fever	62 (46.6)
Sputum	32 (24.1)
Dyspnea	28 (21.1)
General fatigue	8 (6.1)
Wheezing	7 (5.3)
Chest pain	3 (2.3)
Appetite loss	3 (2.3)
Laboratory values, mean $\pm$ SD	
WBC/mm ³	9,430 $\pm$ 3,232
Eos (%)	27.0 $\pm$ 17.0
Eos/mm ³	2,750 $\pm$ 2,340
CRP (mg/dL)	3.98 $\pm$ 4.59
IgE (IU/mL)	936.6 $\pm$ 1,888.2
BAL (n = 126), mean $\pm$ SD	
TCC/BALF (10 ⁵)	5.50 $\pm$ 12.0
MAC (%)	43.4 $\pm$ 26.3
Ly (%)	11.0 $\pm$ 12.8
Eos (%)	38.2 $\pm$ 27.4
Neut (%)	7.0 $\pm$ 13.3
CD4/CD8	1.95 $\pm$ 1.53

Abbreviations: BAL, bronchoalveolar lavage; BALF, bronchoalveolar lavage fluid; CRP, C-reactive protein; Eos, eosinophil; IgE, immunoglobulin E; Ly, lymphocytes; MAC, macrophages; MMF, maximum midexpiratory flow; Neut, neutrophils; TCC, total cell count; WBC, white blood cell.

Corporation, Armonk, New York) software. All analyses were 2-tailed and *P* values less than .05 were considered significant.

Results

Clinical Characteristics

During the study period, 149 patients were diagnosed with CEP and 133 patients were followed up for longer than 1 year (6.1 $\pm$ 4.1 years; [Table 1](#)). There were 84 women (63.2%) and the mean age was 58.3 $\pm$ 14.2 years. Approximately half the patients had asthma and 26.3% had allergic rhinitis. The most common symptoms were productive cough and fever. Increased eosinophil counts, C-reactive protein levels, and serum immunoglobulin E (IgE) levels were observed. A BAL analysis showed an increase of eosinophil proportions (38.2 $\pm$ 27.4%).

HRCT Findings

The HRCT images at the time of CEP diagnosis were available for 122 patients ([eTable 1](#)). HRCT pattern analyses showed that CEP, acute eosinophilic pneumonia, and patchy patterns were found in 68.9%, 8.2%, and 4.1% of patients, respectively. Abnormal HRCT findings were predominantly distributed in the bilateral, upper, and peripheral regions and were infrequent in the lower lung zone. Ground glass opacity, airspace consolidations, and intralobular septal thickening were frequently found, but bronchial wall thickening or traction bronchiectasis was not. Lymph node enlargement and pleural effusion were present in 50 cases (41.0%) and 20 cases (16.4%), respectively.

Therapy and Relapse

Of the 133 patients, 128 were administered corticosteroid, whereas 5 spontaneously recovered without therapy. After diagnosis of CEP, systematic corticosteroid therapy was administered at a mean dose of 28.5 $\pm$ 6.4 mg of prednisolone. The duration of initial therapy and time to relapse varied, with 49 subjects (36.8%) undergoing treatment for longer than 1 year. Forty-nine subjects

Table 2
Initial and Maintenance Treatment of 133 Patients With Chronic Eosinophilic Pneumonia

Initial treatment	
PSL administration, n cases	128
Initial PSL doses, n (%)	
0 mg	5 (3.8)
1–30 mg	51 (38.3)
31–40 mg	62 (46.6)
41–50 mg	8 (6.0)
$\geq$ 51 mg	7 (5.3)
Initial period of PSL administration, n (%)	
0	5 (3.8)
$\leq$ 3 mo	41 (30.8)
$\leq$ 6 mo	38 (28.6)
$\leq$ 1 y	20 (15.0)
$\leq$ 3 y	17 (12.8)
$>$ 3 y	12 (9.0)
Cumulative period of PSL administration, n (%)	
0	5 (3.8)
$\leq$ 3 mo	16 (12.0)
$\leq$ 6 mo	12 (9.0)
$\leq$ 1 y	15 (11.3)
$\leq$ 3 y	36 (27.1)
$>$ 3 y	49 (36.8)
Treatment at last evaluation, n (%)	
PSL administrations (mg), n (%); mean $\pm$ SD	68 (51.1); 5.4 $\pm$ 2.7
ICS use	73 (54.9)
High-dose ICS ($>$ 8,000 μ g) ^a	19 (14.3)
Medium-dose ICS ($>$ 400–800 μ g) ^a	46 (34.6)
Low-dose ICS (200–400 μ g) ^a	8 (6.0)
PSL + ICS use	41 (30.8)
Relapses, n (%)	75 (56.4)
1	37 (27.8)
2	18 (13.5)
3	11 (8.3)
4	5 (3.8)
5	4 (3.0)

Abbreviations: FP, fluticasone propionate; ICS, inhaled corticosteroid; PSL, prednisolone.

^aBudesonide equivalent.

were treated with corticosteroid for longer than 3 years in total. At the time of the last evaluation, 100 patients (75.2%) had maintenance therapy. Sixty-eight patients received oral corticosteroid therapy (mean 5.4 mg of prednisolone), and 73 patients were administered inhaled corticosteroid. Of those, a combination of oral and inhaled corticosteroid therapy was administered to 41 patients. During follow-up, relapse was observed in 75 patients with CEP (56.4%) and 30% of them experienced at least 2 relapses ([Table 2](#)).

Pulmonary Function

At a mean follow-up of 5.4 $\pm$ 4.4 years, spirometry was performed in 114 patients with CEP, of whom 101 underwent spirometry at the onset and follow-up phase of the disease. Overall, spirometric values improved from the initial CEP diagnosis to the last evaluation ([Table 3](#)).

At the initial diagnosis, defect at spirometry was found in 60 patients (51.7%; 12 obstructive, 34 restrictive, and 14 obstructive and restrictive cases). In contrast, at the last evaluation, 42 patients (36.8%) still had defects at spirometry (28 obstructive, 10 restrictive, and 4 obstructive and restrictive cases). Changes in pulmonary function in each patient are shown in [Figure 1](#). Restrictive defects were dominant at the initial diagnosis, whereas obstructive defects were common before the follow-up period. Notably, 73.7% of patients with CEP had persistent impairment at spirometry that was observed at the time of initial CEP diagnosis.

Predictive Factors for Relapse

We first examined factors associated with CEP relapse. A comparison of patients with CEP with or without relapse showed no

Table 3
Pulmonary Function Test at Time of CEP Diagnosis and Follow-up

	At diagnosis of CEP (n = 116)	At follow-up (n = 114)	P value
Pulmonary function test, mean $\pm$ SD			
FVC (% predicted)	84.2 $\pm$ 20.5	101.1 $\pm$ 18.7	<.0001
FEV _{1.0} (% predicted)	80.9 $\pm$ 23.4	96.5 $\pm$ 21.6	<.0001
FEV _{1.0} /FVC (%)	77.8 $\pm$ 12.6	76.7 $\pm$ 10.6	.1190
IC (L)	1.63 $\pm$ 0.55	1.86 $\pm$ 0.51	<.0001
MMF (L/s)	1.89 $\pm$ 1.12	1.80 $\pm$ 0.94	.4020
V50 (L/s)	2.22 $\pm$ 1.19	2.37 $\pm$ 1.07	.1367
V25 (L/s)	0.77 $\pm$ 0.54	0.72 $\pm$ 0.52	.9062
V50/V25	3.45 $\pm$ 1.75	3.90 $\pm$ 1.34	.0020
Pulmonary function defect, n (%)	60 (51.7)	42 (36.8)	.0231
Obstructive	12 (10.3)	28 (24.6)	<.0001
Restrictive	34 (29.3)	10 (8.8)	
Obstructive and restrictive	14 (12.1)	4 (3.5)	

Abbreviations: CEP, chronic eosinophilic pneumonia; FEV_{1.0}, forced expiratory volume in 1.0 second; FVC, forced vital capacity; IC, inspiratory capacity; MMF, maximum midexpiratory flow; V25, flow rate at 25% of forced vital capacity; V50, flow rate at 50% of forced vital capacity.

significant differences in clinical characteristics, laboratory data, pulmonary function results, BAL findings, or radiologic findings (eTable 2). However, the proportion of patients receiving oral corticosteroid therapy at the final follow-up was significantly larger for with relapse than for those without relapse (68.0% vs 29.3%, respectively; $P < .001$). Logistic regression analysis showed that none of the factors at the initial diagnosis of CEP was significantly associated with the occurrence of relapse (Table 4).

Predictive Factors for Persistent Impairment of Pulmonary Function

Persistent defects at spirometry were more prevalent in significantly older men (Table 5). Notably, spirometric values, such as FVC percentage predicted (FVC% pred), FEV_{1.0} percentage predicted

Table 4
Prediction of Relapse: Univariate Analysis

Predictor	HR	95% CI	P value
Age (y)	0.986	0.962–1.011	.265
Female sex	1.610	0.791–3.278	.189
Smoking history	0.881	0.429–1.808	.881
Prior asthma	0.711	0.357–1.415	.331
Reticulation	1.567	0.501–4.896	.440
FVC (% predicted)	1.005	0.987–1.023	.602
FEV _{1.0} (% predicted)	0.995	0.979–1.012	.545
FEV _{1.0} /FVC (%)	0.990	0.961–1.019	.492
Initial impairment by PFT	1.055	0.506–2.196	.887
Initial obstructive defect by PFT (FEV _{1.0} /FVC <70%)	2.059	0.812–5.217	.128
Initial restrictive defect by PFT (VC < 80%)	0.981	0.465–2.072	.960

Abbreviations: CI, confidence interval; FEV_{1.0}, forced expiratory volume in 1.0 second; FVC, forced vital capacity; HR, hazard ratio; PFT, pulmonary function test; VC, vital capacity.

(FEV_{1.0}% pred), and FEV_{1.0}/FVC percentage (FEV_{1.0}/FVC%), were significantly lower in patients with a persistent defect at initial diagnosis.

To identify predictive factors for persistent impairment of pulmonary function, we used logistic regression analysis. For obstructive defects, univariate analysis showed that the comorbidity of asthma, FEV_{1.0}% pred, and FEV_{1.0}/FVC% and initial obstructive defect were significantly associated with persistent obstructive impairment of pulmonary function (Table 6). Next, we performed multivariate analysis in 2 ways: one way included the comorbidity of asthma, FEV_{1.0}% pred, and FEV_{1.0}/FVC% as parameters, and the other consisted of the comorbidity of asthma and patterns of obstructive defects at spirometry. Multivariate analyses showed that the comorbidity of asthma, FEV_{1.0}% pred, and FEV_{1.0}/FVC% and initial obstructive defect were significant independent predictors for persistent obstructive impairment. For restrictive defects, univariate analysis showed that reticulation at HRCT, FVC% pred, and initial restrictive pulmonary function defect were significantly related to persistent restrictive impairment of pulmonary function (Table 7). Similar to obstructive impairments, multivariate analyses were performed in 2 ways. Reticulation at HRCT, FVC% pred, and initial restrictive pulmonary function defect remained significant in multivariate analyses. Unexpectedly, relapse was not a significant predictor for persistent impairment of pulmonary function (neither obstructive nor restrictive).

Discussion

The present study investigated the long-term outcomes of patients with CEP, with a specific evaluation of persistent impairment of pulmonary function, and determined its predictive factors. Of 133 patients with CEP, approximately half of them experienced relapse, but no predictive factors for the relapse were identified. Notably, more than one third of patients showed persistent impairment of pulmonary function, and relapse did not predict this. Persistent obstructive impairment was associated with concurrent asthma and obstructive defect at the initial diagnosis, whereas persistent restrictive impairment was related to reticulation at HRCT and restrictive defect at the time of diagnosis. These data suggest that a prolonged, persistent impairment of pulmonary function is common in CEP and that certain clinical characteristics at the initial diagnosis are associated with this condition.

In the management of CEP, clinicians have focused mainly on decreasing relapse and decreasing doses of corticosteroid to avoid its adverse effects. However, the present study clearly indicated that persistent impairment of pulmonary function was common in patients with CEP, suggesting that this persistent impairment

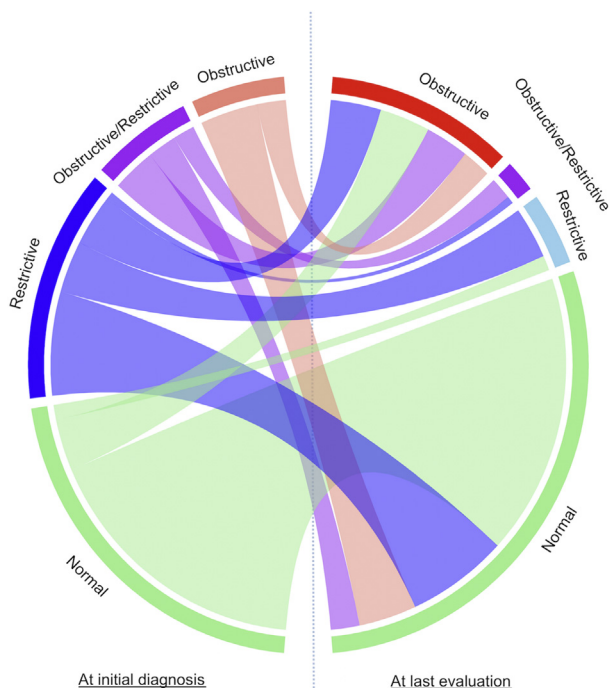


Figure 1. Chord diagram summarizing spirometric alternations from time of diagnosis of chronic eosinophilic pneumonia to follow-up. Patterns of pulmonary function defects at the time of chronic eosinophilic pneumonia diagnosis are depicted on the left side and patterns of pulmonary function defects at follow-up are depicted on the right side.

Table 5

Comparison of Patients With CEP With vs Without Persistent Impairment of Pulmonary Function Test

	Persistent impairment by PFT		P value
	Yes (n = 42; 36.8%)	No (n = 72; 63.2%)	
Women, n (%)	22 (52.4)	54 (75.0)	.0227
Age (y), mean $\pm$ SD	61.3 $\pm$ 12.8	55.4 $\pm$ 12.3	.0141
Observation period (y)	6.8 $\pm$ 5.0	6.4 $\pm$ 3.8	.992
Never smoker, n (%)	24 (57.4)	52 (72.2)	.1057
Prior asthma, n (%)	24 (57.1)	36 (50.0)	.5603
Allergic rhinitis, n (%)	10 (23.8)	19 (26.4)	.8263
Initial PSL treatment period (mo), mean $\pm$ SD	19.9 $\pm$ 38.5	13.0 $\pm$ 23.5	.8979
Cumulative period for PSL administration (mo), mean $\pm$ SD	39.3 $\pm$ 41.5	36.4 $\pm$ 35.6	.9848
OCT use at final follow-up, n (%)	25 (59.5)	36 (50.0)	.3254
Relapses, n (%)	21 (50.0)	45 (62.5)	.2390
Laboratory values, mean $\pm$ SD			
WBC/mm ³	10,109 $\pm$ 2,893	9,275 $\pm$ 3,479	.0843
Eos (%)	29.2 $\pm$ 16.6	27.6 $\pm$ 17.3	.5392
Eos/mm ³	3,123 $\pm$ 2,166	2,764 $\pm$ 2,505	.2401
CRP (mg/dL)	4.81 $\pm$ 5.03	3.55 $\pm$ 4.29	.0867
IgE (IU/L)	1,182.1 $\pm$ 2,699.7	681.7 $\pm$ 953.8	.7949
Initial PFT results (n = 101), mean $\pm$ SD			
FVC (% predicted)	78.1 $\pm$ 18.8	88.5 $\pm$ 20.1	.0039
FEV _{1.0} (% predicted)	72.7 $\pm$ 21.1	84.1 $\pm$ 22.6	.0168
FEV _{1.0} /FVC (%)	73.7 $\pm$ 14.4	79.6 $\pm$ 11.7	.0325
IC (L)	1.66 $\pm$ 0.55	1.61 $\pm$ 0.53	.8541
MMF (L/s)	1.53 $\pm$ 1.03	2.13 $\pm$ 1.19	.0189
V50 (L/s)	1.85 $\pm$ 1.17	2.46 $\pm$ 1.18	.0191
V25 (L/s)	0.62 $\pm$ 0.52	0.85 $\pm$ 0.55	.0330
V50/V25	3.49 $\pm$ 1.40	3.51 $\pm$ 2.04	.7999
Initial defect by PFT, n (%)			
Obstructive	4 (10.5)	8 (12.7)	.0038
Restrictive	15 (39.4)	14 (22.2)	
Obstructive and restrictive	9 (23.7)	4 (6.4)	
BAL, mean $\pm$ SD			
TCC/BALF (10 ⁵)	4.42 $\pm$ 4.50	5.03 $\pm$ 10.6	.4532
MAC (%)	40.9 $\pm$ 24.6	44.8 $\pm$ 27.1	.4926
Ly (%)	10.9 $\pm$ 12.9	9.0 $\pm$ 10.5	.6313
Eos (%)	43.2 $\pm$ 26.6	40.0 $\pm$ 26.9	.4968
Neut (%)	3.95 $\pm$ 6.17	4.82 $\pm$ 8.56	.9946
CD4/CD8	1.64 $\pm$ 1.10	1.96 $\pm$ 1.35	.3787
Pattern classification (n = 104), n (%)			
CEP	26 (68.4)	45 (68.2)	.4991
AEP	2 (5.3)	8 (12.1)	
Patchy	1 (2.6)	3 (4.5)	
Unclassified	9 (23.7)	10 (15.2)	
Zonal predominance, n (%)			
Upper	16 (42.1)	34 (51.5)	.6307
Lower	9 (23.7)	12 (18.2)	
Random or diffuse	13 (34.2)	20 (30.3)	
Lateral predominance, n (%)			
Right	5 (13.2)	15 (22.7)	.2786
Left	9 (23.7)	9 (13.6)	
Right and left	24 (63.2)	42 (63.6)	
Axial distribution, n (%)			
Peripheral	28 (73.7)	51 (77.3)	.8516
Random or diffuse	8 (21.1)	11 (16.7)	
Peri-bronchovascular	2 (5.3)	4 (6.1)	
Radiologic findings, n (%)			
Ground-glass attenuation	36 (94.7)	62 (93.9)	1.0
Airspace consolidation	34 (89.5)	54 (81.8)	.1827
Reticulation	9 (23.7)	5 (7.6)	.0341
Intralobular septal thickening	28 (73.7)	49 (74.2)	1.0
Bronchial wall thickening	11 (29.0)	14 (21.2)	.4754
Traction bronchiectasis	11 (29.0)	13 (19.7)	.3363
Nodules	14 (36.8)	20 (30.3)	.5210
Subpleural curved linear shadow	8 (21.1)	7 (10.6)	.1587
Bronchovascular bundle thickness	5 (13.2)	6 (9.1)	.5250
Lymph node enlargement	17 (44.7)	24 (36.4)	.4133
Pleural effusions	8 (21.1)	6 (9.1)	.1335

Abbreviations: AEP, acute eosinophilic pneumonia; BAL, bronchoalveolar lavage; BALF, bronchoalveolar lavage fluid; CEP, chronic eosinophilic pneumonia; CRP, C-reactive protein; Eos, eosinophils; FEV_{1.0}, forced expiratory volume in 1.0 second; FVC, forced vital capacity; IC, inspiratory capacity; IgE, immunoglobulin E; Ly, lymphocytes; OCT, oral corticosteroid therapy; MAC, macrophages; MMF, maximum midexpiratory flow; Neut, neutrophils; PFT, pulmonary function test; PSL, prednisolone; TCC, total cell count; V25, flow rate at 25% of forced vital capacity; V50, flow rate at 50% of forced vital capacity; WBC, white blood cell.

should be evaluated in clinical settings. In our cohort with a mean observational period of 6 years, 36.8% of patients with CEP had persistent defect at spirometry (27 obstructive, 10 restrictive, and 4

obstructive and restrictive cases). To date, only a few studies have examined the long-term outcomes of patients with CEP. Of these, only a study by Durieu et al⁷ described persistent defect at

Table 6

Prediction of Persistent Obstructive Pulmonary Function Impairment: Univariate and Multivariate Analyses

Predictor	HR	95% CI	P value
Univariate analysis			
Age (y)	1.003	0.971–1.036	.864
Female sex	0.597	0.254–1.402	.236
Smoking history	1.676	0.714–3.935	.236
Prior asthma	2.369	0.995–5.642	.051
Relapse	1.701	0.256–1.351	.211
Reticulation at HRCT	0.709	0.182–2.756	.620
FVC (% predicted)	0.986	0.964–1.008	.202
FEV _{1.0} (% predicted)	0.968	0.946–0.990	.005
FEV _{1.0} /FVC (%)	0.920	0.884–0.958	<.001
Initial defect by PFT	3.636	1.376–9.609	.009
Initial obstructive defect by PFT (FEV _{1.0} /FVC <70%)	4.406	1.675–11.584	.003
Initial restrictive defect by PFT (VC < 80%)	2.905	1.181–7.149	.020
Multivariate analysis			
Prior asthma	3.450	1.098–10.835	.034
FEV _{1.0} (% predicted)	0.986	0.958–1.015	.340
FEV _{1.0} /FVC (%)	0.931	0.884–0.980	.006
Prior asthma	2.952	1.089–8.012	.033
Initial obstructive defect by PFT (FEV _{1.0} /FVC <70%)	4.715	1.723–12.904	.003

Abbreviations: CI, confidence interval; FEV_{1.0}, forced expiratory volume in 1.0 second; FVC, forced vital capacity; HR, hazard ratio; HRCT, high-resolution computer tomography; PFT, pulmonary function test; VC, vital capacity.

spirometry during the course of CEP. They retrospectively analyzed 19 patients with CEP (mean follow-up 4.1 years) and found that 10 patients (52.6%) developed persistent obstructive defects, whereas 1 patient (5.3%) had a persistent restrictive defect. However, in that study, the number of patients with CEP was small and few studies have confirmed their findings thus far. In this context, the present study, which included a larger number of patients with CEP, demonstrated that persistent defect at spirometry is relatively common in CEP. Compared with the study by Durieu et al, the proportion of obstructive defects was smaller in our cohort (52.6% vs 26.3%, respectively), whereas restrictive defects were more frequent (5.3% vs 12.3%, respectively). The precise reasons for these discrepancies are unclear, but the differences in study subjects and/or observation period could account for them. Our observations

Table 7

Prediction of Persistent Restrictive Pulmonary Function Impairment: Univariate and Multivariate Analyses

Predictor	HR	95% CI	P value
Univariate analysis			
Age (y)	1.115	1.046–1.190	.001
Female sex	0.449	0.145–1.391	.165
Smoking history	1.128	0.350–3.634	.840
Prior asthma	0.455	0.142–1.453	.184
Relapse	2.000	0.645–6.201	.230
Reticulation at HRCT	6.587	1.728–25.106	.006
FVC (% predicted)	0.936	0.899–0.974	.001
FEV _{1.0} (% predicted)	0.981	0.954–1.010	.193
FEV _{1.0} /FVC (%)	1.022	0.974–1.071	.379
Initial impairment by PFT	5.756	1.205–27.488	.028
Initial obstructive defect by PFT (FEV _{1.0} /FVC <70%)	0.990	0.227–3.568	.881
Initial restrictive defect by PFT (VC < 80%)	9.935	2.069–47.719	.004
Multivariate analysis			
Reticulation at HRCT	9.197	1.732–48.851	.009
FVC (% predicted)	0.929	0.886–0.974	.002
Reticulation at HRCT	10.186	1.660–62.523	.012
Initial restrictive defect by PFT (VC < 80%)	12.681	2.010–80.007	.007

Abbreviations: CI, confidence interval; FEV_{1.0}, forced expiratory volume in 1.0 second; FVC, forced vital capacity; HR, hazard ratio; HRCT, high-resolution computer tomography; PFT, pulmonary function test; VC, vital capacity.

suggest that persistent impairment of pulmonary function is an important factor that should be evaluated in the management of patients with CEP.

Next, we attempted to elucidate the predictive factors for persistent impairment of pulmonary function in our patients with CEP. Initially, we hypothesized that relapse must be associated with persistent impairment. However, our logistic analysis showed that relapse did not predict persistent impairments, including obstructive and restrictive defects, even after several relapses occurred. Interestingly, we found that significant predictive factors differed based on the type of persistent impairment (obstructive vs restrictive). Based on our observations, patients with CEP and asthma or obstructive defect at the initial diagnosis are more likely to show future persistent obstructive impairment, whereas those showing reticulation at HRCT or restrictive defect at the initial diagnosis tend to develop future persistent restrictive impairments. To date, only a few studies have examined the associated factors for persistent impairment of pulmonary function in patients with CEP. The study by Durieu et al⁷ compared clinical parameters, excluding spirometric values, between patients with and without persistent pulmonary function defects and found that the percentage of BAL eosinophils significantly increased in patients with a persistent obstructive defect. However, the present study found no significant difference in BAL eosinophil counts between patients with and without persistent obstructive defects. Although the predictive factors differed based on the type of persistent impairment of pulmonary function, suggesting that a distinct pathogenesis might be involved, the precise mechanism by which the persistent impairment of pulmonary function occurs in patients with CEP is unclear. Future studies are required to confirm our observations and to elucidate the mechanisms causing persistent impairments in CEP. Based on our results, patients with CEP and asthma or defect at spirometry at the initial diagnosis might be more likely to develop persistent impairment of pulmonary function during the course of this disease.

It is not clear whether persistent impairment of pulmonary function can be prevented in CEP. Because concurrent asthma was associated with persistent obstructive defects, a more aggressive treatment, such as high doses of corticosteroid and/or prolonged therapy, could preclude persistent impairment of pulmonary function for patients with CEP who are likely to develop this impairment. In the present study, there was no difference in corticosteroid doses or duration of therapy between patients with and without persistent defects at spirometry. To clarify further how to prevent persistent impairment in patients with CEP, future prospective studies are necessary.

In addition to persistent impairment of pulmonary function, relapse remains a primary concern in the management of CEP. Thus, we attempted to identify predictive factors for relapse at the initial CEP diagnosis, but did not find them. Laboratory data, spirometric values, and HRCT or BAL findings were not useful in predicting relapse. This finding is consistent with the observations of our previous prospective study. A study by Marchand et al⁶ reported a lower frequency of relapse in patients with asthmatic CEP. In addition, a study by Ishiguro et al²³ recently reported that a smoking habit was associated with a lower risk for relapse, with proportions of current smokers as large as 35.2%. In the present study, however, smoking history or concurrent asthma did not decrease the rate of relapse. Taken together, these results suggest that the predictability of relapse is difficult at the initial CEP diagnosis.

In our cohorts, 68 patients with CEP (51.1%) were still treated with an oral corticosteroid, although at lower doses. Notably, 50% of patients without persistent impairment of pulmonary function and 30% of patients who never experienced relapse still used corticosteroid therapy. Although prolonged corticosteroid use might

contribute to preserve pulmonary functions from further decline or a favorable prognosis in certain cases, it indicated that many patients indefinitely treated with corticosteroid might be overtreated and corticosteroid use in these patients could be decreased. We found several predictors for persistent impairment of pulmonary functions but not for relapse, suggesting a relatively lower risk of persistent decline of pulmonary function in patients with normal pulmonary function at the initial diagnosis. This might encourage physicians to take more care in decreasing corticosteroid use and less care in decreasing relapses, especially for patients without impaired pulmonary function. Therefore, assessment of spirometric values and predictors for persistent impairment of pulmonary function might contribute to the avoidance of excessive corticosteroid use in patients with CEP.

To date, the precise histology and pathophysiology corresponding to the reticular opacities at HRCT in patients with CEP is unclear. Arakawa et al²⁴ reviewed HRCT images of 43 patients with CEP and found that 9.3% of them had reticular opacities, which is compatible with our results in patients with CEP without persistent impairment of pulmonary function. Thus, reticular opacity is a common finding at HRCT for CEP, but they did not perform a histologic investigation of patients with CEP and reticulations. While comparing pathologic findings with radiographic findings of lungs from autopsy cases, Johkoh et al²⁵ found reticular opacities in alveolar filling and interstitial fibrotic processes. In the present study, unfortunately, there were no differences in histology, blood analyses, or BAL findings between patients with and without reticulations (data not shown). Reticulations at HRCT in our patients with CEP were often accompanied by traction bronchiectasis, but it was reversible in response to treatment. Thus, reticulations in CEP seem to differ from those observed in irreversible, persistent fibrosis in idiopathic pulmonary fibrosis. Indeed, Katzenstein²⁶ described interstitial pneumonia with alveolar pneumocyte hyperplasia in CEP, but interstitial fibrosis is not a feature. Thus, reticulations might represent interstitial pneumonia with varying degrees of inflammation, but not mature fibrosis.

This study has several limitations. First, although pulmonary function testing includes spirometry and evaluation of the bronchodilator response, carbon monoxide diffusing capacity, and lung volumes, we performed only spirometry, which is not the ideal way to identify restrictive defects. Airway responsiveness to bronchodilator was not examined in patients with obstructive defects and/or asthma. Second, the data collection method was retrospective in nature, although a large number of patients with CEP were enrolled. Specifically, the pulmonary lung function of 16 of 133 patients (12.8%) was not evaluated at the initial diagnosis. The treatment was not strictly formulated in all patients with CEP. Thus, variation in therapy might have biased our observations. Third, the severity of asthma before CEP diagnosis could not be evaluated, and thus the influence of asthma severity on persistent impairment of pulmonary function remains unknown. Future prospective studies with larger samples of patients with CEP should overcome these limitations.

In conclusion, the present study investigated the occurrence of persistent impairment of pulmonary function and its predictive factors in CEP. Persistent impairment of pulmonary function is common in CEP. Concurrent asthma and obstructive defects at the time of diagnosis were predictors for persistent obstructive impairments, whereas reticulation at HRCT and restrictive defects at the time of diagnosis predicted persistent restrictive impairments. Relapse was not associated with persistent impairment. These data suggest that attention should be paid to prolonged persistent impairment of pulmonary function in the management of CEP.

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Supplementary Data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.anai.2017.08.009>.

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Supplementary Data

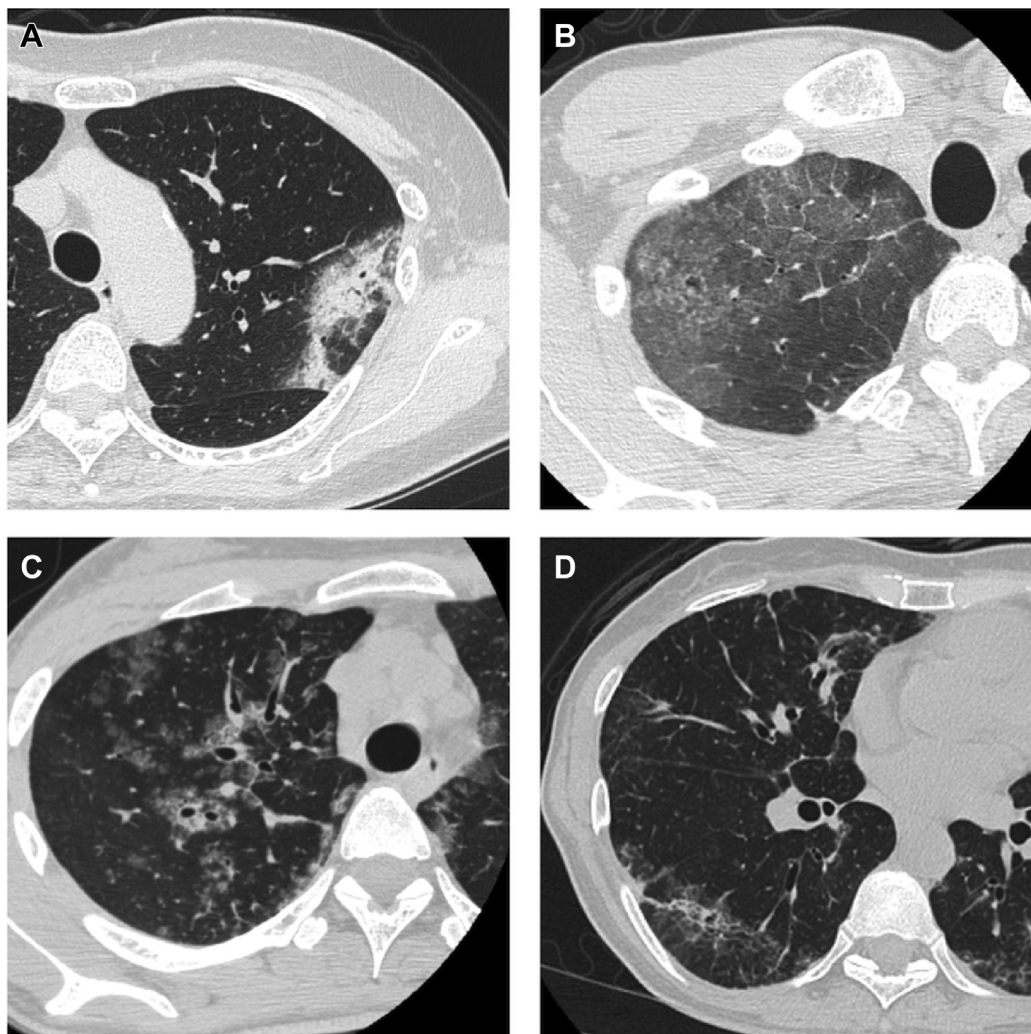


Figure 1. Representative images for each type of high-resolution computer tomographic pattern. (A) Chronic eosinophilic pneumonia pattern: airway space consolidation and ground-glass attenuation involving the peripheral left upper lobe. (B) Acute eosinophilic pneumonia pattern: diffuse areas of ground-glass attenuation and interlobular septal thickening in the upper right lobe. (C) Patchy pattern: patchy unilateral opacities with consolidation and/or ground-glass attenuation in the right upper lobe. (D) Reticulations and ground-glass attenuation in the right lower lobe.

eTable 1

High-Resolution Computed Tomographic Findings of 122 Patients With CEP

Pattern classification, n (%)	
CEP	84 (68.9)
AEP	10 (8.2)
Patchy	5 (4.1)
Unclassified	23 (18.9)
Zonal predominance, n (%)	
Upper	58 (47.5)
Lower	22 (18.0)
Random or diffuse	42 (34.4)
Lateral predominance, n (%)	
Right	25 (18.8)
Left	22 (16.5)
Bilateral	75 (56.4)
Axial distribution, n (%)	
Peripheral	93 (76.2)
Random or diffuse	21 (17.2)
Peri-bronchovascular	8 (6.6)
Radiologic findings, n (%)	
Ground-glass attenuation	116 (95.1) ^a
Airspace consolidation	104 (85.2) ^b
Reticulation	15 (12.3) ^c
Intralobular septal thickening	89 (73.0)
Bronchial wall thickening	28 (23.0)
Traction bronchiectasis	26 (21.3)
Nodules	40 (32.8)
Subpleural curved linear shadow	20 (16.4)
Bronchovascular bundle thickness	14 (11.5)
Honeycombing	0 (0)
Lymph node enlargement	50 (41.0)
Pleural effusions	20 (16.4)

Abbreviations: AEP, acute eosinophilic pneumonia; CEP, chronic eosinophilic pneumonia.

^aPercentage of lung parenchyma: 10% in 85, 20% in 20, 30% in 11.

^bPercentage of lung parenchyma: 10% in 40, 20% in 40, 30% in 24.

^cPercentage of lung parenchyma: 10% in 10, 20% in 4, 30% in 1.

eTable 2

Comparison of Patients With CEP With vs Without Relapse

	Relapses		P value
	Yes (n = 75; 56.4%)	No (n = 58; 43.6%)	
Women, n (%)	51 (68)	33 (56.9)	.2082
Age (y), mean $\pm$ SD	57.1 $\pm$ 14.1	59.9 $\pm$ 14.6	.4363
Never smoker, n (%)	50 (66.7)	37 (63.8)	.8543
Prior asthma, n (%)	35 (46.7)	32 (55.2)	.3834
Allergic rhinitis, n (%)	18 (24.0)	17 (29.3)	.5535
Cumulative period of PSL administration (mo), mean $\pm$ SD	43.9 $\pm$ 33.2	24.3 $\pm$ 33.2	<.0001
OCT use at final follow-up, n (%)	51 (68.0)	17 (29.3)	<.0001
Laboratory values, mean $\pm$ SD			
WBC/mm ³	9,397 $\pm$ 2,925	9,473 $\pm$ 3,615	.6745
Eos (%)	28.7 $\pm$ 17.3	24.8 $\pm$ 16.5	.2172
Eos/mm ³	2,846 $\pm$ 2,127	2,628 $\pm$ 2,600	.2906
CRP (mg/dL)	3.86 $\pm$ 3.91	4.15 $\pm$ 5.39	.4555
IgE (IU/mL)	886.5 $\pm$ 1,506	1,000.8 $\pm$ 2,301	.8020
Initial PFT results (n = 116), mean $\pm$ SD			
FVC (% predicted)	85.1 $\pm$ 20.9	83.1 $\pm$ 2.01	.7618
FEV _{1.0} (% predicted)	79.7 $\pm$ 24.2	82.4 $\pm$ 22.6	.5385
FEV _{1.0} /FVC (%)	77.1 $\pm$ 13.4	78.7 $\pm$ 11.4	.8087
Initial defect by PFT, n (%)			
Obstructive	7 (10.8)	5 (9.8)	.2578
Restrictive	16 (24.6)	18 (35.3)	
Obstructive and restrictive	11 (16.9)	3 (5.9)	
BAL (n = 126), mean $\pm$ SD			
TCC/BALF (10 ⁵)	6.79 $\pm$ 15.3	3.76 $\pm$ 3.96	.5610
MAC (%)	41.7 $\pm$ 26.0	45.6 $\pm$ 26.8	.4099
Ly (%)	11.8 $\pm$ 15.1	9.9 $\pm$ 8.8	.3151
Eos (%)	40.6 $\pm$ 27.6	34.9 $\pm$ 27.1	.2233
Neut (%)	5.46 $\pm$ 9.85	7.48 $\pm$ 13.1	.5858
Pattern classification (n = 122), n (%)			
CEP	49 (70.0)	35 (67.3)	.9546
AEP	6 (8.6)	4 (7.7)	
Patchy	3 (4.3)	2 (3.9)	
Unclassified or other	12 (17.1)	11 (21.2)	

Abbreviations: AEP, acute eosinophilic pneumonia; BAL, bronchoalveolar lavage; BALF, bronchoalveolar lavage fluid; CEP, chronic eosinophilic pneumonia; CRP, C-reactive protein; Eos, eosinophils; FEV_{1.0}, forced expiratory volume in 1.0 second; FVC, forced vital capacity; IgE, immunoglobulin E; Ly, lymphocytes; MAC, macrophages; Neut, neutrophils; OCT, oral corticosteroid therapy; PFT, pulmonary function test; PSL, prednisolone; TCC, total cell count; WBC, white blood cell.