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Review Article

Long-term management and persistent impairment of pulmonary function in chronic eosinophilic pneumonia: A review of the previous literature

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Abbreviations:

CEP, chronic eosinophilic pneumonia;

BAL, bronchoalveolar lavage;

TBLB, transbronchial lung biopsy;

HRCT, high-resolution computed

tomography; PFT, pulmonary function test;

ABPA, allergic bronchopulmonary

aspergillosis; EGPA, eosinophilic

granulomatosis with polyangiitis;

COP, cryptogenic organizing pneumonia;

ICS, inhaled corticosteroid; FVC, forced vital

capacity; FEV1, forced expiratory volume in

1.0 second

ABSTRACT

Chronic eosinophilic pneumonia (CEP) is an inflammatory disease characterized by accumulations of eosinophils in the lung with unknown etiology. Although corticosteroid treatment dramatically resolves these inflammations, relapse is common during the course of the disease. Approximately 50% of patients with CEP experience relapse. Subsequent to persistent disease and repeated relapse, and in cases of combined severe asthma, some CEP patients are administered corticosteroids indefinitely. Similar to patients with severe asthma who are often steroid dependent, a number of CEP patients exhibit prolonged persistent impairment of pulmonary function. Thus, CEP should be considered a potentially chronic disease requiring long-term management, rather than an acute or sub-acute disease requiring short-time therapy only. This review summarizes previous CEP studies, as well as our own cohort data, and discusses the long-term management of CEP with a particular focus on relapse, the prevalence of maintenance therapy, and persistent impairment of pulmonary function.

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Introduction

Chronic eosinophilic pneumonia (CEP) is a rare disease that was first described by Carington *et al.*¹ in 1969. A characteristic feature of CEP is marked accumulation of eosinophils in the lungs that is detectable via bronchoalveolar lavage (BAL) and/or transbronchial lung biopsy (TBLB). While there is reportedly a strong association

between CEP and allergic conditions such as asthma and allergic rhinitis, its etiology remains unknown.^{1–3} CEP responds well corticosteroid administration, but ongoing clinical concerns in CEP patients include a high frequency of relapse, and there is a complete lack of evidence with regard to optimal treatment strategies. In this context, we conducted the first prospective CEP study evaluating relapse rates following short-term (3 months) and long-term (6 months) corticosteroid treatment regimens.⁴ In that study, there was no significant difference in the cumulative relapse rate between the two regimens. We recently reported that considerable patients suffer from prolonged persistent pulmonary function defects, and identified some associated predictive factors.⁵ In that study, accompanying asthma and obstructive defects at the time of diagnosis were predictors of persistent obstructive impairment,

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whereas reticulation on high-resolution computed tomography (HRCT) and restrictive defects at the time of diagnosis predicted persistent restrictive impairment. With regard to relapse and persistent pulmonary function test (PFT) defects, relapse was not a significant predictor of obstructive or restrictive impairment. The current review summarizes previous CEP studies, and discusses the clinical prevalence of persistent impairment of PFT performance in CEP. We also propose a novel suggestion aimed at reducing excessive corticosteroid treatment based on risk factors associated with persistent PFT defects.

Epidemiology and clinical manifestations

CEP is a relatively rare disease, thus its prevalence is yet to be accurately determined. The French GREM“O”P registry reported that 84 cases of CEP were identified from over 700 cases of orphan pulmonary diseases.⁶ Only a few CEP cohort studies have been conducted to date,^{4–10} and the clinical characteristics of CEP reported in these studies are summarized in Table 1. Although CEP can occur in any age group, including childhood^{11,12} and those aged ≥ 80 years,^{5,9} the majority of CEP patients in the studies summarized in Table 1 were diagnosed in their 40s or 50s. There was a clear gender bias, in that women were approximately twice as likely to develop CEP. The prevalence of current-smokers among CEP patients ranged from 0% to 34.2% across the studies, and in all the studies $>60\%$ of the CEP patients had never smoked. A history of allergic disease was common in CEP patients, with approximately 50% reporting that they had asthma prior to CEP diagnosis, and allergic rhinitis was also reported at rates ranging from 15% to 35%. With regard to manifestations of CEP, there were no specific CEP symptoms. Prolonged respiratory symptoms such as coughing, sputum, fever elevation, and dyspnea were commonly found.

Diagnosis of CEP and laboratory findings

In the clinic, CEP was typically diagnosed based on combinations of following: 1) Clinical symptoms, 2) abnormal chest radiographs, 3) eosinophilia detected in BAL, blood eosinophilia, and/or evident eosinophil infiltration in the lung, 4) exclusion of other known eosinophilic pneumonias such as drug pneumonia, parasitic infection, allergic bronchopulmonary aspergillosis (ABPA), and eosinophilic granulomatosis with polyangiitis (EGPA). The diagnostic criteria for CEP and the laboratory findings reported in each study are shown in Table 2.

CEP is typically suspected in patients with progressive and prolonged respiratory symptoms as described above, and

characteristic chest radiography findings such as bilateral or unilateral peripheral opacities. Elevated levels of eosinophils in peripheral blood—one of the key characteristics of CEP—were frequently reported, with a mean of $>20\%$ or $>400/\mu\text{L}$ (Table 2).^{4–10} Elevated IgE levels were also found in some patients, and were reportedly helpful in cases of suspected CEP.³ In our previous CEP cohort study,⁵ blood eosinophilia $> 1000/\mu\text{L}$ and $>20\%$ were found in 73.8% and 64.6% of patients, respectively, and 41.3% had IgE >500 IU/L. Marked eosinophilia evident in BAL is an essential component of a diagnosis of CEP. While the cut-off values utilized differed in the studies reviewed, most were $>25\%$. There was discordance between BAL and lung eosinophilia in some cases, with evident eosinophil infiltration in the lung but eosinophilia in BAL of $<10\%$. Conversely, in other cases there were obvious eosinophils in BAL without eosinophil infiltration in lung tissues identified via TBLB. In one study, such cases comprised 28% (7/25) of the CEP patients.¹³ These discordances may be attributable to differences in sampling areas. While eosinophil infiltration in the lungs was usually detectable via TBLB, some cases of CEP diagnosed by open lung biopsy due to an absence of eosinophils in BAL or TBLB were reported.^{14,15} Proportions of lymphocytes and neutrophils in BAL were also noted in the studies, though to a lesser extent.^{4–6,8,13}

Radiology

Radiological imaging techniques, especially HRCT, were used for the differential diagnosis of CEP. At its onset, bilateral or unilateral airspace consolidation predominantly in the peripheral region, described as a “photographic negative pattern”, is highly indicative of CEP.^{16,17} Notably however, the photographic negative pattern was reportedly not specific for CEP and presented in only a quarter of the CEP patients.^{17–19} A larger study conducted by Johkoh *et al.*²⁰ assessed HRCT findings in diagnosed cases of CEP. They investigated whether subtypes of eosinophilic lung diseases could be differentiated using HRCT data from 111 patients, including 40 CEP, 13 acute eosinophilic pneumonia, 16 ABPA, and 16 EGPA cases. In that study, airspace consolidation with a predominantly peripheral distribution was found in 85% of CEP patients, and 78% of CEP cases were correctly diagnosed via HRCT. We also evaluated HRCT in CEP patients using the same criteria, and found that approximately 70% of patients exhibited a “CEP pattern” defined as patchy unilateral or bilateral airspace consolidation predominantly peripheral in distribution, areas of ground-glass attenuation predominantly in the middle and upper lung zones, and band-like subpleural attenuation.⁵ Via HRCT evaluation, it is also possible to discriminate between CEP and cryptogenic organizing pneumonia (COP), which are

Table 1
Clinical characteristics of CEP.

	Suzuki <i>et al.</i> ⁵	Ishiguro <i>et al.</i> ⁷	Oyama <i>et al.</i> ⁴	Marchand <i>et al.</i> ⁶	Merchand <i>et al.</i> ⁸	Durieu <i>et al.</i> ⁹	Naughton <i>et al.</i> ¹⁰
No of cases	133	73	44	62	53	19	12
Age, yr	58.3 $\pm$ 14.2 (21–84) [†]	56.7 $\pm$ 12.6	61.7 $\pm$ 11.2 (41–79) [†]	45.4 $\pm$ 16.8	43 $\pm$ 17	51 $\pm$ 16 (20–80) [†]	38.5 $\pm$ 9.2 (15–52) [†]
Sex, Female	84 (63.2%)	47 (64.4%)	29 (67.4%)	42 (67.7%)	34 (64.2%)	16 (84.2%)	12 (100%)
Current smoker	4 (3.0%)	25 (34.2%)	1 (2.3%)	4 (6.5%)	7 (13.2%)	0 (0%)	1 (8.3%)
Never smoker	87 (65.4%)	48 (65.8%)	26 (60.5%)	58 (93.5%)	—	18 (94.7%)	11 (91.7%)
Prior asthma	67 (50.4%)	35 (47.9%)	27 (61.4%)	32 (51.6%)	34 (64.2%)	7 (36.8%)	4 (33.3%)
Allergic rhinitis	35 (26.3%)	11 (15.1%)	—	14/59 (23.7%)	—	7 (36.8%)	—
Symptoms							
Cough	86 (64.7%)	54 (73.9%)	29 (65.9%)	57/61 (93.4%)	—	18 (94.7%)	10 (83.3%)
Fever	62 (46.6%)	29 (39.7%)	13 (29.5%)	48/62 (77.4%)	—	10 (52.6%)	5 (41.7%)
Sputum	32 (24.1%)	27 (37.0%)	11 (25.0%)	25/59 (42.4%)	—	7 (36.8%)	10 (83.3%)
Dyspnea	28 (21.1%)	27 (37.0%)	12 (27.3%)	57/62 (91.9%)	—	17 (89.5%)	6 (50%)
General Fatigue/Asthenia	8 (6.1%)	5 (6.9%)	3 (6.8%)	53/60 (88.3%)	—	11 (57.9%)	3 (25%)
Wheezing/rales	7 (5.3%)	16 (21.9%)	—	—	—	6 (31.6%)	6 (50%)
Chest pain	3 (2.3%)	3 (4.1%)	—	10/61 (16.4%)	—	2 (10.5%)	—
Appetite loss/weight loss	3 (2.3%)	2 (2.7%)	3 (6.8%)	45/60 (75.0)	—	13 (68.5%)	8 (66.7%)

[†] Range.

Table 2

Blood and BAL analyses of CEP.

	Suzuki <i>et al.</i> ⁵	Ishiguro <i>et al.</i> ⁷	Oyama <i>et al.</i> ⁴	Marchand <i>et al.</i> ⁶	Merchand <i>et al.</i> ⁸	Durieu <i>et al.</i> ⁹	Naughton <i>et al.</i> ¹⁰
Diagnostic criteria							
Symptoms durations	>2 weeks	>2 months	>1 month	>2 weeks	>2 weeks	—	—
Chest Xp abnormalities	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Definition of Eosinophilia	BAL and/or TBLB	BAL (Eo > 15%) and/or TBLB	BAL and/or TBLB	BAL (Eo > 40%) and/or Eo > 1.0G/L	BAL (Eo > 40%) and/or Eo > 1.0G/L	BAL and/or Blood	Blood
Blood analyses							
WBC (/mm ³)	9430 ± 3232	9931 ± 3464	8800 ± 2987	—	—	—	—
Eos (%)	27.0 ± 17.0	19.4 ± 14.6	26.4 ± 18.6	32.3 ± 15.7	31 ± 15	4232 ± 3461 [†]	1998 ± 1117 [†]
CRP (mg/dl)	3.98 ± 4.59	5.0 ± 6.4	3.89 ± 4.96	4.3 ± 4.75	—	—	—
IgE (IU/L)	936.6 ± 1888.2	620 ± 714	938.9 ± 1672.7	506 ± 633	499 ± 620	580 ± 696	33–1000 [‡]
BAL analyses							
MAC (%)	43.4 ± 26.3	—	45.2 ± 27.5	31.8 ± 20.7	35 ± 20	—	—
Ly (%)	11.0 ± 12.8	—	12.2 ± 12.9	6.1 ± 4.5	6 ± 5	—	—
Eos (%)	38.2 ± 27.4	41.4 ± 28.3	37.7 ± 25.9	58.0 ± 22.6	54 ± 25	50.5 ± 27.6	—
Neut (%)	3.95 ± 6.17	—	4.26 ± 6.68	3.8 ± 4.9	5 ± 6	—	—
CD4/CD8	1.64 ± 1.10	2.1 ± 2.0	1.50 ± 0.91	—	—	—	—

WBC, white blood cell; Eos, eosinophil; CRP, C-reactive protein; IgE, immunoglobulin E; TCC, total cell count; MAC, macrophages; Ly, lymphocytes; Neut, neutrophils; BAL, bronchoalveolar lavage; TBLB, transbronchial lung biopsy.

[†] Absolute number (/mm³).

[‡] Range.

known to share many features.²¹ A nodule or a mass followed by non-septal linear or reticular opacities, and bronchial dilation were reportedly more common in COP, while septal line thickening was more frequent in CEP.²¹ Collectively, the relevant studies analyzed suggest that characteristic HRCT findings may be of invaluable assistance in the diagnosis of CEP, in combination with clinical and laboratory findings.

Treatment

Oral corticosteroid

Once a diagnosis of CEP has been made, corticosteroid administration tends to dramatically improve both clinical symptoms and radiological abnormalities, and clinical and radiological remissions are usually achieved shortly thereafter.^{4–10} Most cases in the studies analyzed in the current review were treated via oral corticosteroid administration, with mean doses of prednisolone (PSL) of approximately 30 mg^{4,5,7,9,10} (Table 3). Intravenous steroid therapy and mini-pulse therapy or less, were also employed in severe cases

or cases exhibiting rapid progression.²² The collective data suggest that if the patient does not respond well to corticosteroid administration, alternative diagnoses should be considered. In some studies, in approximately 10% or less of the patients their CEP spontaneously resolved without corticosteroid administration.^{5–8} Death resulting from CEP is extremely rare, but irreversible fibrosis subsequent to the progression of CEP was reported.²³

Optimal duration of initial treatment

The management goal of CEP has been to control the disease with the smallest cumulative dose of corticosteroid, in order to minimize both the likelihood of relapse and corticosteroid-related adverse effects. However, evidence for an optimal regimen or an optimal duration of initial therapy to accomplish the management goal is entirely lacking. To date, only one study⁴ has prospectively evaluated the initial treatment regimen in the context of relapse rate. That study was a randomized, open-label, parallel group study comparing the relapse rates associated with short-term (3 months) and long-term (6 months) corticosteroid treatment in a 2-year

Table 3

Prevalence of initial treatment, relapse, and maintenance therapy in CEP.

	Suzuki <i>et al.</i> ⁵	Ishiguro <i>et al.</i> ⁷	Oyama <i>et al.</i> ⁴	Marchand <i>et al.</i> ⁶	Merchand <i>et al.</i> ⁸	Durieu <i>et al.</i> ⁹	Naughton <i>et al.</i> ¹⁰
Observation period	6.1 ± 4.1 years (1.1–15.0) [†]	5.3 years (0–28.5) [†]	3.8 ± 1.5 years (1.2–7.2) [†]	6.2 ± 4.6 years	7.3 ± 5.2 years	4.1 ± 3.7 years (1.0–11.8) [†]	10.2 years (4–13) [†]
Initial treatment							
PSL administrations	128 (96.2%)	65 (89.0%)	44 (100%)	61 (98.4%)	—	19 (100%)	12 (100%)
Initial PSL doses, (mg)	28.5 ± 6.4	29.4 ± 7.6	26.5 ± 4.2	0.97 ± 5.0 mg/kg	—	50 ± 17	20–60 [†]
Relapses							
Relapse rate	75 (56.4%)	27 (37.0%)	25 (56.8%)	30 (48.4%)	24/42 (57.1%)	9 (47.4%)	7 (58.3%)
Number of Relapse: once	37 (27.8%)	16.54/year [‡]	—	18 (29.0%)	2.3 ± 1.4 times	8 (42.1%)	0 (0%)
Number of Relapse: 2 >	38 (28.6%)	—	—	12 (19.4%)	0.44 ± 0.5 case/year [‡]	1 (5.3%)	7 (58.3%)
Predictor for relapse	None	Smoking (negative predictor)	None	—	Asthma (negative predictor)	—	—
Maintenance therapy							
PSL administrations	68 (51.1%)	35 (47.9%)	—	31 (68.9%)	56%	9 (47.4%)	10 (83.3%)
PSL doses, (mg)	5.4 ± 2.7	—	—	9.6 ± 7.4	—	11.8 ± 5.8	6.0 ± 2.4
OCT in non-relapsed cases	17/58 (29.3%)	18/46 (39.1%)	—	—	—	6/10 (60.0%)	3/5 (60.0%)
OCT in relapsed cases	51/75 (68.0%)	17/27 (63.0%)	—	—	—	3/9 (33.3%)	7/7 (100%)
ICS use	73 (54.9%)	—	—	—	65%	8 (42.1%)	5 (41.7%)
PSL + ICS use	41 (30.8%)	—	—	—	—	6 (31.6%)	—

PSL, prednisolone; OCT, oral corticosteroid; ICS, inhaled corticosteroid.

[†] Range.

[‡] Frequencies of relapse.

observation period. A 3-month group in which patients received 0.5 mg/kg PSL once daily, and in which PSL was tapered by ~20% every 2 weeks and discontinued after 3 months. A 6-month group in which patients received 0.5 mg/kg PSL once daily, and in which PSL was tapered by ~20% every 2 weeks for 2 months, and thereafter by ~20% every 3 weeks and discontinued after a total of 6 months. All patients in both groups responded well to the initial treatment, and there were no significant differences in the cumulative rates of relapse between the two regimens (3 months 61.9%, 6 months 52.1%, $p = 0.39$), suggesting that the short-term regimen is a viable option for the treatment of CEP in terms of the relapse rate and limiting the cumulative corticosteroid dose.

Relapse

In the studies analyzed, systematic or radiographic relapse frequently occurred during the tapering of steroid treatment or after cessation, though CEP responded well to corticosteroid treatment and a good outcome was common. Unlike at the time of initial diagnosis, for the diagnosis of CEP relapse BAL and/or TBLB are not necessarily required, but physicians should carefully consider the exclusion of infectious diseases and other eosinophilic lung diseases. In the previous studies analyzed, approximately half of the CEP patients experienced relapse^{4–10} (Table 3). Additionally, a considerable number of CEP patients experienced relapse several times. In our previous cohort study, 75 CEP patients (56.4%) experienced relapse, of which 38 (28.6%) relapsed more than twice.⁵ Upon resumption or readministration of corticosteroid therapy, favorable responses were usually observed, even in patients with repeated relapses. With regard to the treatment of relapsed CEP, no prospective studies have evaluated optimal corticosteroid administration duration or dose. Empirically, back to same doses of prednisolone used in the initial treatment or 0.5 mg/kg were employed, and they were variably tapered depending on individual physicians and patients.²²

Factors predicting relapse

Relapse is one of the major concerns in the management of CEP, and the prediction of relapse can change treatment strategies substantially. Accordingly, several studies have investigated factors that potentially predict relapse (Table 3). Merchand *et al.*⁸ retrospectively reviewed 53 CEP patients, and reported that those with asthma at the time of initial CEP diagnosis exhibited lower frequencies of relapse than with those without asthma. They speculated that higher frequencies of inhaled corticosteroid (ICS) use in CEP patients with asthma (88% vs. 31%) may have been responsible for the observed difference. In another retrospective study including 73 CEP patients, those who were current smokers at the time of initial CEP diagnosis exhibited lower frequencies of relapse than those who were non-smokers (8.3%/year vs. 21.1%/year).⁷ In that study, smoking was a significantly negative predictor of CEP relapse in a multivariate analysis ($p = 0.045$). Conversely, in our previous prospective ($n = 44$) and retrospective ($n = 133$) studies in CEP patients, there were no significant differences in asthma status, smoking habits, or CT findings between relapsed and non-relapsed patients.^{4,5} Therefore, to assess the predictive associations between these factors and CEP relapse, further large prospective studies are required.

Maintenance therapy

Because CEP relapse is frequently encountered but difficult to predict, and the relative influences of various factors on the clinical course of CEP have not yet been determined, many patients receive

oral corticosteroid maintenance therapy. A summary of maintenance therapy regimens derived from previous reports is shown in Table 3. Surprisingly, >50% of the CEP patients in the studies reviewed received indefinite maintenance therapy consisting of oral prednisolone with a mean dose of 5–10 mg.^{5–10} CEP patients experiencing relapse were treated more frequently with oral corticosteroid than those with non-relapsed cases.^{5,7,10} Notably, in one retrospective study 18/46 non-relapsed CEP patients (39.1%) were administered a long course of oral corticosteroid maintenance therapy.⁷ Similarly, in the cohort in our previous study, 29.3% of CEP patients without relapse ($n = 17$) received oral corticosteroid maintenance therapy, with no intention to discontinue that therapy.⁵ While prolonged corticosteroid administration may prevent relapse in some cases, in some cases it may constitute over-treatment. Additionally, corticosteroid use is reportedly associated with numerous adverse events such as infections (including Non-tuberculous mycobacterium infection), hyperglycemia, osteoporosis, and psychosis.^{5,7} Therefore, the establishment of optimal treatment strategies for CEP is urgently required, in order to minimize excessive treatment.

Alternative therapy

ICS is essential for the treatment of asthma, which was frequently combined with CEP in the studies reviewed. ICS may have a potent capacity to facilitate a reduction in oral corticosteroid maintenance doses in the context of CEP.^{10,24} In the studies reviewed, approximately half of the CEP patients received ICS and 30% were administered both ICS and oral corticosteroid^{5,8–10} (Table 3). With regard to ICS for the prevention of relapse, CEP patients with long-term ICS use exhibited fewer relapses,⁸ but this observation was not reflected in other studies. A series of studies have shown that ICS monotherapy is not effective as an initial therapy.²⁵ Meanwhile cases of successful treatment with omalizumab, an anti-IgE antibody, to discontinue OCT use have been reported.^{26,27}

Similarities and differences between CEP and AEP

Both CEP and AEP were characterized by accumulations of eosinophils infiltration in the lung that is detectable by BAL and/or TBLB. Thus there were many similarities in clinical manifestations, laboratory and radiographic findings, whereas there were also several differences between the diseases described followings. 1) The causes of CEP and AEP remains unknown, but recently AEP is considered as an acute hypersensitivity reaction to an unidentified inhaled antigen in an otherwise healthy individual.²⁸ Especially, closed associations with cigarette smoking were reported,^{29–31} and the possible role of environmental factors in home was also addressed.³² In contrast, despite associations with allergic diseases were expected, the etiology of CEP is not identified. 2) These pathogenic differences might affect to the distinct epidemiology. AEP and CEP can occur in any ages and both genders, the majority of smoking related AEP was around 20s. The frequencies of men in AEP were approximately twice compared with those of women.^{29,30,33} Conversely, women develop CEP as twice often as men.^{4–10} 3) Patients with CEP and AEP showed similar respiratory symptoms, whereas the durations of AEP were usually less than 7 days, and often had a fulminant onset with severe hypoxia than CEP.^{29,30,33} 4) Peripheral eosinophilia at the time of admission was less common in patients with AEP, and eosinophilia >500 μL were only found with 30–40% of the AEP patients.^{29–31,33} 5) There were marked differences in management of CEP and AEP. Although both diseases were well treated with corticosteroid, certain patients with AEP (6–66%) experienced spontaneous improvements

without corticosteroid,^{29–31,33} and duration of steroid treatment less than 2 weeks were proposed.³⁰ Additionally, relapse in patients with AEP was uncommon.^{29,31}

Pulmonary function at the time of CEP diagnosis

Dyspnea, wheezing/rales, productive cough, and hypoxia are common manifestations of CEP, and impaired pulmonary function as determined via PFT at the time of CEP diagnosis was commonly observed in the studies reviewed. Several cohort studies evaluated the frequencies and patterns of respiratory defects determined via PFTs (Table 4). Approximately 50%–70% of CEP patients exhibited impaired PFT results at the time of initial diagnosis, although the definitions of pulmonary function defects used in the studies differed slightly. Both restrictive and obstructive patterns were reported, of which restrictive defects tended to be slightly more prevalent at the time of CEP diagnosis. In the cohort in our previous study, restrictive patterns were found in 29.3% of the patients, whereas obstructive/restrictive and obstructive patterns were found in 12.1% and 10.3%, respectively.⁵

Persistent pulmonary function impairment in CEP patients

Combined asthma and other allergic conditions were commonly seen in CEP patients, and the severity of combined asthma was reported to increase after the onset of CEP.⁸ In patients with severe asthma, who occasionally suffer from steroid-dependent disease, major concerns were highlighted with regard to long-term declines in pulmonary function. Various factors associated with long-term PFT defects were identified, including late onset, degree of airway hyperresponsiveness, persistent symptoms, severe exacerbations, persistent smoking, and increased levels of inflammatory markers.³⁴ Approximately half of the CEP patients received oral corticosteroid as a complex of combined persistent asthma, repeated relapse, and disease severity, but few studies have evaluated the persistent impairment of pulmonary function in CEP patients. Only 19 CEP patients with were assessed via PFTs, with a mean follow-up of 4.1 years.⁹

To investigate the occurrence of persistent impairment of pulmonary function in CEP patients, and to elucidate predictive factors thereof, we conducted a longitudinal observation study.⁵ We enrolled 133 CEP patients who had follow-up periods of >12 months. With a mean interval of 6.1 ± 4.1 years from the onset of CEP, there were 114 patients with CEP assessed via PFT. Compared with pulmonary function at the time of CEP diagnosis, recovery of pulmonary function following eosinophilic inflammation was roughly found. Notably however, 42 CEP patients (36.8%) still

exhibited persistent defects on PFTs; 28 obstructive, 10 restrictive, and 4 obstructive/restrictive (Table 4). Patterns in PFT defects were also noted. Restrictive PFT defects were dominant at the time of initial diagnosis, whereas obstructive patterns were prior patterns at the last evaluation. We further examined the changes in pulmonary function in each patient. Among the patients, PFTs were performed in 101 at both the onset of CEP and during the follow-up course. Interestingly, patients with persistent restrictive PFT impairment showed significant lower forced vital capacity % (FVC %–pred) at initial diagnosis than those without persistent restrictive defects ($64.9 \pm 15.3\%$ vs. $87.5 \pm 19.2\%$, $p < 0.0001$, Fig. 1A). CEP patients with obstructive PFT defects at follow-up exhibited significant lower forced expiratory volume in 1.0 s/FVC (FEV₁/FVC) at CEP diagnosis compared with those without persistent obstructive defects ($68.2 \pm 12.1\%$ vs. $80.9 \pm 11.6\%$, $p < 0.0001$, Fig. 1B). Subsequently, in long-term PFT evaluations 78.7% of patients exhibiting normal PFT at initial diagnosis had not been PFT impairment. Conversely, approximately half of the patients with PFT defect at initial diagnosis had prolonged persistent impairment of PFT (Fig. 1C).

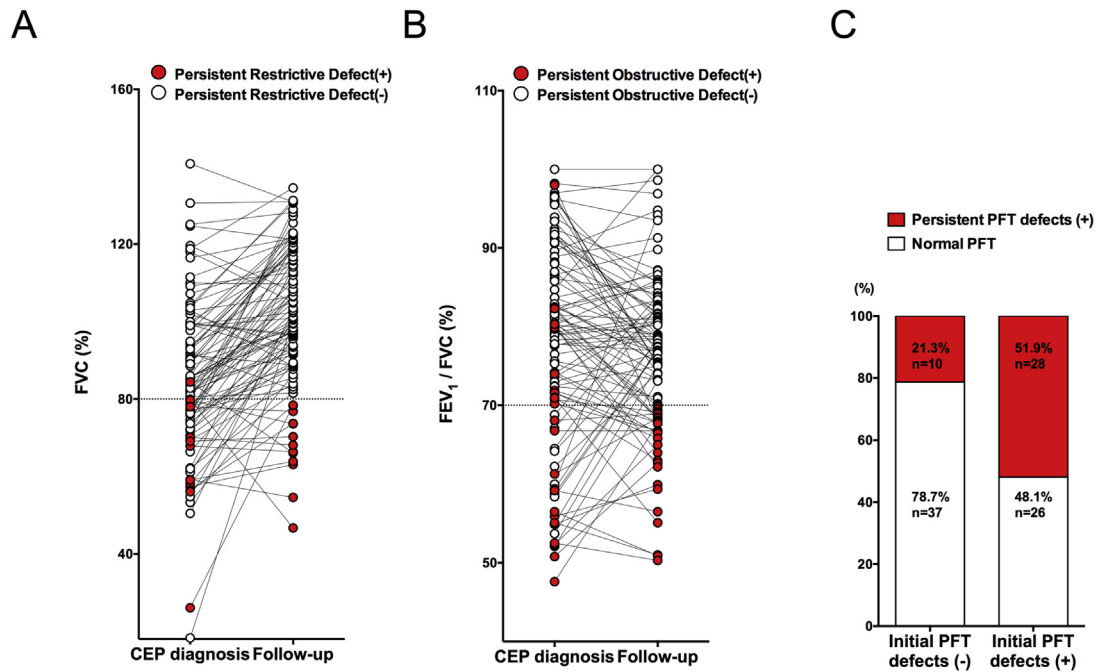
Factors associated with persistent pulmonary function impairment in CEP patients

Identifying factors that predict persistent PFT impairment is important with regard to CEP treatment strategies. For instance, whether relapse is a risk factor for future PFT defects or not, and whether relapse is related to a decline in lung function. The determination of predictive factors may facilitate the identification of cases where short-term therapy is justified, which may in turn facilitate a reduction in steroid-related adverse events. Thus, identification and evaluation of persistent impairment of pulmonary function may help to establish optimized patient-specific therapy based on estimated risk of long-term PFT decline. Notably however, few studies have investigated these issues. Durieu *et al.*⁹ followed 19 CEP patients and reported that BAL eosinophilia tended to be higher in those with persistent obstructive ventilatory defects, but relapses were not more common in that group. In this context, we reported for the first time that there were distinct predictors of obstructive and restrictive PFT defects.⁵ Comorbid asthma, FEV₁-pred, FEV₁/FVC, and initial obstructive PFT defect were significant independent predictors of persistent obstructive PFT impairment. Reticulation on HRCT, FVC%-pred, and initial restrictive PFT defect were significant predictors of persistent restrictive PFT defect. Unexpectedly, relapse was not a significant predictor of obstructive or restrictive persistent impairment of pulmonary function.

Table 4
Evaluations of pulmonary function test in CEP.

	Suzuki <i>et al.</i> ⁵	Ishiguro <i>et al.</i> ⁷	Oyama <i>et al.</i> ⁴	Marchand <i>et al.</i> ⁶	Merchand <i>et al.</i> ⁸	Durieu <i>et al.</i> ⁹	Naughton <i>et al.</i> ¹⁰
At CEP diagnosis	<i>n</i> = 116	<i>n</i> = 49	<i>n</i> = 38	<i>n</i> = 50	–	<i>n</i> = 19	–
PFT Defect	60/116 (51.7%)	N.S.	19/38 (50.0%)	34 (68.0%)	–	13 (68.4%)	–
Obstructive	12/116 (10.3%)	23/49 (46.9%)	4/38 (10.5%)	18/50 (36%)	–	4/19 (21.1%)	–
Restrictive	34/116 (29.3%)	29/49 (59.2%)	11/38 (28.9%)	16/50 (32%)	–	9/19 (47.4%)	–
Obstructive/restrictive	14/116 (12.1%)	N.S.	4/38 (10.5%)	N.S.	–	N.S.	–
At follow-up	<i>n</i> = 114					<i>n</i> = 19	
PFT Defect	42/114 (36.8%)	–	–	–	–	10/19 (52.6%)	–
Obstructive	28/114 (24.6%)	–	–	–	–	9/19 (47.4%)	–
Restrictive	10/114 (8.8%)	–	–	–	–	1/19 (5.3%)	–
Obstructive/restrictive	4/114 (3.5%)	–	–	–	–	N.S.	–
Predictor for long-term impairment of PFT	PFT impairment at CEP diagnosis Asthma Reticulation on HRCT					Eosinophilia on BAL	

PFT, pulmonary function test.



Comparison of %FVC (A), FEV₁/FVC (B), and pulmonary function defects (C) at CEP diagnosis and follow-up.

Fig. 1. Comparison of %FVC (A), FEV₁/FVC (B), and pulmonary function defects (C) at the time of chronic eosinophilic pneumonia diagnosis and during the follow-up period.

Target population for reducing steroid-dependent CEP: a proposed treatment strategy

The primary aims of CEP management are to control the disease and avoid relapse, with minimized steroid usage in order to prevent steroid-related adverse events and long-term impairment of pulmonary function. Relapse currently remains unpredictable

however, and many patients are evidently treated with oral corticosteroid for long periods, including some who have never experienced relapse.^{5,7,9,10} In one prospective study, there was no significant difference in the rates of relapse between patients treated with corticosteroid therapy for 3 months and those treated with corticosteroid therapy for 6 months.⁴ This suggests that short-term therapy may facilitate reduced cumulative steroid doses and

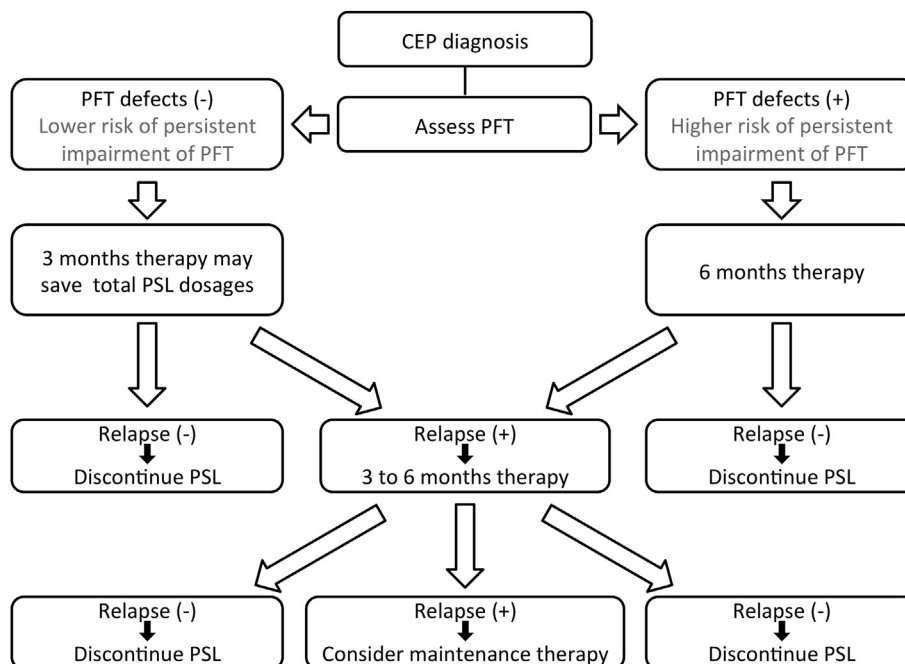


Fig. 2. Proposed pulmonary function test-guided treatment strategy for chronic eosinophilic pneumonia.

help to distinguish benign non-relapsing CEP patients from persistent relapsing CEP patients. Additionally, in one study CEP patients without pulmonary function defects at the time of initial diagnosis were at a relatively lower risk of persistent decline in pulmonary function, and relapse was not significantly associated with persistent PFT impairment.⁵ Therefore, PFT-guided initial CEP management may facilitate a reduction in excessive steroid-dependent CEP (Fig. 2), especially in patients without PFT impairment at the time of initial diagnosis and patients receiving corticosteroid who have not experienced relapse. Notably, persistent impairment of PFT was relatively common in CEP patients.^{5,9} Attention should be paid to these persistent impairments in the course of CEP management.

Conclusion

Although patients with CEP respond well to corticosteroid treatment, several concerns remain such as a high frequency of relapse, overtreatment, and persistent impairment of pulmonary function. CEP patients are heterogeneous with regard to severity, and include persistent and mild cases. Thus, while some CEP patients should remain on corticosteroid therapy for a long time, it is also necessary to avoid excessive steroid use in mild CEP cases. In addition, persistent impairment of PFT was not unusual in CEP patients. Therefore, further studies are required to facilitate the development of disease severity-based treatment regimens for CEP.

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Conflict of interest

The authors have no conflict of interest to declare.

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