Original Article

Predictive factors for relapse in corticosteroid-treated patients with chronic eosinophilic pneumonia

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Background: Chronic eosinophilic pneumonia (CEP) is an idiopathic disorder characterised by an abnormal and marked accumulation of eosinophils in the interstitium and alveolar spaces of the lungs. Systemic corticosteroid (CS) therapy leads to marked improvement. However, relapse is common in the clinical course, and the predictive factors for relapse of CEP are not well known. This study aimed to investigate predictive factors for relapse in CS-treated cases of CEP.

Methods: We identified consecutive patients with CEP at our institution between 1999 and 2019. We retrospectively reviewed 36 CS-treated patients with CEP who underwent bronchoalveolar lavage (BAL) and high-resolution computed tomography (CT) at diagnosis. We examined relapse at least 1 year after the initiation of CS treatment. Statistical analysis included univariate and multivariate Cox proportional hazard regression analyses; $P<0.05$ was considered statistically significant.

Results: The median (interquartile range) age at diagnosis was 59.5 years (47.8–70.0 years). This study included 13 men and 23 women. Twenty-five patients (69.4%) were never smokers and 15 (41.7%) had asthma. The peripheral blood eosinophil percentage was 35.0% (15.6–55.8%), and the BAL eosinophil percentage was 40.8% (10.7–68.5%). The median serum surfactant protein-D (SP-D) level was 135 ng/mL (82.2–176.7 ng/mL). High-resolution CT revealed centrilobular opacities in 23 patients (63.9%). Relapse of CEP was observed in 20 patients (55.6%). Higher serum SP-D levels and the presence of centrilobular opacities on high-resolution CT were significant predictors of relapse in multivariate Cox proportional hazard regression analysis ($P=0.017$ and $P=0.028$, respectively). Additionally, we devised a relapse prediction model for CS-treated CEP using two categorical parameters: the presence of centrilobular opacities and serum levels of SP-D (>135/≤135 ng/mL). Based on these parameters, cases were scored 2, 1, or 0. Patients with a score of 2 experienced relapses earlier than those with scores of 1 and 0 (log-rank test; $P=0.006$, $P=0.003$, respectively).

Conclusions: Centrilobular opacities on high-resolution CT and higher serum SP-D levels at diagnosis may be predictive factors for relapse in CS-treated patients with CEP.

Keywords: Chronic eosinophilic pneumonia (CEP); relapse; corticosteroid (CS); predictive factors

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Introduction

Chronic eosinophilic pneumonia (CEP) was first recognised as a unique pulmonary entity by Carrington *et al.* in 1969 (1). It is an idiopathic disorder with no known infectious, drugs or toxic aetiology and is characterised by an abnormal and marked accumulation of eosinophils in the interstitium and alveolar spaces of the lungs (2). CEP is a rare disease, representing 3% of the cases of various interstitial diseases (3,4) Peripheral blood eosinophilia and a high eosinophilic proportion in bronchoalveolar lavage fluid (BALF) are often included as diagnostic criteria for CEP. In approximately half of the cases, total serum immunoglobulin E (IgE) levels are elevated (5,6). Spirometry in patients with CEP is normal in up to one-third of patients but can demonstrate either a restrictive or obstruction pattern (4). Obstruction is more likely to occur in patients with underlying asthma. The characteristic computed tomography (CT) manifestations of CEP include bilateral peripheral non-segmental consolidation and ground-glass opacities in the upper lobes (4,7). Peripheral distribution of consolidation is seen in only about 25% of the cases (8,9).

Systemic corticosteroid (CS) therapy is the standard treatment for CEP and leads to marked improvement (6,10-12). However, a relapse often occurs during the clinical course of CEP when the CS is tapered or after cessation (4,7). Although previous studies have reported that smoking status or underlying asthma are possible risk factors for CEP relapse (11,13), they have not been sufficiently established because a few studies have reviewed these two factors (10). In a prospective study comparing CEP relapse rates between patients with CEP who underwent 3 and 6 months of CS treatment, recurrence rates were not significantly associated with the duration of CS therapy. They were not an independent factor for recurrence (14). Therefore, this study aimed to investigate the predictive factors for CEP relapse. We present the following article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-511/rc).

Methods

This single-center, retrospective study was approved by the Institutional Review Board of the National Hospital Organization Kinki-Chuo Chest Medical Center (KCCMC) (approval No. 684; approval date: 14 February 2019), and performed in accordance with the Declaration of Helsinki (as revised in 2013). Individual consent for this retrospective analysis was waived. We used an opt-out method, allowing the patients and their families to refuse to participate in the study.

Study population

We checked the database of bronchoalveolar lavage (BAL) of KCCMC between 1999 and 2019 and selected consecutive cases of CEP. CEP diagnosis was based on the criteria (*Table 1*) established by Mochizuki *et al.* (15). The criteria included cases which fulfil two of the following three situations: eosinophilia in BALF ≥10%, eosinophilia in peripheral blood ≥6%, and eosinophil infiltration in the transbronchial lung biopsy (TBLB) specimens. The percentages of eosinophilia in BALF and peripheral blood in the criteria were consistent with the previous reports (9,16).

Since some cases of CEP go into spontaneous remission, we enrolled the CS-treated cases of CEP in this study.

Clinical parameters

We reviewed demographic data, including patient age, sex, smoking history, the coexistence of asthma, and clinical data, including laboratory data, BALF data, pulmonary function, high-resolution CT pattern, and systemic CS therapy.

The serum levels of Krebs von den Lungen-6 (KL-6) and surfactant protein-D (SP-D) were measured using commercially available ELISA kits (ED046; Eizai, Tokyo, Japan; SP-D ELISA; Yamasa, Tokyo, Japan, respectively). The cut-off levels of serum KL-6 and SP-D were 500 U/mL and 110 ng/mL, respectively.

Table 1 CEP based on the criteria established by Mochizuki*

Inclusion in this study required fulfilment of both criteria
(A) CEP was suspected because of clinical symptoms and abnormal chest shadows that had existed for more than 1 month, with the exclusion of other diseases (e.g., infection) and eosinophilic pneumonias of determined origin
(B) At least one of the following conditions was satisfied:
(I) Histopathological diagnosis of CEP as determined by a surgical lung biopsy
(II) Eosinophilia in BALF or blood ≥30%
(III) At least two of the following conditions have to be met:
Many eosinophils in transbronchial lung biopsy specimens
Eosinophilia in BALF ≥10%
Eosinophilia in blood ≥6%

*, diagnostic criteria of CEP in Japanese shown in ref. (15) was translated and assembled into the table by N Takeuchi. CEP, chronic eosinophilic pneumonia; BALF, bronchoalveolar lavage fluid.

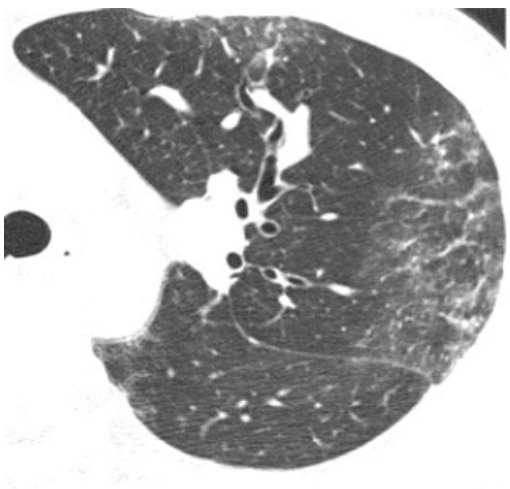

Figure 1 The high-resolution CT of a 39-year-old man with centrilobular opacities in the upper left lung. CT, computed tomography.

BAL was performed by instilling 150 mL of normal saline from three 50 mL aliquots and retrieved using a handheld syringe. This procedure has been previously described in detail (17). All pulmonary function tests were performed using CHESTAC-8800 or 8900 (CHEST, Bunkyo-ku, Tokyo, Japan).

High-resolution CT patterns at diagnosis were reviewed by an expert radiologist (M Akira) and two expert pulmonologists (N Takeuchi and T Arai). The high-resolution CT patterns included consolidation, ground-glass opacity, centrilobular opacity, and pleural effusion. Centrilobular opacities on high-resolution CT generally comprise small 5–10 mm lung nodules anatomically located centrally within secondary pulmonary lobules (*Figure 1*) (18).

Outcome measures

The observational period of CEP was defined as the time from the start of the CS treatment to the last observation (December 2020) or relapse. Relapse was defined as the resumption of or an increased dose of CS when the shadow worsened during the clinical course after starting CS treatment, while clinically ruled out infection, pulmonary edema or embolism, etc. to the extent clinically possible.

Statistical analysis

We investigated the predictive factors for relapse in CS-treated cases of CEP using univariate and multivariate Cox proportional hazard regression analyses. Factors with $P<0.1$ in univariate analysis were used for multivariate analysis. We devised a model to predict the relapse of CS-treated CEP by using significant categorical parameters. Relapse incidence curves were described using the Kaplan-Meier method, and the log-rank test was used to compare the curves. Statistical significance was set at $P<0.05$. JMP® 9.0.3 (SAS Institute, Cary, NC, USA) and SPSS for Macintosh (version 26; IBM Corp., Armonk, NY, USA) were used for all statistical analyses.

Table 2 Clinical characteristics

Parameters	N=36
Age, years	59.5 (47.8–70.0)
Gender (male/female)	13/23
Smoking history (yes/no)	11/25
Asthma (yes/no)	15/21
Laboratory values	
WBC, μL	11,050 (9,525–14,800)
Eosinophils, %	35.0 (15.6–55.8)
Eosinophils, μL	4,000 (1,172.7–7,117.8)
IgE*, IU/mL	488.5 (178–1,089.5)
CRP, mg/dL	4.2 (1.5–10.7)
KL-6*, U/mL	273 (206.3–350.5)
SP-D**, ng/mL	135 (82.2–176.7)
BALF	
Neutrophils, %	1.3 (0.6–3.2)
Lymphocyte, %	8.5 (3.5–14.7)
Eosinophils, %	40.8 (10.7–68.5)
CD4/CD8	1.7 (0.96–2.7)
Pulmonary function test	
%FVC***	73.9 (62.9–88.5)
FEV_1%***	77.4 (67.8–84.0)
Radiological findings on high-resolution CT	
Consolidation (yes/no)	35/1
Ground-glass opacity (yes/no)	35/1
Centrilobular opacity (yes/no)	23/13
Pleural effusion (yes/no)	11/25
Relapse (yes/no)	20/16
Observation period, days	595 (304–1,220)

Each parameter was expressed as number or median (interquartile range). *, n=34; **, n=33; ***, n=30 for the other parameters. WBC, white blood cell; IgE, immunoglobulin E; CRP, C-reactive protein; KL-6, Krebs von den Lunge-6; SP-D, surfactant protein-D; BALF, bronchoalveolar lavage fluid; FVC, forced vital capacity; FEV_1, forced expiratory volume in one second, CT; computed tomography.

Results

We identified 73 consecutive patients with CEP at our institution between 1999 and 2019. We excluded patients with insufficient information (n=6) and those without CS treatment (n=31). The remaining 36 CS-treated patients with CEP were included in the study. Patient characteristics are shown in *Table 2*. All patients underwent TBLB. As for the CS treatment, 12 patients were treated with 500–1,000 mg/day of methylprednisolone for three successive days (8 patients received maintenance prednisolone therapy of 0.5–1.0 mg/kg/day and 4 patients receive no maintenance therapy) and the remaining 24 patients received prednisolone therapy dosing approximately 0.5 mg/kg/day. No other immunosuppressive drugs were used. CEP relapse was observed in 20 patients (55.6%), and the median observation period until relapse was 404 days [interquartile range (IQR), 201–868 days]. The median observation period of the 36 CS-treated cases with CEP was 595 days (IQR, 304–1,220 days) (*Table 2*).

Predictive factors for relapse

Univariate and multivariate analyses showed that higher levels of serum SP-D [hazard ratio (HR), 1.008; 95% confidence interval (CI): 1.001–1.014, P=0.018] and centrilobular opacity (HR, 3.203; 95% CI: 1.182–10.293, P=0.021) were significantly associated with relapse of CS-treated CEP (*Table 3*). In these cases, higher serum SP-D levels and centrilobular opacities showed significantly earlier relapse than those without lower serum SP-D levels (HR, 1.007; 95% CI: 1.001–1.012, P=0.017) and centrilobular opacities (HR, 3.141; 95% CI: 1.126–10.396, P=0.028) by multivariate Cox proportional hazard regression analysis (*Table 4*).

Serum SP-D levels were divided into higher (>135 ng/mL) and lower (≤135 ng/mL) levels by their median values. Multivariate analysis was performed using two categorical parameters (the presence of centrilobular opacities and serum levels of SP-D, >135/≤135 ng/mL), and the two parameters were also significant (*Table 5*). Hence, we devised a relapse prediction model for CS-treated CEP using these two parameters. Based on these parameters, cases were

Table 3 Prediction of relapse: univariate Cox proportional hazard regression analysis

Parameters	HR	95% CI	P value
Age, years	0.996	0.970–1.025	0.770
Gender (male *vs.* female)	0.991	0.379–2.877	0.985
Smoking history (yes *vs.* no)	1.312	0.458–3.343	0.592
Asthma (yes *vs.* no)	0.573	0.220–1.412	0.227
WBC, ×100/μL	1.006	0.999–1.012	0.106
Eosinophils, %	1.009	0.987–1.032	0.426
Eosinophils, ×100/μL	1.007	0.999–1.013	0.091
IgE, ×100 U/L	1.016	0.968–1.056	0.477
CRP, mg/dL	1.057	0.958–1.162	0.262
KL-6, ×100 U/mL	1.088	0.888–1.247	0.359
SP-D, ng/mL	1.008	1.001–1.014	0.018
BALF			
Neutrophils, %	1.047	0.853–1.236	0.627
Lymphocytes, %	0.981	0.934–1.018	0.343
Eosinophils, %	0.996	0.981–1.011	0.580
CD4/CD8	1.284	0.919–1.737	0.137
%FVC	1.008	0.982–1.033	0.524
FEV_1%	1.010	0.971–1.050	0.609
Centrilobular opacity (yes *vs.* no)	3.203	1.182–10.293	0.021
Pleural effusion (yes *vs.* no)	2.501	0.986–6.261	0.054

HR, hazard ratio; CI, confidence interval; WBC, white blood cell; IgE, immunoglobulin E; CRP, C-reactive protein; KL-6, Krebs von den Lunge-6; SP-D, surfactant protein-D; BALF, bronchoalveolar lavage fluid; FVC, forced vital capacity; FEV_1, forced expiratory volume in one second.

Table 4 Prediction of relapse: multivariate Cox proportional hazard regression analysis

Parameters	HR	95% CI	P value
SP-D (ng/mL)	1.007	1.001–1.012	0.017
Centrilobular opacity (yes *vs.* no)	3.141	1.126–10.396	0.028

HR, hazard ratio; CI, confidence interval; SP-D, surfactant protein-D.

Table 5 Prediction of relapse: multivariate Cox proportional hazard regression analysis using higher/lower SP-D

Parameters	HR	95% CI	P value
SP-D (ng/mL) (high *vs.* low)*	4.014	1.575–11.600	0.003
Centrilobular opacity (yes *vs.* no)	3.498	1.251–11.769	0.016

*, median levels of serum SP-D were 135 ng/mL and we defined higher levels as >135 ng/mL, and lower levels as ≤135 ng/mL. SP-D, surfactant protein-D; HR, hazard ratio; CI, confidence interval.

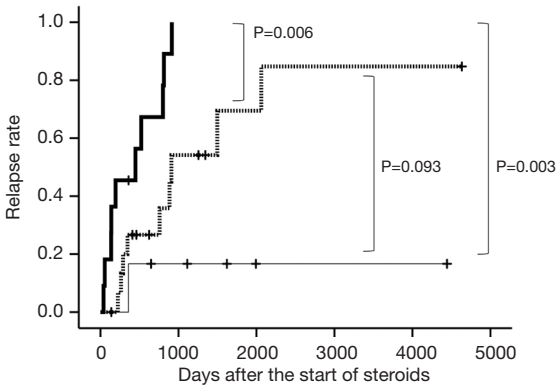

Figure 2 Relapse incidence curves were described according to the relapse predicting model using the presence of centrilobular opacities and serum levels of surfactant protein-D (>135/≤135 ng/mL). Cases satisfying both, either, and neither parameter, were scored 2 (thick line), 1 (dotted line), and 0 (thin line), respectively. Cases with a score of 2 experienced relapses earlier than those scored 1 and 0 (log-rank test; P=0.006, P=0.003, respectively). Cases with a score of 1 tended to experience relapse earlier than those that scored 0 (log-rank test; P=0.093).

scored 2, 1, or 0. Patients with a score of 2 experienced relapses earlier than those with scores of 1 and 0 (log-rank test; P=0.006, P=0.003, respectively). The median relapse time of patients with a score of 1 was between those with scores of 2 and 0 (*Figure 2*).

Discussion

Our findings showed that centrilobular opacities on high-resolution CT and higher SP-D suggest a higher probability of relapse in CEP.

Centrilobular opacities on high-resolution CT suggested a higher probability of CEP relapse. A retrospective study reported that centrilobular nodules within ground-glass opacities were observed in 18% of patients with CEP (19). Thus, centrilobular opacities may be a feature of high-resolution CT in patients with CEP. Centrilobular opacities generally indicate the presence of a lesion in the bronchioles (20).

Since CEP is an eosinophilic lung disease, centrilobular opacities may reflect bronchiolar eosinophilic inflammation and suggest eosinophilic bronchiolitis (21). The first case of eosinophilic bronchiolitis was reported in Japan (22). Although airflow obstruction and peripheral blood eosinophilia were observed, the patient was not diagnosed with asthma. Centrilobular opacities were observed on the high-resolution CT images. TBLB specimens revealed pathological findings of eosinophilic bronchiolitis, and the number of eosinophils in the BALF increased. Airway obstruction improved with CS therapy but relapsed during CS tapering. Following this report, Cordier *et al.* proposed hypereosinophilic obliterative bronchiolitis (HOB) to describe a similar disease entity in case reports including 6 patients showing centrilobular nodules on high-resolution CT (23). In these cases, HOB manifestations recurred when the oral prednisone dose was decreased to 10–20 mg per day. These two reports demonstrate that eosinophilic bronchiolitis may relapse easily with a medium dose of CS. Similar to these two reports, the presence of centrilobular opacity on high-resolution CT, possibly suggesting eosinophilic bronchiolitis in CEP, may be associated with early relapse of CEP.

We also found that higher serum SP-D levels were associated with relapse in CS-treated patients with CEP. SP-D is a hydrophilic protein mainly secreted by alveolar type II cells and plays an important role in the innate immunity of the lung (24). SP-D has beneficial effects in infectious diseases because it functions as an opsonin and participates in pathogen phagocytosis. Its pathophysiological role in non-infectious diseases associated with eosinophilia has been examined. Serum SP-D levels are elevated in patients with allergic asthma (25). Mackay *et al.* found that serum SP-D was increased in severe asthma with mixed eosinophil and neutrophil inflammation and was enriched in SP-D degradation products (26). As for acute eosinophilic pneumonia, elevated serum SP-D reflects disease activity, and its serum levels decrease according to improvement after CS therapy (27,28). These findings could explain why higher levels of serum SP-D were associated with relapse in CS-treated patients with CEP.

What is the physiological role of SP-D in eosinophilic inflammation? In mouse models of allergic bronchopulmonary aspergillosis, SP-D expression in BALF was enhanced, and ablation of SP-D led to enhanced eosinophilia and IgE production. In vitro investigations have also shown that SP-D inhibits eosinophil chemotaxis, binds eosinophils, and attenuate degranulation (29). Hence, SP-D production can be induced to resolve eosinophilic inflammation (30).

Merchand *et al.* retrospectively reviewed 53 patients with CEP and reported that patients with asthma at the time of CEP diagnosis had more relapses during follow-up than those without asthma (11). In another retrospective study of 73 patients with CEP by Ishiguro *et al.*, a history of smoking

was a negative predictor of CEP relapse (13). In contrast, in other previous prospective and retrospective studies of patients with CEP, there were no significant differences in asthma status or smoking habits (14,31,32), similar to the results of our study. Hence, further large-scale prospective studies are needed to determine whether smoking history or asthma status is associated with CEP relapse.

The frequent occurrence of relapse with CEP during tapering or discontinuation of CS demands the need for alternative therapy in case of relapse with CEP. Mepolizumab is a fully humanized antibody against interleukin 5, an important growth factor of eosinophils. Brenard *et al.* reported that treatment with mepolizumab for CEP relapse significantly reduced another relapse (33). This treatment may contribute to future treatment of CEP with centrilobular opacities on high-resolution CT and higher SP-D.

This study had some limitations. It was retrospective study that took over 20 years, and included a limited number of cases. Therefore, the treatment and timing of assessment varied for each patient. Also, this study was conducted in a single centre. However, we reviewed consecutive patients with CEP, and the CEP criteria for the included studies are conventional and have not been changed. Further large, multicentre studies are warranted.

Conclusions

Centrilobular opacities on high-resolution CT and higher serum SP-D levels at diagnosis may be predictive factors for early relapse in CS-treated patients with CEP. We should cautiously observe CEP relapse in CS-treated patients with these two factors at diagnosis.

Acknowledgments

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-511/rc

Data Sharing Statement: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-511/dss

Peer Review File: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-511/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-511/coif). YI has received grants from Japanese Ministry of Health, Labour, and Welfare and Japan Agency for Medical Research and Development regarding interstitial lung diseases. TA has received lecture fees from Boehringer Ingelheim and Shionogi for activities not connected with the submitted work. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that question related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the National Hospital Organization Kinki-Chuo Chest Medical Center institutional review board (approval No. 684) and individual consent for this retrospective analysis was waived.

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