Allergology International 68 (2019) 413–419

Contents lists available at ScienceDirect

Allergology International

journal homepage: http://www.elsevier.com/locate/alit

Invited Review Article

Eosinophilic pneumonia: A review of the previous literature, causes, diagnosis, and management

Yuzo Suzuki*, Takafumi Suda

Second Division, Department of Internal Medicine, Hamamatsu University School of Medicine, Hamamatsu, Japan

ARTICLE INFO

Article history:
Received 10 May 2019
Available online 25 June 2019

Keywords:
Acute eosinophilic pneumonia
Chronic eosinophilic pneumonia
Pulmonary function tests
Relapse
Smoking habit

ABSTRACT

Eosinophilic pneumonia (EP) is a rare disorder, comprising several heterogeneous diseases. Two major types of EP are acute eosinophilic pneumonia (AEP) and chronic eosinophilic pneumonia (CEP), both of which are characterized by marked accumulation of eosinophils in lung tissues and/or BAL fluid. AEP and CEP share some similarities in terms of pathophysiology, radiological findings, and treatment response to corticosteroids. However, they distinctly differ in etiology, clinical manifestations, and the nature of disease course. Especially, although AEP and CEP respond well to corticosteroids, relapse frequently occurs in patients with CEP, but rarely in those with AEP. Although CEP occasionally persists and becomes corticosteroid dependent, most patients with AEP completely recover. This article reviews previous studies and discusses the etiology, clinical manifestations, and treatment of AEP and CEP.

Introduction

Eosinophilic lung disease comprises a rare group of heterogeneous diffuse parenchymal lung diseases, which are characterized by marked accumulations of infiltrating eosinophils in the alveolar space and the interstitium. These pathological conditions have been classified as primary or secondary disorders depending on the absence or presence of a known underlying cause.[1,2] Primary eosinophilic lung disease is further divided into systematic and lung limited diseases. Eosinophilic granulomatosis with polyangiitis (EGPA) and hyper-eosinophilic syndrome belong to the former category. Whereas, acute eosinophilic pneumonia (AEP), chronic eosinophilic pneumonia (CEP), and Loeffler syndrome are classified into the latter category. In this review, we focus on AEP and CEP and describe recent advances, according to our understanding, of these two eosinophilic lung diseases.

CEP was first described by Carrington *et al.* in 1969 as an idiopathic pulmonary disorder characterized by abnormal infiltrations of eosinophils in the lungs,[3] and AEP was originally reported as a cause of respiratory failure in 1989 by Allen *et al.*[4] Both CEP and AEP share some pathophysiological features, such as significant eosinophil infiltrations in the pulmonary parenchyma and prompt response to corticosteroid treatment. However, CEP is clinically distinct from AEP in terms of etiology, disease onset, and the nature of the disease course. In this review, we summarize the clinical manifestations and diagnosis of AEP and CEP and also discuss their treatment and management.

Acute eosinophilic pneumonia (AEP)

Epidemiology and etiology of AEP

AEP was first described by four case series of an idiopathic disease characterized by febrile illness, diffuse pulmonary infiltrates, and pulmonary eosinophilia.[4] Interestingly, the following several studies highlighted a possible association between AEP onset and changes in smoking habits, such as newly starting smoking or alterations in an existing smoking habit (including restarting smoking and increasing the number of cigarettes smoked), suggesting that changes in smoking habits can something cause AEP.[5–11] Importantly, even short-term exposure to passive smoking can cause AEP.[12]

Because AEP is a rare lung disease, its epidemiology remains understudied. One epidemiologic study identified 18 patients with AEP among 183,000 US military personnel deployed in or near Iraq, an estimated 9.1 cases/100,000 person years with this condition.[6] To date, there have been several cohort studies of AEP, which are summarized in Table 1.[5–10] Most patients with AEP are at approximately 20 years of age, with a male sex predominance at 60–100%. Moreover, most patients with AEP are current smokers. A history of

* Corresponding author. Second Division, Department of Internal Medicine, Hamamatsu University School of Medicine, 1-20-1 Handayama Higashi-ku, Hamamatsu, Shizuoka 431-3192, Japan.
E-mail address: yuzosuzu@hama-med.ac.jp (Y. Suzuki).
Peer review under responsibility of Japanese Society of Allergology.

https://doi.org/10.1016/j.alit.2019.05.006

Table 1
Clinical characteristics of AEP.

	Philit *et al.*[5]	Shorr AF *et al.*[6]	Uchiyama *et al.*[7]	Rhee *et al.*[8]	Jhun *et al.*[9]	Sine *et al.*[10]
No of cases	22	18	33	137	85	43
Age, yr	29 ± 15.8[†]	22 (19–47)[‡]	19.3 ± 2.7[†]	20 (19–21)[§]	21 (20–21)[§]	25.5[¶]
Sex, female	9 (40.9%)	2 (11.1%)	10 (30.3%)	0 (0%)	0 (0%)	4 (7.0%)
Current smoker	8 (36.4%)	18 (100.0%)	32 (97.0%)	135 (98.5%)	84 (98.8%)	39 (90.7%)
Never smoker		0	1 (3.0%)	1 (0.7%)		–
Durations of smoking[#]	1 week-3months [‖]	1 month (2w-2 months)[‡]	2 weeks (1 day–2 months)[‡]	17 days (13–26 days)[§]	–	–
Start smoking	6 (27.2%)	14 (77.8%)	21 (63.6%)	71 (51.8%)		33 (76.7%)
Restart smoking		0 (0%)	2 (6.0%)	41 (19.9%)		
Increased smoking		2 (11.1%)	6 (18.2%)	13 (9.5%)		–
No change		2 (11.1%)	3 (9.1%)	10 (7.3%)		6 (14.0%)
Allergic diseases	Dermatitiss 2 (9.1%)	–	Asthma 3 (9.1%) Dermatitiss 2 (6.1%)	Rhinitis 10 (7.3%) Asthma 3 (2.2%) Dermatitiss 3 (2.2%)	–	–

[†] Mean ± SD.
[‡] Median (range).
[§] Median (interquartile range).
[¶] Mean.
[‖] Range.
[#] Time from initiation or increased smoking number to development of AEP.

allergic disease such as bronchial asthma, dermatitis, and rhinitis is uncommon and found in fewer than 10% of cases. Three studies have recorded the detailed smoking history of patients with AEP.[6–8] They showed that 50–80% of patients had started smoking less than 2 months before the onset of AEP. In addition, 11–29.4% of the patients had restarted smoking or had increased the quantity of cigarettes smoked before the onset of AEP. Although smoking is likely to be involved in most cases, it should be noted that a few cases of truly "idiopathic AEP" exist in the real world.[11]

Although the exact etiology of AEP remains unknown, it has been hypothesized that it involves an acute hypersensitivity reaction to an inhaled antigen, such as tobacco smoke, in an otherwise healthy individual. Apart from tobacco smoke, AEP can develop under unusual outdoor circumstances; military personnel working in the desert of the Middle East,[6] a firefighter following the collapse of the World Trade Center towers,[13] inhaled smoke from fireworks,[14] and environmental factors in the home[15] have also been noted. Therefore, epithelial injury following exposure to inhaled antigens or tobacco smoke is postulated to trigger AEP.[16] Alveolar or epithelial damage can elicit activation of the inflammatory signal, leading to secretion of IL-33, IL-25, and thymic stromal lymphoprotein. These epithelial cytokines subsequently stimulate ILC2s and polarize Th2s, resulting in activation and recruitment of eosinophils in the lungs. In fact, several lines of studies have reported elevated levels of IL-5,[17,18] IL-18,[19] IL-33,[20] and other cytokines and chemokines in the BAL fluids and peripheral blood of patients with AEP. Among them, IL-33 is supposed to play central role in AEP[16] because marked IL-33 secretion is caused by epithelial and also endothelial injuries, which strongly activate ILC2s with rapid production of IL-5 and IL-13, that in turn further amplify eosinophil activation and Th2 polarization.

Clinical manifestations and laboratory findings of AEP

A summary of clinical manifestations and laboratory findings from previous studies is presented in Table 2. Generally, AEP is characterized by acute onset of dyspnea accompanied by cough and fever/chills. As shown in Table 2, dyspnea, cough, and fever/chills are found in approximately more than 80% of patients. Sputum production is not commonly observed, but symptoms of chest pain and myalgia (30–50%) are not rare. Importantly, most symptoms can develop within several days after an acute onset. Severe hypoxemia and/or respiratory failure presenting acute respiratory distress syndrome are often found, and most patients with AEP show room-air SpO_2 <90%. Uchiyama *et al.* analyzed the data of 33 patients with AEP with a mean PaO_2 of 60.3 ± 11.6 torr,[7] and Rhee

Table 2
Clinical manifestations, Blood and BAL analyses of AEP.

	Philit *et al.*[5]	Shorr AF *et al.*[6]	Uchiyama *et al.*[7]	Rhee *et al.*[8]	Jhun *et al.*[9]	Sine *et al.*[10]
Symptoms (days)	8.3 ± 8.5 days	1 (1–4 days)	3.5 (1–11 days)	–	3 (2–3 days)	–
Dyspnea	22 (100%)	8/9 (88.9%)	27 (81.8%)	127 (92.7%)	–	–
Cough	18 (81.8%)	6/9 (66.7%)	54 (73.9%)	130 (94.9%)	59 (69.4%)	–
Fever/chills	22 (100%)	8/9 (88.9%)	31 (93.9%)	120 (87.6%)	66 (77.6%)	–
Chest pain	11 (50.0%)	5/9 (55.6%)	–	22 (16.1%)	–	–
PaO_2 or P/F ratio			60.3 ± 11.6 torr	284.3 (232.7–334.1)	256 (225–315)	182
ICU administration	16/22 (72.7%)	–	–	108 (78.9%)	40 (47.1%)	–
Mechanical ventilation	8/22 (36.4%)	12 (66.7%)	–	2 (1.5%)	2 (2.4%)	29 (67.4%)
Blood analyses						
WBC (/mm^3)	20,700 ± 1090	–	15,614 ± 6440	12,070 (9435–16,835)	13,570 (9715–18,485)	
Eos (/mm^3)	980 ± 1500	323 ± 183	623 ± 813	360 (220–583)	318 (169–511)	
Eos > 500/mm^3	8/22 (36.4%)		13/33 (39.4%)	44/137 (32.1%)	24/85 (28.2%)	
Maximum Eo (/mm^3)		2547 ± 1560	2010 ± 1182			
CRP (mg/dl)	12.1 ± 9.4	–	8.4 ± 5.9	16.6 (9.1–36.6)	10.25 (5.67–16.15)	
BAL Analyses						
Ly (%)	12.5 ± 12.7	–	13.4 ± 9.2	19.0 (12–28)[†]	22 (13–29)[†]	37%
Eos (%)	54.4 ± 19.2	40.5 (25–74)[†] 44.0 ± 18.6	52.8 ± 18.6	40.0 (35–53)[†]	44 (33–62)[†]	
Neut (%)	13.0 ± 14.0	–	–	5.0 (2–11)[†]	5 (1–15)[†]	

WBC, white blood cell; Eos, eosinophil; CRP, C-reactive protein; IgE, immunoglobulin E; BAL, bronchoalveolar lavage; Ly, lymphocytes; Neut, neutrophils.
[†] Median range

et al. reported on 137 patients with AEP with a mean median P/F ratio of 284.3 (range, 232–334).[8] Therefore, more than a few patients with AEP require admission to the intensive care unit (30–80%), and cases with severe hypoxemia also need mechanical ventilation.[5,6,9–11]

Blood analyses at the time of admission show increased white blood cell count and C reactive protein levels. Strikingly, peripheral eosinophilia (>500/mm^3) has only been found in 30% of cases.[5–11] Blood eosinophil counts in most patients with AEP remain normal at the time of admission and subsequently increase during the following days. A retrospective study by Jhun *et al.* showed that an initial elevated count of peripheral eosinophils was associated with milder disease course compared to the normal range in terms of oxygen requirements, duration of oxygen administrations, and the rate of intensive care unit admission.[9] Because most patients with AEP have no peripheral eosinophilia, detailed disease history and computed tomography (CT) images comprise cues to suspect AEP. As patients with AEP often have severe respiratory failure, pulmonary function tests (PFTs) cannot be routinely performed.

Consequently, BAL eosinophilia is essential for the diagnosis of AEP. BAL eosinophilia was reported usually over 40%, while proportions of lymphocytes also increased to 10–30%. Additionally, neutrophils in the BAL also increased to some extent. Tissue eosinophilia is usually found in lung tissues obtained by transbronchial lung biopsy (TBLB), and surgical lung biopsy is not necessary unless specified. The histological features of AEP are characterized by dense accumulations of eosinophils in the alveolar space and the interstitium. Interstitial edema, fibrin depositions, and detached type II epithelial cells are frequently found, but airway epithelial architectures are usually preserved.[16,21] In severe cases, diffuse alveolar damage was reported.[22]

Radiology of AEP

Bilateral ground grass attenuations mixed with consolidations are the most common features on chest radiography in patients with AEP. In some cases, Kerley B lines are also present. Evaluations with high-resolution CT (HRCT) are helpful to diagnose AEP. Earlier detailed studies on HRCT findings in AEP cases showed that bilateral areas with ground glass attenuation were found in almost all patients, and 70–90% of the patients had interlobular septal thickening.[8,23] (Fig. 1). Bilateral pleural effusion was also present in most cases (>90%).[8,23] Airspace consolidation was seen in 40–60% of patients. Poorly defined centrilobular nodules were not uncommon (30–50%)[8,23,24] and were occasionally noted as the only abnormality in the early phase of smoking-related AEP.[25] The distributions of these HRCT findings are generally random patterns with cephalocaudal and cross-sectional distributions, while peripheral and lower dominant distributions were found in approximately 30% of cases.[23] A crazy paving pattern, which is not a specific finding in AEP and is seen in various interstitial lung diseases, was reported to be present in 28% of patients with AEP.[23]

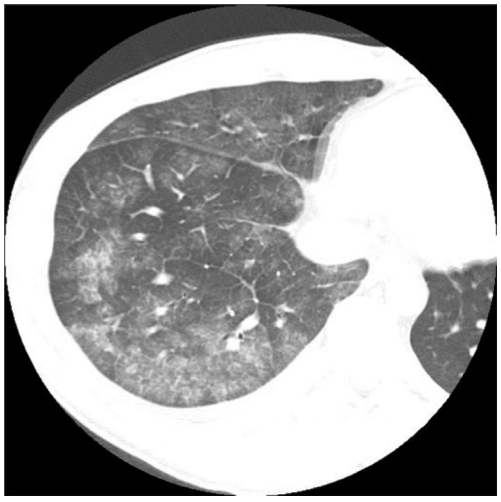

Fig. 1. Chest CT image of a patient with AEP. A 21-years old man showed diffuse ground glass opacities together interlobular septal thickening (presented right lower and middle lobe).

Diagnosis of AEP

There are no formal diagnostic criteria, but the modified *Philit* criteria have been used for the diagnosis of AEP as follows[1,2,16,26]: 1) acute febrile illness of less than 1 month, 2) hypoxemia, 3) bilateral diffuse pulmonary infiltrates on chest radiography, 4) BAL fluid eosinophilia >25% and/or infiltrations of eosinophils in the lung parenchyma on lung biopsy, and 5) absence of known causes of eosinophilic lung disease such as drugs and infections.

Treatment of AEP

Although patients with AEP frequently exhibit progressive respiratory failure or severe hypoxemia, systematic corticosteroid therapy rapidly improves patient condition within several days. In cases with severe respiratory failure, intravenous administration of high-dose corticosteroids is employed. Although no clinical trial has explored the optimal duration of therapy, 2 weeks of steroid treatment may be considered sufficient. Indeed, Rhee *et al.* retrospectively compared the efficacy of 2 week-steroid therapy and 4 week-steroid therapy and found no significant differences in terms of symptomatic and radiographic resolution.[8] In cases with mild hypoxemia, spontaneous resolution may be expected.[7] In contrast to CEP, smoking-related AEP does not usually relapse if the patients discontinue smoking, and complete recovery without impaired pulmonary function can be achieved.[5]

Chronic eosinophilic pneumonia (CEP)

Epidemiology and clinical manifestations of CEP

CEP is a rare disorder among the diffuse parenchymal lung diseases. The incidence of CEP among the interstitial lung diseases (ILDs) was reported to be 0–2.7% in an ILD registry in Europe, and 0.5–1.2% in an ILD registry in the US.[27] Although a small retrospective study estimated the annual incidence of CEP at 0.23 cases/100,000 population,[28] the exact incidence of CEP among the general population remains undetermined. Compared with AEP, the clinical characteristics of CEP have distinct features. The summaries of previous studies are shown in Table 3.[29–36] CEP can develop at any age including during childhood and old age, and most patients with CEP are in their 30 s–50 s, with women being twice as likely to develop this disease.[1,2,26,29] A close association between CEP and allergic diseases has been noted, and more than half of the patients with CEP have an allergic disease, such as bronchial asthma, atopic dermatitis, and allergic rhinitis. These allergic diseases can develop both prior and after the onset of CEP.[34] In contrast to a possible association between smoking and the pathogenesis of AEP, smokers with CEP are uncommon (usually comprising less than 10%) and most patients with CEP (>60%) have never smoked.

Clinical manifestations and laboratory findings of CEP

There are no symptom specific to CEP. Prolonged (several months) respiratory symptoms such as cough (60–90%), and

Table 3
Clinical characteristics of CEP.

	Suzuki *et al.*[30]	Ishiguro *et al.*[31]	Oyama *et al.*[32]	Marchand *et al.*[33]	Marchand *et al.*[34]	Durieu *et al.*[35]	Naughton *et al.*[36]
No of cases	133	73	44	62	53	19	12
Age, yr	58.3 ± 14.2 (21–84)†	56.7 ± 12.6	61.7 ± 11.2 (41–79)†	45.4 ± 16.8	43 ± 17	51 ± 16 (20–80)†	38.5 ± 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%)	–

† Range.

shortness of breath/dyspnea (20–50%) are the most common manifestations, but patients with CEP rarely develop respiratory failure and usually show normal or mild hypoxemia. Temperature elevation, sputum, and wheezing are often found. As a non-respiratory manifestation, patients with CEP also exhibit appetite loss and/or weight loss and occasionally present with chest pain.[29–33,35,36]

The summary of blood and BAL analyses are shown in Table 3. In addition to the prolonged respiratory symptoms, blood analyses are helpful in raising the suspicion for CEP. In contrast to AEP, in which peripheral eosinophilia is unusual at disease onset, blood eosinophilia is observed in most patients with CEP together with elevated IgE levels, being a key characteristic of CEP. Mild elevation of C-reactive protein and white blood cell count are also noted. A review of previous case series showed that the mean peripheral eosinophil and IgE levels were at approximately 30% and >500 IU, respectively.[29–36] In our cohort, including 133 CEP cases, 80% of the patients showed peripheral eosinophilia (>10%), and more than 60% had elevated serum IgE (>300 IU).[30]

When performing bronchoscopy, eosinophilia on BAL and/or tissue eosinophilia on TBLB are observed. The summary of previous cohort studies presented in Table 4 shows BAL eosinophilia with a mean proportion of 40–60%.[29–36] However, discordance between BAL eosinophilia and tissue eosinophilia can occasionally occur. Matsuse *et al.* showed that, among 25 patients with CEP with BAL eosinophilia, 36% showed absence of tissue eosinophilia on TBLB.[37] Taniguchi *et al.* reported a case of CEP without BAL eosinophilia that was eventually diagnosed by surgical lung biopsy with tissue eosinophilia.[38] This discordance may arise from differences in the sample area or small lung specimens obtained by TBLB.

Pulmonary function tests

Assessment of PFTs is helpful to evaluate disease severity and to monitor disease control during follow-up periods. At the time of CEP diagnosis, defects in PFTs are common ranging from 50% to 70%.[30–33,35] Both obstructive and restrictive patterns are noted, and the restrictive pattern is slightly more frequent than the obstructive pattern at the time of diagnosis. Analyses of spirometry in 116 patients with CEP showed an obstructive pattern in 10.3%, a restrictive pattern in 29.3%, and a mixed (obstructive/restrictive) pattern in 29.3%[30] of patients. Diffusing capacity for carbon monoxide is also decreased in approximately half of the patients.[33] Because 30–64% of patients with CEP have asthma and they often presented with wheezing, it should be considered that comorbid asthma affects the results of PFTs in patients with CEP.

Radiology of CEP

Chest radiography shows bilateral or unilateral airspace consolidation predominantly in the peripheral region, described as a “photographic negative pattern,” that is reportedly highly indicative of CEP.[1,29,39,40] However, the photographic negative pattern was reported to be not specific to CEP and was present in only a quarter of patients with CEP.[39,41,42] Airspace consolidation and ground glass attenuations are typical findings of CEP on HRCT. Especially, airspace consolidation with a predominantly peripheral distribution is commonly present[24,30,33,43,44] (Fig. 2). The presence of pleural effusions is uncommon (usually in less than 20% of cases).[24,30,32,33,43,44] HRCT is also helpful to differentially diagnose CEP among the eosinophilic lung diseases. Johkoh *et al.* assessed the HRCT data of 111 patients with a variety of eosinophilic lung diseases, including 40 with CEP, 13 with AEP, 16 with allergic bronchopulmonary aspergillosis (ABPA), and 16 with EGPA and examined the diagnostic accuracy of HRCT. Airspace consolidation with a predominantly peripheral distribution was found in 85% of patients with CEP, and a high accuracy of CEP diagnosis (78%) was achieved via HRCT.[24] Similar to that study, patterns of airspace consolidation with peripheral distribution were found in approximately 70% of patients with CEP in another cohort.[30] Cryptogenic organizing pneumonia (COP) is also known to share HRCT findings with CEP, but several differences have been reported. Arakawa *et al.* showed that nodules or a mass accompanied by non-septal linear or reticular opacities and bronchial dilation were more common in COP, while septal line thickening was more frequent in CEP.[43]

Diagnosis of CEP

CEP is diagnosed based on clinical symptoms, laboratory findings, and exclusions of differential diagnoses of other eosinophilic lung disease. The current working criteria are as follows[1,2,26,29]: 1) clinical symptoms (lasting > 2 weeks), 2) abnormal chest radiographic findings, 3) eosinophilia detected in BAL (usually >25%), blood eosinophilia, and/or evident eosinophil infiltration in the lungs, 4) exclusion of other known eosinophilic pneumonias such as drug pneumonia, parasitic infection, ABPA, and EGPA.

Treatment

Corticosteroids

Patients with CEP usually respond well to corticosteroids. Because spontaneous resolution is rare (<10%), most patients with CEP require systemic corticosteroid treatment once after the CEP diagnosis (Table 4). Generally, administration of corticosteroids is initiated with prednisolone (PSL) 0.5 mg/kg or approximately 30 mg, and is usually sufficient to obtain symptomatic resolution as well as radiological remission within 2 weeks. Intravenous high-dose corticosteroid therapy is also employed in severe cases. In practice, if the patient does not respond well to corticosteroids, an alternative diagnosis should be considered.

Optimal duration of corticosteroid therapy

After resolution with corticosteroid administration, the doses are reduced and ideally censored. In most cases, PSL is tapered for 6–12 months,[1,33] but there are no established or optimal regimens. We prospectively treated patients with CEP with PSL for 3 or 6

Table 4
Clinical manifestations, Blood and BAL analyses of CEP.

	Suzuki *et al.*[30]	Ishiguro *et al.*[31]	Oyama *et al.*[32]	Marchand *et al.*[33]	Marchand *et al.*[34]	Durieu *et al.*[35]	Naughton *et al.*[36]
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							
Eos (%)	38.2 ± 27.4	41.4 ± 28.3	37.7 ± 25.9	58.0 ± 22.6	54 ± 25	50.5 ± 27.6	–
Ly (%)	11.0 ± 12.8	–	12.2 ± 12.9	6.1 ± 4.5	6 ± 5	–	–
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%)
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

WBC, white blood cell; Eos, eosinophil; CRP, C-reactive protein; IgE, immunoglobulin E; BAL, bronchoalveolar lavage; Ly, lymphocytes; PSL, prednisolone.
[†] Absolute number (/mm^3).
[‡] Range.

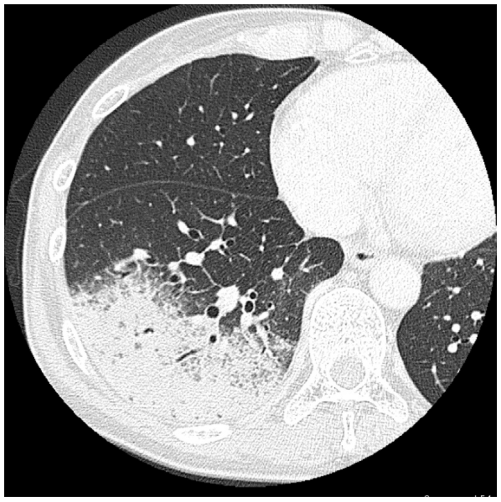

Fig. 2. Chest CT image of a patient with CEP. A 57-years old woman showed air space consolidation predominating in the peripheral (presented right lower lobe).

months and then compared the relapse rate during 2 years. In the 3-month treatment group, patients initially received 0.5 mg/kg PSL once daily, and then PSL was tapered by 20% every 2 weeks and discontinued after 3 months. In the 6-month treatment group, patients initially received 0.5 mg/kg PSL once daily, and subsequently 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. Interestingly, that prospective study found no significant difference in the incidence of relapse between the 3-month treatment group (61.9%) and the 6-month treatment group (52.1%, $p = 0.39$).[32]

Relapse

During tapering and/or after discontinuation of corticosteroid treatment, relapse is common and occurs in more than half of CEP cases[30–36] (Table 4). Additionally, some patients experience relapse several times. Indeed, our previous study showed that, out of 133 patients with CEP, 75 patients (56.4%) relapsed and 38 (28.6%) relapsed more than twice.[30] After relapse, resumption of corticosteroid treatment leads to favorable response similar to that to the initial treatment. Although there have been no clinical studies on the treatment of relapse, it may be treated with PSL 20 mg and/or the same dose used during the initial treatment.[1,29]

Alternative therapy

Because patients with CEP frequently have comorbid asthma, ICS are often used in CEP. Indeed, approximately 50% of patients with CEP receive ICS with or without oral corticosteroids in the clinical setting.[30,34–36] There is a possibility that ICS may potentially save PSL doses and reduce the occurrence of relapse, but this would have to be confirmed by a large prospective study. A retrospective study showed that ICS use was related to lower incidence of relapse.[34] In contrast, four-case series showed that beclomethasone monotherapy as initial treatment failed to control CEP.[45]

Theoretically, biological agents, such as the anti-IgE antibody (omalizumab), anti-IL-5 antibody (mepolizumab), and anti-IL-5 receptor antibody (benralizumab) may be alternative candidates for the treatment of CEP. Indeed, omalizumab[46] and mepolizumab[47,48] showed efficacy for reducing or discontinuing corticosteroid administration in relapsed CEP cases. Although biological agents are a reasonable choice for regulating eosinophilic inflammation in CEP, there remain several concerns regarding adaptation and treatment duration.

Long-term CEP management

Administration of corticosteroids dramatically improves the clinical symptoms and radiological abnormalities in patients with CEP both at initial presentation and at relapse. Thus, CEP-related mortality is extremely rare. However, relapse is commonly encountered as high as over 50% of cases.[30,32–36] Moreover, patients with CEP often have comorbid allergic diseases, such as asthma, and the severity of asthma often worsens after CEP development.[34] Therefore, the long-term management of CEP should mainly focus on CEP relapse and comorbidities. Due to persistent disease, repeated relapse, and/or comorbid severe asthma, more than a few patients with CEP require indefinite maintenance with corticosteroids. Indeed, more than 50% of patients with CEP receive prolonged corticosteroid treatment as maintenance therapy[30,33,34,36] (Table 4). This high frequency of corticosteroid maintenance requirement in the real world is surprising, given the good response to corticosteroids. Additionally, some patients with CEP have prolonged persistent impairment of pulmonary function.[30] Therefore, CEP, or at least some CEP cases,

should be considered a potentially chronic disease requiring long-term management, rather than an acute or subacute disease only requiring short-term therapy. CEP management should aim to control the disease and to prevent relapse and persistent impairment of pulmonary function while avoiding excessive corticosteroid treatment.

Can relapse be predicted?

To date, several studies have attempted to identify predictive factors of CEP relapse. A retrospective study including 53 CEP cases found that patients with CEP with comorbid asthma had lower frequencies of relapse than those without asthma (56% vs 23%).[34] The authors speculated that the higher use of ICS in the patients with asthma (88% vs 31%) might be the reason for this difference. Another retrospective study with 73 patients with CEP found smoking history as a negative factor for relapse.[31] However, these factors have not yet been confirmed by other prospective or retrospective studies so far.[30,32] Therefore, there are no established predictive factors of relapse.

How common is persistent impairment of pulmonary function in patients with CEP?

At the time of CEP diagnosis, approximately 50–70% of patients with CEP exhibit PFT defects with slight dominance of a restrictive pattern.[30–33,35] Interestingly, there has been growing evidence that persistent PFT impairment at follow-up periods is also common in CEP.[30,35] We conducted an observational study with 133 patients with CEP with a mean observation period of 6.1 years, and found that 36.8% of the patients had persistent PFT defects with a predominantly obstructive pattern.[30] Additionally, Durieu *et al.* also reported that 10 of 19 patients with CEP (52.6%) had impaired PFTs with a mean follow-up period of 4.1 years.[35] Thus, the frequency of patients with CEP having persistent impairment of pulmonary function may be higher than we have expected, and this condition should be taken into consideration in the management of CEP.

What are the predictive factors of persistent impairment of pulmonary function?

Because patients with CEP exhibit persistent impairment of pulmonary function, identification of factors associated with such impairment is important. Direu *et al.* reported that BAL eosinophilia was higher in patients with CEP with persistent obstructive PFTs than in those with normal PFTs.[35] In our previous study, comorbid asthma and obstructive PFT defects at the time of initial diagnosis were related to persistent obstructive impairment, whereas restrictive PFT defects and reticulation on HRCT at the time of diagnosis were risks for persistent restrictive impairment.[30] Notably, relapse was not a risk factor for persistent impairment of pulmonary function.[30,35]

Conclusion

This review discussed the current understanding of CEP and AEP in terms of epidemiology, clinical manifestations, and treatment. CEP and AEP share several similarities, including response to corticosteroids, but the clinical manifestations and disease courses differ. Although AEP can cause life threatening severe acute respiratory failure, relapse is rare and corticosteroid therapy can be discontinued with complete recovery. In contrast, more than a half of CEP patients experience relapse, and prolonged corticosteroid treatment is needed in approximately half of these patients. Additionally, persistent impairment of pulmonary function is not unusual. Although successfully-treated cases with biological agents have been reported, further studies are required to facilitate the development of disease severity-based treatment regimens for CEP.

Acknowledgements

This work was supported by a grant-in-aid for scientific research (19K17632 to Y.S.) from the Japan Society for the Promotion of Science and scholarship grant for research in basic medical science and medical care (18KI050 to YS) from the Ichiro Kanehara Foundation for the Promotion of Medical Sciences and Medical Care.

Conflict of interest

The authors have no conflict of interest to declare.

References

1. Cottin V. Eosinophilic lung diseases. *Clin Chest Med* 2016;**37**:535–56.
2. Cottin V, Cordier JF. Eosinophilic pneumonias. *Allergy* 2005;**60**:841–57.
3. Carrington CB, Addington WW, Goff AM, Madoff IM, Marks A, Schwaber JR, et al. Chronic eosinophilic pneumonia. *N Engl J Med* 1969;**280**:787–98.
4. Allen JN, Pacht ER, Gadek JE, Davis WB. Acute eosinophilic pneumonia as a reversible cause of noninfectious respiratory failure. *N Engl J Med* 1989;**321**:569–74.
5. Philit F, Etienne-Mastroianni B, Parrot A, Guerin C, Robert D, Cordier JF. Idiopathic acute eosinophilic pneumonia: a study of 22 patients. *Am J Respir Crit Care Med* 2002;**166**:1235–9.
6. Shorr AFSS, Cersovsky SB, Shanks GD, Ockenhouse CF, Smoak BL, Carr WW, et al. Acute eosinophilic pneumonia among US military personnel deployed in or near Iraq. *J Am Med Assoc* 2004;**292**:2997–3005.
7. Uchiyama H, Suda T, Nakamura Y, Shirai M, Gemma H, Shirai T, et al. Alterations in smoking habits are associated with acute eosinophilic pneumonia. *Chest* 2008;**133**:1174–80.
8. Rhee CK, Min KH, Yim NY, Lee JE, Lee NR, Chung MP, et al. Clinical characteristics and corticosteroid treatment of acute eosinophilic pneumonia. *Eur Respir J* 2013;**41**:402–9.
9. Jhun BW, Kim SJ, Kim K, Lee JE. Clinical implications of initial peripheral eosinophilia in acute eosinophilic pneumonia. *Respirology* 2014;**19**:1059–65.
10. Sine CR, Hiles PD, Scoville SL, Haynes RL, Allan PF, Franks TJ, et al. Acute eosinophilic pneumonia in the deployed military setting. *Respir Med* 2018;**137**:123–8.
11. De Giacomi F, Decker PA, Vassallo R, Ryu JH. Acute eosinophilic pneumonia: correlation of clinical characteristics with underlying cause. *Chest* 2017;**152**:379–85.
12. Komiya K, Teramoto S, Kawashima M, Kurosaki Y, Shoji S, Hebisawa A. A case of acute eosinophilic pneumonia following short-term passive smoking: an evidence of very high level of urinary cotinine. *Allergol Int* 2010;**59**:421–3.
13. Rom WN, Weiden M, Garcia R, Yie TA, Vathesatogkit P, Tse DB, et al. Acute eosinophilic pneumonia in a New York City firefighter exposed to World Trade Center dust. *Am J Respir Crit Care Med* 2002;**166**:797–800.
14. Hirai K, Yamazaki Y, Okada K, Furuta S, Kubo K. Acute eosinophilic pneumonia associated with smoke from fireworks. *Intern Med* 2000;**39**:401–3.
15. Imokawa S, Sato A, Hayakawa H, Toyoshima M, Taniguchi M, Chida K. Possible involvement of an environmental agent in the development of acute eosinophilic pneumonia. *Ann Allergy Asthma Immunol* 1996;**76**:419–22.
16. De Giacomi F, Vassallo R, Yi ES, Ryu JH. Acute eosinophilic pneumonia. Causes, diagnosis, and management. *Am J Respir Crit Care Med* 2018;**197**:728–36.
17. Jhun BW, Kim SJ, Kim K, Lee JE, Hong DJ. Clinical implications of correlation between peripheral eosinophil count and serum levels of IL-5 and tryptase in acute eosinophilic pneumonia. *Respir Med* 2014;**108**:1655–62.
18. Nakahara Y, Hayashi S, Fukuno Y, Kawashima M, Yatsunami J. Increased interleukin-5 levels in bronchoalveolar lavage fluid is a major factor for eosinophil accumulation in acute eosinophilic pneumonia. *Respiration* 2001;**68**:389–95.
19. Katoh S, Matsumoto N, Matsumoto K, Fukushima K, Matsukura S. Elevated interleukin-18 levels in bronchoalveolar lavage fluid of patients with eosinophilic pneumonia. *Allergy* 2004;**59**:850–6.
20. Mato N, Bando M, Kusano A, Hirano T, Nakayama M, Uto T, et al. Clinical significance of interleukin 33 (IL-33) in patients with eosinophilic pneumonia. *Allergol Int* 2013;**62**:45–52.
21. Mochimaru H, Kawamoto M, Fukuda Y, Kudoh S. Clinicopathological differences between acute and chronic eosinophilic pneumonia. *Respirology* 2005;**10**:76–85.
22. Tazelaar HD, Linz LJ, Colby TV, Myers JL, Limper AH. Acute eosinophilic pneumonia: histopathologic findings in nine patients. *Am J Respir Crit Care Med* 1997;**155**:296–302.
23. Daimon T, Johkoh T, Sumikawa H, Honda O, Fujimoto K, Koga T, et al. Acute eosinophilic pneumonia: thin-section CT findings in 29 patients. *Eur J Radiol* 2008;**65**:462–7.
24. Johkoh T, Muller NL, Akira M, Ichikado K, Suga M, Ando M, et al. Eosinophilic lung diseases: diagnostic accuracy of thin-section CT in 111 patients. *Radiology* 2000;**216**:773–80.
25. Abe K, Yanagi S, Imadsu Y, Sano A, Iiboshi H, Mukae H, et al. Acute eosinophilic pneumonia with fine nodular shadows. *Intern Med* 2003;**42**:88–91.

26. Allen J, Wert M. Eosinophilic pneumonias. *J Allergy Clin Immunol Pract* 2018;**6**: 1455–61.
27. Thomeer MJ, Costabe U, Rizzato G, Poletti V, Demedts M. Comparison of registries of interstitial lung diseases in three European countries. *Eur Respir J* 2001;**32**:114S–8S.
28. Sveinsson OA, Isaksson HJ, Gudmundsson G. Chronic eosinophilic pneumonia in Iceland: clinical features, epidemiology and review. *Laeknabladid* 2007;**93**:111–6.
29. Suzuki Y, Suda T. Long-term management and persistent impairment of pulmonary function in chronic eosinophilic pneumonia: a review of the previous literature. *Allergol Int* 2018;**67**:334–40.
30. Suzuki Y, Oyama Y, Hozumi H, Imokawa S, Toyoshima M, Yokomura K, et al. Persistent impairment on spirometry in chronic eosinophilic pneumonia: a longitudinal observation study (Shizuoka-CEP study). *Ann Allergy Asthma Immunol* 2017;**119**:422–8.
31. Ishiguro T, Takayanagi N, Uozumi R, Tada M, Kagiyama N, Takaku Y, et al. The long-term clinical course of chronic eosinophilic pneumonia. *Intern Med* 2016;**55**:2373–7.
32. Oyama Y, Fujisawa T, Hashimoto D, Enomoto N, Nakamura Y, Inui N, et al. Efficacy of short-term prednisolone treatment in patients with chronic eosinophilic pneumonia. *Eur Respir J* 2015;**45**:1624–31.
33. Marchand E, Reynaud-Gaubert M, Lauque D, Durieu J, Tonnel AB, Cordier JF. Idiopathic chronic eosinophilic pneumonia. A clinical and follow-up study of 62 cases. The Groupe d'Etudes et de Recherche sur les Maladies "Orphelines" Pulmonaires (GERM"O"P). *Medicine* 1988;**77**:299–312.
34. Marchand E, Etienne-Mastroianni B, Chanez P, Lauque D, Leclerc P, Cordier JF. Idiopathic chronic eosinophilic pneumonia and asthma: how do they influence each other? *Eur Respir J* 2003;**22**:8–13.
35. Durieu J, Wallaert B, Tonnel AB. Long-term follow-up of pulmonary function in chronic eosinophilic pneumonia. *Eur Respir J* 1997;**10**:286–91.
36. Naughton M, Fahy J, FitzGerald MX. Chronic eosinophilic pneumonia. A long-term follow-up of 12 patients. *Chest* 1993;**103**:162–5.
37. Matsuse H, Shimoda T, Fukushima C, Matsuo N, Sakai H, Takao A, et al. Diagnostic problems in chronic eosinophilic pneumonia. *J Int Med Res* 1997;**25**: 196–201.
38. Taniguchi H, Kadota J, Abe K, Matsubara Y, Kaseda M, Kawamoto S, et al. [Eosinophilic pneumonia without eosinophilia in BALF or peripheral blood and diagnosed by open lung biopsy]. *Nihon Kokyuki Gakkai Zasshi* 1999;**37**: 796–801 (in Japanese).
39. Gaensler EA, Carrington CB. Peripheral opacities in chronic eosinophilic pneumonia: the photographic negative of pulmonary edema. *Am J Roentgenol* 1977;**128**:1–13.
40. Jeong YJ, Kim KI, Seo IJ, Lee CH, Lee KN, Kim KN, et al. Eosinophilic lung diseases: a clinical, radiologic, and pathologic overview. *Radiographics* 2007;**27**: 617–37 (discussion 37-9).
41. Singh I, Kaner R. A woman with asthma and ground-glass opacities. *Ann Am Thorac Soc* 2017;**14**:140–4.
42. Zimhony O. Photographic negative shadow of pulmonary oedema. *Lancet* 2002;**360**:33.
43. Arakawa H, Kurihara Y, Niimi H, Nakajima Y, Johkoh T, Nakamura H. Bronchiolitis obliterans with organizing pneumonia versus chronic eosinophilic pneumonia: high-resolution CT findings in 81 patients. *Am J Roentgenol* 2001;**176**:1053–8.
44. Furuiye M, Yoshimura N, Kobayashi A, Tamaoka M, Miyazaki Y, Ohtani Y, et al. Churg-Strauss syndrome versus chronic eosinophilic pneumonia on high-resolution computed tomographic findings. *J Comut Assist Tomogr* 2010;**34**: 19–22.
45. Minakuchi M, Niimi A, Matsumoto H, Amitani R, Mishima M. Chronic eosinophilic pneumonia: treatment with inhaled corticosteroids. *Respiration* 2003;**70**: 362–6.
46. Kaya H, Gumus S, Ucar E, Aydogan M, Musabak U, Tozkoparan E, et al. Omalizumab as a steroid-sparing agent in chronic eosinophilic pneumonia. *Chest* 2012;**142**:513–6.
47. Lin RY, Santiago TP, Patel NM. Favorable response to asthma-dosed subcutaneous mepolizumab in eosinophilic pneumonia. *J Asthma* 2018: 1–5.
48. To M, Kono Y, Yamawaki S, Soeda S, Katsube O, Kishi H, et al. A case of chronic eosinophilic pneumonia successfully treated with mepolizumab. *J Allergy Clin Immunol Pract* 2018;**6**. 1746–1748.e1.