

A case of chronic eosinophilic pneumonia successfully treated with mepolizumab

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Clinical Implications

- Mepolizumab may be a good treatment option for chronic eosinophilic pneumonia when the disease relapses and/or adverse effects of corticosteroid therapy occur. The therapy has fewer adverse events and is more easily sustainable than conventional corticosteroid therapy.

TO THE EDITOR:

Chronic eosinophilic pneumonia (CEP) is an inflammatory disease characterized by eosinophilic infiltration in the lung of unknown etiology. It is also characterized by the progressive onset of symptoms, including cough and increasing dyspnea.¹ For the treatment of CEP, systemic corticosteroid therapy is recommended, and the response to corticosteroids is usually very good. However, approximately 50% of patients with CEP relapsed after termination of corticosteroid therapy or while corticosteroids were being tapered.²⁻⁴ When prolonged systemic corticosteroid therapy is needed, adverse events caused by corticosteroids, including diabetes mellitus, osteoporosis, and infections, are a serious issue.² Therefore, novel alternative therapeutic strategies are urgently needed for CEP. A case of CEP successfully treated with mepolizumab is presented.

A 65-year-old man visited our hospital because of a chronic cough and abnormal chest X-ray findings. He did not have high fever, dyspnea, massive sputum production, or wheezing. He had no history of lung disease, except for an approximately 20-year history of bronchial asthma. He was a never smoker, and he had no obvious history of occupational dust inhalation. The laboratory data showed an elevated leukocyte count with marked eosinophilia (see Table E1 in this article's Online Repository at www.jaci-inpractice.org). Proteinase 3 antineutrophil cytoplasmic antibody (PR-3 ANCA), myeloperoxidase antineutrophil cytoplasmic antibody (MPO-ANCA), and angiotensin-converting enzyme (ACE) were all negative. Krebs von den Lungen-6, surfactant protein D, and surfactant protein A levels were slightly elevated (Table E1). Chest computed tomography (CT) showed infiltrative shadows in the left upper and lower lobes (Figure 1, A). Fiberoptic bronchoscopy showed no abnormal findings in the bronchial lumen. Bronchoalveolar lavage fluid (BALF) showed an elevated eosinophil percentage (72%; normal range, $\leq 1\%$) (Figure E1, A and B). Bacterial culture of BALF detected only normal flora. On the basis of the high percentage of eosinophils in the BALF, the marked peripheral eosinophilia, the infiltrative shadows on chest CT, and

the negative findings for other potential causes of cough and pulmonary infiltrates, the diagnosis of CEP was established.

Treatment with prednisolone 30 mg/d (0.5 mg/kg/d) was given, with biweekly tapering of the dosage (Figure 2). The patient responded well to corticosteroid therapy, and his symptoms disappeared with the decrease in peripheral blood eosinophil counts (Figure 2). However, after termination of systemic corticosteroid therapy, his symptoms worsened, with increased peripheral eosinophil counts (Figure 2). Infiltrative shadows were newly developed in the right upper lobe, whereas the infiltrative shadows in the left upper and lower lobes had disappeared (Figure 1, B); the CEP had relapsed. Because serious adverse events sometimes occur with prolonged systemic corticosteroid therapy, mepolizumab 100 mg/d every month was administered instead of systemic corticosteroid therapy. He responded well to the therapy. His symptoms decreased several days after the administration of mepolizumab. About 1 month after the administration of mepolizumab, his symptoms disappeared, and his peripheral blood eosinophil counts decreased to the normal range (Figure 2). The infiltrative shadows disappeared on his chest CT taken 3 months after the start of mepolizumab therapy (Figure 1, C). The patient has had no relapse of CEP up to now with the continuation of mepolizumab therapy. No adverse events potentially attributed to mepolizumab therapy were observed. We are planning to continue mepolizumab therapy with careful observation of patients.

Patients with CEP have been reported to show a good response to systemic corticosteroid therapy. However, a substantial percentage of patients suffered relapse of the disease after finishing corticosteroid therapy or while the corticosteroid was being tapered.²⁻⁴ The present case of CEP also had a relapse of CEP after termination of systemic corticosteroid therapy. In contrast, he has had no relapse with continued mepolizumab therapy.

Chronic accumulation of eosinophils in the alveolar space induced by IL-5 is suggested to play a major role in the development of CEP. Although the triggering factors for CEP are usually unknown, the selective migration of T_H2 cells to the lungs, mediated by thymus and activation-regulated chemokine and RANTES, and the chronic release of IL-5 from T_H2 cells have been reported to be evident in CEP lung. The released IL-5 induces accumulation of eosinophils in the lungs. In fact, it has been reported that BALF from the affected area of the lung area has high IL-5 levels, but BALF from the normal area of the lung does not.⁵ Blood IL-5 and BALF IL-5 levels were elevated in CEP, and they were decreased after treatment.⁶ The BALF IL-5 concentration of patients with CEP was higher than that of controls.⁷ Thus, IL-5 seems to play an important role in the pathogenesis of CEP.

Mepolizumab is an mAb to human IL-5 used for the treatment of severe eosinophilic asthma.⁸ Mepolizumab binds to free IL-5 to inhibit it from interacting with IL-5 receptors on the surface of eosinophils. As mentioned in the previous paragraph, IL-5 seems to play an important role in the pathogenesis of CEP. Therefore, it is reasonable to conclude that the administration of mepolizumab suppresses local levels of IL-5 and infiltration of eosinophils, resulting in the resolution of CT findings and decreased symptoms. In addition, mepolizumab therapy can be

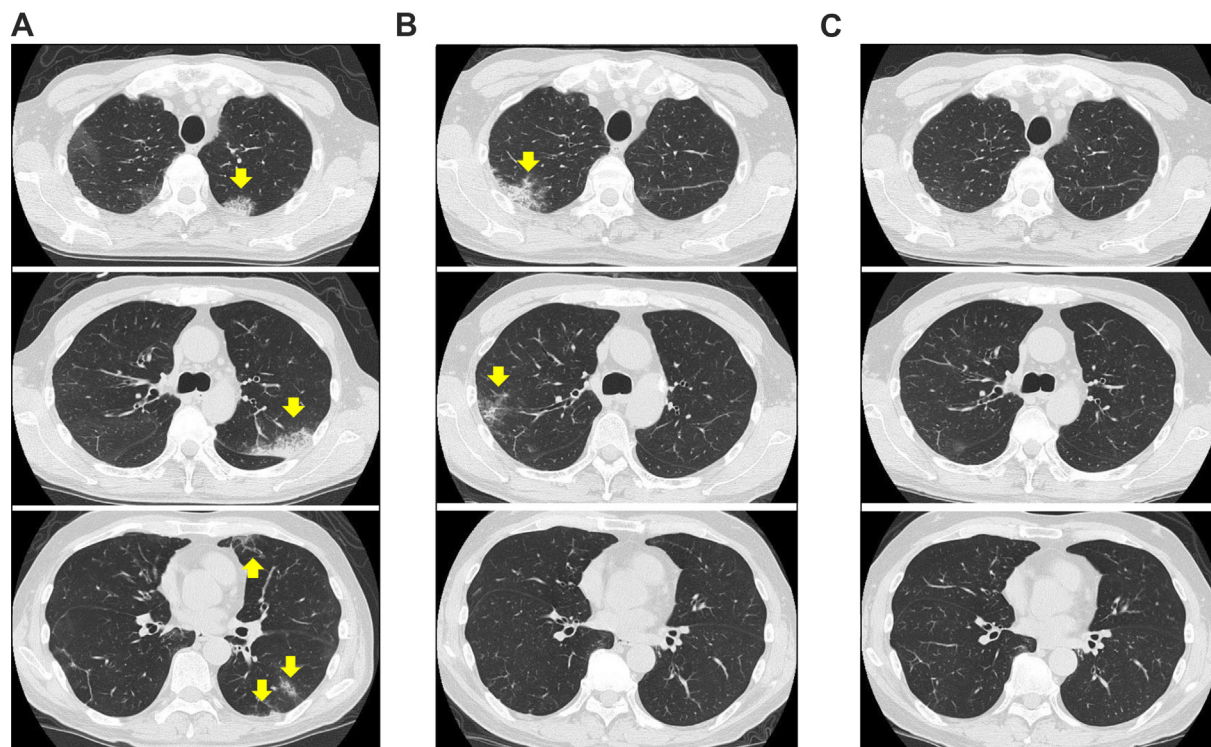


FIGURE 1. Chest CT findings. Chest CT findings on admission (**A**) showed infiltrative shadows in the left upper and lower lobes (indicated by yellow arrows). Chest CT taken at the time of relapse (**B**) revealed that infiltrative shadows were newly developed in the right upper lobe. Chest CT taken 3 months after the initiation of mepolizumab therapy (**C**) showed no infiltrative shadows.

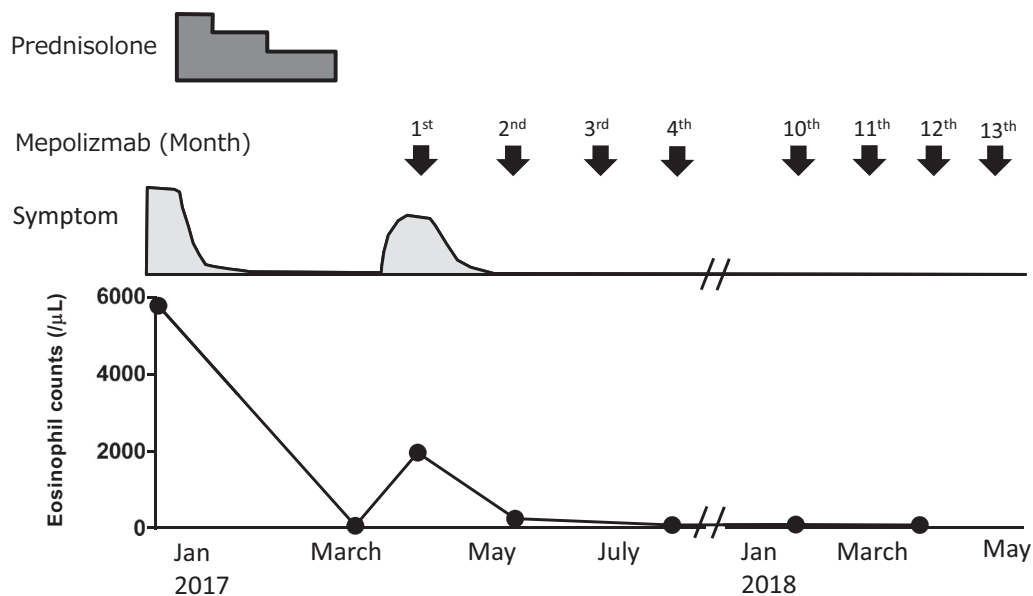


FIGURE 2. Treatment and clinical course. The patient responded to corticosteroid therapy, and his symptoms disappeared with the decrease in peripheral blood eosinophil counts, but his symptoms worsened, with increased peripheral eosinophil counts after termination of systemic corticosteroid therapy. After initiation of mepolizumab therapy, the patient's symptoms disappeared, and his peripheral blood eosinophil counts decreased to the normal range.

continued for a long period of time without obvious adverse effects,⁹ unlike systemic corticosteroid therapy. For this reason, the risk of relapse of CEP may be lower with mepolizumab therapy than with systemic corticosteroid therapy with tapering.

Although long-term safety of mepolizumab treatments is demonstrated, there is no clear evidence to suggest the recommended duration of mepolizumab therapy for either CEP or asthma. Recently, Gunsoy et al¹⁰ tried to establish clinical markers that could help in decisions of continuation of mepolizumab treatments, but they could not find a clear marker. They stated in their article that continuation of mepolizumab treatments should be decided by achieving a reduction in the frequency of acute exacerbation and/or oral corticosteroid dose. On the basis of facts, we are continuing mepolizumab therapy with careful observation of patients.

Thus, CEP seems to be treatable with mepolizumab. Because mepolizumab therapy has far fewer adverse effects than systemic corticosteroid therapy and is suitable for long-term use, relapse of CEP can be inhibited by continuous use of mepolizumab. Mepolizumab therapy might be a good treatment option for CEP when it relapses or serious adverse effects of corticosteroid therapy appear.

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Conflicts of interest: The authors declare that they have no relevant conflicts of interest.

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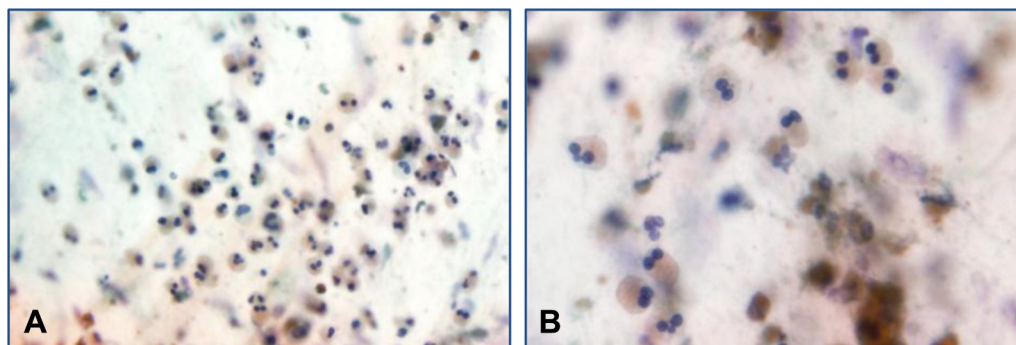


FIGURE E1. A case of CEP successfully treated with mepolizumab BALF cytology. A great number of eosinophils were detected in BALF. Papanicolaou stain magnification $\times 100$ (A), magnification $\times 400$ (B).

TABLE E1. Laboratory data on admission

Hematology			Biochemistry		
WBCs	$10.4 \times 10^3/\text{mm}^3$	TP	7.5 g/dL	IgG	1942 mg/dL
Band	9.0%	Aib	3.6 g/dL	IgA	249 mg/dL
Seg	41.0%	T. bil	0.48 mg/dL	IgM	100 mg/dL
Eosino	29.5%	AST	16 IU/L	β -D glucan	17.8 pg/mL
Baso	0.5%	ALT	13 IU/L	Aspergillus antigen	Negative
Mono	4.5%	LDH	193 IU/L	KL-6	576 U/mL
Lympho	15.5%	CPK	30 IU/L	SP-A	63.6 ng/mL
Hemoglobin	13.4 g/dL	BUN	8.4 mg/dL	SP-D	144 ng/mL
Platelets	$314 \times 10^3/\text{mm}^3$	CRE	0.58 mg/dL	MPO-ANCA	<1.0 U/mL
		Na	138 mEq/L	PR3-ANCA	<1.0 U/mL
ESR	50 mm/h	K	3.6 mEq/L	ACE	4.8 U/mL
		Cl	104 mEq/L	HIV antibody	Negative
		CRP	0.34 mg/dL		
		IgE	290 mg/dL	Sputum	
		RAST		Culture	Normal flora
		<i>Aspergillus</i>	Negative	<i>M tuberculosis</i> DNA	Negative
		<i>Candida</i>	Negative		

CRP, C-reactive protein; KL-6, Krebs von den Lungen-6; SP-A, surfactant protein A; SP-D, surfactant protein D.