

Clinical Communications

Eosinophilic bronchiolitis successfully treated with mepolizumab

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Clinical Implications

- To the best of our knowledge, this is the first case where eosinophilic bronchiolitis complicated by asthma was successfully treated with mepolizumab. The findings highlight the potential of mepolizumab as an alternative medication for eosinophilic bronchiolitis.

TO THE EDITOR:

Eosinophilic lung disease shows diverse pathological characteristics and radiographic findings.¹ Eosinophilic bronchiolitis was first proposed as an atypical eosinophilic lung disease in 2001.² In 2013, Cordier et al³ described a case series and defined this condition as a distinct disease entity called hyper-eosinophilic obliterative bronchiolitis. Because the 2 disorders have several overlapping features, they are recognized as the same disease.

Eosinophilic bronchiolitis is diagnosed on the basis of the following criteria: a blood eosinophil count of $>1 \text{ G L}^{-1}$ and/or a bronchoalveolar lavage eosinophil count of $>25\%$, persistent airflow limitation despite treatment with high-dose inhaled bronchodilators and corticosteroids, and typical findings in lung biopsy and/or direct signs of bronchiolitis (centrilobular nodules and branching opacities) on computed tomography (CT). The etiology of eosinophilic bronchiolitis remains unknown and is considered idiopathic. Because of its rarity, the condition may go unrecognized and managed under a diagnosis of treatment-resistant asthma in several cases. Although some patients respond to systemic corticosteroids, the effectiveness varies among individual cases. Relapse is very common during dose tapering, and there is little evidence for the appropriate treatment strategy. Here we describe a case of eosinophilic bronchiolitis complicated by severe asthma that exhibited an excellent response to mepolizumab, a monoclonal anti-IL-5 antibody, after treatment with high-dose oral corticosteroids proved ineffective.

The patient was a 29-year-old man with a 6-year history of sustained wheezing and exertional dyspnea, a history of infantile asthma, and no allergies to foods or drugs. He was a fisherman by occupation and quit smoking 5 years previously. His living/working conditions did not appear to contribute to his symptoms. He was diagnosed with uncontrolled asthma and treated with all possible options, including an inhaled corticosteroid, a

long-acting β_2 -agonist, a leukotriene receptor antagonist, a long-acting muscarinic antagonist, and theophylline. However, the dyspnea gradually worsened. Endoscopic sinus surgery, an anti-IgE antibody (omalizumab), and bronchial thermoplasty were also ineffective. Because of severe asthma, he regularly received intravenous methylprednisolone (125 mg/day) in the emergency department every 2 weeks. Before the third bronchial thermoplasty, he developed severe respiratory distress and was admitted to our hospital in an emergency. On admission, the peripheral blood eosinophil count was remarkably increased ($745/\text{mm}^3$, 13% of the total white blood cells). The serum total IgE level was slightly elevated (267 IU/mL), whereas a radioallergen sorbent test showed negative results for house dust, animals, plants, and fungi. The specific IgE titer against *Aspergillus fumigatus* was below the threshold. myeloperoxidase anti-neutrophil cytoplasmic antibody was also negative and he did not show any signs of vasculitis, including multiple mononeuropathy (Table 1). Connective tissue disease-related autoantibodies were absent. Chest CT showed diffuse ill-defined centrilobular nodules (Figure 1, A and B) surrounded by prominent ground glass opacities (GGOs) (Figure 1, C and D) in both lungs.

Bronchoscopy revealed severe rubefaction and tortuous capillaries with engorgement on the airway surface (see Figure E1, available in this article's Online Repository at www.jaci-inpractice.org). The percentage of eosinophils in bronchoalveolar lavage fluid (BALF) from the right middle lobe was considerably elevated to 44% (Table 1). There was no evidence of fungi or mycobacteria in BALF. Transbronchial lung biopsy could not be performed because of severe dyspnea. The findings collectively suggested the coexistence of eosinophilic bronchiolitis and asthma.

After bronchoscopy, intravenous administration of a high-dose corticosteroid was immediately initiated, although his respiratory distress progressed. The oral prednisolone dose could not be tapered below 50 mg/day because of relapse. Eventually, we decided to administer mepolizumab as a novel therapy (100 mg, administered subcutaneously). Although dyspnea resolved within 3 days after mepolizumab initiation, the peripheral blood eosinophils as well as GGOs and centrilobular nodules observed on chest CT disappeared within 7 days (Figure 1, E and F). The fractional nitric oxide concentration in exhaled air decreased from 78 to 38 ppb, and airflow obstruction in spirometry was remarkably ameliorated within 1 month (Table 1). The oral corticosteroid was safely tapered within 2 months, and monthly mepolizumab administration was continued for 2 years, during which the patient remained asymptomatic. Bronchoscopy performed at 1 year after treatment initiation showed complete disappearance of the rubefaction (see Figure E1, available in this article's Online Repository at www.jaci-inpractice.org). Moreover, the eosinophil count in BALF had dramatically decreased to 2%.

To the best of our knowledge, this is the first case where mepolizumab was successfully used for the treatment of eosinophilic bronchiolitis. A recent case report by Tomyo et al⁴ involved a patient with eosinophilic pneumonia with a

TABLE 1. Demographics of a patient with eosinophilic bronchiolitis complicated by asthma

Blood count		
WBC		6500/ μ L
Neu		69.0%
Ba		0.9%
Eo		11.3%
Mono		4.9%
Lym		13.9%
Hb		15.1 g/dL
Plt		28.6×10^4 / μ L
Chemistry		
Alb		4.4 g/dL
T-Bil		0.6 mg/dL
AST		17 U/L
ALT		34 U/L
LDH		272 U/L
BUN		9 mg/dL
Cr		0.84 mg/dL
Na		141 mmol/L
K		3.5 mmol/L
Cl		105 mmol/L
CRP		0.19 mg/dL
Serology		
IgE (RIST)		267 mg/dL
Antinuclear antibody		$\times 40$
Anti-CCP antibody		0.6 U/mL
MMP-3		216.0 ng/mL
PR3-ANCA		1.0 U/mL
MPO-ANCA		1.0 U/mL
KL-6		248 U/mL
Aspergillus fumigatus specific IgE		0.10 UA/mL
BAL findings		
	Before mepolizumab	After mepolizumab
Total cell	0.6×10^5 /mL	1.4×10^5 /mL
Neutrophils	14%	80%
Lymph	9%	2%
Eosinophils	44%	5%
Macrophages	33%	13%
Pulmonary function		
	Before mepolizumab	After mepolizumab
VC	4.71 L (106.3%)	5.57 L (126.6%)
FEV ₁	2.09 L	3.29 L
FEV ₁ /FVC	44.8%	62.9%
FeNO	76 ppb	38 ppb

ALT, Alanine aminotransferase; AST, aspartate aminotransferase; BAL, bronchoalveolar lavage; BUN, blood urea nitrogen; CCP, cyclic citrullinated peptide; CRP, C-reactive protein; FeNO, fraction of exhaled nitric oxide; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; KL-6, Krebs von den Lungen-6; LDH, lactate dehydrogenase; MMP-3, matrix metalloproteinase-3; MPO-ANCA, myeloperoxidase-anti-neutrophil cytoplasmic antibody; PR3-ANCA, proteinase 3-anti-neutrophil cytoplasmic antibody; RIST, radioimmunosorbent test; VC, vital capacity; WBC, white blood cells.

somewhat different clinical course. However, a quick treatment response and sustained effects of mepolizumab were observed in that patient as well. These findings highlight the potential of mepolizumab as an alternative medication for eosinophilic bronchiolitis.

Our patient fulfilled all the diagnostic criteria for eosinophilic bronchiolitis,³ including marked serum and BALF eosinophilia, persistent airflow limitation, and diffuse centrilobular nodules on CT images (see Figure E2, available in this article's Online Repository at www.jaci-inpractice.org). One limitation is that pathological improvements could not be evaluated because of the lack of biopsy samples obtained before mepolizumab administration.

Eosinophilic bronchiolitis is often complicated by asthma and/or eosinophilic pneumonia, which is occasionally undistinguishable.⁵ The paroxysmal dyspnea attacks in our patient suggested asthma, although eosinophilia in BALF and radiographic findings were characteristic of bronchiolitis. Therefore, we diagnosed the patient with eosinophilic bronchiolitis complicated by asthma.

There is little evidence concerning the appropriate treatment for eosinophilic bronchiolitis. Because the main symptoms overlap with those of asthma, most patients received standard asthma therapies up to the maximum doses,¹ which generally prove ineffective even when used in combination. Several cases also receive moderate to high doses of systemic corticosteroids and develop exacerbations during dose tapering, as observed in the present case.

Our patient exhibited an excellent response to mepolizumab treatment and could be safely weaned off oral prednisolone. Mepolizumab suppresses the excessive activation of eosinophils by blocking IL-5 and is used for the treatment of allergic asthma and eosinophilic granulomatosis with polyangiitis.⁶ Given that eosinophilic bronchiolitis is also caused by the excessive activation of eosinophils via the IL-5 pathway, we believe that clinicians should consider mepolizumab treatment, particularly for refractory cases. Importantly, mepolizumab exhibits steroid-sparing effects,⁷ and it is well known that the prolonged use of high-dose systemic corticosteroids negatively affects the quality of life and survival.⁸

In summary, mepolizumab may be a promising treatment option for eosinophilic bronchiolitis. Further case reports and clinical studies are necessary for establishing solid evidence.

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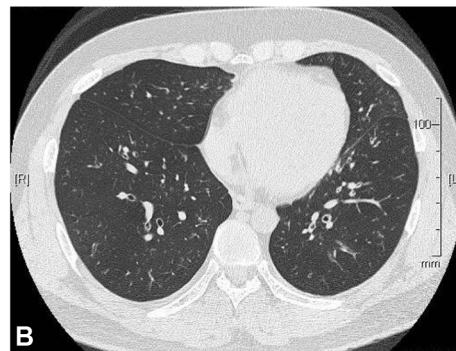
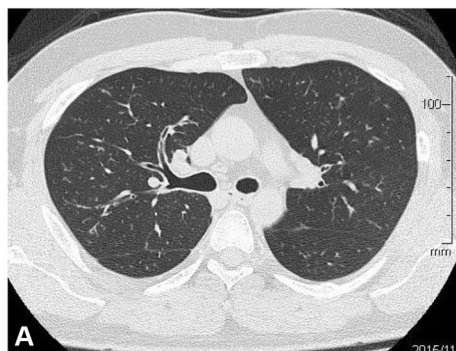
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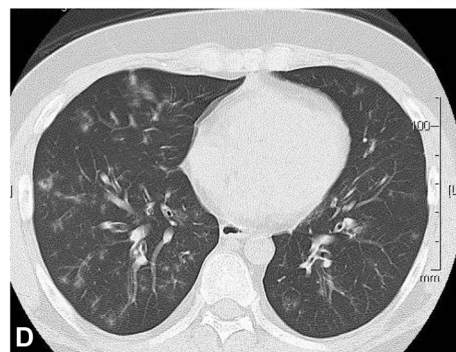
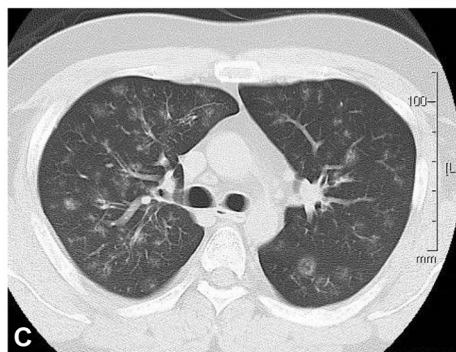
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Conflicts of interest: M. Adachi has received consultancy fees from TOA Pharmaceutical Co., Ltd and Kyowa Hakko Kirin Co., Ltd; and lecture fees from AstraZeneca K.K., GlaxoSmithKline K.K., and Novartis Pharma K.K. The rest of the authors declare that they have no relevant conflicts of interest.

Before
exacerbation



Acute
exacerbation



2 months after
mepolizumab

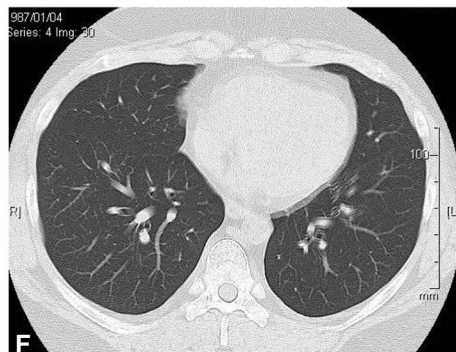
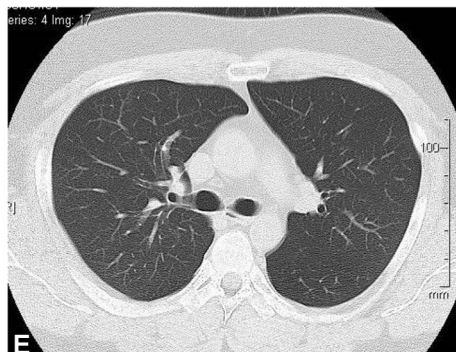


FIGURE 1. Imaging findings for a patient with eosinophilic bronchiolitis complicated by asthma. **A, B,** Initial chest computed tomography shows diffuse centrilobular nodules, Y-shaped shadows, and bronchial wall thickening in both lungs. **C, D,** Prominent ground-glass opacities can be observed around the bronchioles. **E, F,** All abnormalities have resolved after mepolizumab treatment.

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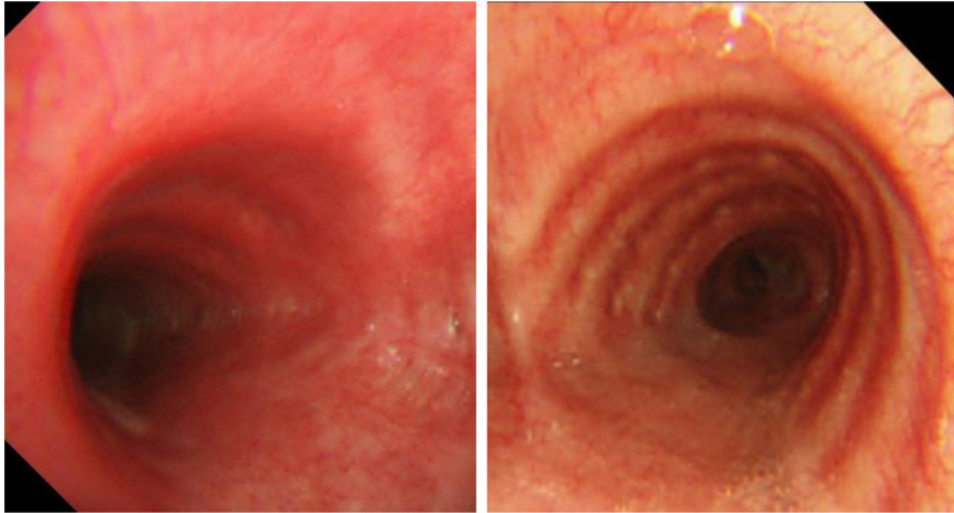


FIGURE E1. Bronchoscopy findings for a patient with eosinophilic bronchiolitis complicated by asthma. Severe rubefaction and tortuous capillaries with engorgement (left). There is an improvement at 1 year after the initiation of mepolizumab treatment (right).



FIGURE E2. Diffuse centrilobular nodules and Y-shaped shadows, suggestive of bronchiolitis, were seen in the computed tomography scan.