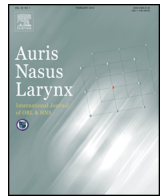




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Case report

Successful treatment of eosinophilic otitis media associated with severe bronchial asthma with an anti-IL-5 monoclonal antibody, mepolizumab

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ABSTRACT

Eosinophilic otitis media (EOM), which is characterized by the accumulation of eosinophils in middle ear effusion and the middle ear mucosa, is a refractory type of otitis media that is often associated with asthma. Although an early diagnosis and appropriate treatment are necessary to prevent the progression of hearing loss in patients with EOM, there are currently no well-established treatments for this condition. We treated a 60-year-old male patient with asthma and EOM. The patient's asthma was poorly controlled, despite the use of high-dose inhaled corticosteroids, long-acting beta-agonist treatment, and the regular use of systemic corticosteroids. Mepolizumab, an anti-IL-5 monoclonal antibody, was started to treat the patient's refractory asthma. At 4 months after the initiation of mepolizumab treatment, the patient's asthma, hearing, and middle ear effusion improved. The present case suggests that mepolizumab therapy can control EOM and asthma.

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1. Introduction

Eosinophilic otitis media (EOM) is characterized by high-viscosity middle ear effusion (MEE) that contains eosinophils;

the condition is often associated with asthma and nasal polyposis [1]. EOM is resistant to conventional treatments for otitis media with effusion or chronic otitis media (*i.e.*, myringotomy or the insertion of a tympanostomy tube). The intratympanic instillation of triamcinolone acetate has been used to control MEE and conductive hearing loss. EOM patients sometimes require systemic corticosteroids to remain stable during exacerbations, when remarkable granulation may occur or the bone conductive threshold may worsen [1]. The administration of optimized asthma treatment is critical for improving the symptoms of EOM, and anti-immunoglobulin E (IgE) therapy is effective for improving the ear symptoms and hearing levels of patients with severe asthma and EOM [2,3]. In

Abbreviations: ACT, asthma control test; ACQ, asthma control questionnaire; ANCAs, antineutrophil cytoplasmic antibodies; BMI, body mass index; CT, computed tomography; EGPA, eosinophilic granulomatosis with polyangiitis; EOM, eosinophilic otitis media; FeNO, exhaled nitric oxide; ICS, inhaled corticosteroids; ILC2s, group 2 innate lymphoid cells; LABA, long-acting beta-agonist; MEE, middle ear effusion.

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Japan, the anti-IL-5 monoclonal antibody, mepolizumab, was approved for the treatment of severe asthma in 2016. We herein report the case of a patient with severe asthma and EOM whose EOM symptoms improved after the administration of mepolizumab.

2. Case report

A 60-year-old man presented with adult-onset asthma and progressive hearing loss. He was a nonsmoker with allergic rhinitis. At 55 years of age, he had been diagnosed with asthma, and had been receiving inhaled corticosteroids (ICS)/long-acting beta-agonist (LABA) treatment. At 57 years of age, he developed hearing loss and prolonged otalgia. Progressive hearing loss and highly viscous MEE containing eosinophils were detected at another clinic. Based on his symptoms, he was diagnosed with EOM. In addition to asthma treatment, the patient had occasionally received myringotomy and systemic corticosteroids as treatment for EOM. At 2 years after the diagnosis of EOM, he developed occasional nasal discharge and nasal obstruction. Nasal polyps were detected by endoscopy, and chronic rhinosinusitis was diagnosed at another clinic. At 3 years after the diagnosis of EOM, his asthma was poorly controlled, despite his regular use of high-dose inhaled

budesonide/formoterol (1280 µg/day), tiotropium bromide, and montelukast, and the occasional use of oral corticosteroids. Although he also received omalizumab, as anti-IgE therapy for refractory asthma for 16 weeks, his symptoms did not dramatically improve. At the same time, his EOM was not well controlled, despite the repeated intratympanic instillation of triamcinolone acetonide at another clinic. At 60 years of age, mepolizumab therapy was initiated to treat the patient's refractory asthma. The department of respiratory medicine of Showa University Hospital consulted our department to evaluate the clinical course of the present patient who had been diagnosed to have severe asthma with EOM and who had been treated with mepolizumab.

A physical examination revealed the patient's body mass index (BMI) to be 22.3 kg/m². The patient's peripheral blood eosinophil percentage was 20% and his serum IgE level was 474 IU/mL. An ImmunoCAP (Thermo Fisher Diagnostics, Tokyo, Japan) Specific IgE blood test was positive for Japanese cedar (6.66 UA/mL, class 3) and house dust mite (1.17 UA/mL, class 2). The patient tested negative for antineutrophil cytoplasmic antibodies (ANCA). A chest X-ray showed no abnormal findings. Both tympanic membranes were thickened, dark and immobile (Fig. 1A). Tympanometry revealed type B findings in both ears. A pure tone audiogram showed 40.0 dB

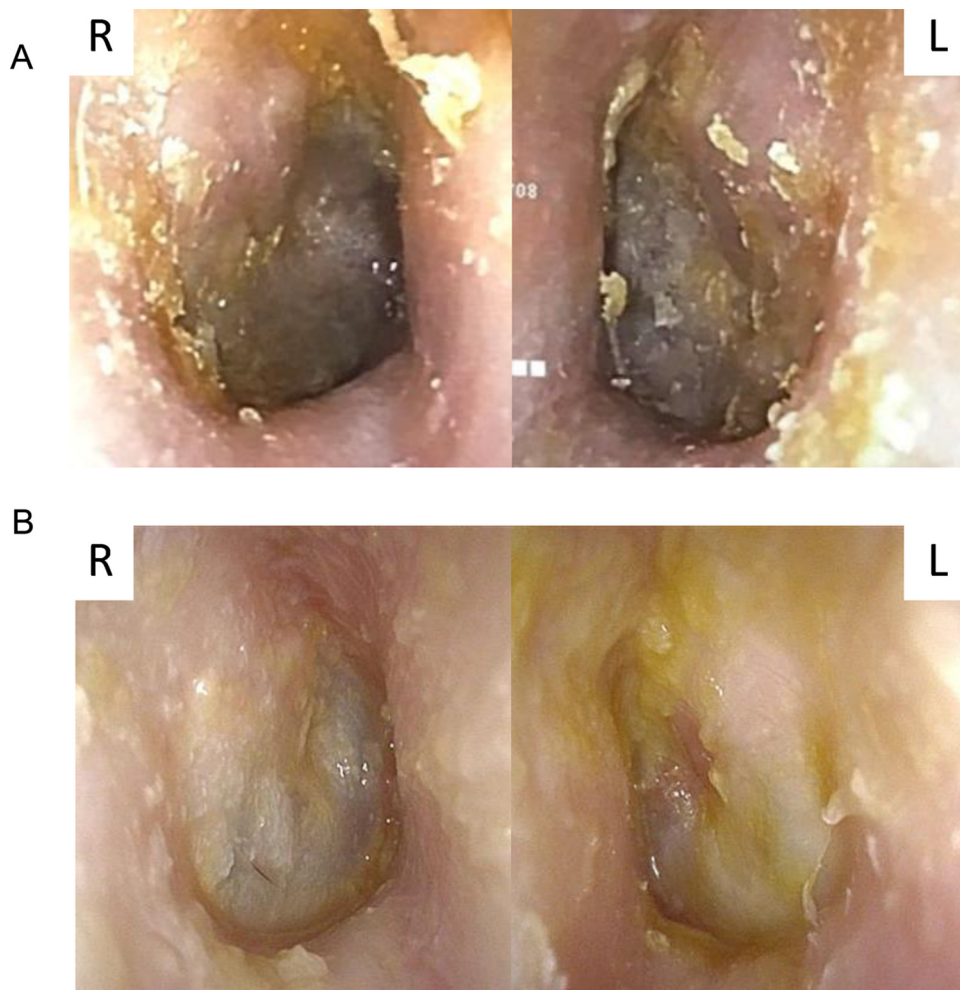


Fig. 1. The otoscopic findings. (A) Prior to mepolizumab treatment. (B) Twelve months after mepolizumab treatment.

(right) and 38.8 dB (left), with mixed hearing loss (average of 500, 1000, 2000, and 4000 Hz) (Fig. 2A). Nasal endoscopy revealed the nasal polyps on both sides of the middle nasal meatus. Computed tomography (CT) scans revealed soft-tissue shadows in the bilateral tympanic cavity and mastoid air cells (Fig. 3A).

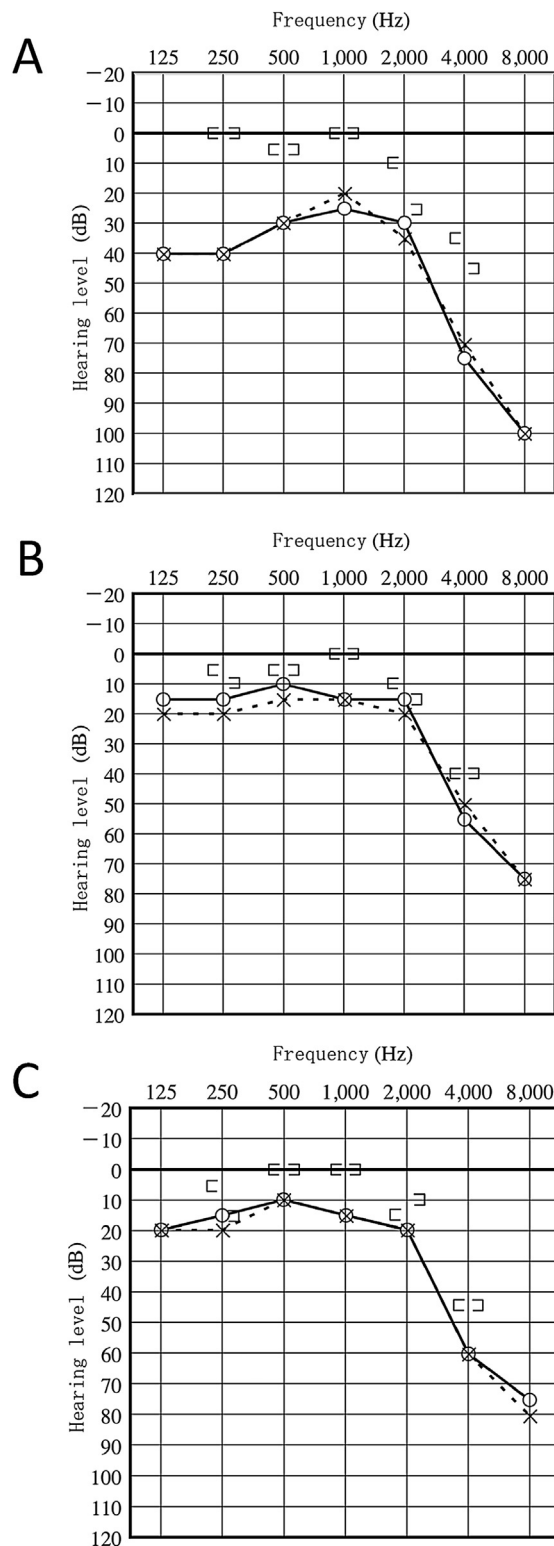


Fig. 2. Pure tone audiometry. (A) Prior to mepolizumab treatment. (B) Four months after mepolizumab treatment. (C) Twelve months after mepolizumab treatment. The air-bone gap was reduced in both ears.

Mepolizumab (100 mg, subcutaneous, every 28 days) was started, and treatment with inhaled budesonide/formoterol and montelukast were continued. At one month after the initiation of mepolizumab therapy, the patient's peripheral blood eosinophil percentage dramatically decreased to 2.6%, whereas the level of serum IgE remained unchanged at 439 IU/mL. Although the patient's lung function and exhaled nitric oxide (FeNO) level showed no change, he did not experience any exacerbation of the symptoms, and his asthma control questionnaire (ACQ) score and asthma control test (ACT) score showed improvement (Table 1).

At 12 months after the initiation of mepolizumab treatment, the thickened tympanic membranes showed increased transparency and a decrease in bulging (Fig. 1B). However, the tympanic membranes did not return to completely normal because some thickening of the tympanic membranes remained. Tympanometry revealed type A findings in both ears at 4 months and 12 months after the treatment. Pure tone audiometry indicated that air and bone conduction hearing had improved in both ears (Fig. 2B, C). At 4 months after the initiation of mepolizumab therapy CT revealed that the soft-tissue shadows in the tympanic cavity and mastoid had disappeared (Fig. 3B). Additionally, his nasal symptoms were well controlled, and the size of his nasal polyps became smaller at 12 months after the treatment. During this observational period, we simply observed the clinical course of the patient and did not perform any additional treatments (*i.e.*, myringotomy or the intratympanic instillation of triamcinolone acetonide). In the 12 months that followed, the patient continued to receive mepolizumab every 28 days for severe asthma. There has been no recurrence of hearing loss, otalgia and the patient has not experienced an exacerbation of asthma. Obviously, the patient's clinical course should be followed for a long time. However, the patient has no need for oral corticosteroid therapy or topical treatment such as intratympanic instillation of triamcinolone acetonide at the time of writing this report.

3. Discussion

IL-5, produced by TH2 cells and ILC2s, is a type of cytokine that targets eosinophils. This is important for their terminal differentiation and maturation [4–6]. IL-5 exerts its effects on target cells via the IL-5 receptors (IL-5Rs), which are composed of IL-5R α and βc subunits. The membrane proximal to the proline-rich motif of the cytoplasmic domain of both IL-5R α and βc subunits is essential to IL-5 signal transduction. Mepolizumab is a humanized monoclonal IgG1 antibody to IL-5 that binds to free IL-5 with high affinity and thus selectively prevents IL-5 from binding to IL-5R α , and which effectively inhibits eosinophilic inflammation [6]. In comparison to a placebo, mepolizumab has been shown to reduce the peripheral blood eosinophil count and the incidence of asthma exacerbations in asthma patients with a history of recurrent exacerbations and signs of eosinophilic inflammation, despite high-dose ICS treatment [7]. Mepolizumab treatment also allowed for the corticosteroid dose to be reduced by 50% in comparison to the asthma patients who received a placebo [8]. In this case, the patient had a history of asthma exacerbations, which necessitated

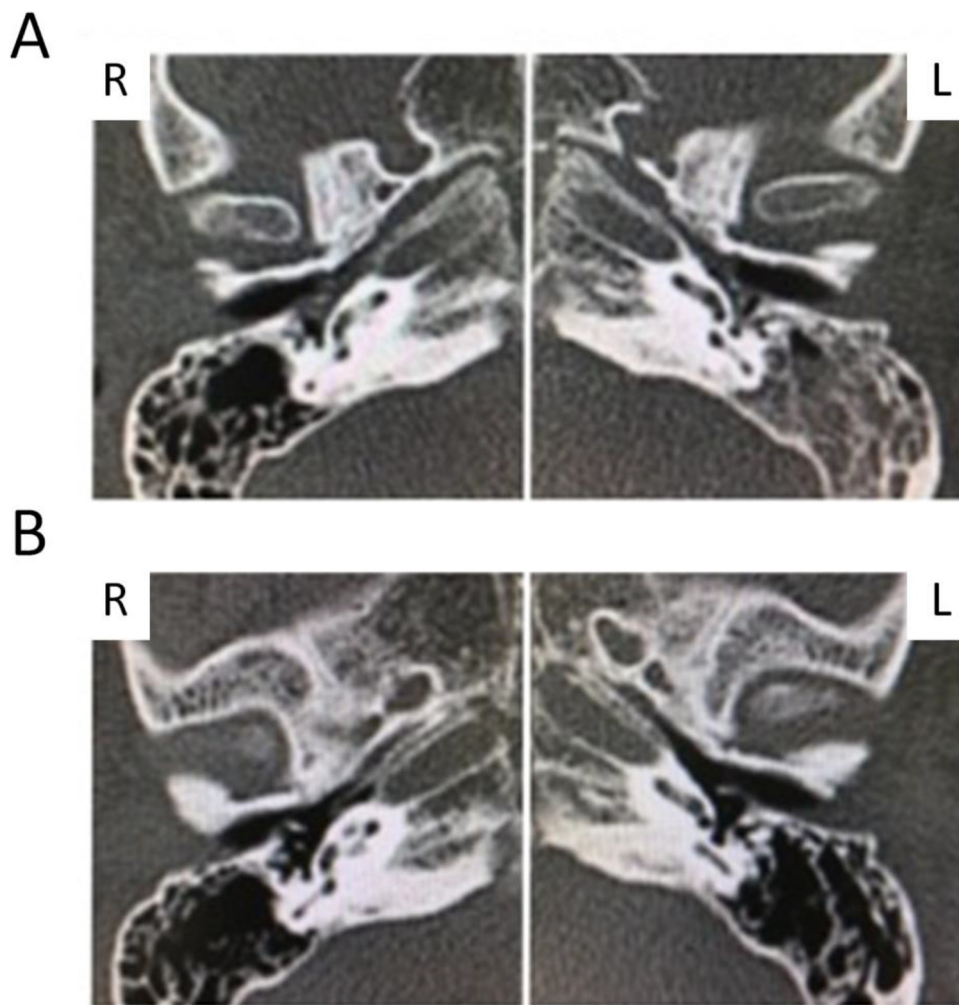


Fig. 3. Temporal bone computed tomography images. (A) Prior to mepolizumab treatment. The soft-tissue shadow extended from the tympanic cavity to the mastoid air cells. (B) Four months after mepolizumab treatment. The soft-tissue shadow had disappeared in both temporal bones.

Table 1
The clinical course before and after mepolizumab treatment.

		Before treatment	Post 1 month	Post 2 months	Post 3 months	Post 4 months	Post 12 months
Blood test	WBC (/μL)	5200	3900	3500	4400	5400	4100
	Eosinophil (%)	20.0	2.6	1.1	1.4	0.9	1.0
	Eosinophil (μL)	1040	101	39	62	49	41
	IgE (IU/mL)	474	439	430	490	559	407
Lung function	FEV1.0 (L)	3.25	3.29	3.29	3.34	3.23	3.16
	% FEV1 (%)	71.9	73.11	70.91	74.39	73.74	71.82
	PEF (L/sec)	8.26	9.15	8.71	8.55	8.32	8.33
FeNO	FeNO (bpm)	59	89	50	43	49	67
Lung symptom	ACT score	22	25	25	25	25	25
	ACQ score	2	0	0	0	0	0

treatment with systemic corticosteroid despite regular use of high-dose ICS/LABA and other long acting drugs. Additionally, anti-IgE therapy, which had previously been attempted, failed to improve his condition. To reduce the risk of an exacerbation and the amount of systemic corticosteroids administered to this

patient with refractory asthma, we initiated anti-IL-5 therapy with mepolizumab. In addition, mepolizumab has been reported to improve the nasal polyp and CT scores of patients with severe eosinophilic nasal polyposis [9]. At present, mepolizumab is only indicated for the treatment of severe asthma; however, it is also

expected to have a therapeutic effect on diseases associated with eosinophilic inflammation.

EOM is a newly recognized intractable middle ear disease that is characterized by the accumulation of eosinophils in MEE and the middle ear mucosa, and which often occurs in patients with asthma, and nasal polyposis. The clinical features of EOM were clarified and the diagnostic criteria were established in 2011 [10]. The major diagnostic criteria for EOM are otitis media with effusion or chronic otitis media with eosinophil-dominant effusion. The minor criteria are as follows: [1] highly viscous MEE; [2] treatment-resistant otitis media; [3] association with bronchial asthma; and [4] association with nasal polyposis. Cases that meet the major criteria, plus two or more of the minor criteria, are considered to be definitive. However, patients with eosinophilic granulomatosis with polyangiitis (EGPA) and hypereosinophilic syndrome are excluded from the diagnosis of EOM [10,11]. EOM is resistant to conventional treatments for otitis media (*i.e.*, myringotomy or insertion of a tympanostomy tube). The standard treatment for EOM is the instillation of triamcinolone acetonide into the mesotympanum; this is expelled through the eustachian tube by applying positive pressure using a pneumatic otoscope [1]. There is a significant association between the severity of EOM and the duration of asthma, and optimized asthma treatment has been shown to improve the symptoms of EOM [3,12]. Iino et al. reported that the long-term treatment of intractable asthma with an anti-IgE agent (omalizumab) was effective for inhibiting eosinophilic inflammation in the middle ear of patients with EOM [2]. In this case, anti-IL-5 therapy was successful, while anti-IgE therapy failed. Omalizumab is reported to be effective in the treatment of allergic asthmatics who show high baseline values of peripheral blood eosinophils, high levels of FeNO and high levels of serum periostin [13]. However, the precise patient factors that predict the efficacy of omalizumab treatment in asthma have not been well established. Taken together, the phenotype of this patient's asthma and EOM might have been eosinophilic-dominant, rather than IgE-dominant. It is essential to maintain good control of asthma in cases of EOM-associated asthma. Although the precise mechanism that leads to the development of EOM is unclear, IgE and several eosinophil chemoattractants (*i.e.*, IL-5, RANTES and eotaxin) are considered to play an important role [14,15]. High levels of IL-5 and eotaxin are detected in the MEE of EOM patients [14]. The clinical features of EOM include a high concentration of eosinophils in the middle ear fluid, and eosinophilic infiltration in the middle ear mucosa, which are similar to the features of asthma. Mepolizumab might inhibit the activation of the eosinophils in the middle ear mucosa and reduce MEE in the tympanic cavity and mastoid. Furthermore, mepolizumab treatment might be expected to have an effect on mild cases of EOM and the early initiation of mepolizumab might be effective for improvement of the condition.

In the present case, mepolizumab, which was used to treat severe asthma, also improved the patient's EOM symptoms. This is the first report to show the efficacy of mepolizumab in the treatment of EOM in a clinical setting. Thus far, mepolizumab therapy is only indicated for severe asthma in

Japan, and its use is not currently permitted for any otorhinolaryngological diseases, including EOM. It is important to carefully follow the clinical course and to hold discussions with respiratory physicians about optimized treatment for EOM that develops in association with severe asthma. This case suggests the possibility that mepolizumab might be an additional treatment choice for patients with intractable EOM and severe asthma.

4. Conclusion

Mepolizumab improved the respiratory symptoms and hearing loss, and reduced MEE in a patient with severe asthma and EOM. Mepolizumab therapy may therefore be useful in the treatment of EOM with severe asthma.

Disclosure statement

The authors declare no conflicts of interest in association with the present study.

Ethical statement

This observational study was approved by Showa University ethical committee (approval number 2018).

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