Dupilumab Remarkably Improved Eustachian Tube Obstruction: A Case of Mepolizumab-Resistant Eosinophilic Otitis Media

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Eosinophilic otitis media (EOM) is a refractory disease characterized by an eosinophil-dominated viscous middle ear effusion, often associated with sinusitis and bronchial asthma [1]. Dupilumab, an anti-interleukin (IL) 4Rα antibody, is a targeted drug that was originally indicated for the treatment of atopic dermatitis, moderate-to-severe asthma, and sinusitis with nasal polyps. However, few reports show the effect of dupilumab on EOM. Herein, we present a case of EOM with tympanic membrane perforation, in which eustachian tube obstruction was significantly relieved by administration of dupilumab.

A 56-year-old woman first visited our hospital because of wheezing despite ongoing treatment for severe asthma, which included oral corticosteroids. She was subsequently hospitalized for asthma exacerbation. She had a medical history of childhood asthma and NSAID-exacerbated respiratory disease (NERD) and had experienced exacerbation of asthma with loxoprofen sodium. She also had chronic otitis media with effusion, which had been treated with myringotomy since the age of 47. Eosinophilia (10%) was detected in otorrhea, and EOM was diagnosed at the age of 54.

The patient's asthma symptoms improved within a few days of systemic corticosteroid therapy, and she was discharged from hospital with a prescription for mepolizumab (Supplementary Figure 1). Sinus computed tomography (CT) was performed owing to the nasal obstruction and olfaction disorder, and the patient was referred to the ENT department. Mucosal thickening was noted in the right maxillary sinus, in both the frontal and the sphenoid sinuses. This finding is typical of chronic sinusitis. Aeration of the tympanic cavity and mastoid cells was normal. Nasal polyps were identified using nasal endoscopy. Analysis of a biopsy specimen revealed ≥50 eosinophil infiltrations/high power field (HPF). The possibility of eosinophilic chronic rhinosinusitis as the diagnosis was likely based on the criteria of the eosinophilic chronic rhinosinusitis score (JESREC score, 15 points) [2]; however, a definitive diagnosis of eosinophilic sinusitis was not made, because the number of eosinophil infiltrations was lower than 70/HPF. The hearing test results were 11.3 dB and 22.5 dB in the right and left ears, respectively. On inspection, tympanic membrane perforation was detected in the left ear, while the right tympanic membrane was normal. The CT scan revealed closure of the left eustachian tube and a normal right eustachian tube. Therefore, the patient was diagnosed with chronic otitis media with perforation in the left ear and otitis media with effusion in the right ear.

The asthma symptoms improved remarkably after initiation of mepolizumab, and systemic corticosteroid therapy was discontinued. We expected mepolizumab to be effective for EOM and chronic rhinosinusitis with nasal polyps (CRSwNP) because it has the potential to improve eosinophilic diseases other than asthma [3,4]. However, nasal and ear symptoms did not improve, even with topical betamethasone administered concomitantly with nasal drops and ear drops (Supplementary Figure 1). Four months after the administration of mepolizumab, the left ear obstruction, runny nose, and nasal obstruction worsened. A CT scan revealed opacities in the ethmoid sinus, bilateral maxillary sinus, and sphenoid sinus (Supplementary Figure 2) and eustachian tube obstruction (Figure, A). Mepolizumab was discontinued because both sinusitis and otitis media were exacerbated.

Immediately after discontinuation of mepolizumab, dupilumab was introduced for CRSwNP, EOM, and severe asthma. Six weeks after initiation of dupilumab, the patient's nasal symptoms improved dramatically (Supplementary Figure 1). The feeling of obstruction in her left ear improved significantly, and the need for betamethasone ear drops was also reduced, although a hearing test revealed no improvements (conductive hearing loss). Examination revealed that the perforation of the tympanic membrane in the left ear had not resolved. However, CT confirmed improved control of CRSwNP and EOM, showing that the eustachian tube had opened (Figure 1B and C). Opacification of the mastoid cells, bilateral maxillary sinuses, ethmoid sinus, and sphenoid sinus had diminished (Supplementary Figure 2). No asthma exacerbations occurred during the period in which the biological agents were switched. No invasive treatment (eg, endoscopic surgery or myringotomy) was necessary for sinusitis.

In this case, dupilumab significantly improved left eustachian tube obstruction despite the resistance to mepolizumab. Three cases of EOM successfully treated with dupilumab have been reported [5]; all 3 cases involved chronic otitis media with perforation and were of the granulomatous type. Other

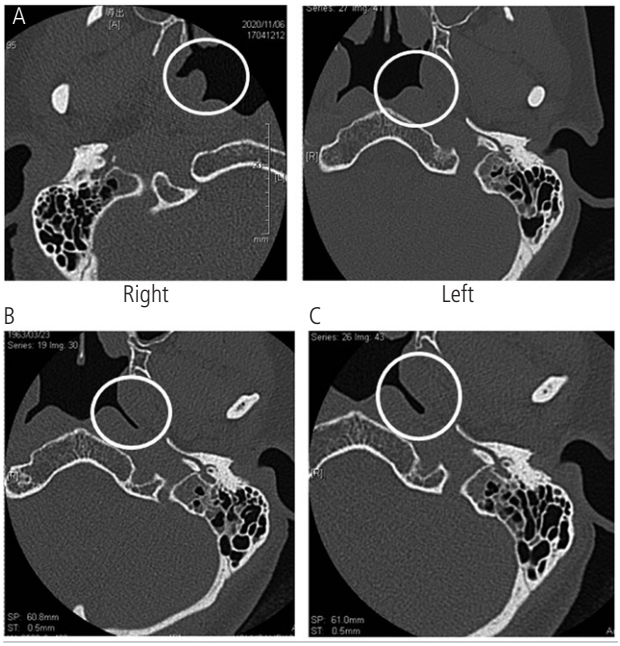

Figure. CT imaging of eustachian tubes before and after treatment with dupilumab. A, CT imaging before dupilumab administration. B, CT imaging 1 month after dupilumab administration (left). C, CT imaging 2 months after dupilumab administration (left). Open circles indicate eustachian tubes. CT indicates computed tomography.

biologics (mepolizumab, benralizumab, and omalizumab) were administered initially but did not prove effective for EOM. Subsequent introduction of dupilumab improved the clinical condition of these patients. Thus, the findings for the case we report are consistent with those of the 3 reported cases of EOM.

Based on the findings of the present case and recent literature, dupilumab may be more effective than other biologics for EOM. One possible explanation of how dupilumab resolved EOM may be the role of periostin in the pathophysiology of the disease [6]. Expression of periostin is induced by type 2 cytokines such as IL-4 and IL-13. It has also been seen in granulation tissue in nasal polyps and in the middle ear [6,7]. In addition, periostin is present in thickened mucosa and is thought to prolong inflammation [8]. Consequently, decreasing IL-4 and/or IL-13 induced by dupilumab may suppress the induction of periostin, thus reducing inflammation and, subsequently, improving eustachian tube obstruction.

In the case we report, CRSwNP also improved with dupilumab. Bachert et al [9] reported that dupilumab reduced the severity of symptoms in adult patients with severe CRSwNP. These results support the benefits of adding dupilumab for patients with severe CRSwNP who have few therapeutic options. Our case was consistent with reported findings. According to Fokkens et al [10], the European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) 2020 steering group recommends using dupilumab in patients with CRSwNP who fulfil the criteria for treatment with monoclonal antibodies. The case we report met these criteria.

In conclusion, eustachian tube obstruction in EOM may be treatable with dupilumab. Dupilumab may be a good treatment option for EOM when it relapses or is resistant to corticosteroid therapy.

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Conflicts of Interest

Y To has received lecture fees from GlaxoSmithKline, AstraZeneca, and Novartis Pharma. The remaining authors declare that they have no conflicts of interest.

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