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Case Report

Complete Remission of Severe Eosinophilic Otitis Media With Dupilumab: A Case Report

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Eosinophilic otitis media (EOM) is a difficult-to-treat otitis media (OM) characterized by eosinophilic accumulation in the middle ear mucosa and secretion. Associated sensorineural hearing loss can eventually lead to (functional) deafness. EOM is strongly associated with type 2 inflammation driven respiratory disease, i.e. asthma and chronic rhinosinusitis with nasal polyps (CRSwNP), for which biological treatment is available. This case report discusses a patient suffering from EOM with severe mixed hearing loss, nearing functional deafness. Dupilumab treatment resulted in complete and enduring remission of the EOM, enabling adequate hearing rehabilitation. Concurrent control of the comorbid asthma and CRSwNP was obtained.

Key Words: Biological, dupilumab, eosinophilic otitis media, human monoclonal antibody.

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INTRODUCTION

Eosinophilic otitis media (EOM) is a difficult-to-treat otitis media (OM) characterized by eosinophilic accumulation in the middle ear (ME) mucosa and ME effusion with a predominant bilateral prevalence (80%).[1,2] Diagnostic criteria were set in 2011 and later supplemented with a severity classification (Table I).[1,3] Alongside bothersome OM symptoms, marked sensorineural hearing loss (SNHL) with gradual and/or sudden deterioration can develop, resulting in functional deafness in ~6%.[2] Treatment is notoriously challenging and comprises local instillation and systemic administration of corticosteroids. Surgery is often ineffective.

EOM is strongly associated with asthma and chronic rhinosinusitis with nasal polyps (CRSwNP).[1] Recently, biologicals directed against type 2 inflammatory pathway components have been approved for and implemented in the treatment strategies of atopic dermatitis, asthma, and CRSwNP. Here, we report on the successful treatment of an adult patient suffering from intractable EOM with severe mixed hearing loss with the anti-interleukin (IL)-4Rα antibody dupilumab, preceded by poor response to (anti-IL)-5 antibodies.

CASE REPORT

A 40-year-old patient with a medical history of nonsteroidal anti-inflammatory drugs (NSAID)-exacerbated respiratory disease (N-ERD), asthma, and CRSwNP developed progressive bilateral hearing loss, aural fullness, and otorrhea irresponsive to topical and systemic antibiotic and corticosteroid therapy. On otoscopy, granulation tissue protruded through the tympanic membrane bilaterally, with remarkably viscous ME secretion (Figure 1A). Cholesteatoma was not suspected otoscopically nor on the CT scan, which showed subtotal opacification of the tympanomastoid space, without ossicular or osseous disruption. Histopathology of the ME granulation demonstrated marked eosinophilic accumulation in the tissue and the ME secretion (Figure 1B,C). Audiometry revealed a severe mixed hearing loss (Figure 2).

Based on fully fulfilling the criteria, EOM was diagnosed. Regular treatment did not obtain disease control. Importantly, the EOM severely compromised the hearing while impeding the use of traditional hearing aids. This negatively affected social and occupational functioning and health-related quality of life. The sensorineural component made rehabilitation with a bone-anchored hearing aid unfeasible, as hearing gain would not result in functional hearing. Continued ME inflammation was disadvantageous for the use of an active middle ear implant. The patient was nearing functional deafness, for which cochlear implantation with subtotal petrosectomy was eventually being considered.

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TABLE I.
Diagnostic Criteria of Eosinophilic Otitis Media (EOM).[1]

Major criteria: Otitis media with effusion or chronic otitis media with eosinophilic dominant effusion

Minor criteria:

1. Highly viscous middle ear effusion
2. Resistance to conventional treatment for otitis media
3. Association with bronchial asthma
4. Association with nasal polyposis

Definitive case: positive for major criteria + two or more minor criteria. Exclusion criteria: Eosinophilic Granulomatosis with Polyangiitis, formerly known as Churg-Straus syndrome, hypereosinophilic syndrome

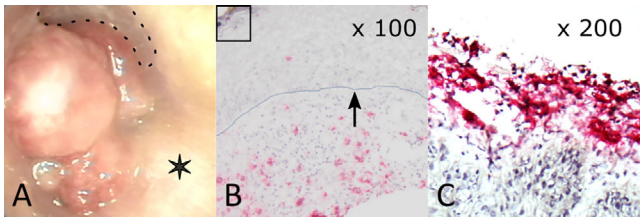

Fig. 1. Micro-otoscopic examination of the right ear of a patient with eosinophilic otitis media and histopathologic examination of the middle ear granulation tissue and secretion. A, Micro-otoscopy showing granulation tissue protruding through the scarcely visible tympanic membrane (dotted line) into the external ear canal (*), alongside viscous secretion. B,C, BMK13-stained granulation tissue slices (Monosan® Eosinophil Major Basic Protein, Clone BMK13; 0,1 μg/mL). B, Eosinophilic infiltration mainly in the lamina propria, below the basement membrane (arrow). Squared area in B, C, eosinophilic mucus on top of the epithelium. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

Meanwhile, insufficient control of his asthma prompted biological treatment as prescribed by his pulmonologist. Successive treatment with mepolizumab and reslizumab, both IL-5-blocking antibodies, transiently resulted in satisfactory control of his asthma and CRSwNP. The EOM, however, demonstrated poor response, resulting in continued nonrehabilitated functional hearing loss.

A switch to dupilumab, an anti-IL-4Rα antibody effectively blocking IL-4 and IL-13 signaling pathways, led to complete remission of the EOM within the course of several months. Normalization of the ME mucosa, cessation of excess ME secretion, and spontaneous bilateral closure of the tympanic membrane resulted in a normal ME physiology, enabling audiologic rehabilitation with traditional behind-the-ears hearing aids. Asthma and CRSwNP control were obtained as well, including recovery of the sense of smell. This therapeutical response sustained during the 12 months of outpatient follow-up as of now.

DISCUSSION

Our report suggests that the anti-IL-4Rα antibody dupilumab is a valuable therapeutic option for severe EOM. Despite poor response to previous anti-IL-5 therapy, complete remission was achieved with dupilumab.

Although EOM is rare, it is expected to be relatively prevalent among patients with type 2 inflammatory respiratory disease. Especially so when both asthma and CRSwNP are present and/or when they are regarded difficult to treat, as is the case when biologicals are indicated by current treatment strategies. Indeed, already 35% of CRSwNP patients in our tertiary referral clinic indicate ear symptoms such as aural fullness.[4] Of these, about a third can be diagnosed with EOM (unpublished data). Therefore, pulmonologists and otorhinolaryngologists should be perceptive for otologic symptoms indicative of EOM when treating type 2 diseases.

EOM-associated hearing loss can become a huge functional impairment for the patient, with cochlear implantation as last available therapeutic resort. Remission of EOM by biological treatment can avert this drastic therapeutical decision. Importantly, it might also prevent (further) SNHL in EOM patients. This should encourage care providers and insurance companies to provide this relatively small group of patients with the proper means to prevent these disabling EOM sequelae.

Biologicals as a treatment modality for EOM is a newly developing field, whose interest from clinicians is reflected in emerging reports in recent years. Its small body of literature consists of case reports and a few small case series, covering most currently available biologicals targeting type 2 inflammation. No direct comparative studies have been performed and the published data so far is not suitable for meta-analysis.

Iino in 2020 also reported on dupilumab treatment in three patients with severe EOM who had poor response to preceding anti-IL-5 antibodies. Pronounced granulation tissue was observed extruding from the patients' middle ears, comparable with our case. Dupilumab substantially reduced the granulation tissue and EOM-severity scores in all three patients. Although complete remission was not achieved and the tympanic perforations persisted, clinically significant symptom control was achieved in two. Interestingly, there is a positive association between EOM severity and periostin levels in both serum and ME mucosa.[5] As the secretion of periostin by fibroblasts is stimulated by IL-4 and IL-13, this might explain the advantageous response to dupilumab in these severe EOM cases compared to anti-IL-5 antibodies.

As with other type 2 inflammatory diseases, it seems likely that endo- and phenotype variability in EOM determines the varying therapeutic response to different biologicals. Further research might entail prognostic biomarkers directing preferential therapy. It might also well be that (difficult to treat or severe) EOM itself will become an indication for biological treatment, or that its comorbid presence guides biological selection in other clinical indications. As long as clear and readily available biomarkers lack, even in far more research advanced diseases like asthma and CRSwNP, the choice for any type of biological will be governed by local availability and experience, healthcare system and insurance issues, patient preference, and responsiveness to previous empirical biological treatment.

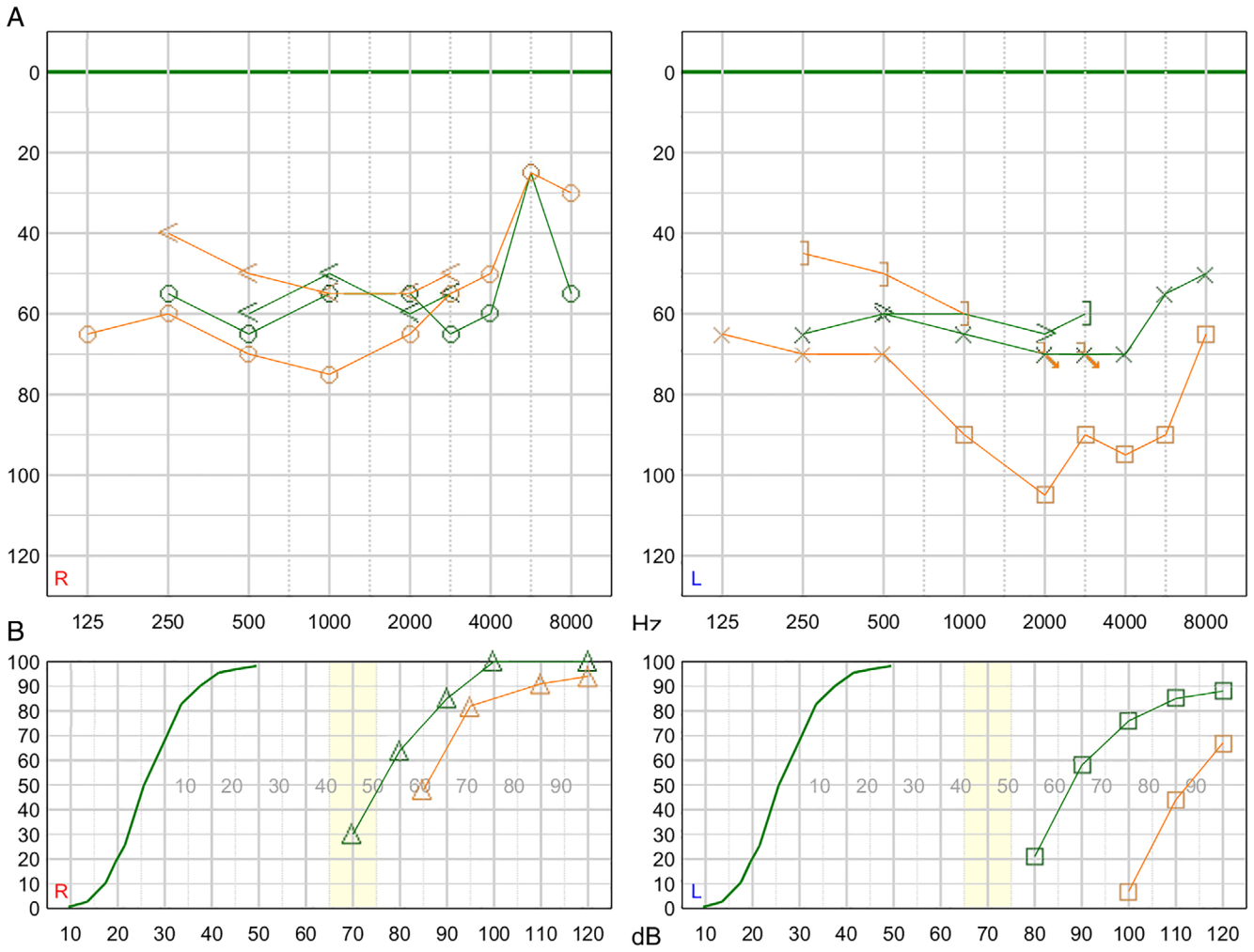

Fig. 2. Pre- and posttreatment audiometry of a patient with eosinophilic otitis media treated with dupilumab. A, Pure-tone audiometry showing profound bilateral mixed hearing loss pretreatment (orange lines) and closed air-bone gaps 12 months into treatment (green lines). B, Unaided speech recognition improved bilaterally. Right ear: from 92% at 120 dB sound pressure level (SPL) to 100% at 100 dB SPL. Left ear: from 68% at 120 dB SPL to 88% at 120 dB SPL (orange versus green lines). [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

CONFLICT OF INTEREST

W.F. is an advisory board member of Sanofi. S.R. has been a consultant for Sanofi. The Department of Otolaryngology & Head and Neck Surgery of the Amsterdam UMC, University of Amsterdam, has participated in premarketing clinical trials with dupilumab. Sanofi cofunds the patient registry PolyREG, dedicated to observational scientific research of patients treated with biologicals for chronic rhinosinusitis with nasal polyps, governed by the nonprofit foundation AERO of which W.F. and S.R. are members of the board and W.F., S.R., and R.L. are member of the steering committee.

BIBLIOGRAPHY

1. Iino Y, Tomioka-Matsutani S, Matsubara A, Nakagawa T, Nonaka M. Diagnostic criteria of eosinophilic otitis media, a newly recognized middle ear disease. *Auris Nasus Larynx* 2011;38:456–461. https://doi.org/10.1016/j.anl.2010.11.016.
2. Suzuki HK, Matsutani S, Kawase T, et al. Epidemiologic surveillance of Eosinophilic otitis Media in Japan. *Otology Japan* 2004;14:112–117.
3. Esu Y, Iino Y, Masuda M, Kanazawa H, Yoshida N. Proposal of a treatment strategy for Eosinophilic otitis media based on middle ear condition. *Otol Neurotol* 2018;39:e671-e678. https://doi.org/10.1097/MAO.0000000000001912.
4. Dietz De Loos DAE, Hopkins C, Fokkens WJ. Symptoms in chronic rhinosinusitis with and without nasal polyps. *Laryngoscope* 2013;123:57–63. https://doi.org/10.1002/lary.23671.
5. Esu Y, Masuda M, Yoshida N. Periostin in middle ear mucosa according to eosinophilic otitis media severity: middle ear pathology-based treatment. *Auris Nasus Larynx* 2020;47:527–535. https://doi.org/10.1016/j.anl.2020.05.014.