

Use of IL-5 Inhibitor Benralizumab as a Novel Therapy for Eosinophilic Otitis Media: Clinical Capsule and Review of Literature

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Objective: We report a case of recurrent eosinophilic otitis media (EOM) successfully treated with the novel monoclonal IL-5 inhibitor benralizumab. We also review literature relevant to EOM diagnosis and potential for biologic treatment.

Patient: A 24-year-old woman with bilateral otitis media with effusion unresponsive to standard treatment.

Intervention(s): Multidisciplinary treatment using subcutaneous benralizumab after diagnosis of EOM.

Main Outcome Measure(s): Behavioral audiometry, peripheral serology, otomicroscopy, and eosinophilic otitis media symptom severity.

Results: Recalcitrant otitis media with effusion (OME) in the setting of nasal polyposis and asthma prompted clinical suspicion for EOM, which was confirmed by pathologic examination of middle ear effusion and soft tissue biopsy.

Treatment with benralizumab was initiated by pulmonology and well-tolerated. Within 2 months of treatment onset there was a cessation of EOM symptoms, a reduction of peripheral eosinophil levels, and an improvement in conductive hearing loss.

Conclusions: Monoclonal antibodies such as benralizumab may be an effective treatment option for EOM. A high level of clinical suspicion in patients with bronchial asthma, nasal polyposis, and recalcitrant OME may allow early diagnosis of EOM. Awareness of emerging biologic treatment options is important in the management of this challenging entity and may prevent long-term sequelae. **Key Words:** Benralizumab—Bronchial asthma—Eosinophilic otitis media—Nasal polyposis—Recalcitrant mucoid effusion.

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Eosinophilic otitis media (EOM) is an uncommon disease characterized by aggregation of eosinophils in the middle ear mucosa accompanied by thick, recalcitrant mucoid effusion. Past cases of EOM have been managed with oral corticosteroids and repeated manual debridement/drainage, with limited success. However, newer monoclonal antibodies have demonstrated efficacy in treatment. We present a challenging case of EOM successfully treated using benralizumab, suggesting a potential role of biologic treatment in otologic disease.

CLINICAL CAPSULE

A 24-year-old female nurse with a history of nasal polyposis, chronic rhinosinusitis, asthma, and eustachian

tube dysfunction presented to our tertiary care center with right-sided otalgia, aural fullness, and dizziness. She had a 1.5 year history of recurrent bilateral otitis media with effusion (OME) unresponsive to conventional treatment with topical nasal steroids, oral antibiotics, and bilateral eustachian tube dilation performed in conjunction with endoscopic nasal polypectomy. Her moderate persistent asthma was controlled with oral corticosteroids, an antileukotriene, and a long-acting β_2 agonist (LABA). Previous nasal cultures suggested presence of *Staphylococcus aureus*. The patient denied any history of aspirin sensitivity, childhood ear infections, tinnitus, vertigo, mastoid pain, exposure to ototoxic drugs, or noise trauma.

Otomicroscopy was consistent with intact, dull, non-mobile tympanic membranes bilaterally with obvious fluid in the middle ear space. Office myringotomy revealed remarkably thick mucus and she underwent repeated bilateral myringotomy with pressure equalization tube (PET) insertions in the office ($n = 6$), secondary to tube obstruction with thick mucoid debris. Topical medication (combination antibiotic and steroid drops as well as steroid drops alone) was attempted to maintain PET patency without success. Repeated courses of oral steroids

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decreased aural fullness and otorrhea. However, symptoms returned following each course.

Behavioral audiometry confirmed moderate conductive hearing loss bilaterally, with normal bone lines, type B tympanograms, and 100% word recognition scores. Serologic testing was negative for Lyme disease, immunodeficiency, and autoimmune dysfunction, including antinuclear antibody (ANA) and antineutrophil cytoplasmic antibodies (ANCA), and was positive for peripheral eosinophilia (8% eosinophils, 1100 cells/ μ L).

Recalcitrant mucoid OME, bronchial asthma, and nasal polyposis prompted suspicion for EOM. Middle ear fluid and mucosal biopsy were obtained in office and sent for pathologic analysis, which revealed periodic acid-schiff (PAS) positive compact mucoid material with scattered inflammatory cells, the majority of which consisted of poorly preserved eosinophils. Inspissated proteinaceous deposits in the form of Charcot-Leyden crystals and hexagonal structures were also observed to be consistent with EOM. After consultation with her pulmonologist, the patient was started on subcutaneous benralizumab for her asthma. Approximately 2 months after treatment initiation, she reported the cessation of aural fullness and hearing loss, with improved eosinophilia on serology (6% eosinophils, 300 cells/ μ L). The medication is well-tolerated, and she remains asymptomatic with patent, dry PET bilaterally for over 6 months, the longest improvement since her diagnosis of EOM.

DISCUSSION

Eosinophilic otitis media is a recently defined intractable middle ear disease that was first identified in 1993 (1). This condition is characterized by the accumulation of viscous eosinophilic mucin in the middle ear (2). A review of 138 EOM patients in Iino et al. (3) found that EOM presented most commonly in women (62%) with mean age of 50.5 ± 13.1 years. Presence of asthma, nasal polyposis, and OME should prompt diagnostic consideration of EOM. In accordance with these findings, Iino et al. (3) outlined diagnostic guidelines characterizing the major criterion for EOM as otitis media with effusion or chronic otitis media (COM) secondary to eosinophil aggregation in the middle ear mucosa and fluid. On gross examination, mucinous yellow effusion and edematous pink mucosa of the middle ear are most commonly observed (4). Symptoms highly associated with EOM include nasal polyposis, viscous effusion, bronchial asthma, and resistance to standard otitis media treatment (odds ratio of 42.17, 201.6, 584.5, and 232.2, respectively). EOM is frequently missed due to its nonspecific presentation (4). Biopsy of the middle ear effusion and hematoxylin and eosin staining is often necessary to identify eosinophils and their state of degranulation for diagnosis. Additional symptoms of lower statistical significance indicating EOM include the formation of granulation tissue, bilaterality of effusion, allergic rhinitis, sudden onset conductive hearing loss, and peripheral hyper eosinophilia (3). In addition, 40% of patients in a

recent EOM cohort ($n = 32$) were found to have a probable history of aspirin intolerance (5).

EOM can present similarly to eosinophilic granulomatosis with polyangiitis (EGPA). Similar symptoms on initial presentation include asthma, chronic rhinosinusitis, recurrent nasal polyposis, elevated serum IgE, hearing loss, and COM (6). However, patients with EGPA had increased rates of peripheral blood eosinophil fractions (mean 45.7% versus 19.8%, respectively) and ANCA positivity (50% versus 0%, respectively). EOM patients were also more likely to have a tympanic membrane perforation, middle ear effusion, and otorrhea on subsequent follow-up (6). Consideration of ANCA test results, blood peripheral eosinophil fraction, and patient history would be necessary to rule out EGPA in favor of EOM (3).

While the exact mechanism for eosinophil accumulation in the middle ear has not been delineated, the presence of eosinophilic chemoattractants eotaxin and interleukin-5 (IL-5) has been previously documented (2). The more active chemotactic agent in EOM pathogenesis, IL-5 is a cytokine that terminally differentiates and stimulates the growth of eosinophils. This ligand has been shown to have significantly increased concentrations in the middle ear mucosa of EOM patients, and is likely responsible for eosinophilic migration from the submucosal region to the middle ear canal (7).

A recent review has proposed that patulous eustachian tubes from T-helper cell Type 2 predisposed asthmatics more readily facilitate antigen entry into the middle ear. The subsequent migration of eosinophils in response to antigen introduction would result in mucin production, forming viscous effusion upon mixing with eosinophilic debris (8). Kanazawa et al. (2) separately suggested that local sensitization against bacteria or fungi, especially *Staphylococcus aureus*, can result in subsequent IgE production and EOM exacerbation. Our patient's history of asthma and *S. aureus* infection of the ear may support this theory.

Previous treatment for EOM involved systemic or topical administration of corticosteroids after unsuccessful conventional treatment of COM (9). Standard COM therapy includes the use of antimicrobial agents, myringotomy, placement of tympanostomy tube, or tympanoplasty. Concurrent treatment of associated bronchial asthma using leukotriene receptor antagonists or antihistamines has also been used. Newer medications studied for EOM intervention included two cases of successfully treated EOM using the thromboxane A₂ antagonist ramatroban (10). In addition, a recent study noted the efficacy of pegylated interferon- α 2a and 2b, albeit with side effects including myalgia and fatigue (11). Nevertheless, advances in molecular-based therapeutics have facilitated the treatment of bronchial asthma using targeted monoclonal antibodies known as biologics. These include lebrikizumab (anti-IL-13), reslizumab (anti-IL-5), dupilumab (anti-IL 4R α), mepolizumab (anti-IL-5), omalizumab (anti-IgE), and benralizumab (anti-IL-5R). Ongoing trials using mepolizumab ($n = 30$) and reslizumab ($n = 24$) have

shown reductions in nasal polyp size relative to controls, demonstrating potential as future treatments of chronic rhinosinusitis (12). Furthermore, dupilumab was recently approved by the Food and Drug Administration as the first drug to treat chronic rhinosinusitis with nasal polyps after two studies reported significant reduction in nasal congestion and polyp size ($n = 724$) (13).

Of these novel drugs, omalizumab and mepolizumab have been moderately successful as EOM treatments in pilot studies (14,15). Iino et al. (14) examined the efficacy of mepolizumab as an add-on treatment to corticosteroids for nine EOM patients. Starting 3 months after initiation of treatment, seven EOM patients reported a reduction in EOM symptoms including middle ear effusion and otorrhea. Moreover, the mepolizumab group showed significant reduction in peripheral blood eosinophilia upon completion of treatment (686 ± 245 cells/ μ L to 70 ± 71 cells/ μ L). One year after beginning treatment, four patients showed full resolution of EOM symptoms (14). However, two EOM patients with granulation showed no improvement. Similarly, Iino et al. (15) tested omalizumab as an EOM treatment in eight patients, with five patients showing resolution of middle ear effusion after 1 year of treatment. Bone conduction hearing deterioration was more common in the control group.

First approved in 2017 by the Food and Drug Administration for treatment of severe cases of eosinophilic asthma, the IL-5R inhibitor benralizumab has been highly effective in depleting blood eosinophil levels (16). However, no literature exists documenting the use of benralizumab in the treatment of EOM. Known side effects are an increased risk for pyrexia (relative risk [RR] 2.26, 95% confidence interval [CI] 1.32–3.87) and headaches (RR 1.42, 95% CI 1.07–1.87), neither of which were experienced by our patient (17). Safety in pregnancy is currently unknown. Further case studies and prospective trials are necessary to further assess the efficacy of benralizumab and other monoclonal antibodies as independent therapies for EOM.

The importance of early diagnosis and intervention for EOM is underscored by the frequent progression of conductive hearing loss to permanent mixed hearing loss in these patients (18). Previous studies have reported that approximately 50% of previously untreated EOM cases resulted in bone conduction hearing level deterioration, and up to 6% resulted in complete deafness (19). Progression of eosinophilic inflammation and bacterial infection have been suggested as the etiology of this inner ear dysfunction.

CONCLUSION

Extrapolating from pulmonary data in asthmatics, there is an emerging understanding of the potential effectiveness of biologic therapy in treating inflammatory disease of the nasal airway. Comparatively little is known about the effectiveness of the immune modulators

in otologic disease, specifically EOM. At present, there are few treatment options for EOM, and biologics appear to represent a promising, novel option for addressing symptoms and preventing complication and progression of this challenging disease. Additional data are necessary to understand the long-term effectiveness and side effects of these medications.

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