

New Insights into Eosinophilic Otitis Media

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Abstract Eosinophilic otitis media (EOM) is a type of intractable otitis media that occurs mainly in patients with bronchial asthma (BA). In 2011, the diagnostic criteria for EOM were established. EOM is characterized by the presence of a highly viscous yellowish effusion containing eosinophils and immunoglobulin E (IgE), eosinophil chemoattractants, such as eosinophil cationic protein, interleukin-5, and eotaxin. Local sensitization against foreign agents such as fungi or bacteria (e.g., *Staphylococcus aureus*) may result in local IgE production in the middle ear and may be responsible for the severity of EOM. The clinical features of EOM closely resemble localized eosinophilic granulomatosis polyangiitis, therefore it is necessary to be vigilant to the symptoms of mononeuritis, polyneuritis, and skin purpura during diagnosis. Standard treatment for EOM is the instillation of triamcinolone acetonide into the mesotympanum. However, severe cases exhibiting strong inflammation and otorrhea are not easily controlled with antibiotics and/or corticosteroids. We proposed the introduction of a severity score to evaluate the severity of EOM. This score correlated with local IgE levels in middle ear effusion. Clinically, the risk factors associated with

this severity score were body mass index, and the duration of bronchial asthma (from the onset of BA to the age of the first consultation of otitis media to our hospital). We emphasize that early diagnosis and adequate treatment are vital in preventing progressive and sudden hearing loss resulting from EOM.

Keywords Eosinophilic otitis media · Bronchial asthma · Viscous middle ear effusion · Eosinophilic chronic rhinosinusitis · Immunoglobulin E · Severity score

Introduction

Eosinophilic otitis media (EOM) was first reported by Tomioka and colleagues in 1994 [1] and is now recognized worldwide as a middle ear disease. In 2011, the EOM study group established diagnostic criteria for EOM [2]. Since then, there have been several case reports, as well as studies concerning the clinical features of EOM from Japan and other countries around the world [3–6]. The pathophysiology and clinical characteristics of this disease are consequently being elucidated.

Early diagnosis and appropriate therapeutic intervention are vital in the treatment of EOM to prevent progressive and sudden hearing loss. To date, EOM has largely been regarded as a type of refractory otitis media. In this review, we collate the literature on EOM and present our current understanding of the pathophysiology (especially immunoglobulin E (IgE)), diagnosis (differential diagnosis for eosinophilic granulomatosis polyangiitis (EGPA)), clinical characteristics (association with rhinosinusitis, condition of middle ear mucosa, change in hearing acuity, severity score), and treatment (especially cochlear implants for deafness) of this disease.

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Pathophysiology

Histological examination of middle ear effusion (MEE) showed that a large number of eosinophils, which are considered to be eosinophilic mucin, in addition to a mucus component were observed [7]. The concentration of eosinophil cationic protein (ECP), which is a marker for eosinophilic inflammation, in the MEE of EOM patients was significantly higher than in their serum. Moreover, a significantly larger number of Eosinophilic Granule 2 (EG2)-positive cells were observed in the middle ear mucosa of EOM patients than in the control patients, proving that active eosinophilic inflammation is occurring in EOM [8]. Regarding eosinophil chemoattractants, the concentration of interleukin (IL)-5 and eotaxin in MEE were significantly higher in EOM patients than in the control group [9, 10]. The concentration of ECP positively correlated with that of IL-5, which is a cytokine involved in local activation of eosinophils and increased cell survival. Furthermore, the expression of eotaxin, regulated on activation normal T cell expressed and secreted (RANTES), and eaelectin messenger RNAs (mRNAs) were detected by in situ hybridization [10]. The fact that chemotactic and activation factors for eosinophils were detected not only at the protein level but also at the mRNA level, indicated that active eosinophilic inflammation occurs in the middle ear itself [7].

IgE in EOM

IgE is an immunoglobulin produced by B cell lymphocytes that plays an important role in type I allergic reactions [7]. The IgE level in MEE was significantly higher than in serum, and hence IgE in the former is considered to have been produced locally in the middle ear [7].

Insufficient closing of the eustachian tube, as evaluated by sonotubometry, was observed in EOM patients [11, 12••]. This anatomical feature may lead to pathogenic EOM because it may allow foreign materials to enter the middle ear and cause eosinophilic inflammation [11]. The foreign material/agent(s) responsible for inducing eosinophilic inflammation remain to be determined, however, candidates include bacterial elements, viruses, or fungi. IgE within the middle ear mucosa was immunohistologically detected on the surface of mast cells and within plasma cells in EOM patients [3]. These

findings suggested that IgE may be locally produced in the middle ear mucosa rather than being derived from serum. Furthermore, antigen-specific IgEs against some fungi and *Staphylococcus aureus* enterotoxin were detected in the MEE of EOM patients [13••]. Okano and colleagues reported that certain fungi, such as *Aspergillus* and *Alternaria*, were also found to be responsible for inducing eosinophilic inflammation in the sinus mucosa or nasal polyps [14]. In addition, it was found that dispersed nasal polyp cells produce IL-5, IL-13, and regulate activation of normal T cells to express and secrete chemokines in response to fungal extracts of *Aspergillus*, *Alternaria*, or *Candida*. This implied that local production of IgE can be induced by both acquired immunity in type I allergic responses and natural immunity from mucoc epithelial cells in middle ear-like nasal mucosa and polyps [15•, 16•, 17].

EOM and EGPA

The diagnostic criteria for EOM proposed by Iino and colleagues in 2011 [2] are shown in Table 1. Major criteria were identification of eosinophils from MEE or middle ear mucosa by histological or cytological examination. Histology of MEE by formalin fixation is more useful because the appearance and degranulation of eosinophils can be detected. If bacterial infection exists, the effusion is found to contain neutrophils rather than eosinophils. Antibiotic therapy and frequent topical saline irrigation are effective at reducing bacterial infection in the middle ear. Following the treatment, re-examination of the MEE was performed to detect eosinophils.

Minor diagnostic criteria for EOM included association with mostly adult-onset bronchial asthma (BA) and nasal polyposis, highly viscous MEE, and resistance to conventional treatments for otitis media.

It is important to note that this set of diagnostic criteria excluded EGPA and hypereosinophilic syndrome. EGPA, formerly Churg–Strauss syndrome, is a form of antineutrophil cytoplasmic antibody-associated vasculitis (AAV). AAV is histologically characterized by systemic necrotizing vasculitis and remains a significant cause of fatal disease despite progress in immunosuppressive therapy. EGPA is characterized by eosinophilic inflammation including severe bronchial asthma

Table 1 Diagnostic criteria for eosinophilic otitis media (adapted from [2])

Major criterion	Minor criteria
Otitis media with effusion or chronic otitis media with eosinophil dominant effusion	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+two or more minor criteria

Exclusion criteria: eosinophilic granulomatosis polyangiitis, hypereosinophilic syndrome (EGPA)

(BA), chronic rhinosinusitis, nasal polyps and eosinophilic bronchitis pneumonia, and eosinophilia. Recently, otological symptoms such as otitis media and acute hearing loss, not previously often associated with AAV, have been reported, described as otitis media with AAV [18•, 19•]. Clinical features relating to eosinophil infiltration, MEE, and mucosal changes are similar in both EOM and localized EGPA. However, EOM does not show a necrotizing vasculitis in the middle ear mucosa. During treatment for EOM, some patients presented numbness in the leg or skin eruptions characteristic of EGPA. It is therefore necessary to pay close attention to the mononeuritis, polyneuritis, or skin purpura-specific nature of EGPA during diagnosis.

Clinical Characteristics

Age

In the 2011 EOM study group report, the majority of first-time EOM patients were found to be aged 50–60 years and 62 % of patients were female [2]. Of this study group, 75 % of patients displayed sinusitis or multiple nasal polyps, and adult-onset BA.

According to questionnaire responses, the average age at onset of BA and rhinosinusitis was earlier than for EOM. Most patients were affected by rhinosinusitis or BA first, with EOM developing more than 10 years later [12••]. EOM may be the endpoint of eosinophilic inflammation involving the upper and lower airway tracts.

Condition of Middle Ear Mucosa

The disease resulting from EOM is generally considered to be bilateral; however, the condition of the middle ear mucosa is not always the same on both sides.

The clinical features of the middle ear during EOM can be roughly divided into two types: otitis media with effusion (OME) and chronic otitis media. Regardless of the existence of perforation of the eardrum, middle ear yellowish effusion is highly viscous. When a tympanostomy tube is placed in OME-type EOM, the lumen of the tube is easily blocked by the viscous effusion. We classified the condition of the middle ear mucosa into three grades (Fig. 1) [20••, 21••]. Grade 1 is normal (unthickened) middle ear mucosa, Grade 2 is thickened but within the tympanum, and Grade 3 is thickened or edematous mucosa beyond the tympanum to the external auditory canal (also known as “granulation type”). Grade 3 middle ear mucosa is the most intractable, being associated with strong inflammation and otorrhea not easily controlled with antibiotics and/or steroids. If the infection is caused by drug-resistant bacteria, such as methicillin-resistant *S. aureus*

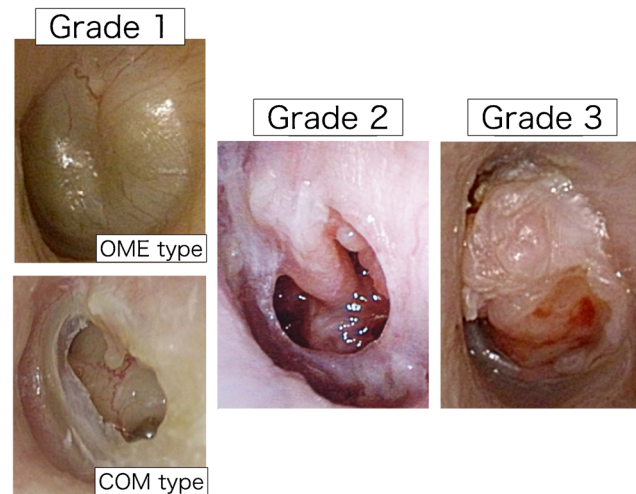


Fig. 1 Middle ear mucosa condition classified into three grades

or *Pseudomonas aeruginosa*, treatment is even more difficult. It is yet to be determined whether bacterial infection is the cause or result of EOM.

Change in Hearing Acuity

Clinical surveillance of EOM in Japan demonstrated that among 190 EOM patients, approximately one-half showed deterioration of the bone conduction hearing threshold and 6 % became completely deaf [2]. Eosinophilic and bacterial inflammatory products of the middle ear may invade the inner ear via the round window to cause inner ear damage.

Matsubara and colleagues [22••] constructed an animal model of EOM by intraperitoneal and intratympanic injection of ovalbumin. As the periods of intratympanic injection of ovalbumin into the middle ear became longer, marked eosinophil infiltration in the perilymphatic and endolymphatic space of the inner ear was observed in addition to the infiltration of eosinophils in the middle ear. The results indicated that eosinophilic inflammation also occurred in the inner ear and caused profound hearing loss [19•].

Generally, the type of hearing impairment in EOM patients is high-tone hearing loss [23]. The concentration of IgE in MEE significantly and positively correlated with bone conduction hearing loss (BCHL) at 2 and 4 kHz [24]. Nakagawa and colleagues evaluated the association between BCHL at 8000 Hz and the length of the duration of EOM [25]. The effect of a thickened middle ear mucosa over the tympanic membrane to the external auditory canal is described as the “granulation type”, which is often accompanied by a significant increase in BCHL [23]. Various other types such as the OME type exist in which the hearing level is usually stable or unstable. To prevent the deterioration of BCHL, the control of eosinophilic inflammation and bacterial infection is mandatory.

Association with Rhinosinusitis

Patients with EOM may exhibit nasal polyposis, which is included within the minor diagnostic criteria. Our survey indicated that 75 % of patients with EOM displayed eosinophilic chronic rhinosinusitis (CRS), which presents with nasal polyps, blood eosinophilia, and an ethmoid dominant shadow in computed tomography scans [26••]. Of cases of eosinophilic CRS, 3 % are associated with EOM. Sometimes, the deterioration of EOM occurs after functional endoscopic sinus surgery [12••]. An increase in nasopharyngeal pressure by habitual nose blowing or sniffing or strong nasal irrigation might be one of the causes leading to EOM, particularly in the post-FESS state. Most of the patients with eosinophilic CRS had already received long-term medication to treat asthma or eosinophilic CRS. This may have reduced mucosal swelling around the eustachian tube, causing impaired tubal closing [12••]. In such cases, we recommend using a low-pressure douche, stopping nasal irrigation, and changing nasal habits.

Much more is now known about the etiology and pathogenesis of CRS [27••]. Because CRS and EOM are closely related to each other, revealing the complexities of CRS may also provide insight into the pathogenesis of EOM.

Severity Score

We previously proposed a severity score to evaluate the severity of EOM [20••, 21••]. The score was evaluated according to five variables: quantity of MEE or otorrhea, condition of the middle ear mucosa, frequency of intratympanic injection of triamcinolone acetonide, frequency of administration of systemic corticosteroids, and antibiotics. This score correlated with the concentration of topical IgE in the MEE and could be used to estimate the efficacy of treatment. Long-term evaluation of EOM is yet to be reported, so this score could be employed for this purpose. Various types of treatment responses have been observed. In some cases, a long-term stable state can be achieved by injection of triamcinolone acetonide into the tympanum, in other cases, otorrhea or granulation cannot be controlled regardless of the type of treatment. Risk factors associated with this severity score are body mass index (BMI), and the duration of BA (from the onset of BA to the patient's age at the first consultation for otitis media at our hospital), which significantly affected EOM ($p < 0.05$) [21••]. The presence of aspirin-intolerant asthma was found to correlate with the severity score. The Lund–Mackay score negatively correlated with the severity score.

BMI is already considered a potential risk factor for severe asthma [28, 29]. There may also be an ethnic difference in the risk of severe asthma [30]. A clear association between body mass index and EOM has not been reported to date.

Treatment

Standard treatment was described by Iino and colleagues in 2008 [31]. As a conservative treatment, we reported the instillation of triamcinolone acetonide, a suspension of corticosteroids, into the mesotympanum and expulsion through the eustachian tube by applying a positive pressure using a pneumatic otoscope [32]. Dorsal positioning is preferred for injection into the tympanic space opening of the eustachian tube, which is thought to be the focus of EOM. A small amount of triamcinolone acetonide is applied to the surface of the middle ear mucosa. It is preferable for EOM patients to undergo this type of local treatment because many patients may be concurrently being treated with inhaled corticosteroids for BA. For most patients, this treatment can be performed once a month or more in outpatient clinics. In less severe cases, the period of injection may be reduced. In infected ears, corticosteroids should be instilled by systemic administration of antibiotics to control the bacterial infection.

As for the association with BA, optimized treatment for BA is important for improving the symptoms of EOM [33]. Smoking history has been reported to be associated with the onset of EOM [34••]. In a recent report, the effects of the anti-IgE monoclonal antibody omalizumab on EOM were investigated [35]. We also previously compared patients with EOM who had received the anti-IgE agent omalizumab, with and without conventional treatments for EOM, by ear symptom scores and severity scores [20••]. Patients who were treated for more than 1 year showed an improvement in their scores with resolution of MEE. The total serum IgE level was significantly elevated after 3 months of therapy ($p < 0.01$). However, the clinical application of omalizumab may be limited by its cost and the need for prolonged use.

To control otorrhea, or to treat hearing impairment due to a large perforation or EOM, tympanoplasty surgery is possible. However, it is important that corticosteroids are administered systemically in the pre- and post-operative periods to prevent eosinophilic inflammation. Complete deafness following surgery has been reported in a small number of patients [1].

Azadarmaki and colleagues performed a tympanomastoidectomy and polypectomy to facilitate middle ear and mastoid ventilation and succeeded in the topical delivery of steroids to the site of deafness [36]. After this type of surgery, it is important that a topical corticosteroid or an oral prednisone is administered.

For patients with bilateral profound deafness, cochlear implantation has been suggested. Two cases (both granulation type) have been reported in which cochlear implantation was performed to treat deafness caused by EOM [37, 38]. The main problem associated with cochlear implantation in patients with chronic ear disease is infection originating from the electrode cable or receiver stimulator package, with the further risk of labyrinthitis or intracranial infection [39•]. In

the first case, systemic administration of oral corticosteroids and antihistamine was employed but difficulties in infection control were experienced. In the second case, a modified Rambo's operation was performed by means of complete removal of the external auditory canal skin, tympanic membrane, malleus, incus, and middle ear mucosa, with exenteration of all mastoid air cells. The external auditory meatal skin was then everted by means of a blind sac closure. Advances in surgical procedures of this type will lead to further cases of cochlear implantation in the future.

Conclusion

In this review, we describe the pathology, clinical characteristics and treatment of EOM. In asthmatic patients who have a T-helper type 2-dominant predisposition, the entry of antigenic material into the middle ear via an impaired eustachian tube may cause EOM. Clinicians should therefore be vigilant regarding ear symptoms in patients with BA.

Further research to understand the etiology and pathogenesis of EOM may lead to the development of novel therapeutic strategies that will decrease our reliance on corticosteroids to treat this disease.

Compliance with Ethical Standards

Conflict of Interest Drs. Kanazawa, Yoshida, and Iino declare no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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