

Eosinophilic Otitis Media: A New Middle Ear Disease Entity

Yukiko Iino, MD, PhD

Corresponding author

Yukiko Iino, MD, PhD

Department of Otolaryngology, Jichi Medical University Saitama Medical Center, 1-847, Amanuma-cho, Omiya-ku, Saitama 330-8503, Japan.

E-mail: yiino@omiya.jichi.ac.jp

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Eosinophilic otitis media (EOM) is intractable otitis media characterized by the presence of a highly viscous yellow effusion containing eosinophils. It occurs mainly in patients with bronchial asthma and is resistant to conventional treatments for otitis media. Here we discuss the clinical features, pathogenesis, and management of EOM. EOM predominantly affects women and presents most often in patients in their 50s. The clinical features of the middle ear in EOM are roughly divided into the otitis media with effusion type and chronic otitis media type. The latter is further divided into two subtypes: simple perforation and granulation tissue formation. EOM is often complicated by rhinosinusitis (eosinophilic sinusitis). High-tone loss is more frequently found and more severe in EOM patients than in chronic otitis media control patients, and EOM patients sometimes become deaf suddenly. Systemic or topical steroid administration is the most effective treatment for patients with EOM. The instillation of triamcinolone acetonide, a suspension of steroids, into the middle ear is very effective for controlling eosinophilic inflammation. It is very important to explain to patients with EOM that the disease may last for a long period and that progressive and sudden hearing loss may occur.

Introduction

Eosinophilic otitis media (EOM) is intractable otitis media characterized by the presence of a highly viscous yellow effusion in the middle ear. It manifests as otitis media with effusion (OME) when there is no perforation of the eardrum and as chronic otitis media (COM) when there is a persistent perforation of the eardrum. It occurs mainly in patients with bronchial asthma and is resistant to conventional treatments for OME and COM. In 1993,

Tomioka et al. [1] first reported three adult patients with a combination of asthma, nasal allergy, and intractable OME. Morinaka [2] also reported a patient with OME with a history of bronchial asthma and nasal allergy. These patients exhibited more or less the same clinical course and symptoms, which were markedly different from those of the more common OME or COM. In 1952, Derlacki [3] termed this type of otitis media with the similar clinical characteristics *allergic otitis media* and summarized the features as follows: 1) a secretion having a remarkably viscous or gelatinous consistency with eosinophils; 2) a middle ear mucous membrane that is fairly thickened with numerous eosinophils; 3) a protracted time of healing; 4) occurrence in individuals of allergic disposition, such as allergic rhinitis; and 5) likely response to antiallergic treatment. Type I allergy (ie, IgE-mediated hypersensitivity to some antigens) is one of the important etiologies of bronchial asthma and nasal allergy. However, Tomioka et al. [4] labeled this type of otitis media *EOM* rather than allergic otitis media because the infiltration of a number of eosinophils is observed in the effusion and mucosa of the middle ear regardless of the presence or absence of type I allergy. Although EOM was considered a rare disease, it is expected that a sizable population of asthmatic patients will be diagnosed as having this disease if it is properly recognized. Here we discuss the clinical features, pathogenesis, and treatment of EOM.

Diagnostic Criteria of EOM

Diagnosing EOM remains controversial. First, it is necessary to prove the infiltration of eosinophils into the effusion or mucosa of the middle ear to diagnose EOM. As for the middle ear effusion, staining the formalin-fixed viscous effusion with hematoxylin and eosin is a more reliable method of determining the extent of infiltration or the condition of eosinophil degranulation than using a smear sample. Some of the eosinophils observed in the effusion or mucosa of the middle ear are degranulated, indicating the presence of a significant eosinophilic inflammation (Fig. 1 and Fig. 2). However, the infiltration of eosinophils may be mild or may not be observed when steroids are used systemically or topically. The infiltration of neutrophils and eosinophils is often observed in the

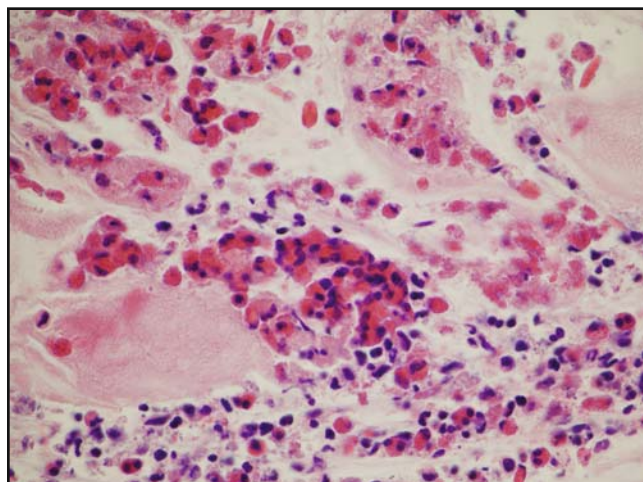


Figure 1. A histologic section of middle ear effusion of eosinophilic otitis media (hematoxylin and eosin staining). Many eosinophils and mucin are found in the effusion.

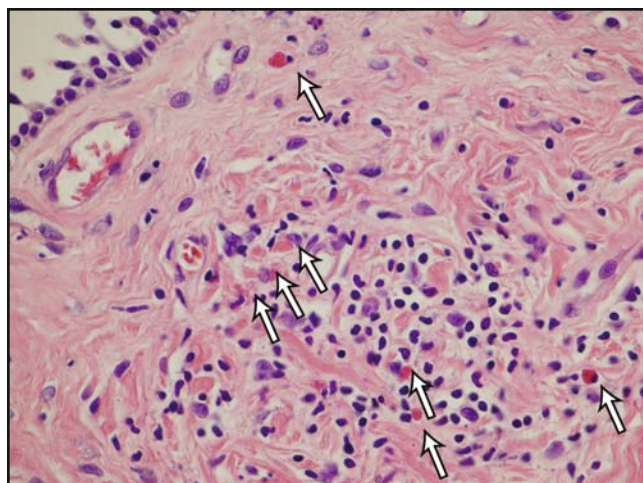


Figure 2. A histologic section of middle ear mucosa of eosinophilic otitis media (hematoxylin and eosin staining). Infiltration of inflammatory cells, including eosinophils (arrows), is observed in the submucosal layer.

effusion and the mucosa of the middle ear when bacterial infection is associated with it.

In 2002, Nagamine et al. [5] reported seven patients with EOM and proposed the diagnostic criteria of EOM as follows: 1) the presence of yellow and extremely viscous middle ear effusion predominantly containing eosinophils and 2) the precedence and association with adult bronchial asthma. Details are shown in Table 1. There has been a series of reports on EOM since. Therefore, in 2003, an epidemiologic and clinical surveillance of EOM was conducted in the ear, nose, and throat departments of 1409 major hospitals throughout Japan. The diagnostic criteria were as follows: a suspected case of EOM was considered when intractable otitis media occurred in adult-onset bronchial asthma patients, which is characterized by the presence of glue-like effusion and is resistant to conventional medical treatment (ie, insertion of tympanostomy

Table 1. Diagnostic criteria for eosinophilic otitis media

Diagnostic criteria

Presence of yellow and extremely viscous middle ear effusion containing predominantly eosinophils
Presence of and association with adult bronchial asthma (atopic or nonatopic)

Other clinical characteristics

Bilateral otitis media
Association with nasal polyposis
Granulation tissue formation in mesotympanum with a large perforation
Bulging, yellowish eardrum without perforation
Deterioration in bone conduction hearing level
Aeration of attic and antrum demonstrated by temporal bone CT images
Presence of patulous eustachian tubes
Resistance to conventional treatment for otitis media with effusion or chronic otitis media
Improvement of the middle ear condition by systemic and/or topical steroid administration

(Adapted from Nagamine et al. [5].)

tube or tympanoplasty); a definitive case of EOM was considered when the characteristics described previously were present and significant infiltration of eosinophils was observed in effusion or mucosa and granulation tissue of the middle ear. As a result, 446 suspected cases and 341 definitive cases were reported [6]. The concept and existence of EOM are now recognized in Japan, and EOM is no longer considered a rare disease.

Clinical Characteristics of EOM

The clinical characteristics of EOM are discussed subsequently as we summarize the 38 cases we have encountered and diagnosed on the basis of the diagnostic criteria previously reported (group 1) [5] and the 190 definitive cases in which detailed clinical features were clarified in the secondary survey of the epidemiologic and clinical surveillance in Japan (group 2) [6].

Gender and age

Among the 38 patients in group 1, 26 (69%) were women. Among the 190 patients in group 2, 116 (61%) were women. In group 1, the ages at onset of otitis media were 25 to 75 years (mean, 48 years), and 11 patients developed otitis media in their 50s, the most in any age group. The ages at first visit were 25 to 74 years (mean, 52 years), and 16 patients were in their 50s at first visit, the most for any age group. These results show that EOM predominantly affects women and occurs most often in patients in their 50s.

Clinical features of EOM

EOM occurs in both ears in most cases. Although the onset periods differ in each ear, bilateral EOM was observed in 87% of the patients in group 1 and 81% of the patients in group 2.

The clinical features of the middle ear in EOM are roughly divided into the OME type and the COM type. In OME, there is no perforation of the eardrum, which is yellow and often bulging, indicating the presence of effusion. When myringotomy is performed, there is a highly viscous effusion in the middle ear cavity that is difficult to remove by aspiration. When a tympanostomy tube is placed, the lumen of the tube is easily blocked by the viscous effusion. Conversely, COM is characterized by persistent perforation occurring in the eardrum caused by various factors. The COM type is further divided into two subtypes. One is the simple perforation subtype, in which yellow and viscous effusion drains from the perforation of the eardrum. The size of the perforation varies. If bacterial infection occurs, the effusion's viscosity tends to decrease. The mucosa of the mesotympanum is nearly unchanged to slightly edematous or thickened. The other subtype is characterized by a significant growth of granulation tissue that may extend into the external ear canal. This is the most intractable type.

EOM complicated by bronchial asthma

EOM is generally accompanied by adult-onset bronchial asthma. It occurs in nonatopic and atopic asthma patients. Among our 38 patients in group 1, 21 were identified as being allergic to specific antigens such as house dust, mites, and pollens. Specific antigens were not identified in the remaining 17 patients; however, approximately one half of those patients had a high serum total IgE level. Also, 9 of the 38 patients showed aspirin intolerance. Haruna et al. [7] reported that 18 of 19 patients with EOM had bronchial asthma, and two of them had aspirin intolerance. There have also been reports of patients with EOM that was not accompanied by bronchial asthma. We encountered a few patients with OME not accompanied by bronchial asthma in which the effusion was highly viscous and the presence of eosinophil infiltration was proven. These patients responded well to treatment, and their otitis media was not as intractable as those with the bronchial asthma complication. Further study is required to clarify cases without bronchial asthma complication.

EOM complicated by nasal and paranasal sinus diseases

EOM is often complicated by rhinosinusitis. Rhinosinusitis was observed in 33 (87%) of the 38 patients in group 1, and nasal polyps or polyposis was observed in many of these patients. Approximately one half of those patients had a history of paranasal surgery, such as polypotomy or endoscopic sinus surgery. In group 2, association of chronic sinusitis was observed in 74% of patients. It was often

accompanied by nasal mucosa hypersensitivity. Infiltration of a number of eosinophils was usually observed in the rhinorrhea and nasal polyps, and the diseased lesion was more significant in the ethmoid sinus than in the maxillary sinus. These patients were considered to have eosinophilic sinusitis [7] or eosinophil mucin rhinosinusitis, as described by Ferguson [8]. In contrast, EOM incidence in patients with eosinophilic sinusitis was approximately 10% [7]. The pathologic conditions of the nasal cavity and paranasal sinuses are strongly related to the onset of EOM.

Change in hearing acuity

Conductive hearing impairment is observed at the initial stage and leads to mixed hearing impairment with deterioration of bone conduction hearing level during the course of EOM development. It has been reported that EOM patients show gradual deterioration of hearing and sometimes become deaf suddenly [1,5]. Surprisingly, in group 2, about one half of the patients showed deterioration in the bone conduction hearing level, and 6% became completely deaf [6]. We encountered two patients who became completely deaf in one ear during the course of the disease's development. Generally, the type of hearing impairment in EOM patients is high-tone hearing loss. However, it is generally accepted that ears with COM without association of bronchial asthma also show gradual sensorineural hearing loss as compared with healthy ears [9,10]. In these studies, a significant increase in bone conduction hearing level was also found at higher frequencies. It seems likely that the bone conduction hearing level deterioration associated with EOM is one of the symptoms sometimes observed in COM. However, Nakagawa et al. [11•] reported that in EOM, bone conduction hearing levels at 4000 and 8000 Hz were higher than those at lower frequencies, and the loss rate was about 10 times that observed in cases of COM, which was reported by Cusimano et al. [12].

In our study, high-tone loss was more frequently found and was more severe in EOM patients than in COM controls, and the infected ear with granulomatous otitis media was often accompanied by a significant increase in bone conduction hearing level [13]. The cause of sensorineural hearing impairment is unclear. However, high-tone hearing loss and profound hearing loss were frequently associated with EOM, suggesting that the eosinophilic and bacterial inflammatory products invade the inner ear via the round window to cause inner ear damage. In practice, although many patients' hearing acuity remains stable for a long period, others rapidly become hearing impaired.

Pathogenesis of EOM

Mechanism of infiltration of eosinophils into the middle ear

The concentration of eosinophil cationic protein (ECP) in middle ear effusion of EOM patients was significantly higher than that in the control group (OME without bronchial

asthma). Moreover, a significantly larger number of EG2-positive cells was observed in the middle ear mucosa of EOM patients than that of the control group (COM without bronchial asthma), proving that active eosinophilic inflammation is occurring in these patients [14]. Regarding eosinophil chemoattractants, the concentrations of interleukin (IL)-5 and eotaxin in middle ear effusion were significantly higher in EOM patients than in controls [14,15]. ECP concentration positively correlated with that of IL-5, suggesting that IL-5 may play a crucial role in the accumulation of eosinophils in the middle ear [16•]. Immunohistochemically, the number of cells immunopositive for IL-5 and ecalectin, which are the chemotactic and activating factors for eosinophils, significantly increased in the middle ear mucosa of EOM patients compared with that of the control group. Furthermore, the expressions of eotaxin; regulated on activation, normal T-cell expressed and secreted (RANTES); and ecalectin mRNAs were detected by *in situ* hybridization [16•]. That chemotactic and activating 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.

Eustachian tube function in EOM

It is generally accepted that eustachian tube function is often impaired in patients with OME and COM. We have often encountered EOM patients in whom hearing impairment occurs after they have blown their nose or in whom air is released from their ears immediately after they have blown their nose, which suggests a patulous eustachian tube or an abnormal patency of the eustachian tube. Our investigation of the eustachian tube function in EOM patients using sonotubometry clarified that the tubal opening duration was significantly longer in EOM patients than in the control groups (ie, asthmatic patients without otitis media; COM controls; and normal, healthy controls), indicating the presence of patulous eustachian tubes [17•]. The patulous state of the eustachian tube is closely related to the pathologic conditions causing EOM in patients with bronchial asthma.

Here the hypothesis for the pathogenesis of EOM is proposed as follows: in asthmatic patients who have a T-helper type 2–dominant predisposition, a patulous eustachian tube easily allows the entry of antigenic materials into the middle ear, causing eosinophil-dominant inflammation. Eosinophils increase the production of mucin; moreover, cytotoxic proteins derived from eosinophils impair epithelial cells. Therefore, the debris of infiltrating cells such as eosinophils and epithelial cells mixes with excessively produced mucin, and they are considered to generate a more viscous effusion.

Management of EOM

Conservative treatment

The effusion is extremely viscous in EOM. Myringotomy is required to drain the effusion if there is no perforation of

the eardrum. The insertion of a tympanostomy tube is not indicated for EOM because the tube is often blocked after the placement. Systemic or topical steroid administration is the most effective treatment for controlling eosinophilic inflammation. Steroids should be administered topically whenever possible. We reported that the instillation of triamcinolone acetonide, a suspension of steroids, into the mesotympanum and eustachian tube is an effective treatment for patients with EOM [18•]. In patients without eardrum perforation, a myringotomy was made, followed by removal of the viscous effusion. Triamcinolone acetonide was then instilled into the middle ear cavity. In patients with persistent perforation, triamcinolone acetonide suspension was applied via the eardrum perforation after the removal of effusion or otorrhea. Then, the triamcinolone acetonide was expelled through the eustachian tube by applying a positive pressure using a pneumatic otoscope. In cases with granulation tissue formation, the granulation of the mesotympanum was removed via the eardrum perforation using a cutting forceps as much as possible, and the previously described procedure was performed several times. In infected ears, steroids should be instilled with systemic administration of antibiotics to control the bacterial infection. The clinical trial comparing the group administered triamcinolone acetonide with the group administered betamethasone eardrops showed the effectiveness in the former group to be significantly higher [18•]. Examination of the relationship between this and the lesion of the middle ear mucosa demonstrated that the effectiveness was slightly lower in patients showing granulation proliferation and greatly thickened middle ear mucosa. However, when the lesion of the mucosa was mild, the effusion could be expected to disappear for a fairly long time after a single injection [18•]. Cell infiltration in the middle ear mucosa became mild after the injection of triamcinolone acetonide into the mesotympanum, and the number of eosinophils and cells immunopositive for ecalectin and RANTES, which are the chemotactic factors for eosinophils, also decreased significantly [16•].

Matsubara [19] reported the effectiveness of topical administration of heparin. Heparin has inhibitory effects on eosinophil chemotaxis and neutralizing effects on cytotoxic proteins such as ECP and major basic protein, which are derived from eosinophils. He reported that topical administration of heparin enabled the withdrawal of steroids and a decrease in the amount of steroids administered. Some types of antiallergy drugs (other than steroids) with inhibitory effects on eosinophil infiltration are used as systemically administered drugs, but they did not seem to exert the same effects as steroids. However, Wada et al. [20] reported two patients with EOM who had been successfully treated with ramatroban, an antagonist of the thromboxane A₂ receptor and the chemoattractant receptor-homologous molecule expressed on T-helper type 2 cells. The accumulation of clinical data is needed to prove the effectiveness of ramatroban for treatment of EOM.

When a rapid increase in bone conduction threshold value or dizziness occurs and an acute exacerbation is observed, steroids should be systemically administered immediately. The patient should be hospitalized, and the high-dose steroids should be administered on a tapering schedule in accordance with the protocol for the treatment of sudden deafness. Steroid pulse therapy is also effective. Because bacterial infection acts as an exacerbating factor, an antibacterial drug also should be administered to infected ears.

Surgical treatment

Controversy exists as to whether surgical treatments are effective for EOM. In the first case reported by Tomioka et al. [1], controlling otorrhea and granulation formation was difficult even after several surgeries, and the patient finally became completely deaf in both ears. We also performed tympanoplasty on an ear with severe granulation tissue formation to control continuous otorrhea infected with *Pseudomonas aeruginosa*, but middle ear aeration was not achieved after the surgery. There have been some reported cases with good postoperative course and some with poor postoperative course. The preoperative pathologic conditions of the middle ear seem to determine the prognosis. Namely, the recurrence should occur more often in patients with severe granular lesion in the middle ear. However, tympanoplasty may be indicated for ears to control otorrhea or for hearing impairment due to a large perforation if the middle ear mucosa shows the mild change. When the tympanoplasty is scheduled, the ear has to have been kept dry for a relatively long period via topical or systemic steroid administration. In the postoperative periods, the systemic administration of steroids is again needed to prevent recurrence of eosinophilic inflammation.

For patients with bilateral profound deaf ears during the course of EOM, cochlear implantation has been indicated. Iwasaki et al. [21] reported that for a patient with EOM who underwent cochlear implantation, the postoperative course was relatively good even 8 years after the surgery with systemic administration of steroids. We should further examine the indication for surgical treatment considering various middle ear conditions.

Conclusions

EOM is no longer considered a rare disease. We should always pay attention to ear symptoms in patients with bronchial asthma. In asthmatic patients who have a T-helper type 2-dominant predisposition, a patulous eustachian tube easily allows the entry of antigenic materials into the middle ear, causing eosinophil-dominant inflammation. It is very important to explain to patients with EOM that the disease may last for a long period and that progressive and sudden hearing loss may occur.

Disclosure

No potential conflict of interest relevant to this article was reported.

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