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Treatment for Eosinophilic Otitis Media

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Abstract

Eosinophilic Otitis Media (EOM) is remarkably characterized by viscous middle ear effusion (MEE) infiltrated with numerous eosinophils. Since EOM is a high risk disease of progressive hearing loss, early diagnosis and management of appropriate treatment along with an understanding of the pathology of EOM are imperative. The treatment strategies for EOM comprise the removal of the highly viscous MEE enriched with a cytotoxic protein derived from eosinophils, and the suppression of local and systemic eosinophilic inflammation.

Here, we introduce how we treat EOM patients in our department concretely. Regarding the management of the acute phase of EOM, topical and/or systemic steroids have proven their efficacy. Regarding the long-term management of EOM, a combination of various antiallergic drugs that have proven efficacy for eosinophilic inflammation is beneficial. In a considerable number of EOM cases, we have succeeded cessation of topical and systemic steroids.

Keywords: Eosinophilic otitis media; Major basic protein; Periostin; Diagnostic criteria; Treatment

Introduction

Eosinophils act in various allergic diseases as effecter cells and are known to play an essential role in the pathogenesis of chronic rhinosinusitis with nasal polyposis and otitis media in the region of the ear, nose, and throat. Although otitis media with eosinophil enriched secretion was reported as allergic otitis over half a century ago [1,2], little investigation has been conducted on this group since then. In 1993, Tomioka et al. reported three cases of intractable otitis media associated with bronchial asthma and allergic rhinitis [3], and termed this disease as eosinophilic otitis media (EOM), because of its most characteristic feature viscous middle ear effusion (MEE) infiltrated with numerous eosinophils [4]. Lately, quite a few case reports and histological and biochemical investigations on EOM have been conducted primarily in Japan [5-8]. EOM is also known as a high risk disease characterized by the progressive hearing loss. To elucidate the characteristics of EOM, the EOM study group in Japan conducted a multicenter study based on the analysis of 138 patients with EOM in five centers participating in the study [9]. This study reported that the deterioration of bone conducting hearing loss (BCHL) was significantly worse in the EOM than in the non-EOM grou, and 8 of 138 (5.8%) patients became unilateral or bilateral deaf [9]. Moreover, other studies highlighted that BCHL of EOM is progressive unless intervened by an appropriate treatment [10,11]. Moreover, our animal model experiments demonstrated that the severe morphological damage of the inner ear was caused as the periods of intratympanic stimulation of allergens to the middle ear became longer [12,13]. Hence, both early diagnosis and management of appropriate treatment along with an understanding of the pathology of EOM are imperative.

Diagnostic Criteria

Based on the analysis of 138 cases registered to the EOM study group, EOM is categorized into two types, otitis media with effusion (OME) and chronic otitis media (COM). Furthermore, the EOM study reported observing numerous eosinophils in MEE of both types (Figure 1A), leading to the formulation of a major criterion "OME or COM with eosinophil-dominant effusion" [9].

In the early stage of EOM, a yellow MEE is observed through the tympanic membrane (Figure 1B) that exhibits substantial viscosity (Figure 1C). The next stage demonstrates bulging of the posterosuperior quadrant of the tympanic membrane. Despite inserting a ventilation tube, swelling does not lessen unless treated adequately (Figure 1D). The COM type demonstrates the formation of tympanic perforation along with middle ear granulation.

Regarding the minor criteria, four items established from the clinical features of EOM are as follows: (a) highly viscous MEE, (b) resistance to conventional treatment for otitis media, (c) association with bronchial asthma, and (d) association with nasal polyposis.

The diagnosis of EOM is based on two or more minor criteria in addition to the major criterion. The exclusion criteria for the diagnosis of EOM were eosinophilic granulomatosis with polyangiitis and hyper eosinophilic syndrome. Although otitis media caused by these two diseases might fulfill the diagnostic criteria of EOM, its pathogenesis is clearly distinct from EOM.

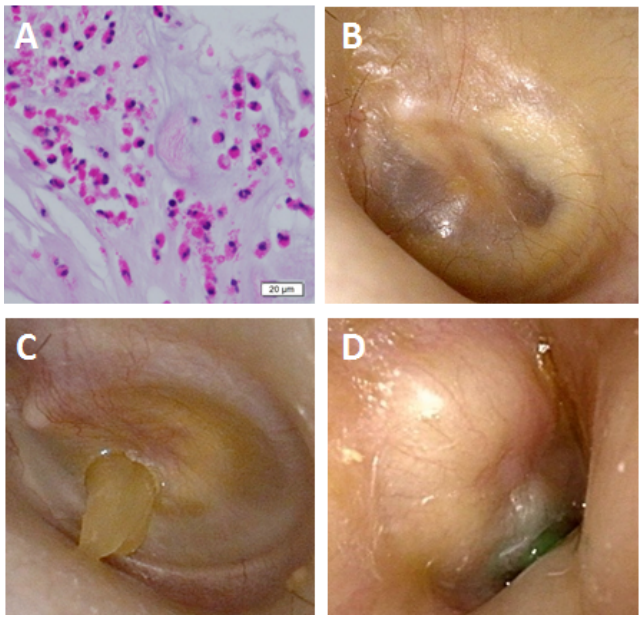

Figure 1: Histological section and endoscopic findings of EOM patients. (A) A large amount of eosinophils is observed in MEE (HE staining). Note that quite a few eosinophils are collapsing and eosinophils granules are released. (B) Endoscopic finding of OME type. (C) After laser assisted myringotomy. Highly viscous MEE. (D) Ventilation tube insertion case. Tube insertion is not necessary useful.

Pathology of EOM

In the 2000s, some studies described the pathological conditions of the middle ear in EOM, and revealed that a majority of eosinophils infiltrated in the middle ear were EG2-positive (the marker of activated eosinophils) and detected a high concentration of eosinophil cationic protein (ECP) in MEE [5,6]. Furthermore, some studies have also proved the presence of eosinophil chemoattractants, such as IL-5 and eotaxin, in MEE [7,8]. All these studies have indicated the occurrence of eosinophilic inflammation in the middle ear. Eosinophils contain some cytotoxic proteins such as ECP and major basic protein (MBP). Apparently, MBP is directly implicated in epithelial cell damage in bronchial asthma. In EOM case, the immunoreactivity for MBP was observed not only in eosinophils in middle ear mucosa but also on the outer side of epithelial cells (Figure 2A). Recently, a study revealed that eosinophils of MEE generate nuclear-derived DNA traps that can entrap eosinophil granules [14], and long-lasting cytolytic effects of eosinophil granules affect middle ear mucosa. Hence, the prompt removal of highly viscous effusion including plenty of entrapped eosinophil granules from the middle ear cavity is imperative.

Reportedly, periostin, an extracellular matrix protein originally isolated from an osteoblast cell line, is secreted by fibroblasts in response to IL-4 and/or IL-13 and is involved in the subepithelial fibrosis of bronchial asthma [15]. In patients with EOM, the periostin immunoreactivity has been observed in the basement membrane and extracellular matrix of the granulated middle ear mucosa (Figure 2B) [12], along with the detection of IL-13 immunopositive cell [16]. Periostin plays an essential role not only in tissue fibrosis but also eosinophil accumulation [17]. Based on these results, periostin could be considered a potential target for the treatment of EOM.

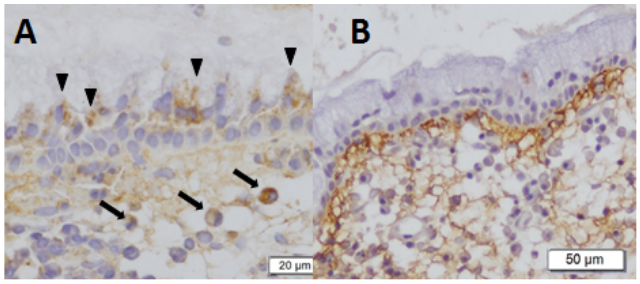

Figure 2: Immunohistochemical staining for MBP and periostin in the middle ear granulation. (A) MBP immunoreactivity was detected on the outer side of epithelial cells (arrow heads) as well as the infiltrated cells of middle ear mucosa (arrow heads). (B) Strong immunoreactivity of periostin is observed in the subepithelial layer of middle ear granulation.

Despite reporting the occurrence of type- I allergic reactions in the middle ear, research has found that the eustachian tube usually acts to prevent the entry of most substances into the middle ear cavity [18]. However, Iino et al. reported that more cases of the patulous eustachian tube in patients with EOM compared with controls [19]. In such condition, antigenic substances could easily enter into the middle ear cavity from the nasal cavity and cause eosinophilic inflammation of the middle ear. Furthermore, a study have reported that the presence of specific IgE for house dust mite, fungi, and staphylococcus enterotoxins in MEE of patients with EOM [20]. Moreover, we recently demonstrated that the expression of thymic stromal lymphopoietin (TSLP), one of the epithelium-derived cytokines, which induces Th2-type responses that trigger several allergic diseases [21], in the middle ear mucosa around the tympanic ostium of the eustachian tube [22]. Since epithelial cells facilitate the release of TSLP in response to allergens and microbial products [23], the systemic suppression of allergic and eosinophilic inflammation locally on both the middle ear and the nasal cavity is essential.

Treatment for EOM

We considered the concept of a treatment strategy for EOM as follows: the removal of highly viscous MEE enriched with cytotoxic protein derived from eosinophils, and the suppression of local and systemic eosinophilic inflammation.

Since MEE of EOM is too viscous to remove and roughly removing might adversely affect the inner ear, we used the intratympanic application of heparin to remove MEE gently. Heparin demonstrates not only inhibitory effects on eosinophilic chemotaxis and neutralizing effects on eosinophil granule cationic proteins but also dissolves highly viscous MEE to facilitate its removal easily [24]. In particular, we used heparin sodium (5,000 IU/5ml) diluted five times by saline for ear dropping or ear instillation, followed by removing MEE gently by suction and administering topical steroids intratympanically.

Notably, the suppression of the eosinophilic inflammation administration of corticosteroids is undoubtedly most effective. We used two types of topical steroids, betamethasone ear drops and

instillation of triamcinolone acetonide into the middle ear. Regarding hearing preservation, although betamethasone ear drops are easy- to-use, the instillation of triamcinolone acetonide is more effective for EOM [25].Thus, in the case of not attaining effect adequate efficacy by betamethasone ear drops; it should be changed to instillation of triamcinolone acetonide. Furthermore, in the case of remarkable granulation formation, progressive sensory hearing loss, and marked eosinophilia, systemic steroid administration is needed.

For the long-term management of EOM, we use a combination of two or three types from various antiallergic drugs that are effective for eosinophilic inflammation, such as Cys-LTs receptor antagonists, phosphodiesterase inhibitors (ibudilast: inhibiting the PDE4 subtype to the greatest extent), a kind of anti H1 receptor antagonist, and a dual antagonist of thromboxane A2 and prostaglandin D2 receptor (ramatroban), which successfully tapered the topical and systemic steroids administration in a lot of cases with EOM (Figure 3). Regarding the suppression of eosinophilic inflammation in the upper and lower airways, adequate dosages of steroid nasal spray and inhaled corticosteroids are also warranted.

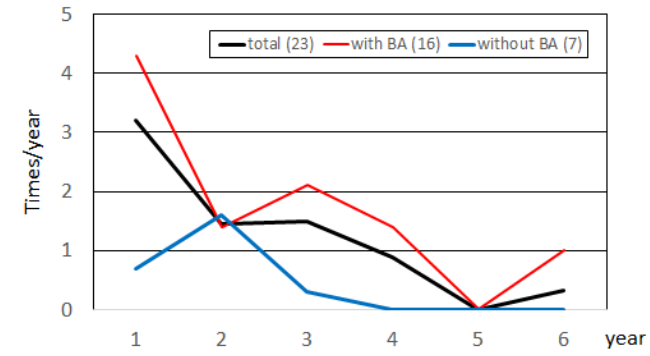

Figure 3: Changes in the number of instillation of triamcinolone acetonide into the middle ear. The number (times/year) of instillation of triamcinolone acetonide into the middle ear was remarkably decreased in 23 cases of EOM to which a combination of 2 or 3 types of anti-allergic drugs was administered with or without bronchial asthma (BA).

The recent advancement of molecular biology has led to the production of various molecular targets, some of which effective in bronchial asthma are also expected to demonstrate efficacy in EOM. Indeed, long-term anti-IgE (omalizumab) therapy could be effective in EOM [26]. Furthermore, anti-IL5 (mepolizumab) is expected to exhibit a stronger effect. From the pathological perspective, the development of anti- IL13 and anti-TSLP modalities could a potential target for new treatments. Nevertheless, further study is warranted to identify more effective treatments for EOM.

Acknowledgments

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