



Eosinophilic otitis media and comorbid asthma

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Purpose of review

Eosinophilic otitis media (EOM) is an intractable otitis media characterized by numerous eosinophils infiltrating the middle ear cavity, which is part of the upper airway. EOM shows a high rate of comorbidity with asthma. They are considered to have a 'one airway, one disease' relationship. Here, we summarize our current knowledge regarding the characteristics of EOM, EOM's relationship with asthma and the efficacy of optimal treatments for EOM.

Recent findings

The greater the severity of asthma, the more pronounced the development of EOM. Asthma control is usually inadequate in asthmatics who develop EOM, and appropriate strengthening of asthma inhalation therapy leads to improvement in the EOM. EOM severity can be divided into mild, moderate, and severe. Intratympanic infusion therapy using a topical steroid such as triamcinolone acetone is effective for mild EOM, whereas moderate EOM requires a systemic steroid in addition to triamcinolone acetone, and severe EOM forms granulation tissue that requires surgical removal. Recently, the effectiveness of molecularly targeted drugs is being reported, but more data need to be accumulated.

Summary

EOM and asthma are closely related. Optimal asthma treatment is important for treating EOM. Treatments commensurate with the severity of EOM are being developed.

Keywords

asthma, eosinophilic otitis media, one airway, one disease, optimized asthma treatment

INTRODUCTION

In 1993, Tomioka *et al.* [1] reported that asthmatic patients developed refractory otitis media with effusion and chronic otitis media. They reported that the middle ear fluid and otorrhea were highly viscous and that there was a high degree of eosinophilic infiltration. The authors named this otitis media eosinophilic otitis media (EOM) because it occurred independently of type I allergy [1]. Similar cases of otitis media have been reported since then [2,3].

In 2011, diagnostic criteria were proposed for EOM [3]. In particular, the probability that EOM patients have asthma is extremely high [4]. EOM, like asthma, is a Th2-type inflammation, and considering that the middle ear cavity is a part of the upper respiratory tract, EOM and asthma can be thought to have a relationship of 'one airway, one disease' [5,6]. The concept of 'one airway, one disease' was first applied to the relationship between allergic rhinitis and asthma. In this concept, the bloodstream and bone marrow are involved, and the upper and lower airways are said to interfere with each other [7–10]. This article reviews the features of EOM, its association with asthma, and its optimal treatment.

CHARACTERISTICS OF EOSINOPHILIC OTITIS MEDIA

EOM is intractable otitis media with numerous infiltrating eosinophils [1]. In the diagnostic criteria, EOM is characterized by either otitis media with effusion or chronic otitis media with eosinophil-dominant effusion. In addition, there must be at least two or more of the following four features for diagnosis: first, highly viscous middle ear fluid; second, resistance to general treatment for otitis media; third, concurrent asthma; and fourth, concurrent nasal polyps (Table 1) [4].

As noted in the diagnostic criteria, EOM can be divided into otitis media with effusion type and chronic otitis media type. Furthermore, the latter is divided into two subtypes (simple perforation and

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KEY POINTS

- EOM develops at a high incidence in asthma patients, and the more severe the asthma, the more readily EOM develops.
- EOM and asthma are considered to have a ‘one airway, one disease’ relationship, a concept that was first applied to allergic rhinitis and asthma.
- EOM is likely to develop if asthma is poorly controlled, and it improves when the asthma treatment is appropriately strengthened.
- EOM is classified according to its severity, and treatment is conducted based on the severity. Intratympanic infusion therapy using triamcinolone acetonide is effective for mild cases.

granulation tissue formation), and it is thought that hearing impairment progresses more when granulation tissue formation occurs [11,12[¶]]. In addition, EOM patients exhibit a very high rate of comorbidity with asthma [4].

EOM, like asthma, is a Th2 type inflammation. It has been reported that Th2 cytokines such as IL-5, periostin, and so on, are produced locally in the middle ear, and high concentrations of IgE can be detected [13–15,16[¶],17]. Furthermore, thymic stromal lymphopoietin (TSLP), a key trigger of Th2-type allergic disease, was reported to be produced by EOM middle ear epithelial cells, and epithelial cells are considered to be the starting point for development of EOM, as they are for airway Th2-type inflammatory conditions such as asthma [16[¶]].

Eosinophils in the EOM effusion undergo cytolysis. A recent report also referred to cytolysis as ‘extracellular trap cell death (ETosis)’. In the process of ETosis, cells undergo degranulation and form sticky chromatin structures (extracellular traps), culminating in cell death. It was suggested that, in EOM, the extracellular traps derived from eosinophils may be related to the viscosity of the middle ear fluid [18].

Table 1. Diagnostic criteria for eosinophilic otitis media [4]

Major	Otitis media with effusion or chronic otitis media with eosinophil-dominant effusion
Minor	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 and ≥2 minor criteria
Exclusion criteria	Churg–Strauss syndrome, hypereosinophilic syndrome

The middle ear cavity is connected to the epipharynx by a narrow orifice called the Eustachian tube, and it is composed of the same pseudostratified, ciliated, columnar epithelium as the airways. Furthermore, it was reported that the more patulous the Eustachian tube is, the more likely EOM is to develop in asthmatics [19].

It was reported that 75% of EOM patients also have eosinophilic chronic rhinosinusitis (ECRS) and, conversely, 3% of ECRS patients were reported to also develop EOM [20,21]. It was reported that EOM sometimes worsens following endoscopic sinus surgery (ESS), which is the most effective treatment for chronic rhinosinusitis, including ECRS [21]. In that regard, following ESS, an increase in the nasopharyngeal pressure due to nose blowing and so on, may lead to the onset of EOM, and care is needed in this regard.

EOSINOPHILIC OTITIS MEDIA AND ASTHMA

The complication rate of asthma in EOM patients is as high as 90% [4]. Patients with aspirin asthma have been reported to develop EOM at a high rate [22]. In addition, asthma that develops EOM is referred mainly to as adult-onset asthma [4]. Asthma is classified into four severity levels according to the Global Initiative for Asthma update 2012: mild intermittent, mild persistent, moderate persistent, and severe persistent. However, onset of EOM in asthmatics with chronic sinusitis is seen only in patients with moderate persistent or severe persistent asthma, and severe persistent cases tended to have a higher incidence than moderate persistent cases (Fig. 1) [6,23]. Furthermore, the EOM onset group showed higher values for smoking history as assessed by the Brinkman index, the eosinophil count in the peripheral blood, and airway wall thickness assessed by high-resolution computed tomography (CT) scanning [6]. Kanazawa *et al.* [24] reported that EOM severity correlated with the duration of asthma and with obesity assessed by the BMI. Based on those findings, EOM and asthma are considered to be closely related and can be thought of as having a ‘one airway, one disease’ relationship.

The concept of ‘one airway, one disease’ was first applied to the relationship between allergic rhinitis and asthma [7]. In that concept, the upper and lower airways are thought to have a systemic link involving the bloodstream and bone marrow [8,9]. It was demonstrated that allergen inhalation by sensitized mice increased the level of IL-5, an eosinophil differentiation inducer, at the sites of inflammation [25]. Wang *et al.* [26] reported that IL-5 in the blood plays a crucial role in eosinophil migration to the

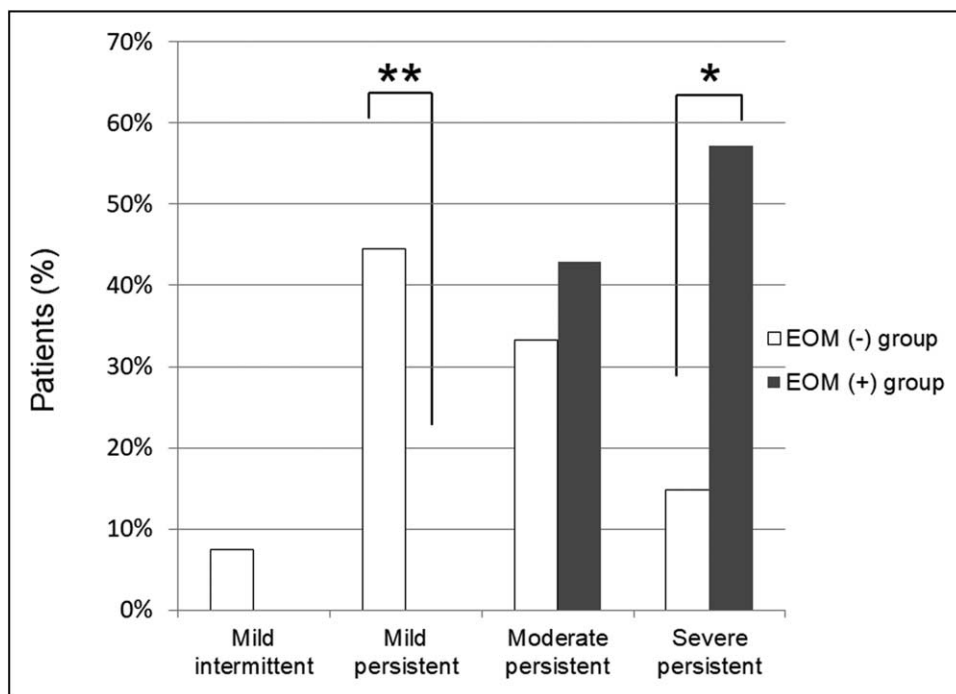


FIGURE 1. Comparison of asthma severity in patients with and without eosinophilic otitis media [6]. Asthma severity is subdivided into four groups (mild intermittent, mild persistent, moderate persistent, and severe persistent). **P* less than 0.05, ***P* less than 0.01: significantly different from the eosinophilic otitis media (–) group.

airways. IL-5 is also involved in eosinopoiesis in the bone marrow.

In fact, it was reported that IL-5 increased in the serum and nasal mucosa when segmental bronchial provocation is performed on nonasthmatic allergic rhinitis patients [27,28]. On the other hand, when patients with allergic rhinitis are subjected to nasal allergen challenge, IL-5 increased in the blood and eosinophils increased in the sputum [29]. Significantly, patients with allergic rhinitis who orally inhaled steroids showed reduced eosinophils in their blood and nasal discharge as well as relief of their nasal symptoms [30]. Allergic rhinitis and asthma are closely related via the bloodstream and bone marrow, and they interfere with each other [10].

Therefore, the inflammatory state of EOM is thought to be affected by the appropriateness of the asthma therapy. In fact, even for patients with EOM, it was reported that, when observed retrospectively, the asthmatics who developed EOM had all had inadequate asthma control (i.e., partially controlled or uncontrolled) [31[¶]]. Therefore, proper control of asthma is considered to be important for EOM treatment.

OPTIMAL TREATMENTS FOR EOSINOPHILIC OTITIS MEDIA

Topical glucocorticosteroids are the treatment of choice for asthma [32]. It is known that airway

Th2-type inflammatory conditions, including EOM, are initiated by such key triggers of Th2-type allergic disease as TSLP. It thus makes sense that the topical airway drug action of steroids controls airway epithelial cells, which are the main producer cells of TSLP and so on [15,16[¶]]. In fact, a systematic study investigated use of intratympanic infusion therapy with triamcinolone acetone, a steroid suspension with a medium length half-life, to treat EOM, and its efficacy was reported to be 81% [33]. Moreover, it was reported to be much more effective than betamethasone eardrops used as the control [33].

In addition, the effectiveness of triamcinolone acetone was greatly influenced by the presence of a mucosal abnormality of the middle ear cavity of EOM patients, and its efficacy was considered poor when there was severe thickening of the middle ear mucosa and when there was a high degree of granulation [33]. Esu *et al.* classified the severity of EOM into three grades depending on the condition of the middle ear mucosa: grade 1 (mild), normal middle ear mucosa; grade 2 (moderate), localized thickened mucosa within the middle ear; and grade 3 (severe), thickened or edematous mucosa with predominant granulation tissue extending to the external auditory canal. Tympanic cavity triamcinolone acetone infusion is effective for grade 1 EOM, whereas grade 2 EOM requires tympanic cavity triamcinolone acetone infusion and/or systemic administration of

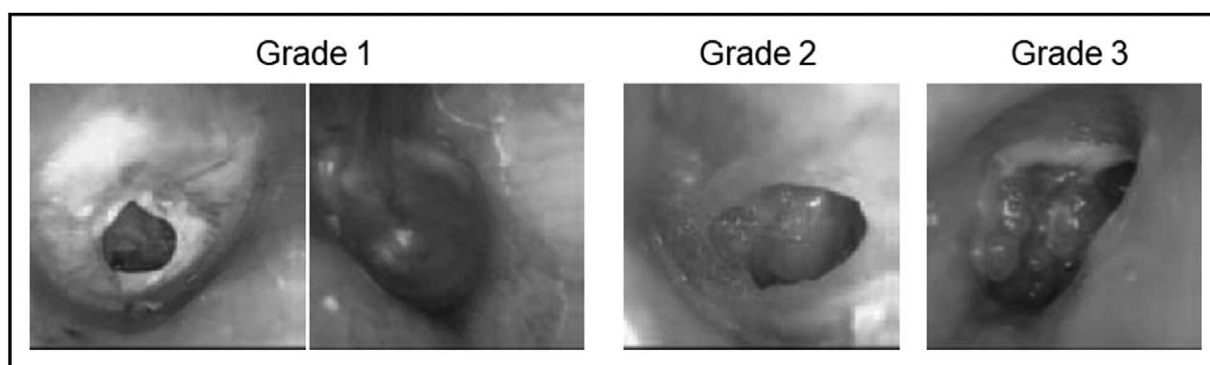


FIGURE 2. Eosinophilic otitis media severity grade according to the middle ear mucosal condition [12[•]]. Grade 1: Normal (not thickened) middle ear mucosa. Grade 2: Localized thickening of mucosa within the middle ear. Grade 3: Diffusely thickened or edematous mucosa with predominant granulation tissue.

steroids. It was reported that grade 3 EOM could be effectively treated by surgically removing the granulation tissue and inserting absorbable gelatin sponges soaked with triamcinolone acetone into the tympanic cavity (Fig. 2) [12[•]].

Seo *et al.* [31^{••}] reported that, in view of the ‘one airway, one disease’ relationship between EOM and asthma, appropriate control of the asthma is important to the onset of EOM. They reported that, in all asthmatics who developed EOM, the asthma was inadequately (partially controlled or uncontrolled) controlled, and if the asthma control was suitably strengthened, lung function improved and the blood eosinophil count decreased. Those changes were accompanied by improvement in the ear symptoms and findings, improvement in the middle ear cavity shadow on CT images, and improvement in hearing [31^{••}]. It is thus clearly important to pay attention to the treatment status of asthma when treating EOM patients.

In 2005, an IgE mAb, omalizumab, was approved by the European Medicines Agency as a treatment for severe asthma [34]. Omalizumab binds to free IgE in the blood, prevents IgE from binding to FcεRI on mast cells, and consequently suppresses allergic reactions by suppressing the release of histamine and interleukins that accompany mast cell degranulation [35].

In asthmatics with EOM, omalizumab has been used to treat the asthma, and effectiveness on the EOM has been reported [36,37]. Although the effectiveness was limited, improvement in the ear symptoms was seen [36,37]. Recently, another molecularly targeted drug, an anti-IL-5 mAb, mepolizumab, was used in asthmatics with EOM – as in the case of omalizumab – for the purpose of treating asthma, and its effectiveness on the EOM were evaluated. However, its effectiveness was often limited to improvement in the ear symptoms [38,39].

We look forward to future reports on the efficacy of several other mAbs, that is, reslizumab (an anti-IL-5 antibody), benralizumab (an anti-IL-5R antibody), and pitrakinra (an anti-IL-4Rα antibody), in the treatment of EOM.

CONCLUSION

The characteristics of EOM, which is an intractable otitis media, are becoming clear. EOM and asthma have a relationship of ‘one airway, one disease’, and achieving optimal treatment of asthma is important for treating EOM. Local steroid infusion using triamcinolone acetone is effective for mild cases of EOM. For moderate or more severe cases, systemic administration of steroids and surgical treatment must also be considered.

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Conflicts of interest

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- of special interest
- of outstanding interest

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