



Eosinophilic Otitis Media: Modern Aspects of Pathogenesis, Clinical Features, Diagnosis and Treatment

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Abstract Eosinophilic otitis media (EOM) is an inflammatory chronic disease of the middle ear, characterized by the presence of a particularly viscous effusion with a high content of protein toxins of eosinophilic origin in the middle ear cavity. The pathology has relationship with bronchial asthma, allergic rhinitis and chronic rhinosinusitis with nasal polyps. EOM is characterized by a sluggish course, a tendency to relapse, which can lead to a gradual hearing decrease up to complete deafness. In this paper, we reviewed the international literature with special attention to pathogenesis and treatment management.

Keywords Eosinophilic otitis media · Bronchial asthma · Viscous middle ear effusion

Eosinophilic otitis media (EOM) is an inflammatory chronic disease of the middle ear, characterized by the presence of a particularly viscous effusion with a high content of protein toxins of eosinophilic origin in the

middle ear cavity, as well as a severe course with a progression to hearing loss up to deafness.

Koch presented this pathology in 1947 for the first time in the scientific literature. He described cases of chronic otitis media with very viscous eosinophilic enriched secretions, accompanied by swelling of the middle ear mucous with a background of allergic rhinitis [1].

The term “eosinophilic otitis media” was first proposed in 1994 by Tomioka et al., who described three clinical cases of sluggish otitis media with a large number of eosinophils in the effusion, regardless of type I hypersensitivity reactions. They also indicated the relationship of this pathology with bronchial asthma (BA), allergic rhinitis (AR) and chronic rhinosinusitis with nasal polyps (CRSwNP) [2].

Epidemiology

The disease is most extensively learnt in Japan, which, probably, can be associated with a higher prevalence of nosology in this region. Thus, according to the results of a questionnaire survey of 1409 ENT—clinics throughout the country, about 340 patients with EOM were identified [3]. The disease developed mainly in women aged 50 to 60 years, both ears were affected in 81% of patients. Concomitant pathology of the nasal cavity and paranasal sinuses were detected in 74% of cases: 75% of patients had a history of chronic rhinosinusitis or CRSwNP in combination with BA that arise already in adulthood. Sensorineural hearing loss developed in 47% of patients, and deafness was observed in 6% of clinical cases [3]. In the majority of EOM patients identified in this survey, the first episodes of the disease appeared more than 10 years ago.

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In publications from Europe and USA, we have found only single descriptions of the clinical cases of EOM [4–8].

Pathogenesis of EOM

According to the literature, EOM mostly develops in adulthood on the background of rhinosinusitis and BA. The pathological process in the middle ear in most cases breaks out approximately 10 years after the development of lung pathology. Thus, EOM with the similar to BA pathogenesis mechanisms, can be considered as the endpoint of the chronic eosinophilic inflammatory process of the respiratory tract. [9]. When interacting with antigens, respiratory tract epithelial cells release inflammatory mediators (TSLP, IL-33, IL-25, etc.), which in turn stimulate the production of cytokines (IL-4, IL-5, IL-13, etc.) T2-helpers, starting an inflammatory process similar to that in BA [10, 11]. An increase in IL-5 expression induces the differentiation of the eosinophilic pool in the bone marrow and stimulates the migration of eosinophils to the bloodstream. Chemokines, for example, eotaxin, are produced by epithelial cells and fibroblasts and further facilitate the migration of eosinophils into the mucous membrane of the respiratory tract. After that the eosinophils are accumulated in the middle ear cavity as a result of the directed migration [12, 13].

Eustachian tube dysfunction and inflammation of the nasal mucosa are important factors in the development of eosinophilic inflammation of the middle ear. When studying the auditory tube function using tubosonometry in 20 patients with EOM, signs of its gaping were revealed [14]. This facilitates the penetration of antigens and cytokines into the tympanic cavity with the subsequent development of eosinophilic inflammation [14, 15].

A histological examination of the mucous membrane of the middle ear reveals signs of chronic inflammation with infiltration by eosinophils and plasma cells with a small number of neutrophils [7, 16].

Examining the middle ear discharge Yukiko Iino and coauthors found a large number of activated cells (EG2-positive cells) among eosinophils. Many of them were degranulated and/or had signs of karyolysis/karyorexis and a high level of eosinophilic cationic protein and eosinophilic chemoattractants (IL-5, eotaxin). In the mucous membrane of the middle ear itself, the number of eosinophils is significantly lower, which indicates their directed migration to the middle ear cavity [16]. Subsequently, local cytolysis of eosinophils promotes the release of not only eosinophilic granules, but also extracellular DNA traps, which leads to exudate thickening.

Thus, the mechanism of programmed cell death, accompanied by the release of extracellular chromatin, the

so-called extracellular chromatin trap—Ethisis plays the key role in the formation of viscous exudate in the middle ear cavity. A chromatin trap consists of a long DNA strand wrapping histone proteins in the form of “beads on a string” [17]. Ejected chromatin traps quickly accumulate surrounding particles (eosinophilic granules and microorganisms) due to hydrophilic compounds, thereby forming stable aggregates. Despite the fact that this process limits the spread of microorganisms, its hyper-purity contributes to an increase in the viscosity of the secretion, which is observed in patients with EOM [18, 19].

When comparing middle ear discharge of EOM patients and otitis media of a different origin, one can find a high concentration of eosinophilic cationic protein (ECP) and EG2—positive cells in the EOM cases, which indicates the activity of eosinophilic inflammation. The concentrations of chemoattractants, IL-5, and eotaxin are significantly higher in EOM patients and correlates positively with the concentration of eosinophilic cationic protein (ECP). Also, it positively correlates with the level of interleukin 5. This chemoattractant is involved not only in the migration of eosinophils, but also in their activation and increases the lifespan of these cells. The authors note that IL-5 is a key link in the pathogenesis of the development of EOM, as it stimulates the migration and local activation of eosinophils and prolonging the cell cycle [16].

Immunohistochemical analysis reveals that the number of cells immunopositive for IL-5 and eaelectin, which are chemoattractants and activating factors for eosinophils, is much higher in the mucous membrane of the respiratory tract and ear in EOM. An increase in the neurotoxin of eosinophils, elastase, IL-2, MIP-1 α , and IL-1ra was also observed in the mucous membrane of the middle ear of EOM patients [20].

The fact that chemoattractants and eosinophil activators were found not only at the protein level, but also at the level of RNA messenger, indicates the active eosinophilic inflammation in the mucous membrane of the middle ear [16, 21]. A significant level of IgE (presumably of local origin), many times higher than the concentration of IgE in blood plasma, is also determined in middle ear effusion [22–24].

The level of IgE in middle ear effusion in EOM patients positively correlates with the level of sensorineural hearing loss, namely with a decrease in bone conduction at 2 and 4 kHz. Local excessive production of IgE in the middle ear ultimately leads to inner ear damage [16].

Matsubara et al. undertook an experimental study on guinea pigs to determine the mechanism of inner ear structures damage in response to eosinophilic inflammation. Experimental animals underwent general peritoneal and local intratympanic sensitization with ovalbumin (egg white albumin) followed by histological and

immunohistochemical analysis of middle and inner ear tissues to assess the damage mechanism. Morphological and histochemical changes were recorded on the 7th, 14th and 28th days of the experiment. On the 28th day significant damage of the middle and inner ear was noted. Inner ear structures contained a vast amount of eosinophils, plasmocytes and lymphocytes. There were a significant number of eosinophils, lymphocytes, plasmocytes, neutrophils and macrophages in the scala tympany. Partial penetration of bacteria and neutrophils through the membrane of the cochlear window was marked. Moreover, there were destructive changes in the capillaries of the basement membrane, severe morphological damage of the Corti organ, the spiral ligament and vascular strip. The presence of nystagmus in several animals could indicate involvement of the vestibular part of the inner ear [25].

Penetration of eosinophils into the inner ear may also be a result of an allergic reaction. Against the background of sensitization with ovalbumin, tympanic epithelial cells begin to produce eotaxin-3 and cytokine A5. With the further development of the process, inflammatory cells such as lymphocytes, plasmocytes, eosinophils also become sources of the above-mentioned chemokines, which penetrate the round window membrane and lead to the migration of eosinophils into the inner ear [25, 26]. Cytotoxic proteins and reactive oxygen species produced by eosinophils lesion the epithelial layer of the round window membrane, increasing its penetrance. The overlay of a bacterial infection and the diffusion of bacterial toxins into the perilymph also contributes to Corti organ damage, causing the development of sensorineural hearing loss [16].

The determination of cytokines involved in the pathogenesis of EOM plays an important role not only in understanding the mechanisms of the disease, but also in the search of treatment methods, for example, the possibility of using targeted biological drugs.

Periostin was found in the basement membrane and extracellular matrix of patients with EOM. This protein is secreted by pulmonary fibroblasts and plays an important role in the development of subepithelial fibrosis in bronchial asthma [27]. Isido et al. observed the production of periostin in nasal polyps in a number of patients, including concomitant BA, as well as in patients with the aspirin triad. Periostin promotes tissue fibrosis and remodeling of the nasal mucosa [28]. According to the authors, periostin plays an important role in the formation of granulations in the middle ear in EOM [29].

Clinical Features

In 2011a multicenter study was conducted in five Japanese clinical centers, to analyse the observation results of 138 EOM patients. As a result, the clinical features of this disease were evaluated and the following diagnostic criteria were proposed (Table 1) [9].

The main clinical signs of EOM are [30]:

1. Bilateral nature of the lesion
2. Visualization of large granulations in the tympanic cavity during perforation of the tympanic membrane; if there is no perforation, then the swelling of the eardrum is yellow
3. Concomitant polypous rhinosinusitis
4. The presence of sensorineural hearing loss
5. Aerial attic and antrum according to CT data
6. Ineffectiveness of standard conservative treatment regimens for exudative/chronic otitis media
7. Improving the condition of the middle ear after applying systemic/local glucocorticosteroids.

The clinical features of the middle ear condition in EOM can be divided into 2 types: otitis media with effusion symptoms or signs of chronic otitis media with the presence of constant perforation. Despite the presence or absence of perforation of the tympanic membrane in all cases of EOM, a particularly viscous exudate is noted in the tympanic cavity. When installing a transtympanic shunt, the lumen of the tube is very easily blocked by the viscous discharge from the middle ear.

Iino et al. proposed a scale for assessing the severity of the of EOM according to the middle ear mucous membrane condition, taking into account the following criteria (Table 2).

Kanazawa evaluated the severity of the aforementioned symptoms in 26 patients every 3 months. Having obtained the average score for 4 three-month periods (1 year), the authors analyzed the influence of the following parameters on the severity of the course of EOM—gender, age, body mass index (BMI), duration of bronchial asthma, relationship with aspirin-dependent bronchial asthma, the sum of the points on a Lund—Mackay scale, the degree of mastoid process pneumatization, the width of the bony part of the auditory tube in the area of the tympanic opening, the values of eosinophils and peripheral blood IgE, the relationship with allergic rhinitis. As a result of the analysis of the created model of multiple linear regression, it was found that excessive BMI and the duration of the course of bronchial asthma (the period between the first episode and the first visit to the clinic) significantly aggravate the course of EOM ($p < 0.05$) [31].

Table 1 Diagnostic criteria for eosinophilic otitis media

Major criteria	Minor criteria
Otitis media with effusion or chronic otitis media with eosinophil dominant effusion.	<ol style="list-style-type: none"> 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 (EGPA), hypereosinophilic syndrome	

Table 2 Scoring system used to evaluate the severity of eosinophilic otitis media (Iino et al.)

1. Quantity of middle ear effusion (MEE)/otorrhea (without eardrum perforation)	
Score 0	No MEE
Score 1	MEE with partial intratympanic aeration
Score 2	Mesotympanum totally filled with MEE
2. Quantity of MEE/otorrhea (with eardrum perforation)	
Score 0	No otorrhea
Score 1	Otorrhea limited to the mesotympanum
Score 2	Otorrhea extrudes to the external auditory canal
3. Condition of the middle ear mucosa Score	
Score 0	Nearly normal or slightly edematous
Score 1	Edematous or thickened
Score 2	Highly thickened or granulated, and extending beyond the eardrum
4. Frequency of intratympanic administration of corticosteroids	
Score 0	None
Score 1	Once in the previous 3 months
Score 2	Two or more times in the previous 3 months
5. Frequency of systemic administration of corticosteroids	
Score 0	None
Score 1	7 days or less in the previous 3 months
Score 2	More than 7 days in the previous 3 months
6. Frequency of systemic administration of antibiotics	
Score 0	None
Score 1	7 days or less in the previous 3 months
Score 2	More than 7 days in the previous 3 months

Bronchial asthma occurs in 90% of cases of EOM and EOM occurs in 10% of BA patients. The relationship between these two pathological processes can be combined into “one airway, one disease” theory. The middle ear cavity, connected with the nasopharynx through the Eustachian tube, can be considered as part of the respiratory tract [4]. Thus, the optimal treatment of bronchial asthma influence the condition of the middle ear in EOM patients. With adequate treatment of bronchial asthma, after selecting a therapy that allows to achieve the stable remission, the condition of the middle ear improves, the otorrhea disappears, the swelling of the mucous membrane

decreases, granulation disappears, which, in turn, leads to better hearing [32, 33].

Diagnosis: Examination Technics

The examination scheme for patients with middle ear pathology, in addition to the standard otorhinolaryngological examination, includes audiological examination, as well as computed tomography (CT), (in rare cases, magnetic resonance imaging (MRI)) of the temporal bones.

Mixed hearing loss is usually observed on the audiograms of EOM patients. The incidence and severity of sensorineural hearing loss in EOM is significantly higher compared with otitis media of another etiology. In the late stages of the disease, patients have bilateral hearing loss with a low degree of bone conduction. Thus, in the course of the disease, conductive hearing loss progresses to sensorineural up to complete deafness [16].

There is very little data in the literature on the X-ray examination results in EOM patients. CT-scans usually shows the filling of the middle ear and mastoid with a soft tissue component. On MRI the soft-tissue mass gives a weak signal in T1 mode and a medium-intense in T2 mode.

Thus, the picture of CT and MRI in EOM is not specific. The following signs may indicative in favour of EOM [34]:

1. Bilateral involvement
2. Signs of rhinosinusitis (thickening of the mucosa of the maxillary sinuses)
3. Patulous Eustachian tubes

Additionally, the diagnostic criteria for EOM require an eosinophil-rich middle ear effusion confirmed morphologically. The quality of the morphologic findings is often suboptimal because of the high effusion viscosity. Some authors propose the flow cytometry as a diagnostic tool, which enables to quantificate eosinophils, redefine the morphology, and estimate the response to therapy [35].

Differential Diagnostics

It is necessary to exclude Charge-Strauss syndrome and hypereosinophilic syndrome in the presence of EOM symptoms.

Eosinophilic granulomatosis with polyangiitis (EGPA), also known as Churg–Strauss syndrome is a rare autoimmune disease characterized by to several organs damage due to the development of eosinophilic infiltration and vasculitis. This disease is often combined into one group with Wegener's granulomatosis due to the frequent appearance of antineutrophilic cytoplasmic antibodies (ANCA) in the blood, however, a distinctive feature of the Charge-Strauss syndrome is an allergic background, which manifests itself in an increase of blood eosinophils, the development of bronchial asthma, as well as eosinophilic inflammation of the upper respiratory tract. Pathology can develop at any age, but the peak incidence occurs at the age of 50–60 years [36]. Currently there are no clear diagnostic criteria for diagnosing Charge-Strauss syndrome. Chapel Hill Consensus (international conferences which addressed the need of standardized classification system for systemic vasculitides) defines it as eosinophil-rich granulomatous inflammation of the airways and necrotic vasculitis

affecting small and medium vessels associated with asthma and eosinophilia [37].

In 1990, the American College of Rheumatology (ACR) established that at least four of the

following six criteria should be fulfilled to diagnose EGPA [35]:

1. A history of asthma
2. Eosinophilia > 10%,
3. Mononeuropathy or polyneuropathy
4. Nonfixed pulmonary infiltrates
5. Paranasal sinus abnormalities
6. Biopsy showing extravascular eosinophils

Otological manifestations are not included in the criteria. However, there are reports of middle and inner ear involvement in the literature, presented by hearing loss, chronic otorrhea with viscous effusion and chronic granulomatous eosinophilic infiltrates in the tympanic cavity and mastoid process [38–40]. The etiology of hearing loss in the case of Charge-Strauss syndrome can be both a consequence of the development of eosinophilic inflammation in the middle ear, and the result of ischemic neuritis.

Due to the analysis of the symptoms of 34 patients with EGPA, otitis media with viscous effusion was presented in 17.2% cases and 52% of patients had hearing loss (mostly conductive).

The otologic symptoms occurred before EGPA diagnosis [41].

Differential diagnosis of EOM and Charge-Strauss syndrome is extremely important, as patients with the syndrome should receive systemic treatment using glucocorticosteroids and cytostatics to prevent life-threatening complications, such as, for example, cardiomyopathy [42].

First, the doctor should pay attention to the presence of neurological disorders or a characteristic rash, indicating the presence of vasculitis.

Also, patients should be tested for antineutrophil antibodies, ANCA (MPO and P3). The Japanese Otological Society has proposed the concept of an early Charge-Strauss syndrome diagnosis, based on a combination of eosinophilic otitis media and ANCA-associated vasculitis [38]. Unfortunately, ANCA is detected in 30–70% of patients with Charge Strauss syndrome [43]; therefore, a number of authors suggest long-term follow-up of patients with EOM due to the risk of the Charge-Strauss syndrome [44].

Hypereosinophilic syndrome is a disease characterized by a constant idiopathic increase of eosinophils in blood (≥ 1500 eosinophils/mm³) for at least 6 months. The heart, nervous system, bone marrow, blood vessels, lungs, and skin may be involved in the pathological process [45]. In 1995 the possible involvement of the middle ear with the development of EOM was described [46]. The diagnosis of

hypereosinophilic syndrome is based on exclusion of clonal and reactive eosinophilia (response to infection, autoimmune disease, atopy, hypoadrenalism, or oncology), as well as tropical eosinophilia. If untreated (glucocorticoids with a possible combination with monoclonal antibodies), hyper-eosinophilic syndrome worsens and leads to death [47, 48].

Treatment

Until recently, the treatment of patients with EOM was based on the use of glucocorticosteroids more often topical, less often systemic [5, 7, 30, 49]. According to Suzuki H. analysis of the treatment of 340 EOM patients, local and systemic steroids were used in 78% and 66% of patients, respectively. The ratio of sensorineural hearing loss was significantly higher in patients who were given systemic steroids than in patients without systemic steroids (52% vs. 34%, $p < 0.05$) [3].

Intrathympanic administration of glucocorticosteroids is crucial for maintaining the function of the inner ear [50]. It is equally important to remove rich in eosinophils and inflammatory mediators exudate from the tympanic cavity as soon as possible. To achieve this, a myringotomy is performed, as well as various shunt procedures. Heparin can be used to dilute and facilitate the removal of viscous effusion. Along with that heparin inhibits the chemotaxis of eosinophils, as well as cationic proteins of eosinophilic granules [51]. In case of bacterial inflammation it is possible to use local antibacterial drugs.

The surgical treatment, such as antromastoidotomy, tympanoplasty is unacceptable for this group of patients, because it leads to the exacerbation of sensorineural hearing loss. The analysis of the treatment methods of 340 patients showed, that only in 13% tympanoplasty was performed. At the same time, significant sensorineural-type hearing loss was recorded in 17% of patients after surgery, and only in 4% without surgical treatment [15].

Yoshihiko et al. evaluated the efficacy of treatment for patients with EOM. The authors identified 3 degrees of the middle ear mucous membrane condition: 1 degree (G1)—unchanged mucous membrane, 2 degree (G2)—thickened mucous membrane of the middle ear, 3 degree (G3)—thickened mucosa with granulations that extend beyond tympanic cavity.

It was found that topical treatment (introduction of triamcinolone into the tympanic cavity) is effective in G1, with G2 additional systemic use of glucocorticosteroids is necessary. G3 changes were observed in case of bacterial inflammation overlay, which required the addition of antibiotic therapy. Local treatment in G3 was effective only after surgical removal of granulation tissue [52].

Along with local treatment, it is very important to conduct adequate therapy for BA. According to observations, when the exacerbation is relieved and the intensity of pulmonary symptoms decreases, the condition of the middle ear also improves [53].

Attempts are currently underway to treat EOM with targeted monoclonal antibodies, known as biologicals. These include lebriuzumab (anti-IL-13), reslizumab (anti-IL-5), dupilumab (anti-IL 4Ra), mepolizumab (anti-IL-5), omalizumab (anti-IgE) and beralizumab (anti-IL) -5R). These drugs have been shown to be effective in treating patients with CRSwNP. According to the results of clinical trials, use of mepolizumab ($n = 30$) and reslizumab ($n = 24$) has led to a decrease of nasal polyps compared to the control group [54]. Based on the results of two studies ($n = 724$), Dupilumab was recently approved by the US Food and Drug Administration (FDA) as the first drug for treating patients with ChRSwithP [55].

In pilot studies Iino et al. demonstrated the efficacy of mepolizumab as an additional treatment for corticosteroid therapy in 13 patients with EOM. After 3 months of therapy, patients taking mepolizumab showed a significant decrease in the EOM symptoms intensity, compared to the control group. After a year of mepolizumab using, almost all patients noted a steady improvement of middle ear condition. Besides a significant decrease in peripheral blood eosinophilia was observed. The therapy was ineffective only in two patients, who had granulations in the tympanic cavity. That enabled the authors to conclude that the use of monoclonal antibodies in the presence of granulation tissue in the tympanic cavity is ineffective. It is important to note that sensorineural-type hearing impairment was more often observed in the control group [56].

Omalizumab was also effective and reduced eosinophilic inflammation in the middle ear. After 3 months of omalizumab administration eosinophil cationic protein concentrations in middle ear effusion significantly decreased [57–59].

The literature describes cases of successful use of an inhibitor of IL-5R beralizumab in the treatment of patients with EOM. First approved by the US Food and Drug Administration in 2017 for the treatment of severe cases of eosinophilic asthma, beralizumab is highly effective in lowering blood eosinophils [60]. Further cases of successful treatment of patients with EOM using a thromboxane A2 antagonist, ramatroban are described in literature [61]. A recent study showed the efficacy of pegylated interferon-2a and 2b in such patients, but with frequent development of side effects, including myalgia and fatigue [6].

Thus, further case studies and prospective trials are needed to evaluate the efficacy of beralizumab and other monoclonal antibodies as an independent therapy for EOM.

The importance of early diagnosis and the need for adequate treatment in EOM is due to the fact that the progression of the disease leads to the development of not only conductive, but also sensorineural hearing loss [62], which is associated with the progression of eosinophilic inflammation and bacterial infection of inner ear. The described above studies report that approximately 50% of previously untreated patients with EOM had a decrease in bone conduction, and in 6%—complete deafness [31].

Such patients need hearing rehabilitation. In 2006, Iwasaki et al. published data on the successful cochlear implantation of a patient with EOM. The surgery has its own peculiarities, since the installation of a foreign body in the structures of the ear can lead to the progression of eosinophilic inflammation. In addition, the ongoing eosinophilic inflammation in the middle ear, the formation of viscous exudate leads to the need for shunting of the tympanic cavity, which, in turn, increases the risk of meningitis. Therefore, in case of cochlear implantation of EOM patients some authors suggest to perform subtotal petrosectomy with removal of the mucous membrane of the tympanic cavity, all mastoid cells, blocking the auditory tube and filling the cavity with adipose tissue. In the pre-operative period, a course of systemic steroid therapy is recommended to a decrease in the volume of granulations and edematous mucous membrane and thus to reduce intraoperative bleeding. [63, 64].

EOM is a relatively rare pathology, however the incidence of the disease seems to be underestimated due to the lack of diagnostic tools. Further studies of the prevalence, clinical features, pathogenesis and treatment tools of this pathological entity as well as the issues of rehabilitation of EOM patients are necessary.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

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