by IL-1β and the enhanced secretion of IL-8 from epithelial cells and neutrophils [6,9], and thus can be identified as neutrophilic CRS with nasal polyps. Recently, polyps found in the Asian population were suggested to represent a neutrophilic disease [10]. A number of studies have confirmed the effectiveness of long-term and low-dose macrolide therapy, which has been established in Japan for the treatment of neutrophilic CRS with or without nasal polyps [11]. One of the major mechanisms of macrolide therapy includes its suppression of the influx of neutrophils through the inhibition of IL-8 production [12], suggesting a strong contribution of neutrophils to formation of nasal polyps.

Since neutrophilic CRS is often influenced by a predisposition to bacterial infection, and eosinophilic CRS is likely to be developed by allergic antigens, differences in the microbiology between the two pathologies of CRS can be expected. In the present study, we prospectively investigated the bacterial findings from the maxillary sinus in eosinophilic and neutrophilic CRS, which were compared in terms of the underlying histopathologies of the sinonasal mucosa.

Material and methods

Patients

Seventy patients with CRS with nasal polyps (19 females and 51 males, ranging in age from 22 to 80 years, mean age 50 years), visiting the Department of Otorhinolaryngology of Juntendo University Hospital between January 2009 and May 2010, were enrolled in this study after giving informed consent. The study was approved by the ethics committee of the Juntendo University Faculty of Medicine. CRS with nasal polyps was diagnosed based on the criteria of the European position paper [2]. None of the patients were treated with antibiotics, systemic or topical corticosteroids or other immune-modulating drugs for at least 1 month before the surgery. Patients with CRS with nasal polyps associated with current signs of purulent nasal discharge, chronic obstructive pulmonary disease, diffuse panbronchiolitis, fungal sinus disease, congenital mucociliary diseases, or cystic fibrosis were excluded from this study.

Sampling of tissue and effusion specimens

Surgically removed human nasal polyps located in the middle meatus were obtained from the patients with CRS. The samples were fixed in 10% formalin, embedded in paraffin wax, processed routinely, and stained with hematoxylin-eosin. The sinus effusion was collected by a microtip cotton applicator through the enlarged ostium of the maxillary sinus.

Criteria of eosinophilic and neutrophilic polyps

To evaluate the degree of the cell infiltration, two of the authors independently counted the numbers of eosinophils and neutrophils in three fields with cell clusters using light microscopy (×400 magnification). The number of neutrophils in the sinus smear was semiquantitatively assessed on a grading scale: (–), absence; (+), sparsely scattered in the field; (++), between (+) and (+++); (+++), forming clusters. Eosinophilic polyps were defined as those with eosinophil counts of more than 200 per microscopic field. Neutrophilic polyps were defined as those with neutrophil counts of more than 20 per microscopic field or neutrophil amounts of more than (++) in the sinus smear cytology.

Bacterial culture

Before surgery, the nasal vestibule was sterilized with 0.02% chlorhexidine gluconate swabs. Samples for bacterial culture were collected with a microtip cotton applicator through the enlarged ostium of the maxillary. The specimens for all bacterial culture were promptly transported in culturette tubes kept moist with Stuart's bacterial transport medium. All specimens were inoculated onto 5% sheep blood agar, chocolate agar, Columbia anaerobic blood agar, and Drigalski agar.

Statistics

Comparisons of the culture were analyzed by a chi-square test. A p value < 0.05 was considered to be significant.

Results

Twenty-nine patients (8 females and 21 males, ranging in age from 27 to 80 years, mean age 48 years) and 41 patients (11 females and 30 males, ranging in age from 22 to 77 years, mean age 53 years) were classified as having eosinophilic and neutrophilic CRS, respectively.

A total of 51 isolates of bacteria were recovered from 26 patients with eosinophilic CRS with nasal polyps. Three patients showed no growth, whereas

neutrophilic CRS with nasal polyps showed 84 isolates in 40 patients and no growth in 1 patient. The isolation rate of bacteria showed no significant difference between eosinophilic (90%) and neutrophilic CRS (98%).

Table I shows the bacterial profiles of eosinophilic and neutrophilic CRS with nasal polyps. Aerobic bacteria were found in 25 patients (86%) in eosinophilic CRS, which was not significantly different from that in neutrophilic CRS (40 patients, 98%). Methicillin-susceptible Staphylococcus aureus (MSSA) was the most frequently detected bacterium in both groups. Although the isolation rate of each type of aerobic bacteria was compared between the two groups of CRS, no significant differences were obtained for any aerobes. The number of detected aerobic bacteria such as MSSA, microaerophilic streptococci, and Klebsiella oxytoca found in eosinophilic CRS was 14 (48%), while 21 species (51%) were found in neutrophilic CRS, which was not significantly different. The rate of isolation for only indigenous bacteria such as coagulase-negative staphylococci (CNS) and Corynebacterium was 31% in eosinophilic CRS and 34% in neutrophilic CRS.

Comparison of the profiles of anaerobic bacteria in eosinophilic and neutrophilic CRS with nasal polyps is summarized in Table II. Five isolates of 3 types of anaerobic bacteria were recovered from eosinophilic CRS, whereas neutrophilic CRS had 11 isolates of 7 types of anaerobes. The isolation rate of anaerobes in eosinophilic CRS (17%) did not differ from that in neutrophilic CRS (15%). Although Prevotella/Porphyromonas, Peptoniphilus asaccharolyticus, and Peptostreptococcus anaerobius represent pathogenic anaerobes, the isolation rate in the patients with eosinophilic (10%) or neutrophilic CRS (15%) was not significantly different.

Table I. Comparison of the aerobic bacteria detected in eosinophilic and neutrophilic chronic rhinosinusitis (CRS) with nasal polyps.

Detected bacteria	Eosinophilic CRS	Neutrophilic CRS
Bacillus	0	1
Citrobacter freundii	0	2
Citrobacter koseri	2	1
Coagulase-negative staphylococci	16	23
Corynebacterium	6	13
Enterobacter aerogenes		2
Enterococcus faecalis	1	1
Eschericha coli	1	1
Haemophilus influenzae	1	0
Klebsiella oxytoca	1	1
Klebsiella pneumoniae	0	1
Microaerophilic streptococcus	1	2
MSSA	7	10
Pasteurella multocida	0	1
Pseudomonas aeruginosa	3	3
Serratia marcescens	0	1
Staphylococcus epidermidis	3	3
Staphylococcus lugnensis	1	1
α-Streptococcus	0	1
β-Streptococcus	0	3
Streptococcus milleri group	0	1

MSSA, methicillin-susceptible Staphylococcus aureus.

Discussion

The present study unexpectedly failed to demonstrate differences between bacterial profiles of eosinophilic and neutrophilic CRS with nasal polyps. We previously proposed that IL-1β derived from bacterial infection induced the secretion of IL-8 from epithelial cells and neutrophils, leading to neutrophil accumulation in the sinus mucosa and cavity even in those subjects without an infection [12]. On the other hand, eosinophil infiltration into the nasal polyps is associated with eotaxin and RANTES, which are driven by Th2 and Th17 cytokines [6,13]. Niederfuhr et al. [14] reported that there was no significant difference in the bacteriologic features between Th2-shifted CRS with nasal polyps and Th1-dominant CRS without nasal polyps. Since the eosinophil response as well as the inflammatory compromise [15] is reported to be much higher in bacterial infection than in viral

Table II. Comparison of the anaerobic bacteria detected in eosinophilic and neutrophilic chronic rhinosinusitis (CRS) with nasal polyps.

Detected bacteria	Eosinophilic CRS	Neutrophilic CRS
Actinomyces	0	2
Micromonas micros	0	1
Parviromonas micra	0	1
Peptoniphilus asaccharolyticus	2	2
Peptostreptococcus	0	1
Peptostreptococcus anaerobius	0	1
Prevotella porphyromonas	1	3
Propionibacterium	2	0

infection, Th2 responses may be triggered by bacterial antigens as well as inhalant antigens. A new paradigm of Th17 has been applied to the recruitment of eosinophils and the remodeling of the nasal polyps of CRS [13]. On the other hand, IL-17 is known to restore neutrophil recruitment resulting in reduced bacterial burden [16]. Thus, underlying pathogeneses of both eosinophilic and neutrophilic polyps could be attributed to the presence of bacteria acting through different mechanisms.

Numerous studies have reported the recovery of bacterial pathogens from patients with CRS and concluded that the predominant isolates are anaerobic. Brook [17] summarized 17 studies of CRS that attempted to recover anaerobes and included 1758 patients. Anaerobes were recovered in 12–93% of the patients. These data indicated that anaerobic bacteria can be isolated in more than half of the patients with CRS when adequate methods are utilized. The present study showed a relatively low rate of isolation of anaerobes as compared with previous studies, which is probably due to the methodologies for collection, transportation and cultivation, and previous antimicrobial treatment.

CNS and Corynebacterium were recovered from CRS as major isolates in the present study, which was similar to previous studies [18,19]. Since these organisms are isolated from the sinus mucosa in healthy patients, they cannot be considered pathogenic per se [19]. They could play a role in CRS only in association with the presence of other bacteria, particularly anaerobes. Actually, eosinophilic and neutrophilic polyps, in which CNS or Corynebacterium were isolated, were also accompanied by the recovery of anaerobes in 17% and 12% of patients, respectively. Determining the pathogenetic significance of these organisms in CRS will require further research.

It has been postulated that Staphylococcus aureus releases enterotoxins acting as superantigens and induces the local formation of multiclonal IgE formation as well as eosinophilic inflammation [20]. However, the present finding of a high rate of isolation of MSSA in both eosinophilic and neutrophilic CRS with nasal polyps suggests that colonization by Staphylococcus aureus in the paranasal sinus is not specific to eosinophil accumulation. Further study is required to determine the role of Staphylococcus aureus-induced enterotoxins in the pathogenesis of CRS with nasal polyps.

In conclusion, we found no significant difference in the bacterial features of the maxillary sinuses between eosinophilic and neutrophilic CRS with nasal polyps. Bacterial infection or colonization may contribute to the underlying pathogenesis in both groups.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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Auris Nasus Larynx 38 (2011) 469–473

AURIS NASUS LARYNX
INTERNATIONAL JOURNAL OF ORL & HNS

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Bacteriology of recurrent exacerbation of postoperative course in chronic rhinosinusitis in relation to asthma

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Received 4 July 2010; accepted 6 October 2010
Available online 8 January 2011

Abstract

Objectives: Co-mobidity of asthma is known to result in a poor prognosis of post-endoscopic sinus surgery (post-ESS). Bacterial infection may play a key role in recurrent pathophysiology of sinusitis in post-ESS.
Methods: Forty-two patients with CRS associated with asthma undergoing ESS were enrolled. Bacterial culture was performed from the sinus cavity at the time of acute infectious episodes. Recurrence of sinonasal disease was analyzed in terms of steroid responsiveness and peak expiratory flow (PEF).
Results: Totally 75 aspirates were obtained during post-ESS; 2 repeat aspirates from 10 patients, 3 from 5 patients, and 4 from 2 patients. Only 6 specimens (8.0%) obtained from 5 patients (11.9%) showed no growth whereas 83 isolates were recovered from 69 specimens. Sixteen patients had at least one episode of a significant decline of PEF. All except one patient complained of symptoms and signs of upper respiratory infections prior to a depression of PEF. Positive culture was obtained in 10 out of 11 patients examined at the time of acute exacerbation of CRS.
Conclusion: Bacterial infection may play a critical role of recurrent polyps and refractory symptoms during post-ESS follow-up. Moreover, worsening of sinusitis accompanies asthma exacerbation.

Key words: Chronic rhinosinusitis; Asthma; Peak expiratory flow; Endoscopic sinus surgery; Steroid responsiveness; Bacteria; Infection

1. Introduction

Chronic rhinosinusitis (CRS) is defined as persistent inflammation of the nasal and paranasal cavity mucosa lasting ≥3 months. Although CRS is a multifactorial disease and a heterogenous group of disease, most clinicians believe that bacteria play a major role in the underlying etiologies and pathogenesis.

Histomorphological patterns of CRS with nasal polyps are characterized by the predominance of eosinophils and mixed mononuclear cells and the relative paucity of neutrophils [1]. Mucosal infiltration with eosinophils in CRS with nasal polyps may be more refractory to surgical cure and is frequently associated with bronchial asthma [2]. Several studies have reported the aspects of the clinical relationship between CRS and asthma [3]. Co-mobidity of asthma is known to be exacerbating factor for CRS and vice verse [3]. Bacterial antigens may elicit IgE-mediated response, which may be important in both exacerbations [4]. The presence of sinusitis can provide a nidus of infection in asthmatics. The most common cause of acute sinusitis, *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis*, mirror those to cause asthma [5].

In contrast to acute exacerbation of CRS without previous surgery [6], the microbiology of acute infectious episodes in post-endoscopic sinus surgery (post-ESS) has not well been studied except for the report by Bhattacharyya and Kepnes [7]. To establish the microbiological characteristics of acute episodes in post-ESS associated with asthma provides not

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0385-8146/$ – see front matter
doi:10.1016/j.anl.2010.10.009

only great interesting, scientific, and practical issues, but also a better understanding of the link with asthma exacerbation. Thus, the present study was designed to evaluate the bacterial microenvironment in sinus cavities of ESS in asthmatics at the time of recurrent diseases, and to study potential contribution of acute bacterial infection after ESS in relation to asthma.

2. Methods

2.1. Patients

Forty-two subjects with CRS associated with bronchial asthma including 3 patients with aspirin sensitivity (22 females and 20 males, ranging in age from 12 to 75 years, mean age of 46 years), who were admitted to the Department of Otorhinolaryngology of the outpatient clinic of the Juntendo University Faculty of Medicine between January 2006 and July 2008, entered the study after giving informed consent. The study was approved by the ethic committee of the Juntendo University Faculty of Medicine. Postoperative follow-up ranged from 12 to 36 months.

CRS with nasal polyps was diagnosed based on the criteria of the European position paper [8], that is, they had two or more symptoms, one of which should be either nasal blockage/obstruction/congestion or nasal discharge (anterior/posterior nasal drip), with/without facial pain/pressure, with/without reduction or loss of smell; and either endoscopic signs of polys and/or mucopurulent discharge primarily from middle meatus, and/or oedema/mucosal obstruction primarily in middle meatus, and/or computed tomographic changes within ostiomeatal complex and/or sinuses.

The diagnosis of asthma was based on the definition of the American Thoracic Society. All patients were treated with bronchodilators including theophylline, β-adrenergics, and inhaled corticosteroids in the same manner and to the same extent after surgery as before.

2.2. Extended endoscopic sinus surgery

ESS in all cases was performed under general anesthesia. Since most of CRS with nasal polyps associated with asthma shows extensive sinonasal disease with multiple polyps, which are protruded from the olfactory cleft and middle meatus, we usually perform extended ESS. The extended ESS implies the elimination of polyps by microdebrider and the resection of the lower half of both superior and middle turbinates and maximal enlargement of each paranasal sinus ostium, to ensure the proper access of topical steroid administration to the lining epithelia of each sinus cavity. Postoperative cleaning of blood and fibrin clots from the operative cavity was meticulously performed daily on postoperative days 3–5 and then weekly for 1–2 months. The patients received oral antibiotics, usually amoxicillin, for a few days postoperatively. All patients were daily received intranasal corticosteroid preparation of two puffs of fluticasone on each nostril in addition to saline nasal douch during postoperative follow-up. A short-term of oral predonisolon (0.5 mg/kg of body weight) was prescribed when severe disturbance of smell and recurrent multiple nasal polyps [9]. Moreover, two hundreds mg of levofloxacin was orally given twice per day in the presence of massive purulent nasal discharge. An asthma exacerbation was treated by short-acting β-agonist rescue.

2.3. Bacterial culture

At the time of acute exacerbation of CRS defined by the presence of purulent sinonasal secretions in conjunction with sinus-related symptoms such as nasal discharge, facial pain, nasal congestion, and loss of smell, bacterial culture was performed by a microtip cotton applicator through the enlarged ostium of the maxillary sinus under endoscopic control. The specimens for bacterial culture were transported in culturette tubes kept moist with Stuart's bacterial transport medium. All specimens were inoculated onto 5% sheep blood agar, chocolate agar, Columbia anaerobic blood agar, and liquid thioglycolate broth. The in vitro antimicrobial sensitivity of the identified bacterial isolates was assessed by an agar disk diffusion method.

2.4. Peak expiratory flow

All patients were assessed for peak expiratory flow (PEF) three times daily during post-ESS according to the National Asthma Education Program. The PEF was measured using a mini-Wright peak flow meter (Clement Clark Ltd., UK). The 20% depression of mean daily PEF was regarded as aggravation of lower respiratory function.

3. Results

Totally 75 aspirates were obtained from 42 patients during post-ESS; 2 repeat aspirates from 10 patients, 3 from 5 patients, and 4 from 2 patients. Only 6 specimens (8.0%) obtained from 5 patients (11.9%) showed no growth whereas bacteria were recovered from 69 specimens (92.0%) obtained from 37 patients (88.1%). One isolate of bacteria was detected in 48 specimens, 2 isolates in 8 specimens, and 3 isolates in 2 specimens (Fig. 1). A total of 83 isolates were recovered (Fig. 2) including 18 isolates of methicillin-susceptible *Staphylococcus aureus* (MSSA), 14 isolate of *S. pneumoniae*, 10 isolates of Coagulase Negative Staphylococci (CNS), 8 isolates of methicillin-resistant *S. aureus* (MRSA), 7 isolates of *Pseudomonas aeruginosa*, 7 isolates of *H. influenzae*, and 6 isolates of *Moraxella catarralis*. The other bacteria includes *Acinetobacter baumannii* (3 isolates), α-*Streptococci* (3 isolates), β-*Streptococci* (2 isolates), *Corynebacterium* (2 isolates), *Staphylococcus*

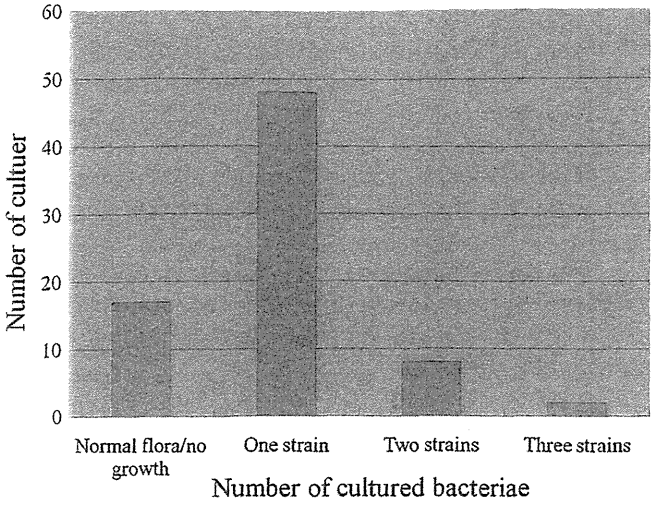

Fig. 1. Culture demographics.

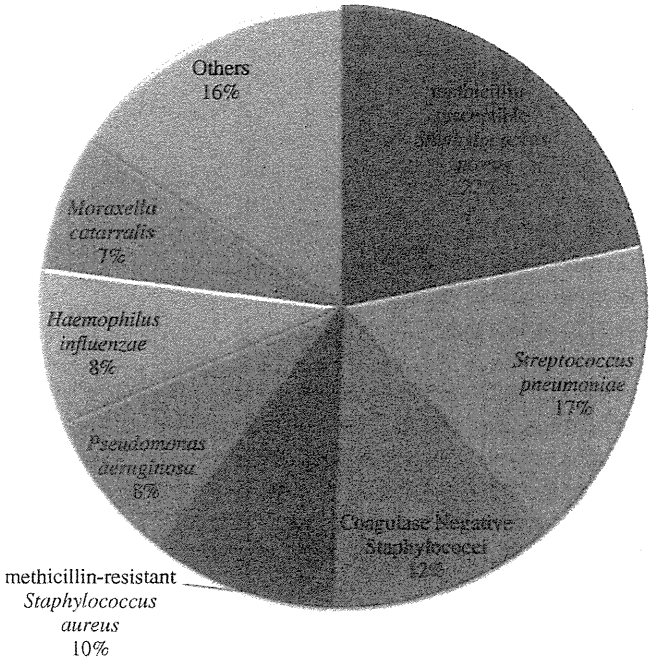

Fig. 2. Distribution of bacterial isolates.

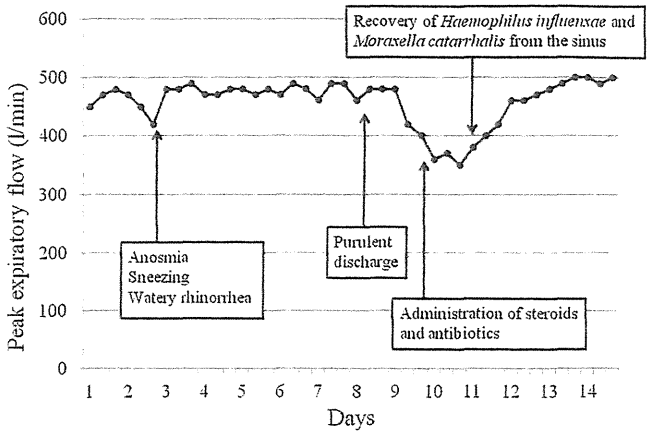

Fig. 3. A representative case of postoperative time course of peak expiratory flow, sinonasal symptoms, and bacterial culture.

epidermidis (1 isolate), *Serratia marcescens* (1 isolate), and *Aeromonas sp* (1 isolate). No anaerobes were detected.

Susceptibility test of 4 pathogens of *S. pneumonia*, MRSA, *P. aeruginosa*, and *H. influenzae* with representative antibiotics were summarized on 35 isolates (Table 1). Penicillin-resistant (the minimum inhibitory concentration, MIC; ≥2 μg/ml), -intermediate resistant (MIC; 0.125–1 μg/ml), and -sensitive *S. pneumoniae* (MIC; ≤0.125 μg/ml) was 7, 4, and 3 isolates, respectively. Levofloxacin showed an excellent efficacy against *S. pneumoniae*. MRSA was remarkably resistant to all antibiotics except for minomycin. Two isolate of *P. aeruginosa* was resistant to ampicillin and the third-generation cephalosporins while levofloxacin showed poor activity against only one isolate. The third-generation cephalosporin and levofloxacin were sensitive to *H. influenzae*.

Sixteen patients had at least one episode of a significant decline of PEF whereas the other 27 patients did not show asthma exacerbations. Fig. 3 shows postoperative time courses of a representative case, in which upper respiratory symptoms were recognized and microorganisms were recovered prior to a depression of PEF. All except one patient (93.8%) complained of symptoms and signs of upper respiratory infections prior to a depression of PEF. Bacterial

Table 1
The rate (%) of antimicrobial sensitivities for selected bactereia (sensitive/intermediate sensitivity/resistant).

	Streptococcus pneumoniae (n = 14)	Methicillin-resistant *Staphylococcus aureus* (n = 8)	*Pseudomonas aeruginosa* (n = 7)	*Haemophilus influenzae* (n = 6)
ABPC	50.0/28.6/21.4	0/0/100.0	71.4/0/28.6	33.3/66.7/0
MPIPC	nd	nd	nd	nd
PIPC	nd	nd	nd	nd
CTX	85.7/7.1/7.1	nd	nd	100.0/0/0
CPZ/SBT	nd	nd	57.1/14.3/28/6	nd
GM	nd	25.0/0/75.0	71.4/0/28.6	nd
MINO	nd	25.0/50.0/25.0	nd	nd
LVFX	100.0/0/0	0/0/100.0	57.1/28.6/14.3	100/0/0

ABPC, ampicillin; MPIPC, methicillin; CTX, cefotaxime sodium; CPZ/SBT, cefoperazone sodium/sulbactam sodium; GM, gentamicin; MINO, minomycin; LVFX, levofloxacin; nd, not determined.

examination from the sinus was carried out in 18 specimens of 11 patients at the time of acute exacerbation of CRS, resulting in positive culture of 17 specimens of 10 patients. Major pathogens included 7 isolates of *S. pneumoniae*, 4 isolates of *H. influenzae*, 3 isolates of *P. aeruginosa*, and 2 isolates of *M. catarralis*, etc.

4. Discussion

The present study revealed that bacteria are related to acute exacerbations in 88.1% of the post-ESS patients associated with asthma. Brook and Frazier [10] reported that the predominant organisms isolated from acute exacerbations of CRS were anaerobic bacteria and that polymicrobial infection was also present. Moreover, aerobic organisms that are generally observed in acute infection emerged in some of the acute episodes. On the other hand, a majority of bacteria recovered in the present findings were aerobic organisms as like detected in acute rhinosinusitis [11]. The difference of bacterial species between CRS with and without previous surgery may be due to the environmental differences, namely that paranasal sinuses of post-ESS were changed into more aerobic conditions by enlargement of sinus ostium. *P. aeruginosa* detected in the present study, which was not recovered in acute exacerbation of CRS without previous surgery, may be characterized in post-operative patients [12].

Bhattacharyya and Kepnes [7] reported the microbiology of recurrent sinus infections after ESS, which was characterized as (i) 30% of the culture resulted in no growth in spite of purulent secretions, (ii) culture data (*S. pneumoniae, H. influenzae* and *M. catarrhalis* accounted for 10.8% of the culture results) differed from those encountered in acute rhinosinusitis, and (iii) the same organisms commonly encountered in preoperative CRS with the exception of an increased prevalence of *Pseudomonas* species (8.5%) and diphtheroids. Our results differed from that of Bhattacharyya and Kepnes [7] regarding the following points: (i) only 8.0% of specimens were no growth of bacteria and (ii) the pattern of bacteria is similar to that of acute rhinosinusitis rather than CRS (three major bacteria encountered acute rhinosinusitis reached 32.5%) in the present study. The difference between two studies may be brought about by the background of the patients, the surgical technique of ESS, and the postoperative care. Our patients were associated with asthma, which may predispose to acute and recurrent bacterial infection. Our technique of ESS for CRS associated with asthma is an extended surgery, in which the natural ostia of each paranasal sinus were enlarged as much as possible in order to gain steroid spray access to the sinus. Acute bacterial infections and recurrent symptoms were promptly treated by administration of steroids and/or antibiotics in the present postoperative regimens. However, the prevalence of *Pseudomonas* species was almost identical in two studies. Al-Shemari et al. [13] documented that CNS, diphtheroids, and *S. aureus* constitute the predominant flora of the healthy post-ESS sinus cavity. Therefore, MSSA, CNS, and MRSA recovered in the present study probably represent colonization of the sinus cavity by nasal flora.

An increase in drug-resistant organisms is an emerging concern in acute and chronic sinonasal infections. In the present study, MRSA was detected in 9.6% of the isolates, which seems to be greater than those of the literature [14]. Although vancomycin is known to represent the gold standard for therapy of MRSA infection, 75% of MRSA recovered in the present study was sensitive to minomycin. Moreover, topical application of mupirocin was reported to be successful in the treatment of MRSA-related CRS [15]. Although a majority of the isolates of *Pseudomonas* species and β-lactamase-producing organisms were sensitive to levofloxacin, a careful attention should be paid to creation of resistance. The combination of a penicillin and a β-lactamase inhibitor is recommended as the first line antibiotic therapy for β-lactamase-producing organisms [16]. We empirically selected levofloxacin as antibiotics in the regiment for sinonasal infection, but culture-directed therapy, which has not yet been performed in the present study, may prevent the emerging of resistant bacteria.

Co-morbidity of asthma is known to result in a poor prognosis of CRS postoperatively, which imply a recurrence of nasal polyps and refractory sinonasal symptoms [3]. Recurrent polyps and refractory symptoms are likely to be derived from steroid-resistance. Allergen exposure, and respiratory virus and bacteria are the most important precipitants of asthma exacerbation, and both produce or worsen sinusitis [17]. Acute exacerbation or recurrence of CRS is known to be developed by a viral infection, especially rhinovirus infection, which is further exacerbated by the secondary bacterial infection [18]. Bacterial antigen induces both Th1 and Th2 responses, which promotes mobilization and activation of neutrophils and eosinophils, respectively. The eosinophil response is reported to be much higher in bacterial infection than in viral infection as well as the inflammatory compromise [19].

A history of asthma has been identified in the literature as poor outcome predictors of ESS [20]. Poor prognosis in CRS associated with asthma is likely to be due to a high likelihood of extensive disease, which is further related to the presence of peripheral eosinophilia. A link between CRS and asthma can be ascribed to a systemic inflammatory process [21,22]. A systemic response to the application of inflammatory stimuli to the sinuses can produce increased inflammation in the lung via the activation of circulating T lymphocytes, eosinophils and basophils as well as inflammatory cytokines. Thus, communications among the sinuses, the lung, and bone marrow may contribute to cell recruitment in airway inflammations, resulting in a refractory sinonasal disorder.

Pulmonary function examined by PEF was disturbed when acute exacerbation related to bacterial infection

occurred. As well as viral infections, bacterial infections potentially play in exacerbation of asthma and the development of sinus disease. The sinonasal and bronchial mucosa present similarities, suggesting the concept of "one airway, one disease". Epidemiologic studies show a link between the upper and lower airways, and mechanistic studies suggest a cause-and-effect rather than a coexistence [23]. The time course of exacerbation of upper and lower airways supports vertical relationship rather than an epiphenomenon of the same infectious and immune-mediated disease. Thus, the present study clearly demonstrated that bacterial infection induces exacerbation of asthma secondary to worsening of sinonasal disease.

In conclusion, bacterial infection may play a critical role of recurrent polyps and refractory symptoms during post-ESS follow-up. Moreover, worsening of sinusitis accompanies asthma exacerbation. Intensive postoperative care of the upper airway after ESS may lead to benefit of asthma control.

Conflicts of interest

There are no conflicts of interest.

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Auris Nasus Larynx 38 (2011) 456–461

AURIS NASUS LARYNX
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Diagnostic criteria of eosinophilic otitis media, a newly recognized middle ear disease

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Received 20 September 2010; accepted 18 November 2010
Available online 19 January 2011

Abstract

Objective: Eosinophilic otitis media (EOM) is a newly recognized intractable middle ear disease, characterised by the accumulation of eosinophils in middle ear effusion and middle ear mucosa. Since EOM patients show gradual or sudden deterioration of hearing, it is important to properly diagnose EOM and to start adequate treatment for EOM. We aimed to investigate the clinical risk factors of EOM and to establish the diagnostic criteria of EOM.

Patients and methods: We reviewed 138 patients with EOM and 134 age-matched patients with the common type of otitis media with effusion or chronic otitis media as controls. We analyzed the incidence of the following clinical variables in both groups: bilaterality of otitis media, viscosity of middle ear effusion, formation of granulation tissue in the middle ear, response to the treatment for otitis media, deterioration of bone conduction hearing level, and association with other diseases such as bronchial asthma, chronic rhinosinusitis, nasal polyposis, and allergic rhinitis.

Results: A high odds ratio was obtained from an association with bronchial asthma (584.5), resistance to conventional treatment for otitis media (232.2), viscous middle ear effusion (201.6), association with nasal polyposis (42.17), association with chronic rhinosinusitis (26.49), bilaterality (12.93), and granulation tissue formation (12.62). The percentage of patients with EOM who were positive for two or more among the highest four items was 98.55%.

Conclusion: A patient who shows otitis media with effusion or chronic otitis media with eosinophil-dominant effusion (major criterion) and with two or more among the highest four items (minor criteria), can be diagnosed as having EOM. Patients with ear symptoms should have the proper diagnosis of EOM using the proposed diagnostic criteria, and then can receive adequate treatment, resulting in prevention of deterioration of hearing and quality of life.

Keywords: Eosinophilic otitis media; Bronchial asthma; Middle ear effusion; Nasal polyposis; Chronic rhinosinusitis; Diagnostic criteria

1. Introduction

Eosinophils are effector cells in the pathogenesis of allergic disease. Historically, Koch [1] first reported that some of the cases with chronic otitis media (COM) showed eosinophil-enriched secretion, and that the macroscopic appearance had characteristics such as highly viscous middle ear secretion with edematous pink mucosa. The high incidence of accompanying nasal allergy has been reported [1]. In 1993, Tomioka et al. [2] reported cases of intractable otitis media with effusion (OME) and COM patients associated with bronchial asthma. Middle ear effusion and otorrhea in those cases contained numerous eosinophils and were very viscous. They named this condition as eosinophilic otitis media (EOM) because the

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0385-8146/$ – see front matter © 2011 Published by Elsevier Ireland Ltd.
doi:10.1016/j.anl.2010.11.016

effusion contains many eosinophils regardless of the presence of type I allergy [3]. Similar case reports have been published in Japan [4].

The mechanism of accumulation of eosinophils in the middle ear has not yet been determined. However, eosinophil chemoattractants such as IL-5 and eotaxin have been detected in middle ear effusion [5,6], and the expressions of eosinophil chemoattractants such as eotaxin, regulated on activation, normal T expressed and secreted (RANTES), and ecalectin mRNAs have also been found in middle ear mucosa by in situ hybridization [6]. These findings indicate that active eosinophilic inflammation locally occurs in the middle ear [7].

EOM is now recognized as an intractable otitis media and is a fairly common middle ear disease not only in Japan but also worldwide. One of the striking events of EOM is the high incidence of gradual or sudden deterioration of hearing [2–4]. Clinical surveillance of EOM in Japan demonstrated that among 190 EOM patients, approximately one-half showed deterioration of bone conduction hearing threshold and 6% became completely deaf [8].

There are several chronic intractable middle ear diseases showing clinical characteristics that are extremely different from the common type of OME and COM. Each disease requires a specific treatment to cure or control the disease; otherwise, patients will suffer persistent otorrhea and progressive hearing loss, resulting in a worsening quality of life (QOL). The following items were nominated for chronic intractable middle ear diseases: otitis media tuberculosa, cholesterol granuloma, anti-neutrophil cytoplasmic autoantibody (ANCA)-related vasculitis syndrome such as Wegener's granulomatosis and Churg-Strauss syndrome (CSS), and EOM.

The concept of EOM has not been properly recognized and EOM tends to be overlooked. Although the clinical characteristics of EOM have been previously reported [4,9], nothing is known about the incidence of each characteristic in EOM and common types of otitis media to make a definitive diagnosis of EOM. Therefore, it is critical to determine risk factors of EOM and to resolve diagnostic criteria of EOM. When diagnosis of EOM is established, early intervention of patients with adequate treatment could prevent deterioration of hearing loss and persistent otorrhea, leading to improvement of their QOL.

2. Materials and methods

2.1. Patients

This analysis was based on the retrospective clinical data of patients from the EOM study group, which is a Japanese multicentre study involving five referral centers. One hundred thirty-eight patients who were diagnosed with EOM were collected from five centers of the EOM study group. The patients included 86 females and 52 males, aged 19–77 years at the first visit to each center (mean ± SD: 50.5 ± 13.1 years). The patients had a middle ear effusion or middle ear mucosa in which the accumulation of eosinophils was detected histologically or cytologically, and they showed clinical characteristics as described by Nagamine et al. [4]. One hundred thirty-four age-matched patients (86 females and 48 males) with non-eosinophilic COM or OME were also enrolled as controls. All of the control patients underwent tympanoplasty or insertion of a tympanostomy tube at Jichi Medical University Saitama Medical Center and were aged between 18 and 77 years (51.6 ± 13.7 years). The difference in the age distributions of both groups was not statistically significant. Informed consent was obtained from all the patients.

2.2. Determination of clinical characteristics

Based on the previous report by Nagamine et al. [4], the following clinical characteristics of each patient in both groups were analyzed: bilaterality of otitis media, viscosity of middle ear effusion, formation of granulation tissue in the middle ear, response to the treatment for otitis media, deterioration of bone conduction hearing level (BCHL), and association with other diseases such as bronchial asthma, chronic rhinosinusitis, nasal polyposis, and allergic rhinitis. Viscosity of middle ear effusion was defined as when middle ear effusion was difficult to remove by Rosen's ear suctioning tube because of high viscosity. If the condition of the middle ear mucosa was grade 3 by the classification of Iino [9], i.e., highly thickened or granulated to an extent beyond the position of a normal eardrum, this was defined as granulation tissue formation. The response to conventional treatments for common otitis media such as myringotomy and insertion of a ventilation tube for OME, and administration of systemic or topical antibiotics and tympanoplasty for COM were investigated. If the treatment was not effective (except for systemic or topical administration of corticosteroids), the condition was defined as resistance to treatment.

2.3. Evaluation of hearing

The air conduction hearing level and BCHL of each patient in both groups were assessed by pure tone audiometry. The latest audiometric results were evaluated. Deterioration of the BCHL was identified if the BCHL of each patient was beyond 30 dB for at least one frequency at 250–4000 Hz.

2.4. Association with other diseases

Patients of both groups were diagnosed with bronchial asthma if they had a history or had been treated by respiratory physicians using inhaled or systemic corticosteroids using the guidelines for the management of bronchial asthma. A diagnosis of chronic rhinosinusitis was made by rhinoendoscopic findings (e.g., mucous or purulent rhinorrhea,

Table 1
Baseline characteristics of EOM and control groups.

	EOM group	Control group	*P* value
No. of patients	138	134	
Sex (F:M)	86:52	86:48	NS
Age (years)[a]	50.5 ± 13.1 (19–77)	51.6 ± 13.7 (18–77)	NS
Bilaterality	114	36	<0.0001
Highly viscous MEE	128	8	<0.0001
Granulation tissue formation	45	7	<0.0001
Resistance to treatment	128	7	<0.0001
Deterioration of BCHL	81	65	0.011
(Deafness)	(8)	(2)	(<0.0001)
Associated diseases			
Bronchial asthma	124	2	<0.0001
Chronic rhinosinusitis	102	14	<0.0001
Nasal polyposis	85	5	<0.0001
Allergic rhinitis	52	39	<0.001

EOM, eosinophilic otitis media; MEE, middle ear effusion; BCHL, bone conduction hearing level; F, female; M, male; NS, not significant.
[a] Mean ± SD (range).

mucosal congestion and nasal polyps) and by the findings of a paranasal computed tomography scan, in addition to a history of nasal symptoms (e.g., nasal obstruction, discharge, postnasal drips, hyposmia, headache and facial pain) for 3 months or more. Patients were considered to have allergic rhinitis if they reported a history and symptoms of nasal allergies and had a high level of serum IgE (≥170 IU/L) or positive specific IgE for inhaled antigens.

2.5. Statistical analysis

All statistical analyses for baseline characteristics between the EOM group and the control group were carried out using the chi-square test, Fisher's exact test (two sided) and multiple regression analysis, except for the patients' age. The difference between the two groups for the patients' age was analyzed using an unpaired *t*-test. *P* values of less than 0.05 were defined as significant. Sensitivity was the true positive rate of the clinical characteristics in the EOM group, and specificity was the true negative rate of the same clinical characteristics in the control group.

3. Results

3.1. Clinical features of patients in EOM and control groups

To characterise more specific clinical features of EOM, the clinical data of 138 patients of the EOM group and 134 patients of the control group (COM/OME) were compared and these data are summarised in Table 1. When the clinical symptoms were analyzed according to previous studies [2–4], a significantly higher incidence of bilaterality, highly viscous middle ear effusion, formation of granulation tissue in the middle ear, resistance to conventional treatment for otitis media ($P < 0.0001$), and deterioration of BCHL ($P = 0.011$) was found in the EOM group than in the control group. The rate of deafness was also significantly higher in the EOM group compared with that in the control group ($P < 0.0001$). Eight patients out of 138 (5.8%) became deaf unilaterally (six patients) or bilaterally (two patients) after the onset of EOM.

Bronchial asthma was the most frequently associated disease with EOM ($P < 0.0001$). Among patients with bronchial asthma, approximately 30% (37/124) showed aspirin intolerance. Chronic rhinosinusitis and nasal polyposis also showed a significantly higher incidence in the EOM group than in controls ($P < 0.0001$). Twenty-seven patients out of 85 with nasal polyposis received endoscopic sinus surgery, and eosinophilic infiltration was histologically identified in polyps in all patients except one. Although allergic rhinitis was also frequently associated with EOM, the association rate was the lowest among the associated diseases studied ($P < 0.001$).

3.2. Sensitivity and specificity

The sensitivity, specificity and odds ratio of each characteristic in both groups are shown in Table 2. The following items showed extremely high odds ratios:

Table 2
Sensitivity and specificity of EOM and control groups.

	Sensitivity	Specificity	Odds ratio[a]	*P* value[b]
Bilaterality	0.826	0.731	12.93	0.5618
Highly viscous MEE	0.928	0.94	201.6	0.0007
Granulation tissue formation	0.321	0.963	12.62	0.1211
Resistance to treatment	0.928	0.948	232.2	0.0054
Deterioration of BCHL	0.591	0.515	1.54	0.2345
Associated diseases				
Bronchial asthma	0.899	0.985	584.5	0.0278
Chronic rhinosinusitis	0.756	0.896	26.49	0.2708
Nasal polyposis	0.62	0.963	42.17	0.0177
Allergic rhinitis	0.426	0.71	1.81	0.1087

EOM, eosinophilic otitis media; MEE, middle ear effusion; BCHL, bone conduction hearing level.
[a] Fisher's exact test.
[b] Multiple regression analysis.

association with bronchial asthma (odds ratio, 584.5), resistance to conventional treatment for otitis media (232.2), highly viscous middle ear effusion (201.6) and an association with nasal polyposis (42.17), followed by an association with chronic rhinosinusitis (26.49). The 4 items such as association with bronchial asthma, resistance to conventional treatment for otitis media, highly viscous middle ear effusion and an association with nasal polyposis also showed statistical significance between the two groups by multiple regression analysis.

3.3. Determination of diagnostic criteria

From the data described above, we tried to establish the diagnostic criteria of EOM. Eosinophils were identified histologically or cytologically in middle ear effusion or middle ear mucosa of all patients in the EOM group. If a patient had bacterial infection, the effusion contained neutorophils rather than eosinophils. In this case, the effusion was re-examined to detect eosinophils after controlling the infection. The presence of eosinophil-dominant effusion as shown in Fig. 1 should be considered as the major criterion to diagnose EOM.

With regard to minor criteria, we selected the following five items, which had high odds ratios: association with bronchial asthma, resistance to conventional treatment for otitis media, highly viscous middle ear effusion, association with nasal polyposis, and association with chronic rhinosinusitis. If the first three items were defined as minor criteria, the percentage of patients with EOM who showed positive for two items or more was 95.7%. Among the first four and five items, the percentages of being positive for two items or more were both 98.6% (Table 3). Therefore, if a patient is positive for at least two items out of the first four items (association with bronchial asthma, resistance to conventional treatment for otitis media, highly viscous middle ear effusion and association with nasal polyposis), they should be diagnosed with EOM. Diagnostic criteria have been accordingly proposed as shown in Table 4.

Table 3
Determination of minor criteria ($N = 138$).

No. of items	No. of cases (%)	95% CI
3 Items (highly viscous MEE, resistance to treatment, associated with bronchial asthma)		
Positive for ≥2 items	132 (95.65)	90.78–98.40
3 Items	109 (85.51)	71.23–85.46
4 Items (highly viscous MEE, resistance to treatment, associated with bronchial asthma, associated with nasal polyposis)		
Positive for ≥2 items	136 (98.55)	94.86–99.84
≥3 Items	119 (86.23)	79.33–91.51
4 Items	71 (51.45)	42.79–60.04
5 Items (highly viscous MEE, resistance to treatment, associated with bronchial asthma, associated with nasal polyposis, associated with chronic rhinosinusitis)		
Positive for ≥2 items	136 (98.55)	94.86–99.84
≥3 Items	125 (90.58)	84.43–94.89
≥4 Items	98 (71.01)	62.68–78.42
5 Items	70 (50.72)	42.08–59.34

MEE, middle ear effusion.

Table 4
Diagnostic criteria of eosinophilic otitis media (EOM).

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 + two or more minor criteria
Exclusion criteria: Churg-Strauss syndrome, hypereosinophilic syndrome

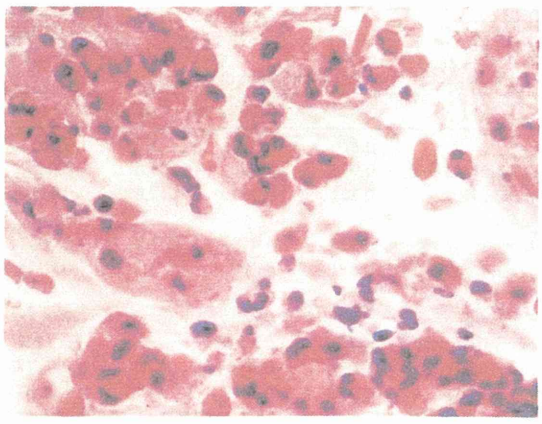

Fig. 1. A histological section of middle ear effusion from a patient with eosinophilic otitis media. Accumulation of eosinophils is seen in the effusion (hematoxyln and eosin stain).

4. Discussion

The members of the EOM study group, who are all ear specialists working in referral centers and have a lot of experience in treating EOM patients, collected data on the 138 EOM patients. The patients had been diagnosed with EOM because they had eosinophils middle ear effusion or middle ear mucosa and had typical characteristics of EOM. To clarify risk factors of EOM and clearly define diagnostic criteria, we compared clinical data of patients with non-eosinophilic OME and COM as controls.

First, we propose that detection of eosinophils in middle ear effusion is the major criterion for diagnosis of EOM. In the middle ear mucosa, eosinophils and EG2 positive cells are also present; however, the number of eosinophils is less than that in middle ear effusion [7]. Formalin-fixed, paraffin-embedded sections of middle ear effusion are useful for detecting eosinophilic mucin, and provide information of eosinophil activation and degranulation [10].

We selected clinical symptoms for minor criteria, because it is easier to diagnose EOM without any laboratory data or imaging. In addition, the detection of nasal polyposis needs only rhinoendoscopy, whereas the diagnosis of chronic rhinosinusitis needs both rhinoendoscopy and paranasal computed tomography. Middle ear effusion is usually viscous. However, the viscosity is reduced with bacterial infection. It is necessary to recheck the viscosity of middle ear effusion after controlling bacterial infection using antibiotics [10]. EOM is resistant to conventional treatment for otitis media including myringotomy and tympanostomy tube insertion for OME, administration of antibiotics, and surgical treatment such as tympanoplasty and mastoidectomy for COM, except for administration of systemic and topical administration of corticosteroids [11].

When Tomioka et al. [2] first reported cases of intractable OME and COM, they noticed the presence of bronchial asthma. In this study, only 10% of the patients had no association with bronchial asthma. EOM is mostly accompanied by adult-onset in both nonatopic and atopic asthma patients including aspirin intolerance, with the incidence being 30%. According to Jenkins et al. [12] the incidence of aspirin intolerance in bronchial asthma in adults is 21% when determined by oral provocation testing, and 3% by verbal history. Therefore, patients with aspirin intolerance are more likely to be associated with EOM. Association with nasal polyposis is another criterion. Multiple nasal polyps are found in the middle nasal meatus and the olfactory hiatus. The present study demonstrated that eosinophilic infiltration was histologically identified in the polyps of 26 of 27 patients (96%) who underwent endoscopic sinus surgery. This condition is called eosinophilic chronic rhinosinusitis [13–15]. Based on these results, the incidence of eosinophilic chronic rhinosinusitis with nasal polyposis in EOM is approximately 60%. In contrast, the incidence of EOM in eosinophilic chronic rhinosinusitis has been reported to be approximately 10% [10].

For the exclusion criteria, we selected two diseases, CSS and hypereosinophilic syndrome (HES). CSS is a rare multisystem autoimmune disease characterised by diffuse eosinophilic infiltration and necrotising vasculitis. Patients with CSS usually show longstanding rhinosinusitis, polyposis and bronchial asthma. There are several recent reports of patients with CSS who manifested intractable otitis media, characterised by viscous otorrhea, granulomatous eosinophilic infiltrate in the mastoid and middle ear with conductive hearing loss, and progressive sensorineural hearing loss [16–18]. These characteristics are similar to those seen in patients with EOM.

HES is characterised by marked blood or tissue eosinophilia and is defined by the presence of a peripheral blood eosinophil count of 1.5×10^9/L or greater for at least 6 months, and exclusion of both secondary and clonal eosinophilia. It involves various organs including the heart, lung, liver, skin and nervous system. It has been reported that the middle ear is also the target organ of HES, manifesting granulation tissue formation containing eosinophils [19,20]. A novel targeted treatment, including tyrosine kinase inhibitors and monoclonal antibodies, has been attempted and has altered the approach to the diagnosis and treatment of HES. These two diseases should be clearly differentiated from EOM because the pathogenesis of CSS and HES is completely different from EOM.

In our study, the incidence of deterioration of BCHL was significantly higher in the EOM than in the control group. It has also been shown that high-tone loss is more frequent and more severe in EOM patients than in age-matched COM control patients [9]. Nakagawa et al. [21] also reported that in cases of EOM, BCHLs at 4 kHz and 8 kHz are higher than those at lower frequencies. The cause of deterioration of BCHL in EOM has not been determined. From the results of our previous study, bacterial infection and eosinophilic inflammation in the middle ear might contribute to the deterioration of inner ear function [22].

It is important to inform a patient who is diagnosed with EOM based on the proposed criteria, that this type of otitis media persists for a long period, and without adequate treatment progressive or sudden onset of severe hearing loss may occur. It is also necessary to evaluate and monitor not only hearing acuity by audiometry but also the severity of the disease by imaging of the temporal bone and paranasal sinuses, and by laboratory tests such as serum IgE levels or eosinophil count in peripheral blood.

Currently, an effective treatment for EOM is administration of systemic and topical corticosteroids [11]. Other treatments such as a combination of anti-histaminergic agents and leukotriene receptor antagonists in addition to topical corticosteroids [21] or administration of ramatroban also result in the relief of subjective symptoms [23]. Since the number of patients was quite limited in these previous studies, further comparative studies will be required to prove the effectiveness of the medication for EOM. It is also possible that novel target treatment could bring about cure of EOM if genetic or molecular analysis unveils the pathogenesis of EOM.

5. Conclusion

A patient who shows OME or COM with eosinophil-dominant effusion (major criterion) and with two or more among the highest four items (minor criteria), can be diagnosed as having EOM. Patients with ear symptoms should have the proper diagnosis of EOM using the proposed diagnostic criteria, and then can receive adequate treatment, resulting in prevention of deterioration of hearing and QOL. In addition, the proposed diagnositic criteria are very useful to select subjects with or without EOM when a comparative study is conducted to evaluate the efficacy of medication and management for EOM.

Conflict of interest statement

We declare that we have no conflicts of interest to disclose.

Acknowledgements

The authors would like to thank Sachio Fukuda for the help of statistical analysis. The study was supported by a Grant-in-Aid for Scientific Research in Japan.

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好酸球性中耳炎の臨床

飯野ゆき子

●はじめに

1997年，Tomiokaらが気管支喘息に合併する難治性中耳炎を報告し[1]，貯留液から多数の好酸球が証明されたことから，好酸球性中耳炎という名称を提唱した．その後，症例も蓄積し，本疾患の臨床像も明らかになってきた．2003年には全国の基幹病院に対してアンケート調査が施行され，好酸球性中耳炎と診断された190例に関して詳細な検討が行われた[2]．さらに，2009年には好酸球性中耳炎study groupが結成され，個々の症例を集め，好酸球性中耳炎の診断基準を提唱するに至った[3]．また基礎的研究も相まって，新たな治療法を見出す努力もされている．

本疾患は，単に従来の中耳炎に対する治療に抵抗する難治性中耳炎というだけではなく，高度難聴（時には聾）を来す危険性の高い疾患という側面をもつ．よって本疾患を正確に診断し，かつ適切な治療をすることが重要である．本稿ではこの好酸球性中耳炎について，その臨床像と治療に関して解説する．

❶好酸球性中耳炎の臨床像

1. 性差・年齢

自験群47例では29例（62%）が女性である．疫学調査群でも61%と同等であった[2]．これらの結果から，好酸球性中耳炎はやや女性優位な疾患といえる．難聴あるいは耳漏を主訴とした初診時の年代は50歳代が最多であった．ただし，中耳炎が発症してから他の医療機関で治療を受けた後に本疾患が疑われ，紹介受診となる症例が多いため，発症年齢はこれより低いと思われる．

2. 中耳病態

中耳病態は滲出性中耳炎型と慢性穿孔性中耳炎型に大きく分類される．滲出性中耳炎型では鼓膜に穿孔はなく，鼓膜は黄色に見え貯留液の存在が示唆される．通常，成人の滲出性中耳炎の貯留液は漿液性が多い．しかし本疾患では非常に粘稠性が高く，膠状と表現される．

一方，慢性穿孔性中耳炎型はさまざまな原因で鼓膜に永久穿孔が生じた状態である．これはさらに2つのタイプに分類される．1つは単純穿孔型で，鼓膜穿孔から黄色で粘稠な貯留液が流出する．細菌感染が生じれば貯留液の粘稠度はむしろ減ずる．もう1つは高度の肉芽の増生を伴う肉芽型で，外耳道にまであふれ出る場合もあり，最も難治なタイプである．自験群47例に肉芽増生をみたものは16例（34%）であり，ほとんどが両側性であった．

3. 気管支喘息の合併

通常，成人発症型の気管支喘息を伴う．気管支喘息症例の1割前後に好酸球性中耳炎がみられるとの報告がある[4]．I型アレルギーの合併に関しては，自験例ではハウスダストや花粉など特異的抗原が同定されたものと同定されなかったものがほぼ同数であった．しかし，後者のなかでも血清総IgE値が高値であるものが約半数を占めた．アスピリン喘息の合併例も多い．気管支喘息非合併例でも貯留液が非常に粘稠で好酸球が証明される場合もある．しかし，これらの症例は比較的治療に良く反応し，それほど難治ではない印象がある．

4. 鼻副鼻腔疾患の合併

副鼻腔炎を高率に合併する．自験群47例中

Clinical Characteristics of Eosinophilic Otitis Media
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表1　好酸球性中耳炎診断基準

大項目 好酸球優位な中耳貯留液を有する滲出性中耳炎/慢性中耳炎 小項目 1）膠状の中耳貯留液 2）中耳炎に対する従来の治療に抵抗 3）気管支喘息の合併 4）鼻茸の合併
確実例：大項目＋小項目2つ以上 除外例：Churg-Strauss症候群，好酸球増多症候群

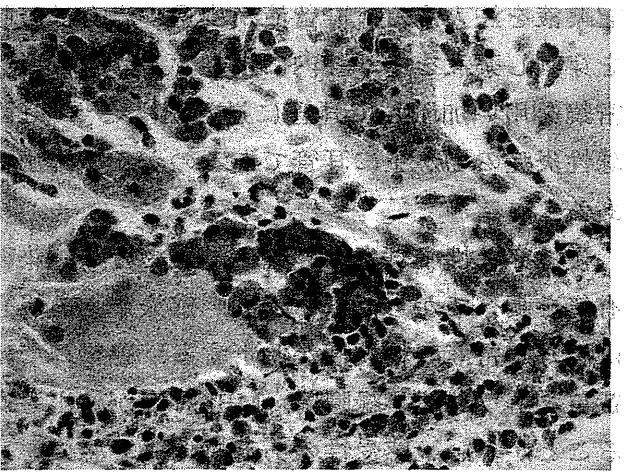

図1　好酸球性中耳炎例の中耳貯留液の病理組織
多数の好酸球が認められる．

40例（85%）に副鼻腔炎を認め，多くが鼻茸あるいは鼻粘膜のポリポイド変性をみた．また約半数に鼻手術の既往を認めたが，これら手術例では鼻茸の再発を認めるものが多い．疫学調査でも74%の症例に副鼻腔炎の合併をみている[2]．鼻汁や鼻茸に多数の好酸球の浸潤が認められ，また上顎洞よりはむしろ篩骨洞病変が強いことから，好酸球性副鼻腔炎と考えられる．好酸球性副鼻腔炎症例における好酸球性中耳炎の合併率は約1割との報告がある[5]．

5. 聴力変化

初期は伝音難聴であるが，経過中に骨導閾値が上昇し，混合難聴を呈してくる．疫学調査では骨導閾値上昇をみたものは47%を占め，そのうち6%が聾となっている[2,6]．自験群でも47例中3例（6.4%）で一側が聾となっている．しかし，長期にわたって聴力が安定しているものから，急激に悪化して聾になるものまで経過はさまざまである．好酸球性中耳炎と診断がついた時点で，患者には急激に難聴が進行し，聾になる危険性がある疾患であることを説明する必要がある．骨導閾値上昇を来す原因は不明であるが，高音域から障害される点や前述した臨床的特徴から，内耳窓を介して好酸球性炎症あるいは細菌感染による炎症産物が内耳に到達した結果生じるものと考えられる[7]．

❷好酸球性中耳炎の診断

前述したように，2009年に好酸球性中耳炎study groupが結成され，おのおのが診断，治療した好酸球性中耳炎症例138例の臨床像に関し詳細に分析した．また，対照例として非好酸球性中耳炎症例を同様に分析して統計学的な解析を行い，表1のような診断基準を提唱した[3]．まず，大項目として中耳貯留液中に好酸球を証明する必要がある（図1）．小項目に関しては，特に煩雑な検査もいらず，主に病歴と臨床所見のみで診断できる点が非常に簡便と考える．貯留液中の好酸球はスメアでの細胞診か，貯留液をそのままホルマリンで固定し組織診断する．後者のほうが好酸球の出現程度や脱顆粒の状況が把握でき，有益な情報が得られる．

❸好酸球性中耳炎の治療

全身的あるいは局所での副腎皮質ステロイドの投与が有効である．なるべく副腎皮質ステロイドの鼓室内投与でコントロールしたい．鼓室内投与には，重症度に応じてトリアムシノロンアセトニド注射薬，デキサメタゾン注射薬，ベタメタゾンの点耳薬を用いる．鼓膜に穿孔のない滲出性中耳炎型で貯留液が大量に存在する場合は，まず鼓膜切開を行い貯留液を排出後，上

記薬液を注入する．貯留液が少量の場合は鼓膜を穿刺し薬液を中耳腔内に投与する．薬液は気密鏡を用い加圧して耳管に逆通気する[8]．好酸球性炎症の場が主に耳管であるのがその理由である．

慢性穿孔性中耳炎穿孔型に対しては，感染の有無を調べてから治療を行う．感染がある場合は中耳貯留液の粘稠性が低下する．感染耳では黄色ブドウ球菌，緑膿菌，MRSA等が検出されることが多い．感受性のある抗菌薬で感染をコントロール後，鼓膜穿孔から副腎皮質ステロイドの鼓室内注入を行う．

慢性穿孔性中耳炎肉芽型では鼓室内に薬液注入のスペースがないため，鼓膜穿孔からこれらの肉芽や肥厚粘膜を裁除鉗子などで除去しスペースを作る．鼓膜穿孔が小さく，かつ鼓室粘膜の肥厚が高度の場合はプレドニゾロンの内服を行い，ある程度のスペースを作ってから同様の治療を行う．いずれのタイプでも鼓室内注入を行う頻度は貯留液の再発をみながら行うため，各症例によって異なる．

好酸球性中耳炎では鼻副鼻腔炎を合併することが多いため，鼻副鼻腔炎に対する治療も重要である．副腎皮質ステロイド鼻噴霧薬の倍量投与が有効である[9]．また，松原はヘパリンを用いた中耳腔洗浄の有効性を報告[10]している．ヘパリンには好酸球の遊走抑制作用や，ECP（eosinophil cationic protein）やMBPなどの好酸球由来細胞性障害蛋白の中和作用があることが知られている．

●おわりに

日本における気管支喘息の有病率が10%内外といわれる今日，かなり多数の好酸球性中耳炎患者が存在する可能性が高い．気管支喘息患者を扱う医師が好酸球性中耳炎の概念を正しく認識し理解していただければ幸いである．

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5 好酸球性副鼻腔炎・好酸球性中耳炎

Eosinophilic chronic rhinosinusitis・
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Key words：好酸球性副鼻腔炎，好酸球性中耳炎，喘息，好酸球性炎症，気道

Abstract

好酸球性副鼻腔炎と好酸球性中耳炎は上気道の慢性好酸球性炎症である。自験例の検討では，好酸球性副鼻腔炎典型例の55％の症例，好酸球性中耳炎の94％の症例が喘息を合併していた。好酸球性中耳炎の平均発症年齢は慢性副鼻腔炎や喘息より約10年遅れて50歳前後であった。好酸球性副鼻腔炎は難治で易再発性であるが，手術と術後の鼻腔洗浄および鼻噴霧用ステロイド治療を継続し，再発時に必要に応じて経口ステロイドを短期間用いればコントロールは良好である。好酸球性中耳炎治療もステロイドの鼓室内注入を基本とし，増悪時には経口ステロイドを用いる。好酸球性中耳炎では，慢性の好酸球性炎症や細菌感染の合併などにより感音難聴を生じることもある。

はじめに

好酸球性副鼻腔炎と好酸球性中耳炎は1990年代中頃から注目されるようになった疾患である。両疾患は喘息を合併することが多く，全身性の特異的IgEには必ずしも依存しない慢性の好酸球性炎症で，従来型の慢性副鼻腔炎や滲出性中耳炎とは臨床的特徴や治療法が異なる。最近では学会や医学雑誌等で取り上げられることも多く，典型例の診断や治療についてはほぼコンセンサスが得られている。しかし，好酸球性副鼻腔炎・好酸球性中耳炎の定義や診断基準はいまだ確立されておらず，多施設共同研究による詳細な疫学データの集積はない。

一方，欧米においても慢性副鼻腔炎の細分類に関しては議論があり，鼻茸の有無でchronic rhinosinusitis with nasal polyps (CRSwNP)とchronic rhinosinusitis without nasal polyp (CRSsNP)の二つに分けているに過ぎない[1)2)]。このように現時点では慢性副鼻腔炎の多様な病態を明確に細分化し定義することは難しい。さらに好酸球性中耳炎は日本から発信された疾患概念であり，好酸球性中耳炎に関する欧米からの研究報告はほとんどない。

そこで本稿では，自験例を中心に好酸球性副鼻腔炎・好酸球性中耳炎の臨床的特徴を簡単に紹介し，喘息との関係も含めて両疾患の

表1　好酸球性副鼻腔炎の臨床的特徴[7]
（従来型の慢性副鼻腔炎との比較）

	好酸球性副鼻腔炎	従来型の慢性副鼻腔炎 （非好酸球性副鼻腔炎）
症状	早期より嗅覚障害、鼻閉 など	鼻汁、後鼻漏、鼻閉 など
鼻内所見	粘稠性鼻汁、多発性鼻茸	膿性鼻汁、中鼻道鼻茸
画像所見（副鼻腔陰影）	初期には篩骨洞優位	初期には上顎洞優位
血液所見	好酸球増多	特になし
鼻過敏症	経過中に症状を示す症例が多い	少ない
気管支喘息の合併	成人発症の非アトピー型が多い アスピリン喘息、Churg-Strauss	少ない
マクロライド療法	効果は不明	有効
全身性ステロイド	再発例に著効	効果は不明
術後の鼻茸再発	高率	少ない
鼻茸の組織学的所見	著明な好酸球浸潤、リンパ球浸潤、 基底膜肥厚	リンパ球浸潤、鼻腺の増生

ナチュラル・ヒストリーを考察する。なお，病態については他総説[3)-5)]を参照されたい。

1. 好酸球性副鼻腔炎の臨床的特徴[3)4)]

慢性副鼻腔炎治療に14員環マクロライド系抗生物質の少量長期投与（マクロライド療法）と内視鏡下副鼻腔手術（endoscopic sinus surgery：ESS）が1990年頃から導入され，慢性副鼻腔炎の治療成績は向上した。一方でこれらの新しい治療法を用いても難治な慢性副鼻腔炎が注目されるようになり，鼻茸中に著明な好酸球浸潤がみられることから，2001年に好酸球性副鼻腔炎という名称が提唱された[6)]。

好酸球性副鼻腔炎の臨床像は従来型の慢性副鼻腔炎（いわゆる蓄膿症タイプ）と多くの点で異なる（表1）[7)]。早期から嗅覚障害を訴え，鼻所見では両側性に多発性の浮腫状鼻茸をみることが多い。画像検査では上顎洞よりも篩骨洞に陰影が強く，従来型の慢性副鼻腔炎が上顎洞に陰影が強いのとは対照的である。そして好酸球性副鼻腔炎で何よりも特徴的なのは，鼻茸中の著明な好酸球浸潤である。さらに末梢血好酸球増多を認め，その程度は鼻茸中の好酸球浸潤に相関する。

臨床経過も特徴的で，マクロライド療法は効果がなくESS手術後にも再発傾向が強いが，鼻腔洗浄や鼻噴霧ステロイドは再発予防に有効であり，再発鼻茸には経口ステロイドが著効する。

このような典型的な経過を示せば診断は確定するが，我々は特徴的なCT所見と末梢血好酸球増多のみから術前に従来型の慢性副鼻腔炎と鑑別する基準を提唱している[8)]。

好発年齢は40歳代で成人発症の非アトピー型喘息を合併する症例も多い。アスピリン喘息に合併する慢性副鼻腔炎はほとんどが好