Eosinophilic Chronic Rhinosinusitis in Japan

Junichi Ishitoya¹, Yasunori Sakuma¹ and Mamoru Tsukuda²

ABSTRACT

Chronic rhinosinusitis is a heterogeneous disease. In Europe and the United States, it has recently been divided into two subgroups: chronic rhinosinusitis with nasal polyps (CRSwNP) and chronic rhinosinusitis without nasal polyps (CRSsNP). The majority of CRSwNP cases have a strong tendency to recur after surgery and show eosinophil-dominant inflammation. However, this definition has proved difficult to apply in Japan and East Asia, because more than half of the CRSwNP cases do not exhibit eosinophil-dominant inflammation in these areas of the world. In Japan in the 1990s, refractory CRSwNP to the standard treatment was focused on in clinical studies and the term “eosinophilic chronic rhinosinusitis” (ECRS) was introduced to identify this subgroup of chronic rhinosinusitis in 2001.

ECRS is different from non-ECRS in terms of many clinical features: symptom appearance, occurrence site of nasal polyps, CT scan findings, the histology of nasal polyps, blood examination findings, clinical course after surgery, and co-morbid asthma, etc. In this review, we describe these clinical features and mention how to make a clinical diagnosis of ECRS as well as how to treat it. Finally, we discuss the pathophysiology of ECRS. The concept of ECRS in Japan would be applicable for CRSwNP in other countries including Europe and the United States.

KEY WORDS
chronic rhinosinusitis, clinical feature, diagnosis, eosinophilic chronic rhinosinusitis, eosinophils

INTRODUCTION

The term chronic sinusitis is usually used for chronic inflammation of the paranasal sinus in Japan. However, because most cases of chronic sinusitis have a proceeding or concomitant involvement of the nasal cavity, and because the term chronic rhinosinusitis is more common in English papers rather than the term chronic sinusitis, the term chronic rhinosinusitis is used in this review.

Although chronic rhinosinusitis is a very common and heterogeneous disease, there are many unsolved issues surrounding its pathophysiology, subclassification, and treatment. While many studies have tried to subclassify chronic rhinosinusitis based on its pathophysiology, a clear definition that can distinguish each subgroup of the disease has not yet been established. In Europe and the United States, chronic rhinosinusitis has been recently divided into two subgroups: chronic rhinosinusitis with polyps (CRSwNP) and chronic rhinosinusitis without polyps (CRSsNP).¹² In CRSwNP patients, there is a strong tendency for recurrence after surgery and a pronounced presence of both eosinophils and interleukin-5 (IL-5) in the nasal polyps.² This definition is simple and convenient for use in clinical studies and clinical practice, but it has proved difficult to apply in Japan and in East Asia (Korea and southern China).³⁶ In these areas, more than half of the CRSwNP cases do not exhibit eosinophil-dominant inflammation. Therefore, another definition for discussion of heterogeneity of chronic rhinosinusitis may be necessary in East Asia. Moreover, chronic rhinosinusitis is often associated with lower respiratory diseases. The association between chronic rhinosinusitis and asthma is clinically important.

HETEROGENEITY OF CHRONIC RHINOSINUSITIS

Chronic rhinosinusitis is defined as chronic inflam-
The diagnosis of chronic rhinosinusitis is based on these symptoms lasting longer than 3 months and sinus opacification in plain sinus x-ray or CT scan. Chronic rhinosinusitis is a heterogeneous disease and patients exhibit various signs and symptoms. The variety of nasal secretions, for example, includes serous, mucous, purulent and very viscous. Inflammatory cells in nasal secretions are also heterogeneous. Figure 1 shows cytology of nasal secretions. Nasal secretions of some patients contain many neutrophils while others contain degraded eosinophils. It is suspected that the former is neutrophilic inflammation and the latter is eosinophilic inflammation. The opacification pattern of sinus imaging is also heterogeneous. If we compare the degree of opacification of the maxillary and ethmoid sinus, some patients show ethmoid sinus-dominant opacification while others show maxillary sinus-dominant opacification. If the disease condition becomes more severe, both types of patients exhibit pan-sinusitis pattern. Figure 2 indicates different sinus opacification patterns.

Low-dose and long-term administration of macrolide antibiotics (macrolide therapy) is basic treatment for chronic rhinosinusitis in Japan, and response of patients with chronic rhinosinusitis to macrolide therapy is also heterogeneous. Macrolide therapy was discovered in Japan as a treatment for diffuse panbronchitis (DPB), and in the late 1980s was shown to be effective for chronic rhinosinusitis associated with DPB. Then, macrolide therapy was proven to
be an effective therapy for chronic rhinosinusitis without DPB. In Japan in the 1990s, macrolide therapy was considered to be the first line of treatment, and the combination of macrolide therapy and newly developed endoscopic sinus surgery (ESS) was the gold standard for chronic rhinosinusitis treatment. After it became possible to successfully improve most chronic rhinosinusitis, understanding of the clinical and histological features of refractory types of the disease in response to this combined therapy has progressed. As one of the features associated with the affliction is abundant eosinophil infiltration in nasal polyps, the term eosinophilic chronic rhinosinusitis (ECRS) was introduced to identify this subgroup of chronic rhinosinusitis in Japan in 2001. In this review, chronic rhinosinusitis with nasal polyps (CRSwNP) is discussed, and the terms ECRS and non-ECRS as a subgroup of CRSwNP are described in the following sections. In Japan, non-ECRS had been the most common type of CRSwNP up until 30 years ago, and nasal polyps of non-ECRS do not exhibit abundant eosinophil infiltration. Patients with non-ECRS exhibit purulent nasal discharge containing neutrophils, and its inflammation is assumed to be non-eosinophilic.

**CLINICAL FEATURES OF EOSINOPHILIC CHRONIC RHINOSINUSITIS (ECRS)**

As ECRS was recognized as refractory chronic rhinosinusitis despite combination of macrolide therapy and ESS in Japan, one of the most characteristic clinical features is a strong tendency for recurrence after ESS. Clinical features of ECRS are listed in Table 1 in comparison with non-ECRS.

**SYMPTOMS**

While a common symptom of ECRS patients is nasal congestion, reduction in or loss of the sense of smell precedes nasal congestion in many cases of the patients. This smell disorder that appears early in the illness is characteristic for ECRS as compared to non-ECRS. ECRS patients may exhibit other nasal symptoms including nasal discharge, postnasal drip, facial pressure, or headache. Nasal discharge of ECRS patients is usually not purulent.

**NASAL POLYPS**

While nasal polyps are raised from the middle meatus in most non-ECRS patients, ECRS patients can exhibit bilateral nasal polyps that are often found in both the middle meatus and inside of the middle meatus. This could explain why ECRS patients complain of smell disorder early in the illness.

**CT SCAN FINDINGS**

It has been previously reported that CT scan images of ECRS patients show ethmoid sinus-dominant opacification. In our recent study, it was found that all CT scores of sinuses, except for the maxillary sinus, were significantly different between ECRS and non-ECRS. The most apparent differences in CT images of ECRS compared to non-ECRS images was involvement of the posterior ethmoid sinus. CT images from the early stage of ECRS can show opacification of posterior ethmoid sinus and the olfactory cleft.

The middle meatus or ostiomeatal complex (OMC) has been demonstrated to have a fundamental role in the pathogenesis of non-ECRS. If drainage from the sinus to middle meatus or OMC is impaired, the sinus becomes secondarily involved. According to this pathogenesis, sinuses that are most likely to be affected are maxillary sinus and anterior ethmoid sinus. These sinuses connect to the middle meatus or OMC through small ostia. In ECRS patients, however, posterior ethmoid sinuses that do not directly connect with the middle meatus are involved in similar to anterior ethmoid sinuses even in the early stage. This suggests that pathological changes in middle meatus or OMC might be of less importance for the pathogenesis of ECRS. Namely, the pathogenesis of ECRS is different from that of non-ECRS. Opacification of the olfactory cleft is also characteristics for ECRS.

**Table 1** Comparison between ECRS and non-ECRS

<table>
<thead>
<tr>
<th>Characteristic symptoms</th>
<th>Eosinophilic Chronic Rhinosinusitis (ECRS)</th>
<th>Non-Eosinophilic Chronic Rhinosinusitis (non-ECRS)</th>
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<tbody>
<tr>
<td>Endonasal findings</td>
<td>reduction/loss of smell in early stages</td>
<td>mucopurulent discharge, nasal polyp in middle meatus</td>
</tr>
<tr>
<td>CT findings</td>
<td>ethmoid predominance (in early stages)</td>
<td>maxillary predominance (in early stages)</td>
</tr>
<tr>
<td>Blood examination</td>
<td>eosinophilia</td>
<td>-</td>
</tr>
<tr>
<td>Coexistence of asthma</td>
<td>frequent</td>
<td>less-frequent</td>
</tr>
<tr>
<td>Macrolide therapy</td>
<td>not effective</td>
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<tr>
<td>Recurrent rate of nasal polyps</td>
<td>very high</td>
<td>low</td>
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<tr>
<td>Systemic steroid for recurrence</td>
<td>higher efficacy</td>
<td>unclear</td>
</tr>
<tr>
<td>Histology of nasal polyps</td>
<td>eosinophilia, lymphocyte infiltration, basement membrane thickening (remodeling)</td>
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**SYSTEMIC STEROID FOR RECURRENCE**

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<th>Recurrent rate of nasal polyps</th>
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This pathological change may exhibit smell disorder in the early stage of ECRS.

**HISTOLOGY OF NASAL POLYPS**

Histological findings of nasal polyps reveal most characteristic features of ECRS. Figure 3 demonstrates massive infiltration of eosinophils in lamina propria, a thick basement membrane, and increased goblet cells. These findings are similar to the remodeling of bronchial mucosa in asthmatic patients. This massive tissue eosinophilia is a reason why this type of CRSwNP is called eosinophilic chronic rhinosinusitis in Japan. Most infiltrating inflammatory cells in nasal polyps in non-ECRS are lymphocytes (plasma cells) (Fig. 3). Even though most inflammatory cells in nasal polyps are lymphocytes, nasal smear cytology of non-ECRS patients shows neutrophilic inflammation.

**BLOOD EXAMINATION**

Peripheral blood eosinophilia is a characteristic blood finding for ECRS. Peripheral blood eosinophil counts significantly correlate with infiltrating eosinophil counts in nasal polyps (Fig. 4). Therefore, peripheral blood eosinophilia is of diagnostic value for ECRS. There is no other routine blood examination which indicates ECRS. Some ECRS patients show total or specific IgE elevation, but more than half of ECRS patients do not exhibit an atopic condition.

**CLINICAL COURSE**

A tendency for recurrence after ESS despite macrolide therapy is of diagnostic value for ECRS. Even if there are no recurrent nasal polyps, after surgery ECRS patients often exhibit edematous changes of sinonasal mucosa in proximity to the middle turbinate. Regardless of such strong tendency of recurrence,
Eosinophilic Chronic Rhinosinusitis in Japan

Table 2 Practical diagnosis for eosinophilic chronic rhinosinusitis

<table>
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<tr>
<th>(1) Clinical history</th>
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<tr>
<td>· Nasal symptoms of chronic rhinosinusitis</td>
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<tr>
<td>· Reduction and/or loss of smell in the early stages</td>
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<tr>
<th>(2) Endonasal examination</th>
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<tr>
<td>· Bilateral polyps (polyposis)</td>
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<td>· High viscous secretion</td>
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<table>
<thead>
<tr>
<th>(3) Clinical examinations</th>
</tr>
</thead>
<tbody>
<tr>
<td>· Peripheral blood eosinophilia</td>
</tr>
<tr>
<td>· CT findings (Ethmoid sinus dominant opacification)</td>
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<th>4. Histological finding</th>
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<tr>
<td>· Massive eosinophilic infiltration in nasal polyps</td>
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<th>5. Postoperative course</th>
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</thead>
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<tr>
<td>· Strong tendency to recur after ESS</td>
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<td>· Effectiveness of systemic steroid for treatment of recurrence</td>
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nasal symptoms of ECRS patients who have undergone ESS are usually well controlled with adequate postoperative treatment described in the following section.

These clinical features resemble CRSwNP (nasal polyposis) as defined in Europe and the United States. In 1995, Klapan and Culo reported that the incidence of polyposis recurrence was significantly higher in patients with increased LTC4 level in nasal polyps. Because the CysLTs level in nasal polyps is an indicator for severity of eosinophilic inflammation, the tendency for recurrence after surgery may be related to the severity of eosinophilic inflammation.

**CO-MORBID ASTHMA**

Asthma co-morbidity is often seen in ECRS. The severity of asthma which is associated with ECRS is usually moderate to severe, and most patients with chronic rhinosinusitis associated with aspirin-intolerant asthma have ECRS. If patients with chronic rhinosinusitis have non-atopic asthma, ECRS might be suspected. However, because about half of ECRS is not associated with asthma, co-morbidity with asthma may not be a diagnostic criterion for ECRS. Even if ECRS patients do not present with asthma, most exhibit airway hyper-responsiveness. This suggests that such ECRS patients are at high risk for developing asthma.

**CLINICAL DIAGNOSIS FOR ECRS**

A clear definition of and diagnostic criteria for ECRS have still not been established in Japan, Europe, or the United States. However, consensus for clinical diagnosis of ECRS is now building in Japan. It is not difficult to diagnose ECRS with the combination of several clinical features as mentioned above (Table 1). Among them, a strong tendency to recur after ESS could be very important. However, this criterion cannot be used for patients who do not undergo surgery.

How to diagnose ECRS precisely with usual clinical diagnostic tools was studied, and the combination of both CT findings and peripheral blood eosinophilia achieved high diagnostic value. If peripheral blood eosinophilia and CT scoring for both posterior ethmoid and olfactory cleft are used as diagnostic criteria, sensitivity and specificity for diagnosis of ECRS are very high. Furthermore, if other clinical features are also taken into consideration in addition to these criteria (Table 2), accurate clinical diagnosis of ECRS could be made in an outpatient clinic.

**TREATMENT FOR ECRS**

ECRS is refractory to conservative medical management. Systemic steroids reduce nasal symptoms of ECRS. However, it is difficult to improve such symptoms completely and to maintain a good condition for a long time. Therefore, surgical treatment (ESS) is an important first-line treatment. The purpose of the surgery is not only to remove the nasal polyps but also to open sinuses widely to enhance the effect of post-operative maintenance therapy. Such post-operative therapy is very important for control of chronic sinonasal inflammation.

The post-operative maintenance therapy includes nasal irrigation, intranasal steroid administration, and oral anti-allergic medicine (anti-leukotrienes). Nasal irrigation and intranasal steroids are basic treatments, and oral medicines are added according to nasal condition of patients as needed. Nasal irrigation is thought to wash out microorganisms and chemical mediators, inducing eosinophilic inflammation like CysLTs and IL-5. If nasal polyps recur despite these maintenance therapies, a relatively high dose of oral steroid (0.5 mg/kg) for 1 or 2 weeks is very effective to cause recurrent nasal polyps to disappear.

While treatment that can bring complete relief of symptoms with ECRS has not yet been established, an adequate combination of surgery and post-operative therapy can maintain a good condition in
most ECRS patients.

**PATHOPHYSIOLOGY OF ECRS**

The pathophysiology of ECRS is still unknown. Because most CRSwNP in Europe and the United States seems to correspond to ECRS in Japan, many studies for CRSwNP are of great help in discussing the pathophysiology of ECRS in Japan.

A primary question surrounding the pathophysiology of ECRS is the mechanism that induces marked eosinophilic inflammation of sinonasal mucosa. The approach to consider this question can be roughly divided in two ways: activation eosinophils and impaired suppression of aggravated inflammation.

Eosinophil counts are significantly higher in nasal polyps of ECRS compared to non-ECRS, but that is independent from atopic status. Some patients with ECRS have IgE specific to common inhalant antigens, but atopic status is not always the case.

Many of the following inflammatory mediators have been reported to be related to eosinophilic inflammation in sinonasal mucosa including cytokines (IL-5, GM-CSF, chemokines (eotaxins) and chemical mediator (CysLTs)). Because eotaxin is produced from epithelial cells and fibroblasts, non-specific stimuli could induce eosinophilic inflammation by stimulating these cells.

Bachert et al. reported correlations between IgE specific to a variety of allergens including Staphylococcus aureus enterotoxins and eosinophilic inflammation in nasal polyps of non-atopic patients. Recently, Sheahan et al. showed that more than half of CRSwNP polyps demonstrated a polyclonal IgE response in sinonasal mucosa and suggested that local mucosal IgE specific to common inhalant allergens play an important role for eosinophilic inflammation even in non-atopic CRSwNP patients. Namely, locally produced IgE by Staphylococcus aureus enterotoxins or other inhalant allergens could induce eosinophilic inflammation of sinonasal mucosa independently with systemic atopy.

In the United States, fungi have received much attention as candidates for inducing ECRS and allergic fungal rhinosinusitis (AFRS, a subgroup of ECRS). Diagnostic criteria for AFRS include type 1 hypersensitivity to fungi, nasal polyposis, and eosinophilic mucin containing fungal elements. Although there is considerable overlap in findings between AFSR and ECRS, the clinical features of AFRS are different from ECRS. In Japan, AFRS is relatively rare compared to ECRS; therefore, the comparison between them is not discussed further in this article.

Fungi have also been postulated to be a trigger for eosinophilic inflammation of sinonasal mucosa even in patients who do not have type I hypersensitivity to fungi. There is a report that suggests non-atopic eosinophilia or local IgE production by fungi in sinonasal mucosa. However, if more sensitive diagnostic techniques are used, fungi could be detected in the nasal passages of not only patients with ECRS but also in normal controls. Fungi could be important in the pathophysiology of ECRS, but further studies are necessary.

**CONCLUSION**

ECRS is a subgroup of CRSwNP in Japan. Although a consensus surrounding diagnosis and treatment for ECRS has been building, a clear definition should be established in the near future, and diagnostic criteria based on these criteria should follow. Moreover, because the heterogeneous presentation of chronic rhinosinusitis in Japan and East Asia is different from that in Europe and the United States, a global consensus for subclassification of chronic rhinosinusitis should be discussed.

**REFERENCES**

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