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MINIREVIEWS

Eosinophilic chronic rhinosinusitis in East Asians

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Abstract

Chronic rhinosinusitis (CRS) is a common disease worldwide, with a prevalence rate of 5%-15% in the general population. CRS is currently classified into two types: CRS with and without nasal polyps. CRS may also be divided into eosinophilic CRS (ECRS) and non-ECRS subtypes based on the presence of tissue eosinophilic infiltration or not. There are significant geographic and ethnic differences in the tissue eosinophilic infiltration, which is predominant in Western white patients and less common in East Asians, despite an increasing tendency for its prevalence in East Asia countries. ECRS differs significantly from non-ECRS in clinical characteristics, treatment outcomes and strategies, and underlying pathogenic mechanisms. ECRS commonly demonstrates more severe symptoms, polyp diseases with a higher incidence of bilateral polyps and sinonasal diseases on computed tomography, and the increase in blood eosinophils. ECRS is considered a special and recalcitrant subtype of CRS, commonly with poor treatment outcomes compared to non-ECRS. The differentiation of specific subtypes and clinical features of CRS will be important for developing novel treatment strategies and improving treatment outcomes for individual phenotypes of CRS. This review discusses clinical features, diagnosis, treatment and prognosis of ECRS in East Asians.

Key words: Chronic rhinosinusitis; Eosinophilic chronic rhinosinusitis; Eosinophils; Chronic rhinosinusitis with nasal polyps; Nasal polyps

Core tip: Chronic rhinosinusitis (CRS) is a common disease and currently classified into two types based on presence or absence of nasal polyps. CRS may also be subtyped into eosinophilic CRS (ECRS) and non-ECRS according to the presence of predominant tissue eosinophilic infiltration or not. ECRS differs significantly from non-ECRS in clinical characteristics, treatment outcomes and strategies, and underlying pathogenic mechanisms. ECRS is considered a special and recalcitrant subtype of CRS. The identification of ECRS is helpful to develop treatment strategies for this CRS subtype. Herein we review the clinical features, diagnosis, treatment and prognosis of ECRS in East Asians.

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INTRODUCTION

Chronic rhinosinusitis (CRS) is one of the most common chronic diseases worldwide, with a prevalence rate of 5%-15% in the general population in Europe and the United States[1] and 7% in South Korea[2]. CRS remains a significant public health problem with a considerable socioeconomic burden[3]. In the current practice guidelines of Europe, the United States and China, CRS is classified into two types based on the presence or absence of nasal polyps: CRS with nasal polyps (CRSwNP) and CRS without nasal polyps (CRSsNP)[1,4,5]. Eosinophilic inflammation is considered a major pathologic hallmark of CRS. Histological studies demonstrate the predominant tissue eosinophilic infiltration with a high proportion of CRS

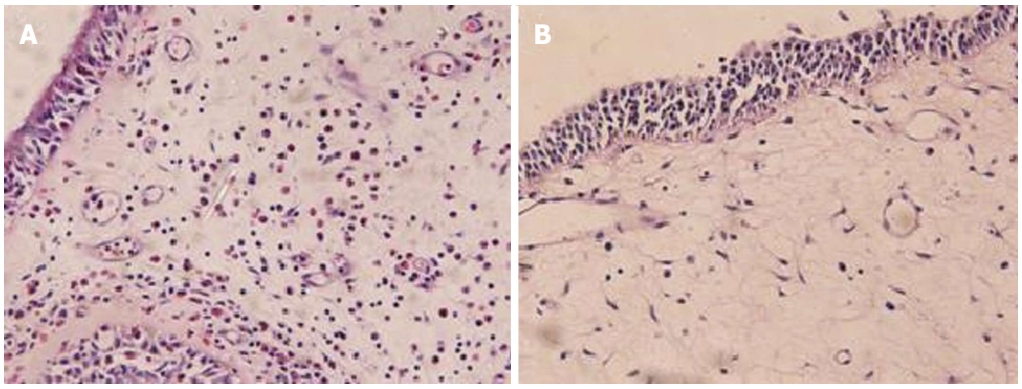

Figure 1 Hematoxylin and eosin staining for nasal polyp tissues. Predominant eosinophil infiltration is showed in the subtype of eosinophilic chronic rhinosinusitis with nasal polyps (A), but other forms of inflammatory cell infiltration in the subtype of non-eosinophilic chronic rhinosinusitis with nasal polyps (B) (× 400).

cases, most prominently with CRSwNP cases[1]. Thus, CRS may be classified into two subtypes: eosinophilic CRS (ECRS) and non-eosinophilic CRS (NECRS). Similarly, CRSwNP may also be subclassified into ECRSwNP and NECRSwNP[6-19]. However, the tissue eosinophilic infiltration in CRS shows significant geographic and ethnic differences. Eosinophilic infiltration is predominantly observed in Western white patients with CRS, accounting for more than 80% of CRS cases[1,4,18], while the eosinophilic phenotype is less than 50% of CRS cases in East Asia countries including Japan[13-15,20], South Korea[17,21,22] and China[11,16,23,24]. However, recent studies indicate an increasing tendency for the prevalence of ECRS in these Asia countries[12,13,15,20,21,25]. Studies show that ECRS differs significantly from NECRS in clinical characteristics, underlying pathogenic mechanisms, treatment outcomes and strategies[1,6,10,11,13,15,16,20,26-28]. ECRS is considered a special subtype of CRS[10,13,15] and also a subtype of recalcitrant CRS, which commonly has worse disease severity[8,18,19,29] and poorer treatment outcomes[19,28,30] compared to NECRS. For example, ECRSwNP is refractory to the combined treatments of endoscopic sinus surgery (ESS) and macrolide therapy and shows a strong tendency for recurrence after surgery but responds to systemic steroid therapy[13-15]. Thus, identifying specific subtypes of CRS and underlying pathogenic mechanisms will be important for developing novel treatment strategies and improving treatment outcomes for individual phenotypes of CRS[10,29].

ROLES OF EOSINOPHILS IN ECRS

CRS is a heterogeneous disease to which numerous etiologies contributed. Although intensive investigations have been performed, the etiology, pathogenesis and underlying mechanisms of CRS are not fully understood[1,15,31,32]. The dominant eosinophilic inflammation for CRS indicates that eosinophils play a key role in the pathogenesis of CRS, especially in CRSwNP[1], although many kinds of other inflammatory cells including neutrophils, mass cells, lymphocytes and plasma cells also have important roles in the pathogenesis of CRS[27,33] (Figure 1).

Eosinophils develop from $CD34^+$ progenitors in the bone marrow and migrate into the bloodstream, and they are recruited to disease sites by chemokines or cytokines, where eosinophils can perform and participate in a variety of functions, including antigen presentation, cytokine or chemokine production, and secretion of granule mediators[34-36]. The ability of eosinophils to process and present antigens has been generally underestimated and this function can be added to the growing list of mechanisms by which eosinophils regulate the immune system[34]. Eosinophils store preformed cytokines in granules that can be released rapidly upon antigenic provocation[36]. These eosinophil-derived cytokines can be T helper 2 (Th2) cytokines such as interleukin (IL)-13 that act directly on T cells, as well as other inflammatory cytokines that can prime antigen presenting cells and the vascular endothelium to secrete chemokines and cytokines that recruit and activate T cells[34].

Studies indicate significant roles of T cell regulation in CRS. CRS appears to be a disease mediated by $CD4^+$ T cells that can be functionally divided into Th1 or Th2 phenotype based on their patterns of cytokine secretion. It is found that among West white patients with CRS, CRSsNP is characterized by Th1 polarization, whereas CRSwNP by predominant Th2, with high levels of Th2-type cytokines including IL-4, IL-5 and IL-13[37]. CRSwNP also is characterized by a Th2-driven eosinophilic inflammation in tissue[37,38]. However, studies suggest that East Asians with CRSwNP present different immunopathologic features compared with West white patients[17,24,39]. For example, CRSwNP in Chinese demonstrates a Th1/Th17 cell pattern with minor eosinophilic inflammation[24]. Th2-dominated reactions can only be found in ECRSwNP instead of all CRSwNP cases, suggesting that Th cell responses may exert different impacts on the pathogenesis of ECRSwNP and NECRSwNP[16,17,24]. There are interactions between T cells and eosinophils. It is conventionally viewed that the T cell–eosinophil interactions are primarily based on the activation of eosinophils by T cells *via* cytokines, but it is suggested that eosinophils also have the capacity to activate T cells to produce cytokines[40,41]. Eosinophils by secreting specific cytokines or chemokines have a more central role in Th2 responses in CRS[34].

Table 1 Demographic and clinical characteristics of eosinophilic chronic rhinosinusitis with nasal polyps and non-eosinophilic chronic rhinosinusitis with nasal polyps

	ECRSwNP	NECRSwNP
n (%)	27 (45%)	33 (55%)
Age (yr), mean ± SD	46.93 ± 12.35	40.27 ± 13.47
M/F	20/7	24/9
With AR (%)	74.10%	48.5%
With asthma (%)	18.50%	12.1%
Duration of symptom (yr)	5.50 ± 3.92	8.55 ± 6.93
VAS	4.04 ± 1.01	3.99 ± 1.09
Score of olfactory dysfunction	5.59 ± 2.54	5.21 ± 2.66
Score of polyps	3.59 ± 1.11[b]	2.06 ± 0.82
Incidence of bilateral polyps	92.6%[b]	39.9%
Score of disease on CT	14.42 ± 3.84[b]	9.64 ± 3.37
Serum IgE (kU/L)	236.72 ± 157.77	167.97 ± 176.77
Blood eosinophil count (× 10^9/L)	0.44 ± 0.24[b]	0.21 ± 0.11
Blood eosinophil percentage (%)	6.49 ± 3.27[b]	3.42 ± 1.87
Tissue eosinophil count/HPF	31.56 ± 21.37[b]	0.91 ± 0.80

[b]$P < 0.01$ *vs* NECRSwNP. ECRSwNP: Eosinophilic chronic rhinosinusitis with nasal polyps; NECRSwNP: Non-eosinophilic chronic rhinosinusitis with nasal polyps; M/F: Male/female; AR: Allergic rhinitis; VAS: Visual analogue scale; HPF: High power field; CT: Computed tomography.

CLINICAL FEATURES OF ECRS

Many studies have shown that ECRS differs from NECRS in clinical features[13,14,15]: (1) ECRS often shows the symptom of olfactory dysfunction in its early stage; (2) ECRS commonly demonstrates multiple and bilateral nasal polyps, with highly viscous mucus secretion, while NECRS mostly with mucopurulent discharge; (3) ECRS tends to have bilateral sinus diseases on sinonasal computed tomography (CT), with a predominant disease in the ethmoid sinus especially in early stage, while NECRS in the maxillary sinus; (4) Co-existence of asthma is more common in ECRS; (5) Most of ECRS cases show the increase of peripheral blood eosinophils; (6) ECRS demonstrates dominant tissue eosinophilic infiltration; (7) In medical treatments, local or systemic steroid therapy is more effective for ECRS compared to macrolide therapy, while macrolide is effective for NECRS; and (8) ECRS shows strong tendency for nasal polyp recurrence after surgery, but systemic steroid is effective for the recurrent nasal polyps.

Symptoms of ECRS

Many studies indicate that ECRS commonly has more severe disease and higher symptom score compared to NECRS[8,18,19,29]. A recent study shows the mean severity score of symptoms including olfactory dysfunction, nasal obstruction, and nasal discharge in ECRS is significantly higher than that in NECRS[42]. Previous studies have shown that there is a close correlation between symptoms and tissue eosinophil infiltration in CRS[18,43]. However, a recent study shows no significant differences in the symptom severities of nasal obstruction, nasal discharge, and facial pain aside from smell dysfunction between ECRS and NECRS cases[10]. Another study also shows no difference in visual analogue scale (VAS) score or duration of symptoms between ECRSwNP and NECRSwNP patients[11], suggesting that the two subtypes may have an equivalent severity of symptoms. Similarly, ECRSwNP and NECRSwNP patients may present with comparable symptom scores[44]. In our recent study, a significant difference in the mean VAS score of symptoms between the ECRSwNP and NECRSwNP patients was also not found (Table 1).

CRS is one of the most frequent causes of olfactory dysfunction (reduction or loss of smell) and accounts for 21%-25% of cases with smell loss[45-48]. Meanwhile, olfactory dysfunction affects about 60% of CRS patients[4]. Olfactory dysfunction is related to the severity of CRS, especially when with nasal polyps[49]. A study shows that 38% of CRS patients present with olfactory dysfunction, which is affected by nasal polyps, and the prevalence of olfactory dysfunction is 57% in CRSwNP and 13.7% in CRSsNP, respectively[20]. A recent report indicates that smell dysfunction is a very common symptom in CRSwNP, even accounting for 96.5% of cases[41]. Olfactory dysfunction is a more predominant and characteristic symptom of ECRS and tends to occur in the early stage of ECRS[10,13-15,20,50]. This symptom is more severe and common in ECRS compared to NECRS[42]. A study shows that there is a high prevalence of olfactory dysfunction in ECRS (78.9%) compared to NECRS (25.9%)[20]. Olfactory dysfunction is reported to be associated with olfactory cleft opacification on CT images[51]. Nasal polyps occur more commonly in the olfactory cleft in ECRS compared to NECRS[42]. Edematous swelling or polyposis of the middle turbinate, which is often observed in ECRS patients, increases the opacification of the olfactory cleft and causes olfactory impairments[13]. Studies indicate that olfaction score is influenced by mucosal eosinophilic infiltration, with lower olfaction score in ECRSwNP as compared to NECRSwNP[29,52]. A study shows that there are no statistically significant differences in the VAS scores of nasal obstruction, nasal discharge, headache or overall symptoms, but a statistically significant difference is found in relation to problems of smell between the patients with high and low infiltration of eosinophils in the ethmoidal sinus mucosa[50]. But in our recent study, no statistically significant difference in olfactory dysfunction scores was found between ECRSwNP and NECRSwNP (Table 1). The patients with ECRSwNP seemed to have a shorter duration of symptoms than NECRSwNP patients although this difference was not significant statistically (Table 1).

Polyps in ECRS

ECRS commonly exhibits multiple and bilateral nasal polyps compared to NECRS[13-15], and the polyps commonly exist in the olfactory cleft[42]. Although a previous study shows that there is not a significant difference in endoscopic scores of nasal polyps between ECRSwNP and NECRSwNP subtypes[29], many studies demonstrate that ECRSwNP often present with a higher endoscopic score of nasal polyps compared with NECRSwNP[10,18]. Our recent study showed that ECRSwNP presented with a higher score of nasal polyps and a higher incidence of

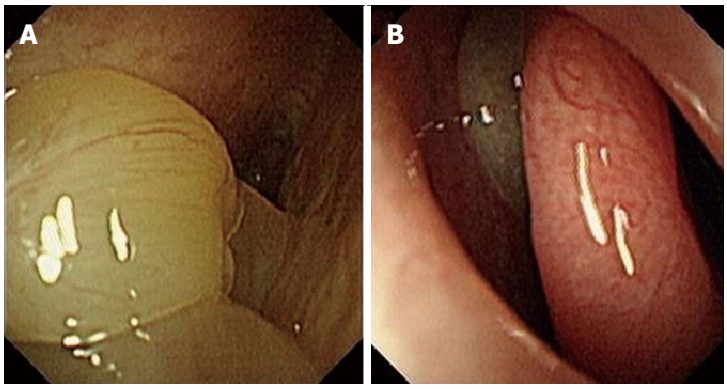

Figure 2 Nasal endoscopic findings. Polyps in eosinophilic chronic rhinosinusitis with nasal polyps (A) and in non-eosinophilic chronic rhinosinusitis with nasal polyps (B).

Table 2 Computed tomography features of eosinophilic chronic rhinosinusitis with nasal polyps and non-eosinophilic chronic rhinosinusitis with nasal polyps

	ECRSwNP (n = 27)	NECRSwNP (n = 33)
Total disease score of sinuses	14.42 ± 3.84[b]	9.64 ± 3.37
Number of involved sinuses	7.88 ± 1.22[b]	5.64 ± 1.49
Percentage of involvement in all sinuses	23.1%[a]	3.0%
Incidence of bilateral diseases in individual sinuses		
Frontal	53.8%[b]	12.1%
Sphenoid	38.5%[a]	9.1%
Anterior ethmoid	53.8%[a]	12.1%
Posterior ethmoid	100.0%[b]	75.8%
Maxillary	96.2%[a]	69.7%
OMC	69.2%[a]	36.4%
Score of diseases in individual sinuses		
Frontal	1.81 ± 1.51[a]	0.88 ± 0.91
Sphenoid	1.23 ± 1.28[a]	0.55 ± 0.76
Anterior ethmoid	3.27 ± 0.90[b]	2.27 ± 0.87
Posterior ethmoid	3.04 ± 1.04[b]	1.52 ± 0.95
Maxillary	2.23 ± 0.43	2.15 ± 0.69
OMC	2.85 ± 1.60	2.27 ± 1.20

[a]$P < 0.05$, [b]$P < 0.01$ *vs* NECRSwNP. Scoring for sinus diseases on computed tomography (CT): 0 = normal, 1 = partial opacification, and 2 = total opacification; these points are applied to individual sinuses on each side; OMC is graded as 0 = not occluded, or 2 = occluded; deriving a maximum score of 12 per side. ECRSwNP: Eosinophilic chronic rhinosinusitis with nasal polyps; NECRSwNP: Non-eosinophilic chronic rhinosinusitis with nasal polyps; OMC: Ostiomeatal complex.

bilateral nasal polyps when compared with NECRSwNP (Table 1 and Figure 2).

In addition, endoscopic examination indicates that most of patients with ECRS demonstrate sinonasal mucus secretion with high viscosity, while NECRS is common with mucopurulent discharge[13-15]. It was found in our recent study that more than half (55.6%) of 27 ECRSwNP patients showed highly viscous mucus secretion, but less than a third (30.3%) of 33 NECRSwNP patients presented with this condition.

CT findings in ECRS

The Lund-Mackay scoring system is widely used to evaluate the disease severity of CRS on sinonasal CT[1,4,53,54]. CRSwNP tends to have a higher score of disease on CT compared with CRSsNP[41]. CT imaging also is a powerful tool to differentiate ECRS from NECRS[13]. Studies show that there are significant differences in the disease scores of most sinuses aside from maxillary sinus between ECRS and NECRS[13,15]. ECRSwNP presents with higher disease scores on CT compared to NECRSwNP[18,27], although an obvious difference in CT scores between ECRSwNP and NECRSwNP subtypes is not found in some studies[11,29]. In addition, CT studies show that sinus diseases commonly occur bilaterally in ECRS compared to NECRS[13-15]. Our recent study showed significant differences in the mean score of total diseases in all sinuses, the mean number of involved sinuses, the percentage of cases with involvement of all sinuses, and the incidence of bilateral diseases in individual sinuses between ECRSwNP and NECRSwNP (Table 2 and Figure 3).

In terms of individual sinuses, ECRS patients especially in their early stages often have predominant diseases in the ethmoid sinuses[13-15,20,42]. A previous study shows that there is a significant correlation between the severity of eosinophilic infiltration in the ethmoidal mucosa and the disease on CT[55]. Ethmoidal sinus lesions are readily detected by CT in patients with CRS accompanied by severe eosinophil infiltration[50]. Involvement of the posterior ethmoid sinus is one of the most apparent differences in CT images between ECRS and NECRS. In the early stage of ECRS, CT images can demonstrate the opacification of the posterior ethmoid sinus[15]. A study shows that the posterior ethmoid sinus is more commonly involved in ECRSwNP compared to NECRSwNP, whereas both the anterior and posterior ethmoid sinuses are similarly involved in NECRSwNP, and CT score of the posterior ethmoid has a good accuracy as a predictor of ECRSwNP in a Japanese population[13]. Our recent study showed that ECRSwNP had a higher incidence of bilateral diseases and a higher disease score in the anterior or posterior ethmoid sinus compared to NECRS, but ECRSwNP had similar disease scores in its anterior and posterior ethmoid sinuses, while NECRS showed a higher disease score in the anterior ethmoid sinus compared with the posterior ethmoid sinus (Table 2).

The maxillary sinus is most often involved in CRS. The middle meatus or ostiomeatal complex (OMC) has a fundamental role in the pathogenesis of CRS[1]. As the drainage from the sinus to the middle meatus or OMC is impaired, the sinus becomes secondarily involved. According to this pathogenesis, sinuses that are most likely

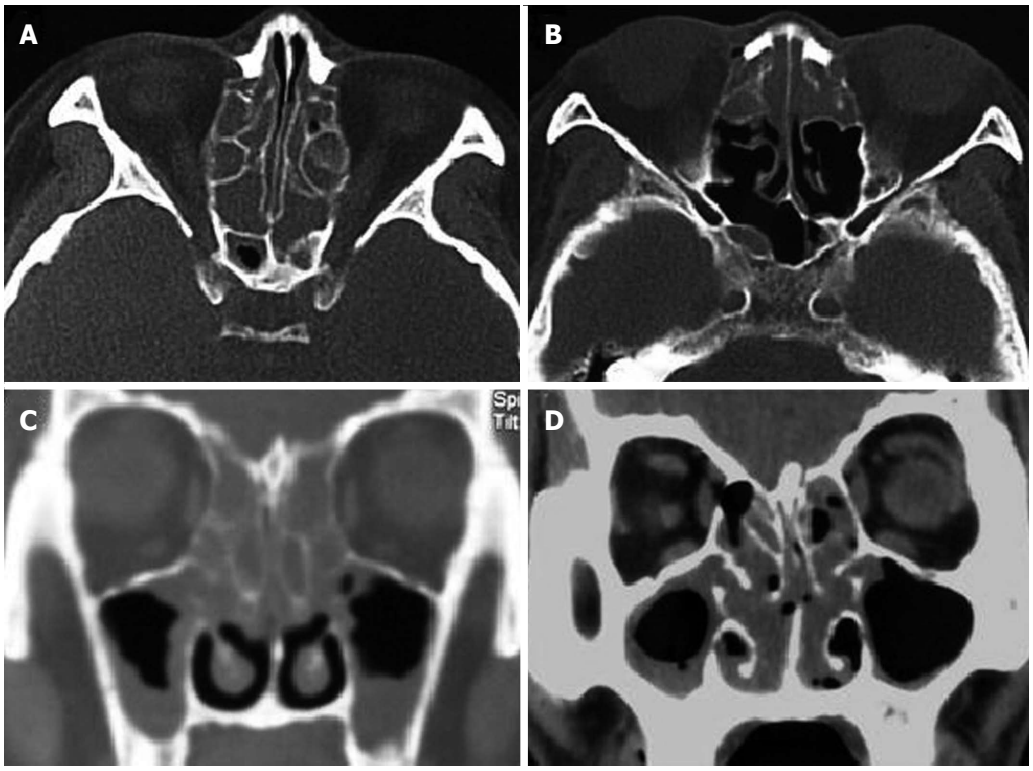

Figure 3 Computed tomography findings. Axial and frontal sections in the subtypes of eosinophilic chronic rhinosinusitis with nasal polyps (ECRSwNP) (A and C) and non-eosinophilic chronic rhinosinusitis with nasal polyps (NECRSwNP) (B and D). Predominant diseases in bilateral anterior and posterior ethmoid sinuses are showed in ECRSwNP, while predominant diseases in anterior ethmoid sinuses in NECRSwNP.

to be affected are the maxillary sinus and anterior ethmoid sinus that connect to the middle meatus or OMC through the small ostia. However, ECRS has predominant disease in the ethmoid sinus, while NECRS in the maxillary sinus[13-15,20], and the posterior ethmoid sinus that does not directly connect with the middle meatus is involved in similar to the anterior ethmoid sinus even in the early stage for ECRS patients. This suggests that pathological changes in the middle meatus or OMC may be of less importance for the pathogenesis of ECRS, namely, the pathogenesis of ECRS is different from that of NECRS[15]. A recent study reveals that OMC obstruction is correlated with sinus disease only for patients with CRSsNP but not CRSwNP[56]. It is thought that ECRS may not be associated with OMC occlusion[8].

In contrast to NECRS patients who have often a predominant disease in the maxillary sinus, patients with ECRS have commonly a predominant disease in the ethmoid sinus especially in the early stage[9,13-15,20]. Our recent study showed that ECRSwNP had higher disease scores in frontal, sphenoid, anterior and posterior ethmoid sinuses than NECRSwNP, but there was not a significant difference in maxillary or OMC disease score between ECRSwNP and NECRSwNP (Table 2), which indicated that ECRSwNP had predominant disease in the ethmoid sinus including the anterior and posterior ethmoid sinuses, while NECRSwNP had similar involvement of the anterior ethmoid and maxillary sinuses but with less involvement in the posterior ethmoid sinus.

Co-morbid allergic rhinitis or asthma in ECRS

Inflammation in the upper respiratory tract affects the lower respiratory tract and *vice versa*. The concept of the unified airway is proposed based on evidence from epidemiological, pathophysiological, and treatment outcome studies, indicating the existence of similar inflammatory responses and the shared pathophysiological mechanisms between allergic rhinitis (AR), asthma and CRS[20,57,58].

Some studies demonstrate that 25%-58% of individuals with CRS have AR[59,60]. A recent study shows that 67.2% of 418 patients with CRS have AR, and 76.8% of 190 patients with ECRS and 59.2% of 228 patients with NECRS have AR[42]. However, some studies show that there is not a statistically significant difference in the coexistent rate of AR between ECRSwNP and NECRSwNP[11,22], and a similar finding was also found in our case cohort (Table 1).

The clinical relationship between CRS and asthma has been known for many years. CRS and asthma coexist often clinically and they share some histopathologic features such as chronic eosinophilic inflammation, epithelial damage, and basement membrane thickening of the airway mucosa[61]. It is reported that the prevalence of asthma in CRS patients is 20%-50%[13,18,20,41,42,62,63] and even more than 50%[61]. However, there is a lower prevalence of asthma (2%-3%) in CRS patients in China compared with the Western population[64]. This difference may result from distinct immunopathologic characteristics of CRS in Chinese patients, specifically from lower levels of eosinophilic inflammation[16,24,64-66]. CRS espe-

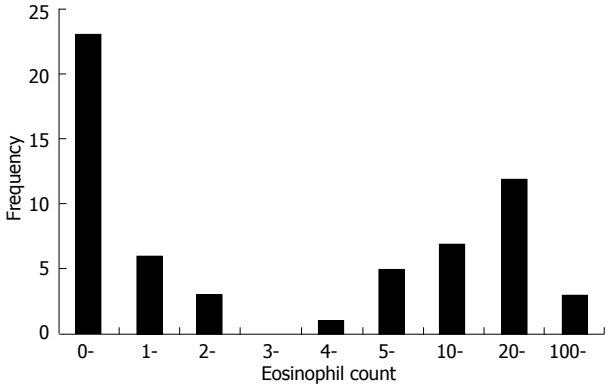

Figure 4 Frequency distribution and range of tissue eosinophil count per high power field for 60 patients with chronic rhinosinusitis with nasal polyps.

cially CRSwNP is commonly associated with asthma[31]. The association of CRSwNP and asthma is well established, and CRSwNP in white population of Europe and the United States represents often a form of severe and difficult-to-treat eosinophilic airway inflammation, which frequently is linked to co-morbid asthma[1]. Eosinophilic inflammation is considered a common mechanism in both CRSwNP and asthma[67]. It is reported that among 2176 cases with CRSwNP, 37.5% present with asthma[68]. A recent study shows that among 182 patients with CRSwNP, the percentage of patients with asthma is as high as 94%[69]. Asthma is known to be often concurrent with ECRS[14,42,70]. A study shows that 34.7% of 190 patients with ECRS, but only 9.6% of 228 patients with NECRS, present the coexistence with asthma[42]. Co-morbid asthma is one of typical features for ECRS[13]. Association of ECRSwNP with asthma is widely accepted[12]. Some authors believe that ECRS and asthma share similar histopathologic features and are the same inflammatory process demonstrating in different sites of the respiratory tract[61,67].

A study shows that in Chinese patients with CRSwNP, the incidence of asthma (15.9%) in ECRSwNP is higher than that (3.6%) in NECRSwNP[9]. Another study shows that the prevalence of asthma in ECRSwNP is higher than that in NECRSwNP, but the difference does not reach statistical significance[11]. And also, there are the studies showing no significant difference in the prevalence of asthma between ECRSwNP and NCRSwNP patients[11,22], which may be due to the low prevalence of asthma among CRS patients in China[64]. A statistically significant difference in the incidence of asthma between ECRSwNP and NECRSwNP patients was also not found in our recent study (Table 1). Although asthma is often seen in patients with ECRS, co-morbidity with asthma may not be a diagnostic criterion for ECRS because about half of ECRS cases are not associated with asthma[15].

IgE and ECRS

CRS is a form of eosinophil-dominated inflammation. Some factors result in local production of IgE, which may contribute to severe eosinophilic inflammation. There is a significant correlation between the concentration of IgE and the number of eosinophils in nasal polyp tissue[38]. Some ECRS patients show the elevation of total or specific IgE level[6,15,44]. ECRSwNP patients demonstrate increased blood IgE levels compared with NECRSwNP[11,27]. A study shows that the amount of tissue eosinophils in CRSwNP is related to eosinophilia of the peripheral blood, but no significant correlation exists between elevated serum IgE and the increase of tissue or blood eosinophils, indicating that atopic conditions may play a minor role in the pathogenesis of CRSwNP in Koreans[17]. It is showed that only less than half of CRS patients present with the increased blood IgE and thus eosinophilic inflammation is not likely driven by an IgE mechanism[61]. A study shows the absence of a significant difference in total serum IgE levels between ECRS and NECRS patients, suggesting that systemic IgE does not greatly contribute to the pathophysiology of ECRS[13]. Also, a recent study shows that although total serum IgE in ECRS is higher than that in NECRS (120.3 *vs* 48.0 kU/L), the difference is not statistically significant[10]. Similarly, a significant difference in serum IgE levels between ECRSwNP and NECRSwNP was not found in our recent study (Table 1).

DEFINITION OR DIAGNOSIS OF ECRS

Currently ECRS is determined primarily based on tissue eosinophilic infiltration, but there is not a well-defined criterion of the tissue eosinophilic infiltration for diagnosis of ECRS. In some studies, ECRS including ECRSwNP is defined as tissue eosinophil count per high power field (HPF) more than 5 eosinophils[18,21,29,64], 10 eosinophils[8,30], or 20 eosinophils[9], even more than 100 eosinophils[27,42], as well as the percentage of eosinophils in tissue-infiltrated inflammatory cells exceeding 5%[17], 10%[16,66,71] or 15%[20]. In our recent study tissue eosinophil count more than 5 eosinophils/HPF was used as a criterion for ECRSwNP based on the frequency of cases with individual eosinophil counts in nasal polyp tissues (Figure 4).

Tissue eosinophilic infiltration, based on which ECRS is determined, is commonly identified after surgery by histopathological examination. Therefore, this approach may be quite unpractical because it is difficult to obtain the diagnostic information before surgery or from the patients treated only with medicines. While peripheral blood eosinophilia has a certain diagnostic value for ECRS[15], because the close correlation between the number of peripheral blood and tissue-infiltrated eosinophils has been shown in several studies[9-11,15,17,18,27,42]. It is easy to understand the close association of blood eosinophils with ECRS because the tissue-infiltrated eosinophils are recruited *via* bloodstream to disease sites of ECRS. Many studies have shown that ECRSwNP presents with a significant increase in the peripheral blood eosinophil count or percentage compared to NECRSwNP[9,11,13,52]. Our recent study also showed the existence of a close correlation between tissue eosinophil count and blood eosino-

Table 3 Diagnostic sensitivity and specificity of blood eosinophil count or percentage for eosinophilic chronic rhinosinusitis

Ref.	Blood eosinophil count				Blood eosinophil percentage			
	AUC	Cutoff value	Sensitivity	Specificity	AUC	Cutoff value	Sensitivity	Specificity
Zuo *et al*[52]	0.873	0.16×10^9/L	84.9%	84.4%	0.863	2.05%	89.0%	84.4%
Wang *et al*[9]	-	-	-	-	0.818	5.65%	79.0%	78.2%
Hu *et al*[11]	0.871	0.22×10^9/L	74.2%	86.5%	0.864	3.05%	80.3%	75.3%
Sakuma *et al*[13]	-	-	-	-	0.880	6.00%	97.4%	70.7%

ECRS: Eosinophilic chronic rhinosinusitis; AUC: Area under receiver operating characteristic curve.

phil count or percentage in ECRSwNP patients, but not in NECRSwNP patients. Thus, the increased peripheral blood eosinophil count or percentage is considered a good marker or predictor of ECRSwNP[9,11,13,52]. Some studies show that blood eosinophil count or percentage in ECRS subtype is significantly higher than that in NECRS subtype[9,11,13,52]. It is found by receiver operating characteristic curve analysis that blood eosinophil count or percentage has high sensitivity and specificity for the diagnosis of ECRS[9,11,13,52] (Table 3).

Our recent study also showed that there was a statistically significant difference in mean blood eosinophil count or percentage between ECRSwNP and NECRSwNP patients (Table 1). However, it was notable that neither all patients with ECRSwNP had the increased circulating eosinophils nor all patients with NECRSwNP showed a normal level of blood eosinophil count. For example, only 10 of 27 patients with ECRSwNP showed blood eosinophil counts more than normal range and 2 of 33 patients with NECRSwNP had the increase of eosinophil count. Therefore, ECRS or NRECR can not be determined only based on if blood eosinophils increase.

The definition or diagnostic criterion for ECRS is very important since ECRS differs from NECRS in treatment strategy. However, there is not yet a clear definition or diagnostic criterion to differentiate ECRS and NECRS subtypes. Recently, new diagnostic criteria for ECRS have been proposed[13], in which the diagnosis of ECRS is finally determined by the clinical symptoms, nasal endoscopy, sinonasal CT imaging, peripheral blood test, and histological examination[13,15].

TREATMENT AND PROGNOSIS FOR ECRS

ESS has been used widely for the treatment of CRS. Outstanding short- and long-term results of ESS in CRS have previously been reported in the literature[41,68,72-75]. The impact of ESS on the improvement in CRS-related symptoms postoperatively is remarkable. However, some of CRS patients are inadequately controlled despite receiving combination of maximal medical therapy and ESS[1]. A wide variety of factors contribute to poor disease control, including patient-related factors such as ECRS[76]. It is believed that NECRS can be relatively well controlled with a combination of ESS and macrolide therapy, whereas ECRS is unresponsive to macrolide therapy[13]. Many studies indicate that ECRS commonly has poorer treatment outcomes compared to NECR[14,19,28,30,76,77]. For example, ECRSwNP is refractory to the combined treatment of ESS and macrolide therapy and shows a strong tendency for recurrence after surgery[13-15,27].

However, a recent study suggests that eosinophilic inflammation in CRS may not be related to the surgical outcome in South Koreans[22]. Another study also shows that the presence or absence of tissue eosinophilic infiltration does not impact significantly on the time interval to revision surgery[78]. Our recent study showed that in terms of the short-term efficacy of ESS in CRSwNP, both ECRSwNP and NECRSwNP patients had significant improvement in symptoms aside from smell dysfunction at one-week follow-up after ESS, but there was no significant difference in symptom improvement between the two subgroups.

CONCLUSION

In conclusion, CRS can be subclassified into two subtypes: ECRS and NECRS. The prevalence of ECRS is increasing in East Asians in the recent years. ECRS differs from NECRS in clinical features and treatment outcomes; however, there is not yet a universally accepted definition or diagnostic criterion for ECRS, and also the underlying pathogenic mechanisms of ECRS are not well-understood. Identification of ECRS subtypes and underlying pathogenic mechanisms is key to developing treatment strategies for the phenotypes of CRS.

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