Highlights of eosinophilic chronic rhinosinusitis with nasal polyps in definition, prognosis, and advancement

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Background: **Tissue eosinophils are characteristic of inflammation in most but not all patients with chronic rhinosinusitis with nasal polyps (CRSwNP) and may be useful for defining subgroups and making treatment choices. However, no consistent diagnostic criteria for CRSwNP with eosinophilic inflammation have been established.**

Methods: **Related literature review was performed and current developments in the diagnosis of eosinophilic CRSwNP were summarized. Details in histopathology, definition of tissue eosinophilia, eosinophil as an indicator of disease recurrence, eosinophilic shift, and related biomarkers in CRSwNP are included in this review article.**

Results: **Mucosal eosinophilia exhibits significant geographic and ethnic differences and may increase over time. Tissue eosinophilia can be defined using a cutoff value based on reference values from healthy mucosa, but typical disease-specific values should also be employed to increase sensitivity and specificity for clinical use. Recent developments highlight the diagnostic criteria for eosinophilic CRSwNP based on cluster analysis, which were also associated with clinical outcomes. Additionally, some promising eosinophil-relevant biomarkers, such as eosinophilic cation protein and interleukin 5 (IL-5), may be clinically applied as diagnostic or predictive tools for CRSwNP in the future.**

Conclusion: **Sinonasal tissue eosinophilia is present in a majority of CRSwNP patients but is currently more common in the West than in the East. Cutoff values of eosinophils as the diagnostic criteria of eosinophilic CRSwNP are subject to change with geographic and ethnic differences over time. It will be important to identify validated eosinophil-related biomarkers in different continents/countries for future research and for the introduction of precision medicine.**

Key Words:
chronic rhinosinusitis; nasal polyps; pathology; diagnosis; prognosis; classification; phenotype; endotype; eosinophils; cluster analysis

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Chronic rhinosinusitis (CRS) is a prevalent inflammatory disorder of the sinonasal mucosa affecting approximately 13%-16% of the U.S. adult population[1–3] and 8% of the Chinese population.[4] Diverse immune cells

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and corresponding inflammatory mediators orchestrate this heterogeneous disease spectrum, which comprises CRS with nasal polyps (CRSwNP) and CRS without nasal polyps (CRSsNP). The inflammatory patterns of CRS have been designated to be eosinophilic and neutrophilic.[5] In general, while CRSsNP is characterized by predominantly neutrophilic inflammation with increased levels of T helper 1 (Th1) cytokines, CRSwNP is often characterized by eosinophilic inflammation with elevated levels of Th2 cytokines.[6,7] The identification of the inflammatory patterns of CRS will not only improve understanding of the pathophysiological mechanism but will aid in selecting treatment strategies. The presence of tissue eosinophilia in CRSwNP is frequently associated with extensive sinus disease,[8,9] higher postoperative symptom scores,[9] less improvement in both disease-specific and general quality of life,[10] and a higher polyp recurrence rate.[11–14] However, no consistent diagnostic criteria for CRSwNP with eosinophilic inflammation have been established. Therefore, this review summarizes the related literature and analyzes current developments in the diagnosis of eosinophilic CRSwNP.

Methods

A literature was performed of papers published in English and Chinese pertaining to CRS, nasal polyps, and eosinophils using the PubMed database. The search employed combinations of the following key words: sinusitis, nasal polyps, pathology, diagnosis, prognosis, classification, phenotype, endotype, eosinophils. Non-human and in vitro studies were excluded. Details in histopathology, definition of tissue eosinophilia, eosinophil as an indicator of disease recurrence, eosinophilic shift and related biomarkers in CRSwNP are included in this review article. As a review, this article is exempt from Institutional Review Board (IRB)/ethical review.

Results

Histopathology of CRSwNP

Nasal polyps, which are semitranslucent, pale gray, grape-like inflammatory outgrowths of sinonasal tissue, typically develop bilaterally in the sinonasal cavity.[15] At present, the gold standard for the diagnosis of eosinophilic CRSwNP is histopathological assessment. Pathologically, nasal polyps are covered by intact respiratory epithelium with underlying edematous stroma containing a mixed inflammatory cell infiltrate that lies beneath the thickened basement membrane.[16] The inflammatory infiltrate is composed of lymphocytes, plasma cells, eosinophils, neutrophils,[16] mast cells, monocytes, and macrophages.[17] While the definition of CRSwNP is nonspecific and solely based on the presence of polypous structures, studies have demonstrated that CRSwNP shows a wide diversity of inflammatory endotypes based on the expression of cytokines and mediators.[7,18]

In 2001, Ishitoya et al.[19] defined eosinophilic chronic rhinosinusitis (ECRS) and non-ECRS as 2 subtypes of CRSwNP. However, Ferguson[20] and Ferguson and Orlandi[21] subclassified ECRS into 4 groups: superantigen-induced ECRS; classic allergic fungal sinusitis (AFS) or rhinosinusitis (AFRS); nonallergic fungal ECRS; and aspirin-exacerbated ECRS (AE-ECRS). Since then, the term "eosinophilic CRSwNP" rather than ECRS has been used to describe a clinical inflammatory phenotype of CRSwNP that is distinct from non-eosinophilic (neutrophilic) CRSwNP. Clinically, the term eosinophilic CRSwNP refers to a CRSwNP phenotype wherein tissue eosinophils are dominant among the inflammatory cells.

More than 20 years ago, Hellquist[22] reported that the edematous eosinophilic type accounted for 86% of all polyps in Sweden. Therefore, eosinophils are probably the most common and important inflammatory cells in the pathogenesis of polyps.[23,24] It has been well accepted that 1 of the most common histological features of nasal polyps is eosinophilia in the mucosa and submucosa.[23,25] CRSwNP is characterized by active sinonasal eosinophilic inflammation; ie, by the presence of tissue eosinophilia with or without other inflammatory cells. Although non-eosinophilic CRSwNP is generally defined by the absence of significant eosinophilic inflammation, it may still present low numbers of tissue eosinophils and a dominant inflammatory type that includes neutrophils and other mixed granulocyte inflammatory cells.

Definition of sinonasal tissue eosinophilia

It is accepted worldwide that eosinophilic CRSwNP can be definitively diagnosed with tissue histopathology for eosinophils or through the quantification of eosinophil-derived mediators (eg, eosinophil cationic protein [ECP]). However, there is a lack of unanimous histopathological criteria for discriminating between eosinophilic and non-eosinophilic CRSwNP. Currently, few studies have investigated the level of mucosal eosinophil density required to meet the definition of tissue eosinophilia. The definition of eosinophilic CRSwNP is not standardized, and no consensus exists regarding the level of eosinophilia that should define the phenotype.

Previous studies defined tissue eosinophilia using either the eosinophil count per high power field (HPF; magnification × 400) or a proportion of eosinophil cell count compared with the total inflammatory cell population, although a semiquantitative evaluation was applied.[26–29] Various eosinophil numbers per HPF were used as cutoff values, including 5 eosinophils/HPF,[9,10,12,30] 10 eosinophils/HPF,[31–34] 15 eosinophils/HPF,[35] 50 eosinophils/HPF,[36] 70 eosinophils/HPF,[37] 100 eosinophils/HPF,[38] 120 eosinophils/HPF,[39,40] and even as high as 350 eosinophils/HPF[41] (Table 1). Regarding the eosinophil percentage used as a cutoff value, different researchers have used 5%,[42] 10%,[6,43–45] 11%,[46] 20%,[47,48] 30%,[49] and as high as 50%[50,51] (Table 2). The discrepancies in the

TABLE 1. Various cutoff values for eosinophilic CRS expressed as eosinophil numbers per HPF

Continent	Country	Reference	Patients	Cutoff values (eosinophils/HPF)
Asia	China	Wen et al.[35]	218 CRSwNP	>15
	Japan	Baba et al.[36]	43 CRSwNP	>50
		Mori et al.[40]	418 CRS	>120
		Matsuwaki et al.[39]	56 CRS	>120
		Yao et al.[41]	33 CRSwNP	>350
		Nakayama et al.[37]	114 CRSwNP and 61 CRSsNP	≧70
		Ikeda et al.[38]	130 CRSwNP	>100
	Korea	Kim et al.[30]	230 CRSwNP	>5
Europe	Belgium	Vlaminck et al.[12]	96 CRSwNP and 125 CRSsNP	>5
	Italy	Brescia et al.[33]	179 CRSwNP	>10
		Brescia et al.[34]	240 CRSwNP	>10
	Turkey	Soy et al.[32]	57 CRSwNP	>10
North America	United States	Kountakis et al.[9]	37 CRSwNP and 15 CRSsNP	>5
		Soler et al.[10]	66 CRSwNP and 81 CRSsNP	>5
		Soler et al.[31]	50 CRSwNP and 52 CRSsNP	>10

CRS = chronic rhinosinusitis; CRSsNP = CRS without nasal polyps; CRSwNP = CRS with nasal polyps; HPF = high power field.

definition of nasal tissue eosinophilia may be caused by differences in genetic (ethnic) or environmental backgrounds of the CRSwNP patients, a lack of consistency in the methods used for expressing eosinophil numbers (eosinophil numbers/HPF or eosinophil percentage), or differences in the preoperative medications used (corticosteroids or antibiotics). Therefore, it is not surprising that the designation of eosinophilia in CRSwNP (eosinophilic CRSwNP) has not reached consensus among researchers.

Theoretically, the presence or absence of tissue eosinophilia can be defined using a cutoff based on reference values for tissue eosinophils derived from healthy subjects. Statistically, subjects with eosinophilia (eosinophil positive) are defined as those who remain outside the normal range based on normal subjects, while subjects

TABLE 2. Various cutoff values for eosinophilic CRS expressed as eosinophil percentage in tissue

Continent	Country	Reference	Patients	Cutoff values (eosinophil %)
Asia	China	Cao et al.[6]	151 CRSwNP and 94 CRSsNP	>10
		Hu et al.[44]	155 CRSwNP (Tongji cohort); 35 CRSwNP (Taizhou cohort)	>10
	Malaysia	Tikaram and Prepageran[51]	80 CRSwNP	>50
	Korea	Kim et al.[42]	30 CRSwNP	>5
		Jeong et al.[46]	118 CRSwNP	>11
Europe	Turkey	Tecimer et al.[50]	40 CRSwNP	>50
	France	Jankowski et al.[43]	263 CRSwNP	>10
		Bonfils et al.[48]	144 CRSwNP	>20
	Finland	Vento et al.[47]	41 CRSwNP	>20
North America	United States	Mahdavinia et al.[45]	296 CRSwNP	>10
South America	Brazil	de Castro et al.[49]	20 CRSwNP	>30

CRS = chronic rhinosinusitis; CRSsNP = CRS without nasal polyps; CRSwNP = CRS with nasal polyps.

without eosinophilia (eosinophil negative) are defined as those who fall within 2 standard deviations of the normal mean for tissue eosinophils.[52,53] Referring to that method,[52] a cutoff value of ≥10% (4.77% + 2 × 2.47% = 9.71%) tissue eosinophils among the total inflammatory cells was used to define Chinese patients with eosinophilic CRSwNP.[6] This cutoff value obtained for the normal mucosa could define tissue eosinophilia in CRSwNP, for the purpose of exploring pathological and immunological mechanisms. However, there is a significant limitation in such a cutoff value because the criterion based on 2 standard deviations from the normal mean is strict and somewhat arbitrary, as has been demonstrated in a similar study of asthma.[52] With this strict criterion, the missed diagnosis rate of eosinophilic CRSwNP is relatively low, because this histopathologic definition focuses on the percentage of eosinophils without considering the severity of neutrophilic inflammation in nasal polyps. Thus, when both eosinophils and neutrophils are above the normal range in CRS, as is the case in some CRSwNP patients,[54] the mixed inflammatory pattern would be misdiagnosed as eosinophilic CRS.

Eosinophilic inflammation in CRSwNP as an indicator of disease recurrence

The major drawback of the abovementioned histological criteria, which are of interest to pathologists rather than surgeons, is that they do not consider the outcome of medical or surgical treatment. Rhinologists have been aware of the differences in responses to the current uniform, stepwise escalation of medical treatments (mostly nasal corticosteroids) or surgical treatment (endoscopic sinus surgery) in CRSwNP patients. Tissue eosinophilia status provides prognostic information about disease severity and treatment outcomes. In a multicenter retrospective study of 1716 patients with refractory CRS, eosinophilic CRSwNP was definitively diagnosed when the number of eosinophils in the mucosal tissues was ≥70 eosinophils/HPF[55]; this study presented the most significant difference in cases of CRS recurrence in Japan.

In supervised classification, the supervised step is to build a classifier describing the predetermined class labels first (eg, the cutoff value of variable), and then the classifier (rules) is then applied to the classification of new data. By contrast, unsupervised clustering does not rely on predefined classes. Thus, in the process of clustering, a set of objects with similar parameters are grouped to identify unique categories, but the class labels and the number of classes are not known in advance. This can facilitate the categorization of heterogeneous disorders into disease subtypes and has recently been used to identify CRS subtypes.

Lou et al.[54] were the first in China to report the results of cluster analysis in Chinese patients with CRSwNP. To our knowledge, the study represents the largest cluster analysis completed to date in Chinese CRSwNP patients. Overall, 5 distinct clusters relevant to recurrence were generated. In the plasma cell–dominant and lymphocyte-dominant CRSwNP clusters, less than 7% of subjects experienced polyp recurrence. Clusters that had a mixed inflammatory pattern or were characterized by neutrophil infiltration mostly had a poor prognosis, with recurrence rates of 75% and 46.4%, respectively. In clear contrast, eosinophil-dominant CRSwNP (tissue eosinophil percentage ≥54.5%) showed the highest polyp recurrence rate of 98.5%.

Recently, Wei et al.[56] performed cluster analyses in Chinese CRSwNP patients to investigate recurrence at 8 years after the primary surgery. In patients with type-2 inflammation (elevated levels of interleukin 5 [IL-5], immunoglobulin E [IgE], and ECP, and a high positive rate of Staphylococcal enterotoxin [SE-IgE]), the highest recurrence rate (72.7%) was reported. For the non–type-2 endotypes, the ECP/myeloperoxidase (MPO) ratio was significantly increased over time after the first surgery in patients with recurrence, suggesting that type-2 inflammation (eosinophilic inflammation) was associated with disease recurrence.

In the search for predictors of surgical treatment response, the polyp recurrence rate after endoscopic sinus surgery was considered the principle clinically relevant end point.[57] Analyses investigated various clinical characteristics, such as the Lund-Mackay score, olfactory score, rhinorrhea score, headache and/or facial pain score, comorbid asthma, fractional exhaled nitric oxide (FENO), and mucosal and blood inflammatory cells, to distinguish which variables predicted higher recurrence rates.[57] The multivariate analysis identified a tissue eosinophil proportion over 27% and a tissue eosinophil absolute count over 55 eosinophils/HPF as the strongest predictors of nasal polyp recurrence after surgery in the Chinese population.[57] Although other highly relevant measurements, such as FENO and blood eosinophil counts, have been correlated with nasal recurrence, further analysis showed that FENO and blood eosinophil counts did not predict the surgical response to the same degree that tissue eosinophil counts did.[57]

Diagnosis of eosinophilic CRSwNP by computed tomography and blood eosinophilia prior to biopsy

Although histopathological examination is considered the gold standard for diagnosing eosinophilic CRSwNP, it is not always possible due to the lack of availability of a sufficient amount of polyp biopsy tissue for examination or unwillingness of the patient to undergo the procedure before surgery. Therefore, other available variables that can be examined less invasively, such as peripheral eosinophils levels and the presence of comorbid asthma,[7] have attracted attention.

Blood eosinophilia may be used as a surrogate for tissue eosinophilic inflammation.[39,44] Compared with histopathological parameters, peripheral eosinophil count is a convenient biomarker because blood is easy to

obtain, and cell counting is standardized and mechanized in laboratories. Hu et al.[44] set an absolute blood eosinophil count $\geq 0.215 \times 10^9$/L or a blood eosinophil percentage $\geq 3.05\%$ as cutoff values for distinguishing eosinophilic and non-eosinophilic CRSwNP in Chinese adults. However, various disorders and causes, including allergies, autoimmune diseases, drug reactions, parasite infections, and corticosteroid therapy, can alter circulating eosinophil counts. Accordingly, blood eosinophilia does not necessarily reflect tissue eosinophilia, and its predictability remains limited, as verified by Lou et al.[57]

As a noninvasive parameter, computed tomography (CT) scores presented as a predictor of eosinophilic CRSwNP. Based on the Lund-Mackay scoring system, Meng et al.[58] found that an optimal cutoff value of >2.59 for the ethmoid sinus/maxillary sinus (E/M) CT score ratio demonstrated a sensitivity of 94% and a specificity of 90% for eosinophilic CRSwNP. Additionally, the Japanese Epidemiological Survey of Refractory Eosinophilic Chronic Rhinosinusitis (JESREC) scoring system was established to diagnose eosinophilic CRSwNP.[55] The scoring criteria consist of bilateral disease sites (3 points), nasal polyps (2 points), shadow of ethmoid cells ≥ shadow of maxillary sinus on sinonasal computed tomography (CT) (2 points), and eosinophilia in the peripheral blood (2% to 5%, 4 points; 5% to 10%, 8 points; >10%, 10 points). For CT imaging of the sinus, the "shadow" referred to opacification by inflammatory soft tissue in CRS. Using this system, non-eosinophilic CRSwNP was determined by a JESREC score ≤10, and eosinophilic CRSwNP was determined by a JESREC score ≥11. The sensitivity and specificity of this criterion were 83% and 66%, respectively, in the Japanese population.[55]

Eosinophilic shift of CRSwNP

Mucosal eosinophilia exhibits significant geographic and ethnic differences and shifts over time in CRSwNP. Studies have demonstrated that pronounced eosinophilic infiltration is predominant in white Western patients with nasal polyps,[28,59] while the eosinophilic phenotype constitutes less than one-half of the cases of polyps in East Asia.[6] More than 2 decades ago, it was reported that moderate-to-high infiltration of eosinophils was found in 77% of 46 nasal polyps cases in Europe.[26] Eosinophilic (edematous) polyps have been considered the most common type, constituting 86% of polyps[22]; however, they constituted only 12% and 44% of polyps in Thailand[60] and Japan,[61] respectively. In Japan, the non-eosinophilic type has been considered the most common subgroup of CRSwNP for more than 30 years.[19]

The few previous studies that directly compared CRSwNP in Western and Eastern populations demonstrated that their inflammatory patterns are distinguishable. Zhang et al.[62] found less activated eosinophils in nasal polyps in South Chinese patients compared with polyps in European patients. Genetic factors or gene/environment interactions are believed to play a role in eosinophil infiltration as evidenced by the reduced eosinophilia in U.S. second-generation Asian patients with CRSwNP compared with white patients,[45] although these findings have been questioned.

However, within the last 2 decades, eosinophilic nasal polyps have shown an increasing tendency in terms of absolute count and percentage in Asian countries.[30,63] Kim et al.[30] found that the proportion of eosinophilic CRSwNP increased from 24% to 51% during a 17-year period using 5 eosinophils/HPF as a diagnosis criterion. Similarly, Shin et al.[64] observed that eosinophilic CRSwNP has significantly increased over the last few years in Korean subjects; from 52.3% in 2001 and 47.7% in 2006 to 62.6% in 2011; suggesting the Korean CRSwNP pattern was adopting a western pattern because of the westernized lifestyle. In Japan,[65] about two-thirds of polyp patients recently investigated were IL-5+, although polyps were described to be mainly neutrophilic in the past, further supporting the concept of eosinophilic shift. Similarly, Katotomichelakis et al.[63] compared absolute counts of eosinophils in CRSwNP and found that the number of eosinophils increased from 5 to 35 per HPF within 12 years in Thailand. A significant increase of ECP/MPO ratio in tissue has also been revealed over 8 years in Chengdu/Southwest China, suggesting a shift to type-2 (eosinophilic) inflammation over time.[56] Consistent with this finding, eosinophil counts and cutoffs are expected to change with time in Asia and possibly throughout the world.

This eosinophilic shift is thought to be due to environmental factors and indicates that the inflammatory patterns may change over time. In particular, the increase of eosinophil numbers in Thai CRSwNP patients was demonstrated at 2 time points 12 years apart, and was accompanied by significant elevation of mucosal *Staphylococcus aureus* (SA) carriage over time.[63] The increase of intramucosal SA carriage has been suggested to be associated with elevation of local IgE levels and eosinophilic shift. Indeed, Wang et al.[66] have demonstrated that the presence of SE-IgE antibodies within the polyp mucosal tissues varied in parallel to the type-2 inflammation signatures. Another study has suggested that non–type-2 recurrent CRSwNP might change over time into type-2 (eosinophilic) inflammation accompanied with SE-IgE increase.[56] Similarly, Ba et al.[67] have demonstrated that IL-5 positive (eosinophilic) nasal polyps were associated with greater gram-positive bacteria colonization, whereas key cytokine–negative nasal polyps (ie, polyps not expressing IL-5, IL-17, or interferon-γ [IFN-γ]) were associated with a greater gram-negative bacteria load. While these studies collectively suggest an important role of bacteria in impacting the inflammatory pattern of nasal polyps, other environmental factors such as air pollution, infectious agents and host factors, and smoking habit might also play a role in influencing CRSwNP pathogenesis.[68] Further studies, however, are needed to clarify this relationship between

environmental factors and inflammatory pattern shift in CRS.

Eosinophil-related biomarkers and Th cells in eosinophilic CRSwNP

The presence of eosinophils does not indicate their activation, and biomarkers such as byproducts of eosinophil and key cytokines may mirror different activation statuses of eosinophils.[62] Histologic methods of eosinophil counts are tissue-based, semiquantitative, and subject to interrater and intraspecimen variations in eosinophilia interpretation. Therefore, more objective eosinophil-related markers have been explored to define eosinophilic CRS, including ECP, ECP/MPO, major basic protein (MBP), eotaxins, total IgE, or SE-IgE.[6,62,66]

Eosinophil counts may not accurately quantitate degranulated eosinophils, whereas ECP has been suggested to be a more accurate reflection of eosinophil infiltration in recent studies. Tan et al.[69] classified CRS as eosinophilic or non-eosinophilic using a 95th percentile threshold of ECP obtained from control tissue. A definition of eosinophilia was established as ECP >131.5 ng/mg from 34 controls,[69] while another criterion was ECP >289.75 ng/mg from 82 controls[70] from the same team. This difference indicates that ECP level varies within a wide range among normal controls and sample size might affect the cutoff value of ECP. Therefore, the ECP-based classification system needs multicenter studies to set up a universal criterion with sufficient samples.

Compared with eosinophil counts, quantification of eosinophil relevant biomarker in tissue reduced interrater and intraspecimen bias. However, the sensitivity and specificity of biomarker determines its stability and credibility in real practice. To date, there is a knowledge gap with respect to the diagnostic accuracy of such markers. Furthermore, their utilization is complicated depending on laboratory availability and they are expensive to apply in clinical practice.

Associated with eosinophils and neutrophils, variable Th cell accumulations manifest in the mucosal tissues of CRS patients. Studies have demonstrated that Th2-biased cytokine profiles, with the release of IL-4, IL-5, and IL-13, are key features of eosinophilic CRS,[71] which is the most common type in Europe and the United States, whereas neutrophilic CRS has been characterized by a significant increase in the Th1/Th17 cell pattern[62] and the expression of elevated amounts of IFN-γ and/or IL-17.

In white subjects, CRSwNP is often skewed toward severe Th2 inflammation with defective regulatory T cell (Treg cell) functions.[72] In contrast, mixed Th1/Th17 reactions with impaired Treg cell function were demonstrated in nasal polyps in Chinese patients.[62] Eosinophilic/type 2 polyps have more asthma comorbidity and disease recurrence, at least in Europe[7] and in China.[57] However, the degree of type 2 cytokines/eosinophilia is lower in the polyps of Chinese patients than in European ones.[66]

Recently, Wang et al.[66] directly compared the Th cytokine profile of CRS among 3 continents: 3 centers in China (Beijing and Chengdu) and Japan (Tochigi) and 3 centers in Europe (Benelux and Berlin) and Australia (Adelaide). They found that CRSwNP patients in Europe, Australia, and Japan showed higher solitary IL-5 expression than the patients in Beijing and Chengdu. In Beijing, a mix of Th2/Th1, Th2/Th17, Th1/Th17, and Th2/Th1/Th17 patterns was predominant in CRSwNP, whereas CRSwNP patients in Chengdu showed a non–Th2/Th1/Th17–dominant pattern.

Cross-sectional cluster studies have identified subsets of asthma patients that share clinical characteristics.[73] This statistical approach might provide a new area for defining CRS diversity. Studies using cluster analysis considered biological markers together with clinical parameters to define endotypes in Chinese CRS patients. Distinct CRS clusters based on inflammatory mechanisms alone have greater potential to aid in the development of individualized treatment strategies for CRS patients than phenotype information only, as demonstrated by Tomassen et al.[7] Liao et al.[18] also reported an analysis of CRS in based on the classical European type 2 pattern of CRSwNP, which presents as high blood and mucosal eosinophil counts and overexpression of type 2 inflammatory mediators (IL-5, IL-13, eotaxin, IgE, and SE-IgE). However, the established cutoff values for these type 2 biomarkers were still inapplicable to eosinophilic/type 2 CRSwNP due to differences in the severity of type 2 inflammation. It will be important to identify validated biomarkers in different continents/countries for future research and for the introduction of precision medicine.

Conclusion

Tissue eosinophilia is present in a majority of CRSwNP patients, but is currently more common in the West than in the East; however, the severity of inflammation also varies within a continent and may further develop to a more severe type 2/eosinophilic inflammation, specifically in Asia. Due to the existence of geographic, ethnic, and environmental differences, location-specific and ethnic-specific cutoff values may be relevant; however, these are also likely to change over time. In fact, eosinophilic CRSwNP, a phenotype with eosinophil dominant inflammation, is closely associated with clinical manifestation of the disease. However, no consensus has been reached on the standardization of this concept. Moreover, it is noteworthy that clinical factors such as prognosis and recurrence rate are also essential to appraise the whole concept of eosinophilic CRS. Furthermore, eosinophil-relevant biomarkers may be clinically used for diagnostic purposes, for classification guidance, or as tools for predicting prognosis and treatment response in CRSwNP.[74,75] Considering future directions in CRS classification, cluster analysis of not only traditional phenotype information but also endotype features should be used. Based on such an analysis, subsequent

discriminant analysis and development of a decision tree could determine the cutoff values of important clinical and immunological parameters for classification of different subgroups. Indeed, a precise identification of the subgroups, based on a better insight into different inflammatory patterns determined using these cutoff values, might allow rhinologists to employ disease-specific values in their regions to optimize the treatment approach and prognosis of the outcome.

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