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Classification of chronic rhinosinusitis according to a nasal polyp and tissue eosinophilia: limitation of current classification system for Asian population

Sung-Woo Cho[1], Dae Woo Kim[2], Jeong-Whun Kim[1], Chul Hee Lee[1], and Chae-Seo Rhee[1,3,4,*]

[1]Department of Otorhinolaryngology-Head and Neck Surgery, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam 13620, Korea
[2]Department of Otorhinolaryngology-Head and Neck Surgery, Seoul Metropolitan Government - Seoul National University Boramae Medical Center, Seoul National University College of Medicine, Seoul 07061, Korea
[3]Research Center for Sensory Organs, and [4]Institute of Allergy and Clinical Immunology, Seoul National University Medical Research Center, Seoul 03080, Korea

Chronic rhinosinusitis (CRS) can be classified according to the presence of a nasal polyp (NP): CRS with NP (CRSwNP) and CRS without NP (CRSsNP). CRSwNP has characteristics with high infiltration of tissue eosinophilia with a burst of Th2 inflammatory cytokine. However recent findings in Eastern Asia countries suggest that CRSwNP can be divided according to the presence of tissue eosinophilia. Thus, CRSwNP can be classified into eosinophilic and noneosinophilic. Eosinophilic CRSwNP seems to have different immunological and clinical feature compared to noneosinophilic CRSwNP. From the same point of view, CRSsNP can also be divided according to tissue eosinophilia. However, the meaning of this dichotomous categorization in CRS seems to be not quite clear. This review focus on the limitations in current subclassification of CRS according to the presence of NP and tissue eosinophilia and discuss other factors related to tissue remodeling and NP generation which may provide clues for the further understanding of CRS pathogenesis.

Key words: Sinusitis; Classification; Nasal polyps; Eosinophilia; Caucasians; Asians

INTRODUCTION

According to the current guideline, mostly lead by the Western countries, Chronic rhinosinusitis (CRS) has been classified phenotypically according to the presence of nasal polyp (NP): CRS with NP (CRSwNP) and CRS without NP (CRSsNP) [1]. It is known

***Correspondence:** Chae-Seo Rhee
Department of Otorhinolaryngology-Head and Neck Surgery, Seoul National University Bundang Hospital, 82 Gumi-ro 173beon-gil, Bundang-gu, Seongnam 13620, Korea
Tel: +82-31-787-6074
Fax: +82-31-787-4057
E-mail: csrhee@snu.ac.kr

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that CRSwNP patients have a greater disease burden compared with those suffering from CRSsNP with respect to disease severity and poor treatment outcomes [2, 3]. Also biologically, CRSwNP and CRSsNP are known to have distinct characteristics. In CRSwNP, inflammation due to the T-helper type 2 (Th2) cell subset used to be the dominant one resulting in tissue eosinophilia with a high prevalence of coexisting asthma [1, 4, 5]. CRSsNP is thought to result from recurrent episodes of acute rhinosinusitis or occlusion of the sinus ostium secondary to anatomic variation, which may contribute to hypoxia development in sinus cavities [6, 7]. Previously, it was thought that inflammation due to the Th1-type subset was the dominant type of inflammation [4, 8]

Although there are conflicting reports, it seems that CRSsNP does not reflect a certain type of T-cell cytokine inflammatory environment. However, it seems evident that cytokine profiles are distinct between CRSwNP and CRSsNP. When compared to CRSsNP or control, CRSwNP has increased levels of Th2 mediators including IL-5, IL-13, eotaxin-2 [5].

Recently, the importance of tissue eosinophilia has been recognized that CRS with tissue eosinophilia seems to have unique characteristics with more disease severity and poor outcome after surgical intervention [9-12]. Studies from Western countries, CRSwNP seems to have more tissue eosinophilia than CRSsNP that about 80% of CRSwNP are presented with tissue eosinophilia with robust Th2 response [4, 13]. Likewise, it is more likely that patient with tissue eosinophilia tended to have NPs compared to patients without tissue eosinophilia [14]. Thus in these circumstances, especially for Western countries, classifying CRS according to the presence of NP has some sort of meaning of classifying CRS according to the presence of tissue eosinophilia.

EOSINOPHILIC VERSUS NONEOSINOPHILIC CRSwNP

In contrast to the United States or Europe, studies showed that in Eastern Asian populations (Korea, Japan, China) about >50% of cases of CRSwNP are non–eosinophil-dominant and that, in some samples, neutrophils are the dominant cell type characterized by mixed Th1 or Th17 type inflammation [8, 15, 16]. This was also demonstrated by a multicenter study performed in Europe, Asia, and Oceania, that CRSwNP tissues from patients from Western countries were Th2 biased, where as those from Beijing mainly demonstrated Th1/Th2/Th17 mixed pattern [17]. Interestingly, NPs from Asian population born in and living in the United States tends to show less eosinophilic compared to those with Caucasian, African American, and Hispanic patients, suggesting that genetic difference may play a crucial role in the development of tissue eosinophilia in NP [18]

Such cases of noneosinophilic CRSwNP seem to have different clinical, histological and immunological features and treatment outcomes. Eosinophilic CRSwNP is known to have more severe symptoms and computed tomography (CT) score compared to noneosinophilic CRSwNP and poorer surgical outcome after surgery [9, 16]. Also, eosinophilic CRSwNP tends to have comorbid asthma more frequently [19, 20]. Aspirin-exacerbated respiratory disease which often presents the most severe manifestations of both asthma and NP also present as eosinophilic CRSwNP [5]. Prominent ethmoidal involvement is related with eosinophilic CRSwNP while noneosinophilic CRSwNP showed more maxillary involvement [21, 22]. It is known that eosinophilic CRSwNP responds well to steroid therapy [23, 24], however noneosinophilic CRSwNP tends to have resistance to steroid therapy, especially if it is neutrophil-dominant [25].

These two have distinct cytokine pattern with eosinophilic CRSwNP skewing toward more Th2 type inflammation with higher expression of interleukin (IL)-5, GATA-3, and eotaxin. As for histology beside the feature of tissue eosinophilia, noneosinophilic CRSwNP is featured by a thinner basement membrane and increased epithelial proliferation [8, 21]. From these observations, many clinicians in Asia think the current classification system according to only the presence of NP is not enough and rather they tend to further classify CRSwNP into "eosinophilic" and "noneosinophilic" according to eosinophil infiltration within NP [8, 15, 16]. One study from Japan performed cluster analysis to generate four clusters based on the presence of NP and tissue eosinophilia [26]. In their study, the presence of NP and tissue eosinophilia were the 2 strongest predictors of clustering.

Thus in overall, it seems that tissue eosinophilia seems to be important for differentiating the NP in the Asian population. One multicenter study in Japan had shown the importance of tissue eosinophilia regardless of the presence of NP [9]. In this study, they have defined eosinophilic CRS in cases where presenting eosinophils in the submucosa of the ethmoid cavity or NP that are more than 70 eosinophils/high-power field (HPF) since this cutoff value presented a significantly increased risk of disease recurrence. They have also made a scoring system for predicting

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eosinophilic CRS by using preoperative clinical features such as CT scan (ethmoid/maxillary ratio), the presence of NPs, peripheral blood eosinophils. With the presence of aspirin or nonsteroidal anti-inflammatory drug intolerance or comorbid asthma, the degree of severity depicted as refractoriness increases. Thus in this study, they have completed the spectrum of severity of eosinophilic CRS according to the clinical features from mild to severe eosinophilic CRS. Even though this study has listed a spectrum of CRS in perspective of tissue eosinophilia regardless of the presence of NP (however there was more likelihood of the presence of NP in cases with eosinophilic CRS), it seems to be evident that eosinophilic CRSwNP is quite distinct and that it should be differentiated from noneosinophilic CRSwNP.

MECHANISM OF TISSUE EOSINOPHILIA: IS THERE A ROLE OF ATOPY?

Then, what is the underlying mechanism that categorizes CRSwNP into eosinophilic and noneosinophilic? Is it underlying atopy? That is, does systemic atopy initiate Th2 inflammation and tissue eosinophilia in NP?

So far, we do not have a clear answer to this question. The role of systemic atopy in CRS pathogenesis is not clear. Some studies (mostly performed in Western countries where CRSwNP is predominantly eosinophilic type) have shown that the prevalence of atopy in patients with CRSwNP is not significantly higher than that in patients with CRSsNP or in healthy controls, and that systemic levels of total/specific IgE in CRSwNP is not high [27, 28].

A variety of IgEs detected in the polyp tissue are known to be somewhat discordant with the serum specific IgEs that are reflected as atopy. Thus the variety of IgEs in the NP tissue is called "polyclonal" rather than "allergic" since they only reflect partially from the serum and skin prick test results [29]. This presence of polyclonal IgE in polyp tissue, especially in cases positive for *Staphylococcus aureus* enterotoxin-specific IgE is one of the evidence of local production of IgE from the NP tissue itself [29, 30]. A study from Western population showed the significant effect of polyp shrinkage after treatment of anti-IgE monoclonal antibody in CRSwNP even without atopy and this further supports the aforementioned assumption [31]

One study showed that superantigen from colonized *S. aureus* leads to activation of T cells and B cells within NP tissue, which results in infiltration of locally produced polyclonal IgE and eosinophils [32]. Our recently developed animal model of NP had also established the role of *S. aureus* superantigen in the pathogenesis of NP. *S. aureus* enterotoxin B when applied at low dose induced nasal polypoid lesion with an increased eosinophilic infiltration in ovalbumin sensitized murine model [33]. Staphylococcal superantigens skew inflammation towards Th2-type inflammation [34], and CRSwNP revealed high concentrations of IL-5 and IL-13 [5]. Originally, these cytokines were thought to be generated only in Th2 cells, but now they are known to also be produced from "innate lymphoid cell 2" (ILC2) and that ILC2 levels are increased in CRSwNP [35, 36].

B cells maturing in a high "burst" of the release of Th2-type cytokines (e.g., IL-4, IL-5, IL-13) will tend to switch to IgE regardless of what the antigen is, and this phenomenon seems to be the main theme in the pathogenesis of CRSwNP [7]. In Th2-type inflammation, expression of many cytokines that is responsible for differentiation, survival, and activation of eosinophils are elevated [5, 37]. Eosinophil itself is also an important source of these mediators, thus burst of Th2 inflammation in eosinophilic CRSwNP will cause tissue eosinophilia itself that results in self-perpetuating tissue inflammation [7].

However, the contribution of atopy in the development tissue eosinophilia cannot be ignored. Studies showed that in cases of atopy, more significant tissue eosinophilia was observed compared to nonatopy cases [24, 38]. Aforementioned study in Japan has shown the significantly higher prevalence of atopy in eosinophilic CRS compared to noneosinophilic CRS, even though the authors have not clarified the role of atopy [9]. Although, not in the key role, systemic eosinophilia in patients with atopy may be nonspecifically recruited into the tissue of CRSwNP where abundant chemotactic factors are expressed, thus augmenting the tissue eosinophilia [39]. Thus in a somewhat portion of the tissue eosinophilia may have resulted from the systemic atopy.

Our previous result also showed that optimal cutoff value for tissue eosinophilia predicting the presence of atopy is 11% [40]. This means that if we define tissue eosinophilia when the proportion of eosinophils among the entire inflammatory cells is above 11%, there is the significantly higher rate of atopy in patients with CRSwNP. However, if the cutoff value is defined above this level, there seems to be no significant difference in the prevalence of atopy. Thus it seems that, until a certain level of tissue eosinophilia, there is an actual effect of atopy. However, in more prominent tissue eosinophilia, there might be a true eosinophilia which resulted from a profound burst of Th2 inflammation which

overwhelms the underlying allergic inflammation.

Unfortunately, so far as we know, there are few studies that evaluated how much the tissue eosinophilia has resulted from the atopy. In the future studies, in order to discover the impact of systemic atopy to the tissue eosinophilia, comparing the degree of eosinophil infiltration along with tissue cytokines that are related would be necessary, and especially for Asians, the status of the tissue eosinophilia (eosinophilic or noneosinophilic) should be controlled. That is, comparison should be performed within eosinophilic CRSwNP or noneosinophilic CRSwNP.

DEFINING TISSUE EOSINOPHILIA

We now know that CRSwNP can be classified into eosinophilic CRSwNP and noneosinophilic CRSwNP. However, one of the major obstacles which limit categorizing CRSwNP into eosinophilic and noneosinophilic type is that, so far, no standard system for the definition of tissue eosinophilia exist. Some authors have described a scoring system according to the severity of eosinophil infiltration in the NP: grade 0, no eosinophil; 1, slight infiltration; 2, moderate infiltration; 3, marked infiltration [41, 42]. However, this system is based on the subjective judgment of the pathologist. Other studies have counted the number of eosinophils per HPF [11, 14] but the number designated as the cutoff point is arbitrary and choosing which field to examine is another problem. Some studies have described "tissue eosinophilia" as a proportion of eosinophils in comparison with the rest of the cell population [43, 44], and this too has limitation since a proportion may change according to the total infiltrated inflammatory cell number. Other study measured the level of eosinophilic cationic protein in tissue to estimate tissue eosinophilia [45]. Despite these efforts, a "gold standard" to define tissue eosinophilia is elusive. Another problem is that tissue eosinophilia has uneven distribution throughout the tissue and this might be the most important reason for the discrepancy [46]. Even with the existence of a standard for tissue eosinophilia, this uneven distribution of tissue eosinophilia will make the clinicians to be confused whether to decide the NP as eosinophilic or noneosinophilic.

If a certain biologic parameter or marker should be used for endotyping, it should characterize the clinical difference and treatment outcomes. Thus if tissue eosinophilia should be used for the parameter for endotyping CRSwNP, the cutoff value for defining tissue eosinophilia should be determined by the difference in clinical outcome. One study showed that ≥10 eosinophils/HPF for the definition of tissue eosinophilia reflects less improvement in symptom scores after endoscopic sinus surgery [11]. Studies from Japan showed that when tissue eosinophilia was defined as ≥70 eosinophils/HPF, a significant difference in disease recurrence after endoscopic sinus surgery was found [9, 16].

Previously, we have reported that there was no difference in clinical outcome between eosinophilic and noneosinophilic CRS after endoscopic sinus surgery [47]. It this study, tissue eosinophilia was defined when eosinophils account for >20% of the total inflammatory cells. Now it seems that the reason for this insignificance is because this "20%" value is somewhat arbitrary and the clinical insignificance might have resulted from the criteria that had been decided without considering the clinical outcome. On the other hand, our result may also reflect the limitation of the current dichotomic classification system. Since even within each subgroup there may be underlying different pathogeneses, there may seem to be no difference between groups. Tissue eosinophilia can give us some proportion of the disease pathogenesis, however, it may not be all and this should be noted as well.

WHAT IS EOSINOPHILIC CRSsNP: IS IT DIFFERENT FROM NONEOSINOPHILIC CRSsNP?

Turing a viewpoint, the categorization according to tissue eosinophilia can also be applied to CRSsNP. Hence, CRSsNP can also be classified as eosinophilic and noneosinophilic.

Few studies have characterized the differences between these 2 groups. However, in contrast to the known differences between eosinophilic and noneosinophilic CRSwNP, there are some conflicting results in CRSsNPs.

One study showed that eosinophilic CRSsNP when compared to noneosinophilic CRSsNP, had higher CT score and worse preoperative and postoperative endoscopy scores [14]. Similarly, another group had reported that eosinophilic CRSsNP had different clinical features compared with noneosinophilic CRSsNP [12]. The same group also compared the outcome as depicted by postoperative symptom scores after surgical intervention by using a different standard in tissue eosinophilia and it turned out that eosinophilic CRSsNP had a worse outcome compared to noneosinophilic CRSsNP [11].

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However, in these studies, the possibility of coexisting atopy was not fully controlled. Some portion of the tissue eosinophilia might have resulted from the underlying atopy and also this coexisting allergic rhinitis might have affected the outcome of surgical intervention. One study showed that eosinophil number in tissue from CRSsNP was higher in an atopic group compared with a nonatopic group [48]. They also showed that levels of markers of Th2-type inflammation (e.g., IL-5, IL-13) were higher in the atopic group.

On contrary, other studies including our own [47, 49], have shown different results. In these study, preoperative CT scores, treatment outcome did not show significant differences among eosinophilic CRSsNP and noneosinophilic CRSsNP. This discrepancy might have resulted from the different definition of tissue eosinophilia, or the lack of clear definition of NP. One of the aforementioned studies has categorized CRS into 4 clusters by using the cutoff score the NP with a score of 2.5 (endoscopic score of 10 in total, with each nostril score of 5) and tissue eosinophilia of 80.5/HPF [26]. It was found out that eosinophilic CRSsNP was not well predicted by using this cutoff value while other groups such as noneosinophilic CRSsNP, noneosinophilic CRSwNP, and eosinophilic CRSwNP fitted well. This group showed that eosinophilic CRSsNP had dissociation between local (tissue) and peripheral eosinophil counts that it clearly showed elevated tissue eosinophilia with only slightly elevated peripheral eosinophil counts. No frank NPs were identified endoscopically, however, during surgery, mucosal edema or polypoid lesions were identified. Thus, this group seems to be in between the border of other groups.

One recent study depicted that CRSsNP is comprised of heterogeneous inflammation patterns that 23%, 36%, and 15% of CRS showed Th1-, Th2-, and Th17-type inflammation [50]. In this study, they found no significant differences in levels of inflammation markers between atopic and nonatopic patients.

The discovery of diverse inflammatory patterns suggests that even in CRSsNP, categorizing according to tissue eosinophilia only does not seem to be enough.

TISSUE REMODELING: A NEW INSIGHT FOR ENDOTYPING?

One could ask "What is the difference between eosinophilic CRSwNP and eosinophilic CRSsNP?" If tissue eosinophilia is a true endotype, does the presence of NP matters? To answer these questions, tissue remodeling of NPs must be understood.

Previous studies depict that in the condition of tissue eosinophilia, the presence of NP is quite significant compared to those without tissue eosinophilia [5, 14]. Thus it seems that in conditions of Th2 inflammation and tissue eosinophilia, tissue remodeling factors are in effect of generating of NPs.

CRSsNP is characterized by fibrosis, thickening of basement membranes, and hyperplasia of goblet cells [51]. Besides eosinophil infiltration, NP histology can be characterized as: edematous stroma with albumin deposition; pseudocyst formation; infiltration of inflammatory cells into subepithelial and perivascular regions; edema formation; absence of collagen production [52].

Levels of transforming growth factor (TGF)-β (a key mediator in the promotion of fibrosis and airway remodeling) have been found to be increased in patients with CRSsNP compared with those suffering from CRSwNP [51]. TGF-β is considered to be a "master switch" in the induction of a "pro-fibrotic program," and acts as chemoattractant and proliferation factor for fibroblasts [53]. TGF-β and its signaling might be universally applicable markers to differentiate distinct CRS entities. However, some studies reported the level of TGF-β expression to be higher in CRSwNP compared with healthy controls or CRSsNP [54, 55]. TGF-β expression is known to have regional variations in that the inferior turbinate and middle turbinate show the lowest expression. Also, stromal cells have increased expression of TGF-β compared with epithelial cells [56]. Such regional and cellular variation in expression seem to have resulted in conflicting data among studies [57].

Factors within the coagulation cascade are involved in the control of tissue remodeling in CRSwNP. The imbalance between clot formation and fibrinolysis (due to increased expression of coagulation factors and decreased fibrinolytic activity, respectively) leads to fibrin accumulation in NP [58, 59]. Increased deposition of fibrin can aid formation of a "scaffold" that traps plasma proteins to enhance tissue edema. Fibrin accumulation in NPs is thought to be related to 2 factors: coagulation factor XIIIa (expression of which is increased by Th2-type inflammation in NPs) and the tissue plasminogen activator (t-PA; a key protein in fibrin degradation). In vitro studies have suggested that Th2-type inflammatory cytokines suppress t-PA expression in cultured human nasal epithelial cells [59]. To summarize, it seems that a Th2-type inflammatory environment shifts towards fibrin

accumulation, thereby leading to edematous tissue in NPs. It is known that TGF-β1 is also affected by t-PA and that TGF-β activates t-PA expression by acting as an autocrine [60, 61].

If this is true, why does eosinophilic CRSsNP have nonpolypoid features? There may be 2 possibilities: (1) Th2-type inflammatory cytokines may not be present at sufficient levels to regulate factors related to tissue remodeling in eosinophilic CRSsNP; (2) factors related to tissue remodeling and NP generation might not be present in CRSsNP even in the presence of tissue eosinophilia.

From this perspective, one may think that in eosinophilic CRSsNP, Th2 inflammation is not as high as in eosinophilic CRSwNP and that its clinical characteristics comparing to noneosinophilic CRSsNP are somewhat lacking.

TISSUE REMODELING IN NONEOSINOPHILIC CRSwNP

Meanwhile, other factors which are not under control of Th2 may affect in NP generation in noneosinophilic CRSwNP. Our previous study described morphologic differences between NPs in patients with noneosinophilic CRS and in those with eosinophilic CRS. Noneosinophilic CRSwNP had contained significantly more pseudocysts compared with eosinophilic CRSwNP [21]. In this study, they have also found that increased epithelial proliferation in noneosinophilic CRSwNP. It is also known that noneosinophilic CRSwNP is often associated with glandular hypertrophy and subsequent fibrosis, thinner basement membrane [15, 62]. These distinct features suggest that other factors related to tissue remodeling and NP generation may be present in non-eosinophilic CRSwNP.

Thus, it seems that the factors related to tissue remodeling and NP generation and their relationship with cytokine profiles should be revealed. It will make more straight-forward in endotyping of CRS.

A MULTIDIMENSIONAL DISEASE SPECTRUM: A KEY TO THE TARGETED THERAPY

Until now, clinicians tended to regard CRS as a dichotomous disease that CRS was classified as CRSwNP or CRSsNP and even within CRSwNP subgroups, clinicians tended to categorize as eosinophilic CRSwNP and noneosinophilic CRSwNP. It is true that these efforts made us understand the pathophysiology of CRS a lot more. However, we all know that CRS has a much diverse disease course with a variety of phenotypes and that there is no single treatment for CRS indicating that there is no common pathophysiology for CRS.

Recently Tomassen et al. [63] had performed a multi-institutional study among European Countries in which they have tried to find out inflammatory endotypes of CRS based on cluster analysis of immunologic biomarkers in a phenotype-free approach. In their study, CRS was composed of 10 clusters based on 5 different groups of cytokines: (1) markers of Th2 inflammation: IL-5, eosinophil cationic protein, total tissue IgE, and *S. aureus* enterotoxin-specific IgE, (2) neutrophilic and proinflammatory cytokines: IL-1B, IL-6, IL-8, and monocyte chemoattractant protein, (3) Th17 or Th22 related cytokines: IL-17A, IL-22, and TNF-α, (4) Th1 marker: IFN-γ, and (5) TGF-β1. Thus the authors urged that CRS is not a dichotomous disease but rather a multidimensional disease with the underlying different inflammatory axis. Interestingly, these clusters were solely based on immunologic or inflammatory endotypes, and yet they were roughly correlated with the phenotypes irrespective of comorbid asthma or the presence of NP. However one phenotype can include several endotypes and at the same time, one endotypes can have several phenotypes. Thus, clinical phenotype does not actually give us direct information about the underlying molecular mechanism.

This categorization according to inflammatory markers has opened up the possibility for the clinicians to use recently developed monoclonal antibody therapies such as omalizumab (anti-IgE), mepolizumab (anti–IL-5), or dupilumab (anti–IL-4/IL-5) targeting specific cytokines in cases of refractory CRS. The therapeutic effects of these targeted therapies had been proven in selected cases of eosinophilic CRSwNP [31, 64, 65]. However, in practice, this kind of approach is not easy to be accepted since tissue needs to be harvested and analyzed for cytokine profile which takes time and economic burden as well as the cost of monoclonal antibodies. Thus it is also important to find practical biomarkers or phenotypes that can be easily accessed and also correlate well to the endotypes.

SUMMARY

Current guideline proposes subclassification using polyp

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status. And we also know that presence of tissue eosinophilia is somewhat related to higher burden of disease, and poorer disease course. In Western countries, about 80% CRSwNP are found to have Th2 inflammation with tissue eosinophilia. Thus for Western countries, categorizing CRS into CRSwNP and CRSsNP seems to be quite acceptable because the presence of NPs also has the meaning of the presence of tissue eosinophilia.

However, although nowadays the proportion is increasing [66], about 35%–45% of Eastern Asian CRSwNP shows this feature. Thus for Eastern Asian countries, subclassification of CRS by only using polyp status is somewhat inadequate. However, as mentioned in our previous study, even if we categorize CRS according to NP and tissue eosinophilia into eosinophilic CRSwNP, noneosinophilic CRSwNP, eosinophilic CRSsNP, noneosinophilic CRsNP, this is still not straight forward. This is because CRS is not a dichotomous disease and nowadays it is rather being accepted as multidimensional disease.

Thus identification of inflammatory cytokines or cellular patterns for endotyping of CRS and their correlation with clinical features seems to be necessary. Also, identification of the factors related to tissue remodeling and NP generation may provide clues for the further understanding of the pathogenesis.

After all, identification of such biomarkers would give us better understanding of the pathogenesis and will guide us to the development of more specific, more precise targeted therapy in refractory CRS.

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