Endotypes of Asian chronic rhinosinusitis with nasal polyps
A narrative review

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ABSTRACT
Chronic rhinosinusitis (CRS) is classified as CRS with nasal polyps (CRSwNP) and CRS without nasal polyps (CRSsNP). CRSwNP is a distinct phenotype with heterogeneous endotypes and complex pathophysiological mechanisms. Inflammation of the sinonasal mucosa that forms NPs causes symptoms such as nasal obstruction, rhinorrhea, and smell loss, and lowers patients’ quality of life. In recent years, researchers have attempted to elucidate the inflammatory endotypes of CRSwNP, and the inflammatory pattern of Asian CRSwNP was found to be different from that of Western CRSwNP. The main endotype of CRSwNP is type 2 inflammation, in which interleukin (IL)-4, IL-5, and IL-13 are key cytokines. In contrast, type 1 inflammation (interferon-γ) and type 3 inflammation (IL-17 or IL-22) play essential roles in Asian CRSwNP. Biological agents, which have recently been highlighted for the treatment of CRSwNP, are very effective in suppressing the type 2 inflammatory response and recovering smell loss. However, little information is available on the efficacy of these biologics in Asian patients with CRSwNP. Herein, we reviewed the endotypes of Asian CRSwNP and compared them to those of Western CRSwNP. We identified changes in the inflammatory patterns and summarized the therapeutic options for Asian CRSwNP.

Keywords: Asians; Chronic rhinosinusitis; Endotype; Eosinophils; Nasal polyps

INTRODUCTION
Chronic rhinosinusitis (CRS) is an inflammatory disease of the sinonasal mucosa that is caused by various environmental factors and an imbalance in host immunity [1]. Infiltration of inflammatory cells in the epithelial and subepithelial layers of the sinonasal mucosa is an important pathophysiological mechanism of CRS. These inflammatory processes cause mucosal swelling and hypersecretion and trigger nasal symptoms such as nasal obstruction, rhinorrhea, posterior nasal drip, smell loss, and facial pain [2]. CRS can be diagnosed if symptoms persist for more than 12 weeks, and endoscopic findings are abnormal, and/or inflammation is confirmed on CT [3]. These bothersome symptoms are related to decreased quality of life and productivity [4].

CRS is one of the most common diseases of the upper respiratory tract and affects approxi-
mately 10 percent of the world’s population [1]. Initial treatment of CRS is appropriate medical therapy with topical or systemic corticosteroids, antibiotics, saline irrigation, and other medications. Endoscopic sinus surgery (ESS) is considered for patients who do not respond to medical treatment. Recently, biologics have emerged as a new treatment option for type 2 inflammation in CRS with nasal polyps (CRSwNP) [5].

The prevalence and burden of CRS varies across countries [6]. Particularly, there is a difference in the phenotype and endotype of CRS between Western and Asian countries [7]. CRS is classified into two phenotypes based on the presence of nasal polyps (NPs): CRSwNP and CRS without nasal polyps (CRSsNP). NP is a distinct CRS phenotype associated with frequent recurrence [8]. CRSwNP is often comorbid with type 2 inflammatory diseases of the lower respiratory tract, such as asthma and aspirin/non-steroidal anti-inflammatory drug (NSAID)-exacerbated respiratory disease (AERD/NERD) [9,10]. Endotypes of CRS are divided into type 2 and non-type 2, according to the inflammatory markers of the sinonasal tissues. CRSwNP was considered type 2 inflammation, and CRSsNP was considered non-type 2 inflammation [11]. However, previous studies were conducted in Western countries. Extensive research conducted on CRS endotypes has revealed differences by race and region [12]. Earlier studies showed that Asian patients with CRSwNP had less eosinophilic inflammation than Western patients.

In this review, we have focused on the endotype of Asian CRSwNP that is different from Western CRSwNP and discuss its clinical importance and application for management with an emphasis on type 2 biologics treatment, which is an emerging novel treatment option for type 2 CRSwNP.

CLASSIFICATION OF ENDOTYPES OF ASIAN CRSwNP

Initial endotyping studies classified CRS according to the presence or absence of eosinophil infiltration in sinonasal tissues [13]. Tissue eosinophilia was defined by the number or percentage of eosinophils measured by microscopic examination. In general, a count of 10 or more eosinophils/high-power field (HPF) is considered tissue eosinophilia, and this is accepted as evidence of type 2 inflammation in CRS [1].

Approximately one-third of Korean patients with CRSwNP are reported to have eosinophilic NPs. Kim et al. [14] conducted a histological evaluation of sinonasal tissues and defined tissue eosinophilia as > 20% of total inflammatory cells. Of 265 patients with CRSwNP, 32% had eosinophilic NPs. Based on an eosinophil count amounting to > 5% of all inflammatory cells, 33% (n = 10) of NPs were eosinophilic in the range of 26.1% ± 8.2% [15]. Early research in Japan reported that 60% (n = 175) of the NPs showed a prominent eosinophilic pattern of inflammation [16]. Yao et al. [17] defined eosinophilic NPs as > 350/HPF, and histological evaluation showed that 36% (n = 12) of the NPs were eosinophilic. In an earlier Japanese study that determined the cutoff value for polyp recurrence, ≥ 70 eosinophils were considered eosinophilic, and 60% (n = 42) of patients with NPs had tissue eosinophilia [18]. Another Japanese study determined a cut-off value of > 100 eosinophils/HPF derived from polyp recurrence. According to this criterion, 32% (n = 42) of NPs were eosinophilic [19].

Histological analysis of 151 Chinese CRSwNP patients showed that 46.4% had eosinophilic NPs with ≥ 10% criterion [20]. These eosinophilic NPs exhibited overexpression of GATA binding protein 3 (GATA-3), Th2 transcription factor, and interleukin (IL)-5, and increased mRNA expression levels of RAR related orphan receptor C (RORC), Th17 transcription factor, and IL-17A. Using the same criterion, 41.5% (n = 66) of CRSwNP patients were classified as having eosinophilic NPs in Tongji, China [21]. In Malaysia, 51% (n = 41) of patients with CRSwNP were diagnosed with eosinophil-dominant NPs (> 50% cells) [22]. CRSwNP patients in Singapore showed that 63% (n = 30) of the NPs had eosinophilia [23]. Lastly, 18% of the NPs (n = 145) were eosinophilic in Thailand [24].

However, the definition of eosinophilic CRSwNP is not standardized, and there is no consensus regarding the diagnostic criteria for tissue eosinophilia [25]. To overcome this limitation, studies have been conducted on the endotypes of CRSwNP using various inflammatory markers. Various clinical features and mucosal inflammatory markers were assessed in 246 Chinese CRS patients [26]. According to the results of cluster analysis of CRS endotypes, eosinophilic CRSwNP was related to severe uncontrolled disease and increased expression of type 2 cytokines (IL-5, IL-13, and eotaxin). In contrast, non-eosinophilic NPs exhibited increased neutrophil infiltration and an inflammatory marker (IL-8). In a cluster analysis of 375 Korean patients with CRSwNP, eosinophilic NPs tended to recur [27]. Tokunaga et al. [28] performed a large multicenter study in Japan and developed the Japanese Epidemiological Survey of Refractory Eosinophilic Chronic Rhinosinusitis (JESREC) scoring system to diagnose eosinophilic CRS, composed of bilaterality, presence of NPs, ethmoid dominance, and blood eosinophil percentage. CRS was classified into four groups according to the presence or absence of comorbid diseases (asthma or AERD/NERD): non-eosinophilic,
mild, moderate, and severe eosinophilic CRS. According to the cutoff value set, tissue eosinophilia ($\geq 70$/HPF) is associated with recurrence.

**DIFFERENCES IN ENDOTYPES BETWEEN ASIAN AND WESTERN COUNTRIES**

In a study comparing Belgian and Chinese CRSwNP patients, 54% of the Belgian patients had eosinophilic inflammation, while 7.5% of the Chinese patients showed eosinophilic inflammation [29]. The authors defined tissue eosinophilia using biomarkers of eosinophils and neutrophils as the ratio of eosinophil cationic protein (ECP) and myeloperoxidase (MPO), and ECP/MPO $> 1$ as eosinophilic inflammation. When measuring cytokines in NP tissues, 83% of Belgian samples expressed IL-5, but only 16% of Chinese samples were IL-5 positive. A European multinational study evaluated the inflammatory endotypes of CRS using cytokines [8]. In this study, 44% of CRS cases were non-eosinophilic, and 56% were eosinophilic. The CRS endotype was evaluated using cluster analysis, and three distinct endotypes were identified. First, type 1 dominant (MPO, IL-6, IL-8, IL-17, IL-22, and interferon [IFN]-γ) endotypes were mostly CRSwNP. Second, the moderate type 2 inflammatory endotypes were positive for IL-5. Finally, severe type 2 was characterized by high levels of type 2 markers, including IL-5, ECP, immunoglobulin E (IgE), and the presence of specific IgE to staphylococcal enterotoxins (SE-IgE), a potent inducer of type 2 inflammation. A similar study was conducted in China, and patients with CRSwNP were categorized into four clusters: cluster 1 with severe type 2 inflammation (IL-5, ECP, IgE, and SE-IgE), cluster 2 with type 1 inflammation (IL-6, IL-8, and MPO), cluster 3 with high tumor necrosis factor-α, and cluster 4 with type 3 inflammation (IL-17) [30]. In these two clustering studies, the proportion of type 2 endotypes was different in the west and east. The overall percentage of type 2 inflammation was 56% in the European cohort and 15.9% in the Chinese cohort. The Chinese severe type 2 inflammation group had a high rate of asthma comorbidity (36.4%) and NP recurrence (72.7%), similar to the Western type 2 endotype.

In 2016, a noteworthy study on the differences in endotypes between Western and Eastern countries was published [8]. Most CRSwNP patients from Europe or Australia had eosinophilic NPs (ECP/MPO $> 1$), whereas 70% of Chinese patients had non-eosinophilic NPs. These findings were consistent with previously reported data from East Asia. According to the JESREC score classification, Japan’s severe eosinophilic CRSwNP is approximately 13%, while the corresponding European severe type 2 CRSwNP accounts for approximately 40% [31].

**Table 1. Differences in CRSwNP endotypes between Asian and Western countries**

<table>
<thead>
<tr>
<th></th>
<th>Asian CRSwNP</th>
<th>Western CRSwNP</th>
</tr>
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<tbody>
<tr>
<td>Eosinophilic NP</td>
<td>About 30%–40%</td>
<td>About 70%–80%</td>
</tr>
<tr>
<td>Tissue eosinophilia</td>
<td>High cut-off value</td>
<td>Relatively low cut-off value</td>
</tr>
<tr>
<td>Eosinophil count</td>
<td>$&gt;70$–100/HPF</td>
<td>$&gt;10$/HPF</td>
</tr>
<tr>
<td>Type 2 inflammation</td>
<td>40%</td>
<td>80%</td>
</tr>
<tr>
<td>Asthma comorbidity</td>
<td>10%–20%</td>
<td>More than 50%</td>
</tr>
<tr>
<td>AERD/NERD comorbidity</td>
<td>Less than 1%</td>
<td>About 20%</td>
</tr>
</tbody>
</table>

Asian chronic rhinosinusitis with nasal polyps

CRSwNP, chronic rhinosinusitis with nasal polyp; NP, nasal polyp; HPF, high-power field; AERD, aspirin-exacerbated respiratory disease; NERD, non-steroidal anti-inflammatory drug-exacerbated respiratory disease.

**EOSINOPHILIC SHIFT IN ASIAN CRSwNP**

In CRS, there has been discussion about whether the differ-
ence in eosinophilic or type 2 inflammation is a genetic or an environmental factor for geographical and ethnic differences. To address this debate, a study of second-generation immigrants was conducted in Illinois [36]. CRSwNP patients whose parents were both from Asia and who were born and raised in the United States showed lower ECP levels in NP tissues than Caucasians. Only 27% of Asian patients had tissue eosinophilia, whereas approximately 60% to 70% of NP tissues from patients of other ethnicities (Caucasian, Hispanic, or African American) were eosinophilic, suggesting a role of genetic causes of CRSwNP.

Although genetic factors play an important role in the pathogenesis of CRSwNP, environmental factors cannot be excluded. The effects of Western lifestyle and dietary habits on chronic inflammatory diseases have been studied [37]. Albeit the mechanisms by which westernization influences CRSwNP in Asian countries have not been elucidated, the eosinophilic endotype of CRSwNP tends to increase in Asia, referred to as “eosinophilic shift.” In Korea, the percentage of eosinophilic polyps (> 5 eosinophils/HPF) has doubled from 24% in 1993–1994 to 51% in 2010–2012 [38]. Another Korean study reported that the prevalence of eosinophilic NPs was higher in 2011 (62.6%) than in 2001 (52.3%) and 2006 (47.7%) [39].

Katotomichelakis et al. [40] reported that the number of tissue eosinophils increased seven-fold over 12 years in Thailand. The median eosinophil count was 5 (interquartile range [IQR], 5 to 15) in 1999 and 35 (IQR, 5 to 95) in 2011. The same phenomenon was also observed in Chinese patients with CRSwNP. From 2003 to 2005, approximately 60% of patients were diagnosed with eosinophilic CRSwNP, and the percentage of eosinophils in NP tissues was 19.8% (IQR, 4.8% to 50.7%) [41]. However, 73.7% of patients were confirmed to have eosinophilic NPs in 2014 to 2016, and the percentage of eosinophils was significantly increased (38.6% [IQR, 8.6% to 61.2%]). In Wuhan, a similar shift toward eosinophilic inflammation was observed [42]. With 10% of the eosinophil criteria, 15.7% of CRSwNP patients were classified into the eosinophilic group in 2000 to 2001, with an increase to 44% in 2014 to 2015. Additionally, as a result of re-analyzing the NP tissues in non-type 2 CRSwNP patients who experienced recurrence after surgery, it was found that the ECP/MPO ratio increased (from 0.64 to 7.25) compared to the first surgery [30].

Interestingly, this increasing tendency was also observed in the West. In a group of Belgian CRSwNP patients divided into two groups (earlier [2007 to 2010] and latter [2016 to 2018]), the authors suggest that this change in endotype might be related to the increase in more severe and refractory CRSwNP cases [43].

### TAILORED MANAGEMENT IN ASIAN CRSwNP

Traditionally, intranasal or systemic corticosteroids are the treatment of choice for eosinophilic or type 2 CRSwNP [1]. Although type 2 inflammation in CRSwNP is responsive to corticosteroid treatment, it tends to recur frequently, making it difficult to repeat medical treatment. Topical treatments such as intranasal corticosteroid spray or budesonide irrigation are generally effective. However, if the drug does not enter the sinuses owing to large NPs, its effectiveness is limited. In addition, type 1 or type 3 dominant inflammatory endotypes are not well controlled with corticosteroids [44].

The benefit of low-dose long-term macrolide therapy has been studied in non-type 2 CRSsNP, particularly in patients with low total IgE levels (< 200 μg) [45]. Macrolides reduce inflammatory markers through antibacterial and anti-inflammatory actions, change the properties of mucus, and improve endoscopic and imaging findings of CRS [46]. Recently, the effectiveness of low-dose long-term macrolides on refractory CRSwNP has been discussed, but its effectiveness remains controversial and requires a well-designed controlled study [47,48].

After adequate medical treatment, ESS is the next step for treating CRSwNP. Surgical treatment can reduce the inflammatory burden by removing NPs and diseased mucosa and improving the patency of the nasal sinuses [1]. However, the recurrence of NPs after surgery is reported to be as high as 40% to 60%, and in particular, it is difficult to improve symptoms such as smell loss after surgery [12]. At present, biological agents targeting type 2 inflammation (anti-IL-4Ra, anti-IL-5, and anti-IgE) have become available for CRSwNP [49]. Omalizumab blocks free IgE in the serum, dupilumab is a monoclonal antibody to IL-4 receptor alpha (IL-4Rα) blocking IL-4 and IL-13, mepolizumab blocks IL-5, and benralizumab blocks IL-5 receptor alpha (IL-5Rα) [50]. The indication for biologics in CRSwNP is severe uncontrolled type 2 inflammation [1]. According to phase 3 studies of these biologics, these drugs effectively reduce the size of NPs and improve their symptoms [51-54]. Most of the studies on these drugs were conducted on Westerners, with very few Japanese and Korean patients [51,54]. Therefore, it is important to perform endotyping of CRSwNPs before using biologics, particularly in Asians, because of the lower frequency of eosinophilic CRSwNP. Japanese studies on dupilumab and benralizumab...
showed that these drugs were effective even in Asian patients with CRSwNP if type 2 endotypes were confirmed [55,56].

There are potential targets for other cytokines and non-type 2 inflammation in CRS [32]. A clinical trial with biologics for epithelial cell-derived cytokines, including thymic stromal lymphopoietin and IL-33, is underway. Anti-IL-17A monoclonal antibody, which is widely used in psoriasis and rheumatologic diseases, may be considered for CRSwNP targeting type 3 inflammation, which is more prevalent in Asian CRSwNP.

CONCLUSION

CRSwNP is a multifactorial and complex disease with various inflammatory subtypes. In particular, the differences in endotypes between Asians and Westerners is an important factor in understanding the pathophysiology and determining the treatment of CRSwNP. Asian CRSwNP patients had a lower proportion of type 2 inflammation than Western patients, but they tended to have an increased burden of type 2 inflammation, called “eosinophilic shift.” It is necessary to identify biomarkers that can easily identify the endotypes of NP in clinical practice. Regarding treatment with biologics targeting type 2 inflammation, further studies are needed on the therapeutic effect in Asians with CRSwNP.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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Drafting the work or revising: GR, YGJ, SDH.
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