

Otolaryngology -- Head and Neck Surgery

<http://oto.sagepub.com/>

Eosinophilic Allergic Polyp : A Clinically Oriented Concept of Nasal Polyp

Woo-Jin Jeong, Chul Hee Lee, Sang-Heon Cho and Chae-Seo Rhee

Otolaryngology -- Head and Neck Surgery published online 20 December 2010

DOI: 10.1177/0194599810391738

The online version of this article can be found at:

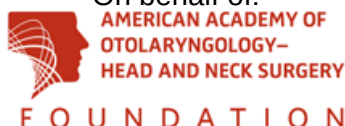
<http://oto.sagepub.com/content/early/2010/12/15/0194599810391738>

Published by:



<http://www.sagepublications.com>

On behalf of:



[American Academy of Otolaryngology- Head and Neck Surgery](http://www.aao.org/)

Additional services and information for *Otolaryngology -- Head and Neck Surgery* can be found at:

Published online 20 December 2010 in advance of the print journal.

P<P

Email Alerts: <http://oto.sagepub.com/cgi/alerts>

Subscriptions: <http://oto.sagepub.com/subscriptions>

Reprints: <http://www.sagepub.com/journalsReprints.nav>

Permissions: <http://www.sagepub.com/journalsPermissions.nav>

Eosinophilic Allergic Polyp: A Clinically Oriented Concept of Nasal Polyp

Woo-Jin Jeong, MD¹, Chul Hee Lee, MD^{1,2}, Sang-Heon Cho, MD^{3,4},
 and Chae-Seo Rhee, MD^{1,2,4}

Otolaryngology—
 Head and Neck Surgery
 XX(X) 1–6
 © American Academy of
 Otolaryngology—Head and Neck
 Surgery Foundation 2010
 Reprints and permission:
 sagepub.com/journalsPermissions.nav
 DOI: 10.1177/0194599810391738
 http://otojournal.org


No sponsorships or competing interests have been disclosed for this article.

Received June 26, 2010; revised October 20, 2010; accepted November 3, 2010.

Abstract

Objective. Tissue eosinophilia is a hallmark of nasal polyposis. However, there is no universally accepted definition for eosinophilic nasal polyp. The aims of this study were to histologically analyze the inflammatory cell population in the nasal polyp and propose the concept of eosinophilic allergic polyp (EAP), a simple and objective concept that would be clinically and practically valuable.

Study Design. A cohort study with histological analysis of tissue sections and chart review.

Setting. A tertiary university hospital.

Subjects and Methods. Nasal polyp tissues were harvested during routine endoscopic sinus surgery from a cohort of 118 patients. Total number of inflammatory cells, including eosinophils, was counted. The presence of allergy and asthma was assessed, which was then correlated with the histologic findings. To determine a criterion for EAP, a receiver operating characteristic curve was used to identify the best cutoff point, which was further validated by comparing the eosinophil proportion in each group with reference to the clinical parameters.

Results. Eosinophil accounted for an average of 18.7% of all inflammatory cells. The proportion of nasal polyps with at least 1 or more eosinophil infiltration accounted for 90.7% of all nasal polyps. When the concept of EAP was applied, a tissue eosinophil count of 11% was found to be significant and clinically most useful. Using this criterion, the proportion of EAP among nasal polyps was 62.7%.

Conclusion. The authors suggest a tissue eosinophil proportion of more than 11% as a criterion for EAP, a clinically useful concept of nasal polyp that bears good correlation with asthma and allergy.

Keywords

asthma, allergy, eosinophil, eosinophilia, nasal polyp

Nasal polyp is a chronic inflammatory condition of the nasal and paranasal sinus mucosa, characterized by edematous masses and infiltration of inflammatory cells. Eosinophils comprise more than 60% of the inflammatory cell population in most of the nasal polyps reported in the Western world.¹ Clinically, nasal polyp is frequently associated with asthma and allergy. Together with its propensity for recurrence, nasal polyp is a challenging clinical entity for the clinician.

The association with nasal polyps and bronchial asthma is well established.² More specifically, nasal polyps with eosinophil infiltration are known to frequently coexist with asthma.^{3,4} Association of allergy in the pathogenesis of nasal polyps is less clear. However, most polyps, especially those with eosinophilia, have allergic traits characterized by a high local level of immunoglobulin E (IgE) and histamine and increased interleukin (IL)-4 and IL-5.¹ Several studies suggest that nasal polyp patients with allergy have a greater recurrence rate after surgery.⁵

However, not all nasal polyps are eosinophil dominant. Based on histological characteristics, polyps may be roughly classified into 1 of 2 types: eosinophilic nasal polyp and

¹Department of Otorhinolaryngology, Seoul National University College of Medicine, Seoul, Korea

²Research Center for Sensory Organs, Seoul National University Medical Research Center, Seoul, Korea

³Department of Internal Medicine, Seoul National University College of Medicine, Seoul, Korea

⁴Institute of Allergy and Clinical Immunology, Seoul National University Medical Research Center, Seoul, Korea

This article was presented at the 2010 AAO-HNSF Annual Meeting & OTO EXPO; September 26–29, 2010; Boston, Massachusetts.

Corresponding Author:

Chae-Seo Rhee, MD, Department of Otorhinolaryngology, Seoul National University Hospital, 101 Daehangno, Jongno-gu, Seoul, 110-744, Korea
 Email: csrhee@snu.ac.kr

noneosinophilic nasal polyp, which is most often neutrophil dominant.

Classifying and reporting of eosinophilic nasal polyp greatly varies between researchers.^{6–12} Although blood eosinophilia is clearly defined as more than 5% of eosinophils among white blood cells, a definition of eosinophilic nasal polyp is ill defined. Classification of eosinophilic nasal polyp has been carried out arbitrarily by pathologists relying on individual experience, which makes the reporting of eosinophilic nasal polyp more inconsistent. More important, although association of eosinophilic nasal polyp with asthma and, to a lesser extent, allergy is widely accepted, classification schemes to date bear no clinical correlation.

This study was designed with a straightforward idea of devising a simple, uniform, and universally applicable term of eosinophilic nasal polyp based on the most basic parameters. We histologically analyzed an inflammatory cell population in nasal polyps to determine a definite criterion for eosinophilic nasal polyp and its proportion among nasal polyps, with an emphasis on an association with asthma and allergy. We propose the term *eosinophilic allergic polyp* (EAP) for this category of nasal polyps.

Materials and Methods

Patients diagnosed as having chronic rhinosinusitis with nasal polyp were subject to study. A cohort of 118 patients was enrolled in the study. Data were prospectively collected for 118 consecutive patients who underwent endoscopic sinus surgery over a 3-year period by a single surgeon at a tertiary referral center. None of the patients was on antihistamine or systemic and/or intranasal corticosteroids for at least a month prior to surgery. The male to female ratio was 65.3% to 34.7%. The mean age was 40 years old, ranging from 6 to 71 years.

All patients were given a thorough explanation of the study, and written consent was obtained. Polyp tissue samples were harvested for histological analysis at the time of surgery. The study was designed and conducted in accordance with the guidelines provided by the Institutional Review Board at Seoul National University Hospital and was subsequently approved (IRB#C-0602-046-168).

Standard hematoxylin and eosin stain was applied on all polyp tissue. Two blinded investigators were assigned to perform a manual inflammatory cell count in 4 different sections at high-power fields ($\times 400$). Complete cell count and inflammatory cell population proportion of the polyp tissue were obtained and calculated. No significant difference in cell population among investigators was observed.

Clinical parameters for each patient were also collected. The multiple allergen simultaneous test (MAST) and skin prick test (SPT) were performed to test allergy. Asthma was diagnosed on the basis of clinical criteria, medical history, and positive methacholine bronchial provocation test. Positive MAST and/or SPT results accounted for 27.5% of all patients. Thirty-five patients had asthma, which accounted for 29.7% of all cases.

Statistical analysis was performed to determine an adequate cutoff point for the best correlation between tissue eosinophil

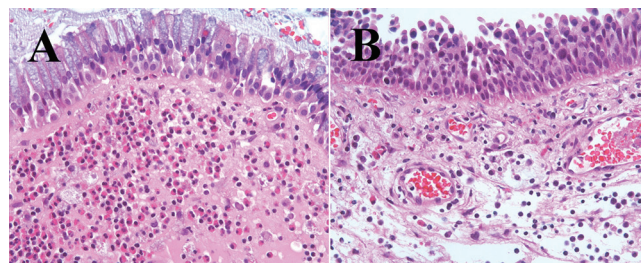


Figure 1. Typical nasal polyp tissue with (A) marked eosinophil infiltration consistent with eosinophilic allergic polyp and (B) little eosinophil infiltration.

proportion and the clinical parameters. The cutoff value was calculated using a receiver operating characteristic (ROC) curve. To further validate the cutoff value, nasal polyps were divided into 2 groups at a certain percentage: a group of nasal polyps with a lower tissue eosinophil count than the particular percentage and another group with a higher tissue eosinophil count. The 2 groups were then compared using the chi-square test for the presence of asthma and allergy to find out whether the 2 groups differed from each other. The *P* value at a given percentage was recorded and plotted from 0% to 40% at 1% intervals. The Kolmogorov-Smirnov test was used to assess the normality of distribution. SPSS 12.0 software (SPSS, Inc, an IBM Company, Chicago, Illinois) was used for the analysis.

Results

Mean $\pm$ SD proportion of eosinophils accounted for $18.7\% \pm 15.5\%$ of all inflammatory cells. The range of eosinophil proportion in each nasal polyp varied from 0% to 74.0%, showing the wide range of eosinophil proportion. The proportion of nasal polyps with at least 1 or more eosinophil infiltrations accounted for 90.7% of all nasal polyps. A typical example of nasal polyp tissue with marked eosinophil infiltration and little eosinophil infiltration, which clearly shows contrast, is shown in **Figure 1**.

The distribution for eosinophil proportion showed a normal distribution ($P > .05$, Kolmogorov-Smirnov test), which was not suitable for clustering into groups based solely on the distribution pattern itself (**Figure 2**).

Statistical analysis was performed to determine a feasible and clinically useful criterion for EAP. An ROC curve obtained to identify the cutoff point for asthma and allergy is depicted in **Figure 3**. The best cutoff value for asthma was at 11.6%, with a sensitivity of 74% and specificity of 47%, and that of allergy was at 10.7%, with a sensitivity of 89% and specificity of 38%.

To further validate the cutoff value, *P* values were plotted as mentioned previously, which is shown in **Figure 4**. The figure shows that *P* values for all clinical parameters are statistically significant at a tissue eosinophil count of 11% (asthma, $P = .035$; allergy, $P = .027$), which is in agreement with the cutoff value obtained from the ROC curve. EAP comprised 62.7% of nasal polyps according to this definition. Cell population in nasal polyps according to this definition is shown in **Table 1**.

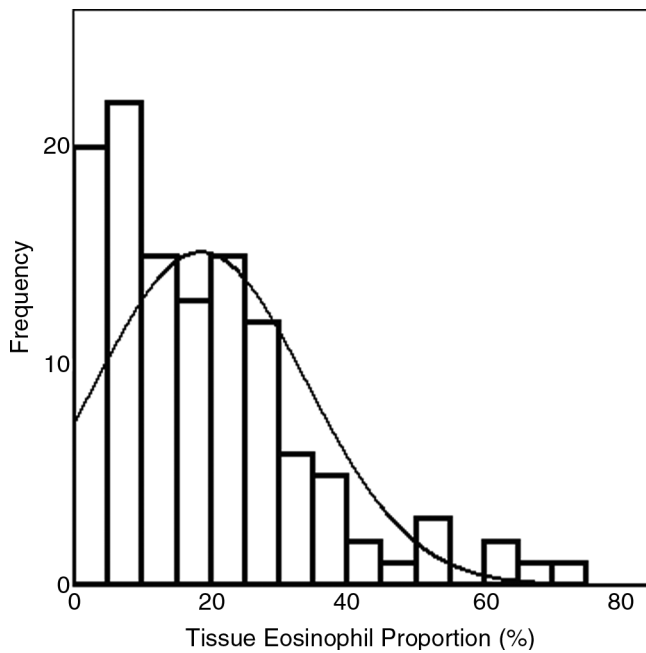


Figure 2. Distribution of tissue eosinophil proportion. A specific cutoff point cannot be inferred from the distribution pattern alone.

Discussion

Because of the histologic diversity of nasal polyps, there have been several attempts at classifying them. One such classical classification scheme was proposed by Mygind,¹³ who classified nasal polyps into 4 categories based on histological findings: eosinophilic edematous type, chronic inflammatory or

fibrotic type, seromucinous gland type, and atypical stromal type.

Hellquist¹⁴ also classified nasal polyps into 4 groups: allergic (edematous, eosinophilic) polyp, fibroinflammatory polyp, polyp with pronounced hyperplasia of seromucinous glands, and polyp with atypical stroma. On the basis of this classification, Hellquist reported that allergic (eosinophilic) polyp accounted for 86% of 107 cases of nasal polyps reviewed. Another study reported eosinophilic nasal polyp with a mere presence of eosinophils, regardless of their absolute count, proportion, and other cell proportions.¹⁵ According to this report, eosinophil-infiltrated polyps accounted for 92.3% of nasal polyps, which is comparable to 90.7% in our study.

The major drawback of these classification methods is that they do not take into consideration the clinical aspects of nasal polyps, which differ with changing proportions of the inflammatory cells. The classification system is purely of a pathologist's interest, but not that of a clinician, because the classification itself does not reveal any clinical information regarding the possibility of associated asthma or allergy.

A more commonly used method of grouping the nasal polyps is to grade the infiltration of eosinophils in the nasal polyp tissue into several categories. Many authors have described the scoring system in a similar manner as the following: grade 0, no eosinophil; grade 1, slight infiltration; grade 2, moderate infiltration; and grade 3, marked infiltration.^{8,10,12}

The biggest shortcoming of the grading method is that it involves a subjective judgment of the pathologist. This implies that when the tissue is examined by a different pathologist, the judgment may become different, putting the same nasal polyp into a different category. Also, this method is not different

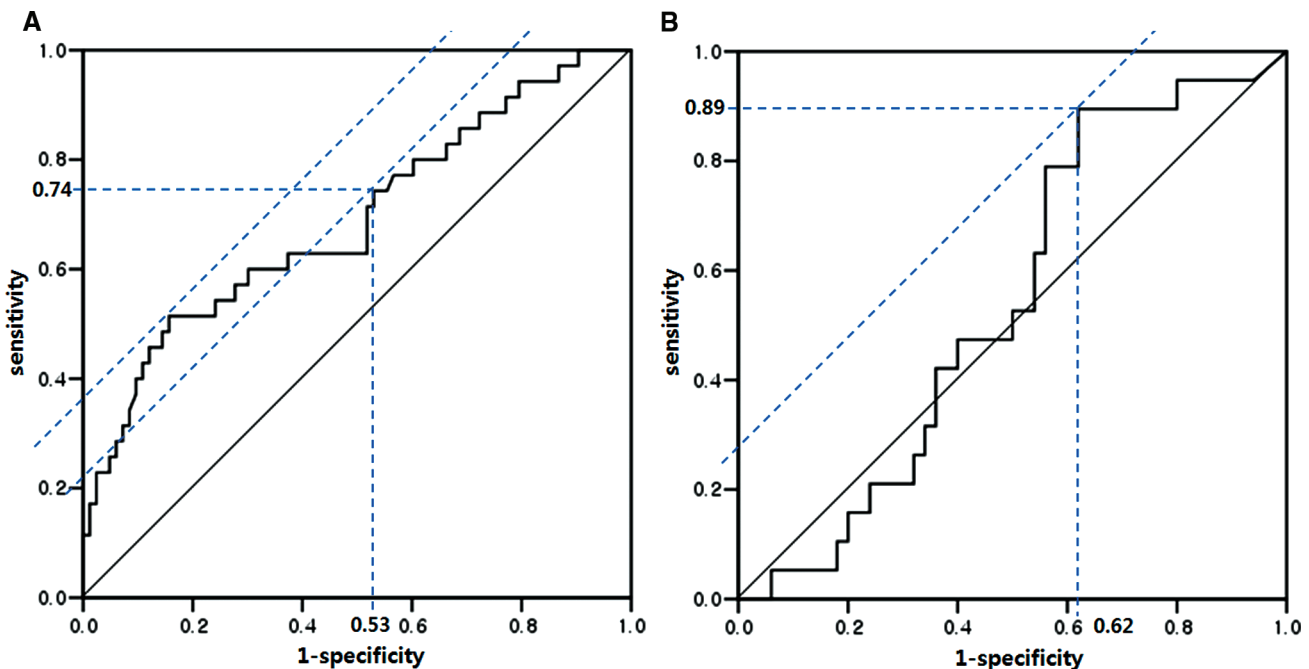


Figure 3. A receiver operating characteristic (ROC) curve for tissue eosinophil proportion. The best cutoff value for asthma was at 11.6%, with a sensitivity of 74% and specificity of 47% (A), and for allergy at 10.7%, with a sensitivity of 89% and specificity of 38% (B).

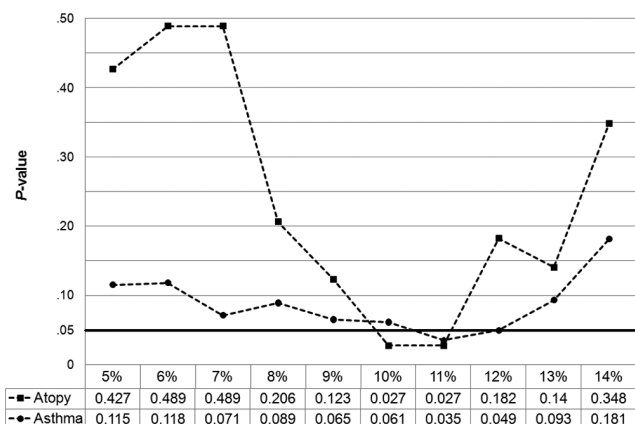


Figure 4. Plotting of P values for verification of cutoff value for eosinophilic allergic polyp. Using the chi-square test, statistical significance was tested at each cutoff point for 2 clinical parameters: asthma and allergy. Cutoff value of 11% is in best correlation with both clinical conditions, which is in agreement with the results from the receiver operating characteristic curve.

Table 1. Inflammatory Cell Proportion in Nasal Polyp Tissue

	EAP	Non-EAP	Overall
No. of cases	74	44	118
Eosinophil, %	26.8	5.1	18.7
Neutrophil, %	26.1	30.8	27.9
Lymphocyte, %	35.0	49.5	40.4
Plasma cell, %	12.2	14.7	13.1

Abbreviation: EAP, eosinophilic allergic polyp. Eosinophils account for an average of 18.7% of all inflammatory cells in the nasal polyp.

from the aforementioned classification schemes in that it does not reflect the clinician's interest.

More recently, Kountakis and his colleagues¹¹ proposed a severity classification system for chronic rhinosinusitis (CRS), which included tissue eosinophilia and the presence of nasal polyp as criteria. In this study, they counted the number of eosinophils per high-power field (HPF) and designated tissues with more than 5 eosinophils per HPF as eosinophilic. Some authors also adopted this method of manually counting the absolute number of eosinophils per microscopic field.^{16,17} A similar method was used in another study but in a slightly different manner. In one study, the infiltrate density of eosinophils was divided into less than 10, 10 to 20, and more than 20 eosinophils per HPF.^{9,10} In another, a grading scale from 0 to 3 was applied, with 0 representing no positive cells, score 1: <10, score 2: 10 to 100, and score 3: >100 positive cells per field.¹⁸

This classification proposes a more practical and clinically oriented approach than the previously mentioned methods. The method bears more objectiveness in that a specific cell population is quantified and also is simple and more intuitive. However, using 5 eosinophils as a cutoff point is purely arbitrary. As seen in the aforementioned studies, different authors use a different number of eosinophils for their own use; hence,

the designation of "eosinophilia" has not reached any consensus among researchers.

Some technical aspects also should be considered. Counting the absolute number of eosinophils poses another problem of choosing which field to examine. A microscopic field that contains a certain number of eosinophils may contain an abundant number of other inflammatory cell populations, whereas another microscopic field may not have any at all. Also, as correctly pointed out by Bhattacharyya and colleagues,¹⁹ the absolute count may show a wide range of variability depending on the thickness of the tissue fixed in the pathology slide.

Few studies expressed eosinophilia as a proportion of eosinophil cell count in comparison to the rest of the cell population.^{6,20,21} The method of recording eosinophils in proportion to other cells minimizes some of the disadvantages of the methods discussed above. The observation is more objective compared to the grading system. Variable thickness should not be as much of a problem when the counting is done relative to other cells. Nevertheless, the cutoff values used in these studies differed from study to study, were arbitrarily determined, and had no clinical implications.

Eosinophil infiltration is a hallmark of nasal polyposis. Eosinophil infiltration in local tissue plays an important role in the pathogenesis of nasal polyposis. Nasal polyp tissue is characterized by T_H2-driven eosinophilic inflammation with high concentrations of eosinophilic cationic protein (ECP), eotaxin, and IL-5.²² Eosinophilia is also associated with clinical conditions such as asthma and allergy.

The association between nasal polyposis and asthma is well recognized, ranging from 7% to 20%.^{1,23} Patients with asthma have worse sinus disease, a higher incidence of polyps, and poorer outcomes than nonasthmatics.¹¹ There is an argument as to whether allergy is associated with nasal polyposis.^{8,10,11} However, studies favoring the allergic origin of nasal polyps have been reported continuously.^{7,24,25} A potential local allergy in the nasal mucosa caused by increased total and specific IgE in polyps has also been suggested.²⁶ Associated allergy has also been found to be a cause of recurrence of nasal polyps.¹ Therefore, we cannot overlook the association between nasal polyposis and allergy.

From this perspective, we sought to devise a simple and objective classification method for analysis of eosinophilia that could be applied in a routine clinical setting as part of the standardized diagnostic regimen for nasal polyp. Most of the previous reports divided the patients into atopic/nonatopic or asthmatic/nonasthmatic groups and then looked at different levels of tissue eosinophilia. We approached this in a reverse manner; that is, we grouped the nasal polyps into eosinophilic and noneosinophilic groups first and then investigated if each group had a correlation with allergy and asthma.

To do so, we implemented 2 elements. First, we manually counted all the inflammatory cells in the histologic specimen for simple and objective judgment appraisal. As mentioned previously, the eosinophil count was determined in proportion to the whole cell population. Second, we correlated the tissue eosinophil count with clinical conditions—asthma and allergy. By doing so, it was possible to calculate a cutoff point for EAP

that would be clinically valuable. It should be mentioned that the best cutoff value for asthma was determined at the second maximum point of deflection because for the purpose of cutoff determination, the sensitivity could not be compromised, although sensitivity itself in this study was not the main issue.

By using this method, we found that 11% is the best cutoff point for the diagnosis of EAP. In other words, nasal polyp patients with a tissue eosinophil count equal to or greater than 11% had a significantly higher incidence of asthma and allergy than those with a tissue eosinophil count of less than 11%. When we applied the 11% criterion, the proportion of EAP among nasal polyps in the Korean population was 67.2%.

Determining EAP in this manner has a number of advantages. First, it is simple and is the most widely adopted way of assessing nasal polyp tissue. It requires no special tools or instruments and no expertise or vast experience in pathology. Therefore, the method is applicable in any clinical setting. This is especially important because many small- to medium-sized hospitals perform surgery for nasal polyps, but they are not equipped with sophisticated diagnostic tools. Most of them are capable of only the standard staining procedure and assessing tissue morphology under light microscopes. Although activated eosinophils and cytokines may be of academic interest, the criteria must be widely acceptable and practically applicable.

Second, this method bears good reproducibility, which eliminates time-to-time, person-to-person variability in assessing the nasal polyp. Proportionate counting can overcome the variability due to the difference in the thickness of the histology slides. Because this method is simple, it allows ease in communication between researchers.

Most important, by diagnosing EAP using this criterion, we can correlate the tissue finding with clinical parameters. As stated previously, classifying nasal polyps based on histologic examination has no clinical significance. However, when a patient is diagnosed as having EAP according to this criterion, the patient may be expected to have higher chances of asthma and allergy, dictating a need for workup for these clinical conditions. The diagnosis of EAP based on this criterion may also suggest that medical treatment with corticosteroids may have a larger impact on the particular patient.

In the current study, it is noteworthy to mention that the distribution of eosinophil proportion of each nasal polyp showed a normal distribution. This pattern of normal distribution was also illustrated in a study by Bonfils and colleagues.²⁰ This, once again, is evidence that for most of the nasal polyps, it should be difficult to decide into which category they would belong just by histologic examination, even for an experienced pathologist.

Another notable finding in this study is the correlation between tissue eosinophilia and allergy. As discussed earlier, some reports favor an association between allergy and nasal polyps, but others do not. Our study shows that the discrepancies may have risen because the criterion for eosinophilia was inconsistent from one report to another. This necessitates further studies using this criterion to determine whether a constant association between tissue eosinophilia and allergy exists.

One point we must consider is the fact that the rate of EAP is known to be lower in the Asian population than in the Western population.²⁷⁻²⁹ Our previous findings are also in accordance with these reports.³⁰ There are certain observations that there has been a rise in eosinophil-infiltrated polyps in Asians.¹⁵ Nevertheless, although the figure 62.7% could be applied to the Asian population, it may not be directly applicable to the Western population. Therefore, there is a need for an analysis of nasal polyps using this criterion in the Western population for a valid comparison.

In conclusion, we suggest a tissue eosinophil proportion equal to or over 11% as a criterion for EAP, a clinically useful concept of nasal polyp that correlates well with asthma and allergy. Using this criterion, the proportion of EAP among nasal polyps in the Korean population is 62.7%.

Author Contributions

Woo-Jin Jeong, acquisition of data, analysis and interpretation of data, writing the article, final approval of manuscript; **Chul Hee Lee**, critical review of manuscript, final approval of manuscript; **Sang-Heon Cho**, conception and design of study, critical review of manuscript, final approval of manuscript; **Chae-Seo Rhee**, conception and design of study, patient selection, critical review of manuscript, final approval of manuscript.

Disclosures

Competing interests: None.

Sponsorships: None.

References

1. Pawankar R. Nasal polyposis: an update: editorial review. *Curr Opin Allergy Clin Immunol*. 2003;3:1-6.
2. Fokkens W, Lund V, Mullol J. European position paper on rhinosinusitis and nasal polyps 2007. *Rhinol Suppl*. 2007;(20):1-136.
3. Steinke JW, Bradley D, Arango P, et al. Cysteinyl leukotriene expression in chronic hyperplastic sinusitis-nasal polyposis: importance to eosinophilia and asthma. *J Allergy Clin Immunol*. 2003;111:342-349.
4. Voegels RL, Santoro P, Butugan O, Formigoni LG. Nasal polyposis and allergy: is there a correlation? *Am J Rhinol*. 2001;15:9-14.
5. Dursun E, Korkmaz H, Eryilmaz A, Bayiz U, Sertkaya D, Samim E. Clinical predictors of long-term success after endoscopic sinus surgery. *Otolaryngol Head Neck Surg*. 2003;129:526-531.
6. Hyo S, Kawata R, Kadoyama K, et al. Expression of prostaglandin D2 synthase in activated eosinophils in nasal polyps. *Arch Otolaryngol Head Neck Surg*. 2007;133:693-700.
7. Cheng W, Zheng C, Tian J, Shi G. T helper cell population and eosinophilia in nasal polyps. *J Invest Allergol Clin Immunol*. 2007;17:297-301.
8. Kirtsreesakul V, Atchariyasathian V. Nasal polyposis: role of allergy on therapeutic response of eosinophil- and noneosinophil-dominated inflammation. *Am J Rhinol*. 2006;20:95-100.
9. Baudoin T, Cupic H, Geber G, Vagić D, Grgić M, Kalogjera L. Histopathologic parameters as predictors of response to endoscopic sinus surgery in nonallergic patients with chronic rhinosinusitis. *Otolaryngol Head Neck Surg*. 2006;134:761-766.

10. Hao J, Pang YT, Wang DY. Diffuse mucosal inflammation in nasal polyps and adjacent middle turbinate. *Otolaryngol Head Neck Surg.* 2006;134:267-275.
11. Kountakis SE, Arango P, Bradley D, Wade ZK, Borish L. Molecular and cellular staging for the severity of chronic rhinosinusitis. *Laryngoscope.* 2004;114:1895-1905.
12. Gerstner AO, Gutsche M, Bucheler M, et al. Eosinophilia in nasal polyposis: its objective quantification and clinical relevance. *Clin Exp Allergy.* 2004;34:65-70.
13. Mygind N. Nasal polyposis. *J Allergy Clin Immunol.* 1990;86:827-829.
14. Hellquist HB. Nasal polyps update: histopathology. *Allergy Asthma Proc.* 1996;17:237-242.
15. Morinaka S, Nakamura H. Inflammatory cells in nasal mucosa and nasal polyps. *Auris Nasus Larynx.* 2000;27:59-64.
16. Soler ZM, Sauer DA, Mace J, Smith TL. Relationship between clinical measures and histopathologic findings in chronic rhinosinusitis. *Otolaryngol Head Neck Surg.* 2009;141:454-461.
17. Armengot M, Garin L, Carda C. Eosinophil degranulation patterns in nasal polyposis: an ultrastructural study. *Am J Rhinol Allergy.* 2009;23:466-470.
18. Van Zele T, Claeys S, Gevaert P, et al. Differentiation of chronic sinus diseases by measurement of inflammatory mediators. *Allergy.* 2006;61:1280-1289.
19. Bhattacharyya N, Vyas DK, Fechner FP, Gliklich RE, Metson R. Tissue eosinophilia in chronic sinusitis: quantification techniques. *Arch Otolaryngol Head Neck Surg.* 2001;127:1102-1105.
20. Bonfils P, Badoual C, Bonfils NA, Gallas D, Malinvaud D. Eosinophil infiltration of nasal polyps in patients with nasal polyposis: role in clinical evolution after medical and surgical treatment. *J Laryngol Otol.* 2009;123:509-516.
21. Lackner A, Raggam RB, Stammberger H, et al. The role of interleukin-16 in eosinophilic chronic rhinosinusitis. *Eur Arch Otorhinolaryngol.* 2007;264:887-893.
22. Van Bruaene N, Perez-Novo CA, Basinski TM, et al. T-cell regulation in chronic paranasal sinus disease. *J Allergy Clin Immunol.* 2008;121:1435-1441, 1441.e1-3.
23. Bachert C, Hormann K, Mosges R, et al. An update on the diagnosis and treatment of sinusitis and nasal polyposis. *Allergy.* 2003;58:176-191.
24. Gosepath J, Mann WJ. Current concepts in therapy of chronic rhinosinusitis and nasal polyposis. *ORL J Otorhinolaryngol Relat Spec.* 2005;67:125-136.
25. Asero R, Bottazzi G. Hypersensitivity to molds in patients with nasal polyposis: a clinical study. *J Allergy Clin Immunol.* 2000;105:186-188.
26. Bachert C, Gevaert P, Holtappels G, Johansson SG, van Cauwenberge P. Total and specific IgE in nasal polyps is related to local eosinophilic inflammation. *J Allergy Clin Immunol.* 2001;107:607-614.
27. Takeno S, Hirakawa K, Ishino T. Pathological mechanisms and clinical features of eosinophilic chronic rhinosinusitis in the Japanese population. *Allergol Int.* 2010;59:247-256.
28. Cao PP, Li HB, Wang BF, et al. Distinct immunopathologic characteristics of various types of chronic rhinosinusitis in adult Chinese. *J Allergy Clin Immunol.* 2009;124:478-484, 484.e1-2.
29. Zhang N, Van Zele T, Perez-Novo C, et al. Different types of T-effector cells orchestrate mucosal inflammation in chronic sinus disease. *J Allergy Clin Immunol.* 2008;122:961-968.
30. Kim JW, Hong SL, Kim YK, et al. Histological and immunological features of non-eosinophilic nasal polyps. *Otolaryngol Head Neck Surg.* 2007;137:925-930.