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What is This?
Changes in Histological Features of Nasal Polyps in a Korean Population over a 17-year Period

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Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

Abstract

Objective. Nasal polyps can be categorized as eosinophilic or non-eosinophilic, depending on inflammatory cell infiltration. There are geographical differences in the prevalence of types of pathologic polyps. The aim of this study was to evaluate the change in the prevalence of histological subtypes of polyps over time in a Korean population.

Study Design. A retrospective cross-sectional study with histologic analysis.

Setting. A single academic medical center.

Subjects and Methods. A total of 230 patients with nasal polyps were enrolled between 1993-1994 (group A) and 2010-2011 (group B). Specimens were fixed in formalin and embedded into paraffin blocks. Slides were stained with hematoxylin-eosin (H&E) and were subsequently reviewed by 2 of the authors. The numbers of eosinophils per high power field (HPF), as well as other cellular, epithelial, and stromal markers, were recorded.

Results. We compared nasal polyp eosinophil counts according to time period. The average eosinophil count/HPF increased from 6.8 in group A to 19.3 in group B (P = .006). The prevalence of eosinophilic polyps also increased from 24.0% in group A to 50.9% in group B (P < .001). Among other histologic markers, lymphocytes, basement membrane thickening, and gland hyperplasia showed significant differences between groups.

Conclusion. After comparison of histopathologic findings of nasal polyps from 1993 and 2011 at 1 academic medical center in Korea, the prevalence of eosinophilic nasal polyps, which are known to be rare among Asians, has significantly increased.

Keywords

nasal polyps, histopathology, eosinophils, eosinophilic polyp, non-eosinophilic polyp.

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of eosinophilic polyps in Asia. However, there are no studies to date that directly assess this hypothesis. This has been further complicated by a lack of consistent criteria used to define eosinophilic polyps in individual studies. Moreover, even when the same criteria are applied, there may still be differences in the interpretation between studies, making it difficult to definitively conclude that eosinophilic polyps have increased by simply comparing recent results with the results from past studies. Therefore, this study aimed to confirm whether the prevalence of eosinophilic polyps in Korea has increased over time.

Materials and Methods

Subjects

Nasal polyp tissue was obtained from 230 subjects referred to the Kyung Hee Medical Center for sinus surgery (e.g., Caldwell-Luc operation or endoscopic sinus surgery with nasal polypectomy). Study subjects were selected on the basis of diagnosis of chronic rhinosinusitis with nasal polyps. The study was approved by the Institutional Review Board of Kyung Hee University Hospital. To include samples separated by the longest possible time period, 110 cases from 1993 and 1994, which were the oldest samples available, were selected and were designated as group A. Group B was composed of 120 cases from 2010 and 2011. Exclusion criteria included cystic fibrosis, primary ciliary dyskinesia, sinonasal tumor or carcinoma, and immunodeficiency. In addition, patients with allergic fungal sinusitis, presence of a fungus ball, and aspirin-exacerbated respiratory disease, each of which is characterized by robust eosinophilic infiltration, were also excluded. Patients who received systemic or topical steroids for at least 2 weeks prior to surgery were excluded due to potential changes in inflammatory cell composition.

Histologic Evaluation and Scoring

Nasal polyp tissue was collected at the time of surgery, promptly fixed in 4% paraformaldehyde, and subsequently embedded in paraffin. Paraffin blocks were sectioned at 4μm thickness on a microtome and stained with hematoxylin-eosin (H&E). All samples were prepared in the same laboratory using the same histopathologic techniques.

Microscopic review was performed by 2 of the authors (a board-certified surgical pathologist and an otolaryngologist). A first review was conducted for diagnosis, and during this process slides that had an insufficient amount of tissue due to squeezing artifact or denuded surface epithelium were excluded. Also, fungal sinusitis or the presence of fungus balls, which show numerous eosinophils with fungal hyphae, were excluded. The pathologic review was done in a blind fashion. Areas exhibiting extremely low cellularity, squeezing artifact, severe inflammatory changes, and abscesses were avoided in selecting the microscopic field. A total of 10 different representative fields were chosen, each of which exhibited dense cellularity while maintaining normal architecture.

Figure 1. Typical histopathology of nasal polyps. (A) Non-eosinophilic polyp (in group A) showing prominent inflammatory cell infiltration, primarily by lymphocytes and plasma cells. (B) Eosinophilic polyp (in group B) showing marked eosinophil infiltration with goblet cells in the surface epithelium and thickening of basement membrane (hematoxylin-eosin staining, ×200).

Eosinophils and eosinophilic polyps. The eosinophil count was obtained by taking the average of the manual cell count of the 10 selected fields in the ×400 high power field (HPF). Polyps were defined as eosinophilic when the average eosinophil count was >5 eosinophils/HPF and as non-eosinophilic when the count was ≤5 eosinophils/HPF.

Other histopathologic markers. In addition to eosinophils, the presence of neutrophils, plasma cells, and lymphocytes was assessed into categorical variables (1 = scanty, 2 = mild, 3 = moderate, and 4 = marked) depending on the degree of cell infiltration. Epithelial markers including goblet cell hyperplasia, squamous metaplasia, and BM thickening were examined. Goblet cells were quantified as a percentage of epithelial cells and categorized into categorical variables (1 = 0%-25% of surface epithelial cells, 2 = 26%-50%, 3 = 51%-75%, and 4 = 76%-100%); squamous metaplasia was assessed into categorical variables (1 = not present-focal, 2 = mild, 3 = moderate, and 4 = marked); and BM thickening was measured and recorded as a categorical variable (1 = <5 μm, 2 = 5-10 μm, 3 = 10-15 μm, and 4 = >15 μm). Additionally, stromal edema, stromal fibrosis, and seromucinous gland hyperplasia were also assessed into categorical variables (1 = not present-focal, 2 = mild, 3 = moderate, and 4 = marked).
Statistical Analysis

All statistical analyses were performed using SPSS v20.0 software (SPSS, Inc., Chicago, Illinois). The Wilcoxon rank-sum test was used to compare eosinophil counts between the 2 groups, and the chi-square test was used to compare the proportion of eosinophilic polyps between the 2 groups. When comparisons of other histologic markers were made, Wilcoxon rank-sum tests or linear by linear associations were used for between-group comparisons. \( P \) values less than .05 were considered to be statistically significant for all analyses.

Results

Subjects

From the 110 cases obtained from 1993 to 1994 initially included in group A, 104 samples were used in the final analysis with 6 cases excluded due to loss or poor tissue condition. From the 120 cases obtained from 2010 to 2011 initially included in group B, 112 samples were used in the final analysis. Among the 8 cases excluded, 5 exhibited fungal sinusitis or fungus balls, and the remaining 3 were excluded because of insufficient tissue due to squeezing artifact or denuded surface epithelium. This study included a total of 216 tissue samples from 216 patients.

Among the 216 patients included, 150 were male (69.4%) and 66 were female (30.6%), with a mean age of 39.4 ± 17.7 years (range, 9-84). Group A (n = 104) consisted of 70 male patients (67.3%) and 34 female patients (32.7%), with a mean age of 37.3 ± 16.4 years (range, 12-71). Group B (n = 110) consisted of 80 male patients (71.4%) and 32 female patients (28.6%), with a mean age of 41.3 ± 18.7 years (range, 9-84). The mean time interval between the 2 groups was 17.6 years. Both groups showed a male predominance, with a male to female ratio of about 2:1. There were no significant differences in sex distribution or mean age between the two groups (\( P > .05 \)).

Eosinophils and Eosinophilic Polyps

The distribution and range of the average eosinophil counts per HPF between the 2 groups are shown in Figure 2. When the average eosinophil counts/HPF were compared, group A exhibited 6.8 ± 15.9 and group B exhibited 19.3 ± 32.1 eosinophils/HPF. These findings showed that group B had a significant increase in the average eosinophil count (\( P = .006 \)). When the proportion of eosinophilic polyps between the 2 groups was compared, eosinophilic polyps comprised 24.0% of the total nasal polyps in group A and 50.9% in group B. These findings indicate that the proportion of eosinophilic polyps also significantly increased in group B (\( P < .001 \)) (Figure 3).

Other Histopathologic Markers

Among the cellular markers other than eosinophils, neutrophils and plasma cells were observed more frequently in group A, but there were no significant differences between groups (\( P = .493 \) and \( P = .281 \), respectively). Lymphocytes, on the other hand, were observed more frequently in group A, and there was a statistically significant difference (\( P = .010 \)). In terms of epithelial markers, goblet cell hyperplasia in the surface epithelium and squamous metaplasia were observed more often in group B, but there were no significant differences between groups (\( P = .386 \) and \( P = .057 \), respectively). However, BM thickening was observed significantly more often in group B (\( P < .001 \)). With regard to stromal markers, stromal edema (\( P = .180 \)) and fibrosis (\( P = .477 \)) were observed more frequently in group A, but there were no significant differences. However, hyperplasia of seromucinous glands was observed significantly more often in group A (\( P < .001 \)) (Figure 4).
Figure 4. Comparison of degrees of other inflammatory cells, epithelial markers, and stromal markers between the 2 groups. (A) Neutrophils and plasma cells were observed more frequently in group A (P > .05). Lymphocytes were observed more frequently in group A, and there was a statistically significant difference (P = .01). (B) Goblet cell hyperplasia and squamous metaplasia were observed more often in group B (P > .05). Basement membrane thickening was observed significantly more often in group B (P < .001). (C) Stromal edema and fibrosis were observed more often in group A (P > .05). Seromucinous gland hyperplasia was observed significantly more often in group A (P < .001). Group A, polyps obtained in 1993-1994; group B, polyps obtained in 2010-2011.
Discussion

According to previous studies, most nasal polyps showed eosinophilic predominance, and comorbidity with bronchial asthma and aspirin intolerance has been reported. In these diseases, eosinophilic inflammation was considered to be the common mechanism, suggesting that activated eosinophils played an important role in pathogenesis by acting as toxic mediators. However, these studies were conducted in Caucasians, making this eosinophilic predominance difficult to apply to Asian populations. In studies conducted in Asian populations including Korean, Chinese, and Japanese patients, it has been reported that non-eosinophilic polyps were the predominant polyp type, in contrast to previous studies.

In a study conducted in Koreans over 5 years beginning in 1996, the results of categorizing nasal polyps according to pathologic findings showed that non-eosinophilic polyps accounted for 74.8%. Likewise, another study conducted on Korean patients in 2007, which defined eosinophilic polyps as those with a tissue eosinophil proportion more than 5%, found that 66.7% of polyps were non-eosinophilic. Additionally, in a study conducted on Chinese subjects in 2009, nasal polyps were classified as eosinophilic when the percentage of eosinophils exceeded twice the SD of the mean controls (10% was chosen as the cutoff). Using this criterion, non-eosinophilic polyps were reported to account for more than half of the total number of cases. However, in a study conducted on Korean subjects in 2010, eosinophilic allergic polyps, defined as those with a tissue eosinophil proportion more than 11%, were reported to be 62.7.

The aforementioned studies suggest that the prevalence of eosinophilic polyps in Asians has increased over time. The criteria for defining eosinophilic polyps, however, differed for each study, making it difficult to conclude that the proportion of eosinophilic polyps had increased by simply comparing past results with recent studies. As there is no universally accepted definition of eosinophilic polyps, different interpretations of the same sample can be made. Moreover, even when the same criteria are applied, there may be differences in technical aspects or subjective observations that render results that are not comparable. To date, there are no studies that directly assess the possibility of increases in the proportion of eosinophilic polyps over time in Asian populations. As a result, this study is meaningful in that it provides evidence that the prevalence of eosinophilic polyps has increased significantly as a function of time.

We examined various criteria for defining eosinophilic polyps, including the classification method that is based on histopathologic findings and the scoring system according to the degree of eosinophil infiltration. These methods are limited by subjective interpretation and ambiguous categorization when histologic findings are not distinct. In addition to these methods, other systems have applied a grade according to eosinophil density or the proportion of eosinophils present compared with other inflammatory cells. Although these methods are more objective in nature, the cutoff values used in these studies were not uniform.

Kountakis et al suggested a staging system to categorize the severity of chronic sinusitis and defined eosinophilic polyps as having >5 eosinophils/HPF in a manual count. This method is objective, though time-consuming, and was applied in the present study. An important consideration when applying this method is that cell counts may vary according to the tissue thickness, as well as with the specific microscopic field that is selected. To minimize the effects of these technical variations, this study used the same laboratory to produce the slides for both groups. As a result, there were no differences in tissue thickness or quality of staining. Also, the microscopic fields were not randomly selected. Rather, the tissue state and cellularity were considered in selecting the 10 representative fields, and the results were averaged in order to minimize different interpretations of the same specimen.

In addition to comparing eosinophil counts, a comparative analysis of other histologic markers was also conducted. Inflammatory cells other than eosinophils, such as neutrophils, plasma cells, and lymphocytes, were more frequently observed in group A, where non-eosinophilic polyps predominated. In terms of epithelial markers, goblet cells within the surface epithelium, squamous metaplasia, and BM thickening were observed more often in group B, where eosinophilic polyps accounted for more than half of the total polyps. Additionally, stromal fibrosis and hyperplasia of seromucinous glands were also observed more frequently in group A, where non-eosinophilic polyps were predominant.

Among the histologic markers, stromal edema was a characteristic that exhibited contrasting results, which may have been due to differences in specimen quality. Group A specimens were collected before the introduction of endoscopic surgery using the Caldwell-Luc approach, and as a result the specimens were mostly intact. On the other hand, endoscopic surgery was performed to obtain most of the group B specimens, in which only a section of the polyp was surgically removed. Therefore, the amount of tissue in group B specimens was small, and a considerable amount of the tissue itself showed a squeezing artifact. Notably, 3 cases in group B lacked a sufficient amount of tissue due to severe squeezing artifact or denuded surface epithelium and were excluded from the study.

This study has limitations in terms of its study design. First, it has some weaknesses given its retrospective nature. A prospective comparison will yield more definite results, but to grasp the current changes, it is reasonable to perform a retrospective cross-sectional study. Another limitation of this study is that it was limited to a single medical center. This, however, can also be seen as an advantage from another perspective as it allows more definite control over other confounding factors, such as the technical aspects. Nevertheless, a multicenter study should be considered in the future so that a conclusion that represents Korea, and by extension Asia, can be drawn.

The pathogenesis of nasal polyps is not yet clearly understood, but T-cell activation and impaired regulatory T-cell...
function seem to be involved in the formation of both eosinophilic and non-eosinophilic polyps. In Caucasians, where eosinophilic polyps are predominant, $T_{H2}$ skewed patterns with NKT cell infiltration has been observed. Asians, on the other hand, primarily express non-eosinophilic polyps in which a $T_{H1}$ predominance has been reported. Accordingly, different underlying pathologic mechanisms seem to apply to the development of each condition. Bronchial asthma and aspirin intolerance, which are known to be concomitant risk factors for eosinophilic polyps, also showed eosinophil-dominated inflammation together with $T_{H2}$-biased cytokine profiles, including IL-5, eotaxin, and IgE formation. In addition, chronic local infections caused by bacterial superantigens or fungi, as well as atopy and allergies, which are all known causes of eosinophilic polyps, showed specific IgE increases together with the $T_{H2}$ cytokine profile, suggesting that there is a different pathologic mechanism for non-eosinophilic polyps.

While there have been many studies that have attempted to clarify the immunopathologic profiles of nasal polyp formation at the cellular level, the reasons for the development of clinically different phenotypes have yet to be clarified. The cause of the recent increase in eosinophilic polyps in Asian populations is thought to be due to concomitant factors such as bronchial asthma, aspirin intolerance, chronic local infections, atopy, allergies, and environmental pollutants. In fact, the prevalence of bronchial asthma has increased both in Asia and worldwide. Increases in environmental pollutants such as tobacco smoke and dust exposure, increases in exposure to bacterial superantigens, and increases in fungal infections due to the recent climate changes are presumed to contribute to the increase in the prevalence of eosinophilic polyps, though further studies will be necessary to test these hypotheses.

**Conclusion**

Comparison of the histopathology of nasal polyps at 1 academic medical center in Koreans obtained 17.6 years apart confirmed that the percentage of eosinophilic polyps has significantly increased. The average eosinophil count/HPF increased from 6.8 to 19.3. The proportion of eosinophilic polyps also increased from 24.0% to 50.9%, with other histopathologic findings supporting these results. Given this new trend, it is necessary to establish new diagnostic and therapeutic strategies specifically targeted toward this disease process in clinical practice.

**Author Contributions**

Su Jin Kim, conception and design of study, acquisition, analysis and interpretation of data, writing the manuscript; Kun Hee Lee, critical review of manuscript, final approval of manuscript; Sung Wan Kim, critical review of manuscript, final approval of manuscript; Joong Saeng Cho, conception and design of study, critical review of manuscript, final approval of manuscript; Yong Koo Park, acquisition and interpretation of data; Seung Youp Shin, conception and design of study, critical review of manuscript, final approval of manuscript.

**Disclosures**

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