Annals of Otology, Rhinology & Laryngology 119(7):455-459.

Relationship Between Postoperative Recurrence Rate and Eosinophil Density of Nasal Polyps

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Objectives: Nasal polyps develop as a result of chronic inflammation, mostly accompanied by pronounced eosinophil leukocyte infiltration. In this study we aimed to investigate the relationship between eosinophil density in nasal polyps and the postoperative recurrence rate of this disease.

Methods: Forty-two patients who underwent endoscopic sinus surgery for massive nasal polyposis by one surgeon were included in the study. The eosinophil leukocyte densities in nasal polyps were determined retrospectively on histologic slides by use of computer-assisted image analysis software. The patients were assigned to group 1, in whom nasal polyps contained up to 3 eosinophils per 1,000 μm^2, and group 2, in whom nasal polyps contained 4 or more eosinophils per 1,000 μm^2. The postoperative recurrence rates of nasal polyps were compared in the two groups.

Results: There were 20 patients in group 1 and 22 patients in group 2. Postoperative polyp recurrence was detected in 5 of 20 patients (25.0%) in group 1 and in 18 of 22 patients (81.8%) in group 2 during the 30-month postoperative follow-up period ($p < 0.05$).

Conclusions: The eosinophil density of nasal polyps can be used to get an estimate of the postoperative recurrence risk. Eosinophil-rich nasal polyps have a higher postoperative recurrence rate.

Key Words: eosinophil, nose, polyp, recurrence.

INTRODUCTION

Nasal polyps develop as a result of chronic inflammation in the nasal passages. Prolonged inflammation in these patients may be associated with chronic bacterial sinusitis, allergic rhinitis, cystic fibrosis, allergic fungal sinusitis, or autonomic nervous system dysfunction. Activation of epithelial cells, macrophages, or mast cells by chronic inflammation results in release of inflammatory mediators and infiltration of inflammatory cells with a prominent eosinophilic leukocyte component. Eosinophils are the most commonly identified cells in chronic sinusitis and in nasal polyps.[1] Eosinophils contain several substances, such as leukotrienes, eosinophilic cationic protein, major basic protein, platelet activating factor, eosinophilic peroxidases, and other vasoactive substances, that cause mucosal injuries and may play an important role in the development of nasal polyps.[1]

Steroid administration and endoscopic sinus surgery are the two most common methods used for the treatment of nasal polyposis.[2,3] Steroid use seems to be the most efficient one among the medical treatments of these patients.[3] It may act by reducing the number and activation of T cells, mast cells, and eosinophils. Steroids provide benefit especially in patients with eosinophilia.[1] However, steroids have several side effects in long-term systemic use, and nasal polyps come back larger shortly after the cessation of steroid therapy. Endoscopic sinus surgery is required for patients with massive nasal polyposis or those in whom medical treatment fails.[3] Endoscopic surgery not only removes nasal polyps, but also opens the narrow clefts in the middle meatus, and thus may help decrease the rate of postoperative recurrence. However, the recurrence rate of nasal polyps is still high in some patients. Aspirin sensitivity and bronchial asthma are well-known factors associated with polyp recurrence, but several other factors also may contribute to the relapsing of nasal polyps.[4,5] If the recurrence rate can be predicted before the surgery by a reliable method, the patients with a higher risk of polyp relapse can be followed up more closely in the postoperative period. In this study we aimed to investigate the relationship between the eosinophil density in nasal polyps and the postoperative recurrence rate of those polyps.

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PATIENTS AND METHODS

The files of patients who underwent endoscopic sinus surgery for massive nasal polyposis at our tertiary referral hospital between 2001 and 2007 were retrospectively reviewed. Patients with massive nasal polyposis, filling at least half of each nasal passage, operated on by the same surgeon and who stayed under follow-up for at least 30 months were included in the study. The surgeries were performed under endoscopic vision and included nasal polypectomy, anterior and posterior ethmoidectomy, and widening of the sinus ostia. The patients below 16 years of age were excluded from the study to eliminate nasal polyposis due to cystic fibrosis. A single dose of 8 mg of dexamethasone sodium phosphate was administered during the operation, and no systemic steroid was used before or after surgery because of potential side effects. However, all patients were put on long-term (at least 3 months) topical nasal steroid treatment after the surgery. The patients were called for intranasal endoscopic examination every 3 months in the first and second postoperative years and every 6 months thereafter to determine the recurrences of nasal polyps.

Eosinophil leukocyte counting in nasal polyps was carried out retrospectively on histologic slides by use of computer-assisted image analysis software. A double-blind control method was used for the determination of eosinophil counts and postoperative recurrence rates of polyps. All tissues were fixed in 10% buffered formalin, routinely processed, and embedded in paraffin. Standard 4-μm-thick sections were obtained from each block and stained with hematoxylin and eosin. Representative areas that were infiltrated most densely by eosinophil leukocytes for each case were selected for taking high-resolution digital images at ×400 magnification. A grid system composed of horizontal and perpendicular parallel lines forming quadrangular chambers with an area of 1,000 μm^2 was superimposed on each image with the aid of image processing and analysis software to determine the degree of eosinophil leukocyte infiltration more objectively.[6] The density of eosinophil leukocytes was evaluated by roughly counting them in each grid chamber and calculating the mean eosinophil count per 1,000 μm^2, which is equal to the area of 1 grid chamber. The cases were assembled into two groups according to the eosinophil leukocyte density as follows: group 1, cases containing up to 3 eosinophils per 1,000 μm^2, and group 2, cases containing at least 4 eosinophils per 1,000 μm^2 (see Figure). A χ^2 test was used to compare the data of the two groups of patients, and a p value of less than 0.05 was considered significant. The statistical analysis was carried out with the SPSS version 15.0 statistical software package.

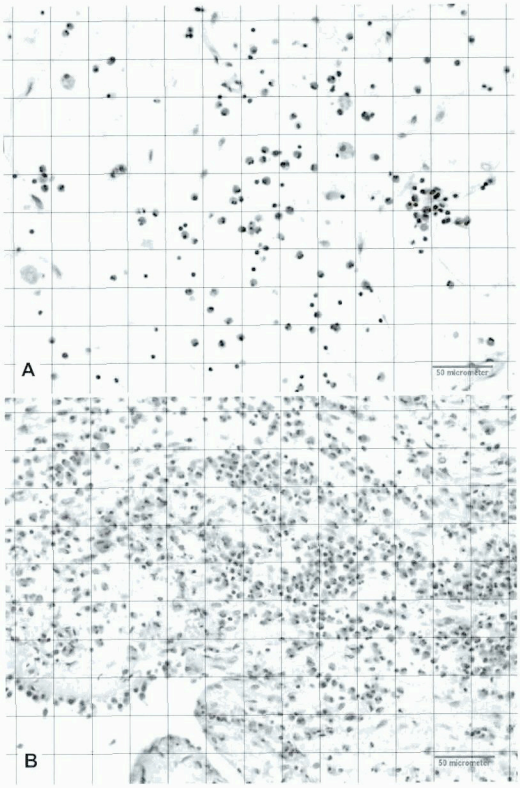
RESULTS

Of the 89 patients who underwent surgery by the same surgeon for massive nasal polyposis, 42 were included whose follow-up period was 30 to 90 months (mean, 53 months); 25 men and 17 women were included in the study. The patients' data are summarized in Tables 1 and 2. The patient ages ranged between 20 and 67 years (mean, 45 years). There were 20 patients in group 1 and 22 patients in group 2. The mean age was 44 years for group 1 and 50 years for group 2. Six patients in group 1 and 7 patients in group 2 had previous surgeries for nasal polyposis. The previous surgeries had no significant effect on postoperative recurrences ($p = 0.453$; 6 of the 23 patients with postoperative polyp recurrences and 7 of 19 patients with no postoperative polyp recurrences had previous surgeries for nasal polyposis in a total of 42 patients). Recurrences of nasal polyps after our surgeries were seen between 18 and 24 months (mean, 23 months) in group 1 and 6 to 36 months (mean, 23 months) in group 2. Postoperative polyp recurrence was seen in 5 of 20 patients (25.0%) in group 1 and in 18 of 22 patients (81.8%) in group 2 during the follow-up periods (Table 3). The recurrence rate was significantly higher in group 2 than in group 1 ($p = 0.0001$). The mean recurrence rate was 53.4% for the whole group of patients in the follow-up period. There was bronchial asthma in 5 patients (25.0%) in group 1 and in 10 patients (45.5%) in group 2, and the rates of asthma did not differ significantly between the two groups ($p = 0.1$). Samter's triad was seen in 2 patients in each group ($p = 0.9$).

DISCUSSION

Recurrence of nasal polyps after treatment is a continuing problem. According to a historical article by Cohen,[7] nasal polyps were considered a horrible and incurable disease 200 years ago. A prominent surgeon who lived during the 18th and 19th centuries in Europe stated that all methods used to remove nasal polyps could remove only the distal end, but not the roots, of polyps, so that they grew back larger than ever in a few days.[7]

Endoscopic sinus surgery provided a great contribution to the treatment of nasal polyposis in the second half of the 20th century. Superior illumination of the middle meatus with endoscopes and magnification of images on a monitor have allowed complete removal of nasal polyps and opening of the narrow clefts in the lateral nasal wall, which may help topically applied nasal sprays to reach the field. How-



Images with **A)** 2 or 3 eosinophils per square and **B)** 6 or 7 eosinophils per square (H & E, original ×400).

ever, recurrence rates after endoscopic sinus surgery in cases of massive nasal polyposis are still high. Wynn and Har-El[4] reported a 60% rate of recurrence after endoscopic sinus surgery in 118 patients with severe nasal polyposis in a 12- to 168-month follow-up period. Nonsteroidal anti-inflammatory drug intolerance, asthma, revision surgery, and polyp extension are the most often reported clinical factors associated with a higher rate of polyp recurrence after treatment.[4,5] The mean recurrence rate was 53.4% for the whole group of patients in the follow-up period in our study.

Several treatment methods have been proposed to decrease nasal polyp recurrence. Rucci et al[8] reported that resection of the vidian nerve in addition to nasal polypectomy prevented intranasal chronic inflammation caused by parasympathic innervation and decreased the rate of postoperative polyp recurrence. Marchioni et al[9] pointed out that middle turbinate resection during endoscopic sinus surgery provided a better control of the relapse of nasal polyposis. Use of steroids, leukotriene inhibitors, and furosemide decreases the rate of polyp relapse.[10,11] Steroids diminish eosinophilic infiltration of the upper airway by decreasing eosinophil viability.[12,13] Eosinophils are the most prevalent inflammatory cells in nasal polyp tissues, except in cases of cystic fibrosis.[1] These cells release mediators such as eosinophil-derived neurotoxin and eosinophil cationic protein and can also synthesize a number of regulatory molecules such as transforming growth factor β and interleukin-4, which can directly or indirectly contribute to the further recruitment and activation of eosinophils capable of causing cellular injury and tissue damage.[14,15] Sun et al[16] reported that preoper-

TABLE 1. CLINICAL DATA FOR GROUP 1, WHO HAD NASAL POLYPS CONTAINING UP TO THREE EOSINOPHILS PER SQUARE MICROMETER

Pt No.	Age (y)	No. of Prior Surgeries for Nasal Polyps	Relapse Time After Surgery (mo)	Follow-Up (mo)
1	43	1	24	90
2	40	0		72
3	60	0		90
4	38	0	24	90
5	44	0	18	90
6	67	1		90
7	40	0		84
8	57	0		48
9	53	0		48
10	20	0		42
11	43	1		36
12	45	1		36
13	41	0	24	36
14	48	0		36
15	35	0		30
16	42	2		90
17	40	0		60
18	60	2		36
19	40	0		48
20	29	0	24	36

TABLE 2. CLINICAL DATA FOR GROUP 2, WHO HAD NASAL POLYPS CONTAINING FOUR OR MORE EOSINOPHILS PER SQUARE MICROMETER

Pt No.	Age (y)	No. of Prior Surgeries for Nasal Polyps	Relapse Time After Surgery (mo)	Follow-Up (mo)
1	48	4	18	72
2	20	2	36	72
3	55	0	12	72
4	56	0		72
5	62	1	60	90
6	61	0	60	84
7	65	0	6	48
8	67	0		42
9	48	0	12	42
10	47	0	18	48
11	61	0	12	36
12	44	1		42
13	65	2	24	36
14	50	0	18	36
15	44	1		30
16	53	0	18	30
17	59	0	24	72
18	35	2	18	30
19	62	0	12	30
20	37	0	6	84
21	32	0	30	48
22	31	0	24	36

ative eosinophilic cationic protein and interleukin-5 levels in nasal secretions were higher in patients with postoperative polyp recurrence. Moreover, a significant reduction of eosinophilic cationic protein level was observed during the follow-up period in patients without recurrence in the same study.[16] In a similar study by Matsuwaki et al,[17] patients with peripheral or mucosal eosinophilia and asthma showed a higher incidence of recurrence of chronic sinusitis after endoscopic sinus surgery.

On the other hand, Eweiss et al[18] investigated the effect of eosinophilia and vascular cell adhesion molecule–1 expression on postoperative recurrence of diffuse sinonasal polyps in 50 patients who underwent endoscopic sinus surgery followed by use of local steroids for 1 year and found no significant difference in the number of infiltrating eosinophils between patients who developed and those who did not develop recurrent nasal polyps. In our study, the patients with 4 or more eosinophils per 1,000 μm^2 of the polyp's sectional area showed a higher incidence of postoperative recurrence (81.81%) of nasal polyps than did those with 3 or fewer eosinophils per 1,000 μm^2 (25%; $p < 0.05$).

The relationship between chronic sinusitis and bronchial asthma has been widely documented in recent years. It is a well-known clinical fact that the presence of chronic sinusitis with or without nasal polyposis exacerbates the symptoms of asthma. Nasal polyposis and bronchial asthma involve two different components of the respiratory tract, and in most cases they share a similar pathogenesis, which represents a mucosal susceptibility to chronic stimuli. Eosinophilic inflammation as the main source of chronic stimuli plays an important role in the pathogenesis in both diseases. Nasal polyps in patients with asthma and aspirin intolerance recur frequently. Ogata et al[1] found that the levels of activated eosinophils in the nasal polyps of patients with aspirin-induced asthma were significantly higher and that they decreased after steroid treatment. However, the results of clinical studies on the effects of bronchial asthma on polyp recurrence are different. In a study by Wynn and Har-El,[4] patients with bronchial asthma and previous sinus surgeries had a significantly higher postoperative recurrence

TABLE 3. RECURRENCE RATES FOR TWO GROUPS

	No. of Patients	No. of Patients With Postoperative Recurrence	Bronchial Asthma	Samter's Triad
Group 1	20	5 (25.0%)	5	2
Group 2	22	18 (81.8%)	10	2
p		0.0001	0.1	0.9

rate. On the other hand, Garrel et al[19] reported that bronchial asthma was not related to the frequency of recurrence of sinonasal polyposis during a 5-year follow-up of 132 patients after endoscopic sinus surgery. The rate of asthma was almost twofold higher in the second group of patients in our study, but the difference between the two groups was not statistically significant ($p > 0.05$), probably because of the relatively small size of the patient groups. Previous surgeries for nasal polyposis had no significant effect on postoperative polyp recurrences ($p = 0.453$) in our study.

The degree of eosinophil leukocyte infiltration in nasal polyps can be determined more objectively by applying a virtual grid composed of horizontal and perpendicular parallel lines forming quadrangular chambers, and determining the number of the inflammatory cells per chamber as in the method used in manual differential blood cell counting with the aid of computer-assisted image analysis software.[6] If the postoperative recurrence rate of nasal polyps can be predicted by this method before the surgery, patients can be informed about the prognosis, and patients with eosinophil-rich nasal polyps may be put on a long-duration postoperative regimen of topical steroids and leukotriene inhibitors.

In conclusion, eosinophil counting in nasal polyps by histopathologic examination can be used as a relatively easy method for prediction of the postoperative recurrence rate of polyps. The findings of this study indicate a high rate of postoperative relapse of eosinophil-rich nasal polyps. However, the study groups were relatively small, and similar studies are needed.

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