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Original article

Incidence of Nasal Polyps Recurrence Rate in Patients with Eosinophilic Esophagitis after Endoscopic Endonasal Surgery

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ABSTRACT

Background: Nasal polyps [NPs] are frequently encountered in otorhinolaryngology practice. It had been proposed to share etiological origin with eosinophilic esophagitis [EOE]. However, there is not yet adequate estimations of this association and incidence of NPs recurrence after endonasal surgery in patients with EOE.

Aim of the work: To evaluate incidence of recurrence of NPs after endoscopic endonasal surgery for patients with EOE.

Patients and Methods: 150 patients were included and divided into three groups: the control [CG] [50 patients indicated for gastroscopy]. The nasal polyp's subgroups consisted of 100 patients and further subdivided into two groups according to result of nasal biopsy into two subgroups, eosinophilic nasal polyps [ENP] group IIA; non-eosinophilic nasal polyps [NENP] group IIB. In NPs subgroups, sinonasal outcome test [SNOT22] had been performed to measure the health status and quality of life in patients with NPs through questions relating to their symptoms. The recurrence of nasal polyps were investigated after endoscopic sinus surgery and during follow up and outcome had been compared between groups.

Results: 22% suffered polyp recurrence after surgery during the follow-up period. Patients with EOE had a significantly higher recurrence rate of nasal polyps [100%] in comparison to 16.4% in EOE patients. These results indicate that, mucosal eosinophilia is a determinant factor in the recurrence of nasal polyps. Hence in patients with EOE [had mucosal eosinophilia] who underwent endonasal surgery, the recurrence of nasal polyps should be highly expected.

Conclusion: Mucosal eosinophilia in patients with EOE, and ENP are a more important prognostic factor in recurrence of nasal polyps.

Keywords: Nasal polyps; Eosinophilic esophagitis; Allergic rhinitis; Eosinophilia; Sinonasal Outcome Test.

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* Main subject and any subcategories have been classified according to research topic.

INTRODUCTION

Nasal polyps defined as blue gray protuberance masses in the nasal cavity, characterized by eosinophil inflammation, and accompanied by acetylsalicylic intolerance in up to 25% of cases^[1]. Forty percent of cases of nasal polyposis are associated with intrinsic asthma, linked to aspirin sensitivity or may represent part of a systemic disease such as cystic fibrosis^[2]. Rhinologist and allergist had hard duties to understand etiology and pathophysiology of nasal polyps, so recurrences are frequent regardless of treatment, making repeated surgical interventions necessary^[3].

Histologically polyps were edematous and fibrotic with decreased vascularization. In addition, there is a reduction in nerve endings and the number of glands with epithelial damage^[4]. The typical manifestations are a cold that persisted over months or years, nasal obstruction and discharge are cardinal symptoms^[5].

By time anosmia develops, which is a typical symptom for nasal polyps, differentiating it from chronic sinusitis without polyposis, anosmia may serve as a valid marker to estimate the duration and extent of disease^[6].

The main etiology of nasal polyps and eosinophilic esophagitis point towards an atopy: clinical symptoms similar to allergic rhinitis, the association with late-onset asthma and elevated local IgE in polyp fluid as well as a pronounced tissue eosinophilia^[7]. Medical treatments of nasal polyps include intranasal steroids, which relieve most of symptoms such as nasal blockage, rhinorrhea and occasionally hyposmia, but recurrence of symptoms occurs within weeks to months^[8].

Topical corticosteroids are indicated post-operatively to reduce the incidence of polyp recurrences and surgery is mainly to establish ventilation and drainage of sinuses for better irrigation by steroids^[9]. However, topical corticosteroids may be insufficient in severe bilateral polyps^[10], and polyp growth may be observed despite treatment.

Eosinophilic esophagitis [EOE], also defined as [allergic esophagitis] is a specific condition of esophagus characterized by the presence of abundant eosinophils. Eosinophils is a common

type of cells, present in EOE and ENP. Symptoms are dysphagia, food impaction, vomiting, and heartburn^[12]. EOE originally defined in pediatrics, but it also affect adult patients. EOE is not well understood, but food allergy proposed to play a crucial role^[13]. The treatment include eradication of suspected stimuli and immune-suppressive medications. Endoscopic esophageal dilatation may be indicated in sever forms of the disease^[14].

The relation between EOE and recurrence of nasal polyps is not well-addressed. Hence, we designed the current study.

AIM OF THE WORK

To evaluate incidence of recurrence of nasal polyps [NPs] after endoscopic endonasal surgery between patients with eosinophilic esophagitis [EOE].

PATIENTS AND METHODS

Design: A double-blinded, randomized, controlled, clinical-trial design was chosen to perform the current study.

Setting: Departments of Otorhinolaryngology and Clinical Pathology, the site of this study was at the Al-Jafel International hospital in Riyadh, Saudi Arabia, during the period from May 2017 to January 2019.

The study protocol was approved by the local Ethics Committee of Al-Azhar Faculty of Medicine, Egypt. Also, approval had been obtained from the hospital administration to conduct the study. Furthermore, an informed consent was taken from each patient.

This study recruited a total of 150 patients were included in the study. This study consisted of three groups, the control group I [CG] consisted of 50 patients indicated for gastro-scopy, which had been evaluated in GIT outpatient Clinic due to dyspepsia symptoms.

The nasal polyps subgroups consisted of 100 patients examined in our outpatient ENT Clinic , with a diagnosis of nasal polyps , this group subdivided into two groups according to result of nasal biopsy into two subgroups.

Group I is the control group consisted of 50 patients. All patients were complaining of epigastric pain, dyspepsia, reflux, and dysphagia. For diagnosis of EOE, upper gastroscopy was

done, biopsies were taken from the esophagus from different levels together with stomach [multiple biopsies]. Eosinophilic infiltration was accepted as being positive if, under high power magnification, there were ≥ 60 and ≥ 70 eosinophils for patients taking PPI [twice a day/two months] in the esophageal squamous epithelium, and no eosinophils in the gastric or duodenal biopsies under the same magnification. After modified Giemsa stain, the presence of *H. pylori* was investigated in the biopsy materials taken from antrum and corpus [15].

For group II Patients with nasal polyps were classified on the basis of the presence of nasal polyps and histological detection of mucosal eosinophilia as defined by the eosinophil cut point into the following groups: eosinophilic nasal polyps [ENP] group IIA, non-eosinophilic nasal polyps [NENP] group IIB. All patients underwent to full history details including age, sex, and history of previous sinus surgery, special habits [e.g., smoking], bronchial asthma, or allergic rhinitis. Investigations included skin prick test [SPT], and serum total IgE and findings of computed tomography, were classified by Lund-MacKay method [16].

The minimum follow up duration for all patients was 6 months, and only those who completed the minimum duration, were subjected to data analysis. Polyps were graded as described elsewhere [17].

In NPs subgroups, Sino-nasal outcome test [SNOT] [18] was performed to measure the health status and quality of life in patients with NPs through questions relating to their symptoms. SNOT results, IgE levels, SPT positivity, presence of *H. pylori*, endoscopic and biopsy findings, presence of major symptoms were noted and polyp recurrence were compared between EoE and non-EoE patients of group IIA,B. Also, the recurrence of nasal polyps were investigated after endoscopic sinus surgery and during follow up and compared between all groups.

Exclusion criteria: In this study, we exclude patients with cystic lesions [excluded by sweat test], unilateral disease like antrochoanal polyps, and any pathology that will increase eosinophilic cells as in patients with parasitic infections [19].

Histological analysis: All nasal polyps were biopsied during surgery; the biopsy included also mucosa of ethmoid cavity [Figure1], and immediately fixed in formalin [10%], and prepared for Haematoxylin-Eosin staining.

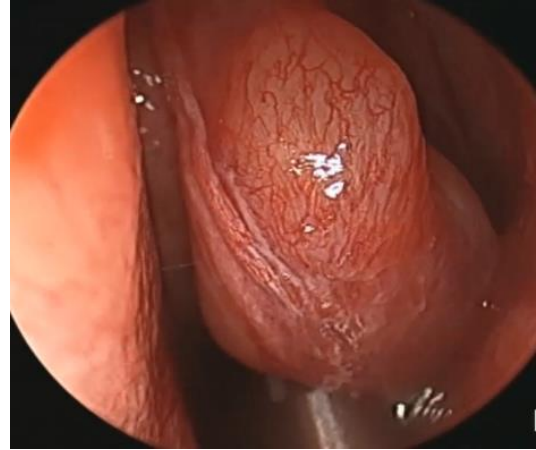


Figure [1]: Patient with nasal polyps removed by shaver during endoscopic endonasal surgery using 0 degree endoscope

The eosinophilic number had been counted under the HPF [high-power field] [$\times 400$]. Eosinophils appeared as a dense cellular infiltrate below the surface of epithelium. Three histologists carried out the examinations and there were unaware of the patient clinical data[20]. The endoscopic appearance of eosinophilic and erosive esophagitis are depicted in figures 2 and 3.

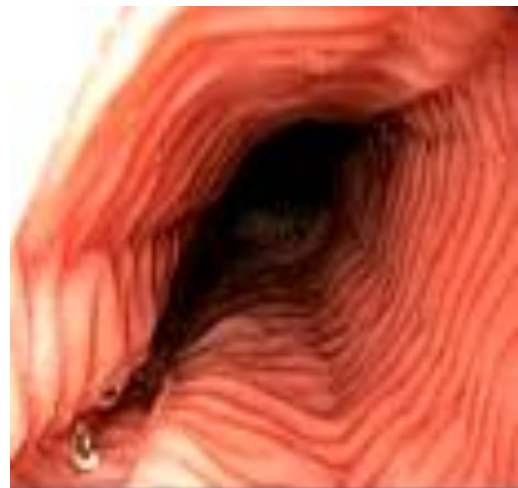


Figure [2]: Eosinophilic esophagitis Endoscopic appearance of esophageal mucosa with longitudinal furrowing, mucosal white plaques, loss of capillary markings along the entire length of the esophagus, and mucosal white plaques in the esophagus.

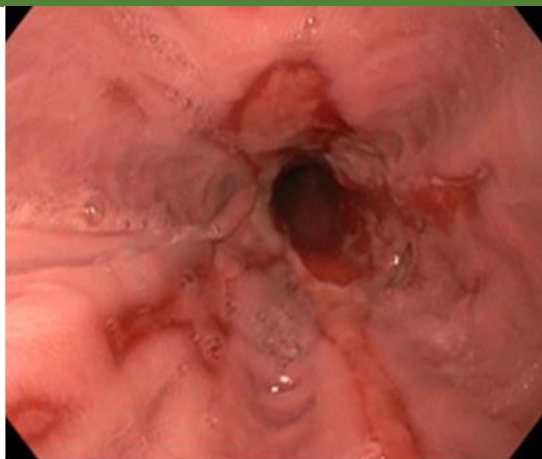


Figure [3]: Erosive esophagitis

Statistical analysis: Data were verified, coded, and analyzed using IBM-SPSS 20.0 [IBM-SPSS Inc., Chicago, IL, USA]. Data were presented as mean, standard deviation [SD] for quantitative variables, and frequency and percentage for qualitative variables. For quantitative groups' comparison, independent sample t-test [two groups] or analyses of variance [more than two groups] were used, while, for qualitative variables, chi-square [χ^2], Fischer's exact, Wilcoxon signed ranks were used as appropriate. A significant P-value was considered significant when it is less than 0.05^[21].

RESULTS

A total of 150 enrolled patients had adequate data for analyses. Studied groups were comparable as regard to patient age, gender, smoking habit and symptoms [Detailed are presented in table 1].

On other side, there was significant increase of allergic rhinitis and asthma in ENP group when compared to MENP or control groups [62.3%,

22.9% vs 13.3%, 6.7% and 34.0% and 6.0% respectively]. In addition, values of IgE and polyp scores were significantly higher in ENP and MENP groups when compared to control group [269.66 ± 109.17 , 259.96 ± 132.04 and 3.33 ± 0.75 , 3.55 ± 0.89 vs 140.10 ± 10.63 , 0.67 ± 0.04 respectively] [see table 2].

Table [3] revealed that, ENP group had the higher rate of EOE [14 patients; 20.0%] followed by control group [4 patients; 8.0%] and finally NENP group [1 patients 3.3%] with significant difference between groups. The biopsy results was identical to EOE and finally there was significant increase of H.Pylori infection in ENP and NENP groups when compared to control group [52.9%, 60.0% vs 30.0% respectively].

Comparing patients with EOE to those who did not have EOE revealed that, EOE was significantly associated with significant increase of IgE levels, increase percentage of patients with positive H.Pylori, increased Epigastric pain, reflux, positive skin prick test [SPT] and all had polyp recurrence [only 16.5% of negative groups had polyp recurrence] [Details are presented in table 4].

Table [5] revealed that, the follow up duration was comparable between studied groups [the mean duration was 12.80 ± 5.23 , 13.07 ± 4.01 and 11.72 ± 3.61 months, in control group, ENP and MENP groups respectively. However, the incidence of polyp recurrence was significantly increased in ENP group [37.1%] when compared to control group [8.0%]. However, the difference between MENP group [10.0%] and control group was statistically non-significant.

Table [1]: The overall clinical and demographic profile

		CG group I [n=50]	ENP group IIA [n= 70]	NENP group IIB [n= 30]	Test	P value
Age		44.74±12.34	45.30±7.70	43.83±7.4	F=0.38	0.68
Gender	Male	[27][54.0%	[37][52.9%	[17][56.7%	0.12	0.94
	Female	[23][46.0%	[33][47.1%	[13][43.3%		
[Current smoker [n, %		[16][32.0%	[21][30.0%	[13][43.33%	χ^2	0.40
Symptoms[n,%]	Dyspepsia	[19][38%	[29][41.4%	[11][36.7%	0.25	0.88
	Epigastric pain	[6][12.0%	[18][25.7%	[5][16.7%	3.68	0.15
	Reflux	[22][44.0%	[23][32.9%	[7][23.3%	χ^2	0.15
	Dysphagia	[3][6.0%	[1][5.0%	[1][10.0%	χ^2	0.86

ENP eosinophilic nasal polyp, NENP: non eosinophilic nasal polyp.

Table [2]: Comparison between groups as regard to incidence of allergic rhinitis, asthma, levels of IgE and polyp score

	CG group I [n=50]	ENP group IIA [n= 70]	NENP group IIB [n= 30]	Test	P value
Allergic rhinitis [n, %]	17[34.0%]	43[62.3%]	4[13.3%]	22.93	<0.001*
Asthma [n, %]	3[6.0%]	16[22.9%]	2[6.7%]	8.55	0.014*
IgE [IU/ml] [mean±SD]	140.10±10.63	269.66±109.17	259.96±132.04	28.94	<0.001*
Polyp score	0.67±0.04	3.33±0.75	3.55±0.89	289.3	<0.001*

CG: control group; ENP eosinophilic nasal polyp, NENP non eosinophilic nasal polyp; * indicates significant difference.

Table [3]: Results of EOE, biopsy and H pylori among studied groups

	CG group I [n=50]	ENP group IIA [n= 70]	NENP group IIB [n= 30]	Test	P value
EOE [n, %]	4[8.0%]	14 [20.0%]	1[3.3%]	6.75	0.03 ± *
Biopsy [eosinophil ≥ 60/hpf]	4[8.0%]	14 [20.0%]	1[3.3%]	6.75	0.03 ± *
H. Pylori [positive] [n, %]	15[30.0%]	37[52.9%]	18[60.0%]	Λ, Λ *	0.01 ± *

CG: control group, ENP eosinophilic nasal polyp, NENP non eosinophilic nasal polyp; * indicates significance of difference

Table [4]: Results between EOE and non-EoE of NP [IIA, IIB] subgroups:

	EOE [-] [n=85]	EOE [+] [n=15]	Test	P value
Age	46.80±8.23	44.58±7.54	1.03	0.30
IgE level	248.18±115.33	362.00±63.73	3.71	<0.001*
SNOT test score	53.05±3.93	55.00±2.26	1.84	0.067
Gender	Male	9[60.0%]	*, 20	*, 61
	Female	6[40.0%]		
H pylori	Positive	12[80.0%]	ε, ε0	0.031*
	Negative	3[20.0%]		
Symptoms	Dyspepsia	5[33.3%]	0.32	0.56
	Epigastric pain	8[53.3%]	9.16	0.002*
	Reflux	8[53.3%]	4.57	0.032*
	Dysphagia	0[0.0%]	0.36	0.54
SPT	47[55.3%]	13[86.7]	5.22	0.02 ± *
Polyp recurrence	14 [16.5%]	15 [100%]	43.20	<0.001*

EOE eosinophilic esophagitis, NP nasal polyps; * indicates significance of difference.

Table [5]: Results of incidence of polyp recurrence and follow up between CG [I] and NPs [IIA, IIB] subgroups

	CG group I [n=50]	ENP group IIA [n= 70]	NENP group IIB [n= 30]	P value
Follow up [m]	12.80 ± 5.23	13.07 ± 4.01	11.72± 3.61	0.07
Polyp recurrence	4 [8.0%]	26[37.1%]	3[10.0%]	<0.001*

CG: control group, ENP eosinophilic nasal polyp, NENP non eosinophilic nasal polyp; * indicates significance of difference.

DISCUSSION

Eosinophils usually not present in the nasal mucosa, but we must expect tissue eosinophilia when it exceed more than 15 eosinophils/HPF ×400, as described by **Fokkens et al.**[22]. However in our study, we set the value to above 60 eosinophils/HPF as the polyps mostly developed in atopic patients where there were abundant tissue eosinophilia due to type-1 hypersensitivity reaction.

In this study, the incidence of recurrence of NPs was significantly higher in patients with EOE, with abundant mucosal eosinophilia. This supports the previous study reported that, mucosal eosinophilia is associated with the severe for of the disease and recurrence of nasal polypi after surgery[23].

Many studies have described the association between mucosal eosinophilia and outcome of the endoscopic surgery, but few studies assessed density of the tissue eosinophils for definition of

mucosal eosinophilia. **Bachert et al.** characterized mucosal eosinophilia by values > 15 eosinophils/HPF and eosinophilia when present was associated with low quality of life scores^[24]. **Noguchi et al.** defined it as values > 5 eosinophils/HPF and linked it to poor surgical outcome^[25].

The current study showed that levels ≥ 60 /HPF had the greatest effects on the surgical outcome. Thus, we defined mucosal eosinophilia as ≥ 60 /HPF. This agree with **Nakayama et al.**^[26] who found it as a significant and important predictor than the nasal polyps itself when consider the surgical end-results.

In the current work, EOE was significantly higher among ENP groups, especially in atopic patients. This is in line with a study done by **Soylu et al.**^[27] who concluded that, the co-existence of EOE in allergic rhinitis is substantially noteworthy.

The esophageal reflux seems to be the main symptom of EOE refractory to treatment in about 1-4% of the patients^[28]. In our study, patients with EOE were found to have a significantly higher percentage of reflux [53.3%] when compared to patients without esophagitis [25.9%]. Epigastric pain showed similar significant increase as reflux in EOE subgroup when compared to non-EOE subgroup [53.3% vs 17.6% respectively].

Dysphagia and food impaction were not significantly different. These results agree with a retrospective study of 156 EOE patients, and reflux was reported to be observed in 40% of EOE patients in one study^[29], and in another study a high percentage of dysphagia [67.5%], food impaction [80%] and history of atopy [80%] were reported^[30]. Similar to our research, **Dellon et al.**^[31] and **Joo et al.**^[32] observed reflux symptoms in 70% and 61.5% of patients, respectively.

In patients with mucosal eosinophilia, there was a high polyp recurrence rate. Therefore, we considered that eosinophils together with thickness of basement membrane are the main factors predispose to recurrence of NPs. Recurrence rate of nasal polyps is significantly high among such group.

Chronic rhinosinusitis [CRS] associated pathology with ENP revealed many differences from that of patients with CRS and NENP^[26,33]. Mucosal eosinophilia is a characteristic of ENP,

but not NENP. However, we recognized that mucosal eosinophilia could also be considered as a key predictor of CRS without NP. These data suggested that chronic rhinosinusitis with ENP might be understood as variables degrees of inflammation and moreover may be considered as an entity of the same disease.

On contrary, patients with NENP did not have a higher recurrence rate of nasal polypi. This agree with study done in Chinese populations and showed that NENP share some similarities in granulocyte activation and T-helper cell responses^[34] indicating that CRS with NENP and non-eosinophilic CRS without NP may be the same disease entity.

Nasal polyps are inflammatory process rather than infective conditions, so its management needs multiple approaches include medical treatment, mainly based on the use of topical or systemic corticosteroids and surgical procedures to eradicate all polyp tissue and to decrease inflammatory load and long use of nasal steroids, but still there is high risk of recurrence in spite of a combined treatment strategy. Biopsy is strongly indicated from mucosa for detection of eosinophilia and thickness of basement membrane; and mucosal eosinophilia could be considered as a biomarker to detect [predict] for relapse. If mucosal eosinophilia more than 60/HPF which approved in our study, it indicate a bad prognosis with high rate of recurrence^[35].

In line with the current work, a previous study revealed that, the prevalence of atopic diseases such as environmental or food allergies is 50% higher in adults and children with EOE when compared to the general population^[36]. EOE is seen more in atopic patients, which has increased with the increase in diagnosis and prevalence of allergic disease^[37]. Another work reported that, allergic rhinitis had been observed in 10-20% of the general population. It is important to diagnose EOE early for the control of symptoms and prevention of complications. In patients with EOE, incidence of AR, eczema and

asthma are reported to be 40-75%, 4-60%, and 14-70% respectively^[38].

Conclusion: Mucosal eosinophilia in EOE, and ENP is an important prognostic factor in prediction of nasal polyp's recurrence after surgery.

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