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The Evaluation of Nasal Polyps in Terms of Smoking, Proliferative Processes, and Inflammation: Cross-Sectional Study

Nazal Poliplerin Sigara İçimi, Proliferatif Süreç ve Enflamasyon Açısından Değerlendirilmesi: Kesitsel Çalışma

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ÖZET

Amaç: Bu çalışmada Türk toplumunda Nazal poliplerin (NP) sigara içimi, proliferatif süreçler ve enflamasyon ile ilişkisini histopatolojik ve klinik parametreler doğrultusunda detaylı bir şekilde değerlendirmeyi amaçladık.

Gereçler ve Yöntem: Mart-Ağustos 2021 tarihleri arasında hastanemizde endoskopik sinüs cerrahisi yapılan 36'sı erkek, 19'u kadın toplam 55 nazal polip hastasının patolojik materyalleri incelendi. Hematoksilin ve Eozin (H&E) boyama ile histolojik alt tipler skuamöz metaplazi, epiteliyal hiperplazi gibi histolojik değişikliklerin değerlendirilmesi yapıldı. Ayrıca eozinofil, nötrofil, lenfosit oranları ve yoğunluğu gibi çeşitli inflamatuar durumları değerlendirildi. Bununla birlikte, dokularda sigara içimi ile ilgili gelişebilecek proliferatif değişiklikler immünohistokimya (IHK) yöntemi ile Ki-67 ve p53 boyama değerlendirmeleri yapılarak araştırıldı. Hastane sisteminden elde edilen klinik bilgiler, laboratuvar sonuçları ve Lund-Mackay sınıflaması verileri dahil edildi. Çalışmada R 4.2.2 programı kullanılarak Ki-Kare ve Fisher testleri ile T-testi analizleri gerçekleştirildi.

Bulgular: Hastaların yaş ortalaması 37,22±16.96'dir. Bunlardan 34'ü (61,82%) sigara içmezken, 21'i (38,18%) sigara içmekteydi. Sonuçlarımızda sigara içenlerde ve Lund-Mackay sınıflaması puanı yüksek olanlarda eozinofilik infiltrasyon ile anlamlı bir ilişki gösterdi ($p<0.05$). Ayrıca, Lund-Mackay puanı yüksek olanlarda eozinofilik ve lenfoplazmositik inflamasyon türleri ile de anlamlı korelasyon saptandı ($p<0.05$). Nazal poliplerde skuamöz metaplazinin bulunması ile Ki-67 ve p53 immünhistokimyasal boyanma skorları arasında anlamlı ilişki bulunurken, epiteliyal hiperplazi ile bu değerler arasında ilişki bulunmadı.

Sonuç: Çalışmamızda nazal polip hastalarında sigara içimi ile Lund-Mackay sınıflaması sonuçları, inflamasyon tipi ve eozinofilik inflamasyon arasında ilişkiyi gösterdik. Ayrıca, proliferatif belirteçler olan Ki-67 ve p53 bulguları ile metaplazik değişiklikler ve epitel hiperplazi gelişimi arasında korelasyon tespit edildi. Türk toplumunda NP'lerdeki eozinofilik inflamasyon dereceleri Asya ve Avrupa toplumları arasında bir noktada olduğu sonucuna varıldı.

Anahtar Kelimeler: Nazal polip, proliferatif süreç, sigara içimi, Ki-67, p53

ABSTRACT

Objective: This study aimed to evaluate the relationship between nasal polyps (NP) in the Turkish population and smoking, proliferative processes, and inflammation, based on histopathological and clinical parameters.

Materials and Methods: Nasal polyp materials from 36 male and 19 female patients who underwent endoscopic sinus surgery at our hospital between March and August 2021 were examined. Histological changes, such as histological subtypes, squamous metaplasia, and epithelial hyperplasia, were evaluated using Hematoxylin and Eosin (H&E) staining. Various inflammatory conditions, such as the proportions and density of eosinophils, neutrophils, and lymphocytes, were also assessed. Furthermore, proliferative changes in tissues related to smoking were investigated using immunohistochemistry (IHC) using Ki-67 and p53 data. Clinical information obtained from the hospital system, laboratory results, and Lund-Mackay classification data were included. In the study, Chi-square and Fisher's tests, as well as t-test analyses, were performed using the R 4.2.2 program.

Results: Thirty-four (61.82%) of the patients were non-smokers, while 21 (38.18%) were smokers. Our results showed a significant association between eosinophilic infiltration in smokers and those with high Lund-Mackay classification scores ($p<0.05$). Furthermore, a significant association was found with eosinophilic and lymphoplasmacytic inflammation types in those with high Lund-Mackay scores ($p<0.05$). While there was a significant association between the presence of squamous metaplasia in nasal polyps and Ki-67 and p53 immunohistochemical staining scores, no association was found between these values and epithelial hyperplasia. **Conclusion:** In our study, we demonstrated the relationship between smoking and Lund-Mackay classification results, inflammation type, and eosinophilic inflammation in patients with nasal polyps. Additionally, an association was found between the proliferative markers Ki-67 and p53 and the development of metaplastic changes and epithelial hyperplasia. It was concluded that the degree of eosinophilic inflammation in NPs in the Turkish population appears to be intermediate between those of Asian and European populations.

Keywords: Inflammation, nasal polyp, proliferative processes, smoking, Ki-67, p53

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INTRODUCTION

Nasal polyps (NPs) are nonneoplastic, chronic inflammatory growths in sinonasal tissues and are seen in 2-4% of the population (1,2). In NPs, there are histological developments in the form of epithelial proliferation, squamous metaplasia, thickening of the basal membrane, inflammation, and vascular and glandular proliferation (1,3). Genetic factors, anatomical disorders, allergic inflammations, infections, mastocytosis, and environmental factors play a role in the etiopathogenesis of NPs under the headings of proliferative processes, and infective-immunological and genetic conditions (4,5). NPs are more common among males and adults due to the intensity of smoking and higher exposure to occupational chemicals (6). Recurrence is observed in 15-40% after polypectomy (7).

Smoking is an important environmental factor, and it has been reported that NPs are more commonly seen in smokers than non-smokers, respond less to surgery, and have a higher recurrence rate (5,8). Smoking increases the aggravation of eosinophilic inflammation and inflammatory responses, decreases mucociliary clearance, and paves the way for the formation of polyps (9-11). Proinflammatory mediators and inflammatory cells may contribute to the formation of polyps (12). Reducing immune resistance is also considered to lead to NPs. Most individuals with NPs have an increased level of immunoglobulin E (IgE) and reveal skin test positivity against inhalant allergens (9). Potent regulatory molecules are increased in NPs (13). Despite the prevalence of polyps, sinonasal cancers account for less than 1% of all malignancies (14). Malignancy development in inverted papillomas (IPs) is 10%, whereas it is very rare in NPs (15).

Fewer eosinophils have been shown to exist in the nasal mucosa normally (16). The eosinophil activation contributes to the formation and development of polyps. Eosinophils have also been demonstrated to be effective on CD-3-positive cells (17). T lymphocytes are involved in the pathogenesis of diffuse and chronic rhinosinusitis. In polyps, polymorphonuclear neutrophils (PMNs) also participate in inflammation at various rates. It is known that eosinophilic chronic rhinosinusitis with NPs (CRSwNP) responds well to steroid therapy, but non-eosinophilic cases are resistant to the therapy with steroids (12). In addition, nasal polyps refractory to more than eight weeks of appropriate local therapy or more than two courses of systemic steroid therapy are the most acceptable indication for surgery. Furthermore, biologics (i.e., Dupilumab, Benralizumab, Omalizumab, and Mepolizumab) are a treatment option in patients who do not respond to topical medical therapy or cannot tolerate surgery (18).

Epithelial hyperplasia, squamous metaplasia, and hyperplasia of goblet cells are witnessed as remodeling in the sinonasal mucosal epithelium (1). Smoking leads to more squamous metaplasia than airways (5). A tumor suppressor protein, p53, plays a key role in maintaining the integrity of the genetic code by screening for likely mutations and is responsible for repairing the damaged DNA and inducing apoptosis of mutated cells (12,19). On the other hand, Ki-67 is a proliferation marker and generally increases inflammation and carcinogenic processes (20). About 3800 chemical and carcinogenic substances have been detected in cigarette smoke (21).

In our study, we aimed to evaluate NPs in terms of smoking, proliferation processes, and inflammation in the Turkish population. In this context, we immunohistochemically investigated in detail the histological subtypes, types, and grades of inflammation, eosinophil inflammation grading, formation of eosinophilic aggregates, PMNs, and lymphocyte infiltration through the staining of Ki-67 and p53.

MATERIAL AND METHODS

Design and ethical approval

Approval was obtained from the Ethics Committee of Hamidiye Health Sciences University (Date and number: 02/19/2021-2021/7). Informed consent was also obtained from the participants. All procedures in this study adhered to the ethical standards of the institutional and national research committees and conformed to the principles of the Declaration of Helsinki and its later amendments.

Patients and samples

In our study, 55 patients (36 males and 19 females) undergoing endoscopic sinus surgery between March and August 2021 were evaluated at Konya City Hospital, University of Health Sciences, Konya, Turkiye.

The study plan was applied to the patients who applied to our hospital with complaints of nasal polyps and underwent surgery. Patients with unavailable demographic data or without adequate pathologic specimens were excluded from the study Demographic data (age and gender), hemogram values including eosinophil (%), polymorphonuclear neutrophils (%), lymphocyte (%), monocyte (%), basophil (%), Red blood cell (M/Ul), Hemoglobin (g/Dl), hematocrit (%), MCV (fL), MCH (pg), MCHC (g/dl) values and smoking status(smoking history or not) were obtained from data from the hospital. All patients were evaluated with the Lund-Mackay classification (22).

While 23 (41.81%) of the patients were <35 years old, 32 (58.18%) were ≥ 35 years old. Of the smokers, 10 (47.62 9%) smoked for more than 20 years, 8 (38.09%) smoked for less than 5 years, and the remaining 3 (14.29%) smoked for 5-20 pack-years.

IHC and H&E staining

The tissues of NPs were prepared by cutting 4-5 micron-thick sections for the hematoxylin-eosin and immunohistochemistry (IHC) studies. Anti-Ki-67 and anti-p53 were stained according to protocols. Anti-Ki-67 antibody for immunohistochemistry (Mouse monoclonal, Biogenex, The Hague, The Netherlands), Anti-p53 (Mouse monoclonal, Zeta, Sierra Madre, CA, USA.

To grade eosinophils and PMNs, the counts were classified as Grade 0 (G0) if the count was 0, G1 between 1-2, G2 between 3-10, G3 between 11-30, and G4 if the count was >30 in 5 high-power fields (HPF). Even so, the eosinophil infiltration in tissues was evaluated as <10% and >10% of the inflammation. While the histological types were also grouped as edematous, fibroinflammatory, angioectatic, and glandular, the types of inflammation were grouped as lymphocytic,

lymphoplasmacytic, and eosinophilic. In terms of stromal degeneration and fibrosis, the severity of inflammation was evaluated as mild (1), moderate (2), and severe (3). Also, the presence of eosinophilic aggregates, lymphocyte infiltration, squamous metaplasia, epithelial hyperplasia, and goblet cells was evaluated with the presence and absence (0/1). For Ki-67 and p53, no staining was considered as G0, between 1-25 cells as G1, between 25-50 cells as G2, and >50 cells were evaluated as G3. Preliminary evaluation was made regarding the presence and intensity of staining in preparations stained with Ki-67 and p53 of the cases at x20 magnification. Then, epithelial cells, which were considered positive for nuclear staining, were counted in all areas at x40 magnification. Absence of staining in all areas was evaluated as G0, and according to the number of positively stained cells, 1-25 cells were evaluated as G1, 25-50 cells as G2, and >50 cells as G3.

Ulceration in the epithelium, infarction in the stroma, hemorrhage, and cystic changes were evaluated as degeneration. The presence of hyalinized connective tissue in the stroma and fibrosis was evaluated with H&E. In 6 suspicious cases, evaluation was performed using Masson Trichrome (blue staining).

Lund-Mackay classification

In chronic rhinosinusitis, the Lund-Mackay classification is used radiologically. The six subdivisions of the paranasal sinuses, including the maxillary sinus, anterior ethmoid sinuses, posterior ethmoid sinuses, sphenoid sinus, frontal sinus, and osteomeatal complex, are divided into 12 regions when evaluated as right and left. Mucosal inflammation or fluid collection of the sinus is scored as (0) completely radiolucent, (1) partially radiolucent, or (2) completely radiopaque. In addition, mild mucosal thickening without fluid collection is scored 0; mild mucosal thickening with fluid collection causing a partial radiolucent appearance is scored 1; and moderate or severe mucosal thickening without fluid collection causing a partial radiolucent appearance without complete radiopaque is scored 1. In addition, since the osteomeatal complex is a difficult region to grade, it is scored as 0, no obstruction, and 2, obstruction. As a result of these evaluations, all sinuses are completely radiolucent: 0; all sinuses are completely radiopaque: 24, and a total bilateral Lund-Mackay score is determined. Based on the Lund-Mackay scoring system, patients with scores of 1–12 were categorized into the low-score group (A), whereas those with scores of 13–22 were categorized into the high-score group (B).

Statistical Method

Descriptive statistics were presented as mean ± standard deviation for quantitative variables and as frequency and percentage for categorical variables. For comparisons between categorical variables, Chi-Square or Fisher's Exact Tests were used as appropriate. For normally distributed numerical variables, Student's t-test or analysis of variance (ANOVA) was applied. All analyses were performed using R software (version 4.2.2). A two-tailed p-value <0.05 was considered statistically significant.

RESULTS

The average age range of the study population was 37.22±16.96 (ranging between 7- 77 years). Of 55 patients, 36 (65.45%) were males and 19 (34.55%) were females, and while 34 (61.82%) were non-smokers, 21 (38.18%) were smokers. The package-years of smoking were 6.79±12.64 (ranging from 0 to 45 years). Histopathological evaluation of nasal polyps revealed that the majority of cases were of the edematous type (80%), followed by angioectatic (7.27%), glandular (7.27%), and fibroinflammatory types (5.45%). Regarding the type of inflammation, lymphoplasmacytic infiltration was most common (54.55%), while eosinophilic (30.91%) and lymphocytic inflammation (14.55%) were less frequent. The severity of inflammation was predominantly moderate (44.45%), with mild (30.91%) and severe inflammation (23.64%) observed in fewer cases. Eosinophilic infiltration ≥10% was present in 56.36% of the samples. According to the grading of eosinophilic inflammation, Grade 3 was most frequent (25.45%), followed by Grade 1 (23.64%), Grade 2 (16.36%), and Grade 0 (5.45%). Eosinophilic aggregates were detected in 52.73% of cases. In addition, neutrophilic inflammation was identified in 63.64% of specimens, while lymphoid aggregates were less common (18.18%). Evaluation of other histopathological parameters showed that macrophage counts <5 were more frequent (60%) than ≥5 (40%). Epithelial hyperplasia was observed in 36.36% of cases, mucosal ulceration in 58.18%, and squamous metaplasia in 45.45%. Goblet cells were preserved in most cases (78.18%), and subepithelial edema was identified in 54.55%. Concerning stromal changes, stromal degeneration was most commonly observed at Grade 2 (36.36%) and Grade 3 (34.55%), while Grade 1 (20%) and Grade 0 (9.09%) were less frequent. Stromal fibrosis was predominantly absent or mild

Table 1. Findings related to smoking status and the Lund-Mackay classification

Smoking Status	Sex	Low (Group A: 1–12) n (%)	High (Group B: 13–22) n (%)	Total n (%)	p-value1
Non-Smoking	Female	7 (12.72)	11 (20.00)	18 (32.72)	
	Male	8 (14.54)	8 (14.54)	16 (29.08)	
	Total	15 (27.26)	19 (34.54)	34 (61.80)	0.9270
Smoking	Female	0 (0.00)	1 (1.81)	1 (1.81)	
	Male	9 (16.36)	11 (20.00)	20 (36.36)	
	Total	9 (16.36)	12 (21.81)	21 (38.17)	
Overall Total	24 (43.62)	31 (56.38)	55 (100.00)		

Abbreviations: N, number; %, percent. [1]Pearson's Chi-squared test.

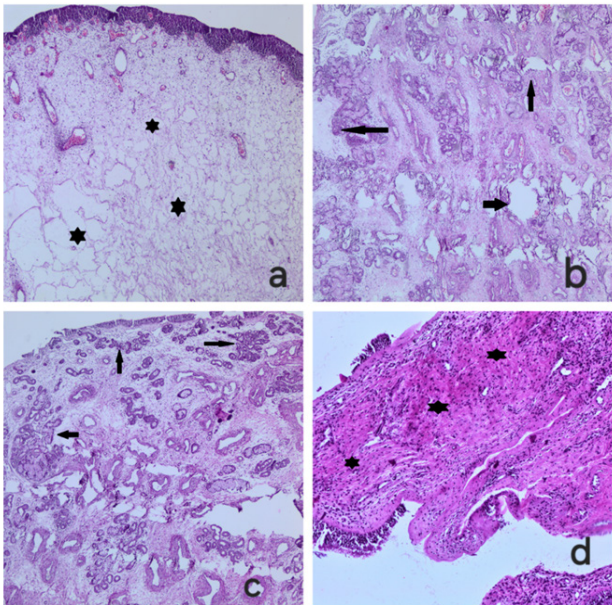

Figure 1. Histological subtypes of nasal polyps: A- Edematous, widespread edematous changes in the stroma (stars), H&E x100; B- Angioectatic, vascular structures with wide lumens between glands (arrows), H&E x150; C- Glandular, increased number of glandular building communities (arrows), H&E x100; D- Fibroinflammatory, Inflammation in diffuse fibrotic stroma (stars), H&E x100
Abbreviations: H&E: Hematoxylin & Eosin

(41.82% for both Grade 0 and Grade 1), whereas Grade 2 and Grade 3 changes were found in 9.09% and 7.27% of cases, respectively (Figure 1). According to Lund-Mackay's findings, the patients were divided into two groups: low, 31 (% 53.37%), and high, 24 (% 46.63%). The smoking status in both groups is shown in Table 1.

Those with higher scores of the Lund Mackay classification were more likely to have the eosinophilic and lymphoplasmacytic types of inflammation, and a significant association was detected between those types of inflammation (p=0.0306). Among those with higher scores of the Lund-Mackay criteria, eosinophilic aggregates were observed at a higher rate (64.52%), and the rate of inflammatory >10% was higher than 70.97%, a significant associate with was found between those parameters (p=0.0466, p=0.0131, respectively). A significant association was found between the scoring (p=0.0324) and the increase in blood eosinophil values among the patients with higher Lund-Mackay scores that displayed higher blood eosinophil values. Even so, no significant relationship was detected between this scoring and other histopathological changes, proliferative processes, rates of Ki-67 and p53, and other blood values (p>0.05). Given the comparisons between smokers and non-smokers, the fact that eosinophil aggregates were more marked (p=0.0236), and the rate of inflammatory

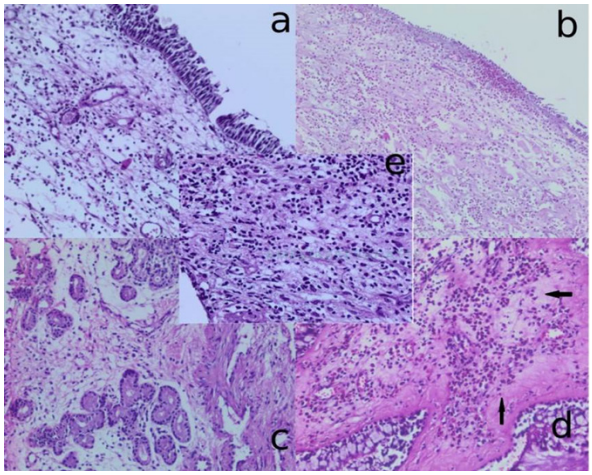

Figure 2. Inflammatory features of nasal polyps: A- Lymphoplasmacytic, H&E x100; B-Eosinophilic, H&E x100; C- Lymphocytic, H&E x100; D- Eosinophilic aggregate, densely eosinophilic cells form distinct clusters (arrows), H&E x200; E- Neutrophilic, H&E x200
Abbreviations: H&E: Hematoxylin & Eosin

cells was eosinophilic >10% (p=0.0318) among smokers suggested that there was a significant relationship between high hemoglobin values (p=0.0408), high hematocrit values (p=0.0256) (Figure 2), and mean corpuscular hemoglobin (MCH) values (p=0.0296). No significant association was found between smoking status and other histopathological changes, proliferative processes, rates of Ki-67 and p53, and other blood values (p>0.05).

Various histological findings of histological eosinophilic grading and aggregates were determined to be prominent, and some blood values were also found to be high. Significant correlations were observed between eosinophilic grade and blood eosinophil (p=0.0013), neutrophil (p=0.0014), and lymphocyte counts (p=0.0200). Similarly, the presence of eosinophilic aggregates correlated with these three blood parameters (p=0.0012, p=0.0003, and p=0.0032, respectively). In addition, with the higher rates of eosinophilic aggregates in smokers, all these significant relationships are shown in Tables 2 and 3. No significant association was detected between the out-of-histological and other blood values of these two entities and the scores of Ki-67 and p53 (p>0.05) (Table 4). The differences in Figure 4 and the scoring results of Ki-67 IHC staining in Table 4 were evaluated, and a trend was observed (p=0.0563), but it did not reach statistical significance.

Due to the presence of higher values of Ki-67 in the cases with squamous metaplasia, while a significant association was found between the values of Ki-67 and squamous metaplasia (p=0.0032), no significant association was seen between Ki-67 and epithelial hyperplasia (p=0.2897) (Figure 3). Given the assessment of the differences (Figure 5) and scoring results of p53 IHC staining (Table 4), a significant association was found in the patients with squamous metaplasia due to higher values

Table 2. Association of Clinicopathological Parameters with Eosinophilic Aggregate

Variable Parameter	Category	Eosinophilic Aggregate Present (N,%)	Eosinophilic Aggregate Absent (N,%)	p – value1
Smoking	Yes	7 (24.14%)	14 (53.85%)	p=0.0236
	No	22 (75.86%)	12 (46.15%)	
Degree of Inflammation	Mild	2 (6.90%)	15 (57.69%)	p=0.0002
	Moderate	18 (62.07%)	7 (26.92%)	
	Severe	9 (31.03%)	4 (15.38%)	
Type of Inflammation	Lymphocytic	2(6.90%)	6 (23.08%)	p<0.0001
	Lymphoplasmacytic	10 (34.48%)	20 (76.92%)	
	Eosinophilic	17 (58.625)	0 (0.00%)	
Eosinophilic Grade	Grade 0	0 (0.00%)	3 (11.54%)	p<0.0001
	Grade 1	0 (0.00%)	13 (44.83%)	
	Grade 2	0(0.00%)	9 (34.62%)	
	Grade 3	13 (50.00%)	1 (3.85%)	
	Grade 4	16 (55.17%)	0 (0.00%)	
Eosinophil Inflammation >10%	Yes	28 (96.55%)	3 (11.54%)	p<0.0001
	No	1 (3.45%)	23 (88.46%)	
Neutrophilic Inflammation	Yes	23 (79.31%)	12 (46.15%)	P=0.0107
	No	6 (20.69%)	14 (53.85 %)	

Abbreviations: N, number; %, percent. [1]Pearson's Chi-Squared Test.

Table 3. Association of Clinicopathological Parameters with Eosinophilic Grade

Variable	Category	Eosinophilic Grade 0 (N,%)	Eosinophilic Grade 1 (N,%)	Eosinophilic Grade 2 (N,%)	Eosinophilic Grade 3 (N,%)	Eosinophilic Grade 4 (N,%)	p – value1
Smoking	Yes	2 (66.67%)	7 (53.85%)	5(55.56%)	3(21.43%)	4(25.00%)	0.1728
	No	1 (33.33%)	6(46.15%)	4(44.44%)	11(78.57%)	12(75.00%)	
Degree of Inflammation	Mild	3(100.00%)	8 (61.54%)	4(44.44%)	1(7.14%)	1(6.25%)	0.0046
	Moderate	0(00.00%)	4 (30.77%)	3(33.33%)	9(64.29%)	9(56.25%)	
	Severe	0(00.00%)	1 (7.69%)	2(22.22%)	4(28.57%)	6(37.50%)	
Type of Inflammation	Lympho-plasmacytic	2 (66.67%)	8 (61.54%)	9(100.00%)	8(57.14%)	3(18.75%)	<.0001
	Eosinophilic	0(00.00%)	0 (00.00%)	0(00.00%)	4(28.57%)	13(81.25%)	
	Lymphocytic	1 (33.33%)	5(38.46%)	0(00.00%)	2(14.29%)	0(00.00%)	
Eosinophilic Aggregate	Yes	0 (0.00%)	0(00.00%)	0(00.00%)	13(92.16%)	16(100.00%)	<0.0001
	No	3(100.0%)	13(100.0%)	9(100.00%)	1(7.14%)	0(00.00%)	
Eosinophil Inflammation >10%	Yes	0(00.00%)	0(00.00%)	2(22.22%)	13(92.86%)	16(100.00%)	<0.0001
	No	3 (100.0%)	13(100.0%)	7(77.78%)	1(7.14%)	0(00.00%)	
Neutrophilic Inflammation	Yes	1(33.33%)	6(46.15%)	4(44.44%)	13(92.86%)	11(68.75%)	0.0460
	No	2(66.67%)	7(53.85%)	5(55.56%)	1(7.14%)	5(31.25%)	

Abbreviations: N, number; %, percent. [1]Pearson's Chi-Squared Test.

Table 4. Scoring values of immunohistochemical staining of Ki-67, p53, and the relationship between smoking

	Grade 0 (N,%)	Grade 1(N,%)	Grade 2(N,%)	Grade 3(N,%)	p – value1
Ki-67 Values n (%)	13 (23.63)	14 (25.45)	20 (36.36)	8 (14.54)	
Smoking	4 (7.27)	4 (7.27)	8 (14.54)	5 (9.09)	0.410
Non-smoking	9 (16.36)	10 (18.18)	12 (21.81)	3 (5.45)	
p53 Values n (%)	27 (49.09)	19 (34.54)	8 (36.36)	1 (14.54)	
Smoking	10 (18.18)	7 (12.72)	3(5.45)	1(1.81)	0,648
Non-smoking	17 (30.90)	12 (21.81)	5 (9.09)	0 (0.00)	

Abbreviations: N, number; %, percent. [1]Pearson's Chi-squared test.

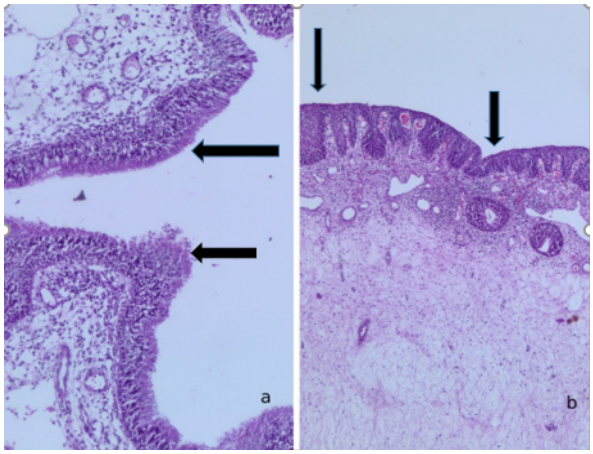

Figure 3. A- Epithelial hyperplasia, increased number and order of pseudostratified columnar epithelium (arrows), H&E x200; B- Squamous metaplasia, transformation of pseudostratified columnar epithelium into squamous epithelium (arrows), H&E x100
Abbreviations: H&E: Hematoxylin & Eosin

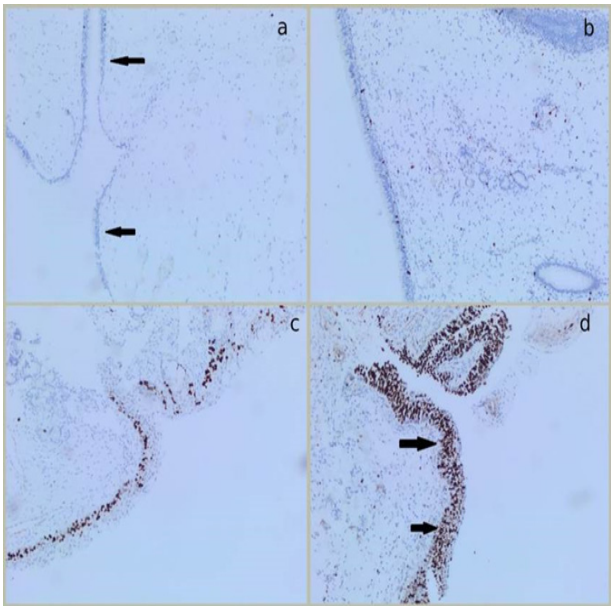

Figure 4. Ki-67 Scoring: A- Grade 0. No staining with Ki-67 in epithelial cells (arrows), Ki-67 x100; B- Grade 1, Ki-67 x100; C- Grade 2, Ki-67 x100; D- Grade 3, Strong staining with Ki-67 in epithelial cells (arrows), Ki-67 x200

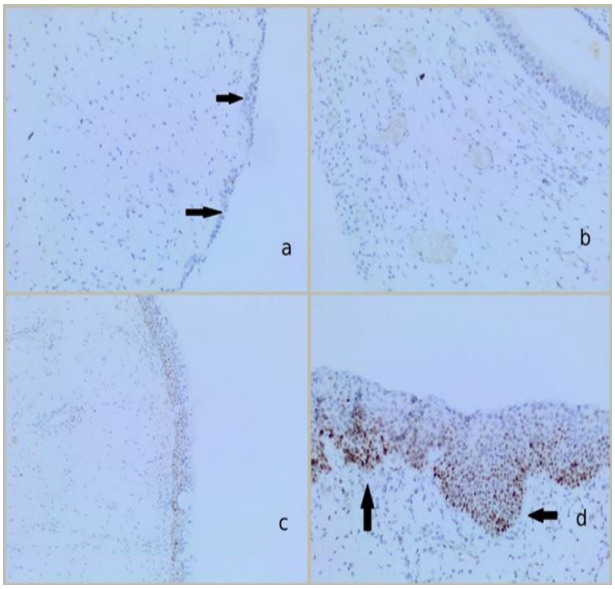

Figure 5. p53 Scoring: A- Grade 0. No staining with p53 in epithelial cells (arrows) p53 100X; B- Grade 1, p53 x100; C- Grade 2, p53 x100; D- Grade 3, Strong staining with p53 in epithelial cells (arrows), p53 x200

of p53 scores (p=0.0237). Even so, no significant relationship was detected between epithelial hyperplasia and values of p53 scores (p=0.0847).

DISCUSSION

NPs are among the commonly encountered phenomena in the community [1]. Here, we aimed to carry out a wide-parameter study including the inflammatory-proliferative processes and also the clinical-radiological evaluations of NPs. In addition, we strove to demonstrate the place of Turkish society between Asian and European societies regarding the evaluations of eosinophilic inflammation. Due to a higher rate of smoking and greater exposure to environmental pollution, NPs are more commonly encountered in males. In a study with 172 patients, the rate of the development of polyps was found to be 1.72 times higher in males than in females (23). In our study, this rate was detected to be 1.89 times higher among male patients. It is considered that the difference has decreased due to the increased exposure to environmental pollution. In the study carried out by Erbek et al. with 125 patients, no significant relationship was detected between smoking status and the diameter of NPs, paranasal NPs. Scores of computed tomography (CT), total IgE levels, and blood eosinophil levels (24). In our study, there was no significant relationship between the evaluations of similar parameters and the Lund-Mackay scoring of smoking.

Studies investigating the relationship between smoking status, inflammation, and NPs have also generally found similar results to each other. In the study by Lee et al., chronic smoking was emphasized to aggravate the eosinophilic inflammation and formation of NPs (25-27). In two separate studies by Kule et

al. and Li et al., however, it was demonstrated that the number of total inflammatory cells and PMNs increased in the NPs of cigarette smokers (5,27). In a study, it was shown that serum IgE, Th2 cytokines, N-cadherin, α-SMA, and vimentin increased, while E-cadherin levels decreased in smokers compared to non-smokers (28). In our study, no significant association was determined between smoking status and other findings related to inflammatory cells, except for the evaluations of eosinophilic infiltration. Even so, various values of complete blood count, such as hemoglobin, hematocrit, and MCH, were found to be higher in cigarette smokers.

In studies of the airway, a significant association has been shown between smoking and squamous metaplasia. However, in different studies, controversial findings have been reported. In the study by Kule et al., squamous metaplasia and hyperplasia of goblet cells were found to be significantly higher in smokers, compared to non-smokers (5). Likewise, Li et al. also reached identical findings in the study carried out with 48 patients (29). In a study of 285 people, including smokers, quitters, and non-smokers, it was shown that smokers had more squamous hyperplasia, metaplasia, and basement membrane thickness (27). Contrary to the findings mentioned above, Gao et al. stated that smoking did not affect the development of squamous metaplasia in NPs (1). Parallel to this, in our study, there was no significant relationship between smoking status and the development of squamous metaplasia and epithelial hyperplasia.

In routine pathologic practices, the Sydney classification systems, such as numerous benefits have been achieved in terms of the clinical-pathological association, with classification used in reporting gastritis can also be recommended for NPs [30]. In addition, clinical and age-related information on atypia, dysplasia, and cancer development in NPs can be collected, as in some large studies, although not seen in our study (2,31). In the diagnoses of NP in routine histopathological examinations, in general, various parameters (Table 3) such as the histological types of the polyps, type of inflammation, and rate of eosinophilic inflammation can be specified in interpreting the report. Thanks to this standard practice, a larger series of data can be acquired for the treatment, follow-up, and clinicopathological features of further studies.

Studies related to the Lund-Mackay classification and pathological findings are limited. Tezer et al. found no statistically significant association between the Lund-Mackay classification and the evaluation of Ki-67 (32). Erbek et al. did not detect a significant relationship between smoking status and the Lund-Mackay classification (24). In our study, while no significant relationship was detected between the scores of the Lund-Mackay classification, smoking status, and rates of p53 and Ki-67, a significant relationship was revealed between the inflammatory characteristics of polyps, eosinophil inflammation and formation of aggregates, and blood eosinophil values. Studies have found a high rate of eosinophilic cells in NPs in Europe. In two studies, one with 107 patients, conducted by Hellquist, and the other with 123 patients, these rates were found to be 86% and 83% (33). This rate has also been found to be 80%-90% in non-European Western societies and 98% in North Africa (34,35). Unlike Western societies, the rate of eosinophilic polyps has been found to be lower in Asian societies, including South Korea (9). In a study conducted in Malaysia, the rate of neutrophil-predominant polyps in the country was demonstrated as 67.2% (36). In various recent comparative studies in South Korea between 1993 and 2011, the rates of eosinophilic NPs have been demonstrated to increase (9). The socioeconomic and environmental conditions (bacterial superantigens, smoking, dust, climate changes, fungal infections, etc.) of Asian societies are increasingly similar to those of Europe. Because of these, the prevalence of eosinophilic polyps is also increasing among Asian populations (9,33). In fact, in an old study, the rate of eosinophil infiltration in NPs was found to be 92.3% in Japanese, as high as among Europeans (37). In the study by Yu et al., the ratio of the eosinophil-dominant phenotype of CRSwNP increased significantly (38).

There are more significant challenges in the treatment of non-eosinophilic polyps compared to eosinophilic polyps. In different studies, it has been stated that there will be differences in treatment regimens since the etiologies of NPs may be different in the Caucasian and Asian populations. In the method used in the Asian population, more antibiotics are needed to treat NPs, and there is less response to steroids (39,40). Eosinophilic NPs have a poorer prognosis than other groups due to reasons such as increased serum eosinophilia, atopic presentation and more widespread disease. A study has shown that all these parameters have been shown to have adverse effects (39). The rate of the least part of the inflammation was eosinophilic in 31 (56.36%) of the polyps evaluated in our study; with such a rate, our country ranks between the values of the Asian and European populations in terms of eosinophilic infiltration in NPs. In the study conducted by Ikeda et al., the serum eosinophil values and recurrence rates were found to be higher in the eosinophilic groups, compared to the other two groups. In addition, the symptomatic and CT scores, and the expressions of eotaxin, interleukin-17A, MUC5AC, and CD68 were also detected to be high [40]. High IgE levels have been found in the serum of patients with CRSwNPs (41). It has also been reported that treatment is more difficult in patients with a high eosinophilic aggregate/infiltration ratio (42).

In our study, a significant association was also determined between eosinophilic grades and blood eosinophil values. In various studies, the effects of lymphocytic factors and PMNs on the formation of polyps and eosinophilic inflammation were also investigated. Cho et al. emphasized that, as well as the presence of eosinophils in 80% of the cases with NPs in the tissues, the inflammation of T helper-2 cells is present in Western countries. Although now increasing in distant Asian countries, the rate is approximately between 35-45% (42). The Japanese population showed a significant association between CD4 and IL-17A (Th17) cells in terms of eosinophil count and mucosal remodeling. In previous studies, a moderate number of PMNs was shown to be present in eosinophilic CRSwNPs (39). In our study, a significant association was found between

neutrophil inflammation in NPs, blood neutrophil values, and eosinophilic infiltration criteria. In their study, Enache et al. demonstrated a higher proportion of lymphocytes in NP tissues compared to normal tissues. They reported that most of the lymphocytes in NPs were CD8 positive (44). In our study, however, a significant association was detected between the levels of blood lymphocytes and eosinophilic infiltration criteria.

P53 and Ki-67 studies in NPs and IPs were compared with more malignant conditions. Based on the literature, the number of studies investigating NPs and the effects of smoking on NPs is limited. An increase is also observed in the cells in the positive S-phase via Ki-67 staining in NPs (14). In the study that evaluated the diagnosis of NPs or IPs, a significant association was found in both with Ki-67 staining (45). In the study by Karagianni et al., the amount of Ki-67 staining showed an increase in the epithelium of patients with NPs, compared to the controls (46). However, in the study, no difference was found in terms of Ki-67 index values between recurrence of NPs (24,23). Haznedar et al. reported that Ki-67 also has an immunostimulant effect in their study (47). Barouh et al. didn't find any significant difference in proliferative cell nuclear antigen (PCNA) expression between nasal polyps and chronic rhinosinusitis [18]. In our study, the activity of Ki-67 was 76.36% in polyps. While there was a significant relationship between Ki-67 expression and squamous metaplasia, there was no significance between epithelial hyperplasia.

Encoding c-Jun, p63, vascular endothelial growth factor (VEGF), and IL-19, a large number of promoting genes associated with aberrant remodeling patterns have been found in NPs (48). In a study, the levels of IL-17, TNF-alpha, and rafftin, which are remodeling factors, were increased, especially in patients with nasal polyps who were smokers (48). Katori et al. demonstrated the expression of p53 in 11 (38%) of 29 patients with NP [49]. In two studies, p53 and Ki-67 were found to be more expressed in squamous cell carcinomas than in IPs (50). In a study where Sham et al. investigated NPs, the focal immunoreactivity of p53 was found as 19% in IPs and 40% in NPs (51). Contrary to the findings in other studies, the study evaluated 35 patients with NPs and IPs and detected that no significant association was present (44). When evaluating all these data, it should be taken into consideration that only smoking increases p53, p21, and Ki-67 values (52). In the study, staining rates of p53 in imprint smears of patients with NPs were determined as 50% for polyps, 60% for simple hyperplasia, 80% for significant hyperplasia, and 0% for metaplasia (53). However, while p53 expression was observed at a rate of 50.01% in NPs, a significant relationship between p53 expression and squamous metaplasia, and an insignificant relationship between epithelial hyperplasia were found in our study. The retrospective nature of this study means that the clinical outcome of patients, such as relapsed cases or response to drug treatment, was not investigated, which is one of the limitations of the present study.

CONCLUSIONS

In conclusion, the outcomes of the present study related to smoking status and evaluations through the Lund-Mackay classification revealed that there was an association between the inflammation types of polyps and data on eosinophilic inflammation in NPs. This is different from the findings of previous studies investigating Ki-67 and p53 at a higher rate in IPs and nasal squamous cell carcinomas, but at a limited rate in NPs; a significant relationship was shown between the scoring values of Ki-67 and p53, and squamous metaplasia, one of the proliferative processes. It was also concluded that the eosinophilic inflammation data in the polyps in the Turkish population were between those in the Asian and European populations. In the pathological reporting of NPs, with the advent of such methods as the "Sydney Gastritis Scoring" in gastritis, extensive data can be

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