

Distribution of inflammatory cells, adhesion molecules, intermediate filaments, and chemokine receptors in subgroups of nasal polyp patients

Metin Onerci, M.D.,¹ Cagdas Elsurur, M.D.,¹ Elif E. Guzel, M.D.,² and Attila Dagdeviren, M.D.²

ABSTRACT

Background: The pathogenesis of nasal polyps (NPs) is incompletely understood. The aim of this study was to investigate the distribution of inflammatory cells, adhesion molecules, intermediate filaments, and chemokine receptors in subgroups of NP patients.

Methods: In total, 35 patients were enrolled (group 1, 10 patients with Samter syndrome; group 2, 10 patients with diffuse polyposis without signs of Samter syndrome; group 3: 5 patients with solitary nasal polyps; group 4, 10 controls). Immunohistochemical staining was performed for CD105, CD106, CD62E, CD4, CD8, CXCR4, CD147, CD90, CD104, BF45, vimentin, pancytokeratin, and muscle-specific actin (MSA) in all patients' specimens.

Results: Expression of CD4, CD8, and CD106 were similar between the groups. Number of patients expressing CD4 in groups 1, 2, and 3 were higher than the controls. Number of patients expressing CD8 antigen were significantly higher in all three groups than in the control group. Expression of CD147 in groups 3 and 4 was significantly higher than in groups 1 and 2. CD98 expression was higher in groups 1, 2, and 3 than in group 4. The number of patients expressing vimentin in groups 1, 2, and 3 was significantly higher than in group 4. Immunostaining for pancytokeratin was positive in all patients.

Conclusion: In conclusion, inflammatory cell, adhesion molecule, intermediate filament, and chemokine receptor profiles in nasal polyps differ among different patient groups and control subjects. Additional specific immunohistochemical studies are necessary for development of more specific immunotherapies.

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Nasal polyps (NPs) are edematous masses of nasal mucosa characterized by squamous metaplasia, secretory hyperplasia, inflammatory cell infiltration, extracellular matrix accumulation, and fibrosis.¹ Incidence of NPs is 2.7%.² Several factors may have a role in NP pathogenesis, including chronic infections (*i.e.*, stimulation of human nasal epithelial cells by staphylococcal enterotoxin B), allergy, bronchial asthma, aspirin intolerance, genetic factors, mucosal contact, Bernoulli phenomenon, and nasal mastocytosis.^{1,3–11} Although individual etiologies may differ, NPs result from chronic inflammation of nasal mucosa in response mediators and cytokines.¹² Various cytokines, arachidonic acid metabolites, growth factors, adhesion molecules, and chemokines may also play a role in pathogenesis.^{12–20}

Immunohistochemical analysis relies on strong mutual interaction between antigen and its antibody and identifies antigen–antibody complex *via* an enzyme or a fluorescent dye. Immunohistochemical markers are composed of adhesion molecules, apoptosis markers, T- and B-lymphocyte markers, lectins, carbohydrates, leukocyte molecules, chemokine receptors, dendritic cells, myeloid cells, natural killer cells, thrombocytes, and erythrocytes.²¹ The aim of this study was to investigate the distribution of inflammatory cells, adhesion molecules, intermediate filaments, and chemokine receptors in subgroups of NP patients.

MATERIALS AND METHODS

The research was conducted in accordance with the principles set forth in the Helsinki Declaration and was approved by the institutional ethical committee. Twenty patients operated for NPs, who did not have any systemic disease, ciliary dyskinesia, or cystic fibrosis, and five patients who had surgery for solitary NPs were enrolled. None of the patients were previously treated (including topical and systemic steroids) for NPs. Ten patients who had undergone septo-

plasty + partial inferior concha resection were included as controls. The mucosal specimen was obtained from the inferior concha in controls. All specimens were routinely sent for histopathological examination and none of the specimens had findings of malignancy. None of the patients in the control group had bronchial asthma, aspirin intolerance, or NPs. Patients were assigned to one of four groups: group 1 (*n* = 10), patients with Samter syndrome; group 2 (*n* = 10), patients with diffuse NP without Samter syndrome; group 3 (*n* = 5), patients with solitary NP; or group 4 (*n* = 10), controls.

Postoperative NP specimens were examined by monoclonal antibodies against adhesion molecules, antigens for lymphoid cell groups, and activation antigens. The histology was graded by the same histologist in a blinded fashion with regard to the diagnostic group. Immunohistochemical staining included antibodies against CD105, CD106, CD62E, CD4, CD8, chemokine receptor 4 (CXCR4), CD147, CD90, CD104, BF45, vimentin, pancytokeratin, and muscle-specific actin (MSA). Table 1 shows the relevance of each marker for the specific cell type.

All tissue specimens were immediately frozen (within 1–25 minutes) in liquid nitrogen and stored at –196°C until sectioned. Cryostat sections (Leica Frigocut 2800E; Leica, Wetzlar, Germany) of 7 µm thick were taken on gelatin-coated slides and kept in humidity-free containers (K. no. 1.01925; Merck, Darmstadt, Germany) at room temperature until the staining was performed (ideally within 1–4 days).

Sections were fixed in acetone for 10 minutes and air-dried for at least 30 minutes. Sections were then incubated for 60 minutes with monoclonal antibodies. After washing in 0.01 M of phosphate-buffered saline (PBS), pH 7.4, the slides were covered with a 1:200 dilution of anti-mouse IgG peroxidase (cat. no. A9044; Sigma-Aldrich, St. Louis, MO) in PBS containing 0.2% bovine serum albumin (cat. no. A-7034; Sigma-Aldrich) and 1% normal human serum. After washing in PBS the slides were stained for peroxidase activity with 3,3'-diaminobenzidine-tetrahydrochloride (cat. no. D-5637; Sigma; 0.5 mg/mL of Tris-HCl buffer, pH 7.6, containing 0.01% H₂O₂). Counterstaining with hematoxylin was done. The control staining was performed by omitting the first (primary antibody) step and using an irrelevant monoclonal antibody. For indirect immunofluorescence staining the same steps were applied up to the secondary antibody step. Sections were then incubated with fluorescein isothiocyanate-labeled anti-mouse IgG (code no. F-0479; DAKO, Glostrup, Denmark)

From the Departments of ¹Otorhinolaryngology Head and Neck Surgery, and ²Histology and Embryology, Hacettepe University Faculty of Medicine, Ankara, Turkey. The authors have no conflicts to declare pertaining to this article. Approved by the Institutional Review Board, Hacettepe University. Address correspondence and reprint requests to Cagdas Elsurur, M.D., Kultur Mah. Caldiran Sok. Dogan Apt. 34/18, Kolej 06420, Ankara, Turkey. E-mail address: cagdaselsurur@yahoo.com. Copyright © 2011, OceanSide Publications, Inc., U.S.A.

Table 1 The relevance of each marker for the specific cell type

Antigens for	Expression
Inflammatory cells	
CD4	Helper T-lymphocytes
CD8	Cytotoxic T-lymphocytes
CD90	Activated, proliferated and differentiated cells (e.g., leukocytes)
CD98	Fibroblasts
CD62E	Vascular endothelium
CD104	Epithelial cells, Schwann cells, tumoral and endothelial cells, and basal membrane
CD105	Endothelium, activated monocytes, and tissue macrophages
CD106	Vascular endothelium, dendritic cells, and macrophages
BF45	Myofibroblasts and smooth muscle cells
MSA	Myofibroblasts and smooth muscle cells
Intermediate filaments	
Vimentin	Stromal elements
Pancytokeratin	Epithelial elements
Adhesion molecules	
CD147	Endothelial cells
Chemokines	
CXCR4	Vascular endothelium, epithelial cells, B-lymphocyte maturation, differentiation, and angiogenesis

MSA = muscle-specific actin.

for 30 minutes, washed in PBS 3×10 minutes and covered by 1 drop of propidium iodide/antifade (cat. no. S1370-6; Oncor, Gaithersburg, MD) solution. Both peroxidase and fluorescein isothiocyanate-labeled sections were then examined and photographed by using Leica DMR-reflection contrast microscope-RCM (Leica) with a DC200 digital camera (Leica).

The degree of expression of each specific antigen was scored as follows: 0, negative; 1+, weak; 2+, moderate; and 3+, strong. The number of patients with and without expression of the specific antigen was determined.

Statistical Analysis

Statistical analysis was performed using SPSS 10.0 for Windows (SPSS, Inc., Evanston, IL). Data were shown as mean $\pm$ SD and as a percentage (%). Comparisons between groups were assessed by means of Kruskal-Wallis test for continuous variables. For the analysis of categorical variables, *viz.*, the number of patients expressing and not expressing the specific antigen, χ^2 - and Fisher's exact tests were used. Results were considered statistically significant if two-tailed *p* was <0.05 .

RESULTS

Among 35 patients, 21 (60%) were men 14 (40%) were women. Mean age was 43.0 ± 15.3 years. Demographic characteristics and results of immunohistochemical analysis are shown in Tables 2 and 3, respectively. Anti-CD105 antibody expression was present in vascular endothelium, including high endothelial venules (HEVs) and some macrophages. HEVs were observed to be more abundant in NP specimens in group 1 (Fig. 1) than in group 2 (data not shown), whereas distribution of macrophage infiltration was similar. Number of patients expressing CD105 antigen was different between the four groups ($p = 0.001$). Number of patients expressing CD105 antigen was significantly higher in group 1 than in groups 3 and 4 ($p = 0.022$

and $p < 0.0001$, respectively). Number of patients expressing CD105 antigen was higher in group 2 than in group 4 ($p = 0.007$).

CD62E reactivity was shown in two patients in group 1, four patients in group 2, and three patients in group 3. None of the patients in group 4 had CD62E reactivity. Number of patients showing CD62E reactivity did not differ between the four groups ($p > 0.05$).

CD106 expression was shown in 10 patients in group 1 (100%), 4 patients in group 2 (40%), and 5 patients in group 3 (100%). However, none of the patients within group 4 showed CD106 reactivity. CD106 expression was different between groups ($p < 0.0001$); number of patients expressing CD106 was higher in group 1 (Fig. 2) than in groups 2 and 4 ($p = 0.005$ and $p < 0.0001$, respectively). Number of patients expressing CD106 was higher in group 2 when compared with group 4 ($p = 0.043$) and in group 3 when compared with groups 2 and 4 ($p = 0.042$ and $p < 0.0001$, respectively). None of the specimens showed any evidence of germinal center formation. In group 1, lymphoid elements were observed to be abundant (3+), which was 1+ in other groups (1+), and were seen as diffuse lymphoid aggregates with a patchy distribution. Each patient disclosed CD106 reactivity in endothelium of some vessels. In group 2, CD106 reactivity was shown in a few vascular endothelia. In group 2, a venule displayed endothelial CD106 reactivity and surrounding infiltrate. In group 3, lymphoid elements showed a more diffuse distribution pattern, and all patients showed endothelial CD106 reactivity. CD106 reactivity in lymphoid cells and in endothelium was 3+ in group 3 and 1+ in groups 1 and 2.

T-helper lymphocytes and macrophages in stroma disclosed CD4 reactivity. Number of patients showing CD4 expression did not differ between groups 1, 2, and 3, which was higher than controls ($p = 0.003$, $p = 0.003$, and $p = 0.002$, respectively). In group 1, CD4-expressing cells were shown in connective tissue. In group 2, CD4-reacting T-lymphocytes and macrophages organized forming a small number of foci in connective tissue (Fig. 3). Although the percentage of patients with CD4 expression (%100) was higher in group 3, this was not statistically significant. In group 4, CD4-expressing cells were dispersed among connective tissue (Fig. 4).

CD8 expression, a marker of cytotoxic T cells, differed among groups ($p = 0.013$); number of patients with CD8 expression was higher in groups 1, 2, and 3 than in group 4 ($p = 0.003$, $p = 0.007$, and $p = 0.003$, respectively). Except for group 4, cytotoxic T-lymphocytes expressing CD8 were demonstrated in epithelium.

Number of patients showing CD184 (CXCR4) reactivity was similar among groups ($p > 0.05$). In groups 1 and 2, CXCR4 staining was disclosed in glandular epithelium, *viz.*, in apical luminal cell membranes, and in surface of exfoliated cells. Among five patients in group 3, four displayed CXCR4 reactivity. In one patient, reactivity was observed in some connective tissue cells and in vascular endothelium and surface epithelium in others.

CD147 expression differed among the four groups ($p = 0.001$). Number of CD147 expressing patients in groups 3 and 4 was significantly higher than in groups 1 and 2 (for groups 1-3, $p = 0.042$ for groups 3-4, $p = 0.019$; for groups 1-4, $p = 0.005$; and for groups 2-4, $p = 0.002$). CD147 antigen expression was marked in NP surface epithelium and in glandular epithelium.

CD98 antigen was expressed in connective tissue cells and expression significantly differed between groups ($p = 0.003$). In groups 1, 2, and 3, number of patients with CD98 expression was significantly lower than in group 4 (for groups 1-4, $p < 0.0001$; for groups 2-4, $p = 0.005$; and for groups 3-4, $p = 0.022$).

Some connective tissue fibroblasts and mononuclear cells expressed CD90. Expression was prominent in fibroblasts and was also seen in macrophages and lymphocytes, vascular endothelium, vascular smooth muscle, and pericytes in groups 1 and 2. Lymphocytes migrating through the vascular wall into tissues were reactive for CD90. CD90 expression was different among groups ($p < 0.0001$). Patients with CD90 expression in group 1 was significantly higher than in groups 3 and 4 ($p = 0.004$ and $p = 0.002$, respectively), and

Table 2 The comparative analysis of demographic parameters of 35 patients within four groups

Parameter	Group 1 (n = 10)	Group 2 (n = 10)	Group 3 (n = 5)	Group 4 (n = 10)	p	Test
Age (yr)	50.6 ± 13.8	47.4 ± 14.9	36.0 ± 11.8	34.6 ± 14.8	0.073	Kruskal-Wallis
Gender (female/male)	4/6	5/5	2/3	3/7	0.841	χ^2

Table 3 The results of the immunohistochemical analysis of 35 patients enrolled in the study

Antigen*	Group 1 (n = 10)	Group 2 (n = 10)	Group 3 (n = 5)	Group 4 (n = 10)
CD4	8	8	5	1
CD8	7	7	5	2
CD90	10	10	1	3
CD98	2	4	2	10
CD62E	2	4	3	0
CD104	0	3	4	5
CD105	10	8	2	2
CD106	10	4	5	0
BF45	10	10	5	10
MSA	10	10	5	10
Vimentin	7	7	4	0
Pancytokeratin	10	10	5	10
CD147	4	3	5	10
CXCR4	3	3	4	0

*Results indicate the number of specimens stained for the specific antigen. MSA = muscle-specific actin.

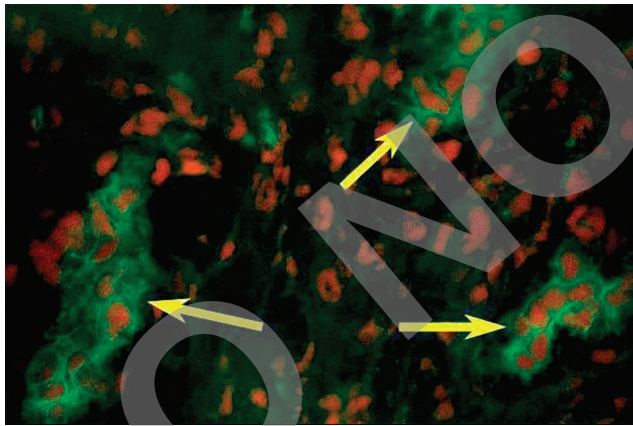


Figure 1. CD105 reactivity in high endothelial venules in a specimen of a patient in group 1. The vessels show typical high endothelial venule characteristics through which lymphocytes migrate (arrow; fluorescein isothiocyanate-labeled indirect immunofluorescence, propidium iodide nuclear staining; magnification, $\times 40$).

expression was higher in group 2 than in groups 3 and 4 ($p = 0.004$ and $p = 0.002$, respectively). Immune reactivity in group 1 was prominent in connective tissue adjacent to epithelium, and inner connective tissue was edematous and loosely organized.

Anti-CD104 staining was positive in basement membrane in three patients in group 2, in four patients in group 3, and in five patients in group 4. Number of patients with CD104 expression was significantly higher in groups 3 and 4 than in group 1 ($p = 0.004$ and $p = 0.016$, respectively).

Vimentin expression was significantly different among groups ($p = 0.002$). Number of patients with vimentin expression in groups 1, 2, and 3 was significantly higher than in group 4 (for groups 1–4, $p = 0.002$; for groups 2–4, $p = 0.002$; and for groups 3–4, $p = 0.004$). Fibroblasts, vascular endothelium, and pericytes showed vimentin expression.

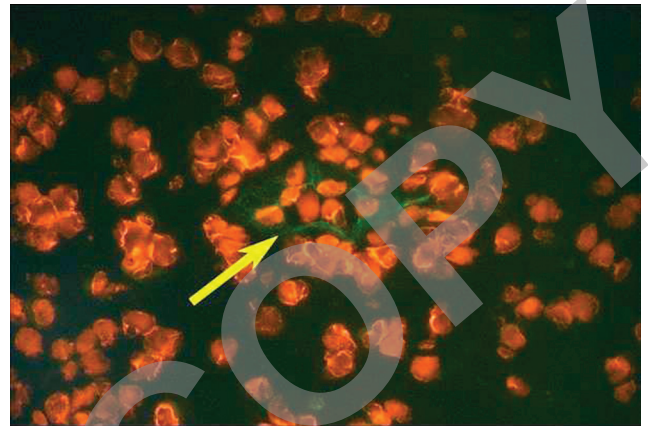


Figure 2. CD106 reactivity in the vascular endothelium of a polyp specimen of a patient in group 1 (arrow; fluorescein isothiocyanate-labeled indirect immunofluorescence, propidium iodide nuclear staining; magnification, $\times 40$).

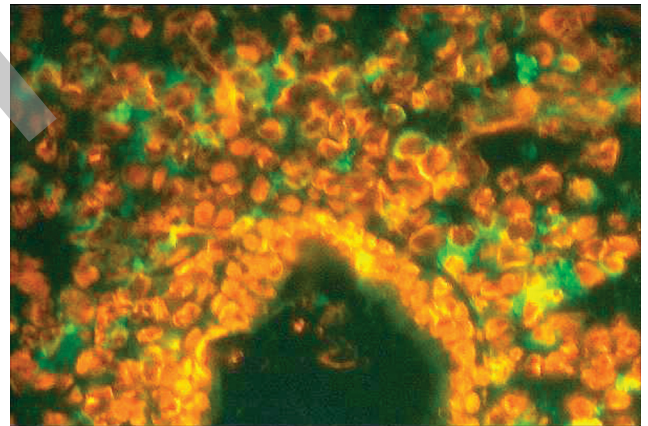


Figure 3. CD4 expressing lymphocytes and macrophages in a polyp specimen of a patient in group 2 (fluorescein isothiocyanate-labeled indirect immunofluorescence, propidium iodide nuclear staining; magnification, $\times 40$).

Pancytokeratin reactivity in groups 1, 2, and 3 were observed in surface epithelium, in indentation of surface epithelium into connective tissue, and in glandular epithelium. Pancytokeratin reactivity in indentation of surface epithelium and in glandular epithelium was 3+ in group 2, which was 1+ in other groups. In group 3, although pancytokeratin reactivity was observed in surface epithelium, indentation of surface epithelium and glandular epithelium lacked reactivity. In controls, reactivity was observed in surface and glandular epithelium.

BF45 antigen expression was 3+ in epithelial basement membrane, in pericytes surrounding vascular endothelium, fibroblasts in connective tissue, and in myofibroblasts in all groups. Number of patients with expression of BF45 did not differ between groups ($p > 0.05$).

MSA was expressed in vascular smooth muscle, vascular endothelium, and myofibroblasts-like cells in groups 1, 2, and 3. MSA was expressed in all specimens of the four groups in our study.

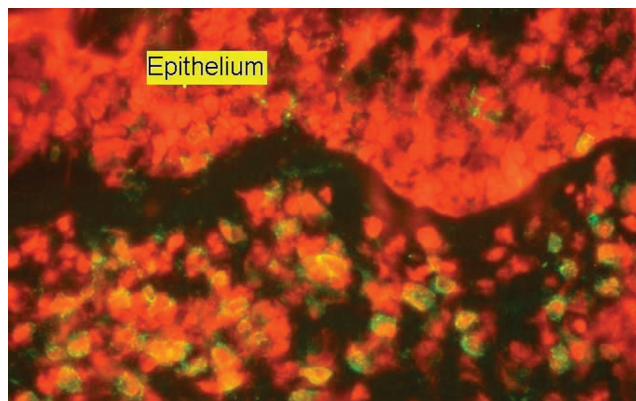


Figure 4. CD4 expressing cells in the epithelium and subepithelial connective tissue in an inferior concha specimen of a patient in group 4 (fluorescein isothiocyanate-labeled indirect immunofluorescence, propidium iodide nuclear staining; magnification, $\times 40$).

DISCUSSION

Inflammation in upper respiratory tract mucosa has a role in NP pathogenesis.^{22–24} Germinal centers, where active humoral response is localized, are abundant in nasopharynx, bronchus, and tonsils, especially in chronic inflammation. CD106 is expressed in response to inflammation and cytokines, mainly in vascular endothelium, in dendritic cells, and macrophages, and plays a role in adhesion and migration of leukocytes and proliferation of T-lymphocytes.²¹ We did not observe germinal center formation in any specimens, suggesting absence of local effector cell production in NPs. However, lymphoid component, as determined by CD106 expression, was abundant in group 1 (3+). CD106 was expressed in more patients in group 1 than in group 2, suggesting a more active inflammation in vascular endothelium. Inflammation may also have a pathogenetic role through mechanisms of extravasation and angiogenesis.²⁵ Patadia *et al.* showed elevated levels of selected B-cell chemokines (*viz.*, B-cell attracting chemokine 1 and stromal cell-derived factor 1 α) in polyp tissues in patients with chronic rhinosinusitis.²⁶ Our results suggest that in NPs in Samter syndrome (in contrast to NPs without Samter syndrome), inflammatory stimulus and cytokines may predominate.

Anti-CD4 is a marker of helper T-lymphocytes.²¹ Classic T-helper 2 eosinophilic reaction is seen in most forms of chronic rhinosinusitis with NPs. Alternatively, chronic rhinosinusitis without NPs displays more of a T-helper 1 or mixed T-helper 1/T-helper 2 adaptive responses. Schlosser *et al.* showed an up-regulation of the complement pathway, particularly the alternate pathway and the common pathway in patients with chronic rhinosinusitis and NPs.²⁷ Sinonasal epithelial cells can promote T-helper inflammation with various mediators. In another study by Reh *et al.*, epithelial cells in treatment-recalcitrant chronic rhinosinusitis with NPs had increased baseline expression of IL-33.²⁸ In our patient population of NPs, none had chronic rhinosinusitis, we also showed T-helper cells and macrophages in stroma of NPs; number of patients with CD4 (+) expression was not different between groups. A minority of mononuclear cells was CD4 (+) in controls (1+). Our results show that polypoid tissues in groups 1, 2, and 3 were immunologic active. Distribution of cytotoxic T-lymphocytes was determined by anti-CD8 antibodies. Majority of specimens, except for controls, showed significant CD8 reactivity (3+), which predominated in connective tissue in group 3 (data not shown), suggesting a more effective cellular immune response. Our results indicate that besides cellular immunity, humoral immunity also plays a role in NP pathogenesis and humoral immune response seems to take place without germinal center formation.

CD98 is expressed in activated, proliferating, and differentiated cells and its expression is up-regulated in leukocytes during inflam-

mation. CD90 is also expressed in fibroblasts, which may be involved in NP pathogenesis, especially the hyperplastic type.^{15,21} We found that the number of patients with CD98 staining was significantly higher in controls than other groups. All specimens of patients in groups 1 and 2 were stained for CD90, which was higher than in groups 3 and 4. Although CD90 staining observed in groups 1 and 2 indicated some degree of fibroblast activation, CD98 staining, being highest in controls, was not in accordance with the literature. Therefore, we did not observe fibroblast activation and a relationship between NP subgroups and fibroblast activation.

CD105 is expressed in endothelium of small and large vessels, activated monocytes, and tissue macrophages.²¹ We showed that a higher number of patients expressed CD105 in group 1 than in groups 3 and 4. We observed CD105 expression in vascular endothelium, including HEV and macrophages. HEV, which mediate lymphocyte migration from circulation to lymphoid tissues, were relatively more abundant in group 1 than in group 2 (data not shown). We think that in NPs in Samter syndrome, lymphocyte migration is enhanced as a result of inflammation.

Myofibroblasts are involved in extracellular matrix production.^{29–31} We showed a strong (3+) BF45 reactivity in epithelial basal membrane, vascular endothelium, pericytes around vessels, resident fibroblasts in connective tissue, and myofibroblasts (data not shown). BF45 was reactive in all NP specimens in all groups. MSA staining was seen in vascular smooth muscle and vascular endothelium, which identified patchy dense infiltrates of myofibroblast-like cells. In group 1, MSA was strongly (3+) reactive in capillaries, venules, and pericytes surrounding HEV (data not shown). We observed an increased number of myofibroblast-like cells in NP stroma. Our results are in parallel with literature reporting increment of myofibroblasts in NPs.³²

Imbalance of matrix metalloproteinases and tissue inhibitors of metalloproteinases lead to extracellular matrix degradation and tissue edema. Erbek *et al.* reported that the immunopositivity score for a disintegrin and metalloproteinase (ADAM)-33, a member of matrix metalloproteinases, was significantly higher in epithelial cells and mesenchymal cells in patients with NPs than those of controls.³³ CD147 is expressed in endothelial cells.³⁴ CD147 reactivity in NPs has not been reported so far. In our study, number of patients with CD147 expression was higher in groups 3 and 4 than in groups 1 and 2. We observed a predominant expression of CD147 in NP surface and glandular epithelial cells. We suggest that this finding may be a marker of both decreased (a possible adhesion molecule) and increased (by stimulating metalloproteinase and collagenase) tissue penetration of cells; however, decreased expression of CD147 in groups 1 and 2 favored the former.

CD62E is expressed abundantly in vascular endothelium in early phases of inflammation and plays a role in tissue migration of circulating leukocytes.³⁵ Ural *et al.* reported that CD147 expression in allergic and nonallergic polyps was no different than controls.³⁶ In our study, CD147 expression was not significantly different between groups.

CD104 is a transmembrane glycoprotein expressed in epithelial cells, Schwann cells, keratinocytes, tumoral and endothelial cells, and basal membrane. CD104 is involved in cellular migration.^{21,37} In our study, the number of patients with CD104 expression was significantly higher in groups 3 and 4 than in group 1.

Pancytokeratin and vimentin antigens were examined for discrimination of epithelial and stromal elements, respectively. We observed a relative increase in epithelial component in patients without Samter syndrome when compared with patients with Samter syndrome (data not shown). Number of patients with vimentin expression was higher in groups 1 and 2 than in groups 3 and 4. Vimentin was predominantly expressed in fibroblasts, vascular endothelium, and pericytes; however, vessel involvement did not differ between groups. In patients with Samter syndrome, there was less cellular involvement in stroma favoring an increment of extracellular matrix (data not shown). This finding is compatible with diffuse submucosal edema in patients with Samter syndrome.

Chemokines have an important role in placement of immature dendritic cells in airway mucosa as well as in maturation and migration of dendritic cells to lymph nodes.³⁸ CD184 (CXCR4) is a chemokine expressed in hematopoietic cells, vascular endothelium, and epithelial cells, which is involved in lymphocyte (especially B-lymphocytes) maturation, differentiation, and angiogenesis.³⁹ In our study, in groups 1 and 2, CD184 reactivity was seen in glandular epithelium, especially in apical membrane and on the surface of exfoliated cells (data not shown). We observed 3+ reactivity in patients with Samter syndrome, which was 1+ in those without Samter syndrome. In one patient in group 1, a very strong CD184 reactivity was shown in apical membrane of glandular epithelium and in exfoliated cells. In group 3, reactivity was seen in some cells of connective tissue in one patient and in vascular endothelium and surface epithelial cells in others. In another study in 10 chronic rhinosinusitis patients, CCL20 ligand of chemokines family, involved in antigen presentation and host immune response development in human paranasal sinus epithelial cells, was up-regulated. As CCL20, CD184 expression may be involved in chemokine microenvironment regulation of paranasal sinus mucosal epithelial cells, thereby influencing immature dendritic cell migration.⁴⁰ We observed a relatively stronger CD184 reactivity in patients with Samter syndrome and we conclude that in patients with Samter syndrome, inflammation was more severe.

In conclusion, our study disclosed the distribution of inflammatory cells, adhesion molecules, intermediate filaments, and chemokine receptors in subgroups of NP patients. Additional specific immunohistochemical studies are necessary for development of more specific immunotherapies.

REFERENCES

- Önerci M. Burun Poliplerinin Patogenezi. In Nazal Polipozis, Önerci, M. (Ed). Ankara, Turkey: Hacettepe Üniversitesi Hastaneleri Basımevi, 7-14, 2006.
- Johansson L, Akerlund A, Holmberg K, et al. Prevalence of nasal polyps in adults: The Skovde population-based study. *Ann Otol Rhinol Laryngol* 112:625-629, 2003.
- Yu RL, and Dong Z. Proinflammatory impact of *Staphylococcus aureus* enterotoxin B on human nasal epithelial cells and inhibition by dexamethasone. *Am J Rhinol Allergy* 23:15-20, 2009.
- Bernstein JM, and Kansal R. Superantigene hypotesis for the early development of chronic hyperplastic sinusitis with massive nasal poliposis. *Otol Head Neck Surg* 13:39-43, 2005.
- Geavert P, and Holtappels G. Organisation of secondary lymphoid tissue and local IgE formation to *staf. aureus* enterotoxins in nasal polyp tissue. *Allergy* 60:71-79, 2005.
- Pitzurra L, Bellocchio S, and Neocenti A. Antifungal immune reactivity in nasal polyposis. *Infect Immunol* 72:7275-7781, 2004.
- Eskiizmir G, and Ünlü HH. Nazal polipoziste medikal tedavinin rolü. İleri, F. (Ed.). TKBV Akademi Toplantıları Mezuniyet Sonrası Eğitim Kitapçıkları Serisi, Nazal Polipler; Ankara, Turkey: Deomed Yayıncılık, 121-131, 2007.
- Settipane GA. Nasal polyps: Epidemiology, pathology, immunology and treatment. *Am J Rhinol* 1:119-126, 1987.
- Drake-Lee A. The pathogenesis of nasal polyps. In Nasal Polyps: Epidemiology, Pathogenesis, and Treatment. Settipane GA, Lund VJ, Bernstein JM, and Tos M (Eds). Rhode Island: OceanSide Publication, 57-64, 1997.
- Maloney J, and Oliver R. HLA antigens, nasal polyps and asthma. *Clin Otolaryngol* 5:183-189, 1980.
- Kenedy DW, Bolger WE, and Zinrach SS (Eds). Özkarakaş H, Yıldırım N (çeviri ed). Sinüs hastalıkları. İstanbul: Nobel Tıp kitabevleri, 57-60, 2003.
- Sin AB. Nazal Polip Etiyopatogenezi. In Nazal Polipozis, Önerci, M. (Ed). Ankara, Turkey: Hacettepe Üniversitesi Hastaneleri Basımevi, 74-95, 2006.
- Mullol J, Xaubet A, and Gaya A. Cytokine gene expression and release from epithelial cells: A comparison study between healthy nasal mucosa and nasal polyps. *Clin Exp Allergy* 25:607-615, 1995.
- Wittekindt C, Hess A, and Bloch W. Immunohistochemical expression of VEGF and VEGF receptors in nasal polyps as compared to normal turbinate mucosa. *Eur Arch Otorhinolaryngol* 259:294-298, 2002.
- Nonaka M, Nonaka R, and Wolley K. Distinct immunohistochemical localization of IL-4 in human inflamed airway tissues: IL-4 is localized to eosinophils in vivo and is released by peripheral blood eosinophils. *J Immunol* 155:3234-3244, 1995.
- Norlander T, Westermarck A, and van Setten G. Basic fibroblast growth factor in nasal polyps immunohistochemical and quantitative findings. *Rhinology* 39:88-92, 2001.
- Alam R, Forsythe P, Stafford S, et al. Transforming growth factor beta abrogates the effects of hematopoietins on eosinophils and induces their apoptosis. *J Exp Med* 179:1041-1045, 1994.
- Jahnsen FL, Haraldsen G, Haye R, et al. Adhesion molecules and recruitment of eosinophils. In Nasal Polyposis. An Inflammatory Disease and Its Treatment. Mygind N, and Lildholdt T (Eds). Copenhagen: Munksgaard, 88-97, 1997.
- Bartels J, Maune S, and Meyer JE. Increased eotaxin-mRNA expression in nonatopic and atopic nasal polyps: Comparison to RANTES and MCP-3 expression. *Rhinology* 35:171-174, 1997.
- Shin SH, Park JY, and Jeon CH. Quantitative analysis of eotaxin and RANTES messenger RNA in nasal polyps: Association of tissue and nasal eosinophils. *Laryngoscope* 110:1353, 2000.
- Shaw S. CD guide. In Leukocyte Typing VI. Kishimoto T, Kikutani H, and von dem Borne AEG (Eds). New York: Garland Publishing, Inc., 1109-1220, 1998.
- Slavin RG. Sinusitis in adults and its relation to allergic rhinitis, asthma and nasal polyps. *J Allergy Clin Immunol* 82:950-956, 1988.
- Winther B, and Innes DJ. Lymphocyte subsets in normal airway mucosa of human nose. *Arch Otolaryngol Head Neck Surgery* 113:59-62, 1987.
- Hameleers DMH, and Stoop AE. Intra epithelial lymphocytes and non lymphoid cells in human nasal mucosa. *Int Arch Allergy Appl Immunol* 88:317-322, 1989.
- Hu KH, Lee FP, Cheng JC, et al. Vascular endothelial growth factor and children featuring nasal polyps. *Int J Pediatr Otorhinolaryngol* 71:23-28, 2007.
- Patadia M, Dixon J, Conley D, et al. Evaluation of the presence of B-cell attractant chemokines in chronic rhinosinusitis. *Am J Rhinol Allergy* 24:11-16, 2010.
- Schlosser RJ, Mulligan RM, Casey SE, et al. Alterations in gene expression of complement components in chronic rhinosinusitis. *Am J Rhinol Allergy* 24:21-25, 2010.
- Reh DD, Wang Y, Ramanathan M Jr, et al. Treatment-recalcitrant chronic rhinosinusitis with polyps is associated with altered epithelial cell expression of interleukin-33. *Am J Rhinol Allergy* 24:105-109, 2010.
- Sappino A, and Següch W. Differentiation repertoire of fibroblastic cells: Expressions of cytoskeletal proteins as a marker of phenotypic modulations. *Lab Invest* 63:144-161, 1990.
- Kuhn C, and Mc Donald J. The roles of myofibroblast in idiopathic pulmonary fibrosis. *Am J Pathol* 138:1257-1265, 1991.
- Vyalov S. Rat alveolar myofibroblast acquire alpha smooth muscle actin expression during bleomycin induced pulmonary fibrosis. *Am J Pathol* 143:1754-1765, 1993.
- Wang QP, and Escuder E. Myofibroblast accumulation induced by transforming growth factor beta is involved in the pathogenesis of nasal polyps. *Laryngoscope* 107:926-931, 1997.
- Erbek SS, Erinanc H, Erbek S, et al. Expression of a disintegrin and metalloproteinase 33 protein in nasal polyposis: An immunohistochemical study. *Am J Rhinol Allergy* 24:79-82, 2010.
- Jian-Li J, and Juan T. CD147 and its interacting proteins in cellular functions. *Acta Physiol Sinica* 59:517-523, 2007.
- Naclerio RM. Pathophysiology of perennial allergic rhinitis. *Allergy* 52(suppl 36):7-13, 1997.
- Ural A, Tezer MS, and Yücel A. IL-4, IL-8 and E-selectin levels in intranasal polyposis patients with and without allergy: A comparative study. *J Int Med Res* 34:520-524, 2006.
- Turni L, Shaw S, Watson B, and Mason D. CD guide. In Leukocyte Typing VII. Mason D, Andre P, and Bunussan A (Eds). New York: Oxford University Press, Inc., 1-945, 2002.
- Stick SM, and Holt PG. The airway epithelium as immune modulator: The LARC ascending. *Am J Respir Cell Mol Biol* 28:641-644, 2003.
- Oelschlaegel U, Bornhauser M, and Boxberger S. Kinetics of CXCR-4 and adhesion molecule expression during autologous stem cell mobilization with G-CSF plus AMD3100 in patients with multiple myeloma. *Ann Hematol* 86:569-573, 2007.
- Lee JH, Kang HJ, and Woo JS. Up-regulation of chemokine ligand 20 in chronic rhinosinusitis. *Arch Otolaryngol Head Neck Surg* 132:537-541, 2006. □

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