

ORIGINAL RESEARCH–SINONASAL DISORDERS

The comparison of histopathological characteristics of polyps in asthmatic and nonasthmatic patients

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ABSTRACT

INTRODUCTION: Considering the different clinical aspects of polyps in asthmatic and nonasthmatic patients, we aimed to explore their histopathological characteristics.

MATERIAL AND METHODS: Twenty-five asthmatic patients and 25 nonasthmatic patients with polypoid chronic rhinosinusitis (29 male, 21 female; mean age 41.3 ± 13.27 ; range 15–78 years) were enrolled in the study to be compared on the basis of histopathological characteristics. They were compared according to the following seven light microscopic findings: basement membrane thickness, goblet cell hyperplasia, subepithelial edema, submucous gland formation, eosinophilic infiltration, lymphocytic infiltration, and polymorphonuclear infiltration.

RESULTS: Basement membrane thickening, goblet cell hyperplasia, and eosinophilic and lymphocytic infiltration were more prominent in the asthmatic compared with the nonasthmatic group ($P < 0.05$), whereas polymorphonuclear infiltration was more prominent in nonasthmatics ($P < 0.05$). No statistically significant differences were found between the two groups with regard to submucosal gland hyperplasia or subepithelial edema.

CONCLUSION: Asthmatic patients present histopathological characteristics of a marked chronic inflammatory reaction, which might explain the negative effect on chronic rhinosinusitis outcome and the severity of the disease in this group.

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Polypoid chronic rhinosinusitis (CRS) is a common disorder that accompanies asthma about half of the time.^{1,2} Although the pathogenesis of the polyposis is still unclear, a proliferative process associated with fibrosis, atypical gland formation, goblet cell hyperplasia, subepithelial edema, and mononuclear cell infiltration were supposed.^{3,4} Many studies have shown these histopathological changes in the sinus mucosa to have an important prognostic value for long-term outcome.^{5–8}

Endoscopic sinus surgery (ESS) has been well established as a successful surgical procedure, with failure rates

as low as 5 to 10 percent. However, the cause of failure in responding to surgical treatment is still controversial.^{5,9} A history of asthma and allergy, previous sinus surgery, and nasal polyposis has been identified as poor outcome predictors in large series of ESS-treated patients. Dinis et al¹⁰ and Sobol et al¹¹ have documented a significant negative effect of asthma on the outcome of sinus surgery in polypoid rhinosinusitis. Asthma is a widespread respiratory systemic disease that is supposed to predominantly affect the lung and bronchia. Still few reports are available on the histological characteristics among different types of CRS as a possible contributory factor. We hypothesized that analysis of histopathological findings in the sinus mucosa of two different groups of polypoid CRS (asthmatic and nonasthmatic) might reveal some histological characteristics to enable us to distinguish the two groups. In addition, the analysis might provide some histological clues to explain the variety of outcomes in the two reported groups in previous studies. Therefore we designed our study to approach this goal.

MATERIALS AND METHODS

From April 2006 to January 2008, we registered 50 cases of chronic polypoid sinusitis (29 males, 21 females) at the Department of Otorhinolaryngology, Amir Alam Educational Hospital, affiliated with Tehran University of Medical Sciences. The study protocol was reviewed and approved by the Tehran University of Medical Sciences Research Ethics Review Board.

All patients underwent ESS, and they were all initially examined in the respiratory clinic for the evaluation of asthma. Twenty-five cases with established mild to moderate asthma were selected as the study group (group 1). Asthma was diagnosed by means of clinical symptoms, medical history, physical findings and pulmonary function testing, according to the guidelines laid down by the Global Initiative for Asthma.¹² Methacholine provocation test was

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performed only for those with a history of intermittent dyspnea who were asymptomatic at the time of examination. They had experienced asthma symptoms for at least 2 years and had been treated with appropriate asthmatic medication for at least 12 months.

Twenty-five chronic polypoid sinusitis patients without asthma (14 males, 11 females) were randomly selected as the control group (group 2) for comparison of histopathological characteristics. All patients in both groups were older than 15 years.

Chronic sinusitis was diagnosed both clinically as the presence of a combination of symptoms (ie, purulent rhinorrhea, postnasal discharge, headache, hyposmia, facial fullness, and nasal obstruction) and on the basis of CT findings. Patients who had undergone surgery for fungal sinusitis, allergic fungal sinusitis, mucocele, antrochoanal polyps, acute rhinosinusitis, and underlay disorders (eg, Wegener's granulomatosis, sarcoidosis, and systemic lupus erythematosus) were excluded.

ESS was performed by a rhinologist using the standard technique under general anesthesia. All candidates had received a 10-day course of systemic corticosteroid (according to a tapering schedule) and 4 weeks of topical nasal corticosteroid in addition to irrigation of the nose with normal saline 4 times a day. Sinus mucosa samples were obtained from all the patients during surgery and stained with hematoxylin-eosin. The light microscopic findings of the following seven histopathological characteristics, taken as pathological parameters, were compared between the asthmatic and nonasthmatic groups: thickness of the basement membrane, goblet cell hyperplasia, subepithelial edema, submucous gland formation, eosinophil infiltration, lymphocyte infiltration, and polymorphonuclear leukocyte (PMN) infiltration. The first evaluation was made under low-power magnification ($\times 40$) to determine whether any regions of the epithelium were preferentially affected and, if so, the three most affected regions were selected. Each of the selected regions was then thoroughly reviewed under high-power magnification ($\times 100$ or $\times 400$) and scored as described by Dhong et al¹³ and discussed in the following subsections.

Thickness of the Basement Membrane

At a magnification of $\times 100$, a score was assigned according to the degree of visible basement thickening: 0, none; 1, mild; 2, moderate; or 3, marked.

Goblet Cell Hyperplasia

At a magnification of $\times 400$, a score was assigned according to the number of goblet cells visible: 0 (less than three cells); 1 (three to 10 cells); 2 (11-20 cells); or 3 (>20 cells).

Subepithelial Edema

At a magnification of $\times 100$, a score was assigned according to the degree of subepithelial edema: 0 (none); 1 (mild); 2 (moderate); or 3 (marked).

Submucous Gland Formation

At a magnification of $\times 100$, a score was assigned according to the number of submucous glands visible in a section: 0 (less than three glands); 1 (three to 10 glands); 2 (11-30 glands); or 3 (>30 glands).

Eosinophil Infiltration

At a magnification of $\times 400$, the number of eosinophils present within epithelial cells and in the submucosa was scored as follows: 0 (none); 1 (one or two eosinophils); 2 (three to 10 eosinophils); 3 (11-30 eosinophils); or 4 (>30 eosinophils).

Lymphocyte Infiltration

At a magnification of $\times 400$, the number of lymphocytes present in the submucosa was scored as follows: 0 (<20 lymphocytes); 1 (21-50 lymphocytes); 2 (51-80 lymphocytes); 3 (81-120 lymphocytes); 4 (>120 lymphocytes).

PMN Infiltration

At a magnification of $\times 400$, the number of PMNs present in submucosa was scored as follows: 0 (none); 1 (one or two PMNs); 2 (three to 10 PMNs); or 3 (>10 PMNs).

Statistical Analysis

The Mann Whitney *U* test was used to analyze the differences between the two groups in terms of the degree of preoperative polyposis, the extent of the disease, and the seven histopathological parameters. $P < 0.05$ was considered significant.

RESULTS

The mean age of the asthmatic group was 42.15 years (range 15-67 years), and that of the nonasthmatic group was 40.45 years (range 15-78 years). The mean Lund score was 10.4 and 9.6 among asthmatic and nonasthmatic patients, respectively. There was no significant difference between two groups from the standpoint of age and Lund score ($P > 0.05$).

Duration of the disease in asthmatics was 4.6 ± 0.6 years and 5.8 ± 0.5 years for the other group, which did not show a significant difference ($P = 0.71$). The most common symptom in both groups was nasal obstruction. Other symptoms are summarized in Table 1.

Basal membrane thickness, goblet cell formation, and lymphocyte and eosinophil infiltration were more prominent in the asthmatic group than in the nonasthmatic group ($P < 0.05$), whereas PMN infiltration was significantly prominent among nonasthmatic patients ($P = 0.001$). However, no statistically significant differences were found between the two groups in terms of subepithelial edema and submucous gland hyperplasia ($P > 0.05$) (Table 2).

Table 1
Frequency of symptoms and signs among asthmatic and nonasthmatic group

Symptom	Asthmatic patients No. (%)	Nonasthmatic patients No. (%)
Nasal obstruction	16 (64%)	15 (60%)
Postnasal discharge	10 (40%)	11 (44%)
Headache	9 (36%)	8 (32%)
Mouth breathing	7 (28%)	6 (24%)
Facial pressure	3 (12%)	4 (16%)
Anosmia	3 (12%)	2 (8%)
Hyposmia	5 (20%)	4 (16%)
Nasal sniffing	4 (16%)	4 (16%)
Rhinorrhea	2 (8%)	3 (12%)
Sneezing	5 (20%)	3 (12%)
Snoring	8 (32%)	7 (28%)

DISCUSSION

CRS remains one of the most challenging entities in the practice of otolaryngology. CRS generally manifests an inflammatory component regardless of the cause of the disease. Expression of inflammatory cells and molecules may vary among patients. The most prevalent and studied pathological entity associated with CRS is nasal polypsis. Polyps are more prevalent in the asthmatic population with CRS. Basic science investigations are evolving to improve our knowledge about the cause and mechanism of nasal polyp formation.^{14,15}

Asthma as a widespread respiratory disorder often coexists with rhinosinusitis (as many as 50 percent of patients with CRS have asthma¹⁶). Respiratory epithelium lines not only the lower airway in the trachea and bronchi but also the upper airway and paranasal sinuses. The relationship between upper and lower airway inflammatory diseases has been mentioned in the literature; the sinus and lung passages are lined with similar respiratory epithelium, and subsequently respond to inflammatory mediators in a parallel manner.

It has been shown that asthmatic patients with chronic sinusitis have a more severe disease as determined by imaging or by evaluations performed during surgery,¹⁷ and that the recurrence rate among asthmatics after sinus surgery is higher than that of nonasthmatics.¹⁸ Furthermore, asthma is a critical factor known to negatively affect the outcome of sinus surgery.^{10,11} Although the clinical impact of asthma on sinusitis may be affected by many factors, the histopathological findings of sinus mucosa have not been well documented in the past. Several studies of the histopathological findings in chronic sinusitis have been undertaken, and characteristics of basement membrane thickening, atypical gland formation, goblet cell hyperplasia, subepithelial edema, and inflammatory cell infiltration have been studied.^{19,20} In asthmatic patients, thickened basement membranes, mucous plugs in the airways, varying degrees

of bronchial epithelial damage, and lymphocyte cell infiltration have been shown in lung specimens.²¹ In addition, Bousquet et al²² showed an increased number of eosinophils in the bronchoalveolar lavage fluid and in bronchial biopsies of asthmatics, and they also found thickened basement membranes, goblet cell hyperplasia, and an increased number of lymphocytes among them.

We found that chronic inflammatory reactions such as basement membrane thickening and goblet cell hyperplasia were more prominent in patients with chronic sinusitis and asthma. These histopathological findings are similar to those found in bronchial biopsy specimens,¹⁶ supporting the fact that a severe chronic inflammatory reaction can occur in the sinus as well as the bronchus of the asthmatic patients. Furthermore, in our study we found a significant eosinophilic infiltration in the asthmatic group, which correlates with the results of Harlin et al²³ and Dhong et al.¹³ In our survey, lymphocytic infiltration and PMN infiltration were prominent among asthmatics and nonasthmatic patients, respectively. Dhong et al¹³ reported such findings; however, they were not statically significant.

We did not perform the methacholine challenge test for those who were clinically asymptomatic and had no history of dyspnea. This is our study limitation, but it does not have a great negative effect on our conclusion because some asthmatic patients might have been mistakenly placed in the control group, which ultimately would have decreased our data difference (between the two groups) without changing the ultimate conclusion. Furthermore, we excluded severe asthmatic patients from the study; if included, they possibly could have enhanced our results.

Chronic inflammation including chronic sinusitis shows marked subepithelial edema and submucous gland formation.^{19,20} We also observed such findings in both groups without a significant difference. However, the values of these parameters were higher in the asthmatic group compared with the nonasthmatic group. Histopathological differences that indicate significantly different patterns of inflammation may explain differences in surgical outcome.

Table 2
Comparison of histopathological characteristics of asthmatic and nonasthmatic patients

Histological parameters	P value	Significant group
Basal membrane thickness	0.014	Asthmatic
PMN infiltration	0.001	Nonasthmatic
Subepithelial edema	0.363	Not significant
Eosinophil infiltration	0.026	Asthmatic
Lymphocyte infiltration	0.004	Asthmatic
Submucosal gland formation	0.884	Not significant
Goblet cell formation	0.013	Asthmatic

CONCLUSION

Patients with both polypoid sinusitis and asthma present histopathological characteristics of a marked chronic inflammatory reaction, which may contribute to a poorer postoperative outcome. Our results indicate that significant lymphocytic and eosinophilic infiltration could be a major characteristic of chronic sinusitis with asthma. Therefore, severe inflammation of the sinus mucosa is expected when an otorhinolaryngologist performs sinus surgery in such patients. These histopathological characteristics might be indicators of poor prognosis even among nonasthmatic patients with CRS; complementary study to draw such a conclusion is necessary.

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