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Correlation of histopathology and symptoms in allergic and non-allergic patients with chronic rhinosinusitis

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Introduction

Chronic rhinosinusitis (CRS) is a common and well-recognized clinical syndrome that is likely to have a number of different causes. Its considerable morbidity and often refractory symptoms, are leading to significant reduction of health-related quality of life and increased healthcare resource usage [6,10]. As CRS is a multifaceted disease, interaction of different predisposing factors and comorbid disorders may have impact on symptoms profile and objective findings, including type and severity of inflammation in sinus mucosa [3].

Endoscopic sinus surgery (ESS) is a well-established strategy for the treatment of CRS, which has not responded to medical treatment, regardless of predisposing factors mentioned above.

Cellular infiltration and local cytokine activity in the sinus mucosa collected at surgery may have important prognostic value for long-term outcome [7,11,13].

The purpose of this study is to evaluate and to compare the predictive value of some histopathologic parameters and to asses the efficacy of ESS in a larger group of allergic and non-allergic patients with CRS. Determining predictors may help in choosing better management strategy and help surgeons in estimating prognosis of the treatment.

Subjects and methods

The study is a continued research on predictive value of graded histological features of sinus mucosa obtained at surgery on mid-term (at least 2 years) surgical treatment outcomes [2]. One hundred patients, 50 allergic (persistant allergic rhinitis) and 50 non-allergic (44 male, 56 female, with a mean age of 41 ± 17.8), with CRS were randomly selected from a prospective study group of more than 600 patients who underwent ESS, performed by a single surgeon between February 1998 and February

2004. The study was approved by the Ethics Committee of the Sestre Milosrdnice University Hospital in Zagreb, Croatia**.** All patients fullfilled the following criteria: age between 18 and 70, CRS confirmed by symptoms, endoscopy and computed tomography (CT), (Lund-Mackay score range 8 – 16), bilateral sinus disease (followed by bilateral complete ethmoidectomy). The current AAO-HNS set of guidelines for the diagnosis of CRS was applied.

Patients with systemic evidence of bronchial asthma, nasal polyposis, previous sinus surgery, and systemic steroid or antimicrobial treatment within one month were excluded. Criteria for allergy group were a positive skin prick test for at least one symptom relevant airborne allergen and the total serum IgE higher than 40 IU/ml. All patients underwent medical treatment (several courses of topical steroids and antibiotics) with unsatisfactory results at least one year before surgery. Postoperative medical treatment during the follow-up consists of topical steroids courses and antibiotics according to the guidelines.

Patients completed a questionnaire on rhinosinusitis symptoms before the intervention, and at 12 and 24 months after surgery, grading severity and frequency of congestion, postnasal secretion, nasal secretion, headache, sneezing, cough, facial swelling and olfaction from 0 to 3 both for intensity + frequency, respectively (total subjective symptom score /TSS/ range from 0 to 6) [2].

During ESS, uncinectomy was performed and bilateral uncinate process specimens were fixed in buffered 4% formaldehyde, and paraffin embedded, standard 5 μm sections stained with hematoxylin–eosin and examined. Semiquantitative grading was performed in comparison with normal uncinate process histology (0, 1+, 2+, 3+) scored in a control group of 11 patients without CRS, who underwent intranasal

endoscopic orbital decompression as a treatment of thyroid eye disease refractory to conventional treatment.

The observed parameters of severity of inflammation were: the number of goblet cells, thickening of the basement membrane (subepithelial thickening), and inflammatory cells count. Initially, low-power survey of the slide was performed at x 100 magnification to identify the area with greatest density of eosinophils and mastocytes. Counting of eosinophils was done in 10 non-overlapping consecutive high power magnification fields (x 400 / 0,196 mm^2), and average number of eosinophils was calculated. Infiltrate density of eosinophils was recorded as + for < 10 Eo/HPF, ++ for 10-20 Eo/HPF, and +++ for > 20 Eo/HPF.

Infiltrate density of mastocytes was recorded as 0 for no inflammatory cells, + for scattered inflammatory cells, ++ for diffuse but not confluent infiltrate and +++ for confluent infiltrate [2,5,12,14].

Basement membrane thickness was measured in 5 high power magnification fields (x 400 / 0,196 mm^2) in the same area where cells were counting and mean value was calculated. Basement membrane thickness was recorded as 0 for ≤ 5μm, + for > 5 -10 μm, ++ for > 10-15 μm, and +++ for > 15 μm.

The side with the higher grade of inflammation (that with the worse total score of histopathological changes) from these two uncinate process specimens was used in statistical analysis.

Statistical Analysis - Descriptive statistical methods were used to describe the distributions of variables. The quantitative variables did not follow the normal distribution which has been tested by Kolmogorov-Smirnov test. A correlation was calculated between the scores of histolpathological findings (0-3) and symptom scores (0-6) after 12 and 24 months postoperatively. Spearman rank correlation coefficients

were then calculated. The Pearson Chi-square test was used for testing the differences in categorical variables between two groups of patients. The Mann-Whitney test was used for testing differences in quantitative variables between two groups of patients. All conclusions were based on a significance level of $p<0.05$. Statistical software Statistica 7.1 (StatSoft Inc., Tulsa, USA) has been used.

Results

CORRELATION BETWEEN HISTOPATHOLOGIC PARAMETERS AND SYMPTOMS - *Correlation to Goblet Cells and Symptoms* - A significant positive correlation ($P<0.005$) of goblet cells with itching and negative ($p<0.005$) with congestion, nasal secretion, headache, olfaction, swelling and TSS was found in the allergic group, 12 months postoperatively (Table 1), while 24 months postoperatively a significant positive correlation ($P<0.005$) with congestion, headache and cough, and negative with postnasal secretion, itching and olfaction was found (Table 2). In non-allergic group correlation was positive ($P<0.005$) with itching and sneezing at 12 months postoperatively, and negative ($p<0.005$) with congestion, nasal secretion, headache, cough and swelling (Table 3), and 24 months postoperatively a significant negative correlation was found with congestion, secretion, headache and cough ($p<0.005$) (Table 4).

Correlation to Subepithelial Thickening and Symptoms - A significant positive correlation ($p<0.005$) of subepithelial thickening with congestion, postnasal secretion, headache, olfaction, swelling, and TSS, and a negative correlation ($p<0.005$) with itching was found 12 months postoperatively in the allergic group (Table 1). *Correlation remained* positive ($p<0.005$) with olfaction, swelling and TSS 24 months postoperatively, and it was negative ($p<0.005$) for sneezing and cough (Table 2).

In non-allergic group, 12 months postoperatively we found a significant positive correlation ($p<0.005$) with postnasal secretion, and a negative correlation ($p<0.005$) with congestion, headache and cough (Table 3), while 24 months postoperatively a significant positive correlation ($p<0.005$) with postnasal secretion and negative correlation ($p<0.005$) with congestion and cough was found (Table 4).

Correlation to Mast Cells and Symptoms – In the allergic group, 12 months postoperatively a significant positive correlation ($p<0.005$) with secretion, olfaction and total symptom score (Table 1), and 24 months postoperatively a significant positive correlation ($p<0.005$) with postnasal secretion, itching, sneezing and olfaction was found. A significant negative correlation ($p<0.005$) was found with congestion and cough (Table 2). In non-allergic group, 12 months postoperatively we found a significant positive correlation ($p<0.005$) with postnasal secretion and a negative correlation ($p<0.005$) with secretion and cough (Table 3), and 24 months postoperatively we found a significant positive correlation ($p<0.005$) with postnasal secretion and a negative correlation ($p<0.005$) with secretion (Table 4).

Correlation to Eosinophils and Symptoms - In the allergic group, 12 months postoperatively we found a significant negative correlation ($p<0.005$) with congestion.(Table 1), and 24 months postoperatively a significant positive correlation ($p<0.005$) with olfaction and negative correlation ($p<0.005$) with swelling (Table 2). In non-allergic group, 12 months postoperatively we found a significant positive correlation ($p<0.005$) with postnasal secretion and a negative correlation ($p<0.005$) with congestion, headache and cough (Table 3), while 24 months postoperatively a significant positive correlation ($p<0.005$) of eosinophils with postnasal secretion and a negative correlation ($p<0.005$) with congestion was found (Table 4).

Discussion

CRS is predominantly a proliferative process associated with fibrosis of the lamina propria, in which lymphocytes, plasma cells and eosinophils predominate along with, perhaps, changes in bone [10]. The basement membrane is thickened with atypical gland formation, goblet cell hyperplasia, subepithelial oedema, and mononuclear cell infiltration [6].

It was proven that analyzing histopathologic changes in the sinus mucosa taken at surgery may have important prognostic value for long-term outcome [7,11,13]. Significant correlations between severity of certain symptoms and inflammation parameters indicate that there is a potential prognostic value of the analysis of impact of these parameters on some symptoms and outcomes after surgical treatment, even in non-allergic patients [2,13].

Goblet cells and subepithelial thickening are histopathologic parameters which were found to correlate with the largest number of symptoms in both groups of patients at all observed terms. This typical characteristic for chronic inflammatory disease seems to be more consistent in allergic group. Furthermore, it seems to depend on a fewer number of factors and inflammatory processes than cellular infiltration [6].

We have not found statistically significant difference in eosinophilic infiltration in allergic and non-allergic groups of patients. Our findings confirm data from the literature that eosinophilia occurred in rhinosinusitis and in particular those with asthma and that the presence of atopy did not predict tissue eosinophilia [1,15]. Furthermore, eosinophilic infiltration significantly correlated with more symptoms in non-allergic group. Although eosinophilic infiltration was shown not to be a valuable predictive factor for total symptom score, it was shown to be a predictive factor for certain symptoms in both observed groups.

Interestingly, mast cell infiltration correlates with more symptoms in non-allergic patients than in allergic patients. Although difference between allergic and non-allergic is not significant, number of 3+ mast cell infiltration specimen is higher in non-allergic group.

It is interesting that histopathologic scores significantly correlate with total symptom scores before surgery and at 12 and 24 months after treatment only in allergic group of patients.

These data may suggest that, in non-allergic patients, either single or in combination the parameters of inflammation have a greater impact on certain symptom than all parameters of inflammation on total symptom scores, when put together. Our findings confirm previous findings in the literature, that correlations between severity of symptoms and objective extent of disease (CT or endoscopy) are usually not significant, although may have an impact on treatment outcome [4,8,9]. This means that a rhinosurgeon does not have a general predictive parameter after surgical specimen is analyzed, at least in non-allergic patients with CRS but has to analyze a single symptom and relate it to different parameters of inflammation, considering predisposing factors in an individual patient, in order to predict, to a limited extent, persistence of some bothersome symptoms after sinus surgery.

Conclusion

Quantification of certain histopathologic changes was found to be predictable for the persistence of certain bothersome symptoms after ESS in allergic and nonallergic patients. Histomorphometric analysis in these patients was found to be a significant global outcome predictor for allergic patients, but not for non-allergic patients. Consultation with a pathologist may help the ENT surgeon predict persistence of certain CRS symptoms after ESS.

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Table 1 Correlation between histopathologic parameters and subjective symptoms improvement after 12 months in allergic patients

Spearman Rank Order Correlations				
Symptoms after 12 months	Goblet cells	Subepithelial thickening	Mast cells	Eosinophils
Congestion	0,036	0,589*	-0,027	-0,285*
Secretion	-0,425*	0,003	0,477*	0,152
Postnasal	-0,237	0,372*	0,224	0,213
Itching	0,400*	-0,624*	0,032	0,099
Sneezing	-0,059	0,115	0,077	-0,255
Headache	-0,503*	0,414*	-0,047	0,074
Olfaction	-0,679*	0,577*	0,577*	0,261
Cough	-0,276	0,506*	0,017	-0,175
Swelling	-0,556*	0,662*	0,070	-0,246
Total scores	-0,465*	0,362*	0,372*	0,007

*P<0.005

Table 2 Correlation between histopathologic parameters and subjective symptoms improvement after 24 months in allergic patients

Spearman Rank Order Correlations				
Symptoms after 24 months	Goblet cells	Subepithelial thickening	Mast cells	Eosinophils
Congestion	0,518*	0,150	-0,441*	-0,242
Secretion	0,247	0,051	0,020	-0,190
Postnasal	-0,466*	0,223	0,366*	0,147
Itching	-0,385*	-0,181	0,368*	-0,080
Sneezing	-0,140	-0,322*	0,477*	-0,084
Headache	0,475*	-0,195	-0,512*	0,260
Olfaction	-0,499*	0,540*	0,540*	0,426*
Cough	0,396*	-0,472*	-0,398*	0,189
Swelling	-0,270	0,624*	-0,208	-0,334*
Total scores	-0,311*	0,562*	0,185	-0,217

*P<0.005

Table 3 Correlation between histopathologic parameters and subjective symptoms improvement after 12 months in non-allergic patients

Spearman Rank Order Correlations				
Symptoms after 12 months	Goblet cells	Subepithelial thickening	Mast cells	Eosinophils
Congestion	-0,597*	-0,641*	-0,188	-0,353*
Secretion	-0,305*	-0,256	-0,701*	-0,263
Postnasal	0,211	0,293*	0,503*	0,303*
Itching	0,438*	0,183	-0,137	0,220
Sneezing	0,457*	0,307	-0,037	0,301
Headache	-0,451*	-0,315*	-0,029	-0,280*
Olfaction	-0,165	-0,082	0,171	0,049
Cough	-0,521*	-0,655*	-0,554*	-0,496*
Swelling	-0,422*	-0,179	0,065	0,000
Total scores	0,061	-0,087	-0,019	0,046

*P<0.005

Table 4 Correlation between histopathologic parameters and subjective symptoms improvement after 24 months in non-allergic patients

Spearman Rank Order Correlations				
Symptoms after 24 months	Goblet cells	Subepithelial thickening	Mast cells	Eosinophils
Congestion	-0,571*	-0,556*	-0,123	-0,289*
Secretion	-0,285*	-0,255	-0,432*	-0,179
Postnasal	0,260	0,296*	0,477*	0,289*
Itching	0,182	0,003	-0,016	0,069
Sneezing	0,084	-0,010	0,042	0,090
Headache	-0,289*	-0,082	0,020	-0,238
Olfaction	-0,179	0,059	-0,053	0,089
Cough	-0,466*	-0,586*	-0,298	-0,274
Swelling	-0,014	-0,059	0,276	-0,033
Total scores	-0,190	-0,159	0,004	-0,094

*P<0.005