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Histopathologic Parameters as Predictors of Response to Endoscopic Sinus Surgery in

Non-allergic Patients with Chronic Rhinosinusitis

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ABSTRACT

OBJECTIVE: To estimate the predictable value of histopathologic parameters in chronic rhinosinusitis (CRS) for response to endoscopic sinus surgery (ESS).

STUDY DESIGN: Symptomatology was rated in 100 patients prior to as well as 12 and 24 months after surgery. Specimens taken during the procedure were examined and scored for goblet cells, subepithelial thickening, mast cells and eosinophils. Multiple regression analysis was performed to predict the total score of subjective symptoms before treatment by histopathologic parameters. The correlation between histopathologic parameters and postoperative symptoms was then evaluated.

RESULTS: Goblet cells were the best predictor correlating with 5 symptoms. Subepithelial thickening correlated with 4 symptoms. Mast cells infiltration correlated with 3 symptoms. Eeosinophilic infiltration correlated with only one symptom ($P<0.05$).

CONCLUSION: Certain histopathologic parameters in CRS are predictive of favorable response to ESS.

SIGNIFICANCE: Pathologic evaluation may help the ENT surgeon to predict the persistence of certain CRS symptoms after ESS, even in patients at low risk for surgical failure.

INTRODUCTION

Chronic rhinosinusitis (CRS) is a common disease with a significant impact on health-related quality of life. Due to its increasing prevalence, CRS is associated with a significant social-economic burden. The pathogenesis of CRS still remains unclear. As the diagnosis is based on persistence of subjective symptoms related to rhinosinusitis for longer than 12 weeks, empirical conservative treatment may go on for months or even years before confirmation by radiology and/or endoscopy. Surgery, however, is necessary in certain patients with CRS when medical therapy fails.[1,2]

Despite the many controversies in understanding the etiology of CRS, sinus ostial obstruction has been established as one of the most important pathogenetic pathways. The functional approach to surgical treatment of CRS hypothesizes the recovery of the diseased sinus mucosa by enabling ventilation through the natural ostia and restoring mucociliary clearance. Endoscopic sinus surgery (ESS) has been well established as a successful surgical procedure, with failure rates as low as 5% to 10%. However, the cause of failure to respond to surgical treatment is still controversial.[3,4]

A history of asthma and allergy, previous sinus surgery and nasal polyposis have been identified in the literature as poor outcome predictors in large series of ESS treated patients. The objective stage of severity of CRS, based on imaging studies, does not correlate with symptoms but may be a relevant long-term outcome predictor. Cellular infiltration and local cytokine activity in the sinus mucosa collected at surgery may have high prognostic value for long-term outcome, mostly indicating poorer prognosis in allergic and asthmatic patients, with increased local eosinophilia and IL-5 activity.[3,5,6]

Prediction of treatment failure and detection of potential responders among candidates for surgical treatment would be of a great clinical value. However, no study on histopathologic prognostic parameters in a larger group of non-allergic, non-asthmatic, non-polyposis, non-

revision patients, with CRS has been published in the literature. Our hypothesis is that analyzing histopathologic findings in sinus mucosa even in patients with expected good outcome following surgical treatment, could help in prediction of the response to ESS. The aim of this study was to determine whether there exists a correlation between histopathologic parameters and symptoms before and after the ESS in non-allergic, non-asthmatic patients with CRS who underwent primary surgical treatment and to evaluate the prognostic value of these findings.

MATERIALS AND METHODS

One hundred patients (48 male, 52 female, with a mean age of 43 ± 16.3) with CRS were selected from a prospective study group of more than 500 patients who underwent ESS, performed by a single surgeon between February 1998 and February 2003. All patients have been followed-up for evaluation of the relationship between histopathologic inflammatory parameters of the sinus mucosa at surgery with mid- to long-term outcome. The study was approved by the Ethics Committee of the Sestre Milosrdnice University Hospital in Zagreb, Croatia. Patients were selected according to the following criteria: age between 18 and 70, CRS confirmed by symptoms, endoscopy and computed tomography (CT), (Lund-Mackay score range 8 – 16). The current AAO-HNS set of guidelines for the diagnosis of CRS was applied.

Patients with systemic evidence of allergy, bronchial asthma, nasal polyposis, previous sinus surgery, and systemic steroid or antimicrobial treatment within one month were excluded. Allergy was excluded when the skin prick test for inhalatory allergens was negative and the total serum IgE lower than 40 IU/ml.

All patients underwent medical treatment with unsatisfactory results at least one year before surgery.

Anterior and posterior bilateral ethmoidectomy were performed in all patients.

Patients completed a questionnaire before the intervention, and at 12 and 24 months after surgery, with respect to the following sinusitis symptoms: congestion, discharge, nasal secretion, headache, sneezing, cough, facial swelling and olfaction. Symptoms were scored for their intensity from 0 to 3 (0 - no symptom, 1 - mild, 2 – moderate, 3 - severe) and for the frequency of the symptoms from 0 to 3 (0 – never, 1 rarely, 2 – sometimes, 3 – often). The total subjective symptom score was the sum of the intensity and frequency scores (i.e. from 0 to 6).

During ESS, uncinectomy was performed with a sickle knife and a Blekesly forceps. Mucosal biopsy specimens were fixed in buffered 4% formaldehyde, and paraffin embedded. Standard 5 μm sections were stained with hematoxylin–eosin and light microscopic examination was then conducted and recorded semiquantitatively. Semiquantitative grading was performed in comparison with normal sinus mucosal histology (0, 1+, 2+, 3+).

The normal sinus mucosa is observed in mucosal specimens fo uncinate process taken in control group of 11 patients without CRS. This group of patients underwent intranasal endoscopic orbital decompression as a treatment of medically refractive thyroid eye disease. The assessed parameters were as follows: number of goblet cells, thickening of the basement membrane (subepithelial thickening), and inflammatory cells.

Infiltrate density of goblet cell was recorded as 0 for no inflammatory cells, + for scattered inflammatory cells, ++ for diffuse but not confluent infiltrate, and +++ for confluent infiltrate. Semiquantitative grading was performed in comparison with normal sinus mucosal histology (0, 1+, 2+, 3+) for subepithelial thickening. Initially, a low-power survey of the slide was performed at 10x magnification to identify the area with the greatest density of eosinophils and mastocytes. Counting of eosinophils was done in 10 non-overlaping consecutive high power magnification fields (x 400/ 0,144mm^2), and the average number of eosinofils 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 well as for goblet cells.[7,8]

As we analyzed both left and right uncinate processes in every patient, we used the side with the higher grade (that with the worse total score of pathohistological changes) from these two specimens for statistical analysis.

Statistical Analysis

The improvement of particular symptom scores, as well as the improvement of total symptom scores after 12 and 24 months were calculated as a percentage of the initial score value before treatment. Multiple regression analysis was performed to estimate a prediction of the total score of subjective symptoms before treatment by pathohistological parameters.

A correlation was calculated between the scores of pathohistological findings (0-3) and symptom scores (0-6) after 12 and 24 months postoperatively. Spearman rank correlation coefficients were then calculated. All conclusions were based on a significance level of $p < 0.05$.

RESULTS

All patients had improvement in symptom scores 12 months after the surgery. Six patients had improvement between 1% to 25%, 2 between 26% to 50%, 63 between 5% to 75% and 29 patients with more than 75%. The improvement rate was lower 24 months after surgery: 3 patients reported no improvement, 5 of them had improvement between 1%-25%, 7 between 26%-50%, 67 between 51%-75%, and 18 more than 75% (Table 1).

We performed a multiple linear regression analysis to investigate the prediction of total scores before treatment by "goblet cells", "subepithelial thickening", "mast cells" and "eosinophils". Analysis of variance tables indicates that at least one of the explanatory variables is related to the total score before treatment ($F_{(5.95)} = 109.88$ $P < 0.001$). An adjusted R^2 value of 0.815 indicated that 81.5% of the variability of total scores can be explained by differences in pathohistological examination (Table 2).

Total scores before treatment = 13.957 + (5.483*goblet cells) + (4.318*subepithelial thickening) + (2.114* mast cells) – (2.158*eosinophils).

Every analyzed predictor was found statistically significant.

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Multiple linear regression analysis to investigate the prediction of improvement in total scores in 12 and 24 months after treatment by "goblet cells", "subepithelial thickening", "mast cells" and "eosinophils" was not statistically significant. Correlation data are shown in tables 3 and 4.

Correlation to Goblet Cells and Symptoms. At 12 and 24 months postoperatively we found a significant positive correlation ($P<0.005$) of goblet cells with itching. A significant negative correlation ($p<0.005$) was found with congestion, nasal secretion, headache and cough. The correlation between goblet cells and postnasal secretion, olfaction and total symptom score was not significant.

Correlation to Subepithelial Thickening and Symptoms. At 12 and 24 months postoperatively we found a significant positive correlation ($p<0.005$) of subepithelial thickening with postnasal secretion. A significant negative correlation ($p<0.005$)was found with congestion, nasal secretion and cough. The correlation between subepithelial thickening and itching, facial swelling and total symptom score was not significant.

Correlation to Mast Cells and Symptoms. At 12 and 24 months postoperatively we found a significant positive correlation ($p<0.005$) of mast cells with postnasal secretion. A significant negative correlation ($p<0.005$) was found with nasal secretion and cough. We did not find any significant correlation between mast cells and itching, sneezing, headache, olfaction, facial swelling and total symptom score.

Correlation to Eosinophils and Symptoms. At 12 and 24 months postoperatively we found no symptom which correlated with a significant positive association with eosinophils at both observed terms. We found a significant negative correlation ($p<0.005$) with nasal secretion. There was no significant correlation between eosinophils and itching, sneezing, olfaction, facial swelling and total symptom score.

DISCUSSION

The prediction of mid to long-term prognosis of ESS has been evaluated in numerous retrospective and a few prospective trials. Most of these studies have determined epidemiological parameters from the patient's history which may be predictive of poor response to surgical treatment, such as presence of allergy, asthma, nasal polyposis or previous surgery. Fewer studies have focused on local inflammatory parameters determined by quantification of cellular infiltration or cytokine activity in the sinus mucosa collected at surgery. However, these studies have included patients with lower and higher risks for surgical failure, or included only those with a higher risk for poor prognosis.[3,4,6,9-11] These results have confirmed previous risk factors for failure, detected by retrospective epidemiological studies (for example, IL-5 upregulation or eosinophilia, which can be found in asthmatic or allergic patients).[5] Data in the literature indicates that an association of allergy and asthma with CRS has a negative effect on subsequent response to surgery, suggesting that allergic patients will need a more intensive or allergy specific management after surgery. Given the unfavorable results in patients with upregulated IL-5 in sinus mucosa, it was hypothesized that surgical widening of the sinus ostia might increase exposure of the sinus cavities to environmental allergens, infectious agents, and irritants which might perpetuate chronic allergic inflammation that was previously present in the nasal cavity before surgery.[5,9] Eosinophil infiltration, basement membrane thickening and goblet cell hyperplasia were more prominent in the asthmatic compared to the non-asthmatic group.[12] Although improvement in the overall management of the asthmatic patients with CRS following sinus surgery has been demonstrated, asthma is correlated to poor outcomes after ESS in some studies.[13,14] However, some studies show that asthma is not associated with earlier relapse of sinusitis symptoms.[15] CRS patients with serum eosinophilia have a worse prognosis when compared with controls. A higher proportion of patients with serum eosinophilia had a history of asthma, polyp

disease, and allergic fungal sinusitis.[11,14] While we did not correlate serum eosinophilia in our study, local eosinophilic infiltration was correlated with only one major symptom on both observing terms. Regarding this finding, eosinophilic infiltration was shown not to be a valuable predictive factor in this selected group of patients.

Nasal polyps, especially recurrent ones, were found to be a predictor of poor prognosis of success after ESS.[9] Similarly, previous sinus surgery is strongly associated with lower individual symptom scores.[5,16] This trial was undertaken to establish the prognostic value of quantification of previously well-established histopathologic parameters of inflammation in CRS in the literature (goblet cells, subepithelial thickening, mast cells and eosinophils) to the mid-term prognosis after ESS in a selected group of patients with CRS, which should be a predictor of better outcome, based on epidemiological data, but not on the patients' symptoms and CT scores.

Strict selection criteria for this study were established to avoid patients who are already at high risk for surgical failure, and to decrease the variability in the study group. On the other hand, our selection criteria included only those with moderate to severe disease stages according to symptomatology (>50% maximal total symptom score) and CT scores (≥5 Lund Mackay on the worse side), which may lead to an unsatisfactory surgical outcome. Considering Lund Mackay CT scores, patients with low, as well as high scores were excluded, as patients with nasal polyposis were not included in the study. This staging system exhibited the best correlation between nasal symptom scores and CT stage in CR. The degree of correlation however remained small.[6] Higher CT disease stage is correlated with poor outcomes after EES.[16] Stewart and coauthors have found that symptom severity as assessed by a pretreatment CT scan is a strong predictor of outcome.[17]

Our group as a whole was homogeneous (adults, non-allergic, non-asthmatic, non-polyposis, non-revision, CT score 8-16 pts, moderate to severe according to total symptom score). All

procedures were performed by a single surgeon to exclude the influence of different approaches and surgeon skill on the outcome after ESS. Pathohistological samples analyzed were taken from the same site (the uncinate process), to avoid variability of findings in different sinus cavities. The uncinate process was selected as it is the cornerstone of the ostiomeatal complex, the site where early pathology is detected in patients with no other risk factors for CRS and is hypothesized to be responsible for impaired sinus ventilation and clearance.

Our study confirmed the efficacy of ESS as have many previous studies looking at ESS outcomes.[18,19] In our study 92% of the patients showed a marked global improvement (total score improvement >51%) 12 months after the surgery, and 85% of patients at 24 months after surgery. We have to stress that our subjects belong to the specific group of CRS without previously established poor prognostic background.

Multiple linear regression analysis of the impact of histomorphometric scores of "goblet cells", "subepithelial thickening", "mast cells", and "eosinophils" on total symptom scores before the treatment, as well as at 12 and 24 months after treatment did not reveal the prognostic value of histomorphometric analysis on global response to surgery. However, except for eosinophils, a strong impact of the observed parameters was found on the baseline scores. Out of these data, it can be suggested that only an increased proportion of activated eosinophils (found in asthma, allergy or polyposis, excluded in this trial) may be predictive of symptom severity and prognosis of surgical outcome. To test the relationship between histopathological changes in the uncinate process mucosa and symptoms severity after sinus surgery, we calculated the correlation between histopathologic findings with total score and each separate symptom at both postoperative terms.

Both multiple linear regression and Spearman Rank correlation have shown that histopathologic findings are not predictive of total symptom score outcomes at 12 and 24

months after treatment. Regarding this data, there is no predictive value of the histopathologic findings in sinus mucosa to asses the 'global' prognosis of response to surgery.

However, a correlation between some of the histopathologic parameters and certain symptoms is significant. Such histomorphometric analysis, at least for those where the correlation is not only significant, but strong, may indicate better or worse surgical outcome considering specific symptoms. Patients with a higher goblet cell score may expect better improvement in ithching, but less improvement in congestion, secretion, headache and cough after ESS. A higher subepithelial thickening score may predict better improvement in postnasal secretion, but less improvement in congestion, nasal secretion and cough. Those with higher mast cell scores would probably have better improvement in postnasal secretion, but less improvement in nasal secretion and cough. Higher eosinophil scores may predict less improvement in nasal secretion after surgery.

These data and our speculations concerning these results can be retested in a specific group of CRS subjects who are chosen by the same inclusion and exclusion criteria.

Only a few studies have considered correlation between the surgical subjective outcomes. No valid correlations have been found between histopathology in chronic maxillary sinusitis and congestion, nasal secretion and facial pain in a study of patients operated by ESS or the Caldwell-Luc procedure.[8] Moran and coauthors evaluated sections of sinus tissue for the presence of lymphocytes, plasma cells, eosinophils, and macrophages. They did not find a difference in the magnitude or specific type of inflammatory cells present at the time of surgery, nor any specific inflammatory cell predominance to be predictable of surgical outcome. However, since patients who received less preoperative medication seemed to improve less after surgery, we concluded that patients with less symptom severity are less likely to benefit from ESS. Both studies had different and less strict selection criteria, they

included less patients operated by ESS and analyzed less symptoms to give adequate prognosis to the value of histopathology in CRS.

Some studies have identified a potential link between CRS, inflammatory cells and other mediators present in sinonasal mucosa. The degree of tissue eosinophilia correlates with extension of the disease.[11] Lavigne and coauthors have suggested that an increased number of cells expressing IL-5 mRNA in the ethmoid sinuses at the time of surgery might be predictive of poor surgical outcome.[5] The same group of authors indicated that topical endosinusal steroid benefited allergic patients with persisting CRS symptoms after ESS. The results of our previous study were in concordance with these data where we have found that the level IL-5 in sinus lavage may be a good predictor of response to endosinusal steroid-antibiotic therapy in patients with chronic maxillary sinusitis. Patients with a higher improvement rate had a significantly higher level of IL-5 in sinus lavage.[20]

Although we did not analyze the cytokine pattern in the sinus mucosa specimen, the selection criteria of our study have probably excluded those with a high IL-5 activity. This may be the reason for the poor prognostic value of eosinophilia in our trial.

CONCLUSION

The results of our study have confirmed:

1. ESS is a highly effective treatment for CRS in non-allergic, non-asthmatic patients without nasal polyposis or previous sinus surgery, when long-term conservative treament fails.

2. In this selected population of CRS patients, who were without previously established poor prognostic background, quantification of certain histopathologic changes was found to be predictable for the persistence of certain bothersome symptoms for years after surgery.

3. Histomorphometric analysis in these patients was not found to be a significant global outcome predictor following surgical treatment for CRS.

4. Pathologic consultation may help the ENT surgeon to predict the persistence of certain

CRS symptoms after ESS, even in patients at low risk for surgical failure.

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Tables

Table 1 -Total score improvement in 12 and 24 months after treatment

Total score improvement	12 month after treatment	24 month after treatment
0%	0	3
1-25%	6	5
26-50%	2	7
51-75%	63	67
>75%	29	18
Total	100	100

Table 2. Prediction of total score before treatment – results of regression analysis

Independent variables	Beta	Std.Err.	B	Std.Err.	t(94)	P-level
Intercept			13.957	1.018	13.708	<0.001
Goblet cells	0.568	0.061	5.483	0.586	9.350	<0.001
Subepithelial thickening	0.451	0.065	4.318	0.628	6.880	<0.001
Mast cells	0.239	0.051	2.114	0.451	4.688	<0.001
Eosinophils	-0.218	0.064	-2.158	0.633	-3.412	<0.001

Table 3. Correlation between histopathologic parameters and subjective symptoms improvement after 12 months

Spearman Rank Order Correlations				
Improvement after 12 months in:	**Goblet cells**	**Subepithelial thickening**	**Mast cells**	**Eosinophils**
congestion	-0.537*	-0.650*	-0.239*	-0.329*
secretion	-0.261*	-0.265*	-0.718*	-0.321*
postnasal	0.087	0.265*	0.477*	0.199*
itching	0.489*	0.165	-0.168	0.080
sneezing	0.512*	0.259*	-0.063	0.182
headache	-0.392*	-0.282*	-0.072	-0.210*
olfaction	-0.156	-0.182	0.084	-0.172
cough	-0.346*	-0.689*	-0.430*	-0.525*
swelling	-0.411*	-0.116	0.164	-0.092
total scores	0.162	-0.061	-0.104	-0.044

* = correlations are significant at P<0.05

Table 4. Correlation between histopathologic parameters and subjective symptoms improvement after 24 months

Spearman Rank Order Correlations ∗= correlations are significant at P<0.05				
Improvement after 24 months in:	Goblet cells	Subepithelial thickening	Mast cells	Eosinophils
congestion	-0,487*	-0,512*	-0,140	-0,195
secretion	-0,271*	-0,288*	-0,523*	-0,227*
postnasal	0,158	0,278*	0,452*	0,188
itching	0,289*	0,041	-0,076	0,001
sneezing	0,165	0,020	0,018	0,056
headache	-0,364*	-0,070	0,060	-0,191
olfaction	-0,181	-0,082	-0,166	-0,066
cough	-0,304*	-0,584*	-0,046	-0,294
swelling	-0,062	-0,028	0,205	-0,052
total scores	-0,125	-0,116	-0,066	-0,077