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Histopathologic analysis in chronic rhinosinusitis: Impact on quality of life outcomes

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ABSTRACT

Objective: This study investigates the impact of histopathologic parameters on quality of life outcomes in patients with chronic rhinosinusitis.
Setting: Hospital of Zhejiang University.
Study design: Retrospective analysis of collected data.
Subjects and methods: One hundred and twenty patients with chronic rhinosinusitis (CRS) who underwent endoscopic sinus surgery were recruited. Clinical features, CT evaluation, pre and postoperative SNOT-22 scores and histopathologic findings were collected. Tissue eosinophils and mucosal remodeling were analyzed relative to clinical features and outcomes 12 months postoperatively.
Results: Symptom improvement was seen for the entire population. Eosinophilic CRS had significantly worse preoperative and postoperative SNOT-22 scores than non- eosinophilic CRS. Symptom improvement in eosinophilic CRS after surgery was less than that of non-eosinophilic CRS. There was no significant association between preoperative and postoperative SNOT-22 scores and remodeling markers. However, patients with basement membrane thickening showed less reductions of SNOT-22 score postoperatively.
Conclusions: Presence of mucosal eosinophilia and basal membrane thickening appear to be the main factors adversely affect the symptom control of surgical intervention. Routine histopathology analysis can provide meaningful information for prognostication of surgical outcome.

1. Introduction

Chronic rhinosinusitis is a heterogeneous disease with various inflammatory mechanisms [1]. Although current management of CRS such as endoscopic sinus surgery (ESS) has been shown to provide significant improvement in patient outcomes [2–4], a large number of CRS patients continue to suffer from uncontrolled symptoms [5]. There is often no adequate explanation for divergent management outcomes in equivalent phenotypic groups. Commonly used phenotypic clarifying and clinical measures such as the severity of Lund-Mackay computed tomography (CT) have failed to reliably predict treatment outcomes [6,7].

New research in the pathogenesis of CRS has shed light on an emerging classification system based on endotypes defined by the distinct pathogenesis that may be identified by corresponding biomarkers. Better identification of endotypes might permit individual therapy that targeting against the pathophysiologic processes of a patient's endotype, with potential for more effective treatment outcomes [8,9]. The ensuing histopathologic changes of inflammation have been documented in CRS. To evaluate the feasibility of endotyping from histopathology that differ from the standard phenotypic classification system, a growing number of reports have investigated the histopatholgic changes including tissue remodeling in CRS and its role in clinical decision-making using structured histopathologic analysis [4,10–16]. Of specific importance is its association with the phenotypes of CRS, objective and subjective disease severity. For example, basement membrane thickening (BMT), resulting from ongoing subepithelial collagen deposition, is associated with a prolonged duration of symptoms, comorbid asthma, and atopy [17], and may adversely affect the symptoms of CRS [11]. However, the extant literature focuses on the features to reliably differentiate between phenotypes and gets mixed results. Little is known about the impact of mucosal remodeling on symptom control after surgical intervention.

The use of 22-item Sino-Nasal Outcome Test (SNOT-22) is rapidly

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Table 1
Demographic and clinical characteristics by subtypes.

	CRSsNP $n = 56$	CRSwNP $n = 64$	P	eCRS $n = 48$	neCRS $n = 72$	P
Age (years)	39.6 ± 5.3	41.2 ± 7.9	0.34	42.3 ± 6.4	38.9 ± 7.2	0.41
Gender (male, %)	51.7	57.8	0.51	47.9	55.5	0.20
Asthma (%)	8.9	14.1	0.38	18.9	6.9	0.048
Allergic rhinitis (%)	14.3	20.3	0.38	29.8	9.7	0.01
Previous sinus surgery (%)	17.8	23.4	0.45	27.1	16.7	0.17
Lund-Mackay score (mean ± SD)	9.3 ± 0.7	10.2 ± 0.8	0.4	11.4 ± 0.9	8.5 ± 0.7	0.01

CRSsNP = CRS without nasal polyps; CRSwNP = CRS with nasal polyps; eCRS = eosinophilic CRS; neCRS = non-eosinophilic CRS.

growing in studies of clinical effectiveness and quality of care in CRS. It accurately reflects patient-reported control of CRS symptomatology, and can be used to accurately distinguish patients with poor vs well-controlled CRS symptoms [18–20]. This study aims to investigate the influence of remodeling features on symptom improvement measured by SNOT-22 after ESS.

2. Materials and methods

This study was performed with approval of the Institutional Review Board of the first affiliated hospital of Zhejiang University. Patients with CRS who underwent ESS at our hospital were included. No patients received oral corticosteroids for 4 weeks prior to surgery. Written informed consent was obtained from all participants. The diagnosis of CRS met the criteria of EPOS [1]. Exclusion criteria included patients under 18 years of age, use of oral steroids or immunomodulatory agents within 30 days prior to surgery, antro-choanal polyp, cystic fibrosis and allergic fungal rhinosinusitis. Demographic data and medical history was collected preoperatively, including age, gender, asthma, allergic rhinitis, and history of previous sinus surgery. Evaluation was performed comparing demographic factors, CT evaluation (Lund-Mackay score, LMS), histopathologic findings, and SNOT-22 scores. All patients received a similar initial postoperative care protocol with oral prednisone for 2 weeks and intranasal budesonide twice a day for 12 weeks. Then the steroid rinses tapered down to once a day until complete sinonasal mucosal normalization was achieved. If patients demonstrate persistent low-grade mucosal disease, they were continued on steroid rinses at the discretion of the operating surgeon.

2.1. Histological evaluation

Sinus mucosal tissue was collected from the ethmoid cavity at the time of surgery. Tissue specimens were prepared using standard laboratory techniques for hematoxylin and eosin (H&E) staining. Histological review was performed according to the system previously described by Snidvongs et al. [10]. The reporting pathologist was blinded to other data.

Tissue absolute counts of eosinophils were calculated, and eosinophilic CRS (eCRS) was histologically defined when tissue eosinophils > 10 per high power field. Histopathologic variables assessed included basement membrane thickening (< 7.5 μm, 7.5 to 15 μm, > 15 μm) squamous metaplasia (absent or present) and fibrosis (absent or present).

2.2. Disease severity measurements

Preoperative LMS was recorded to provide an objective assessment of disease severity. Subjective disease severity was evaluated with the SNOT-22 preoperatively and 12-months postoperatively.

3. Statistical analysis

Data were analyzed using IBM SPSS Statistics version 23 (IBM Corp, Armonk, NY). Proportions were assessed using chi-square analysis. Descriptive statistics (means, standard deviations, and frequencies) were calculated for all measures. Changes in SNOT-22 scores were calculated for all patients from preoperative to postoperative time points. The Student *t*-test or Mann-Whitney *U* test (two-tailed) was used for comparison of continuous variables. The one-way analysis was used to compare means for more than two independent groups. Results with a p value of < 0.05 were considered significant.

4. Results

4.1. Demographic and histopathological data

A total of 120 patients were recruited, including 56 CRSsNP and 64 CRSwNP patients. Forty-eight patients had eCRS (40%). Demographic data are summarized in Table 1. There was no difference in gender distribution, age, and ESS history between the subgroups classified by phenotype or endotype. Comorbid asthma and allergic rhinitis were significantly associated with eCRS. ECRS patients had higher average baseline LMS than non-eCRS patients.

The proportion of BMT did not differ significantly between CRS subtypes. Although the incidence of fibrosis tended to increase from CRSwNP to CRSsNP, and from eCRS to non-eCRS, there was no significant difference between subtypes respectively. Similarly, the frequency of squamous metaplasia also increased in CRSwNP and eCRS respectively, however, they did not reach statistical significance either (Table 2).

4.2. Clinical severity: SNOT-22

Mean preoperative and postoperative SNOT-22 scores were 45.9 ± 14.3 and 21.75 ± 13, respectively ($P < .001$). The overall reduction in SNOT-22 score of the entire patient cohort was 24.2 ± 7.1. The association of SNOT-22 scores with phenotype and endotype is detailed in Table 3. Patients with CRSwNP, when compared

Table 2
Remodeling changes by subtypes.

	CRSsNP n = 56	CRSwNP n = 64	P	eCRS n = 48	neCRS n = 72	p
BMT (μm, %)			0.66			0.63
< 7.5	19.6	26.6		25.0	22.2	
7.5–15	48.2	45.3		50.0	44.4	
> 15	32.1	28.1		25.0	33.4	
Fibrosis (%)			0.2			0.33
Absent	44.6	56.3		56.3	47.2	
Present	55.4	43.7		43.7	52.8	
Squamous metaplasia (%)			0.08			0.14
Absent	91.1	79.9		79.9	88.9	
Present	8.9	20.1		20.1	11.1	

CRSsNP = CRS without nasal polyps; CRSwNP = CRS with nasal polyps; eCRS = eosinophilic CRS; neCRS = non-eosinophilic CRS. BMT = basement membrane thickening.

Table 3
Mean pre/postoperative, and absolute change in SNOT-22 by subtypes.

Subtype	Pre-ESS	p	Post-ESS	p	Change	p
CRSsNP	42.5 ± 18.1	0.02	17.7 ± 8.6	0.004	24.8 ± 7.9	0.40
CRSwNP	48.9 ± 16.2		25.3 ± 7.9		23.6 ± 8.1	
eCRS	56.1 ± 22.5	0.001	34.8 ± 12.2	0.0001	21.3 ± 9.8	0.01
neCRS	39.1 ± 15.2		13.1 ± 3.8		26.0 ± 10.9	

CRSsNP = CRS without nasal polyps; CRSwNP = CRS with nasal polyps; eCRS = eosinophilic CRS; neCRS = non-eosinophilic CRS; ESS = endoscopic sinus surgery.

to CRSsNP, had higher preoperative and postoperative SNOT-22 scores. However, reductions in SNOT-22 scores 12 months postoperatively were not significantly different between CRSwNP and CRSsNP groups. Patients with eCRS also had significantly higher preoperative and postoperative SNOT-22 scores than non-eCRS. In contrast, the improvement of SNOT-22 score after ESS in eCRS was less than that of non-eCRS (Table 3). Table 4 illustrated the association of SNOT-22 scores and remodeling features. There was no significant association between preoperative and postoperative SNOT-22 scores and remodeling markers. With respect to the SNOT-22 changes postoperatively, there was significant difference in the reduction of SNOT-22 scores among these three groups. Patients with BMT shew less reduction of SNOT-22 scores postoperatively.

5. Discussion

Chronic rhinosinusitis is a complex, heterogeneous disorder with differing underlying mechanisms underpin the inflammation [1]. This heterogeneity of CRS results in divergent treatment outcomes in equivalent phenotypic groups. Thus, clarifying CRS based on distinct pathophysiological mechanisms, or “endotypes”, may facilitate to improve therapeutic modalities for patients with refractory CRS [8.9]. Endotyping from histopathologic analysis was investigated to determine subtypes that differ from the standard clinical classification system in recent years [4,10–16] However, the exact role and influence of the histopathologic profile in clinical outcomes have not yet been fully elucidated. In the present study, all patients did well after ESS indicated by a significant preoperative to postoperative reduction in SNOT-22 score. Further analysis of histopathology revealed that patients with eCRS and BMT had less reduction in SNOT-22 score after surgery.

Tissue eosinophils are thought to be effective for simply differentiating CRS endotype. Snidvongs et al. demonstrated that tissue eosinophilia may be a good marker for eCRS regardless of CRS phenotype [10]. Several previous studies have recognized the importance of tissue eosinophilia with respect to disease severity and prognosis [4,10–16,21]. Increased tissue eosinophils were correlated with higher disease severity indicated by endoscopic score and LM score; patients with eosinophilic aggregates which may represent vigorous eosinophilic activation, had more severe disease than those without aggregates [10,16]. Furthermore, tissue eosinophilic aggregates may increase the requirement of steroid therapy postoperatively to control mucosal inflammation [4]. This may have important prognostic implication as higher tissue eosinophilia is associated with less quality-of-life improvement and increased relapse after surgery [15,21]. In this study, patients with eCRS also had higher baseline LMS. However, our study illustrated that patients with eCRS had worse pre and postoperative SNOT-22 scores, which was in contrary to other reports [10,13,16,22]. Of note, Chowdhury et al. also observed significant inverse correlation between Extranasal Rhinologic Symptoms of SNOT-22 and mean eosinophil counts [22]. The discordance between our study and others was hard to explain. One likely reason may be the ethnic background of the patients and the variance of endotype features in Western and Eastern people. In our study, eCRS demonstrated less reduction of SNOT-22 score after ESS, suggesting that patients with eCRS may experience poor symptom control after surgery. Thus, more aggressive either systemic or topical steroid therapy in these patients may need to better control mucosal disease [4].

The impact of remodeling changes on asthma treatment and the unified airway disease hypothesis has driven the attention toward the mucosal remodeling of CRS [23–25]. Mucosal remodeling occurs in up to 80% of CRS patients and predicts increased steroid requirements postoperatively than those without remodeling [14]. Therefore, the mucosal remodeling occurring in CRS may have a prognostic implication. Subepithelial collagen deposition, leading to BM thickening, is a hallmark of remodeling in CRS, similar to that seen in asthma [25]. Rehl et al. found that BMT was correlated positively with the duration of CRS symptoms [17]. Their observation may evidence the hypothesis that mucosal remodeling accumulated as untreated sinusitis progressed, which may be one of the reasons for the results observed in Hopkins' study that symptom duration of > 12 months had a negative influence on postoperative outcomes [26]. In our study, BMT was significantly associated with symptom improvement after ESS, which was in line with Soy et al., who also demonstrated that BMT adversely affected symptoms of CRSwNP measured by the Rhinosinusitis Disability Index [11]. Ongoing collagen deposition appears to respond poorly to traditional surgical techniques and steroids [27]. However, earlier steroids treatment may decrease remodeling through acting on various precursor steps, including fibroblast proliferation and myofibroblast differentiation [28]. Meanwhile, as surgery leads to improved ventilation of the sinuses and thus better irrigation and instillation of topical steroids, patients with CRS refractory to medical management may do better with earlier surgical intervention.

Several caveats need to be considered when interpreting our results. First, there is inherent difficulty in controlling for variability and bias due to retrospective nature of the study. Second, follow-up of up to 12 months postoperatively cannot capture patients with later deterioration of the disease. At last, a larger sample size is needed to provide sufficient power for multivariate analysis. Nonetheless, this study shows that histologic inflammatory markers can provide important

Table 4
Mean pre/postoperative, and absolute change in SNOT-22 by remodeling variables.

Variables	Pre-ESS	P	Post-ESS	P	Change	P
BMT (μm, %)		0.72		0.10		0.000
< 7.5	47.5 ± 11.1		18.5 ± 7.63		29.0 ± 7.7	
7.5–15	45.6 ± 13.7		21.5 ± 13.4		24.1 ± 5.2	
> 15	44.5 ± 22.2		26.4 ± 21.6		18.1 ± 6.8	
Fibrosis (%)		0.84		0.81		0.77
Absent	45.5 ± 18.1		21.7 ± 14.9		23.8 ± 8.1	
Present	46.1 ± 14.1		21.8 ± 12.4		24.3 ± 7.7	
Squamous metaplasia (%)		0.33		0.15		0.44
Absent	47.9 ± 18.8		24.6 ± 10.8		23.3 ± 6.7	
Present	45.1 ± 13.6		20.5 ± 11.6		24.5 ± 8.2	

BMT = basement membrane thickening; ESS = endoscopic sinus surgery.

predictive information in determining disease severity and treatment outcomes. Further work investigating the role of medications inhibiting remodeling can add significantly toward individualization of care based upon histopathology profile.

6. Conclusions

In this study, patients experienced symptom improvement after ESS. Presence of mucosal eosinophilia and basal membrane thickening appear to be the main factors adversely affect the symptom control of surgical intervention. This work, coupled with the previous studies, supports the notion that histopathology analysis can provide very meaningful information for prognostication of surgical treatment outcomes. Patients with tissue eosinophilia and basal membrane thickening may need more aggressive postoperative management.

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Conflict of interest

The authors declare that they have no conflict of interest

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