Relationship Between Mucosal Inflammation, Computed Tomography, and Symptomatology in Chronic Rhinosinusitis Without Polyposis

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Objectives: This study was an attempt to determine whether sinus mucosal inflammation is related to computed tomographic findings and patients’ reported symptoms in chronic rhinosinusitis (CRS) without polyposis.

Methods: Retrospectively reviewed the clinical symptom scores according to the Rhinosinusitis Symptom Inventory (RSI), the radiographic findings, and the histopathologic findings in the paranasal sinus mucosa for a consecutive series of adult patients who underwent endoscopic sinus surgery for CRS. Linear regression analysis was conducted for the relationship between tissue pathology inflammatory severity score graded on a 5-point Likert scale and the RSI symptom domains. A similar analysis was conducted for the relationship between the pathology inflammatory score and the total Lund score.

Results: The study cohort consisted of 115 adult patients (mean age, 40.2 years). The mean Lund score for the cohort was 8.8 (95% confidence interval, 7.9 to 9.7), and the mean pathology severity score was 2.1 (median, 2.0). The mean total symptom score for the overall cohort was 41.3; the mean total symptom scores for pathology severity grades 0, 1, 2, 3, and 4 were 25.0, 43.8, 41.8, 42.4, and 32.8, respectively. No significant association could be identified between pathology severity and any of the 5 RSI symptom domains (nasal, facial, oropharyngeal, systemic, and total symptoms; all \( p > .436 \), linear regression). A statistically significant relationship between total Lund score and pathology severity was identified (\( p < .001 \)).

Conclusions: Poor correlation exists between the histopathologic severity of sinonasal inflammation and self-reported symptom scores in CRS. Histopathologic inflammatory grade alone fails to stratify CRS cases according to disease symptom severity. Histopathologic inflammation and computed tomographic findings correlate strongly.

Key Words: chronic rhinosinusitis, histopathology, staging, symptom.

INTRODUCTION

Chronic rhinosinusitis (CRS) is one of the most common chronic disease conditions in the United States, affecting more than 20 million Americans. Despite its widespread prevalence and advances in imaging, molecular biological, and microbiological techniques, the pathophysiology of CRS remains poorly understood. However, central to almost all of the pathophysiological models of CRS is the concept of mucosal inflammation. As CRS is a disease entity with substantial and various degrees of severity, investigators have long sought to stage or stratify patients with CRS in order to determine treatment protocols and predict outcomes for CRS. Previous investigators have reported on radiographic staging methods for CRS, but unfortunately, to date, very little usable correlation has been demonstrated between radiographic stage and disease symptom severity. Another potential option for disease severity staging would be the degree of histopathologic inflammation of the sinonasal mucosa. The potential relationship between sinonasal symptoms and histopathology in CRS has received little attention in the literature. Therefore, I sought to determine whether the degree of mucosal inflammation in CRS, as determined by standard histopathology, correlated with disease symptom severity scores. If such correlation or stratification existed, this then might allow stratification of patients with CRS according to their mucosal pathological status.

METHODS

A consecutive series of adult patients who underwent endoscopic sinus surgery (ESS) for CRS was retrospectively reviewed. Patients were included in the study according to the following inclusion criteria: age over 16 years, satisfied diagnostic criteria (clinical symptom criteria and radiographic criteria) for CRS without nasal polyposis, failed standard medical management, standard ESS undergone with...
tissue submitted for histopathology, and pathology findings available for review. All patients were also required to have completed a preoperative Rhinosinusitis Symptom Inventory (RSI) cataloging their symptom severity scores for the major and minor symptoms of CRS and reporting their medication usage with respect to CRS. For each patient, standard demographic information was collected, and the scores on the individual elements of the RSI and RSI symptom domains were tabulated and calculated. Symptom domain scores may range from 0 (no symptoms) to 100 (maximum symptoms). Separately, with the investigators blinded to the demographic and RSI data, pathologic specimens were reviewed and scored according to a 5-point Likert severity scale, with 0 representing absence of inflammation (ie, normal respiratory mucosa) and 4 representing maximum inflammation (ie, severe eosinophilia, lymphoplasmacytic infiltrate, etc) according to the scale of Biedlingmaier and Trifillis. Pathology severity was graded for each side, and both a mean pathology reading (simple average of the left and right side scores) and maximum pathology severity (overall severity assigned according to the side with the more severe pathology severity score) were tabulated. The preoperative paranasal sinus computed tomography (CT) scans were also reviewed and staged according to the Lund system. Because tissue histopathology specimens are primarily obtained from the ethmoid sinuses during ESS, cases in which the ethmoid sinuses were radiographically negative (ie, total ethmoid Lund score of 0) were excluded after review.

Standard descriptive statistics were computed for the study cohort. A linear regression analysis was performed to determine the relationship between pathology severity score and the scores on RSI symptom domains and total Lund score. For each RSI symptom domain score (dependent variable), a linear regression equation was computed with maximum pathology severity score as the independent (predictor) variable. In order to adjust for the influence of medication use on CRS symptoms, the additional independent variables — total weeks of intranasal steroid use, total weeks of non-sedating antihistamine use, and number of weeks of antibiotic use in the previous 12 months — were included as covariates in the linear regression model. Statistical significance was set at a p value of less than .05 with an intercept included in the model. The analysis was repeated with the mean pathology score (severity score average between sides) as the independent variable in the linear regression model along with the previously noted covariates.

RESULTS
A total of 140 adult patients were initially eligible for study inclusion. Eight patients were excluded for incomplete pathology data, and an additional 17 patients were excluded because their CT scans demonstrated no evidence of ethmoid sinus inflammation, leaving 115 patients for analysis (80 female and 35 male) with a mean age of 40.2 years. Figure 1 dis-

| Table 1. Values for RSI Symptom Domains and Lund Score According to Maximum Pathology Severity Grade |
|-------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Variable    | 0               | 1               | 2               | 3               | 4               | Overall         |
| Nasal domain | 40.0            | 58.4            | 51.2            | 54.2            | 47.6            | 52.4            |
| Facial domain | 33.3            | 53.3            | 52.3            | 55.5            | 36.2            | 51.7            |
| Oropharyngeal domain | 8.3            | 32.5            | 32.3            | 29.7            | 25.4            | 30.7            |
| Systemic domain | 23.3            | 40.6            | 34.5            | 36.4            | 22.9            | 34.8            |
| Total symptoms | 25.0            | 43.8            | 41.8            | 42.4            | 32.8            | 41.3            |
| Total Lund score | 10.7            | 7.2             | 7.8             | 10.7            | 14.4            | 8.8             |

RSI — Rhinosinusitis Symptom Inventory (score of 100 represents maximal symptoms).
Fig 2. Distribution of A) nasal symptom domain scores, B) facial symptom domain scores, C) oropharyngeal symptom domain scores, D) systemic symptom domain scores, E) total symptom scores, and F) total Lund scores according to maximum pathology score.

plays the distribution of pathology severity scores for the cohort. The mean Lund score for the cohort was 8.8 (95% confidence interval, 7.9 to 9.7). Table 1 presents the RSI symptom domain scores according to the maximum pathology severity score. Figure 2 depicts the box plots for the distribution of RSI
symptom domains and total Lund score according to the pathology inflammation severity score.

Table 2 lists the results of the regression analysis for the relationship between pathology score and RSI symptom domain scores, as well as total Lund scores. The maximum pathology severity score failed to predict any of the RSI symptom domain scores; the statistical significance of all coefficients was greater than 0.372. Similarly, on repeat analysis with the mean pathology score (averaged between the left and right sides), once again the mean pathology score failed to predict any of the RSI symptom domain scores. The maximum pathology severity score did statistically significantly predict the total Lund score with the mean pathology score (averaged between the left and right sides), once again the mean pathology score was greater than 0.372. Similarly, on repeat analysis with the mean pathology score (averaged between the left and right sides), once again the mean pathology score failed to predict any of the RSI symptom domain scores. The maximum pathology severity score did statistically significantly predict the total Lund score with a significant regression coefficient (Table 1), as did the mean pathology score (p = .001). In order to test for the influence of time interval between the RSI survey and the date of surgery on the correlation analysis, the group was divided into “short” interval and “long” interval groups by the median time interval, and the statistical analysis was again performed. In neither the “short” nor the “long” interval groups did the pathology score correlate with the total symptom score (p = .685 and p = .144, respectively), suggesting a limited impact on the statistical analysis due to the time interval between RSI survey and histopathologic analysis.

**DISCUSSION**

Investigations into the correlation between patients’ self-reported symptom scores and objective measures in CRS have proven problematic. A substantial body of work has been elaborated concerning the lack of correlation between patients’ reported symptoms and findings on paranasal sinus CT scans. Several authors have found in large-scale studies that the paranasal sinus CT scan fails to correlate with or predict total symptoms and individual symptoms of CRS.2-7 Similarly, it has been difficult to predict the presence or absence of true CRS on the basis of symptom criteria alone.3,10 Thus, simple stratification of patients according to CT findings or CT stage fails to capture much of the variability in patients’ self-reported symptoms.

Part of this discordance could be due to the fact that the paranasal sinus CT scan demonstrates a similar appearance whether or not the radiographic abnormality is secretions, mucosal inflammation, or polyposis. Perhaps the degree of mucosal inflammation demonstrates better correlation with or influence on patients’ self-reported symptom scores than the radiographic score of the paranasal sinus CT scan. This idea offers some intuitive appeal, because certain symptoms of CRS, such as facial pain, headache, and discharge, may be more likely to correlate with the level of mucosal inflammation than with other objective measures. If, in fact, various degrees of mucosal inflammation did correlate with or predict reported sinonasal symptom scores, then histopathology might be another tool for disease stratification in CRS.

Unfortunately, as is intuitively evident from examination of the box plots of the reported RSI symptom domains according to pathology severity score, the study failed to identify any meaningful relationship between CRS symptoms and pathology severity score. This lack of correlation between pathology and symptom scores remains, whether we consider the mean pathology score averaged across the two nasal cavities or whether we consider the maximum pathology score (the greater of the inflammatory scores from the left and right sides). The maximum pathology score was chosen for study primarily because in certain cases, patients may have unilateral disease or disease that is much more prominent on one side, and their reported symptoms may more accurately reflect the inflammation they are perceiving unilaterally. In other words, it may not be the case that a patient with zero inflammation on the left and maximum inflammation on the right would necessarily report half the level of symptoms (if only averaged pathology scores were examined) as would a patient with pathology inflammation scores of 4 and 4, bilaterally. Nonetheless, neither the mean pathology score nor the maximum pathology severity score predicted the level of symptoms in CRS.

The current study examines only CRS without polyposis. This was done to avoid potential problems with regard to sampling error. In CRS with polyposis, at the time of surgery, polyp tissue may be sampled, as well as sinonasal mucosa. These 2 samples may in fact demonstrate differing levels of inflammation due to location within the nasal cavi-
ty, proximity to application of topical nasal steroids, and other factors. In the current study, only ethmoid mucosa was consistently sampled. Polzehl et al\textsuperscript{11} compared ethmoid mucosa between CRS patients with and without nasal polyps and found significant differences in the degrees of round cell infiltration, eosinophil infiltration, and plasma cell infiltration, highlighting such potential histopathologic differences. Therefore, only patients with non-polyp CRS were included in the current study for purposes of cohort homogeneity.

It is interesting that the 2 most objective measures of the level of disease severity in CRS, namely, the paranasal sinus CT scan score and the mucosal pathology severity score, did correlate well with one another. This held true whether the maximum pathology score or the mean pathology score was utilized. Thus, there is a relationship between volumetric measurement of disease and degree of mucosal inflammation. Few studies have examined the relationship between radiographic findings and histopathology and CRS. Cousin et al\textsuperscript{12} examined 60 patients with respect to the agreement between paranasal CT scan findings and histopathology and found that overall agreement between mild, moderate, and severe ratings for each was relatively poor. In contrast, Szucs et al\textsuperscript{13} found that Lund scores correlated significantly with the inflammatory cell counts in the sinonasal mucosa among 48 specimens. The current data are interesting, because some of the cardinal symptoms of CRS may be due to volumetric level of disease (for example, nasal obstruction and nasal congestion), whereas other symptoms of CRS may be more related to pure inflammation (for example, nasal discharge, fever, or cough), and still others may be a combination of both (for example, dysosmia). Understanding how inflammation leads to increased volumetric disease may provide substantial further insight into the actual pathogenesis of CRS.

A few limitations of the current study merit mention. First of all, there were relatively small numbers in the extreme pathology groups (pathology severity scores of 0 and 4), as might be expected. This limitation potentially prevents an analysis of extreme symptom severity scores. Second, although the pathology scores were determined with the investigator blinded to the CT scores and the symptom scores, only a single reviewer determined the pathological grade. However, our previous studies have shown good interrater and intrarater reliability for evaluation of histopathology in CRS.\textsuperscript{14} One potential confounder in the analysis of the data are the time intervals between the RSI evaluation, the CT scan, and the date of surgery. However, since the CT stage correlation with mucosal inflammation was positive and significant, it is likely that the inflammatory process due to CRS was still active and was likely stable during that interval. Furthermore, in the analysis comparing correlations according to median split time intervals, I did not find significant variation in the lack of correlation according to time. Finally, not only is CRS a complex disease with protein symptom manifestations, but patients present for evaluation and treatment with substantially varying degrees of prior medical management. I attempted to adjust for factors that would modify both symptoms and/or pathological findings by including total nasal steroid use, total non-sedating antihistamine use, and weeks of antibiotic use prior to surgery in the multivariate linear regression model. Despite their inclusion in the predictive models, pathology severity scores failed to predict symptom severity scores. It is possible that there are other confounders that I did not include in the models that may help establish a relationship between pathology severity and symptoms, such as allergy, tobacco use, or other factors. Historically, the rate of tobacco use in our patient population is extremely low, averaging less than 10\%, so I was unable to ascertain its influence on the data. The role of allergy in CRS has been controversial, and the correlation between symptom reporting and allergic findings specifically in CRS has been inconsistent.\textsuperscript{15,16} Nonetheless, the potential correlation between allergy and pathological findings may merit further investigation.

**CONCLUSIONS**

The degree of histopathologic inflammation does not correlate with or predict patients' self-reported symptom scores in CRS. There is a significant relationship between increasing degree of histopathologic inflammation and increasing radiographic involvement in CRS. Unfortunately, histopathologic inflammation does not account for a significant portion of the variability in patients' symptoms with CRS.

**REFERENCES**

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