

Inter-pathologist Agreement on Structured Histopathology Reporting in Chronic Rhinosinusitis

Annals of Otolaryngology, Rhinology & Laryngology
2021, Vol. 130(8) 899–903
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DOI: 10.1177/0003489420987970
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Abstract

Background: Structured histopathology reporting is increasingly being utilized in rhinology to characterize endotypes in chronic rhinosinusitis and guide management decisions after sinus surgery.

Objective: The goal of this investigation is to evaluate inter-observer agreement in structured histopathology reporting.

Methods: Two experienced head and neck pathologists independently compiled structured histopathology reports for tissue samples collected during functional endoscopic sinus surgery. Cohen's standard kappa (κ) coefficients were calculated for each histopathologic variable to assess inter-pathologist agreement.

Results: A total of 92 cases were analyzed. Substantial inter-pathologist agreement was reached on tissue eosinophil count ($\kappa=0.64$, $P<.001$), the presence of eosinophil aggregates ($\kappa=0.62$, $P<.001$), and the presence of fungal elements ($\kappa=0.74$, $P<.001$). There was moderate agreement on the degree of inflammation ($\kappa=0.56$, $P<.001$) and the presence of squamous metaplasia ($\kappa=0.46$, $P<.001$). There was fair agreement on the presence of neutrophil infiltrates ($\kappa=0.33$, $P<.001$), the presence of hyperplastic changes ($\kappa=0.40$, $P<.001$), and the presence of fibrosis ($\kappa=0.24$, $P=.022$). There was only slight agreement on the degree of subepithelial edema ($\kappa=0.20$, $P=.008$). The κ coefficients for basement membrane thickening and mucosal ulceration were not statistically significant.

Conclusion: High inter-pathologist agreement was demonstrated for several salient histopathologic variables, including tissue eosinophil count and the presence of eosinophil aggregates. However, refining the definitions of certain histopathologic variables may improve the reproducibility of structured histopathology reporting.

Keywords

chronic rhinosinusitis, structured histopathology, sinus surgery

Introduction

Chronic rhinosinusitis (CRS) is a heterogeneous disorder characterized by persistent sinonasal symptoms that last longer than 12 weeks with endoscopic or computed tomography (CT) evidence of sinonasal inflammation.¹ Classically, CRS has been classified into 2 subtypes: CRS with nasal polyps (CRSwNP) and CRS without nasal polyps (CRSsNP). However, this binary classification is insufficient to adequately explain CRS pathogenesis as it fails to account for patients with overlap between the 2 phenotypic categories.

In 2012, Snidvongs et al² proposed the use of structured histopathology reporting after functional endoscopic sinus surgery (FESS) to better elucidate mechanisms underlying CRS pathophysiology. Since then, numerous studies have demonstrated associations between structured histopathology and patient outcomes.³⁻⁷ In 2017, an analysis by Kuhar

et al⁸ showed that several markers of inflammation on structured histopathology correlated with higher Lund-McKay scores. In 2020, Tajudeen et al⁹ demonstrated that the presence of eosinophil aggregates on structured histopathology correlates with increased postoperative

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prednisone requirements. These findings reaffirm the utility of structured histopathology reporting in understanding CRS pathogenesis.¹⁰

Although structured histopathology reporting is being increasingly utilized, no study to date has investigated inter-pathologist agreement in reporting. In addition, no study has analyzed the current definitions of structured histopathology variables and identified areas where definitions can be further refined. Thus, the purpose of this study is to determine interobserver agreement for each variable included in the structured histopathology report in an effort to improve the reproducibility of reporting.

Materials and Methods

A retrospective review was conducted on patients who underwent surgical management of medically recalcitrant CRS at Rush University Medical Center (RUMC) between June 2014 and January 2019. Patients were included in the study cohort if they met the following criteria: age 18 or older, CRS diagnosis based on 12 weeks of continuous sinonasal symptoms, positive findings on CT scan and underwent FESS due to insufficient clinical improvement with appropriate medical management. Patients were excluded from the cohort if they were diagnosed with sinonasal malignancy or autoimmune disease. Patients undergoing revision surgery were included in the analysis; however, no 2 specimens included in the analysis were taken from the same patient. All procedures were performed at RUMC by 2 fellowship-trained rhinologists.

About 46 patients whose sinonasal tissue specimens were evaluated by a dedicated head and neck pathologist at RUMC and 46 patients whose specimens were evaluated by a second dedicated head and neck pathologist at RUMC were randomly selected from this patient cohort. Each set of cases was then submitted for secondary review by the pathologist who did not perform the original evaluation. To mitigate bias, second review of slides was completed independently by each pathologist. In addition, the pathologists were not involved in any part of the data analysis. The findings of the investigation were only discussed with the pathologists after subsequent statistical analyses were completed.

Analysis of tissue specimens obtained exclusively from the sinonasal tract was completed using structured histopathology reporting (Table 1). The 13 variables assessed by subspecialty pathologists included: tissue present (respiratory mucosa, mucoserous tissue, or bone), degree of inflammation (absent, mild, moderate/severe), neutrophilic infiltrate (absent, focal, diffuse), basement membrane thickening (absent, mild, moderate/severe), mucosal ulceration (absent or present), sub-epithelial edema (absent, mild [focal], moderate [perivascular or distortion of mucosal structure]/severe [diffuse, polypoid change]), hyperplastic

or papillary changes (absent or present), squamous metaplasia (absent or present), fungal elements (absent or present), fibrosis (absent, partial, extensive), Charcot-Leyden crystals (absent or present), eosinophil aggregates (absent or present), and number of eosinophils per high-power field (less than 5, between 5 and 10, greater than 10).

Cohen's standard kappa (κ) coefficients were then calculated for each histopathologic variable to assess inter-pathologist agreement. Cohen's κ coefficients were interpreted as follows: 0.81 to 1.00 represents almost perfect agreement, 0.61 to 0.80 represents substantial agreement, 0.41 to 0.60 represents moderate agreement, 0.21 to 0.40 represents fair agreement, 0 to 0.20 represents slight agreement, and less than 0 represents less than chance agreement. Statistical analysis was performed using SPSS Statistics software (IBM Corporation, Version 24, Armonk, NY). Significance was established as $P < .05$.

All patient identifiers were removed from the data prior to performing analysis. This study received prior approval from the Rush Institutional Review Board (IRB #14120806).

Results

A total of 92 cases were analyzed; the average age of the cohort was 50 years. CRSwNP was diagnosed in 85 (92.4%) of cases; the remaining patients were diagnosed with CRSsNP. Cohen's κ values and results of the secondary review structured histopathology analysis are summarized in Table 2. Substantial inter-pathologist agreement was reached on tissue eosinophil count ($\kappa=0.64$, $P < .001$), the presence of eosinophil aggregates ($\kappa=0.62$, $P < .001$), and the presence of fungal elements ($\kappa=0.74$, $P < .001$). There was moderate agreement on the degree of inflammation ($\kappa=0.56$, $P < .001$) and the presence of squamous metaplasia ($\kappa=0.46$, $P < .001$). There was fair agreement on the presence of neutrophil infiltrates ($\kappa=0.33$, $P < .001$), the presence of hyperplastic changes ($\kappa=0.40$, $P < .001$), and the presence of fibrosis ($\kappa=0.24$, $P = .022$). There was only slight agreement on the degree of subepithelial edema ($\kappa=0.20$, $P = .008$). The κ coefficients for mucosal ulceration ($\kappa=0.20$, $P = .052$) and basement membrane thickening ($\kappa=0.07$, $P = .362$) were not statistically significant.

Discussion

To our knowledge, this investigation is the first to date to assess inter-pathologist agreement in structured histopathology reporting. Our analysis demonstrated substantial agreement on the tissue eosinophil count, the presence of eosinophil aggregates, and the presence of fungal elements. A commonality of these variables is that all are objectively well-defined. Tissue eosinophil count is based on quantitative assessment of the number of eosinophils per high-power field. Eosinophil aggregates are defined as clusters

Table 1. Chronic Rhinosinusitis Structured Histopathology Report.

Histopathologic variables	
Tissue present	Respiratory mucosa Mucoserous glands Bone
Overall degree of inflammation	Absent Mild Moderate or severe
Neutrophilic infiltrate	Absent Focal Diffuse
Basement membrane thickening	Absent Mild Moderate or severe
Mucosal ulceration	Absent or present (with reactive changes)
Sub-epithelial edema	Absent Mild (focal or perivascular) Moderate (distortion of mucosal structure) or severe (diffuse/polypoid change)
Hyperplastic/papillary changes	Absent or present
Squamous metaplasia	Absent or present
Fungal elements	Absent or present
Fibrosis	Absent Partial Extensive
Charcot-Leyden crystals	Absent or present
Eosinophil aggregates	Absent or present
Eosinophil count per HPF	<5 Between 5 and 10 >10

Abbreviation: HPF, high-power field.

of greater than 20 eosinophils per high-power field that are generally prominent histologically. Finally, fungal elements are also distinct features that are readily recognized by pathologists. The finding of substantial agreement suggests that current definitions of these variables are sufficient to allow high inter-observer reliability. This finding is especially important given that recent literature on structured histopathology reporting has demonstrated important implications of tissue eosinophilia and eosinophil aggregates on CRS pathophysiology and patient outcomes.^{5,6,9,11,12}

Variables that demonstrated moderate or fair agreement include degree of inflammation, squamous metaplasia, hyperplastic changes, presence of Charcot-Leyden crystals, neutrophil infiltrate, and fibrosis. For many of these histologic features, the subjectivity in variable definitions adversely affects inter-pathologist agreement. For example, the degree of inflammation may be classified as absent, mild, moderate, or severe; however, there are no objective features based on which mild inflammation is distinguished from moderate inflammation. Diffuse neutrophilic infiltrates can be easily identified, but in cases with sparse infiltrates, pathologists must subjectively decide whether the

neutrophils are present in the tissue or extravasated from vessels. Similarly, the distinction between partial and extensive fibrosis is also based on an individual pathologist's subjective assessment. Thus, although these variables demonstrate moderate to fair agreement, further refinement of the definitions of categories for each variable may improve inter-observer reliability.

Variables demonstrating slight agreement or statistically non-significant agreement, namely basement membrane thickening, sub-epithelial edema, and mucosal ulceration, may require updated definitions to improve agreement. At our institution, evaluation of the degree of basement membrane thickening is based on subjective assessment by the pathologist. However, the initial investigation of structured histopathology profiling conducted by Snidvongs et al² categorized the degree of basement membrane thickening using a quantitative assessment of thickening. Incorporating these objective measurements into descriptions of the degree of basement membrane thickening may improve inter-observer agreement. On the other hand, each degree of sub-epithelial edema is accompanied by a histologic description; for example, mild sub-epithelial edema is

Table 2. Inter-Pathologist Agreement for Structured Histopathology Variables.

Variable	Number of cases (%)		Cohen's $\kappa \pm$ SE	P-value
	Pathologist 1	Pathologist 2		
Fungal elements			0.74 \pm 0.18	<0.001
Absent	87 (94.6)	89 (96.7)		
Present	5 (5.4)	3 (3.3)		
Total	92 (100)	92 (100)		
Eosinophil count per HPF			0.64 \pm 0.07	<.001
<5	25 (27.5)	30 (33.0)		
Between 5 and 10	11 (12.0)	8 (8.8)		
>10	56 (60.9)	53 (58.2)		
Eosinophil aggregates			0.62 \pm 0.08	<.001
Absent	58 (63.0)	71 (77.2)		
Present	34 (37.0)	21 (22.8)		
Degree of inflammation			0.56 \pm 0.10	<.001
Absent	0 (0)	0 (0)		
Mild	27 (29.3)	28 (30.4)		
Moderate or severe	65 (70.7)	64 (69.6)		
Squamous metaplasia			0.46 \pm 0.10	<.001
Absent	63 (68.5)	61 (66.3)		
Present	29 (31.5)	31 (33.7)		
Hyperplastic changes			0.40 \pm 0.15	<.001
Absent	79 (85.9)	86 (94.5)		
Present	13 (14.1)	5 (5.5)		
Charcot-Leyden crystals			0.38 \pm 0.18	<.001
Absent	86 (93.5)	84 (91.3)		
Present	6 (6.5)	8 (8.7)		
Neutrophil infiltrate			0.33 \pm 0.07	<.001
Absent	47 (51.1)	67 (73.6)		
Focal	25 (27.2)	20 (22.0)		
Diffuse	20 (21.7)	4 (4.4)		
Fibrosis			0.24 \pm 0.10	.022
Absent	47 (51.1)	54 (58.7)		
Partial	45 (48.9)	38 (41.3)		
Extensive	0 (0)	0 (0)		
Mucosal ulceration			0.20 \pm 0.16	.052
Absent	84 (91.3)	85 (92.4)		
Present (with reactive changes)	8 (8.7)	7 (7.6)		
Subepithelial edema			0.20 \pm 0.08	.008
Absent	26 (28.3)	23 (25.6)		
Mild	38 (41.3)	32 (35.6)		
Moderate or severe	28 (30.4)	35 (38.9)		
Basement membrane thickening			0.07 \pm 0.08	.362
Absent	22 (23.9)	20 (21.7)		
Mild	40 (43.5)	41 (44.6)		
Moderate or severe	30 (32.6)	29 (31.5)		

Abbreviation: HPF, high-power field; SE, standard error.

characterized by focal perivascular edema while moderate sub-epithelial edema is characterized by distortion of the mucosal architecture. One explanation for low agreement is that sub-epithelial edema may be present only focally

within tissue; as a result, the edema may not be properly visualized or may be misinterpreted as myxoid change.

There are several limitations of this study that warrant discussion. A known disadvantage of using Cohen's κ is

that the statistic may underestimate interobserver agreement when variables have low prevalence or when there is a significant imbalance of cases in variable categories.¹³ In our analysis, fungal elements, Charcot-Leyden crystals, and mucosal ulceration each were present in under 10% of cases; therefore, the κ values for these variables may be underestimated. In addition, our analysis demonstrated that agreement on mucosal ulceration was not statistically significant. When present in tissue, this finding is readily recognizable to pathologists. Thus, the lack of significance suggests that the study may have been underpowered to assess inter-pathologist agreement on this finding. Second, given that a “gold standard” does not exist in histopathology reporting, our study was only able to evaluate interobserver agreement and not accuracy of pathologist assessments. Finally, our study included very few patients diagnosed with CRSsNP; further investigation is necessary to assess inter-pathologist agreement among CRSwNP and CRSsNP subgroups. Future studies are also necessary to evaluate inter-pathologist agreement between institutions.

Conclusion

Overall, there is high inter-pathologist agreement for salient variables on structured histopathology, such as tissue eosinophil count and eosinophil aggregates. However, improved consensus on the definitions of other structured histopathology variables may improve interobserver reliability.

Authors' Note

These findings were accepted for virtual poster presentation on September 11 to 12, 2020 at the 66th American Rhinology Society Annual Meeting in Boston, MA, USA.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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