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ORIGINAL RESEARCH

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Inflammatory cell predominance and patterns in chronic rhinosinusitis with and without nasal polyposis patients

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Abstract

Objectives: There is interest in identifying chronic rhinosinusitis (CRS) endotypes that align pathophysiology with clinical observation and outcomes. CRS with polyps (CRSwNP) has classically been studied with reference to tissue eosinophilia, but the role of other cellular infiltrates remains uncharacterized. No particular tissue prognosticators have been described for CRS without nasal polyps (CRSsNP). Predominance of leukocytes seen in surgical tissue may be useful for differentiating CRS subtypes, severity of inflammation, and outcomes.

Methods: Structured histopathology reports were examined for 277 patients undergoing endoscopic sinus surgery for CRSwNP (n = 115), CRSsNP (n = 141), and recurrent acute rhinosinusitis (RARS, n = 21). Inflammatory predominance was examined for associations with nasal polyposis, asthma, allergic rhinitis, aspirin exacerbated respiratory disease (AERD), immune deficiency, preoperative Lund-Mackay score, and outcome (SNOT-22 score change).

Results: In order of frequency, the prevalence of predominant inflammatory patterns accounting for 93.5% of CRS patients were: lymphoplasmocytic (n = 111), lymphocytic (n = 74), eosinophilic (n = 50), and lymphoplasmocytic with eosinophilic (n = 24). Eosinophilic predominance was 97.4% specific for nasal polyps (95% confidence interval [CI], 93.4%-99.3%), although sensitivity was 43.4% (95% CI, 33.8%-53.4%). The absence of eosinophilic predominance was 100% sensitive for RARS (95% CI, 82.4%-100%), however specificity was 30.8% (95% CI 25.1%-37.1%). There were no significant differences in preoperative SNOT-22 scores or change postoperatively.

Conclusions: Eosinophilic inflammatory predominance was predictive for nasal polyps and against RARS. Nevertheless, the majority of CRSwNP patients had a different inflammatory predominance, demonstrating heterogeneity in CRS, even among patients with nasal polyps. Symptomatic outcomes were not associated with inflammatory predominance through 12 months follow up.

Level of Evidence: 4.

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KEYWORDS
chronic rhinosinusitis, histopathology, inflammation, nasal polyps, recurrent acute rhinosinusitis

1 | INTRODUCTION

Chronic rhinosinusitis (CRS) is typically classified into CRS with nasal polyps (CRSwNP) or CRS without nasal polyps (CRSsNP).[1] CRS phenotypes, while feasible to apply in the clinic, likely oversimplify the heterogeneous molecular, cellular, and inflammatory mechanisms that underlie CRS. Endotyping has been described to categorize CRS according to pathophysiological mechanisms.[2] Cluster analysis of inflammatory markers has identified CRS endotypes, which overlap with phenotypic descriptions, but that also describe the common inflammatory mechanisms for each endotype.[3,4] This approach to characterizing CRS may be helpful in personalizing patient treatment plans.[2]

Structured histopathology reporting has also been introduced for identifying histologic features that may differentiate CRS subtypes.[5] These reports can be generated from histopathologic analysis of surgical specimens, and routinely applied to clinical practice in patients having endoscopic sinus surgery (ESS). Some of the histologic parameters tracked in these reports have been used to differentiate CRS phenotypes,[6] in addition to CRS associated with odontogenic infection, immunosuppressive therapy, and prior radiation treatment.[7-9] Gender differences have also been described according to histopathologic features.[10] Structured histopathology reports, when routinely applied to the examination of surgical specimens in CRS, may be useful in clarifying the diagnosis and identifying prognostic markers. This may also guide treatment which is targeted to the patient's histopathologic features.

Inflammatory predominance, a component of structured histopathologic reporting, has not been fully investigated in previous studies differentiating CRS subtypes by histologic parameters.[7-9] Neutrophil infiltrate, which is also a component of structured histopathology, has not been shown to be different according to CRS subtypes or gender.[7-10] Inflammatory cell infiltrate may be a useful marker for differentiating CRS phenotypes, disease severity, and outcomes. The present study aimed to examine an association of inflammatory cell predominance, including neutrophil infiltrate, with CRS phenotype, related comorbidities, and disease severity. The relationship of these histologic features with patient reported outcomes was also investigated.

2 | PATIENTS AND METHODS

Patients undergoing ESS for the treatment of CRSwNP and CRSsNP in the senior author's (DL) practice between July 1, 2011, and December 31, 2016 were considered for study inclusion. Diagnosis of CRS was made in accordance with the American Academy of Otolaryngology clinical practice guideline on adult sinusitis,[11] and all patients had a sinus computed tomography (CT) scan prior to surgery. Patients having ESS for recurrent acute rhinosinusitis (RARS) were also considered for study inclusion. The diagnostic criteria for RARS included four or more episodes of acute bacterial rhinosinusitis in 1 year, resolution of symptoms between episodes, and objective confirmation of an episode of acute sinusitis by CT or nasal endoscopy.[11] Exclusion criteria were incomplete structured histopathology reports from surgery and age less than 18 years. Patients did not routinely receive antibiotics or oral steroids in the immediate preoperative period, although patients were treated with appropriate medical therapy[12] prior to decision for surgery. Appropriate medical therapy was defined as twice daily topical nasal steroid, nasal saline irrigations, and oral steroid (30 mg prednisone taper over 12 days). Culture directed antibiotics were prescribed prior to the decision for surgery when applicable. All patients were maintained on topical nasal steroids and nasal saline irrigations prior to surgery. Patients prescribed oral steroid at the time of surgery was obtained from the medical record. For patients with RARS, surgery was generally not during an episode of acute sinusitis. Patients were prescribed maintenance therapy of twice daily topical nasal steroids and saline irrigations in the first postoperative week.

Structured histopathology reports were completed by the reviewing pathologist from sinonasal contents collected during surgery. Specimens primarily represent ethmoidal tissue and mucin, and do not include tissue outside of the paranasal sinuses. For all patients tissue was fixed in formalin, and histopathological analysis of hematoxylin and eosin stained slides was performed. These reports were reviewed for the reported inflammatory predominance and the presence of neutrophil infiltrates. Inflammatory predominance was reported as lymphocytic, lymphoplasmacytic, eosinophilic, lymphohistiocytic, neutrophilic, or other.[5] In some instances the inflammatory predominance was reported as two of the possible categories. Neutrophil infiltrates were reported as either absent or present.

The medical record was retrospectively reviewed for the primary diagnosis prior to ESS, and assigned as CRSwNP, CRSsNP, or RARS. Comorbid diagnoses including asthma, allergic rhinitis, aspirin exacerbated respiratory disease (AERD), and immune deficiency were also recorded. Preoperative SNOT-22 and Lund-Mackay (LM) scores were also determined from the medical record. SNOT-22 scores at 6 and 12 months follow up were included when available, and change relative to the preoperative SNOT-22 score was calculated.

For continuous variables, two-sample independent t-tests were used to compare two groups, while one-way analysis of variance (ANOVA) was used to compare three or more groups. Post-hoc testing was performed for significant ANOVA comparisons using Tukey honestly significant difference (HSD). Chi-square test was used to compare categorical variables, except when frequency counts were <5, in which case Fischer exact test was used. Sensitivity and specificity analysis was performed to describe the predictive value of inflammatory predominance for selected clinical conditions. Statistical analysis was performed using JMP Pro, version 14.1.0 (SAS Institute Inc., Cary, North Carolina), and *P*-values less

than .05 were considered significant. The study was approved by the institutional review board of the Mayo Clinic, Phoenix, Arizona.

3 | RESULTS

A total of 277 patients met inclusion and exclusion criteria. The primary diagnosis prior to ESS was either CRSsNP (n = 141, 50.9%), CRSwNP (n = 115, 41.5%), or RARS (n = 21, 7.6%). Neutrophil infiltrates were present in 87 (31.4%) patients, and absent in 190 (68.6%) patients. Inflammatory predominance was reported as lymphocytic (n = 74), lymphoplasmacytic (n = 111), eosinophilic (n = 50), or lymphoplasmacytic and eosinophilic concurrently (n = 24) in 259 of 277 cases (93.5%). The remaining 18 cases were categorized as lymphohistiocytic (n = 1), neutrophilic (n = 3), other (n = 4), lymphocytic and lymphoplasmocytic (n = 2), lymphocytic and eosinophilic (n = 5), lymphocytic and neutrophilic (n = 1), lymphoplasmacytic and neutrophilic (n = 1), and eosinophilic and other (n = 1). These remaining 18 cases were excluded from further statistical analysis due to the low number of patients in each category.

Patient age was statistically different by inflammatory predominance (P = .014, Table 1), although post-hoc analysis using Tukey HSD did not reveal any difference between the individual groups. There were no differences in sex according to inflammatory predominance (P = .428, Table 1). There no significant differences in patient age (P = .764) or sex (P = .320) according to neutrophilic infiltrate (Table 1). A total of 37 (13.4%) patients had been prescribed oral steroid at the time of surgery, and this was more common among the patients with eosinophilic or lymphoplasmacytic and eosinophilic inflammatory predominance (P = .004). There was no statistical difference in the number of patients prescribed oral steroid at the time of surgery according to neutrophil infiltrate (P = .813, Table 1). The average prescribed dose at the time of surgery was 16.4 mg of prednisone.

Preoperative SNOT-22 scores were not associated with inflammatory predominance (n = 259, P = .310), although eosinophilic predominance was associated with higher CT scores preoperatively (P < .001, Table 2). Eosinophilic predominance was also associated with nasal polyps (P = <.001), asthma (P = .049), and AERD (P < .001, Table 2). Inflammatory predominance was not associated with comorbid allergic rhinitis (P = .927) or suspected immune deficiency (P = .142). RARS

TABLE 1 Demographic characteristics of study population by inflammatory predominance and neutrophil infiltrate

	Age in years (95% CI)	Male	Female	Oral steroid at time of surgery
Inflammatory predominance				
Lymphocytic (n = 74)	51.6 (48.2, 55.0)	37 (50.0%)	37 (50.0%)	6 (8.1%)
Lymphoplasmacytic (n = 111)	56.8 (54.0, 59.6)	54 (48.6%)	57 (51.4%)	10 (9.0%)
Eosinophilic (n = 50)	49.2 (45.0, 53.4)	25 (50.0%)	25 (50.0%)	12 (24.0%)
Lymphoplasmacytic + Eosinophilic (n = 24)	51.5 (44.5, 58.5)	8 (33.3%)	17 (66.7%)	7 (29.2%)
P-value	.014	.428	—	.004
Neutrophil infiltrate				
Absent (n = 190)	53.5 (51.4, 55.6)	93 (48.9%)	97 (51.1%)	26 (13.7%)
Present (n = 87)	52.8 (49, 56.6)	37 (42.5%)	50 (57.5%)	11 (12.6%)
P-value	.764	.320	—	.813

Abbreviation: CI, confidence interval.

TABLE 2 Clinical features according to inflammatory predominance

Clinical Feature	Lymphocytic	Lymphoplasmacytic	Eosinophilic	Lymphoplasmacytic + Eosinophilic	*P*-value
Nasal Polyps	14 (18.9%)	33 (29.7%)	46 (92%)	13 (54.2%)	<.001
RARS	10 (13.5%)	9 (8.1%)	0 (0%)	0 (0%)	.018
Asthma	31 (41.9%)	47 (42.3%)	32 (64%)	13 (54.2%)	.049
Allergic Rhinitis	16 (21.6%)	20 (18%)	9 (18%)	5 (20.8%)	.927
AERD	7 (9.5%)	8 (7.2%)	18 (36%)	4 (16.7%)	<.001
Suspected IMD	12 (16.2%)	14 (12.6%)	4 (8%)	0 (0%)	.142
Preoperative SNOT-22	43.5 (38.4, 48.6)	41.0 (37.1, 44.9)	47.5 (42.6, 52.4)	45.4 (35.4, 55.4)	.310
Preoperative LM Score	9.7 (8.5, 10.9)	10.2 (9.1, 11.3)	15.0 (13.9, 16.1)	10.6 (9.1, 12.1)	<.001
6 Month SNOT-22 Change	27.1 (20.1, 34.1)	24.1 (20.2, 28)	30.0 (24.2, 35.8)	20.6 (8.8, 32.4)	.339
12 Month SNOT-22 Change	23.2 (15.5, 30.9)	15.8 (10.6, 21.0)	27.2 (19.2, 35.2)	27.6 (14.4, 40.8)	.076

Note: Values are counts with percentage, or mean with 95% confidence interval.
Abbreviations: AERD, aspirin exacerbated respiratory disease; IMD, immune deficiency; LM, Lund-Mackay; RARS, recurrent acute rhinosinusitis.

TABLE 3 Clinical features according to neutrophil infiltrate

Clinical feature	Neutrophil infiltrate absent	Neutrophil infiltrate present	*P*-value
Nasal Polyps	77 (40.5%)	38 (43.7%)	.621
RARS	15 (7.9%)	6 (6.9%)	.771
Asthma	92 (48.4%)	38 (43.7%)	.463
Allergic Rhinitis	33 (17.3%)	20 (23.0%)	.27
AERD	22 (11.6%)	16 (18.4%)	.126
Suspected IMD	23 (12.1%)	10 (11.5%)	.884
Preoperative SNOT-22	43.6 (40.6, 46.6)	44.0 (39.2, 48.8)	.889
Preoperative LM Score	10.6 (9.8, 11.4)	11.6 (10.3, 12.9)	.166
6 Month SNOT-22 Change	26.9 (23.4, 30.4)	23.5 (18.4, 28.6)	.273
12 Month SNOT-22 Change	21.3 (16.8, 25.8)	21.3 (14.9, 27.7)	1

Note: Values are counts with percentage, or mean with 95% confidence interval.
Abbreviations: AERD, aspirin exacerbated respiratory disease; IMD, immune deficiency; LM, Lund-Mackay; RARS, recurrent acute rhinosinusitis.

was associated with lymphocytic or lymphoplasmacytic inflammatory predominance (P = .018, Table 2). Eosinophilic inflammatory predominance was specific (97.4%; 95% confidence interval [CI], 93.4%-99.3%), although not sensitive (43.4%; 95% CI, 33.8%-53.4%) for nasal polyps. A majority of CRSwNP patients had an inflammatory predominance other than eosinophilic (60%). Finally, the absence of eosinophilic inflammatory predominance was sensitive (100%; 95% CI, 82.4%-100%), although not specific (30.8%; 95% CI 25.1%-37.1%) for RARS. Postoperative SNOT-22 score change was not statistically significant according to inflammatory predominance at 6 months (n = 160, P = .339) or 12 months follow up (n = 115, P = .076).

Neutrophil infiltrate was not associated with differences in preoperative SNOT-22 (n = 277, P = .889), or LM score (P = .166, Table 3). There were also no differences in the presence of neutrophil infiltrate according to the primary diagnosis of CRSsNP, CRSwNP, or RARS. None of the investigated comorbidities was associated with the presence of neutrophil infiltrate. Postoperative SNOT-22 score change was not statistically significant according to neutrophil infiltrate at 6 months (n = 175, P = .273) or 12 months follow up (n = 129, P = 1).

4 | DISCUSSION

CRS is often divided into phenotypic subgroups of patients with and without nasal polyps, and this classification has been used in multiple guidelines and consensus statements on the diagnosis and management of CRS.[11-13] CRSwNP is typically associated with T_H2 cell and eosinophil predominance, while CRSsNP has been associated with T_H1 cell predominance.[14,15] Description of CRS endotypes has demonstrated correlations with clinical phenotypes, but that distinct and multidimensional inflammatory patterns exist.[3,4] Structured histopathologic reporting has been suggested as means for recognizing histologic features which may have implications for diagnosis and prognosis of CRS.[5] This approach was first described for the identification of eosinophilic CRS,[5] and subsequently histologic differences have been described between CRSsNP, CRSwNP, and additional subtypes.[6-10] Inflammatory predominance, a component of the structured histopathology report, has not been completely defined for its association with CRS subtypes, comorbidities, disease severity, and outcomes.

Eosinophilic inflammatory predominance was associated with several clinical factors. Comorbid asthma and AERD were more common in patients with eosinophilic predominance, and this is consistent with previous reports.[16,17] Radiographic disease burden was higher in patients with eosinophilic predominance, although patient reported preoperative SNOT-22 scores were not statistically different. Eosinophilic predominance was specific for nasal polyps, while the absence of eosinophilic inflammatory predominance was sensitive for RARS. Collectively, this may have diagnostic and prognostic utility for the clinician in interpreting surgical specimens. These results are also consistent with and further support the findings by Snidvongs et al which described the identification of eosinophilic CRS through structured histopathology reports and that advocated for the routine use of these reports.[5]

Despite the association of eosinophilic inflammatory predominance with several clinical factors, the heterogeneity of CRS phenotypes was also apparent. The majority of CRSwNP patients (60%) had an inflammatory predominance other than eosinophilic. Therefore, CRSwNP is not exclusively due to eosinophilic inflammation, and this is consistent with recent to work to describe CRS endotypes.[3,4] Differentiation of CRSwNP and CRSsNP according to other structured histopathologic parameters has also failed to reveal a consistently predictive feature.[6] These factors contribute to the low sensitivity of eosinophilic predominance for CRSwNP. The presence of neutrophil infiltrate was not associated with the primary diagnoses, comorbidities, or preoperative disease severity, and is also suggestive of heterogeneity of CRS phenotypes.

SNOT-22 score change was not significantly different at 6 or 12 months follow up according to either inflammatory predominance or neutrophil infiltrate. The utility of inflammatory predominance or neutrophil infiltrate in predicting patient reported outcomes is therefore unclear among a general population of patients with CRS. This may reflect the heterogeneity and complexity of inflammatory mechanisms underlying CRS that cannot be captured by leukocyte predominance alone. Nevertheless, correlation of histologic features with CRS subtypes,[6-10] may be useful for directing postsurgical treatment in accordance with inflammatory mechanisms and deserves further study.

Lymphocytic and lymphoplasmacytic inflammatory predominance represent a majority of CRS and RARS patients. Furthermore, lymphoplasmacytic inflammation represents the plurality of CRS patients. This study and previous studies,[5,16,17] however, have more often linked eosinophilic inflammation with comorbid conditions and prognostic value. SNOT-22 score is not significantly different according to inflammatory predominance at 6 or 12 month follow up. Therefore, future study devoted to patients with lymphocytic and lymphoplasmacytic predominance might identify pathophysiological mechanisms or other comorbid conditions specific to these groups.

This in turn may have prognostic value and utility in guiding targeted therapies for these patients. Specifically, RARS is associated with lymphocytic and lymphoplasmacytic inflammation, and the absence of eosinophilic inflammation is sensitive for this condition. 10% of patients in this study with lymphocytic or lymphoplasmacytic inflammation had a diagnosis of RARS, and may represent a subgroup of patients with this inflammatory finding in surgical specimens.

There are limitations noted with the current study, and include difficulty interpreting patient reported outcomes. While the reported inflammatory predominance or presence of neutrophil infiltrate did guide treatment following surgery, specifics could not be ascertained due to the retrospective study design. Another potential limiting factor is that preoperative medical therapy was not used in a standardized fashion. Oral steroid had been prescribed at time of surgery in a limited number of patients, and this was more common in patients with eosinophilic or lymphoplasmacytic and eosinophilic inflammatory predominance. These patients were also more likely to have nasal polyps, AERD, and asthma, which may account for the increased use of oral steroid in these patients. Details on dosage and compliance with use of nasal corticosteroids or antibiotics were not prospectively collected and are difficult to reliably ascertain from the medical record. Last, not all categories of inflammatory predominance were represented with sufficient sample sizes for meaningful statistical analysis. This makes understanding the clinical relevance of lymphohistiocytic and neutrophilic predominance difficult, and further study of the prevalence of these categories would help understand whether these should be included in structured histopathologic reporting.

5 | CONCLUSION

Eosinophilic inflammatory predominance was specific for CRSwNP, and associated with comorbid asthma and AERD. Sensitivity, however, was low and the majority of CRSwNP patients had an inflammatory predominance other than eosinophilic. The absence of eosinophilic predominance was sensitive for RARS. Overall, heterogeneity of inflammatory predominance and neutrophil infiltrate among patients with CRS, and a subgroup with nasal polyps, was apparent. Patient reported outcomes were not associated with inflammatory predominance or neutrophil infiltrate, although targeted therapies according to histopathologic features may be useful and deserve further study. Additional study of patients with lymphocytic or lymphoplasmacytic predominance, who represent the majority of cases, may also identify additional prognostic factors and therapeutic targets.

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CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

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