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Defining the allergic endotype of chronic rhinosinusitis by structured histopathology and clinical variables

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Abbreviations:

Chronic rhinosinusitis (CRS), atopic CRS (aCRS), non-atopic CRS (non-aCRS), eosinophilic CRS (eCRS), non-eosinophilic CRS (non-eCRS), CRS with nasal polyps (CRSwNP), CRS without nasal polyps (CRSSNP), nasal polyps (NP), functional endoscopic sinus surgery (FESS), sinonasal outcome test (SNOT-22), Lund-Kennedy (LK), aspirin exacerbated respiratory disease (AERD), allergic rhinitis (AR), T-helper cell (Th₂), computed tomography (CT), Rush University Medical Center (RUMC), high power field (HPF), kiloUnits/liter (kU/L)

Abstract

Background: Atopy has a strong association with chronic rhinosinusitis (CRS).

Objective: To understand whether patients with atopy and CRS can be defined by markers of tissue histopathology, systemic biomarkers, and clinical factors, that may guide their response to new pharmacologic agents.

Methods: In a retrospective cohort of CRS patients who underwent functional endoscopic sinus surgery (FESS), a structured histopathology report consisting of 12 variables, comorbid conditions, preoperative total serum IgE levels, and preoperative modified Lund-Kennedy (LK) endoscopic and Sinonasal outcome test (SNOT-22) scores were compared between aCRS and non-aCRS control patients in a multivariable model.

Results: 380 CRS patients were enrolled. 286 had comorbid atopy (aCRS). Compared to non-aCRS, aCRS patients had significantly higher preoperative total SNOT-22 scores (40.45 ± 22.68 vs. 29.70 ± 20.68 , $P=0.015$) and symptom-specific SNOT-22 scores in all domains except psychological dysfunction. Relative to non-aCRS, aCRS patients had: increased tissue eosinophilia ($P<0.0001$), eosinophil aggregates ($P<0.0001$), Charcot Leyden crystals ($P<0.04$), fibrosis ($P<0.02$), total serum IgE levels ($P<0.04$), polypoid disease ($P<0.001$), and a prevalence of comorbid asthma ($P<0.0001$) and Aspirin Exacerbated Respiratory Disease (AERD) ($P<0.003$). Patients with aCRS demonstrated increased tissue eosinophilia compared to non-aCRS patients even after controlling for polypoid disease, asthma, and AERD.

Conclusion: In the context of CRS, atopy appears to be a specific predictor of CRS severity linked to specific histopathological variables, including enhanced eosinophilic aggregates. Moving forward, allergic status, may be a useful way to identify an atopic endotype of CRS patients. Furthermore, following surgery, patients are often maintained on intranasal corticosteroids. In patients whose disease is unresponsive to steroids, we may look to atopic status to identify another management therapy. Atopic CRS patients, irrespective of polyp and asthmatic status, could be optimal candidates for biologic agents such as Th₂, eosinophil, and/or IgE-targeted therapies.

Highlight Box

1. What is already known about this topic?

An association exists between chronic rhinosinusitis (CRS) and atopy. However past studies have evaluated this link with conflicting results which could have been due to small sample sizes or not capturing and analyzing confounding factors.

2. What does this article add to our knowledge?

This study investigates the associations between atopy and several clinical and histopathologic variables in CRS in a comprehensive way using a statistical model. Our results demonstrate that atopy in CRS is significantly linked to certain sinus tissue pathologic features, and is associated with higher disease burden, patient-reported symptoms and poorer quality of life.

3. How does this study impact current management guidelines?

Linking atopy and established metrics of CRS disease, including tissue eosinophilia and SNOT-22 and modified LM scores, independent of nasal polyp and asthma diagnosis, positions allergic status as a clinical feature that can help identify CRS patients who may benefit from differential treatments.

Introduction

Chronic rhinosinusitis (CRS) is a heterogeneous inflammatory disorder of the sinonasal mucosa.(1) Clinical management of CRS relies on classifying each case as belonging to a phenotype and endotype that correlate with clinical characteristics and underlying pathophysiological mechanisms, respectively.(2) Classically, patients with CRS have been placed in one of two phenotypic camps based on the presence (CRSwNP) or absence (CRSsNP) of nasal polyps.(3) In terms of endotypic characterization, CRSsNP is thought to result from a predominately neutrophilic inflammatory response, with increased mononuclear cell infiltration, goblet cell hyperplasia, and fibrosis.(4) CRSwNP has been linked to innate lymphoid cell (ILC) and T-helper cell (Th₂) inflammation, featuring eosinophilic infiltration, edematous stroma, albumin deposition, and pseudocyst formation.(4)

The staying power of CRS delineation based on nasal polyps is rooted in its correlation with clinical presentation, which has subsequently shaped management. On average, CRSwNP patients demonstrate more extensive sinus disease assessed by endoscopy and computed tomography (CT) imaging than CRSsNP patients.(5-7) Subjectively, CRSwNP patients more commonly report symptoms of severe sinonasal disease.(8) Moreover, CRSwNP patients are more likely than CRSsNP patients to require revision functional endoscopic sinus surgery (FESS).(9, 10) However, newer data suggest this categorization alone is insufficient. While CRSwNP has historically been considered the eosinophil-predominant CRS phenotype, a portion of CRSwNP cases do not display eosinophilic infiltration.(11, 12) Additionally, eosinophilic inflammation has been identified in the hyperplastic tissue of patients without NPs.(13-17) Accordingly, it has been suggested that the presence or absence of NPs should not be used as the

only disease differentiator guiding treatment, as this tissue finding is not a reliable indicator of underlying histopathology.(18)

Though the presence or absence of NPs has historically driven decisions about disease management, tissue eosinophilia has recently been posited as a more appropriate marker of CRS disease severity. Bassiouni et al. found that tissue eosinophilia was associated with postoperative refractory disease independent of polyploid status.(19) Kuhar et al. demonstrated that the presence of eosinophilic aggregates on histopathology was associated with higher preoperative Lund-Kennedy (LK) endoscopic scores.(20) It should be noted that certain studies have challenged the idea of decreasing eosinophilic burden as a treatment for CRS. Laidlaw and colleagues found that, in a population of CRSwNP patients, reduction of tissue and blood eosinophilia using dexamipexole treatment, did not correlated with a decrease in NP burden or improvement in CT evidence of sinonasal disease or sinonasal outcome test (SNOT-22) scores.(21) This analysis is limited by the quantity and quality of the study population (i.e. small sample size [n=13] of CRSwNP patients only). Therefore, although tissue eosinophilia alone may not fully explain CRS pathophysiology, there is an abundance of compelling evidence that this cytologic finding may influence polyploid as well as nonpolyploid CRS disease severity. Based on the growing body of literature correlating eosinophilic inflammation with disease pathogenesis, additional studies have proposed endotyping CRS into eosinophilic CRS (eCRS) and non-eosinophilic CRS (non-eCRS).(22-24)

A barrier to physician evaluation of histopathologic disease burden and determination of whether patient presentation is consistent with eCRS is that these assessments rely on analysis of tissue specimens collected during surgery. Given the evidence that tissue eosinophilia may have a significant impact on CRS pathogenesis and medical management of disease, there is a need

for clinical tools that can more readily aid in making these assessments. One tool for assessing the likelihood of tissue eosinophilia preoperatively is atopic status. Atopic diseases, specifically asthma and allergic rhinitis (AR), have a strong association with CRS.(25) A recent comprehensive study showed that more than two-thirds of CRS patients demonstrate atopy.(26) The relationship between CRS and asthma has been extensively explored – with more severe CRS disease identified in patients with this comorbidity – and is not the focus of the present study.(27-31) The interplay between AR and CRS is less well-defined, with several studies noting a difference in CRS disease severity based on LK scores between atopic and non-aCRS patients,(5, 32, 33) and others reporting no significant difference in CRS severity between these patient groups.(34, 35) Discrepancies in findings are likely in part due to the inaccuracy of Lund-Mackay (LM) CT scoring in measuring the extent of sinus disease. Regardless, these analyses indicate an ambiguous association between CRS and atopy, meriting further investigation to better characterize the relationship between allergic sensitization to inhalant allergens and histopathology of CRS.

In this study we investigate the interplay between atopy and CRS, with a specific focus on the differences in clinical variables, total serum IgE, and several histopathologic biomarkers of disease between CRS patients with and without atopy. Through this work, we seek to further define an atopic endotype of CRS disease. These findings may refine preoperative targeted disease management, ultimately optimizing patient outcomes.

Materials and Methods

Inclusion criteria were adult patients (>18 years old) with a formal diagnosis of CRS and who required FESS for medically recalcitrant disease at Rush University Medical Center (RUMC) between June 2015 and December 2019. CRS diagnosis was based on at least 12 weeks of continuous sinonasal symptoms, endoscopic findings positive for sinusitis, and sinus CT scan consistent with clinical guidelines.(36) In accordance with the most recent clinical guidelines, diagnosis of atopy was based on clinical symptomatology in addition to positive skin prick test sensitization to aeroallergens, including tree, grass, ragweed, mold, dustmite, animal (cat/dog), and cockroach.(37) Each case was reviewed and formally diagnosed by a fellowship-trained, board-certified allergist-immunologist. A positive prick test indicated that the patient had IgE antibodies specific for the allergen being tested on the skin's mast cells. In a subset (n=105) of atopic (n=93) and nonatopic (n=12) CRS patients, total serum IgE levels were available. A value >200kiloUnits/liter (kU/L) was considered elevated, a cutoff value determined by the RUMC laboratory and based on manufacturing-recommended normal intervals (2-200 kU/L) for a healthy adult. This level is very close to 2-214 kU/L normal interval levels reported in a recent article.(38) The study protocol was submitted to and approved by RUMC's Institutional Review Board.

Two independent head and neck pathologists analyzed the sinus tissue extracted during FESS. Their analysis consists of 12 histopathology variables (**Table 1**), including type of tissue (respiratory mucosa, mucoserous glands, bone), degree of inflammation (none to mild or moderate to severe), number of eosinophils per high power field (HPF) (<10/HPF or 10+/HPF), neutrophil infiltrate (absent or present), inflammatory predominance (lymphocytic or non-lymphocytic), basement membrane thickening (absent or present), sub-epithelial edema (absent

or present), hyperplastic/papillary changes (absent or present), mucosal ulceration (absent or present), squamous metaplasia (absent or present), fibrosis (absent or present), Charcot-Leyden crystals (absent or present), and eosinophil aggregates (absent or present). Based on the latest criteria for eosinophilic CRS, tissue eosinophilia and eosinophilic aggregates were defined as one or more groups of >10 eosinophils/HPF and >20 eosinophils/HPF within the lamina propria of the sinonasal mucosa, respectively.(24, 39)

A thorough chart review was performed to collect pertinent clinical information including patient demographic data, comorbid conditions, current medications, and pre-operative modified LK.(40) These data can be found in **Table 2**. All patients, regardless of atopy status, used intranasal steroids. 24 patients were on immunotherapy, 34 were on a biologic, and 22 were on low-dose chronic oral corticosteroids. Diagnoses of asthma and Aspirin Exacerbated Respiratory Disease (AERD) were obtained from manual review of the medical record and confirmed by fellowship-trained allergist-immunologist at RUMC based on clinical guidelines.(41) Specifically, to obtain a diagnosis of AERD, patients required documented evidence of respiratory symptoms associated with exposure to a COX-1 inhibitor detailed in a medical record note from allergy-immunology or otorhinolaryngology clinics. All patients completed the SNOT-22 preoperatively. Total and domain SNOT-22 scores were calculated. SNOT-22 domains include three sinus-specific symptoms domain (Rhinologic, Extra-nasal rhinologic, Ear/facial symptoms), and two general health-related quality of life domains (Psychological and Sleep dysfunction). The Rhinologic symptom domain assesses: need to blow nose, nasal blockage, sneezing, and runny nose. The Extra-nasal rhinologic symptom domain assesses: cough, post-nasal discharge, and thick nasal discharge. The Ear/facial domain symptom assesses: ear fullness, dizziness, ear pain, and facial pain/pressure. The Psychological dysfunction domain

assess: fatigue, reduced productivity, reduced concentration, frustrated/restless/irritable, sad, and embarrassed. The sleep dysfunction domain assessed: decreased sense of smell/taste, difficulty failing asleep, nighttime awakening, lack of a good night's sleep, and waking up tired.

Regarding statistical analysis, a student's t-test (two-tailed) was used to compare parametric data. A one-way ANOVA test was used to compare means between more than two independent groups. A chi-square test was used to compare nonparametric qualitative variables. Linear and logistic regression analyses were used to adjust the comparisons for relevant factors when appropriate. All statistical analyses were performed using SPSS, version 26.0.0.0 (IBM SPSS Statistics for Macintosh, Version 26.0. Armonk, NY). A P-value of 0.05 or less was considered significant for all statistical analyses. When presenting data, any number following "±" represents one standard deviation.

Results

380 CRS patients who underwent FESS were included in this study. 75.3% (286/380) of this CRS cohort exhibited atopy, as determined by sensitization to at least one aeroallergen by percutaneous testing. Within the aCRS cohort, 76.2% of patients demonstrated poly-sensitization and 23.8% demonstrated mono-sensitization to tested allergens. The aCRS cohort was 43.7% female and 56.3% male, while the non-aCRS cohort was 53.2% male and 46.8% female ($P=0.087$). There were no differences in medication usage (i.e. oral corticosteroids, immunotherapy, and biologics) at the time of surgery between aCRS and non-aCRS groups. On average, aCRS patients were significantly younger than non-aCRS patients (49.4 ± 15.6 years vs. 56.4 ± 17.1 years, $P < 0.0001$). The majority (60.8% of aCRS and 60.7% of non-aCRS) of patients identified as Caucasian race, followed by 18.5% and 16.0% Black, 9.2% and 14.9% Latino, 3.8%

and 4.3% Asian, and 7.7% and 4.3% Other, respectively ($P=0.370$). In terms of tobacco exposure, 65.7% of aCRS and 63.8% of non-aCRS patients were never smokers, 27.3% of aCRS and 25.5% of non-aCRS patients were past smokers, and 7.0% of aCRS and 10.7% of non-aCRS patients were current smokers ($P=0.436$).

Variables with established associations with more severe CRS (e.g. polypoid disease, asthma, AERD, and IgE serum level) were compared between patients with and without atopy (**Table 2**). (30, 42-44) Significantly higher percentages of aCRS patients had elevated total serum IgE levels (33.3% vs. 8.3%, $P<0.04$), polypoid disease (56.3% vs. 35.9%, $P<0.001$), and comorbid asthma (44.8% vs. 17.0%, $P<0.0001$) and AERD (9.4% vs. 1.1%, $P<0.003$), compared to non-aCRS patients.

Structured histopathological findings of CRS patients with and without atopy were compared (**Table 3**). Relative to non-aCRS patients, aCRS patients demonstrated increased eosinophils/HPF (10+/HPF) (45.8% vs. 23.4%, $P<0.0001$), eosinophil aggregates (27.3% vs. 8.5%, $P<0.0001$), Charcot Leyden crystals (6.3% vs. 1.1%, $P=0.034$), and fibrosis (46.5% vs. 27.7%, $P=0.015$).

aCRS patients showed significantly higher average preoperative total SNOT-22 scores (40.5 ± 22.7 vs. 29.7 ± 20.7 , $P<0.015$) compared with non-aCRS patients. Moreover, aCRS patients exhibited higher symptom-specific SNOT-22 scores within the rhinologic (13.1 ± 7.81 vs. 10.0 ± 8.22 , $P=0.001$), extra-nasal rhinologic (6.10 ± 4.25 vs. 4.48 ± 4.44 , $P=0.001$), ear/facial (6.61 ± 5.66 vs. 4.82 ± 4.86 , $P=0.003$), and sleep dysfunction (10.0 ± 8.04 vs. 7.85 ± 7.59 , $P=0.020$) domains, relative to non-aCRS patients. No significant difference was identified within the psychological dysfunction domain between aCRS and non-aCRS patients (10.7 ± 9.63 vs. 9.02 ± 9.34 , $P=0.132$). In terms of endoscopic scoring, relative to non-aCRS patients, aCRS

patients showed higher preoperative modified LK scores (5.88 ± 2.85 vs. 4.80 ± 2.97 , $P=0.003$) (Table 4).

After controlling for polypoid disease, asthma, and AERD on binary logistic regression analysis, aCRS patients still demonstrated a significantly higher rate of tissue eosinophilia and preoperative SNOT-22 scores compared to non-aCRS patients. The adjusted odds ratio (95% CI) of having tissue eosinophilia in aCRS compared to non-aCRS was 2.84 (1.11-6.24), and the adjusted regression coefficient (95% CI) for total SNOT-22 score in aCRS compared to non-aCRS was 1.24 (1.02-1.89).

We next attempted to compare the association of “asthma and sinus tissue eosinophilia” to the association of “atopy and sinus tissue eosinophilia” in our group. Patients with aCRS showed enhanced tissue eosinophilia, eosinophilic aggregates, and preoperative total SNOT-22 and modified LK scores, relative to non-aCRS patients, even after adjusting for the presence of asthma and NPs (adjusted $P=0.011$ and $P=0.034$ for 10+ eosinophils/HPF and eosinophilic aggregates, respectively). However, after adjusting for atopy, patients with CRS+asthma did not exhibit significantly increased tissue eosinophilia or eosinophilic aggregates (adjusted $P=0.463$ and $P=0.213$ for 10+ eosinophils/HPF and eosinophilic aggregates, respectively).

Lastly, we assessed the association between tissue eosinophilia and sensitivity to individual aeroallergens. Specific sensitivities for all aeroallergens were more often identified in atopic CRS patients with tissue eosinophilia relative to non-eosinophilic atopic CRS patients (Fig. 1). Only sensitization to tree allergen was significantly correlated with tissue eosinophilia ($P=0.022$).

Discussion

The present study's findings suggest that CRS patients with atopy have significantly more severe CRS disease linked to distinct tissue-level modifications observed on structured histopathologic analysis. In agreement with previous studies, we found that the aCRS group showed enhanced CRS severity by objective and subjective measures.(45) Eosinophilic infiltration is a significant feature of allergic airway inflammation.(46) This type of inflammation in CRS has been previously correlated with more severe disease by both endoscopic scores and patient-assessed metrics.(47, 48) Our data show a very strong association between sinus tissue eosinophilia and atopy in CRS. In fact, among CRS patients with 10+ eosinophils/HPF, 85.1% demonstrated atopy, leaving only 13.5% of patients who demonstrate an eosinophilic predominant infiltrate without atopy. Similarly, among patients with eosinophilic aggregates, 92.9% were atopic. These findings point to atopy as a specific predictor of dense eosinophilic disease in the context of CRS and may explain the severity of symptoms in aCRS patients.

In western countries, CRSwNP is a predominantly eosinophilic inflammatory disease and reportedly exhibits a stronger association with atopy than CRSsNP.(26) To answer the question of whether the observed association between atopy and enhanced tissue eosinophilia in our patients could be explained instead by a higher rate of NPs in aCRS patients, we performed a logistic regression analysis correcting for the presence of NPs. After normalizing for polypoid disease, aCRS patients continued to demonstrate increased tissue eosinophilia compared to non-aCRS controls. In an analysis of CRSsNP patients alone, atopic patients demonstrated increased tissue eosinophilia relative to nonatopic-patients ($P<0.019$). A recent study by Benjamin et al. found that atopic CRSsNP patients demonstrate significantly more severe radiographic disease, which they define as increased sinus mucosal thickening on CT imaging, compared to non-atopic CRSsNP patients.(49)

Another recent study by Delemarre et al. aimed to categorize and understand the clinical significance of Th₂-predominant inflammatory changes in patients with CRSsNP who underwent FESS.(50) Of patients with CRSsNP, 49% exhibited type 2 inflammation based on cytokine expression; these patients demonstrated increased levels of tissue IL-4, IL-5, eosinophilic cationic protein, IgE, and *Staphylococcus aureus* enterotoxin-specific IgE, relative to non-type 2 CRSsNP patients based on ELISA analysis of tissue homogenate. Moreover, these patients exhibited higher rates of disease recurrence.(50) The step-wise inflammatory response to allergens is a well-established immunologic phenomenon resulting in type 2 inflammation.(51) The immediate allergic reaction caused by mast-cell or basophil degranulation is followed by a more sustained inflammation, known as the late-phase response, which involves the recruitment of effector cells, notably Th₂ lymphocytes, eosinophils, and basophils. The data from Delemarre et al. suggest that in almost half of CRSsNP patients who have an increased recurrence rate, the inflammation is driven by the type 2 inflammatory pathway. In agreement with these findings, our findings suggest that in CRS patients with a history of atopy, including atopic CRSsNP patients, tissue-level type 2 inflammatory changes, specifically enhanced tissue eosinophilia, underlie the increased disease severity.

Because both asthma and atopy are viable clinical factors with prognostic potential for identifying patients with severe CRS, we compared their association with tissue eosinophilia in CRS. Our analysis showed that atopy but not asthma can independently predict sinus tissue eosinophilia. While there is less dissent in terms of the impact of atopy on patient-reported CRS symptomatology, there are certainly discrepancies in the effects of atopy on CRS disease severity.(45) Two previous studies in particular that failed to find an association between atopy and severity of CRS have notable limitations.(34, 35) First, these studies use LM score, a metric

known for standardization challenges, as the chief measurement of CRS burden. Second, these studies both have relatively small sample sizes. Our study mitigates both of these shortcomings. The present analysis utilizes structured histopathology reports to comment on CRS disease severity. Further, it is the largest of its kind (i.e. the largest group of atopic medically-refractory CRS patients having undergone percutaneous aeroallergen testing, n=286). This is more than double the sample size of any previously published study. Though always important in terms of maximizing the power of a study, a high sample size is particularly critical in this particular analysis because there are so many variables, in terms of atopic categories (e.g. asthma), classification of CRS disease (e.g. polypoid, eosinophilic), and different aeroallergens (e.g. tree, grass, ragweed, mold, dustmite, animal, cockroach).

Moreover, the finding that atopy, but not asthma, is an independent predictor of sinus tissue eosinophilia, a well-established indicator of CRS disease severity, suggests that atopy is a stronger and more reliable marker than asthma for preoperatively identifying CRS patients with eosinophilic disease. This conclusion is relevant for the purposes of optimizing medical management. New biologic agents targeting Th₂ and eosinophilic inflammation might be of use in aCRS patients regardless of asthma or polypoid status.

Given this link between atopy and the presence of tissue eosinophilia and eosinophilic aggregates in aCRS patients, we attempted to investigate which specific aeroallergens guide observed tissue eosinophilia. Tissue eosinophilia was associated with sensitivity to all tested allergens, which indicates the process of allergic sensitization is linked to eosinophilia in sinus tissue regardless of the type of inhalant allergen.

aCRS patients had a higher degree of tissue fibrosis compared to non-aCRS patients. In CRS, tissue fibrosis is linked to reduced reticulin network in the mucosa and tissue

remodeling.(52) Fibrosis in sinus tissue is also associated with pro-inflammatory microbiota changes.(53) Previous studies have shown that aCRS patients have unique microbiota changes including lower relative abundance of *Corynebacterium* species, compared with non-aCRS patients.(54) Decreased abundance of *Corynebacterium* species is predictive of worse surgical outcomes in CRS.(54) The increased tissue fibrosis and associated unique microbiota changes in patients with aCRS, provide additional rationale for why an atopic endotype of CRS portends worse outcomes and higher disease severity. These findings underscore the need for patients with aCRS to undergo differential medical management.

In addition to observed histopathologic features, aCRS patients demonstrated increased prevalence of elevated serum IgE levels, relative to non-aCRS patients. These results were limited to a subgroup of patients, and largers studies are needed to confirm this association.

There are several limitations of the present study. First, as a retrospective cohort analysis, there is potential for selection bias. The major limitation of the present study is that it excludes patients in whom CRS is well-controlled with medication and therefore do not require surgery. All of the study samples were retrieved from patients who failed medical management and required sinus surgery. For this reason, the study represents only patients with moderate to severe CRS disease. Another limitation of our study is that total serum IgE levels were not measured in every patient; this laboratory value was available in 105 of the 380 patients. This additional information would more definitively corroborate the claim that serum IgE may act as a surrogate for CRS disease severity, similar to or even more than blood and tissue eosinophilia. Future studies exploring this question would continue to strengthen current approaches for clinical identification and management of CRS disease. Moreover, the field and this patient population would benefit from additional investigations into whether observed elevations in level of tissue

eosinophilia are influenced by patient-specific factors (e.g. spring surgery in a patient with seasonal allergies or pet ownership in a patient with a dog/cat allergy).

Our analysis draws an association between atopic CRS patients and subjective measures of disease (e.g. increased serum IgE levels and histopathologic features, in particular increased eosinophilic aggregates, tissue eosinophilia, Charcot Leyden crystals, and fibrosis), as well as increased patient-reported outcome measures (e.g. SNOT-22). These findings indicate that aCRS patients, regardless of polypoid or asthmatic status, have evidence of type 2 inflammation and may benefit from management of disease with agents targeting type 2 inflammation such as Dupilumab, IgE-targeted therapies, like the anti-IgE monoclonal antibody, omalizumab, and/or agents that directly target eosinophilis, either through inducing eosinophil apoptosis, like Siglec-8, or depleting eosinophils through enhanced antibody-dependent cell-mediated cytotoxicity, like human epidermal growth factor (EGF)-like module containing muscin-like hormone receptor 1 (EMR1). These data call for future investigations and potential secondary analyses of clinical trials of these medications with a focus on atopic status of CRS.

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Figure Legends

Figure 1. Specific aeroallergen sensitivities among atopic CRS patients with and without eosinophilia. Grey bars represent patients without tissue eosinophilia and blue bars represent patients with tissue eosinophilia. Animals tested include cat and dog.

Tables

Table 1. Structured histopathology report.

Variables	Options
Tissue present	Respiratory mucosa, mucoserous glands, bone
Overall degree of inflammation	Mild/moderate, severe
Eosinophil count per HPF	<5, 5+
Neutrophil infiltrate	Absent, present
Inflammatory predominance	Lymphocytic or non-lymphocytic
Subepithelial edema	Absent, present
Hyperplastic/papillary changes	Absent, present
Mucosal ulceration	Absent, present
Squamous metaplasia	Absent, present
Fibrosis	Absent, present
Charcot-Leyden crystals	Absent, present
Eosinophil aggregates	Absent, present

Table 2. Comparison of demographic data, comorbid conditions, and disease-specific variables between atopic and non-atopic CRS patients.

Variables	Atopic CRS (n=286) n (%)	Non-atopic CRS (n=94) n (%)	P-value
Age	49.4 ± 15.6years	56.4 ± 17.1years	<0.0001
Sex			
Male	125 (43.7%)	50 (53.2%)	0.087
Female	161 (56.3%)	44 (46.8%)	
Race			
Caucasian	174 (60.8%)	57 (60.7%)	0.370
Black	53 (18.5%)	15 (16.0%)	
Latino	26 (9.2%)	14 (14.9%)	
Asian	11 (3.8%)	4 (4.3%)	
Other	22 (7.7%)	4 (4.3%)	
Smoking status			
Never	188 (65.7%)	60 (63.8%)	0.436
Past	78 (27.3%)	24 (25.5%)	
Current	20 (7.0%)	10 (10.7%)	
Polypoid disease	162 (56.3%)	33 (35.9%)	0.001
Comorbid asthma	128 (44.8%)	16 (17.0%)	<0.0001
Comorbid AERD	27 (9.4%)	1 (1.1%)	0.003
Comorbid GERD	76 (26.6%)	34 (36.2%)	0.075
Elevated total serum IgE (>200 kilounits (kU) /L)	31/93* (33.3%)	1/12* (8.3%)	0.032
Allergen sensitization			
Mono (1)	68 (23.8%)	n/a	n/a
Poly (2+)	218 (76.2%)		

*Total serum IgE levels were only available in a subset of patients (n=105): 93 atopic CRS and 12 non-atopic CRS.

Table 3. Comparison of structured histopathologic variables between atopic and non-atopic CRS patients.

Variables	Atopic CRS (n=286) n (%)	Non-atopic CRS (n=94) n (%)	P-value
Degree of inflammation			
Mild inflammation	120 (42.0%)	42 (44.7%)	<i>0.337</i>
Moderate-severe inflammation	166 (58.0%)	52 (55.3%)	
Number of eosinophils per HPF			
<10	155 (54.2%)	72 (76.6%)	<0.0001
10+	131 (45.8%)	22 (23.4%)	
Neutrophil infiltrate	80 (28.0%)	30 (31.9%)	<i>0.195</i>
Basement membrane thickening	210 (73.4%)	62 (66.0%)	<i>0.106</i>
Sub-epithelial edema	181 (63.3%)	53 (56.4%)	<i>0.241</i>
Hyperplastic/papillary changes	31 (10.8%)	5 (5.3%)	<i>0.097</i>
Mucosal ulceration	14 (4.9%)	1 (1.1%)	<i>0.090</i>
Squamous metaplasia	66 (23.1%)	22 (23.4%)	<i>0.440</i>
Fibrosis	133 (46.5%)	26 (27.7%)	0.015
Fungus	5 (1.7%)	13 (13.8%)	<0.0001
Charcot Leyden crystals	18 (6.3%)	1 (1.1%)	0.034
Eosinophil aggregates	78 (27.3%)	8 (8.5%)	<0.0001

Table 4. Comparison of SNOT-22 and modified LK scores between atopic and non-atopic CRS patients.

Score	Atopic CRS (n=286)	Non-atopic CRS (n=94)	P-value
Total SNOT-22	40.5 ± 22.7	29.7 ± 20.7	0.015
Rhinologic Symptoms	13.1 ± 7.81	10.0 ± 8.22	0.001
Extra-Nasal Rhinologic Symptoms	6.10 ± 4.25	4.48 ± 4.44	0.001
Ear/Facial Symptoms	6.61 ± 5.66	4.82 ± 4.86	0.003
Psychological Dysfunction	10.7 ± 9.63	9.02 ± 9.34	0.132
Sleep Dysfunction	10.0 ± 8.04	7.85 ± 7.59	0.020
Modified LK	5.88 ± 2.85	4.80 ± 2.97	0.003

