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Defining the allergic endotype of CRS by structured histopathology, IgE, and clinical variables

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INTRODUCTION

Researchers have sought to identify targeted, phenotype-based approaches to diagnosis and management of chronic rhinosinusitis (CRS). In addition to polyploid status, several CRS patient subgroups have been identified as having phenotypes that may help guide diagnosis and management. CRS, especially CRSwNP is associated with increased risk of allergic rhinitis (AR), chronic non-allergic rhinitis, asthma, gastroesophageal reflux disease, and sleep apnea.[1]

Though the association between CRS and asthma has been extensively explored,[2] the role of atopy in CRS is less well-researched. Tan and colleagues found that between 51-86% of CRSwNP patients are sensitized to at least one aeroallergen. The link between aeroallergen sensitization and sinus disease severity remains unknown. Some studies report that sinus CT and endoscopy scores are significantly worsen in patients with inhalant allergies,[3] while others do not report a difference in sinonasal disease severity. [1, 4, 5]

In this study we have investigated the interplay between AR and CRS, with a specific focus on the differences in clinical variables, serum IgE, and histopathological biomarkers of disease between CRS patients with and without AR. Through this work we seek to further define atopic endotypes of CRS disease. These findings may contribute to the development of more targeted disease management, whether in the form of pharmacotherapies or surgical approaches, to optimize CRS disease management and patient outcomes.

METHODS

In a two-armed prospective cohort of CRS patients who underwent functional endoscopic sinus surgery (FESS), a structured histopathology report consisting of 13 histopathological variables, comorbid conditions, preoperative total serum IgE levels, and preoperative SNOT-22 scores were compared between CRS+AR and nonallergic-CRS patients in a multivariable model.

RESULTS

310 CRS patients who underwent FESS were included in this study. 78.06% (242/310) of this CRS cohort had comorbid AR (i.e. was sensitized to at least one aeroallergen according to IgE levels obtained by percutaneous testing). The CRS patient cohort was 47% male and 53% female with an average age of 50.41 ± 15.42 years.

Variables that have been associated with more severe CRS (e.g. IgE serum level, polyploid disease, asthma, and AERD) were compared between patients with and without AR (**Figure 1**).

CRS+AR patients had elevated total serum IgE levels ($p<0.05$), increased polypoid disease (48.5% vs. 34.3%, $p<0.03$), and a higher prevalence of comorbid asthma (41.9% vs. 11.6%, $p<0.0001$) and AERD (10.7% vs. 1.4%, $p<0.008$), compared to nonallergic-CRS patients (**Figure 1**).

Structured histopathological findings of CRS patients with and without AR were compared (**Table 1**). Relative to nonallergic-CRS patients, CRS+AR patients had increased eosinophil aggregates (55.5% vs. 27.9%, $p<0.0001$), eosinophils/HPF (>5/HPF) (26.9% vs. 7.2%, $p<0.0001$), and fibrosis (44.2% vs. 30.4%, $p<0.03$) (**Figure 2**).

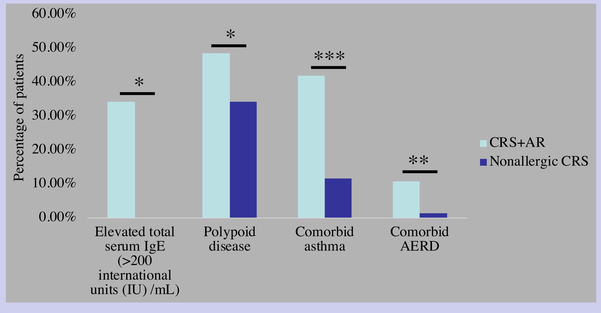

Figure 1. Comparison of variables associated with severe sinus disease between allergic and nonallergic CRS patients. $P<0.001$***, $p<0.01$**, $p<0.05$*

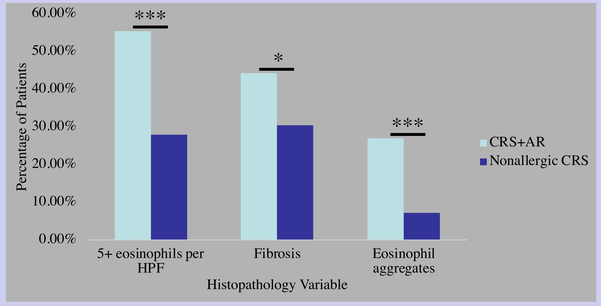

Figure 2. Comparison of histopathological variables that showed significant differences between patients with CRS+AR and nonallergic CRS. $P<0.001$***, $p<0.01$**, $p<0.05$*

CRS+AR patients had significantly higher average SNOT-22 scores (40.45 ± 22.6 vs. 29.70 ± 20.6, $p<0.001$) compared with nonallergic CRS group. Furthermore CRS+AR patients had a trend towards higher endoscopic CRS severity scores measured by Lund-Mackay scoring compared with nonallergic CRS group ($p=0.058$) (**Table 2**).

Table 2. Comparison of SNOT-22 and LM scores between CRS+AR and nonallergic CRS patients

Scores	CRS+AR (n=242)	NONALLERGIC CRS (n=68)	p-value
SNOT-22	40.45 ± 22.683	29.70 ± 20.677	**0.001**
LM	5.93 ± 2.828	5.15 ± 3.010	0.058

Variables	CRS+AR (n=242)	NONALLERGIC CRS (n=68)	p-value
Polyp status			
CRSwNP	48.5%	34.4%	**0.030**
CRSsNP	51.5%	65.6%	
Degree of inflammation			
Mild inflammation	43.4%	47.8%	0.683
Moderate-severe inflammation	56.6%	52.2%	
Number of eosinophils per HPF			
<5	44.6%	72.1%	**0.0001**
5+	55.4%	27.9%	
Neutrophil infiltrate			
Present	29.3%	33.3%	0.310
Absent	70.7%	66.7%	
Basement membrane thickening			
Present	70.7%	60.9%	0.082
Absent	29.3%	39.1%	
Sub-epithelial edema			
Present	60.7%	52.2%	0.128
Absent	39.3%	47.8%	
Hyperplastic/papillary changes			
Present	9.9%	4.3%	0.109
Absent	90.1%	95.7%	
Mucosal ulceration			
Present	5.0%	2.9%	0.362
Absent	95.0%	97.1%	
Squamous metaplasia			
Present	23.6%	21.7%	0.445
Absent	76.4%	78.3%	
Fibrosis			
Present	44.2%	30.4%	**0.027**
Absent	55.8%	69.6%	
Fungus			
Present	2.1%	13.0%	0.001
Absent	97.9%	87.0%	
Charcot-Leyden crystals			
Present	5.8%	0%	0.116
Absent	94.2%	100%	
Eosinophil aggregates			
Present	26.9%	7.2%	**0.0001**
Absent	73.4%	92.8%	

Table 1. Comparison of structured histopathologic variables between allergic and nonallergic CRS patients

SUMMARY

- In the context of CRS, AR appears to be a specific predictor of CRS severity linked to histopathological variables, namely enhanced eosinophilic aggregates.
- A large number of CRS patients regardless of presence of nasal polyp remain symptomatic even after surgical and medical treatment.
- Moving forward, allergic status, may be a useful way to identify an atopic endotype of CRS patients.
- These patients, irrespective of polyp and asthmatic status, could be optimal candidates for biologic agents such as eosinophil-targeted therapies.

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