Original Article

Lack of Efficacy of Symptoms and Medical History in Distinguishing the Degree of Eosinophilia in Nasal Polyps

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What is already known about this topic? Studies have demonstrated that nasal polyps can be eosinophilic or non-eosinophilic and this knowledge can direct treatment; however, there is no way to distinguish these conditions other than by histology.

What does this article add to our knowledge? No clinical biomarker other than absolute eosinophil count was able to help distinguish patients with eosinophilic polyps from patients with noneosinophilic polyps.

How does this study impact current management guidelines? This study emphasizes the importance of histologic examination of surgically obtained tissue to direct treatment.

BACKGROUND: Distinguishing eosinophilic nasal polyps (NP) from noneosinophilic NP will impact prognosis and therapeutic responsiveness.

OBJECTIVE: To investigate the ability of clinical history and biomarkers to distinguish these conditions.

METHODS: A total of 74 consecutive patients undergoing surgery for NP were enrolled. Clinical presentations were evaluated using the 22-item sinonasal outcome test (SNOT-22). Biomarkers included absolute eosinophil count, IgE, and extent of tissue hyperplasia on sinus computed tomography scan. Tissue eosinophilia was quantified in 10 random hpf and data analyzed addressing both peak and average results.

RESULTS: No component of the SNOT-22 was predictive of tissue eosinophilia. Similarly, a medical history of allergic rhinitis, asthma, or aspirin-exacerbated respiratory disease was not predictive. An absolute eosinophil count of more than 300 was associated with NP tissue eosinophilia. In contrast, neither IgE nor extent of sinus computed tomography hyperplasia was predictive.

CONCLUSIONS: The ability to individualize therapies for NP is dependent on identifying clinical features or biomarkers of eosinophilia. However, with the exception of circulating eosinophilia, we could not identify a clinical feature or biomarker that robustly predicted the presence of tissue eosinophilia. Even more problematic, even the seeming "criterion standard" determination of tissue pathology was of limited value, as our cohort displayed a continuous spectrum of tissue eosinophil expression, making arbitrary any definitive cutoff distinguishing these conditions. **(J Allergy Clin Immunol Pract 2017;■:■-■)**

Key words: *Chronic rhinosinusitis; Nasal polyps; Eosinophils; Sinonasal outcome test; CT scan*

The importance of properly distinguishing chronic rhinosinusitis (CRS) phenotypes is essential because of its impact on prognosis and therapeutic decisions. The presence of eosinophilic inflammation will define patients responsive to biotherapeutics that target eosinophils or type 2 cytokines. This is certainly understood in asthma where the presence of eosinophils is essential in not only defining subjects responsive to systemic and inhaled corticosteroids[1-3] but also those who will respond to IL-5–targeting therapeutics.[4-6] And, similarly, the presence of an IL-13^{high} signature predicts response to its antagonists.[7,8] Although topical and systemic corticosteroids (CCSs) are considered the mainstay of medical therapy for CRS,[9-11] the requirement for infiltrating eosinophils has not been investigated

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Abbreviations used
AEC- Absolute eosinophil count
AERD- Aspirin-exacerbated respiratory disease
AR- Allergic rhinitis
CCS- Corticosteroids
CRS- Chronic rhinosinusitis
CRSwNP- Chronic rhinosinusitis with nasal polyps
CT- Computed tomography
ECP- Eosinophil cationic protein
NP- Nasal polyp
SNOT- Sinonasal outcome test

as the basis for predicting their therapeutic responsiveness. But given the histological and immunological similarities of asthma and CRS, it is likely that this "eosinophil dependence" regarding steroid responsiveness in asthma will extend to CRS. Although not as well studied in CRS, at least 1 trial of an IL-5 antagonist in this condition reported efficacy in an IL-5^{high} phenotype subgroup of patients.[12]

Current guidelines phenotype CRS according to the presence (chronic rhinosinusitis with nasal polyps [CRSwNP]) or absence (CRS without nasal polyps [NPs]) of NPs.[13,14] This dichotomy was driven largely by the concept that CRSwNP is a disease more commonly characterized by prominent tissue eosinophilia along with a type 2 (IL-4^{high}/IL-5^{high}/IL-13^{high}) cytokine profile. In contrast, CRS without NPs usually presents as an IL-5^{low} noneosinophilic disease. However, although the diagnosis of NPs strongly suggests the presence of a type 2 helper lymphocyte^{high} (T_H2^{high})/IL-5^{high} phenotype, this is far from absolute. In a recent comprehensive study investigating regional differences in CRS presentation, between 17% and 42% of patients from Europe, Australia, and China did not demonstrate a T_H2^{high} signature in their NPs and, similarly, anywhere from 20% to 75% of patients did not demonstrate an eosinophil^{high} profile.[15] Thus, although the presence of NPs has been used as presumptive evidence for an eosinophilic/T_H2-driven process, given the frequency with which NPs can comprise a noneosinophilic disease there is increasing recognition of the inadequacies of this approach.

With the importance of defining eosinophil status as the basis for determining individualized therapeutic approaches, a means of easily distinguishing noneosinophilic from eosinophilic NPs is required. The "criterion standard" determinant of inflammation would arguably be quantifying eosinophil number, and/or perhaps also eosinophil-derived mediators such as eosinophilic cationic protein (ECP), in tissue samples. However, this approach requires obtaining a surgical specimen and pathologists may not always be prepared to provide definitive reporting of eosinophilia or be able or to perform proper immunohistochemical analyses for eosinophil byproducts.

We speculated that eosinophilic NPs and noneosinophilic NPs would present with distinct profiles in their medical history, symptom profile, or circulating biomarkers that would predict NP pathology. We therefore addressed the utility of the 22-item sinonasal outcome test (SNOT-22) to predict NP tissue diagnosis. In addition, we investigated whether the extent of hyperplastic changes in the sinuses, as assessed by Lund-Mackay score, along with the history of allergic rhinitis (AR), asthma, or aspirin-exacerbated respiratory disease (AERD) or circulating absolute eosinophil counts (AECs) or total IgE would support the diagnosis of eosinophilic CRS.

TABLE I. Subjects' demographic characteristics (total n = 74)

Characteristic	n (%)
Sex: female	35 (47.3)
Age (y), mean ± SD	46.4 ± 14.9
Asthma	39 (53.4)
Allergies	38 (51.4)
AERD	16 (21.6)
Smoking	12 (16.2)

METHODS

Subjects

Our study group consisted of 74 subjects consecutively evaluated at the University of Virginia for CRSwNP and referred for functional endoscopic sinus surgery. Eligibility for surgery required a failure of medical therapy to control symptoms that included a course of oral followed by topical CCSs. Immediately preoperative oral steroids were not used. All subjects completed a SNOT-22 before surgery and, as part of their medical evaluation, AECs and total IgE concentrations were determined using standard clinical laboratory methodologies. The presence of AR was based on specific allergen testing or a strong clinical history of seasonal variation with sneezing and ocular complaints. Comorbid asthma was based on physician diagnosis and did not include remote and/or resolved childhood disease. AERD diagnosis was based on a compelling history of exacerbation of upper and/or lower airway symptoms after exposure to aspirin or other nonselective cyclooxygenase inhibitors. Finally, we quantified the extent of sinus hyperplasia via Lund-Mackay scoring of subjects' sinus computed tomography (CT) scans. This study was performed with the approval of the University of Virginia Institutional Review Board.

Pathological scoring

A portion of each polyp was placed in 4% paraformaldehyde (Sigma, St Louis, Mo) overnight at 4°C. The next day specimens were washed in PBS and stored in 70% ethanol until paraffin embedding. Paraffin embedding, tissue sectioning, and hematoxylin-eosin staining were performed by the Histology Core Laboratory of the University of Virginia. NPs were scored for eosinophilia on the basis of the number of eosinophils in hematoxylin-eosin–stained sections. Sections were examined under 400× magnification in a blinded fashion and positive cells were counted in 10 random sections for each sample with the final number analyzed as both the peak and as the average number of cells per 10 hpf.

Surgical outcome

All patients were treated postoperatively with twice daily large volume nasal saline irrigation and topical nasal corticosteroid. Repeat SNOT-22 scoring was performed at a follow-up visit as close as feasible to 3 months postoperatively.

Statistical analyses

For complete details, see this article's Online Repository at www.jaci-inpractice.org. Briefly, data were summarized by frequencies and percentages, and continuous scaled data were summarized by the mean and SD of the distribution. Spearman rank correlation analyses were conducted to examine the relationship of the preoperative