

Biomarkers in Chronic Rhinosinusitis with Nasal Polyps



Alan D. Workman, MD, MTR^a, Michael A. Kohanski, MD, PhD^a,
Noam A. Cohen, MD, PhD^{a,b,c,*}

KEYWORDS

• Chronic rhinosinusitis • Biomarkers • Polyps • Microbiome • Genetics

KEY POINTS

- Chronic rhinosinusitis is a complex disease that exists along the inflammatory spectrum between types 1 and 2 inflammation.
- The classic phenotypic differentiation of chronic rhinosinusitis based on the presence or absence of inflammatory polyps remains one of the best differentiators of response to therapy.
- Biologics for the treatment of atopic disease and asthma, and perhaps a new look at topical therapies for sinusitis, have placed renewed emphasis on understanding the pathophysiology of inflammatory sinus polyp pathogenesis.
- Identification of key markers of polyposis will allow for better stratification of inflammatory polyp disease endotypes to objectively identify tailored medical therapies and track response to medical and surgical treatment.

INTRODUCTION

Chronic rhinosinusitis (CRS) is a prevalent and heterogeneous disease associated with a high degree of morbidity. Although there exist specific conditions for diagnosis, it has been increasingly appreciated that CRS exists as a spectrum of clinical conditions with distinct pathophysiology and presentation.¹ Targeted biologics for treating asthma are now being used for CRS with nasal polyps (CRSwNP), which has

^a Department of Otorhinolaryngology–Head and Neck Surgery, Division of Rhinology, University of Pennsylvania, Perelman School of Medicine, 3400 Spruce Street, Philadelphia, PA 19104, USA; ^b Philadelphia Veterans Affairs Medical Center, 3900 Woodland Avenue, Philadelphia, PA 19104, USA; ^c Monell Chemical Senses Center, 3500 Market Street, Philadelphia, PA 19104, USA

* Corresponding author. Division of Rhinology, Department of Otorhinolaryngology–Head and Neck Surgery, University of Pennsylvania Medical Center, 5th Floor Ravdin Building, 3400 Spruce Street, Philadelphia, PA 19104.

E-mail address: Noam.Cohen@uphs.upenn.edu

predicated the need for improved classification and diagnosis of different presentations of the disease in an effort to improve therapeutic efficacy.

Traditionally, a dichotomous classification system has been used to describe CRS based on the presence or absence of nasal polyps. CRSwNP represents a subset of those with CRS,² and CRSwNP is often associated with more severe sinonasal symptoms and asthma. The division of CRS by polyp status was initially supported at the cellular level, with CRS without nasal polyps (CRSsNP) thought to be characterized by a T-helper type 1 (T_H1)-predominant inflammatory pattern and CRSwNP characterized by a T-helper type 2 (T_H2)-predominant inflammatory pattern. However, recent work has demonstrated that CRS may be better evaluated as a continuum of inflammatory processes, with variable and nonmutually exclusive immunologic markers. This complexity can potentially be captured with endotype or cluster classification based on consistent pathologic mechanisms that may not be evident at the level of phenotypic observation. Endotypes are often defined by the presence or absence of one or more biomarkers, and the use of biomarkers can be helpful in achieving accurate diagnosis, evaluating optimal therapeutic strategy, and determining patient prognosis.

Chronic Rhinosinusitis with Nasal Polyps Pathophysiology

Inflammatory sinonasal polyps manifest bilaterally from the ethmoid sinuses and can often present with hyposmia and/or nasal obstruction as major symptoms (Figs. 1 and 2). It is thought that nasal polyp growth is present in 1% to 4% of the US population.³ As stated, T_H2 inflammation often predominates and is associated with elevated levels of eosinophils and type 2 inflammatory cytokines including IL-4, IL-5, and IL-13.⁴ Asthma is frequently a comorbid condition in patients with CRSwNP, affecting 20% to 60% of diseased individuals.⁵ An additional hallmark of CRSwNP is the loss of healthy barrier function in sinonasal epithelial cells. There is generally increased permeability, decreased epithelial resistance, and a high degree of tissue remodeling observed⁶ in cells harvested from patients with CRSwNP compared with cells from CRSsNP patients and control individuals. This loss of barrier function is reflective of a general inflammatory process, but it is unclear whether the epithelial cells are inherently abnormal or if the state is induced.⁷ Treatment for CRS is most frequently glucocorticoid based, but response is quite variable in patients with nasal polyps and the side effects from oral steroids limits their long-term efficacy in the treatment of this disease. Hamilos and colleagues⁸ demonstrated an inverse relationship between glucocorticoid receptor- β expression in nasal polyp tissue and steroid efficacy, and another study showed that neutrophil accumulation in nasal polyp tissue is also related to corticosteroid insensitivity.⁹ Some individuals exhibit a very high level of resistance to steroid therapy, and this underscores the need for therapeutics targeted toward non-steroid-responsive pathophysiologic mechanisms involved in sinus polyp formation.



Fig. 1. Visible nasal polyps on external nares examination.

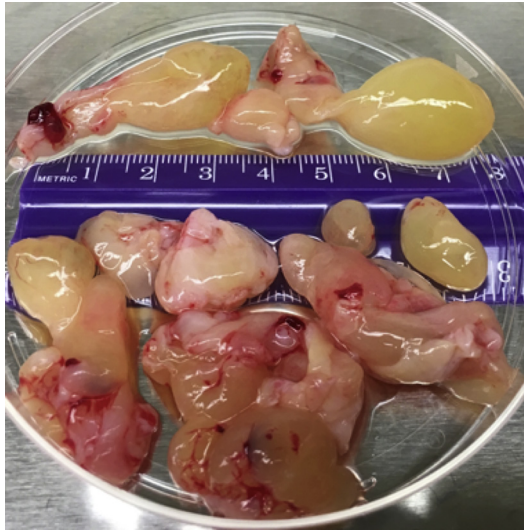


Fig. 2. Removed nasal polyps after functional endoscopic sinus surgery.

BIOMARKERS AND THERAPEUTICS IN CHRONIC RHINOSINUSITIS WITH NASAL POLYPS

An ideal biomarker is easy to obtain and has a high sensitivity and specificity for the disease or disease subtype in question. The most frequently used mediums to obtain CRS biomarkers are peripheral blood, nasal secretions, tissue biopsies from the sinuses, and nasally exhaled breath. A peripheral blood draw is significantly easier to obtain than a nasal biopsy, and requires less time, expertise, and expense. However, peripheral blood may not always reflect local nasal inflammatory processes and is often a poor proxy for the nasal microenvironment. Nasal lavage is more useful in many situations, but several studies have demonstrated a somewhat inconsistent correlation between cytokines and proteins in nasal secretions and those in the tissue itself.⁴ Much of this is likely due to geographic variability in inflammatory microenvironments in the sinonasal environment. Many CRS biomarkers have been preliminarily evaluated in recent years (Table 1), with most of the literature expanding on proof-of-concept studies of markers that have been evaluated in related diseases, including asthma, environmental aeroallergens, and atopic dermatitis.

Eosinophilia and IgE

Classically, CRSwNP is an eosinophilic disease and CRSsNP is generally noneosinophilic. However, there are many random and regional exceptions, with up to 50% of patients with CRSwNP in East Asia presenting without eosinophilic inflammation.¹⁰ Wang and associates¹¹ further showed that 20% to 75% of nasal polyp specimens can be noneosinophilic, contrasted with tissue obtained from CRSsNP patients that can show very high eosinophilia in a minority of cases. Although this substantial overlap prohibits the use of eosinophilia as a definitive marker for polyp disease, eosinophilia itself can be a predictive tool. Eosinophilic nasal polyps are associated with increased objective and subjective disease severity, as well as an increased risk of recurrence of disease after sinus surgery.¹² Conversely, eosinophilic polyps are generally more glucocorticoid responsive than their noneosinophilic counterparts.⁹

Table 1 List of current biomarkers		
Biomarker	Source Medium	Targeted Therapy
Eosinophilia	Tissue, peripheral blood	
IgE	Tissue	Omalizumab
Cytokines		
IL-4	Tissue	Dupilumab
IL-5	Tissue	Mepolizumab, reslizumab
IL-13	Tissue	Dupilumab
IL-25	Tissue	
IL-33	Tissue	
Thymic stromal lymphoprotein	Tissue	
Periostin	Tissue, nasal secretions	
P-glycoprotein	Tissue, nasal secretions	Verapamil
CXCL-12/CXCL-13	Tissue	
Type 2 innate lymphoid cells	Tissue	
IgG and IgA autoantibodies	Tissue	
Nitric oxide	Exhaled breath	
Bitter and sweet taste receptors	Tissue, genotype, taste test	
Microbiome	Nasal secretions	
IgE antibody to <i>Staphylococcus aureus</i> enterotoxin	Tissue	
Matrix metalloproteinases	Tissue, nasal secretions	Doxycycline
Oncostatin M	Tissue	

Classification of an eosinophilic-rich environment is most often achieved using tissue microscopy, with different groups establishing optimal cutoffs for grading levels of eosinophilia. Kountakis and colleagues¹³ established a cutoff point of greater than 5 eosinophils per high power field, whereas Soler and colleagues¹⁴ had a higher cutoff of 10 eosinophils per high-power field based on a measurement of quality of life improvement after surgery. Importantly, degree of tissue eosinophilia is extremely difficult to determine based on clinical symptoms, and it cannot be predicted by SNOT-22 scores or the concomitant presence of asthma or aspirin-exacerbated respiratory disease.¹⁵ Whereas many studies establish that it is possible to identify a cohort of patients with noneosinophilic nasal polyp and a cohort of hypereosinophilic nasal polyp patients, most patients fall along an expression continuum that makes grouping solely on eosinophilia difficult.¹⁵ Further experiments have used blood eosinophilia to predict disease relapse after surgery, but this is complicated by the fact that blood eosinophilia is not definitively correlated with that in tissue.¹⁶

IgE, an inducer of eosinophilia, has also been investigated as a biomarker for CRS phenotyping and treatment. Patients with CRS frequently express high levels of serum and local IgE, in addition to allergic sensitization to bacterial antigens.¹⁷ Specifically, *Staphylococcus aureus* enterotoxins can serve as both conventional and superantigens to activate basophil degranulation in those with CRSwNP.¹⁸ High local IgE in tissue itself was also predictive of recurrence requiring repeat surgical intervention.¹⁹ The anti-IgE therapeutic omalizumab was also tested in patients with CRSwNP to see if it could reduce polyp burden and lead to symptomatic improvement. Omalizumab reduced nasal polyp size and improved sinus computed tomography scores in

patients with CRSwNP, but decreases in local nasal mucosal inflammation were not unequivocally observed.²⁰

Cytokines

Cytokine profiles are perhaps the most currently investigated and initially promising biomarkers for CRS phenotyping and therapeutic targets. The classic characterization of CRSsNP is with a T_H1 or T_H17 phenotype with prominent neutrophilia, expressing transforming growth factor- β , type I interferons, and IL-6, IL-8, or IL-17. This is contrasted with the characterization of CRSwNP as a T_H2 microenvironment with increased expression of thymic stromal lymphoprotein and type 2 inflammatory cells, such as type 2 innate lymphoid cells, which produce IL-4, IL-5, IL-13, IL-25, and/or IL-33. Type 2 innate lymphoid cells play a role in T- and B-cell activation, and activated epithelial cells contribute to leaky barriers as they apoptose.¹ Both IL-4 and IL-13 induce local IgE production and stimulate mucus secretion, whereas IL-5 induces eosinophilia through the recruitment, activation, and survival of eosinophils.¹ IL-13 affects epithelial differentiation resulting in decreased ciliation and goblet cell metaplasia, further contributing to a leaky epithelial barrier of sinonasal epithelial cells.²¹ IL-13 also increases hyperreactivity of the airway and causes subepithelial fibrosis. More recently, studies show that IL-25 seems to be involved in the IL-13 regulatory cascade, with IL-25 stimulation inducing IL-13-dependent changes in an asthma mouse model.²²

Cytokine signatures are extremely valuable in determining T_H classification and are more specific than eosinophilia or even the presence of nasal polyps themselves, even though both are more common in T_H2 high states.²³ The T_H1 and T_H2 dichotomy is useful but also an oversimplification as a proxy for nasal polyp status. Eighty-five percent of nasal polyps do have high concentrations of IL-5, but there is intermittent concomitant expression of IL-17 and interferon- γ that is more characteristic of a T_H1 process.¹¹ The subset of patients with IL-5-enriched nasal polyps has an increased percentage of asthma and revision surgery patients.²⁴ The presence of IL-5 may be defining for a specific endotype of CRSwNP individuals with more severe disease. IL-25, IL-33, and thymic stromal lymphoprotein are also epithelial-derived cytokines that are important in the pathogenesis of CRSwNP and asthma, and may be important biomarkers for CRSwNP. IL-25 expression is upregulated in CRSwNP tissue,²⁵ is associated with elevated eosinophil counts and increased severity in computed tomography scoring parameters,²⁶ and can potentially serve as a sensitive biomarker.²⁷ IL-33 participates in less well-defined pathways, but also plays a role in T_H2 inflammation. IL-33 expression levels are increased specifically in patients with CRSwNP with severe and recalcitrant disease.²⁸

Many anticytokine agents are currently in production and development as asthma treatments, and it is a logical extension that they may have a potential role in treating T_H2 inflammation in CRS. It has been well-demonstrated that asthmatic patients with a T_H2 phenotype with eosinophilia derive benefit from IL-5 antagonists.²⁹ In fact, nasal polyps were a good biomarker for predicting anti-IL-5 response in these studies, owing to the relationship of nasal polyps with a T_H2 -skewed state. Antibodies to IL-5 already are approved for refractory asthma, and an anti-IL-5 receptor antibody will be available in a short time. Initial trials of IL-5 antagonism with mepolizumab and reslizumab in CRSwNP demonstrated a reduction in nasal polyp size and reduced necessity for revision surgeries.^{30,31} However, these trials have not definitively shown improved nasal symptom scores, and careful patient selection may be critical for derivation of benefit. An IL-5-enriched endotype seems to be necessary to predict efficacy, because eosinophil markers themselves were not predictive of mepolizumab response magnitudes.³²

Dupilumab is an anti-IL-4 receptor antibody that blocks the actions of both IL-4 and IL-13 that is currently used in atopic dermatitis and has shown efficacy in treating asthmatics with an elevated type 2 inflammatory response.³³ Just as with anti-IL-5 treatments, dupilumab also improves several outcomes in patients with CRSwNP from clinical, endoscopic, and radiologic standpoints.³⁴ Nasal polyps decrease in size and sinus computed tomography scores are less severe after treatment, although objective sinus symptomatology measures and smell tests also show improvement in patients with a confirmed T_H2 /eosinophil endotype.³⁴ Again, the effectiveness of these treatments is predicated on a well-defined and compatible inflammatory signature, so appropriate patient selection for therapy is important.³⁵ Murine studies also show promise for IL-25 blockade, because polypoid lesions are reduced and edematous inflammation is decreased at the cellular and mucosal level.³⁶ These novel cytokine pathways are very promising targets for CRSwNP therapies in the coming years, and diagnostic tools incorporating these cytokines will be concomitantly necessary for patient selection. Some studies have purported that the cytokines in nasal secretions correlate with tissue levels to a degree that allows for alternative evaluation, and can be useful when assessment of structural and cellular patterns of expression are not necessary.³⁷ Longitudinal tracking of biomarkers will also be important to objectively measure therapeutic efficacy, because the cost of biologics is currently prohibitive for CRS. The current cost of dupilumab treatment for nasal polyps is greater than treating the condition with surgery every 6 months for the duration of symptomatology.³⁸

Periostin

Periostin is an extracellular protein that is secreted in response to IL-4 and IL-13 and it plays a role in airway subepithelial fibrosis through interactions with integrin molecules involved in tissue remodeling.³⁹ Additionally, it participates in eosinophil recruitment and activation cascades as well as in angiogenesis through the action of vascular endothelial growth factor.⁴⁰ Periostin is elevated in patients with CRSwNP regardless of asthma or atopic comorbidity status and it is especially high in patients with active disease. Conversely, periostin levels seem to decrease after effective treatment and can be helpful in evaluating the efficacy of therapy.⁴¹ Specifically, an established cut-off value of 48.5 ng/mL of s-periostin had a sensitivity of 93.5% for the presence of tissue IL-5. Because periostin seems to regulate protein expression of other inflammatory molecules and tissue remodeling factors, there is potential for periostin itself to serve as a viable target for the reduction of inflammation.⁴⁰

P-glycoprotein

P-glycoprotein is an ATP-dependent transmembrane efflux pump that is upregulated in T_H2 disease, and can cause a portion of CRS-related inflammation through promotion of cytokine secretion.^{42,43} It is of particular interest as a biomarker for CRSwNP and as a therapeutic target. P-glycoprotein is also secreted into nasal fluids, making clinical specimen collection and fluid assays more convenient and tolerable for patients than a tissue biopsy. P-glycoprotein levels are elevated in all CRS subtypes, and even higher levels are seen in CRSwNP, specifically with correlation of inferior subjective and objective measures of disease severity with higher levels of P-glycoprotein.⁴⁴ Verapamil is an antagonist of p-glycoprotein, and preliminary trials show that low-dose verapamil therapy is safe and effective for CRSwNP treatment. Improvements in SNOT-22 with verapamil resulted in improvements that were comparable with those achieved with steroids or biologic agents.⁴⁵

Immune Cells and Autoantibodies

Immune cell activation and proliferation occurs locally within nasal polyps themselves, with substantially elevated immunoglobulin levels that are not raised at a systemic level. Plasmablasts and plasma cell populations expand rapidly and parallel the growth seen in the T- and B-cell populations in CRSwNP.⁴⁶ CXCL-12 and CXCL-13 molecules also are present at increased levels, which enhance B-cell chemotaxis.⁴⁷ Type 2 innate lymphoid cells are independently linked with high tissue and blood eosinophilia and are shown to correlate with worse nasal symptom scores.⁴⁸ Beyond these cell populations, Tan and colleagues⁴⁹ showed IgG and IgA autoantibody elevations within polyp tissue, and the presence of antinuclear, anti-DNA, and anticytokine antibodies is significant. Anti-dsDNA IgG antibody is correlated with a more severe clinical course, whereas the presence of antineutrophil cytoplasmic antibody in patients with CRS may be associated with a subset of individuals difficult-to-treat disease.⁵⁰ Autoimmunity and autoantibodies may play a greater role as further work elucidates how these biomarkers may be associated with other phenotypic findings.

Nitric Oxide

It is known that patients with CRSwNP have decrements in exhaled nasal nitric oxide (nNO) owing to ostial occlusion and disruption of gas exchange with the nasal cavity.⁵¹ Patients with CRSsNP also have lower nNO than control patients on average as well, but significantly higher than those observed in CRSwNP.⁵² Jeong and colleagues⁵³ revealed a specific nNO cutoff point with a sensitivity of 81.3% and a specificity of 93.3% for the presence of nasal polyps and, further, nNO levels correlate with the extent of disease.^{51,53,54} However, atopic patients in both control groups and patients with nasal polyps have significantly higher nNO levels, confounding some of these findings.⁵² Exhaled oral NO is currently used as a marker of asthma control, with lower levels correlating with better disease control. Overall, nNO is a noninvasive biomarker that may have some usefulness for alternative identification of nasal polyp disease and as a marker for disease severity.

Taste Receptors

Over the past several years, a growing body of literature has identified a role for bitter and sweet taste receptors in immune defense in the airway.^{55,56} Bitter taste receptors respond to bacterial products, including acyl-homoserine lactones produced by gram-negative bacteria such as *Pseudomonas aeruginosa*.⁵⁷ When bitter taste receptors on ciliated cells are stimulated, there is a downstream antimicrobial NO response, resulting in direct bacterial killing and increases in ciliary beat frequency.⁵⁸ When a separate cohort of bitter taste receptors on solitary chemosensory cells, another airway cell type, are stimulated, antimicrobial peptides are released.⁵⁹ Bitter taste receptors are genetically diverse, and specific genetic polymorphisms correlate with in vitro antimicrobial activity of sinonasal epithelium.⁵⁶ This translates to the clinical realm; patients with a nonfunctional polymorphism in a specific taste receptor, T2R38, have inferior outcomes after functional endoscopic sinus surgery and require increased intervention.⁶⁰ Furthermore, sinonasal specimens from patients with nonfunctional polymorphisms exhibit increased bacterial biofilm formation.⁶¹ Some in vitro studies also show that bitter taste receptor hyperactivation can be deleterious and potentially proinflammatory, because sinonasal cultures obtained from patients with CRSwNP have increased disease recurrence after sinonasal surgery.

Sweet taste receptors act in opposition to bitter taste receptors, and inhibit the antimicrobial cascade in solitary chemosensory cells. Depletion of airway surface liquid

glucose is a harbinger of bacterial infection, because the bacteria consume the sugar rapidly. It is hypothesized that this decrease in glucose deactivates the sweet receptors, which then release their inhibition on the actions of the T2R receptors.⁵⁹ Patients with CRS are known to have increased airway glucose levels,⁵⁹ similar to those of diabetic patients, who have nasal microbiologic cultures that include far more gram-negative bacteria, including *P aeruginosa*.⁶²

Because bitter taste receptors are expressed both on the tongue and in the upper airway, inexpensive phenotypic taste tests can be used as a proxy for the functionality of sinonasal taste receptors. Patients with CRSsNP are significantly more likely to be less sensitive to denatonium, a broad bitter taste receptor agonist, and patients with CRSwNP and CRSsNP are more sensitive to sucrose, which is a sweet receptor agonist.⁶³ Thus, it may be possible to use bitter and sweet taste tests as biomarkers to evaluate CRS disease status and potentially stratify patients into taste-specific endotypes.

Microbiome

The nasal microbiome is thought to play an important role in the pathogenesis of CRS, and several studies have shown that bacterial diversity is decreased in disease and overall bacterial abundance is increased.⁶⁴ This finding suggests that dysbiosis is correlated with CRS status.^{65,66} Beyond this, Cope and colleagues⁶⁷ demonstrated specific microbiota classifications that correlated with patient phenotypes, including the presence of nasal polyps. A higher than expected proportion of patients with CRSwNP are colonized with *S aureus*,⁶⁸ and IgE antibodies to *S aureus* enterotoxins are frequently found in diseased tissue specimens. Both *S aureus* and *P aeruginosa* bacteria can disrupt the epithelial barrier contributing to presumed physiologic mechanisms for CRSwNP development. Compounding the problem, antimicrobial compounds including lysozyme, S100 proteins, and β -defensins all are decreased in patients with CRSwNP compared with matched controls.⁶⁹ This reduction in natural defenses could play a key role in shifting the balance toward dysbiosis. Finally, an alternative proposed pathogenic mechanism for T_H2-biased sinusitis is that T cells are allergically sensitized to fungi in the ambient environment, leading to allergic inflammation characterized by a T_H2-high state.⁶⁴

Genetics and Proteomics

Large-scale genetic and proteomic studies hold promise for CRS biomarker identification. It is known that first-degree relatives of patients with CRSwNP have a 4-fold increased risk of developing nasal polyps themselves, but no specific mutation or polymorphism has been individually explanatory, other than those for cystic fibrosis mutations.⁷⁰ Genetics are also known to play an important role in other eosinophilic diseases, including eosinophilic esophagitis, suggestive of an inherent predilection to eosinophilia.⁷¹ Gene expression patterns, rather than genetic polymorphisms themselves, are of particular interest. Liu and colleagues⁷² revealed 192 upregulated and 156 downregulated genes in polyp tissue using DNA microarray methods. Altered transcription factors include Foxp3 and SOCS3, involved in T-cell regulation,⁷³ and GATA-3, a T_H2 transcription factor that has been leveraged in early therapeutic trials to decrease asthmatic responses.

Proteomics analysis by Upton and colleagues⁷⁴ showed 300 differentially expressed mucosal proteins in patients with CRSwNP compared with matched controls. A separate study identified an even larger cohort of differentially expressed proteins, including mucin 5B, lipocalin-1, mucin 5AC, and arfinase-1. These latter proteins were elevated specifically in patients with nasal polyps.⁷⁵ The possibility of proteomic

analyses on nasal lavage fluids offers a noninvasive way to obtain a set of secreted biomarkers with potentially rich information.

Other biomarkers

Matrix metalloproteinases are involved in tissue remodeling and are increased specifically in nasal polyp disease. Doxycycline has an anti-matrix metalloproteinase effect that lowers matrix metalloproteinase levels in secretions and causes decreases in polyp size.⁷⁶ This property makes doxycycline a potentially beneficial antibiotic choice, whereas other antibiotics such as clarithromycin are more targeted to neutrophilic disease.^{77,78} Other compounds of interest include Oncostatin M, an IL-6 related molecule, that is elevated in CRSwNP and causes increased tissue permeability in *in vitro* sinonasal epithelial cells.⁷⁹

ENDOTYPE CLASSIFICATION

Endotype classification of patients with CRS can use many of these biomarkers to attempt to identify nonphenotypic patient cohorts. This process is not merely an academic exercise; tailored medical and surgical interventions spare an inordinate amount of patient morbidity and unnecessary treatment. If endotype-specific drugs are used, but patients are selected for treatment based only on phenotype, then this patient selection approach may result in many incompletely or inappropriately treated individuals. For example, CRSsNP disease with prominent fibrosis can show severe scarring after aggressive sinonasal surgery, whereas highly eosinophilic CRSwNP disease is much more appropriately treated aggressively. It is thought that aggressive surgery for this extremely eosinophilic endotype of nasal polyp disease eliminates local immune memory and that this intervention is associated with a recurrence-free interval after sinonasal surgery.⁸⁰ This is just one example. For the practicing rhinologist, patient subclassification allows for guided preoperative treatment, appropriate surgical management, and improved long-term maintenance.

There are many ways to define patient endotypes. Tomassen and colleagues¹⁷ performed a cluster analysis of patients with CRS with a clinical phenotype-free approach, aiming to identify inflammatory endotypes with immune markers alone. This resulted in 10 defined clusters, generally segregating into 4 clusters with low IL-5 concentrations, eosinophilic cationic protein, and IgE and 6 clusters with increased levels of these compounds. Interestingly, increased IL-5 expression was observed in clusters containing high and low proportions of nasal polyp patients, whereas 1 of the 4 IL-5-negative clusters had a mixed CRSsNP and CRSwNP phenotype with a T_H17 profile. *S aureus* enterotoxin-specific IgE was observed in all patients with high IL-5 levels and a clinical polyp phenotype. Overall, the study suggests that patient classification by inflammatory endotype provides a more accurate description of the disease than phenotype alone, and that there is a high degree of diversity in CRS inflammation. Although certain inflammatory markers segregate together more frequently, it may be a more multidimensionally heterogeneous disease than previously thought, with separation on T-helper subtype, eosinophilic, and antigenic parameters.

Although not uniformly nonphenotypic, 2 recent studies have identified CRS clusters based on disease characteristics. Soler and colleagues⁸¹ used patient-reported outcome measures after medical and surgical therapy for clustering, identifying a cohort of patients with failure to improve after surgical therapy. A follow-up study proved that these clusters could be applied to a larger, prospective cohort, and that differences in outcomes could be identified in patients treated surgically and those who continued with medical treatment.⁸² A second study by Wu and colleagues⁸³

clustered 110 patients into 3 distinct groups based on course of disease with clinical, functional, and inflammatory parameters. These schema for patient classification may have high usefulness in identifying subsets of patients with a predilection for recalcitrant disease.

SUMMARY

CRS, and specifically CRSwNP, is a substantially heterogeneous disease that exists on a multidimensional spectrum of inflammatory pathology. Endotyping helps to explain some of the differences in clinical manifestations of disease, as well as the variations in therapeutic response and prognosis. Biomarkers provide critical information for endotyping, and it is likely that a panel of CRS biomarkers will be necessary to fully identify T_H2 status associated with nasal polyposis and can be used to guide appropriate therapeutic intervention. The use of high throughput-based studies to identify inflammatory endotypes based on genomics and proteomics holds promise for a future with more accurate CRS diagnosis and tailored medical therapy.

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