The Molecular Genetics of Inflammatory, Autoimmune, and Infectious Diseases of the Sinonasal Tract

A Review

Kathleen T. Montone, MD

Context.—The sinonasal tract is frequently affected by a variety of nonneoplastic inflammatory disease processes that are often multifactorial in their etiology but commonly have a molecular genetic component.

Objective.—To review the molecular genetics of a variety of nonneoplastic inflammatory diseases of the sinonasal tract.

Data Sources.—Inflammatory lesions of the sinonasal tract can be divided into 3 main categories: (1) chronic rhinosinusitis, (2) infectious diseases, and (3) autoimmune diseases/vasculitides. The molecular diagnosis and pathways of a variety of these inflammatory lesions are currently being elucidated and will shed light on disease pathogenesis and treatment.

Conclusions.—The sinonasal tract is frequently affected by inflammatory lesions that arise through complex interactions of environmental, infectious, and genetic factors. Because these lesions are all inflammatory in nature, the molecular pathology surrounding them is most commonly due to upregulation and down-regulation of genes that affect inflammatory responses and immune regulation.

The sinonasal tract is frequently affected by a variety of nonneoplastic inflammatory disease processes that are often multifactorial in their etiology but commonly have a molecular genetic component. These inflammatory diseases result in billions of dollars in health care costs annually. The molecular diagnoses and pathways of a variety of these inflammatory lesions are currently being elucidated and will shed light on disease pathogenesis and treatment.

Inflammatory lesions of the sinonasal tract can be divided into 3 main categories: (1) chronic rhinosinusitis (CRS), which encompasses a heterogeneous group of entities, all of which result in sinonasal mucosal inflammatory patterns with or without polyps and eosinophils; (2) infectious diseases, which can be bacterial, viral, fungal, or parasitic in origin; and (3) autoimmune diseases/vasculitides, which can result in mucosal necrosis and nasal cartilage destruction. This review will focus on the molecular genetics of a variety of nonneoplastic inflammatory diseases of the sinonasal tract, with emphasis on chronic rhinosinusitis, select infections that may have significant sinonasal tract involvement, and autoimmune diseases/vasculitides that affect the sinonasal tract.
Biofilms are collections of microorganisms that grow in a self-produced matrix that attaches to moist surfaces including sinonasal mucosa.\textsuperscript{4,5,10} Biofilms allow bacteria survival advantages by providing protection from antibiotics and the host inflammatory response.\textsuperscript{4,3,10} Interestingly, bacteria in biofilms show upregulation and down-regulation of several genes compared with free-floating bacteria.\textsuperscript{11} A recent prospective study observed biofilms in 65% of CRS patients, with the most common cultured pathogens being \textit{S. aureus} and \textit{Pseudomonas aeruginosa}.\textsuperscript{20} On the other hand, fluorescence in situ hybridization targeting \textit{Streptococcus pneumoniae}, \textit{S. aureus}, \textit{Haemophilus influenzae}, and \textit{P. aeruginosa} ribosomal RNA in conjunction with confocal microscopy revealed biofilm production in more than 70% of specimens, with no examples of \textit{P. aeruginosa} and no correlation with the conventional cultures of the specimens.\textsuperscript{7} Using similar techniques and a panfungal ribosomal RNA gene probe, the presence of fungal organisms in bacterial biofilms in patients with CRS and allergic fungal rhinosinusitis (AFRS) was seen.\textsuperscript{12} The identification of fungi in biofilms does lend some support for fungi having a potential role in the pathogenesis of CRS, as will be further discussed in this review.

Finally, a third means in which bacteria have been implicated in CRS is through host immune responses through superantigen production.\textsuperscript{1,2,13–16} Superantigens are toxins produced in inflammatory and allergic conditions that elicit T-cell activation by binding to major histocompatibility complex class II molecules.\textsuperscript{1,2,13–16} Toxins produced by \textit{S. aureus}, the bacterium that has been most commonly associated with CRS, act like superantigens.\textsuperscript{13–16} Superantigens alter immune reactions by promoting a switch from a T helper cell (Th1) 2 to a Th11 response through interleukin (IL)-12 production.\textsuperscript{13–16} This change in the immune response, as well as the expression of Th11 cytokines (tumor necrosis factor [TNF] \(\alpha\) and interferon [IFN] \(\gamma\)), can lead to glucocorticoid insensitivity by increased expression of glucocorticoid \(\beta\) receptor.\textsuperscript{2} It is proposed that \textit{S. aureus}, either in biofilms or in epithelial or inflammatory cells, secretes toxins that result in stimulation of T cells and recruitment of inflammatory cells, particularly eosinophils, resulting in polyp formation.\textsuperscript{2}

**Hereditary Conditions Associated With CRS**

There are at least 2 inherited disorders that are commonly associated with CRS with polyp formation: cystic fibrosis (CF) and primary ciliary dyskinesia syndrome. Cystic fibrosis is a relatively common autosomal recessive disorder characterized by a defect in chloride channel transport in systemic mucus glands, leading to the production of thick, tenacious mucus, which results in significant pulmonary disease. Cystic fibrosis is caused by mutations in the 250-kb, 27-exon CF transmembrane conductance regulator gene, \textit{CFTR}, located at chromosome 7q31.2.\textsuperscript{17} The protein product of the \textit{CFTR} gene is a chloride channel protein identified in mucus glands.\textsuperscript{17} Although CF was once considered fatal in early childhood, CF life expectancy has increased with improved treatment and management of disease symptoms. As a result, other disease manifestations have become evident. Eventually most CF patients will develop CRS with polyps.\textsuperscript{18–20} Microarray profiling shows similar glandular gene expression in CRS patients with and without CF, with the exception that CF patients with CRS also show increased expression of the orthodenticle homeobox 2 gene, \textit{OTX2}, suggesting this glandular gene is CF associated.\textsuperscript{21}

Primary ciliary dyskinesia syndrome, or immotile cilia syndrome, is a heterogeneous collection of rare autosomal recessive disorders characterized by defects in the structure and function of cilia, leading to CRS with polyps and recurrent infections.\textsuperscript{20,22} About 50% of patients with primary ciliary dyskinesia syndrome have situs inversus, CRS, and bronchiectasis (Kartagener syndrome). The disorders are characterized by ultrastructural defects in proteins in the outer or inner dynein arms of the ciliary unit. Several genes and loci have been implicated in the disease process, with the 2 most common being dynein intermediate chain 1 (DNAI1), located on 9p13.3, and dynein heavy chain 5 (DNAH5), located on 5p15.2.\textsuperscript{22} Together these 2 loci are associated with about 40% of primary ciliary dyskinesia syndrome cases. Other genes and loci involved in the disorders include thioredoxin domain–containing protein 3 (TXNDC3), located at 7p14.1; dynein heavy chain 11 (DNAH11), located at 7p21; radial spoke head (RSPH) 4 homologue A (RSPH4A), located at 6q22.1; and RSPH9, located at 6p21.1, as well as loci for which the genes are unknown: 9q13.42–q13.43, 15q13.1–q15.1, 16p12.1–p12.2, and 15q24–q25.\textsuperscript{22} Clinically available tests for the most common mutations are available.

**Molecular Genetics of CRS**

A genetic basis for CRS is supported by familial tendencies as well as the association of CRS with genetic syndromes such as CF and primary ciliary dyskinesia syndrome, as discussed above.\textsuperscript{2,4,23,24} It is known that CRS with nasal polyps shows familial tendencies; however, environmental factors are also likely involved. Gene expression profiling using microarray technology, reverse transcriptase-polymerase chain reaction, and immunohistochemistry comparing CRS patients with nasal polyps with normal controls as well as with those CRS patients without polyps shows upregulation of numerous genes and their gene products, particularly those associated at least in part with inflammatory responses, immune cell trafficking, respiratory pathways, and cell movement.\textsuperscript{2,4,23,24} The most commonly upregulated genes include mammaglobin (a marker associated with mammary gland neoplasia but having an unknown role in CRS) and inflammatory mediators IL-6, IL-12a, IL-13, and TNF-\(\alpha\), whereas down-regulated genes include the Clara cell 10 protein (uteroglobin) gene and other genes, although the significance of these findings is not completely understood.\textsuperscript{23–26} Recent studies using gene expression profiling have also shown upregulation of glandular-associated genes in CRS.\textsuperscript{27} Polymorphisms in a number of genes such as uteroglobin (which has anti-inflammatory/immunomodulatory properties), TNF-\(\beta^2\), human leukocyte antigen (HLA) B54 (HLA-B54), \textit{CFTR}, lymphotyoxin \(\alpha\) (LTA), transforming growth factor \(\beta\) (TGF\(\beta1\)), IL-1 receptor agonist (IL1RN), IL-12, \(\alpha\)-1 antitrypsin, mesenchymal-epithelial transition (MET), and \(\beta2\) adrenoceptor (ADRB2) have also been observed in CRS patients.\textsuperscript{24–26} Genome-wide association studies have detected a locus with CRS predisposition on 7q31.1–7q32.1 in the area of the \textit{CFTR} gene, so it is likely that this gene plays a role in CRS.\textsuperscript{42–43} Interestingly, heterozygotes for the \textit{CFTR} mutation have a greater incidence of CRS than controls.\textsuperscript{43}

Chronic rhinosinusitis with polyps is distinct from CRS without polyps clinically, pathologically, phenotypically, and genetically.\textsuperscript{2,23,25,26,37} Chronic rhinosinusitis without polyps is commonly characterized by chronic inflammation without a significant number of eosinophils and expression of T\(\gamma\)1
cytokines (IFN-γ, TNF-α, and IL-2), whereas CRS with polyps shows marked chronic inflammation with eosinophils and overexpression of T1,2 cytokines (IL-4, IL-5, IL-6, IL-10, and IL-13). A genetic predisposition to nasal polyps has been reported. DNA microarray technology has shown differential expression of a number of genes in CRS with and without polyps, with the most significantly upregulated gene in CRS with polyps being lipophilin, butyrophilin, prostate stem cell antigen, and prostate-specific antigen compared with CRS patients without polyps. Galectin-1 and annexin-1 genes, both modulators of immune response and anti-inflammatory roles, are upregulated in CRS with polyps. Treatment with corticosteroids results in down-regulation of annexin-1 but not galectin-1, indicating that these genes have anti-inflammatory effects by different means. By oligonucleotide microarray in patients with CRS with polyps, differential transcriptional activity of hundreds of genes compared with normal controls has been shown. Most of the upregulated genes and their products appear to be related to inflammatory and immune modulated responses.

There are associations of CRS with polyps with certain HLA types, particularly alleles HLA-DRB1*03 and *04, HLA-DQA1*02,1, and HLA-DBQ1*02.62-63 The HLA-B*07 and HLA-Cw*12 alleles have been more commonly identified in CRS patients with polyps. In addition, polymorphisms in the IL-1α gene have been associated with nasal polyposis. Arg16 to Gly polymorphisms in the ADRB2 gene, the product of which effects smooth muscle contraction, have been observed in blood samples from CRS patients with polyps compared with controls.64

Genetic predisposition to glucocorticoid resistance has been observed in some CRS patients via increased numbers of glucocorticoid β receptors that lack the ability to bind glucocorticoids. Corticosteroid resistance has been documented in patients with increased glucocorticoid β receptor expression. There appears, in part, to be a genetic predisposition to aspirin sensitivity. Genotyping of HLA-DRB1 shows a predisposition to aspirin sensitivity polyps in patients with haplotypes HLA-DR7-DQ1*0201 and HLA-DR7-DQB1*0202. In addition, HLA-A*24, HLA-Cw*12, and HLA-DRB1*04 alleles are significantly higher in CRS patients with aspirin sensitivity. Single-nucleotide polymorphisms have been observed in the promoters of prostaglandin E2 receptor subtype 2 gene and IL-13 genes as well as the leukotriene C4 synthase (LTC4S) gene.65,66,67 Using microarrays for global gene expression, 2 genes, indoleamine 2,3 dioxygenase (INDO) and IL receptor type 2 (IL1R2), were found to be related to aspirin sensitivity. Genome-wide expression microarray studies found upregulation of the periostin (POSTN) gene compared with CRS with polyps. Other upregulated genes include MET and protein phosphate 1 regulatory subunit, whereas downregulated genes include prolactin-induced protein and zinc α-2 glycoprotein.

**Aspirin Sensitivity Syndrome**

**Background.**—About 15% of patients with nasal polyps have aspirin sensitivity syndrome (Samter triad).68 Aspirin sensitivity syndrome is an underrecognized entity characterized by the clinical triad of adult-onset asthma, nasal polyps, and sensitivity to aspirin or other nonsteroidal anti-inflammatory drugs. The condition is more commonly seen in young adult women. The incidence is unknown because it is only clinically unrecognized. The pathogenesis of the syndrome is not considered allergic in nature because patients have baseline CRS symptoms, but they are worsened following the use of aspirin or other nonsteroidal anti-inflammatory drugs. Histologically, aspirin-sensitive patients show persistent and severe inflammation of the sinonasal mucosa with numerous eosinophils and are often described as having a hyperplastic eosinophilic rhinosinusitis with polyposis formation. In addition, eosinophilic mucin (allergic mucin) may be observed.69 Aspirin sensitivity has a poor response to corticosteroids and a progressive clinical course with worsening of asthma and CRS.

**Molecular Genetics.**—The pathogenesis of aspirin sensitivity is poorly understood, but it is believed to be due to a defect in the arachidonic acid cascade, leading to overproduction of leukotrienes, especially cysteinyl leukotriene, a mediator of bronchoconstriction, mucus secretion, inflammatory cell infiltration, and increased eosinophil survival.

**CRS and Association With Fungal Infection**

In 1999, a controversial study indicated that most, if not all, cases of CRS are due to fungi. In this study, using sensitive culturing techniques that took advantage of proteolytic agents that helped degrade mucin, essentially all CRS patients grew fungal pathogens with multiple fungi often cultured per patient; however, all control subjects also had positive fungal cultures, although the number of fungi per patient was fewer. Although this study has not been universally accepted, there have been more recent studies that have supported this initial work. Association of fungi, particularly fungal proteases, with the production of marked inflammatory reactions mediated by T1,2 cytokines and the identification of fungi using ultrasensitive culturing and in situ techniques has led support for the potential role of fungi in CRS. On the other hand, antifungal therapy has resulted in little, if any, improvement in CRS patients, although more recent studies indicate that perhaps the most useful antifungal agents have yet to be trialed. The most commonly described form of CRS associated with fungi is AFRS.

**Allergic Fungal Rhinosinusitis**

**Background.**—Allergic fungal rhinosinusitis occurs in immunocompetent patients who develop an allergic reaction to extramucosal fungal antigens. The pathogenesis of AFRS is not completely understood. Although type 1 and type 3 hypersensitivity had initially been considered essential for the development of AFRS, more recent studies have suggested that fungi induce production of T1,2 cytokines and the subsequent inflammatory reaction produces results in the disease entity. Grossly, the sinus contents from AFRS patients are described as inspissated, claylike material that is green, brown, or grayish in color. Microscopic examination shows eosinophilic (“allergic”) mucin that contains mucin admixed with sloughed epithelial cells, eosinophils, Charcot-Leyden crystals, and other inflammatory cells arranged in a laminar pattern and associated with rare, scattered fungal hyphae. Allergic mucin has also been described in patients without evidence of fungal infection. Ferguson coined the term *eosinophilic mucinous rhinosinusitis* to describe a patient population that showed characteristic eosinophilic mucin but no histologic or culture evidence of fungus. However, more recent studies have called into question whether eosinophilic mucinous rhinosinusitis is a separate entity, using more sensitive
culturing techniques or more sensitive methods for detecting fungi in eosinophilic mucin, including protease digestion with trypsin prior to GMS stain, immunofluorescence for chitinase and fungal antigens, and fluorescence in situ hybridization techniques, particularly in evaluating biofilms. When positive, cultures from AFRS patients most often grow dematiaceous fungi or *Aspergillus* sp., depending on the geographic location. A limited study using in situ hybridization found that about 50% of AFS patients contained *Aspergillus or Penicillium* ribosomal RNA.

**Molecular Genetics.**—Initial DNA microarray analyses have not observed significantly different expression profiles between AFRS and eosinophilic mucinous rhinosinusitis, although these results are preliminary. However, in a recent study using polymerase chain reaction amplification to perform HLA DNA genotyping in CRS and AFRS, at least 1 class II HLA-DQB1*3 allele was observed in 66% of AFRS patients, and 50% of patients with hypertrophic sinus disease with DQB1*301 and *302 allelic variants in AFRS but not hypertrophic sinus disease, suggesting that these 2 conditions that may both histologically demonstrate allergic mucin have different molecular profiles. An additional study using automated surface enhanced laser desorption/ionization time-of-flight mass spectrometry on serum samples, a technology that identifies relative concentrations of low-molecular-weight proteins, the proteomic profile of patients with AFRS in comparison with those with aspirin sensitivity syndrome and CRS with nasal polyps has shown that the proteomic profile among the groups is different and that analysis can distinguish among the 3 groups with high sensitivity and specificity. The molecular differences between CRS and AFRS support that AFRS is a different entity than CRS.

**SINONASAL INFECTIONS**

The sinonasal tract is a common place for infectious diseases. Numerous bacterial, fungal, mycobacterial, viral, and parasitic disease entities can involve the nasal cavity and paranasal sinuses. This section will focus on some of the sinonasal infectious diseases that have a genetic predisposition.

**Rhinoscleroma (Klebsiella rhinoscleromatis)**

**Background.**—Rhinoscleroma ("hard nose") is a chronic self-limited, granulomatous disease that involves upper respiratory tract structures. The disease is caused by *K. rhinoscleromatis*, a gram-negative organism that is endemic to Central America, Egypt, Africa, India, and Indonesia and rarely seen in the United States. Klebsiella rhinoscleromatis is contracted by prolonged direct inhalation of contaminated material. The pathogenesis of the disease is unknown, but infection is associated with crowded conditions and poor hygiene; however, more recent studies indicate a possible genetic factor, and the disease may be related to a genetically predisposed inflammatory reaction to the bacterium, particularly because host histiocytes are able to engulf but not destroy the bacteria. Clinically, patients present with inflammatory polyps that involve the nasal septum and spare the sinuses. There are 3 stages of rhinoscleromatosis:

1. The catarrhal or atrophic stage, in which patients have a nonspecific rhinitis that then develops into a purulent nasal discharge with mucosal crusting.
2. The granulomatous or hypertrophic stage, in which there is the development of nasal polyps, bleeding, nasal enlargement, and nasal cartilage destruction.
3. The sclerotic or fibrotic stage, in which the inflammatory changes undergo fibrosis. This stage can result in significant facial deformities.

Tissue biopsies reveal distinctive findings, the most characteristic of which is the granulomatous phase, in which there is a lymphoplasmacytic infiltrate with Russell bodies, pseudoepitheliomatous hyperplasia of the mucosa, and groups of large vacuolated histiocytes (Mikulicz cells) that contain the bacterial organisms. If numerous, the bacteria can be seen on hematoxylin-eosin stain, but Gram, periodic acid Schiff, silver, or immunohistochemical staining may be required to confirm the diagnosis.

**Molecular Genetics.**—Although rhinoscleroma is clearly due to a bacterial infection, there have been reports of potential genetic predisposition with familial cases and the potential that the inflammatory reaction generated toward the organism may be related to a defect in immune regulation. The HLA-DQ3 allele has been seen in a family with rhinoscleromatosis, and more recent investigations have shown the HLA haplotype HLA-DQA1*301-DQB1*301 in almost 50% of patients with the disease. It is believed that this HLA haplotype can bind to *K. rhinoscleromatis* and as a result enables the production of the inflammatory reaction, which causes the clinical and pathologic manifestations.

**Leprosy (Mycobacterium leprae)**

**Background.**—Leprosy is a chronic granulomatous disease caused by *M. leprae*. The infection usually affects superficial peripheral nerves, skin, and mucous membranes, and involvement of the nasal cavity and paranasal sinuses may present before the clinical skin lesions. Leprosy is a spectrum of disease ranging from a localized, deforming, self-limited process (tuberculous leprosy [TT]) to systemic disease that, left untreated, may be fatal (lepromatous leprosy [LL]). Most cases of leprosy are concentrated in Brazil, India, Madagascar, Mozambique, and Nepal. Histologic findings vary according to the form of leprosy, and the histology varies with the immune response to the infection. In TT (T1 response—IL-2, IFN-γ), there are noncaseating granulomas that destroy nerves, and organisms are difficult to identify. In LL (T2 response—IL-4 and IL-5), there is diffuse inflammatory reaction consisting of macrophages, foamy histiocytes (Virchow or lepra cells), and many intracellular organisms. Assays have been developed for demonstration of *M. leprae*—specific DNA and ribosomal RNA sequences in various specimens including nasal smears and blood. Polymerase chain reaction for bacterial DNA is most sensitive and can detect fewer than 10 organisms. In situ hybridization can be used to establish the diagnosis if necessary.

**Molecular Genetics.**—Genetic factors are important for disease susceptibility, including the type of inflammatory response as well as the types of cells infected by the organism. The genetics behind leprosy is complex, with polymorphisms in a variety of genes associated with different forms of the disease. Polymorphisms in the following genes have been observed in populations with LL (or forms of disease close to the LL side of the spectrum): SLCT1A1 (solute carrier family member 1), COL3A1 (procollagen III α 1), CTLA4 (cytotoxic T lymphocyte—associated antigen), TLR2 (toll-like receptor 2), MICA/HLA B haplotype, TNF-α, TNF-α-LTA (lymphotoxin α) haplotype, complement component 4B, and VDR (vitamin D receptor). Tuberculous leprosy (or forms of disease close to the TT side of the spectrum) is
associated with polymorphisms in TAP2 (transporter 2, ATP binding cassette, subfamily B) and heat shock protein 1A genes.\textsuperscript{97} In population studies, TT and LL have been associated with HLA class II genes, predominantly DQw1, DR3, DQB1, DQA1, and DRB1, with DRB1*1501 associated with LL and DRB8*1502 with TT. A genome-wide association study on TT patients has shown an area of linkage of chromosome 10p13 that includes the macrophage mannose receptor gene, the product of which mediates pathogen phagocytosis.\textsuperscript{7} An area of weaker linkage has been identified on chromosome 20p12 that seems related to immune response to the organism.\textsuperscript{97}

**Leishmaniasis**

**Background.**—Leishmaniasis is caused by the protozoan *Leishmania*, which is transmitted by the female sand fly. There are many different species, and the spectrum of disease is broad and includes 3 major forms: (1) cutaneous (most common), (2) visceral, and (3) mucocutaneous (rarest). The forms of disease vary with the geographic location, with cutaneous and mucocutaneous forms more commonly encountered in Afghanistan, Brazil, Iran, Iraq, Peru, and Saudi Arabia and visceral forms most common in Bangladesh, Brazil, India, Nepal, and Sudan.\textsuperscript{101,102} Mucosal leishmaniasis is caused by *Leishmania braziliensis*, *Leishmania panamensis*, and, rarely, *Leishmania amazonensis*.\textsuperscript{102} Mucosal involvement alone is rare, and the nasal cavity is the most frequent site of involvement.\textsuperscript{102} Mucosal lesions may develop as a result of disseminated disease or direct contact with cutaneous lesions. Diagnosis is usually made by identification of the organisms in tissue or cytologic specimens, with material taken from the ulcer base usually having the highest yield.\textsuperscript{102,103}

Detection by polymerase chain reaction is usually the most sensitive method for the diagnosis of cutaneous and mucocutaneous disease.\textsuperscript{103} Immunohistochemistry and in situ hybridization have been used to identify the organisms in tissue.\textsuperscript{104} Microscopically, the parasites appear as 1.5- to 3-μm ovoid to round organisms within histiocytes. The organisms are identified on hematoxylin-eosin and Giemsa stains on smears. In tissue sections, Giemsa stains are not usually useful, but the organisms may be highlighted with Brown and Hopps modified Gram stain. The complications of leishmaniasis include secondary bacterial infection of ulcerated lesions, bleeding, disfigurement, and, rarely, splenic rupture. With early treatment, the majority of patients are cured, but untreated cases can be fatal. Death is usually secondary to bacterial infection of ulcerated lesions.

**Molecular Genetics.**—There have been documented familial clusters of leishmaniasis, but it is unknown whether this is due to contamination from family members being in close proximity.\textsuperscript{105} However, the host immune response to the organism likely has a genetic component.\textsuperscript{102,105} Polymorphisms in TNF-α, particularly the TNF-308 lymphotoxin and major histocompatibility complex class II genes, have been reported.\textsuperscript{105} In addition, there are other associations, including HLA-Cw7, HLA-DQw3, HLA-Bw22, DRB1*407, DPA*401, and DPB1*101, with mucosal lesions showing increased frequency of HLA-DQw3 and decreased frequency of HLA-DR2.\textsuperscript{105}

**AUTOIMMUNE DISEASE/VASCULITIS**

**Sarcoidosis**

**Background.**—Sarcoidosis is a chronic systemic disease of unknown etiology characterized by nonnecrotizing granulomas that may involve multiple sites, including the sinonasal tract in approximately 4% of patients.\textsuperscript{106–108} Women aged 20 to 40 years are more commonly affected. Grossly, sinonasal mucosal lesions are friable and crust-d.\textsuperscript{106–108} In addition, submucosal nodules formed by fibrosis and granulomatous inflammation may be present, and extensive cartilage destruction may be seen.\textsuperscript{106–108} Histologically, well-formed epithelioid granulomas with or without fibrosis are characteristic. Infection and other causes of granulomatous inflammation, such as bacterial, mycobacterial, and fungal infections; prior surgical intervention; vasculitis; and autoimmune diseases need to be excluded prior to making a diagnosis of sinonasal sarcoidosis. Treatment with corticosteroids is recommended as well as surgical management to alleviate sinonasal symptoms.

**Molecular Genetics.**—The pathogenesis of sarcoidosis, although unknown, is considered multifactorial, with genetic, environmental, and possibly infectious factors likely. Familial cases of sarcoidosis are well known.\textsuperscript{109} In addition, certain ethnic backgrounds have higher incidences of sarcoidosis, with the disease being 3 times more frequent in African Americans in comparison with whites in the United States. Because the disease is characterized by granulomatous inflammation, it is not surprising that HLA genes appear to be affected. Polymorphisms in the HLA haplotype HLA-B8/DR3 gene are considered a risk factor for the disease.\textsuperscript{109}

In addition, the HLA-DRB1 gene with DRB1*1101 allele is associated with sarcoidosis in Caucasians and African Americans. Interestingly, HLA-DPB1 Glu 69 is not associated with sarcoidosis but is associated with chronic beryllium exposure, another entity characterized by systemic nonnecrotizing granulomas.\textsuperscript{109} Polymorphisms in a variety of genes, including Clara cell 10KD protein, complement receptor 1, CF transmembrane regulator, heat shock protein 70-like, IL-1β, IL-4 receptor, IL-18, IFN-γ, toll-like receptor 4, transforming growth factor β, TNF-α, vascular endothelial growth factor, and vitamin D receptor have all been reported.\textsuperscript{109}

**Antineutrophilic Cytoplasmic Antibody–Associated Vasculitides in the Sinonasal Tract (Wegener Granulomatosis and Churg-Strauss Syndrome)**

**Background.**—Necrotizing vasculitides associated with antineutrophilic cytoplasmic antibodies (ANCA) include Wegener granulomatosis (WG), microscopic polyangiitis, and Churg-Strauss syndrome (CSS). Wegener granulomatosis and CSS both can involve the sinonasal tract. Wegener granulomatosis is a systemic ANCA-related disease that is most commonly associated with necrotizing granulomatous vasculitis of the upper and lower respiratory tract and kidneys. Wegener granulomatosis is characterized by associated with c-ANCA, in which patients have autoantibodies to proteinase 3, a protein found in neutrophilic granules.\textsuperscript{110} Although WG is of unknown etiology, the pathogenesis is believed to be multifactorial, with a combination of environmental, genetic, and possibly infectious factors involved.\textsuperscript{110} Environmental factors, including geographic location and time of year, are considered important. Although infection is believed important in disease pathogenesis, unlike in animal models, an associated organism has not been identified in humans.\textsuperscript{110} Men and women are equally affected, and the disease can be seen in any age, although most patients are older than 45 years. Up to 80% of patients present with sinonasal involvement, and in rare cases just the sinonasal cavity is affected. Clinically, patients
present with symptoms ranging from mild obstruction to nasal cartilage destruction. Histologically, necrotizing vasculitis and inflammation consisting of histiocytes, lymphocytes, plasma cells, and multinucleated giant cells surrounding geographic areas of basophilic necrosis are characteristic. Well-formed granulomas are usually not seen. A diagnosis of WG is difficult to make on nasal biopsies, and usually multiple biopsies are necessary before a definitive diagnosis can be rendered. The mainstay of therapy is cyclophosphamide, usually combined with steroids.

Churg-Strauss syndrome is a rare ANCA-associated vasculitis (usually p-ANCA) syndrome characterized by bronchial asthma, systemic necrotizing vasculitis, and peripheral eosinophilia. Although uncommon, the disease may present with sinonasal involvement. Sinonasal tract involvement consists of sinonasal polyps, chronic sinusitis with eosinophilia, and, rarely, diagnostic necrotizing vasculitis.

### Molecular Genetics

The characteristic cytokine profile in WG is a T_{H}1/T_{H}17 response with the production of cytokines such as TNF-α and IFN-γ, which may play a role in inciting the characteristic granulomatous inflammatory reaction. Because there are known familial cases of WG, genetic associations have been proposed. Rare mutations in the TAP gene have been reported to have a clinical scenario similar to that of WG, but the defect in these patients is believed to be due to class I HLA deficiency and not an ANCA-associated vasculitis. This does indicate, though, that WG likely involves alterations in the class I HLA system. DNA-based HLA typing by sequence-specific priming or sequence-specific oligonucleotides shows an association of WG and other ANCA-associated vasculitides with DR4 and A1B8DR3 and decreased association with DR13(6) and DR1 (in WG only). The strongest association to date, though, has been the association with the HLA-DPB1 gene, which has also been linked to chronic beryllium exposure, another disease characterized by granulomatous inflammation. Recent studies have also shown an association of HLA-DR4, although to a lesser degree than HLA-DPB1*0401. Interestingly, the HLA-DPB1*0401 allele shows increased risk factor for WG in ANCA-positive but not ANCA-negative patients. Using a microsatellite screen and tag single-nucleotide polymorphism genotyping, a strong association of WG with a 280-kb region on chromosome 6p21.3 has been observed in the area of the retinoid X receptor on chromosome 6p21.3 has been observed in the area of the retinoid X receptor gene (RXRα), which may play a role in regulating transcription and immunity.

Polymorphisms in the CD226 gene, a gene that has been associated with other autoimmune diseases, have been linked to chronic inflammatory disorders, such as uveitis, multiple sclerosis, and inflammatory bowel disease. Polymorphisms in the IFN regulatory factor 5 (IRF5) gene, a gene that has been associated with autoimmune diseases, have been linked to chronic inflammatory disorders, such as uveitis, multiple sclerosis, and inflammatory bowel disease. Polymorphisms in the protein tyrosine phosphatase, nonreceptor type 22 (PTPN22) 620 allele, which is seen in many inflammatory disease processes, have been identified in WG.

In contrast to WG, the inflammatory reaction in CSS is predominantly T_{H}2. Genetically, CSS is associated with HLA-DRB1, HLA-DRB3, and HLA-DRB4 genes but not with HLA-DPB1*0401, which is strongly associated with strong association with the IL10.2 haplotype, which is linked to IL-10 expression, is observed in CSS but not WG. A case of CSS and WG in first-degree relatives associated with the HLA haplotype A*03 B*07 C*07 DRB1*0404, DQB1*0302 has been described.

### SUMMARY

In summary, the sinonasal tract is frequently affected by inflammatory lesions that arise through complex interactions of environmental, infectious, and genetic factors. Because these lesions are all inflammatory in nature, the molecular pathology surrounding them is most commonly

<p>| <strong>Table 1. Human Leukocyte Antigen (HLA) Associations with Inflammatory Sinonasal Disease</strong> |</p>
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<tr>
<td>Rhinoscleroma</td>
<td>HLA-DRB1, HLA-DQA1, HLA-DQB1</td>
</tr>
<tr>
<td>Leprosy</td>
<td>HLA-DRB1, HLA-DQA1, HLA-DQB1</td>
</tr>
<tr>
<td>Leishmaniasis</td>
<td>HLA-DRB1, HLA-DQA1, HLA-DQB1</td>
</tr>
<tr>
<td>Churg-Strauss</td>
<td>HLA-DRB1, HLA-DQA1, HLA-DQB1</td>
</tr>
</tbody>
</table>

**Abbreviations:** AFRS, allergic fungal rhinosinusitis; CRS, chronic rhinosinusitis.

<p>| <strong>Table 2. Known Chromosomal Linkages of Select Inflammatory Sinonasal Disorders</strong> |</p>
<table>
<thead>
<tr>
<th><strong>Chromosome Location</strong></th>
<th><strong>Gene</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>CRS</td>
<td>Cystic fibrosis: 7q11.2, CFTR</td>
</tr>
<tr>
<td>Primary ciliary dyskinesia: 9p13.3, DNAH1</td>
<td></td>
</tr>
<tr>
<td>5p15.2, DNAH5</td>
<td></td>
</tr>
<tr>
<td>7p14.1, TXDNC3</td>
<td></td>
</tr>
<tr>
<td>7p21, DNAH1</td>
<td></td>
</tr>
<tr>
<td>6q22.1, RSPH4A</td>
<td></td>
</tr>
<tr>
<td>6p21.3, RSPH9</td>
<td></td>
</tr>
<tr>
<td>Infection: Leprosy, 10p13, 20p12</td>
<td></td>
</tr>
<tr>
<td>Autoimmune Wegener: 6p21.3</td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviation:** CRS, chronic rhinosinusitis.
due to upregulation and down-regulation of genes that affect inflammatory responses and immune regulation (see Tables 1–3). Elucidation of these molecular pathways and gene polymorphism will further our understanding not only of diagnosing but of treating these inflammatory disorders that affect a large proportion of the population.

References


Table 3. Gene Polymorphisms and Gene Expression in Select Sinonasal Inflammatory Lesions

<table>
<thead>
<tr>
<th>Gene Polymorphisms</th>
<th>Gene Expression</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRS with/without polyps IL-1α, ADRB2, uteroglobin, TNF-β2, HLA-B54, CFTR, LTA, TGF-β1, IL1RN</td>
<td>Upregulated: mammaglobin, lactoferrin, TNF-α</td>
</tr>
<tr>
<td>Aspirin sensitivity Sarcoidosis PG receptor type 2, IL-13, LTC4 synthase Clara cell 10KD, complement receptor 1, CFTR, HSP-70-like protein, IL-1α, IL-4 receptor, LI-18, IFN-γ, toll-like receptor 4, TGF-β3, VEGF, VDR</td>
<td>IL-4, L-5, IL-13, IL-4 receptor, IL-5 receptor, galecetin 1, annexin 1</td>
</tr>
<tr>
<td>Wegener CD226 (DNAM1), TNFAP13, CDK6, IRF5, PTPN226</td>
<td>Downregulated: Clara cell 10, S100 family, lipophilin, butyrophilin, prostate stem cell antigen, proplatelet basic antigen, IL-12, SPINK 5</td>
</tr>
<tr>
<td>Churg-Strauss FCGRB3, CTLA4 IL10, CD226</td>
<td>IND0, IL1R2, peroxin</td>
</tr>
</tbody>
</table>

Abbreviation: CRS, chronic rhinosinusitis.