Historically, chronic sinusitis (CS) was considered a single disease entity or, at best, could be separated into two diseases, CS with nasal polyps (NPs) and CS without NPs. It is now recognized that there exist multiple variants of CS including presentations characterized by chronic infection, noneosinophilic inflammation, chronic hyperplastic eosinophilic sinusitis (CHES), aspirin-exacerbated respiratory disease, allergic fungal sinusitis, the disease associated with cystic fibrosis, and, presumably, many others, each with specific pathogenic mechanisms and each requiring individualized approaches to management. Each of these conditions can variably present as more likely (CHES, aspirin-exacerbated respiratory disease, allergic fungal sinusitis, and cystic fibrosis) or less likely (chronic infection, non-eosinophilic sinusitis) to present with NPs. CHES with or, less commonly, without NPs is primarily defined by the prominent expression of eosinophils. This disease is frequently associated with NPs but also with asthma and allergic (IgE) sensitization to aeroallergens (atopy). Because of the similarities of CHES to allergic disorders and this association with atopy, the potential role of allergy in CHES will be the primary focus of this article.

**IMMUNE MECHANISMS OF CHES**

CHES is an inflammatory disease characterized by the prominent accumulation of eosinophils in the sinuses and, when they are present, in the associated NP tissue. NPs frequently complicate this condition, and, as such, their presence (especially in the concomitant presence of asthma) has been proposed as presumptive diagnostic evidence for an underlying eosinophilic disease. However, CHES can only be unambiguously diagnosed on histochemical staining of tissue for eosinophils or via quantification of eosinophil-derived mediators (such as eosinophil cationic protein or major basic protein). In CHES, the sinus tissue shows a marked increase in cells that express cytokines (IL-5, granulocyte macrophage colony-stimulating factor, etc.), chemokines (CCL5, CCL11, CCL24, etc.), and proinflammatory lipid mediators (e.g., cysteinyl leukotrienes) that are responsible for the differentiation, survival, and activation of eosinophils. Because eosinophils themselves are a prominent source of many of these mediators, CHES can best be thought of as a disease of unrestrained self-perpetuating inflammation and that once eosinophils are recruited, they provide the growth factors necessary for their further recruitment, proliferation, activation, and survival. This certainly is consistent with the chronicity of this disorder and the requirements for frequent surgical revisions. As such, although allergy might be important in precipitating or possibly exacerbating the disorder, it has to be recognized that ongoing allergen exposure may not be required for its persistence.

**EPIDEMIOLOGY OF ALLERGY IN CS**

More than 50% of individuals with allergic rhinitis (AR) have clinical or radiographic evidence of CS and, conversely, 25–58% of individuals with sinusitis have aeroallergen sensitization. Elevated total IgE is a risk factor for the presence of severe CS and both sensitivity to multiple allergens and sensitivity to perennial allergens (e.g., dust mites) are independently associated with increased likelihood of having CS. Together, these studies support the concept that CS could be an atopic disease driven by IgE sensitization to aeroallergens. However, the mechanisms by which aeroallergens might produce CHES are not inherently obvious and the presence of allergy in CHES patients may simply reflect the coincidental occurrence of two relatively common clinical conditions. Given these caveats there remains tentative arguments supporting a role of allergy in CS.

**PUTATIVE MECHANISMS LINKING AR TO CS: DIRECT AEROALLERGEN REACTION**

Aeroallergens gain access to the nares (and lungs) by inspiration into the respiratory tract. However, breathing alone can not directly drive aeroallergens into the sinuses. This process can be accomplished via diffusion, a process dependent on the particles remaining airborne within the nares for a sufficient period of time, something unlikely, in part, reflecting their size. Mucociliary flow can not contribute, because—even when functioning—the movement is in the opposite direction. Furthermore, CHES is generally associated with occlusion of the ostiomeatal complex, often with NPs, and this occlusion will categorically preclude entry of aeroallergens. Studies performed with insufflated radiolabeled ragweed particles and contrast media have...
confirmed the inability of these particles to enter the sinuses.\textsuperscript{25,26} Interestingly, nose blowing does enable particulate access to the healthy sinuses. Early studies with single-photon emission computed tomography imaging suggested increased metabolic uptake in the sinuses of CS patients with AR during a sensitization-relevant allergy season, and these changes became less active out of season.\textsuperscript{27} However, more recent and more comprehensive studies by the same group have not been able to confirm this finding using single-photon emission computed tomography, indium, or positron emission tomography imaging of the sinuses, suggesting that seasonal allergen exposure alone does not drive or exacerbate sinus disease.\textsuperscript{28} In contrast, another recent study did show increased eosinophilia in the maxillary sinuses of allergic subjects during the season of exposure.\textsuperscript{29}

**SYSTEMIC ALLERGIC INFLAMMATION**

Given the limitations of direct inhalation of aeroallergens with diffusion into the sinuses as an allergic mechanism in CHES, the link between inhalant allergies and sinusitis, if present, must be ascribed to a systemic inflammatory process. This concept involves a systemic interaction between the local nasal airway, nasal-associated lymphatic tissue, the bone marrow, and the sinuses (Fig. 1). In sensitized subjects, allergen exposure engages resident nasal dendritic cells. Allergenic peptides loaded on dendritic cells readily migrate to nasal-associated lymphatic tissue where they will activate effector T-helper lymphocytes. However, in these previously sensitized subjects, inhaled aeroallergens can also be processed by nonprofessional antigen-presenting cells in the nares including macrophages, B lymphocytes, mast cells, and even eosinophils themselves, which can also activate allergen-specific effector T lymphocytes both in secondary lymphoid tissue and in those that are residing in the nasal tissue. The cytokines associated with allergic inflammation do not function hormonally. Thus, Th2-associated cytokines such as IL-4, IL-5, and IL-13 can not be readily identified in serum samples and are certainly unlikely to access the bone marrow at a concentration sufficient to drive hematopoietic differentiation. In contrast, these effector memory T cells that have been reactivated in the nasal or nasal lymphatic tissue migrate to the bone marrow.\textsuperscript{30,31} Once delivered to the bone marrow, cytokines derived from these Th2-like cells will stimulate the production of inflammatory cells including primarily eosinophils, but presumably also basophils and mast cell precursors.\textsuperscript{32–34} Newly generated eosinophils are released into the circulation where they are programmed to recognize adhesion molecules ("addressins" such as vascular cell adhesion molecule 1) and chemotactic signals (such as CCL11 [eotaxin] and the cysteinyl leukotrienes) that will recruit them into the inflamed tissue. This mechanism underlies the eosinophilia in the nares that progresses with seasonal nasal allergen exposure.\textsuperscript{13} However, these newly elicited eosinophils (and presumably also mast cell precursors and basophils) will be nonspecifically recruited into any tissue displaying relevant addressins and chemotactic factors including the sinuses of CHES patients (and lungs of asthmatic patients).\textsuperscript{33,34} All of the factors requisite for eosinophil uptake are expressed in CHES/NP tissue.\textsuperscript{33,34} In addition to systemic mechanisms involving the bone marrow, cells newly activated in the nasal airway by allergen also include locally expressed eosinophil precursors (Fig. 1)\textsuperscript{36} so direct recirculation of allergic inflammatory cells between the nares, local lymphatic tissue, and the sinuses likely also occurs. Obviously, subjects without preexisting CHES do not express addressins or chemotaxins in their sinon tissue and thus do not have the machinery necessary to recruit inflammatory cells into their sinuses during allergen-induced exacerbations of rhinitis.

Several clinical studies have now produced compelling evidence supporting relevance of such a mechanism in CHES. This includes studies showing a significant increase in eosinophils and eosinophil cationic protein not only in the nose but also in the maxillary sinus.
after allergen exposure. In a more recent seminal study, nasal allergen challenges were performed in one side of the nose, and lavage specimens from both maxillary sinuses were analyzed. Eosinophil numbers significantly increased not only in the ipsilateral but, to an equivalent extent, also in the contralateral maxillary sinuses. These findings show the systemic nature of allergic inflammatory responses and a viable mechanism whereby inhalant aeroallergen exposure in the nares could drive CHES.

**SENSITIZATION TO COLONIZING PATHOGENS**

**Bacteria**

Patients with CHES routinely become colonized with bacteria. These bacteria primarily exist within biofilms, which are present in 29–72% of CS patients. In eosinophilic disease, these bacteria commonly include *Staphylococcus* spp. These bacteria can drive the recurrent acute infections that plague CS patients, when they transform into their planktonic state and emerge from the biofilm. However, even in their indolent biofilm-associated state, these bacteria are not innocuous and can be a robust source of superantigens, immune adjuvants, and of allergenic (IgE inducing) proteins (Fig. 2). Superantigens are proteins that bind directly to the major histocompatibility complex or β-chain of the T-cell receptor, leading to the nonspecific activation of large numbers of T lymphocytes thereby producing a barrage of cytokine secretion. Bacterial-derived superantigen expression can be identified in up to 90% of patients with CS. Because the T cells infiltrating the sinuses of CHES generally display a Th2 cytokine signature, this superantigen-mediated surge in cytokines will include IL-4 and IL-13, production of which will drive any B cells present to synthesize IgE antibodies to any humoral antigen to which that B cell is responding at that moment. As a specific example of this mechanism, this interaction leads to the formation of IgE in the sinus tissue to the *Staphylococcus* enterotoxin itself, and these IgE antibodies can be identified in 27.8% of CS with NP's and 53.8% of CS with both NP's and asthma. IgE antibodies to *staph* enterotoxin cross-link FcεRI on mast cells and basophils in the nose, further expanding the inflammatory response. The antibodies also bind FcεRI on dendritic cells in the nose and sinus promoting facilitated antigen uptake and leading to a vicious cycle of ongoing Th2 cytokine secretion.

**Fungi**

Mold present as commensals in the sinuses can engage pathogen-associated molecular pattern receptors and thereby activate innate immune pathways, ultimately eliciting robust Th2-lymphocyte and eosinophilic inflammatory responses. These pathways underlie the pathogenesis of allergic fungal sinusitis and because these mechanisms are not controversial in this disorder, this will not be further discussed here. What is controversial is whether allergic sensitization to colonizing fungi could contribute to the pathogenesis of CHES. This concept is supported by intriguing observations regarding the colonization within the sinuses and associated striking sensitization especially to *Alternaria* spp. displayed by CHES patients when analyzed as T-cell activation and associated IL-5 secretion. These CHES patients universally did not display IgE sensitization to any of the relevant fungi. The concept that Th2-like helper “allergic” responses can produce eosinophilic inflammation can be identified in 27.8% of CS with NP's and 53.8% of CS with both NP's and asthma. IgE antibodies to *staph* enterotoxin cross-link FcεRI on mast cells and basophils in the nose, further expanding the inflammatory response. The antibodies also bind FcεRI on dendritic cells in the nose and sinus promoting facilitated antigen uptake and leading to a vicious cycle of ongoing Th2 cytokine secretion.
nization) and, as such, a role for fungal colonization in CHES remains intriguing.

THERAPEUTIC IMPLICATIONS

If allergic, then allergen-targeting therapies arguably would have efficacy in the treatment of CHES and, by satisfying Koch’s postulates, this would establish causality. Arguments have been made regarding an allergic mechanism in CHES based on the usefulness of “allergy”-targeting therapeutics such as corticosteroids and leukotriene modifiers in CHES. However, these treatments nonspecifically target the types of inflammation seen in allergic and nonallergic Th2-associated inflammatory disorders, so even if verified, their efficacy cannot be used to support an allergic mechanism. For example, leukotriene modifiers and corticosteroids are equally efficacious in allergic and nonallergic presentations of asthma. Similarly, only one study has suggested beneficial effects of immunotherapy in CHES. However, this study did not sufficiently use objective outcome criteria that could distinguish beneficial influences on the CHES from the expected improvement of the underlying AR.

ANTI-IMMUNOGLOBULIN E

At present, one of the strongest arguments supporting a role for allergy in CHES is derived from studies suggesting benefit of IgE-targeting therapies. A preliminary study providing rationale for these interventions for NPs was a study that functional IgE-expressing mast cells are present in this disease as evinced by the ability of anti-IgE to drive immediate Fgβ2 synthesis. It is intriguing and consistent with the concept that this IgE might be directed against bystander pathogens such as Staphylococcus spp that, in contrast to parallel studies performed on the nasal tissue of grass-allergic subjects, in the NP samples, no inhalant allergen specificity could be identified. Most compelling is tentative suggestion of a role for omalizumab in the treatment of CHES. In a very recent double-blind placebo-controlled study of 24 subjects with asthma and NPs, significant improvements were shown in the treatment arm for symptom, endoscopy, and sinus CT scores after only 16 weeks of treatment and this was associated with significantly improved quality of life. Importantly, this improvement occurred irrespective of the presence of allergy, again suggesting that it may be IgE sensitization to bystander pathogens and not inhalant allergens that is really driving this disease process.

SUMMARY

CHES is an inflammatory disease characterized by an “allergic” inflammatory process with prominent eosinophil infiltration. Aeroallergen sensitization in CHES occurs regularly, but the causality between allergen sensitivity, exposure, and disease is unclear and this may just be a coincident presentation of two relatively common disorders. Allergen can not readily directly enter the healthy sinuses either by diffusion or by ciliary flow, and, even more problematic remains the loss of patency of the sinus ostia with sinusitis. Therefore, if driven by aeroallergen sensitization, it seems more likely that the inflammation and tissue eosinophilia found in this disease is driven by nasal allergen exposure with secondary systemic recirculation of allergic cells (Th2 lymphocytes, eosinophil progenitors, and eosinophils) that are activated by nasal allergic disease but are nonspecifically recruited back to the diseased sinuses of CHES. Through these mechanisms, intranasal aeroallergen challenges induce eosinophil influx within not only the ipsilateral sinuses but, more intriguingly, within the contralateral maxillary sinuses. An additional allergic mechanism of CHES comprises generation of IgE to pathogens that colonize or reside in biofilms within the sinuses including especially those derived from Staphylococcus spp. Support for these concepts is derived from evidence regarding therapeutic efficacy of omalizumab, which has shown promise even in patients without obvious allergen sensitization. Although many aspects of the role of allergy in CHES remain a mystery, the mechanisms that have been elucidated allow for improved understanding of this disease, which, ultimately, will lead to better treatments for the patients who live with this disease.

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