Differential Diagnosis of Eosinophilic Chronic Rhinosinusitis

John C. Sok, MD, PhD, and Berrylin J. Ferguson, MD

Eosinophilic chronic rhinosinusitis (ECRS) encompasses a wide variety of etiologies. To date, a unifying pathophysiologic mechanism remains elusive. Eosinophilia is frequently, but not exclusively, caused by immunoglobulin (Ig)E-mediated hypersensitivity and is dominated by the associated cytokine milieu of Th2 inflammation. The provisional subcategories of ECRS include superantigen-induced eosinophilic chronic rhinosinusitis, allergic fungal sinusitis, nonallergic fungal eosinophilic chronic rhinosinusitis, and aspirin-exacerbated eosinophilic chronic rhinosinusitis. Within each subcategory, recent findings supporting distinct mechanisms that promote eosinophilic infiltration are presented, and, therefore, targeted therapeutic interventions with specific antibacterial, antifungal, or immune modulation may be indicated.

Introduction

Chronic rhinosinusitis (CRS) affects more than 30 million people in the United States each year and accounts for 11.6 million visits to physicians’ offices [1–3]. It is increasingly apparent that CRS represents a variety of subtypes, each of which may differ in severity, associated comorbidities, optimal therapies, and prognosis. Past studies of CRS, which lump all subtypes together, provide only limited insight with regard to comorbid associations and the efficacy of various targeted medical or surgical therapies. In 2004, a consensus, which was drawn from representatives from the organized academies of general allergy, otolaryngology, otolaryngic allergy, and rhinology, was reached in defining CRS and recommending research parameters [4]. A general grouping of CRS into forms with nasal polyps (NP) and without nasal polyps was proposed. A further subgrouping of CRS, into either eosinophilic or noneosinophilic histopathologies, was suggested. This strategy could potentially aid in identifying targeted therapies for each subtype of CRS, which might not have been appreciated in studies of a more heterogeneous collection of patients with CRS. The most refractory of the subgroups of CRS are those associated with eosinophilia. In this article, we review the epidemiologic evidence of eosinophilic CRS (ECRS) with regard to severity of disease and prognosis, as well as mechanisms that may account for more extensive disease in the eosinophilic conditions. Additionally, potential different and possibly overlapping mechanisms and associations that might serve as a further subgrouping of ECRS are discussed, both pathophysiologically and in the context of potential logical targeted therapeutic interventions.

Review of Studies of Chronic Rhinosinusitis and Eosinophilia

Both serum eosinophilia and histologic eosinophilia in patients with CRS are associated with more extensive disease and a decreased likelihood of surgical success. In 1994, Newman et al. [5] reported the first large series of patients with symptoms of CRS, uncovering the association between eosinophilia and extensive sinus disease. In their landmark study of 98 patients, serum and tissue samples were assayed for various immunologic parameters, including immunoglobulin (Ig)E antibodies and total eosinophil counts and were compared with radiologic analysis of sinus disease extent by CT scan. This study found a strong positive correlation between extent of disease and eosinophilia. Sixty-five percent of those with extensive disease had eosinophilia compared with only 7% of patients with limited disease ($P < 0.001$). In vitro allergy positivity was present in only 19 of 95 patients (20%), whereas 8 of 13 patients (62%) with both extensive disease and serum eosinophilia had negative in vitro allergy tests. Therefore, more than half the patients with ECRS did not have evidence of allergy. Although all patients had at least one bacterial organism cultured, most were coagulase-negative staphylococci. The significance
of this as a pathogen is questioned, because normal subjects and asymptomatic patients have an equal incidence of coagulase-negative staphylococcal presence in cultures from their nose and sinuses [5]. This same investigative group reported on additional immunologic parameters in 80 patients with CRS in a subsequent publication in which 37 (46%) patients demonstrated extensive sinus disease. The peripheral eosinophil count (> 200 cells/μL) had the strongest correlation to greater disease as measured by the CT scoring criteria. Eosinophilia was observed in 76% of patients with extensive disease compared to 21% in limited disease. The association of eosinophils with extent of disease was independent of asthma, atopy, or age. There was no correlation with extent of CT disease and any of the following: IgE, IgA, IgG1, IgG2, and IgG3 [6].

In a study of 48 adult CRS patients, Szuks et al. [7] reported that the intensity of the eosinophilic infiltration in the diseased sinus mucosa correlated significantly with the severity of the mucosal inflammation, independent of atopic status. However, 20% to 40% of the patients with CRS had no eosinophilic inflammation of the mucosa. Baroody et al. [8] reported similar results in 34 children with CRS; specifically, there were significantly more eosinophils in the lamina propria of CRS sinuses (median 32.8 cells/0.5 mm², \(P = 0.0004\)) than in normal ethmoid sinus mucosa (median 0 cells/0.5 mm²).

Sobol et al. [9•] compared the tissue inflammation in CRS in adults with tissue inflammation in CRS in children, and in control subjects. T lymphocytes, eosinophils, and basophils were higher in subjects with CRS, whether adult or child, than in control subjects. The degree of tissue eosinophilia was significantly greater in adults with CRS than in children with CRS. Similarly, Chan et al. [10] also reported that adults had a higher density of submucosal eosinophils than children with CRS. In addition, children with CRS had a higher density of submucosal lymphocytes, a thinner and more intact epithelium, a thinner basement membrane, and fewer submucosal mucous glands compared with adult CRS controls. They interpreted the lower eosinophilia and fewer morphologic abnormalities in young children compared to adults as evidence of a greater potential for reversibility of CRS and higher potential for cure in children than in adults [10].

Zadeh et al. [11•], in a retrospective review of 620 patients with CRS, found that 31 patients (5%) had elevated serum eosinophilia. Despite this low incidence of peripheral eosinophilia, these patients were significantly more likely to have polyps (77% vs 15%), allergic fungal sinusitis (AFS: 39% vs 3%), and asthma (35% vs 24%), compared with CRS patients with normal eosinophil counts. Postoperatively, patients with serum eosinophilia were more likely to be diagnosed with recurrent sinus infections (94% vs 32%) and recurrent polyps (35% vs 3%), and to require revision surgery (84% vs 24%). In summary, presence of increased serum eosinophilia was associated with a worse prognosis in every parameter compared with CRS patients without an increase in serum eosinophilia.

Despite the increased awareness of eosinophilia, both histologically and serologically as a marker of increased disease and a worse prognosis with regard to surgical intervention in CRS, no study to date has subcategorized patients regarding possible etiologic factors for tissue eosinophilia. Allergy is one cause, but certainly not the only cause of eosinophilia, and in multiple studies, the correlation of eosinophilia to atopic status is weak or absent.

Pathophysiologic Role of the Eosinophil

The eosinophil is a granular, bi-lobed leukocyte that comprises approximately 2% to 5% of granulocytes in a nonallergic person. Eosinophil progenitors are released from the blood marrow into the circulation and are chemically attracted to the sites of inflammation by chemotrophic factors. Locally, tissue eosinophilia is induced by three canonical pathways. The dominant pathway is mediated by the TH₂-type immune response, with interleukin (IL)-5 as the major mediator. However, both innate immunity and TH₁ immune response are also capable of inducing tissue eosinophilia in the absence of a TH₂ response [12•]. Nonetheless, the role of these leukocytes in the context of tissue inflammation remains poorly understood. Eosinophils contain a variety of toxic pro-inflammatory mediators, including preformed granule proteins (such as the major basic protein, eosinophil cationic protein, and eosinophil-derived neurotoxin), reactive oxygen species, lipid mediators, and cytokines that could contribute to inflammation [12•,13•]. When these preformed granules are released, the mediators can inflict damage to the surrounding tissue. In the asthma model, the major basic protein antagonizes M2 muscarinic receptors in the airways and contributes to neural mechanisms of airway hyperreactivity. The role of M2 muscarinic antagonism by major basic protein in the upper airway is unexplored.

Eosinophils are also a major source of tissue remodeling factors. A study by Dunnill [14] demonstrated that eosinophil-induced myofibroblast differentiation can be blocked by an antibody against transforming growth factor β (TGFβ), indicating a crucial role of TGFβ-mediated eosinophilia in tissue remodeling. In addition, the presence of other tissue remodeling factors, such as TGFα, heparin-binding epidermal growth factor, platelet-derived growth factor-β, and vascular endothelial factor have been reported [15]. Although