Allergic Fungal Sinusitis

To the Editor: We read with interest the article on allergic fungal sinusitis (AFS) by Dr Ponikau and associates[1] and agree that this disorder needs to be better defined. The authors have done an excellent job to raise awareness of this syndrome and encourage careful handling of nasal secretions and pathologic specimens for fungal isolation. However, we doubt that such a high percentage of chronic rhinosinusitis (CRS) cases, 93% of 101 consecutive surgical cases as reported in this series, are caused by this disorder. Importantly, the authors note that 100% of 14 normal volunteers had fungal culture–positive nasal washings, as did 96% of 210 patients with CRS, limiting the importance of this finding. Thus, fungal colonization per se adds little positive predictive value for AFS.

The authors argue that correlation of fungal culture with evidence of type I hypersensitivity to specific fungal allergens is not relevant. We disagree and believe that positive radioallergosorbent test (RAST) results, skin test results, or presence of serum precipitins for fungal allergens, in combination with fungal culture results matching that fungal species, are essential in making the diagnosis of AFS, as outlined by Morpeth et al.[2] This is analogous to the related and well-characterized condition of allergic bronchopulmonary aspergillosis.[3] In the CRS patients of this study, skin tests positive for fungi were found in 42%, and RAST results for fungi were positive in 28%, as compared with 21% of controls. However, data regarding the species of fungi reactivity identified by RAST and skin testing were not shown. Furthermore, no data were presented to demonstrate a relationship between immediate hypersensitivity to fungal allergens and these specific isolates from patients' nasal cultures.

An allergic diathesis is not uncommon in patients with chronic sinusitis, and nasal eosinophilia suggests an allergic component may be prominent in some patients with CRS. However, the presence of a positive skin test result to 1 species of fungus does not indicate that colonization with a different fungal species is pathological. Furthermore, eosinophils in nasal smears may also be seen in nonallergic conditions, such as nonallergic rhinitis with eosinophilia syndrome, which probably accounts for some of the skin test–negative patients found in this study.

Given the lack of specificity of nasal eosinophilia and the ubiquitous nature of fungal colonization of the nose, we propose that the term *allergic fungal sinusitis* be applied only to patients with CRS who have nasal eosinophilia and either positive skin test results, RAST results, or presence of precipitins (or a combination of these tests) for the specific fungus isolated from their sinuses.

Donald A. Dibbern, Jr, MD
Stephen C. Dreskin, MD, PhD
University of Colorado Health Sciences Center
Denver

1. Ponikau JU, Sherris DA, Kern EB, et al. The diagnosis and incidence of allergic fungal sinusitis. *Mayo Clin Proc*. 1999;74:877-884.
2. Morpeth JF, Rugg NT, Dolen WK, Bent JP, Kuhn FA. Fungal sinusitis: an update. *Ann Allergy Asthma Immunol*. 1996;76:128-139.
3. Greenberger PA. Diagnosis and management of allergic bronchopulmonary aspergillosis. *Allergy Proc*. 1994;15:335-339.

To the Editor: I read with great interest the article by Ponikau et al,[1] and I am writing to offer an alternative interpretation of their findings.

The authors state that the unrefuted diagnostic criteria for AFS are (1) CRS; (2) presence of allergic mucin, ie, clusters of eosinophils and their by-products; and (3) the presence of fungal organisms within that mucin.

In their study, they compared 210 patients with CRS and 14 controls. They found that the 2 groups differed on criteria 1 and 2, but not 3, the presence of fungus in their nasal mucus. Ninety-six percent of cases had positive fungal cultures from their noses, compared with 100% of controls. Cases averaged 2.7 organisms per person, compared with 2.3 in controls. Thirty-three percent of cases had an elevated total immunoglobulin E (IgE), compared with 29% of controls. There was no significant difference in specific IgE values between groups.

The authors conclude that type I hypersensitivity is an unlikely mechanism for AFS because there was no difference in total or specific IgE between the groups. Given that the authors state that (1) histologic markers of CRS patients are the striking number of eosinophils in contrast to the near absence of eosinophils in controls and (2) many different fungi colonize everyone's nasal secretions, it would also seem reasonable to conclude that fungi play no role in the pathophysiology of this disorder. Nevertheless, the authors conclude that fungi are responsible for AFS. Perhaps this entity should be termed *eosinophilic rhinosinusitis*. This would provide for the possibility of 1 or more other etiologies (eg, pollen, dust mites) responsible for the presence of the eosinophilic mucin in these patients.

Elena H. Page, MD, MPH
National Institute for
Occupational Safety and Health
Cincinnati, Ohio

1. Ponikau JU, Sherris DA, Kern EB, et al. The diagnosis and incidence of allergic fungal sinusitis. *Mayo Clin Proc*. 1999;74:877-884.

In reply: As Drs Dibbern and Dreskin state, Morpeth et al[1] and others[2] have suggested that evidence of fungal-specific or -nonspecific IgE-mediated atopy (Gell and Coombs type I) should be a diagnostic criterion for AFS. Unfortunately, these suggestions have never been validated. To our knowledge, there is not a single evidence-based reference in the literature proving or even strongly indicating a role for an IgE-mediated allergy in the pathophysiology of AFS.

Eleven percent of our CRS patients had either elevated fungal-specific IgE RAST or positive specific skin test results to the species of fungi growing from their nasal cultures. Given the known cross-reactivity between the mold antigens and the poor

standardization of the test assays, we did not want to draw incorrect conclusions from those findings. The presence of elevated specific IgE and of a correlating fungus in the nasal mucus is not uniformly pathologic, as demonstrated by our control group of healthy volunteers among whom 2 (14%) of 14 had this finding.

It is rather our finding that AFS clearly exists on histopathology regardless of the presence or absence of atopy. The presence of eosinophils or eosinophilic mucin does not implicate IgE-mediated allergy, because their presence in our CRS patients clearly occurs in nonatopic patients as well. The destructive changes on the mucosa we see in AFS (or CRS) are eosinophil protein mediated (major basic protein) and not IgE mediated.[3] They do not occur in diseases with an IgE-mediated pathophysiology such as allergic rhinitis. Certainly patients who have both allergic rhinitis and CRS may have worse symptoms, as both diseases share some major symptoms, like nasal obstruction, postnasal drip, and rhinorrhea. But allergic rhinitis is not a prerequisite to developing either CRS or AFS.

Limitation of the diagnostic criteria and terminology used in this disease, without validation of those limitations, would certainly narrow our view of this disease. This may prevent us from further uncovering the pathophysiology of this common disorder. Therefore, we have proposed a change in terminology from AFS to *eosinophilic fungal rhinosinusitis*.

As Dr Page states, extramucosal fungi were found in almost all patients with CRS and also in all controls. From an infectious disease perspective, if the mere presence of those organisms is assumed to cause disease, the conclusions we drew from our study can certainly be challenged. But if the presence of fungi is viewed as a hypersensitivity reaction that is not IgE mediated, then our hypothesis seems plausible. For example, everyone inhales pollens, but only a sensitized patient develops the symptoms of hay fever (in that case, IgE mediated).

The presence of eosinophils in the tissue and the formation of the typical eosinophilic mucin were the histologic hallmarks in our CRS cases, a finding absent in the healthy controls. The eosinophils were found to leave the tissue and formed clusters in the "eosinophilic mucin." We hypothesized that their target in the mucin is the extramucosal fungi. Recently, we were able to further validate this hypothesis and demonstrated that the eosinophils are indeed targeted against fungal organisms in CRS, a phenomenon that was absent in healthy controls as well as in patients with allergic rhinitis.[4-7]

Thus, the mere presence of fungi is nonspecific in this disease, but fungi are still essential in CRS as a trigger to stimulate the immunologic (eosinophilic) response to them in a sensitized individual. This is another reason for adopting the term *eosinophilic fungal rhinosinusitis*.

Jens U. Ponikau, MD
Eugene B. Kern, MD, MS
David A. Sherris, MD
Mayo Clinic Rochester
Rochester, Minn

1. Morpeth JF, Rupp NT, Dolen WK, Bent JP, Kuhn FA. Fungal sinusitis: an update. *Ann Allergy Asthma Immunol*. 1996;76:128-139.
2. Bent JP, Kuhn FA. The diagnosis of allergic fungal sinusitis. *Otol Head Neck Surg*. 1994;111:580-588.
3. Harlin SL, Ansel DG, Lane J, Myers J, Kephart GM, Gleich GJ. A clinical and pathologic study of chronic sinusitis: the role of eosinophils. *J Allergy Clin Immunol*. 1988;81:867-875.
4. Ponikau JU, Sherris DA, Gaffey TA, Kern EB. Understanding the cause for chronic sinusitis: the role of the eosinophil. Paper presented at: plenary session of the XIII International Symposium on Infection and Allergy of the Nose and Congress of the European Rhinologic Society; July 31, 1998; Vienna, Austria.
5. Ponikau JU, Sherris DA, Kern EB. Pathophysiology and future treatment of chronic rhinosinusitis. Paper presented at: panel discussion at the Annual Meeting of the American Academy of Otolaryngology-Head and Neck Surgery; September 14, 1998; San Antonio, Tex.
6. Ponikau JU, Sherris DA, Kern EB. Chronic rhinosinusitis: an immune response to fungi. Paper presented at: Third Symposium on Experimental Rhinology and Immunology of the Nose; November 14, 1998; Ghent, Belgium.
7. Ponikau JU, Sherris DA, Kern EB, Charlesworth JE, Kita H. Chronic rhinosinusitis and allergic rhinitis: the different role of the eosinophil. Paper presented at: Annual Meeting of the American Rhinologic Society; September 25, 1999; New Orleans, La.

The Editor welcomes letters and comments, particularly pertaining to recently published articles in *Mayo Clinic Proceedings*, as well as letters reporting original observations and research. Letters pertaining to a recently published *Proceedings* article should be received no later than 1 month after the article's publication. A letter should be no longer than 500 words, contain no more than 5 references and 1 table or figure, be signed by no more than 3 authors, be in double-spaced, typewritten format, and not be published or submitted elsewhere. The letter must be signed and include the correspondent's full address, telephone and fax numbers, and e-mail address (if available). It is assumed that appropriate letters will be published, at the Editor's discretion, unless the writer indicates otherwise. The Editor reserves the right to edit letters in accordance with *Proceedings* style and to abridge them if necessary. Letters may be submitted by surface mail to Letters to the Editor, *Mayo Clinic Proceedings*, Room 770 Siebens Building, Rochester, MN 55905; by fax to (507) 284-0252; or by e-mail to proceedings@mayo.edu. (Note: Authors who submit letters by fax or e-mail must also send a copy by surface mail.)