Guest editorial

The fungal conundrum

Just more than 10 years ago, our group was asked to see a 7-year-old boy from Mobile, AL, who had undergone 5 previous sinus operations and presented with recurrent sinusitis and proptosis of his right eye. Sinus computed tomography showed an expansible mass from the ethmoid area into the orbit and surgery was performed. Dense collections of polyps and peanut butter–like mucin formed the mass that was removed at surgery. Review of the surgical pathology showed that the peanut butter–like material was composted of laminated mucin with a dense collection of eosinophils, many Charcot-Leyden crystals, and sparse degenerating fungal elements. There was a lymphoplasmacytic cellular infiltrate within the intact sinus mucosa. Further evaluation showed intact immunity, with high total IgE and specific IgE levels to most inhalant allergens tested, including *Curvularia lunata,* which grew from the mucin.

Not having seen such a patient before, we performed a literature search and, to our surprise, found 99 similar reports. The review was complicated by the fact that there were no established clinical criteria for this syndrome, which had been termed *allergic aspergillus sinusitis* on the basis of histopathologic findings.[1] We sent letters to local otolaryngologists and immediately identified 8 additional cases. On the basis of a detailed evaluation of our 9 patients, we submitted a manuscript that offered clinical criteria for diagnosis of allergic fungal sinusitis (AFS).[2] Unknown to us, Drs Bent and Kuhn in Georgia submitted a paper that proposed similar diagnostic criteria contemporaneously.[3] More work led us to propose a new classification for syndromes of fungal sinusitis, which placed AFS within a much broader spectrum.[4] Subsequently, other authors have proposed additional diagnostic criteria for AFS.[5,6]

A unifying diagnostic criterion in all of the proposed criteria for AFS is the presence of allergic mucin. This material appears to be the result of mucous hypersecretion associated with an eosinophil-driven inflammatory response in the upper airway and, on occasion, in the lower airway as well. Viscid mucus, often in combination with polyps, forms a mucoid mass within the sinuses that obstructs drainage, promotes secondary bacterial infection, and is sometimes expansible. This mass is capable of crossing the lamina papyracea into the orbit, causing proptosis and expanding posteriorly into the brain or expanding anteriorly out of the frontal sinus to cause facial bone abnormalities. These abnormalities are more common in children, whose bones are not fully ossified. Thus, the high prevalence of proptosis with AFS in children reported by Campbell et al[7] in this issue of the *Annals* is consistent with previous reports of AFS.

This said, it is interesting that those authors included 9 patients in their series who did not have allergic mucin present at surgery. Although the patients may have had other features of AFS, in my opinion, that diagnosis cannot be confirmed without histopathologic evidence of eosinophilic mucin containing fungal elements. Rhinosinusitis with allergic mucin but *no* fungal elements detectable by standard histopathologic and culture techniques has been reported to occur as an entity distinct from but clinically similar to allergic fungal sinusitis.[8] This *eosinophilic mucin rhinosinusitis* may be a unique clinical syndrome with a different distribution of clinical findings. Thus, both chronic hypertrophic sinusitis with nasal polyps and eosinophilic mucin rhinosinusitis may simulate AFS clinically but appear to be separable on the basis of histopathologic evaluation. In that regard, it would have been useful if Campbell et al would have compared the clinical findings in their patients with and without allergic mucin.

Ponikau and colleagues[6] from the Mayo Clinic reported that fungi could be grown from processed mucus obtained from nasal lavages in 202 of 210 patients with chronic rhinosinusitis. Most of these patients were said to have allergic mucin at surgery, but few had fungal specific IgE. They concluded that most patients with chronic rhinosinusitis met criteria for AFS and that chronic rhinosinusitis should be renamed *eosinophilic fungal rhinosinusitis*. In subsequent studies, that group used highly sensitive immunofluorescent techniques to demonstrate fungal protein in the mucus as well. Demonstration of fungi in the upper airways of most individuals with or without sinusitis has not been considered to be a confounding variable to the original conclusions in that or subsequent publications. A single publication suggested the presence of fungal specific immune responses in patients with eosinophilic fungal rhinosinusitis vs controls, but this issue requires further investigation.

The fallout from work at the Mayo Clinic and the eosinophilic fungal rhinosinusitis hypothesis has been considerable. New classifications have been proposed for chronic rhinosinusitis that allow in various ways for the presence of nasal polyps, allergic mucin, and fungal elements or aspirin sensitivity. A method patent for the treatment of all chronic rhinosinusitis has been filed by the Mayo Clinic, and widespread use of antifungal antibiotics in the treatment of rhinosinusitis has occurred.[9] An open clinical trial by the Mayo Clinic group that suggested the therapeutic utility of intranasal amphotericin B in chronic rhinosinusitis was not confirmed by a controlled trial.[10,11]

There are many cofounders in clinical trials for treatment of rhinosinusitis. It will take time to sort all this out before we arrive at an evidence-based approach to diagnosis and treatment. I believe that AFS is a clearly definable syndrome using the criteria and techniques we initially proposed and that the techniques used by Ponikau et al are too sensitive and not specific enough for the diagnosis. In hindsight, I wish we had not included fungal culture in our criteria (we were forced to do so by the reviewers) and had tightened up the association with fungal specific IgE, which is inevitably detectible in patients with AFS.

Finally, we have reported the coexistence of AFS and allergic bronchopulmonary mycosis using the acronym SAM for sinobronchial allergic mycosis.[12] Since AFS and allergic bronchopulmonary mycosis appear to be the same disease process operative at different locations in the respiratory tract, it would also have been useful if Campbell et al had evaluated their patients to determine whether the asthmatic patients clustered in the group with allergic mucin and whether allergic bronchopulmonary aspergillosis was present in the asthmatic patients vs the nonasthmatic patients.

RICHARD D. DESHAZO, MD
University of Mississippi Medical Center
Jackson, Mississippi

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