



MOC-CME Review

Possible allergic fungal sinusitis

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Release Date: April 1, 2016**Expiration Date:** March 31, 2018**Target Audience:** Physicians involved in providing patient care in the field of allergy/asthma/immunology**Learning Objectives:**

At the conclusion of this activity, participants should be able to:

- Discuss recent advances in the diagnosis and treatment of allergic fungal sinusitis
- Discriminate between allergic fungal sinusitis and eosinophilic mucin rhinosinusitis

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Clinical Vignette

A 55-year-old African American man was referred by his otolaryngologist for further evaluation and treatment of probable “allergic fungal sinusitis” (AFS). The patient had a long history of chronic rhinosinusitis, although neither he nor his first-degree relatives had rhinitis, eczema, or asthma. He reported 3 previous endoscopic sinus surgeries spaced roughly at 3-year intervals. The recent revision sinus surgery leading to this referral was preceded by symptoms of nasal obstruction. A sinus computed tomogram showed postsurgical changes, complete opacification of the paranasal sinuses, and obstruction of the remaining components of the osteomeatal complex (Fig 1). There were areas of hyperattenuation in the ethmoid and maxillary areas bilaterally, which the radiologist commented, “suggest the presence of polyps or fungal elements.” The bony margins of the sinuses were intact.

His most recent operative and surgical pathology reports were obtained for review. The surgeon reported that during functional endoscopic sinus surgery, he had attempted to remove all the mucoid material, thought to be eosinophilic mucin (allergic mucin) and polyps. The surgical pathology report confirmed the presence of eosinophilic mucin with dense accumulations of eosinophils in mucin containing Charcot-Leyden crystals (Fig 2). Numerous attempts to demonstrate fungal elements in the allergic mucin



Figure 1. Computed tomogram showing evidence of extensive previous endoscopic sinus surgery to open the osteomeatal complex. There is maxillary and ethmoid pansinusitis with nasal septal deviation to the left. Hyperattenuation of material (white areas) within the sinuses is present and most visible in the right ethmoid sinuses, suggesting the presence of eosinophilic mucin. The right nostril is completely obstructed by mucous or polyps. The orbits are intact and the frontal sinuses appear uninvolved.

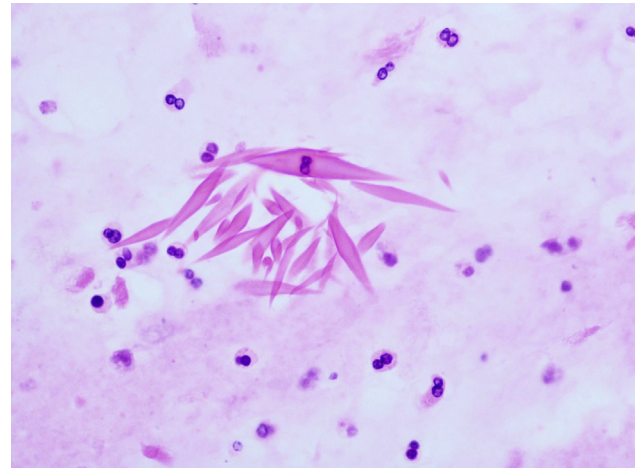


Figure 2. High-power photomicrograph of eosinophilic mucin showing dense accumulations of eosinophils and Charcot-Leyden crystals (hematoxylin and eosin stain, magnification $\times 100$). No fungal elements (hyphae or hyphal fragments) were present here or on the required fungal stains.

obtained directly from the sinuses by culture and appropriate fungal stains, including Gomori methenamine silver, were unsuccessful. A diagnosis was made and a treatment plan was developed.

Introduction

The pathophysiology of AFS is still debated. Most believe it reflects the same eosinophilic inflammation seen in the IgE-dependent late-phase allergic reaction best described in skin after injection of allergen and present in the bronchi in allergic fungal mycosis.¹ In AFS, the inflammatory response occurs within a closed space with access to cytokines that not only attract and activate eosinophils to perpetuate inflammation but also stimulate the production of large quantities of mucus. The fungal elements present in allergic mucin stain darkly with silver stains and are usually fragmented and nonviable. They have been postulated to present a persistent stimulus for ongoing IgE production and allergic inflammation. This hypothesis does not explain the mechanism by which eosinophilic mucus is produced when fungal elements are not present. Nonetheless, eosinophilic mucin can become an expansive inflammatory mass within the sinuses that can obstruct the osteomeatal complex, promote bacterial superinfection with probable superantigen functionality, and induce compression necrosis and breach of the bony sinus margins. Breaches of the sinus walls can result in serious complications outside the sinuses and result in the mis-diagnosis of invasive sinusitis.^{2–4}

Confusion in the Medical Literature

Diagnostic Criteria for Syndromes of Fungal Sinusitis

Several years ago, to establish a contemporary classification of fungal sinusitis, the authors set out to establish evidence-based diagnostic criteria for the known forms. The results of that work were published in 1997 and have subsequently been used widely in the clinical management of patients with fungal sinusitis⁵ (Table 1).

Table 1
Classification of syndromes of fungal sinusitis, 2015

Noninvasive
Allergic fungal rhinosinusitis
Fungus ball (sinus mycetoma)
Invasive fungal sinusitis
Acute invasive sinusitis
Chronic invasive fungal sinusitis
Granulomatous invasive fungal sinusitis
Overlap syndromes (?)

Adapted from deShazo and Swain.⁹

Those diagnostic criteria were designed to facilitate multicenter studies to better understand AFS because multicenter studies require as close to absolute certainty of the diagnosis as possible. Thus, these criteria were not developed for clinical purposes, although many find them useful in practice because they include clinical findings in the usual patient. The authors have seen patients, including those who have developed AFS after exposure to fungal antigens from contaminated continuous positive pressure humidification systems, who present with nasal symptoms only, normal to mildly elevated total serum IgE levels, have negative fungal allergen radioallergosorbent test results, and require intradermal skin testing to demonstrate fungal specific IgE. The authors conclude that the only essential criterion for diagnosis of AFS is the presence of hyphae or hyphal fragments in eosinophilic mucin obtained at surgery or by aspiration of a sinus. However, there has been ongoing controversy about the diagnostic criteria and classification of fungal sinusitis and the existence of possible overlap syndromes with histopathologic features of more than 1 type.^{6,7} This includes an international controversy concerning a hypothesis that most chronic rhinosinusitis is allergic fungal rhinosinusitis.⁸

That hypothesis also stirred controversy about the accepted and congruent existing diagnostic criteria for AFS published almost simultaneously by deShazo and Swain⁹ and Bent and Kuhn¹⁰ (Table 2). The controversy arose from the erroneous assertion that AFS could be diagnosed by the culture of fungi commonly associated with AFS from nasal secretions of patients with chronic rhinosinusitis.⁸ The authors and others previously demonstrated that such fungi can be cultured from the noses of healthy, normal volunteers. Normal controls were not used in the original study, which led to the controversy.⁸

The suggestion that most forms of chronic rhinosinusitis were fungal led to the widespread use of oral and intranasal antifungal antibiotic treatment for chronic rhinosinusitis. Subsequent controlled trials have not demonstrated efficacy of this treatment.^{11,12}

Table 2
Diagnostic criteria and features of allergic fungal rhinosinusitis^a

1	Chronic rhinosinusitis
2	Nasal polyposis
3	Increased total IgE with the presence of fungal specific IgE
4	Characteristic computed tomographic findings to include pansinusitis often with areas of hyperattenuation of opacified material within them
5	Characteristic histopathologic findings to include eosinophilic mucin with a positive fungal stain of sinus contents for fungi and no evidence of fungal invasion into sinus tissue ^b
6	Immunocompetent patient

^aDiagnostic criteria and clinical features are the same in allergic fungal sinusitis and eosinophilic mucin rhinosinusitis except for items 3 and 5.

^bRequired for diagnosis. The fungi in eosinophilic mucin are usually dead or dying fungal fragments. If cultures of purported eosinophilic mucin are to be performed, then they should be carefully obtained directly from the sinuses at the time of surgery. Nasal culture results are not helpful because they frequently grow fungi in healthy controls.

Eosinophilic Mucin Rhinosinusitis

The previous controversy confirmed that the presence of fungal elements within eosinophilic mucin is an essential diagnostic criterion for AFS and highlighted the treatment dilemma of patients with chronic rhinosinusitis associated with eosinophilic mucin in which fungi are not present. Such patients appear to have a separate and unique entity, namely eosinophilic mucin rhinosinusitis (EMRS). This was the case with the present patient. The controversy also has reinforced the requirement for the presence of fungal specific IgE in AFS and reflects the observation that most patients with AFS have atopy.

Thus, for now, when fungi cannot be demonstrated in eosinophilic mucin removed from the sinuses of patients with what otherwise appears to be AFS, the diagnosis of EMRS (previously termed allergic mucin rhinosinusitis) is the correct one.¹³ The authors have observed nasal polyps in both entities. This recommendation is based primarily on the desire to limit the inappropriate use of the multiple therapies necessary to prevent recurrence of AFS. For instance, in patients with EMRS, there is no rationale or data to suggest efficacy for allergen immunotherapy unless patients have co-existent allergic rhinosinusitis. Although patients with EMRS typically do not have atopy or high levels of total serum IgE or fungal specific IgE, they frequently have asthma and aspirin sensitivity.^{13,14} As is the case of AFS, patients with EMRS must be carefully followed for recurrence of the syndrome after surgery, although the authors' experience suggests that recurrence is less frequent after adequate surgery, and the patients' clinical course is less severe than that for AFS. The authors hypothesize that when the pathogenesis of EMRS is elucidated, it will be similar to that of the nonatopic form of chronic persistent asthma, where eosinophils are prominent histopathologic findings.

Bony Compression vs Bony Invasion

Another controversy concerning AFS and EMRS is whether the expansion of eosinophilic mucin outside the bony margins of the sinuses into the orbit, brain, or vascular structures reflects invasion and thus conversion to invasive fungal sinusitis.² Computed tomography in such patients is often read as "erosion of bony margins," suggesting fungal invasion of bone when the process is actually ischemic necrosis from compression of an expanding mass of eosinophilic mucin within a closed space. Collaboration with a radiologist with experience in bone disease and use of the extensive information provided in the radiologic literature about imaging in this complication are helpful.¹⁵

The authors and others have reported individuals with concurrent AFS and sinus fungal balls, but the evolution of noninvasive to invasive forms or the coexistence of the 2 forms have not been reported in the United States.

Complications

Complications of AFS and EMRS fall into discrete categories and include ophthalmic and cerebral complications as the result of entry of allergic mucin into the orbit or cranium causing visual changes, proptosis, or cavernous venous thrombosis.² Most patients with AFS and serious complications have pre-existing asthma and/or allergic rhinitis and frequently have nasal polyps. However, approximately one fourth have no history of rhinosinusitis or polyps at presentation. Prevention and/or early diagnosis of complications in AFS and EMRS are facilitated by regular follow-up with endoscopic and radiologic surveillance. There are too few reports about complications in EMRS to compare the type, frequency, and severity with AFS.

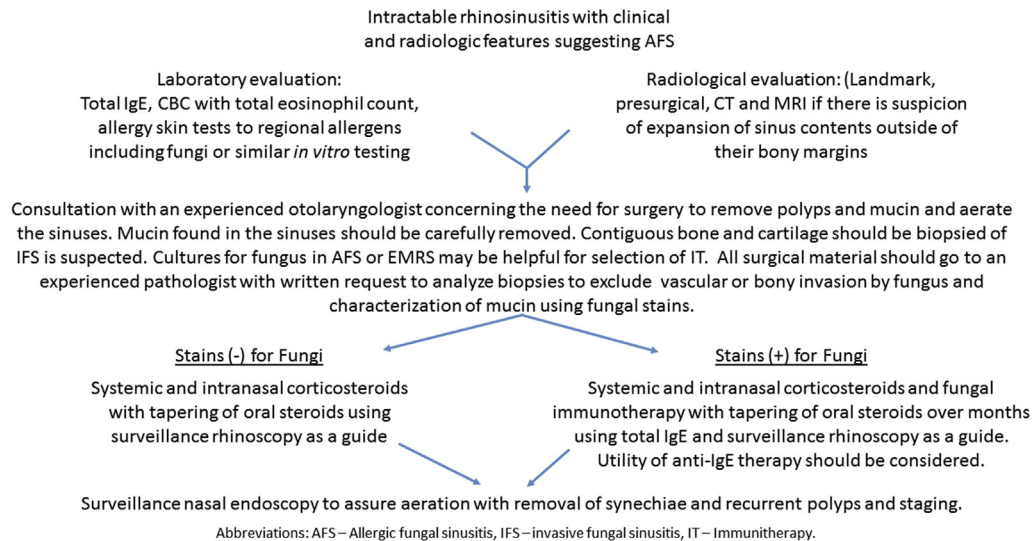


Figure 3. Approach to the patient with possible allergic fungal sinusitis. CBC, complete blood cell count; CT, computed tomography; MRI, magnetic resonance imaging.

Treatment

Diagnosis First

The first step in evaluating a patient referred for possible fungal sinusitis is to determine whether alarm signs requiring emergency evaluation and treatment are present. Does the patient have neurologic findings to suggest disease outside the sinuses, features of invasive fungal sinusitis such as fever or mental status changes, or is the patient immunocompromised? If so, then emergency surgery for diagnosis and/or treatment and antifungal antibiotic treatment might be required¹⁶ (Fig 3).

Surgery is performed to obtain bone and tissue containing blood vessels and sinus contents for histopathologic study and to remove all necrotic and mucoid material to assure complete sinus aeration. In the presence of alarm signs or when the diagnosis remains unclear, antifungal antibiotic treatment is started immediately.

Surgery and Follow-up

Preoperative oral corticosteroid therapy improves the visibility of anatomic landmarks and is preferred by many surgeons. AFS and EMRS can recur if surgery is not effective in removing all mucin and polyps so that recurrent allergic inflammation can be assessed and treated. Treatment of allergic rhinitis in patients with AFS has been shown to decrease recurrences of AFS in uncontrolled trials. Postoperative treatment for the 2 conditions includes daily nasal irrigation with saline and topical nasal steroid treatment, preferably in lavage or aerosol form, and oral anti-leukotriene therapy.^{17,18}

Regular surveillance rhinoscopy and restaging (Table 3) yearly after sinus surgery is essential to prevent recurrence associated with obstruction. This approach seems to be effective in preventing the chronic inflammation and multiple surgeries that result in atrophic rhinosinusitis and the “syndrome of the nasal crumple.”¹⁹

Table 3
Endoscopic grading system for allergic fungal sinusitis

Stage	Criteria
0	No evidence of disease
1	Edematous mucosa and eosinophilic mucin
2	Polypoid mucosa and eosinophilic mucin
3	Polyps and fungal debris

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Medical Therapies

There are no convincing controlled trials to demonstrate the effectiveness of antifungal antibiotic treatment for AFS or EMRS by any route.²⁰ To the contrary, daily oral corticosteroid treatment before and after surgery followed by low-dose or alternate-day corticosteroid treatment for at least 3 months is helpful.^{17,21} During the period of oral steroid treatment, high-dose topical nasal steroids are introduced by nebulization or with incorporation into lavage. The authors recommend daily nasal lavage with warm saline using a Waterpik device with a Grossan tip or squeeze-bottle devices. Lavage helps prevent mucus impaction, removes inflammatory debris and cytokines, and aids in the assessment of acute or chronic infection. The authors incorporate budesonide in the lavage.¹⁸

The authors recently reviewed their experience with subcutaneous allergen immunotherapy for AFS and found it definitely safe and more likely than not effective.²² They do not use immunotherapy for EMRS unless the patient has concurrent allergic rhinitis.

The current understanding of the pathogenesis of AFS suggests that anti-IgE therapy would be a logical treatment for this condition. Case reports have suggested this might be the most promising current treatment option.²³ For those patients with EMRS and elevated IgE levels, clinical trials of anti-IgE therapy might also be worthwhile.

There are no clinical trials to establish best practice in the treatment of EMRS. The authors have found good results with the use of endoscopic surgery to remove mucous and polyps with clearing of the osteomeatal complex, postoperative oral corticosteroids, surveillance for recurrence, and ongoing nasal lavage with saline and topical steroids.

Conclusion

The present patient had EMRS, a condition that usually presents with the same clinical signs and symptoms as AFS. Too few cases of EMRS have been reported to determine whether distinctive clinical features exist between the 2 conditions. High serum levels of IgE and fungal specific IgE are uncommon in EMRS and suggest AFS. The approach to diagnosis and treatment of AFS and EMRS are similar except that immunotherapy to fungal allergens and use of anti-IgE therapy are less likely to be of benefit in EMRS in the absence of coexistent allergic disease. The reported experience suggests that the management regimens of these conditions are effective in controlling symptoms and in some cases resolving the

disease process altogether. Nevertheless, long-term follow-up is required to observe for recurrence and prevent complications.

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