



Maintenance of certification-CME review

Allergic fungal rhinosinusitis

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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:

- Describe the pathophysiology and presenting features of patients with allergic fungal rhinosinusitis
- Discuss the best management approaches to patients with allergic fungal rhinosinusitis

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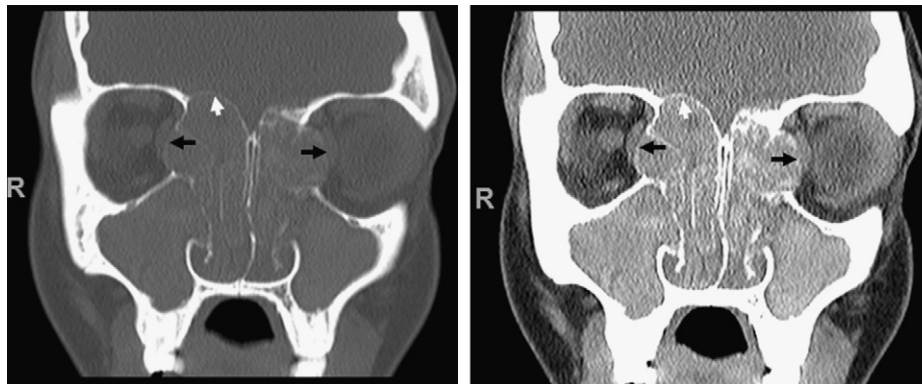


Figure 1. Coronal computed tomographic images of the paranasal sinuses. Bone density (left) and soft tissue density (right). Both cuts are at the level of the ethmoid and maxillary sinuses and show complete opacification of all the sinuses with the typical central increased attenuation, which is characteristic of allergic fungal sinusitis. The nasal cavity is also filled with soft tissue masses, representing the clinically visualized nasal polyps. Of importance is the obvious impingement on the lamina papyracea bilaterally with lateral displacement of the medial rectus muscle (black arrows). Displacement of the bone of the anterior cranial fossa superiorly into the cranial vault is also obvious (white arrows).

Clinical Vignette

A 30-year-old, African American woman presented with a 4- to 5-month history of bilateral nasal obstruction and drainage. She had received many antibiotics with minimal or no symptomatic improvement before finally being referred for additional treatment. She was also experiencing intermittent headaches that lasted less than an hour, occurring 2 or 3 times a week without nausea or emesis. Although relatively healthy overall, the patient has year-round allergies and exercise-induced asthma, for which she takes albuterol on as needed basis. She has no history of prior surgery.

During her initial physical examination, the patient was determined to be a mouth breather, and external nasal examination revealed a widening of the nasal bridge. Anterior rhinoscopy revealed significant bilateral polyposis, leading to almost complete bilateral nasal obstruction. Nasal endoscopy could not be performed. The results of the rest of the physical examination were unremarkable.

A radioallergosorbent test revealed an elevated total IgE level of 3,025 IU, with positive responses to most of the molds tested, including *Aspergillus fumigatus*, *Candida albicans*, *Alternaria alternata*, *Curvularia lunata*, and others, as well as a positive response to dust mites, white ash tree, and giant ragweed. A complete blood cell count with differential obtained in preparation for surgery was essentially normal except for peripheral eosinophilia, with 4% eosinophils on the differential count. Computed tomography (CT)

revealed opacification of all paranasal sinuses and the nasal cavity by hyperdense and expansible masslike lesions, which were impinging on the orbits and anterior cranial fossa, with mass effects on the inferior frontal lobes and medial rectus muscle alongside diffuse bone thinning of the lamina papyracea, findings likely suggestive of allergic fungal sinusitis with polyposis (Figs 1 and 2).

Because of involvement of the orbit and brain, magnetic resonance imaging (MRI) was performed, the results of which revealed significant thinning and deficient bone at the level of the anterior cranial fossa secondary to expansible fungal sinusitis of the bilateral ethmoid and sphenoid sinuses, with resultant elevation of the contents of the sinuses into the intracranial space (Figs 3 and 4). There was a mass effect and displacement of the brain parenchyma but with no evidence of edema. All images were compatible with allergic fungal sinusitis. There was also evidence of sinus expansion into the bilateral orbits and bilateral retro-orbital space, resulting in displacement of the medial rectus muscles laterally; however, no abnormal signal intensity or enhancement was evident, and the retro-orbital contents and globes appeared normal.

Because of possible involvement of the orbits, the patient was sent to an ophthalmologist, who noted mild optic nerve papilledema bilaterally with a cup-disc ratio of less than 0.1. However, the results of the rest of the examination were within normal limits, including her visual acuity and extraocular mobility. The neurosurgery department was also consulted in the event that assistance was required intraoperatively.

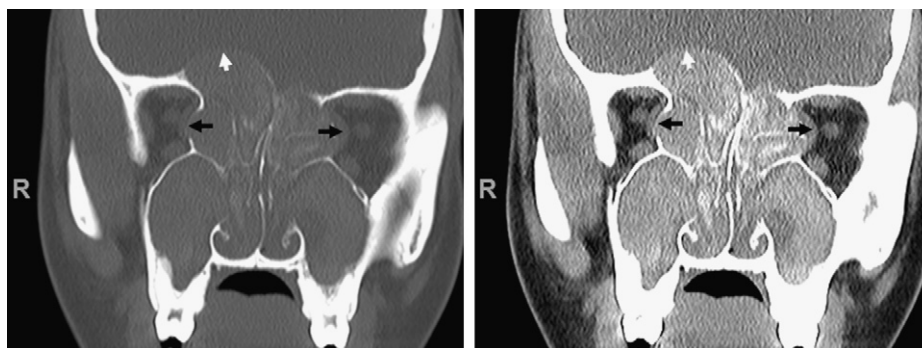


Figure 2. Coronal computed tomographic images of the paranasal sinuses with bone density (left) and soft tissue density (right) windows. Both cuts are at the level of the posterior ethmoids and maxillary sinuses and, again, show complete opacification of all the sinuses with the typical central increased attenuation, which is characteristic of allergic fungal sinusitis and is best seen on the soft tissue windows. The nasal cavity continues to be filled with soft tissue masses, representing nasal polyps. As in Figure 1, there is obvious impingement on the lamina papyracea in the posterior orbit, which is more marked on the left than the right side (black arrows). There is also continued displacement of the bone of the cranial fossa superiorly into the cranial vault (white arrows).

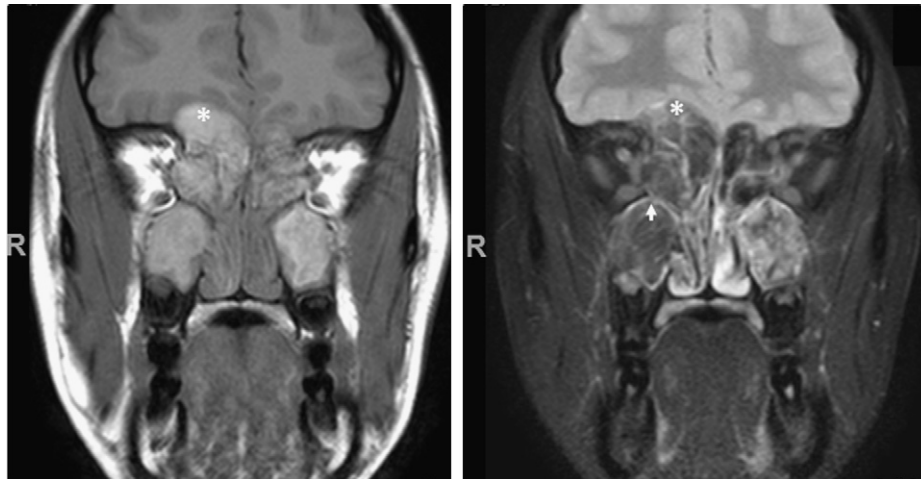


Figure 3. T1 (left) and T2 (right) coronal magnetic resonance images of the paranasal sinuses taken at approximately the same level as the computed tomogram in Figure 2. Enhancement of the inflamed mucosal lining of the right maxillary sinus can be seen in the T2 image (white arrow), and the central signal void corresponds to inspissated secretions. There is obvious impingement on the bone of the cranial fossa with superior displacement of the brain into the cranial vault (white asterisk).

Introduction

Allergic fungal rhinosinusitis (AFRS) was first described in 1983 by Katzenstein et al.^{1,2} Although once considered somewhat uncommon, the condition has recently been reported with increasing frequency worldwide.³ It is thought to represent 5% to 10% of all cases of chronic rhinosinusitis, although the incidence varies, depending on geographic areas.⁴ Ferguson et al.⁵ surveyed otolaryngology practices across the United States and found that southern areas of the country had incidences of AFRS of 10% to 23%, whereas northern areas reported lower frequencies of 0% to 4%. Classic allergic fungal sinusitis develops primarily in young adults and adolescents and is more common in temperate regions with high humidity.⁶



Figure 4. Sagittal T1 magnetic resonance image of the head showing complete opacification of the nasal cavity and paranasal sinuses and displacement of the brain superiorly by the expansile polypoid lesions of allergic fungal sinusitis (black arrows).

Clinical Presentation

AFRS is a noninvasive form of chronic sinus disease and is most frequently found in immunocompetent, atopic individuals who present with difficult-to-treat sinusitis and nasal polyposis. This process is associated with a type 1 hypersensitivity reaction against fungal antigens.⁷ The sinuses are usually filled with characteristic, inspissated, thick secretions with concretions that are found to be eosinophil rich with Charcot-Leyden crystals on microscopy. The mucus also contains fungal elements that can be identified through culture and by light microscopy using periodic acid–Schiff stain and Gomori methenamine silver stains for identification of fungal organisms. It is important to perform these stains because culture results are sometimes negative and the presence of the fungi on light microscopy helps cement the diagnosis. This thick substance blocks the sinus ostia, leading to secondary bacterial infection and other complications, including extension beyond the walls of the sinuses.⁷

The process starts when fungal spores are deposited within the sinuses. Unknown factors promote fungal growth within the sinuses, followed by a type 1 allergic reaction triggered by the fungus and leading to mast cell degranulation and cellular inflammation. Eosinophils are then attracted to the site of inflammation, releasing toxic proteins that contribute to tissue destruction and the formation of allergic mucin.⁸ The disease does not usually progress rapidly or aggressively, but, with time, the process may eventually extend outside the sinuses and possibly lead to bone destruction and the compression of adjacent structures, such as the orbit and the brain.^{9,10} Some patients may even present with proptosis of slow onset and facial deformity secondary to the expansile process.

On the basis of the clinical findings, Bent and Kuhn⁸ proposed the following 5 major criteria for diagnosis: (1) nasal polyposis, (2) allergic mucin/eosinophilic mucus with absent fungal tissue invasion of the paranasal tissues, (3) CT findings consistent with chronic rhinosinusitis, (4) positive fungal histologic test or culture results, and (5) skin test or serologic test results suggesting a type 1 hypersensitivity reaction to fungal allergens.⁸ Several minor but relevant criteria include a history of asthma, predominance of unilateral disease, radiographic evidence of bone erosion, and peripheral eosinophilia.⁷

In a study of 62 patients with AFRS, Dall'Igna et al.¹¹ report that the most common presenting symptoms were nasal obstruction, nasal discharge, postnasal drip, cough, smell problems, sore throat,

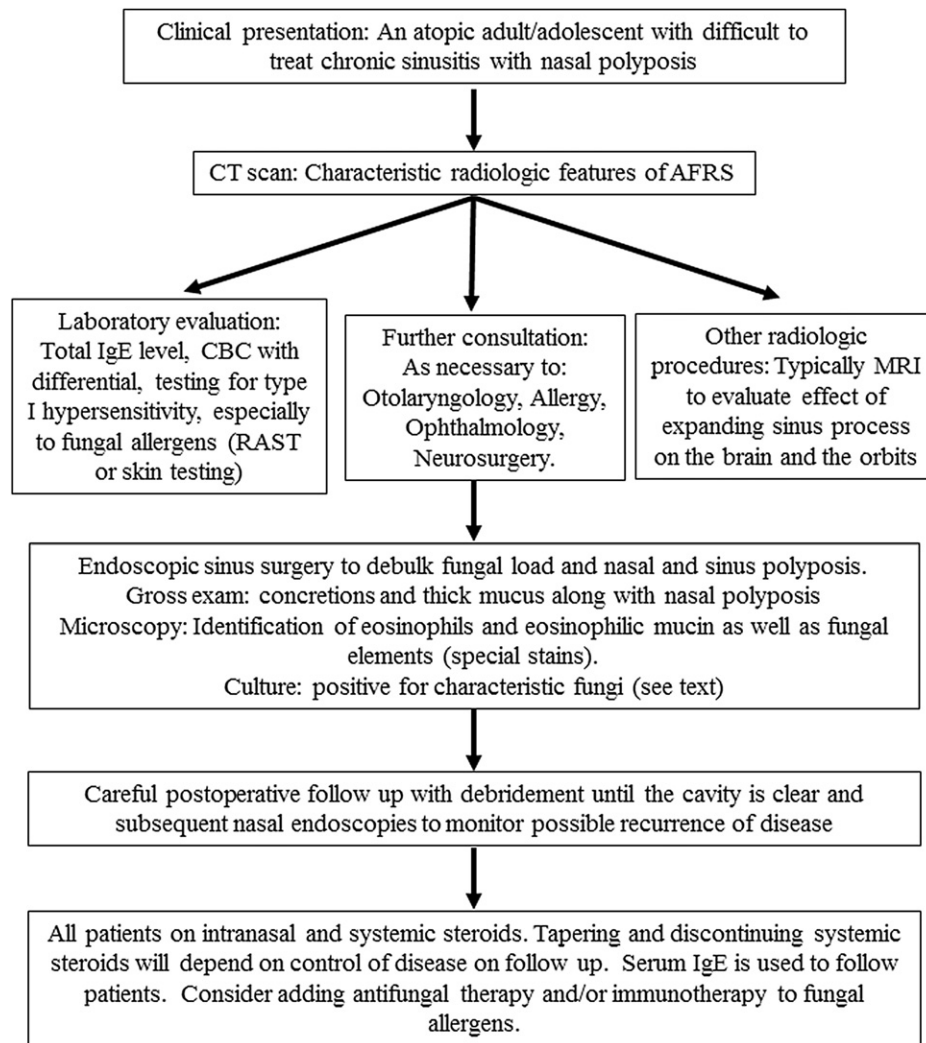


Figure 5. Approach to management of the patient with allergic fungal rhinosinusitis.

fatigue, and facial pain. Many patients also had allergic rhinitis and asthma, in some cases with aspirin sensitivity.

The fungal organisms most frequently involved in the development of AFRS may themselves vary, depending on the geographic region. In 1991, Manning et al¹ reported on 22 patients diagnosed as having AFRS and found that the genus *Bipolaris* was the most commonly cultured at the time of surgery, followed by *Exserohilum*, *Curvularia*, and *Alternaria*, whereas *Aspergillus* was only found in 1 patient. In 1996, Cody et al¹² reported the same distribution in 31 patients who fulfilled the criteria of AFRS. Meanwhile, in a 2003 study of 139 patients, *Aspergillus* was the most common isolated fungal species, accounting for nearly 20% of cases.¹³

Radiologic Findings

The most common CT scan findings include central areas of increased attenuation within the sinuses on both soft tissue and bone window settings that usually correspond to surgical findings of thick allergic mucin with surrounding areas of lower attenuation.¹⁴ The typical MRI findings as reported by Manning et al show higher signal characteristics at the periphery of involved sinuses, corresponding to the contrast-enhancing inflamed mucosa. Reduced central signal intensity on both T1 and T2 images corresponds to fungal concretions. Peripheral enhancement, along with a dark center, on MRI images is characteristic of AFRS.¹⁴ Proptosis

and impingement on the brain and orbit can be seen, as in our case. The clinical presentation, along with imaging studies, is crucial for early and effective diagnosis and treatment.¹⁵

Management

Management usually involves a team approach, with the allergist and otolaryngologist coordinating care, especially because these patients usually have significant asthma and allergies that need to be kept under control. Other specialists are consulted, depending on the extent of the disease (Fig 5). The first step in the management of patients with AFRS is the removal of the fungal allergenic load and the opening of the sinuses by performing functional endoscopic sinus surgery (FESS). Because this is an inflammatory disease, intranasal and systemic steroids are used postoperatively. Rupa et al¹⁶ completed a prospective, placebo-controlled trial in 24 patients, trying to determine the role of postoperative oral steroids in controlling symptoms and recurrence of AFRS. The patients underwent ESS and were subsequently randomized into 2 separate groups: one group was treated with prednisolone, 50 mg once daily for 6 weeks, tapered for a further period of 6 weeks, and the other group was treated with placebo at the same dose. All patients received fluticasone propionate nasal spray and oral itraconazole at a dose of 200 mg once daily for 12 weeks. Evaluation, performed at 6 and 12 weeks, revealed that

8 patients receiving steroids were disease free, whereas only 1 receiving placebo treatment had significant improvement. These results indicate that systemic steroid therapy administered for at least 3 months after FESS can be effective in controlling disease and preventing early recurrence.

Ikram et al¹⁷ reported on 63 patients with AFRS who underwent FESS and were then divided into 2 groups. Thirty patients had no further treatments, and 33 had oral and nasal steroid therapy. All patients were followed up for at least 24 months. There was a statistically significant difference in recurrences: 50% of the group not receiving postoperative steroids had disease recurrence compared with only 15% of the group receiving steroid therapy.

Schubert et al¹⁸ reported on 67 patients diagnosed as having allergic fungal sinusitis. Postsurgical patients were treated initially with prednisone at 0.5 mg/kg twice a day for a period of 2 weeks. This dose was then progressively reduced until the end of the treatment. Along with the systemic corticosteroids, the patients received a combination of anti-inflammatory nasal sprays, antihistamines with or without decongestants, and allergen immunotherapy against seasonal and perennial allergens they may have tested positive for in a previous skin test (with the exception of those fungi not commercially available for immunotherapy, such as *Bipolaris*, *Exserohilum*, and *Curvularia*.) The duration of these treatments was individually decided according to the clinical presentation. The follow-up also included IgE measurements before surgery and at 2 and 6 months after the surgical procedure.

Schubert et al reported that increases of 10% or more in the IgE level for postsurgical patients were correlated with increased risk of recurrence, with 77% sensitivity and 79% specificity. Likewise, the study illustrated with statistical significance that higher levels of IgE were associated with increases in disease severity. The researchers also compared patients who received systemic corticosteroids after surgery with patients who did not, demonstrating that at the time of follow-up, the patients taking steroids had reduced clinical severity of AFR, and an increased time between subsequent sinus operations for recurrence of the disease. Furthermore, the data revealed that the best results were obtained in patients treated with steroids for as long as 12 months. Adverse effects were not reported to any significant extent in the patients receiving systemic steroids according to this protocol.

In a retrospective study of 139 patients, Rains et al¹³ found that patients diagnosed as having AFRS could be safely managed postoperatively with high doses of itraconazole, 400 mg/d for 1 month, reducing the dose within 2 months without observing serious adverse reactions. These patients also received systemic corticosteroid and topical nasal steroids. The protocol of Rain et al found a reduced rate of subsequent surgery when compared with other studies.

In these studies, antifungals and corticosteroids (systemic or intranasal depending on the study) were 2 common medical treatment modalities. The studies using steroids alone reported relatively convincing results, supporting the use of these potent anti-inflammatories after the initial surgical debulking procedures. Patients taking these agents seemed to have less severity of disease over time and a longer interval before revision surgery was needed for recurrent disease. In the studies using antifungals, steroids were also given, making it difficult to deduce whether systemic antifungals had a significant effect or whether the positive observed effects were mostly related to the potent anti-inflammatory effects of corticosteroids. Thus, the mainstay of medical therapy remains in the form of anti-inflammatory treatment with intranasal and/or systemic steroids, whereas the role of antifungals requires further study for confirmation. Furthermore, although the efficacy of oral corticosteroids therapy is well

documented, no conclusive steroid dosing regimen has yet been established.¹⁹

In more recent studies, immunotherapy has been found to be effective in treating AFRS, eliminating the need for oral corticosteroids and decreasing the need for topical steroids. Mabry et al²⁰ published results on the use of immunotherapy for these patients, basing their protocol on preoperative and postoperative testing for common molds and nonfungal antigens. Therapy was initiated 4 to 6 weeks after surgery for a period of 1 to 3 years. For 11 of the patients receiving this treatment, there was no subsequent need for the regular use of oral corticosteroids, and only 3 patients required intranasal steroids. Likewise, this study found no need for subsequent operations because of the AFRS for the period of follow-up.

A 2000 follow-up report subsequently published by Mabry et al²¹ described 8 patients with AFRS who underwent FESS and received antifungal immunotherapy for at least 3 years. After a mean of 13 months from discontinuation, none showed a recurrence of fungal disease.

In 2001, Bassichis et al²² reported a retrospective study of 82 adult patients with AFRS who were monitored for at least 1 year after sinus surgery. They were divided into 2 groups: a control group of 24 patients undergoing sinus surgery without immunotherapy and a study group of 36 patients receiving postoperative immunotherapy for fungal and nonfungal antigens based on a previously positive skin test result. The study found a statistically significant lower recurrence of the disease and lower rates for revision surgery in the immunotherapy group. The study also reported that earlier initiation of fungal immunotherapy decreased the mean number of office visits when compared with patients who delayed initiation of immunotherapy.

After diagnosis of AFRS and discussion of the available therapeutic options, the patient underwent ESS. Polyps and thick secretions were removed from all cavities with a microdebrider. Samples were collected and sent to the pathology department for culture. These samples were stained with periodic acid–Schiff stain and Gomori methenamine silver stain for identification of fungal organisms. The stains showed chronic inflammatory changes, prominent eosinophils in the nasal mucosa, and fragments of tissue debris and inflammatory exudates with fungal growth. Cultures yielded *A. fumigatus*. Intraoperatively, the fungal expansion was found to have eroded a portion of the floor of the cranial fossa, exposing the dura, but there was no leak of cerebrospinal fluid intraoperatively or postoperatively.

Twelve days after first undergoing surgery, the patient also underwent bilateral nasal endoscopy with debridement and was given intranasal fluticasone. Adult patients will usually have all these debridements performed in the office using nasal endoscopy, whereas younger patients might require a general anesthetic for a more complete cleaning. On further follow-up at 3 months, the patient was doing well and breathing freely through her nose, and nasal endoscopy revealed no recurrence of disease. She was instructed to continue with daily administration of intranasal fluticasone. No systemic steroids were administered.

Conclusion

AFRS is an entity that presents with rhinosinusitis and nasal polyposis and has a characteristic clinical and radiologic picture. Diagnosis should be prompt, and treatment should be initiated in the form of ESS to remove all secretions and diseased tissues and eliminate the offending fungal allergens while attempting to preserve normal mucosa and normal nasal anatomy. The mainstay of postoperative medical management is the administration of intranasal and systemic corticosteroids and careful follow-up. The benefit of systemic antifungals and immunotherapy requires further study.

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