

# Allergic Fungal Sinusitis

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**A**llergic fungal sinusitis (AFS) is a distinct form of noninvasive fungal disease characterized by a hypersensitivity reaction to fungal elements in the paranasal sinuses. It is a cause of recurrent or refractory sinusitis in immunocompetent patients. This entity is probably underdiagnosed and should be considered in patients with chronic, intractable sinusitis if there is a history of atopy or asthma. When fungal elements are detected by histopathology or culture from sinus material, AFS must be differentiated from invasive disease, as treatment and prognosis are radically different. We report a case of AFS, review proposed criteria for diagnosis, and discuss current therapeutic concepts.

## CASE PRESENTATION

### Initial Presentation and History

A 20-year-old man with a history of mild asthma and chronic refractory sinusitis since age 8 years presented to the emergency department with blurred vision in his left eye and diplopia of 4 weeks' duration. He also complained of nasal congestion and bilateral frontal headaches. The patient denied trauma to his left eye, pain with eye movement, discharge, fever, or chills. His past medical history was notable for 2 endoscopic sinus surgeries. His daily medications were fexofenadine, albuterol metered-dose inhaler, and ibuprofen. There was no history of diabetes, and he denied smoking, alcohol use, or parenteral or intranasal drug use as well as food and drug allergies.

### Physical Examination

On examination, the patient was alert, afebrile, and able to provide a clear history. There was no discrete sinus tenderness. Visual acuity was 20/40 in the right eye and 20/60 in the left eye. Pupils were equal and reactive. No nystagmus was elicited; however, the patient could not abduct his left eye. Funduscopic examination showed no signs of papilledema or retinal disease. There were thick, green-colored, tenacious, inspissated secretions in both nares. The remainder of the general and neurologic examination was unremarkable.

### Laboratory and Imaging Studies

A complete blood count was normal except for an

eosinophil value of 9% (normal, 2.7%). An HIV antibody test was negative. The patient's serum IgE levels were 1123 mg/dL (normal, 0.01–0.04 mg/dL). All other laboratory results, including sodium, potassium, blood urea nitrogen, serum creatinine, and serum glucose levels, were within normal limits. No allergy testing was performed. A computed tomography (CT) scan of the sinuses demonstrated complete opacification of all paranasal sinuses (**Figure**). There was a soft tissue expansile enhancing mass centered in the ethmoid and sphenoid sinuses, with osseous erosion of the sphenoid. Magnetic resonance imaging (MRI) demonstrated dense inspissated mucoid material involving the sphenoid and ethmoid air cells, without intracranial or orbital extension. The signal intensity on the T2-weighted sequences of the ethmoid and sphenoid sinuses was extremely dark, indicating very high protein content.

### Diagnosis and Treatment

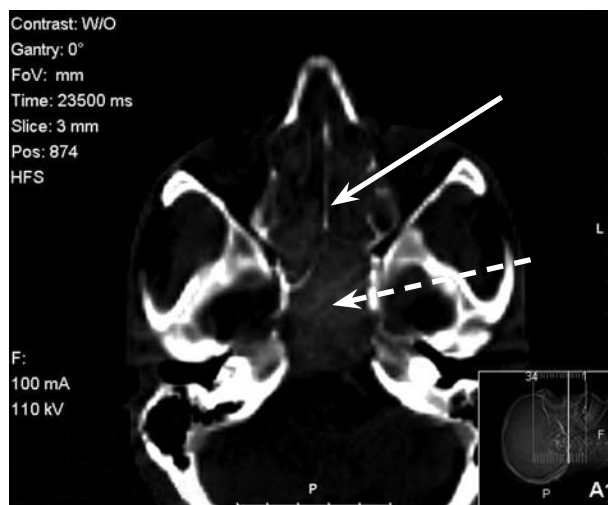
The patient underwent endoscopic polypectomy of the left nasal cavity and ethmoid sinus with removal of thick, inspissated greenish mucoid secretions. Biopsy showed fibrinous inflammatory material with septate fungal hyphae and numerous eosinophils. There was no fungal invasion of respiratory submucosa, bone, or blood vessels. Based on these findings, the patient was diagnosed with AFS. *Bipolaris spicifera* was later identified from fungal culture. The patient was treated with oral prednisone, with significant improvement of visual acuity in his left eye, elimination of diplopia and headache, and decreased nasal congestion. He was discharged on a tapering dose of oral prednisone. The patient was lost to follow-up.

### DISCUSSION

AFS is a noninvasive fungal infection of the paranasal sinuses that is usually seen in young immunocompetent patients with atopy and/or asthma. These patients often present with nasal polyps, severe rhinosinusitis, and

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**Figure.** Computed tomography scan with contrast of the case patient showing a large and heterogeneously enhancing soft tissue mass centered in the ethmoid and sphenoid sinuses. Osseous erosion or dehiscence (*solid arrow*) is noted in the sphenoid region, and there is expansion of the ethmoid and sphenoid sinus cavities (*dashed arrow*) to accommodate the mass.

occasionally proptosis from extension of disease into the orbit. Patients are frequently misdiagnosed with invasive fungal sinusitis. Many of these patients have had multiple sinus operations before the correct diagnosis is made.<sup>1</sup>

### Diagnostic Features of AFS

AFS can be distinguished clinically, histopathologically, and prognostically from other forms of chronic fungal sinusitis. There are 3 forms of invasive fungal sinusitis (acute, chronic, and granulomatous) and 2 types of noninvasive fungal sinusitis (fungal ball and AFS). The main differentiating features are delineated in **Table 1**.<sup>1</sup> AFS must be distinguished from invasive disease, as treatment and prognosis are radically different. **Table 2** lists the proposed diagnostic criteria for AFS.<sup>2</sup> All of these criteria must be met to make the diagnosis of AFS.

The presence of allergic mucin suggests the diagnosis of AFS. Allergic mucin is a brown or greenish-black material with the consistency of peanut butter or cottage cheese and is found in the sinus during surgery or grossly during the physical examination,<sup>3</sup> as was seen in the case patient. Allergic mucin contains laminated accumulations of intact and degenerating eosinophils, Charcot-Leyden crystals, cellular debris, and fungal hyphae. The adjacent mucosa has a mixed cellular infiltrate of eosinophils, plasma cells, and lymphocytes but no invasion by fungal hyphae. Allergic mucin with polypoid sinus mucosa may form a partially calcified

expansive mass, which can obstruct the ostia and decrease aeration of the sinus, leading to superimposed bacterial infection. Pressure-induced erosion through the intra-ethmoidal septae, the lamina papyracea into the orbit, and even through the cribriform plate or posterior wall of the frontal sinus into the epidural space has been reported.<sup>4</sup>

The disease process in AFS is an IgE-mediated hypersensitivity reaction to fungal elements in the sinuses.<sup>5</sup> Patients usually have multiple positive immediate hypersensitivity skin tests to inhaled allergens, including the causative organism. The most common species associated with AFS are the dematiaceous fungi, including *Curvularia*, *Bipolaris*, and *Pseudallescheria*, and the hyaline molds, such as *Aspergillus* and *Fusarium*.<sup>8</sup> Serum IgE levels are often elevated; however, a normal total serum IgE level does not exclude AFS.<sup>6</sup> The white blood cell count is usually normal with a variable degree of eosinophilia.

The characteristic CT findings of AFS are complete unilateral or bilateral opacification of multiple paranasal sinuses, sinus expansion, erosion of the involved sinus wall, and scattered intra-sinus high attenuation areas and mucosal thickening on nonenhanced CT scans.<sup>6</sup> Although this type of erosive process might seem to be indicative of an invasive infection, the histology in AFS does not show fungal penetration into tissue or bone. MRI findings can also be helpful in diagnosing AFS. MRI typically shows a hypodense signal on T1-weighted images and a very decreased signal on T2-weighted images.<sup>6</sup>

### Treatment

The initial treatment for AFS is complete surgical debulking of allergic mucin and reactive hypertrophied/hyperplastic mucosa and reventilation of sinuses.<sup>7,8</sup> Debulking must be thorough to avoid relapse. After surgery, oral prednisone (0.5 mg/kg daily) is initially used to downregulate the IgE-mediated hypersensitivity response. Following tapering of the oral dose, patients usually are switched to intranasal corticosteroids at 6 months when the mucosa is normal or there is no mucin present.<sup>9</sup> Administration of oral corticosteroids resulted in prompt resolution of sinonasal symptoms in 68 cases.<sup>10,11</sup> The duration of corticosteroid treatment was individually determined but usually lasted 1 year. Some patients had a return of AFS symptoms while tapering corticosteroids.

Despite treatment, patients usually have recurrence of the disease and require repeat surgery and oral corticosteroid therapy. Therefore, follow-up is very important. Repeat total serum IgE levels should be measured during patient follow-up. Progressive declining levels

**Table 1.** Features of Noninvasive and Invasive Fungal Sinusitis

	<b>Common Causes</b>	<b>Characteristics of Host</b>	<b>Histopathologic Features</b>	<b>Treatment</b>	<b>Prognosis</b>
Allergic fungal sinusitis	<i>Bipolaris</i> species, <i>Curvularia lunata</i> , and <i>Aspergillus fumigatus</i>	Immunocompetent, frequently atopic	Fungal elements in allergic mucin; no invasion of mucosa, submucosa, or bone	Débridement, aeration, oral and topical steroids, and (?) allergen immunotherapy*	Recurrence common
Sinus mycetoma (fungal ball)	<i>A. fumigatus</i> and dematiaceous fungi	Immunocompetent, sometimes atopic	Dense accumulation of fungus in mucoid matrix forming an expansile mass	Débridement, aeration; no antifungals	Excellent
Acute invasive fungal sinusitis	<i>Mucorales</i> species and <i>A. fumigatus</i>	Immunocompromised, diabetes mellitus, immunosuppressive therapy	Fungus invades mucosa, submucosa, blood vessels, or bone with extensive tissue necrosis	Radical débridement, antifungal agents, treatment of underlying conditions	Fair if disease is limited to sinus and poor with intracranial involvement
Chronic invasive fungal sinusitis	<i>A. fumigatus</i>	Immunocompromised	Necrosis of mucosa, submucosa, bone, and blood vessels with inflammation	Radical débridement and antifungals	Poor
Granulomatous invasive fungal sinusitis	<i>A. flavus</i>	Immunocompetent	Granuloma with multinucleated giant cells and palisading histiocytes	Débridement, aeration, and itraconazole therapy	Good but disease can recur

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\*There is no evidence that oral antifungal agents are helpful.

of IgE are associated with improvement, whereas increasing levels of IgE are associated with disease recurrence or worsening. Disease recurrence or worsening requires increasing the dose of prednisone or surgical intervention.<sup>10</sup>

Recently, immunotherapy has been proposed as a treatment for AFS. Patients usually have elevated total and fungal-specific IgE levels as well as hypersensitivity to multiple fungal and nonfungal antigens as demonstrated by allergy skin testing. In a study by Mabry and colleagues<sup>12</sup> of 11 patients who had received immunotherapy for 1 to 3 years, patients had less nasal crusting and required no systemic steroids or repeat surgeries for recurrent AFS. Immunotherapy should be administered 6 to 8 weeks after surgical debulking of the sinuses because there is concern about worsening of the disease in patients with a high burden of fungal antigen.<sup>13</sup> In another small study by Mabry and colleagues,<sup>14</sup> there was no disease recurrence in 8 patients 7 to 17 months after discontinuation of immunotherapy. Immunotherapy, however, remains a controversial treatment because of the potential for worsening AFS.

There are no data to suggest that systemic antifungal therapy will be beneficial. Bent and Kuhn,<sup>15</sup> however, have proposed that topical amphotericin B and itracon-

**Table 2.** Five Proposed Criteria for the Diagnosis of Allergic Fungal Sinusitis

1. Allergic mucin is seen histologically and/or grossly
2. Allergic mucin fungal stain is positive and/or surgical sinus fungal culture is positive
3. An inflammatory infiltrate comprised of eosinophils and lymphocytes is seen in the sinus mucosa
4. Necrosis, granuloma, or fungal invasion of blood vessels, submucosa, or bone is not present
5. Diabetes, immunosuppressive disease, and use of immunosuppressive medication are absent, and other fungal diseases are excluded

Data from deShazo RD, Swain RE. Diagnostic criteria for allergic fungal sinusitis. *J Allergy Clin Immunol* 1995;96:24–35.

azole might be used as an adjunct to surgery to lower the fungal antigen loads via postoperative sinus irrigation.

## CONCLUSION

AFS should be considered in all patients with intractable sinusitis and a history of atopy or asthma. Early diagnosis of noninvasive sinusitis may prevent multiple surgical procedures and lead to effective treatment. Postoperative follow-up is critical as the relapse rate is very high.

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