Allergic Fungal Sinusitis/Polyposis

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ABSTRACT

In the last decade, the medical community has recognized allergic fungal sinusitis as an unique clinical entity strongly associated with nasal polyps. We will review the differential diagnosis, clinical features, diagnosis, treatment, and prognosis. Appropriate management requires distinguishing allergic fungal sinusitis from other forms of chronic fungal and bacterial sinusitis. Surgical treatment initially results in dramatic improvement, and oral steroids help maintain postoperative success. However, recurrent disease eventually prevails, leaving a glaring need for improved medical treatment. (Allergy and Asthma Proc 17:259–268, 1996)

Allergic fungal sinusitis (AFS) is a newly appreciated diagnosis, first described in the early 1980s. Over the last decade, it has come to be acknowledged as a significant cause of nasal polyposis and the most common form of fungal sinusitis in the United States. Although much has been learned about AFS since its discovery, it remains a mysterious and chronic condition for which there exists no effective long-term treatment.

In order to properly diagnose and treat AFS, the full spectrum of fungal sinusitis must be understood. Currently, most rhinologists recognize four types of fungal sinusitis: acute/fulminant (invasive), chronic/indolent (invasive), fungus ball, and allergic fungal sinusitis (AFS).[1–3] This system can be broken down into two invasive and two noninvasive, or one acute and three chronic (Table I). Other forms of fungal sinusitis may exist that have not yet been described. This article will outline the four recognized types of fungal sinusitis, highlighting the differences among each category. Emphasis will be placed on the pathophysiology, diagnosis, and treatment of AFS.

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ACUTE/FULMINANT (INVASIVE) FUNGAL SINUSITIS

Fulminant (invasive) fungal sinusitis is the only form of acute fungal sinusitis. It occurs exclusively in diabetic or immunosuppressed patients, most typically among oncology or transplant patients. The patient generally presents with ischemic tissue in the paranasal region, but not with polyps. Fungal penetration progresses rapidly, within hours or days, destroying mucosa and bone while invading blood vessels, orbit, brain, and skin. Histologic exam demonstrates vascular occlusion and necrosis (Fig. 1), and fungal cultures usually reveal Phycomycetes (*Mucor* or *Rhizopus*) or *Aspergillus* species. The term "mucormycosis," which describes acute fungal sinusitis caused by *Mucor,* frequently appears in the medical literature.

This condition requires emergency surgical attention. Necrotic tissue should be debrided until viable tissue is encountered, which may require orbital enucleation or craniotomy. The goal is to minimize the number of fungal organisms present, but complete fungal eradication is usually not possible with surgery alone. Adjuvant antifungal therapy with amphotericin B helps improve survival, but morbidity and mortality rates are quite high. Outcome does not appear to be dependent on whether the etiologic organism is *Mucor* or *Aspergillus.* Survival rates range from 20%–75% and correlate with the control of underlying disease.[4] Aggressive correction of any metabolic or immune disorder is therefore of paramount importance. Diabetics tend to fare better than patients with more refractory systemic disorders, such as leukemia and chronic renal failure,[4] probably because diabetes can be more readily controlled.

HIV-related immunosuppression does not predispose patients to acute fungal sinusitis, but AIDS victims may be at risk for fungal sinusitis caused by *Pseudallescheria boydii, Cryptococcus,* or *Histoplasma.*[5]

CHRONIC/INDOLENT (INVASIVE) FUNGAL SINUSITIS

Chronic invasive fungal sinusitis features insidious symptomatology complicated by fungal penetration into tissue. It occurs in immunocompetent individuals who usually have a longstanding history of rhinosinusitis. The

TABLE I	
Classification of Fungal Sinusitis	
Acute	
acute fulminant	invasive
Chronic	
chronic indolent	invasive
fungus ball	noninvasive
allergic fungal sinusitis	noninvasive

disease progresses slowly, producing chronic granulomatous inflammation and extension beyond sinus walls. Polyps may be present. It has been compared to a locally aggressive neoplasm.[6] Plasmocytes and eosinophils may be seen in sinus mucosa, a finding also seen in AFS. Many of these patients have allergic histories,[7] making differentiation from AFS difficult. Fungi must be microscopically visualized within sinus tissue to distinguish this entity from the two noninvasive forms of fungal sinusitis.

Aspergillus species and members of the *Dematiaceous* family are the usual causative organisms. Chronic invasive fungal sinusitis is virtually endemic in some areas, such as Sudan[6] and northern India.[7] Reports of this disease have decreased significantly in the United States over the last decade. We have seen no cases since 1980 and believe that it is quite rare, certainly the least common of the fungal sinus infections.

When pathologic examination confirms fungal invasion, the physician is obligated to treat the patient aggressively. Complete surgical excision with wide exposure and generous bone removal is indicated. Extensive antifungal therapy, directed by *in vitro* fungal culture sensitivities, should also be used. Although recurrences commonly occur, some patients achieve cure,[8] and the prognosis is much better than for acute fungal sinusitis.

FUNGUS BALL

Older names for this noninvasive form of chronic fungal sinusitis include mycetoma and aspergilloma. It affects immunocompetent, nonatopic patients and usually produces either no symptoms or a mild sensation of pressure. The disease may involve any sinus, but usually occurs in a single sinus, most frequently the maxillary antrum. Bone erosion and mucosal invasion does not occur. Fungal proliferation produces a tangled and tightly packed mass with a clay-like appearance. The lack of sinus inflammation distinguishes this disorder from other forms of chronic fungal sinusitis.

The etiologic organism is almost always *Aspergillus fumigatus*.[9] Treatment consists of debridement of the fungus and sinus aeration; cure rates should approach 100%. In our recent review of 20 consecutive cases of chronic fungal sinusitis, 2 had fungus balls, equating to an incidence of 10%. This is unlike the European experience, where it appears to be the most common form of fungal sinusitis.[9]

ALLERGIC FUNGAL SINUSITIS

Historical Background

AFS was first appreciated in the early 1980s because of its histologic resemblance to allergic bronchopulmonary aspergillosis (ABPA). This connection was first appreciated in 1981 by Millar et al., who noted a similarity between the sinus contents removed from five chronic sinusitis patients and the typical pathologic appearance of ABPA.[10] Two years later, Katzenstein et al. independently made the same observation, stimulating a retrospective review of 119 chronic sinusitis surgical specimens in which they identified seven patients (5.9%) with septate fungal hyphae scattered among necrotic eosinophils and amorphous mucin. They termed this condition "allergic *Aspergillus* sinusitis" based on the assumption that *Aspergillus* species were the causative organisms.[11] Gourley et al.'s retrospective review of 200 patients demonstrated a 7% prevalence of AFS among chronic sinusitis patients requiring surgery,[14] corroborating Katzenstein et al.'s study. No prospective data exists regarding true disease prevalence, but the 6–7% rate established in retrospective studies may be an underestimate. As it became apparent that *Dematiaceous* fungi, not *Aspergillus* species, were the primary etiologic agents, the name was changed to AFS.[12,13]

Clinical Characteristics

Warm humid climates, typified by the southeastern United States, seem to foster fungal proliferation. AFS patients are usually adolescents or young adults. We have now diagnosed over 40 cases in the last 4 years, with an age range of 9 to 69 years, but have observed no sexual or ethnic predilection. Atopy and asthma have been present in most reported cases. Patients typically give a history of sinonasal polyposis, recurrent sinusitis, and multiple previous surgeries. Usually, the inflamation affects all paranasal sinuses, but asymmetrically involves one side.

Computerized tomography (CT) scans have a characteristic appearance (Fig. 2). Fungal elements release ferromagnetic elements (magnesium and calcium), creating a serpinginous area of high attenuation.[20] CT scans often demonstrate bone erosion and deviation of adjacent structures. Investigators have reported bone destruction ranging from 19%[27] to 80%[16] of AFS cases. Such a CT appearance in an allergic patient complaining of chronic sinus obstruction is highly suggestive of AFS. Magnetic resonance imaging (MRI) also has a characteristic appearance, as the ferromagnetic elements have a decreased signal intensity, leading to a hypointense T1 image and a markedly hypointense T2 image (Figs. 3 and 4). Some surgeons recommend MRI as the optimal imaging method,[21] but we believe that CT adequately displays AFS while providing superior bone definition.

Nasal endoscopy demonstrates a characteristic allergic mucus, which is thick and viscous, often stained brown, yellow, or green by bacterial superinfection or fungal ma-

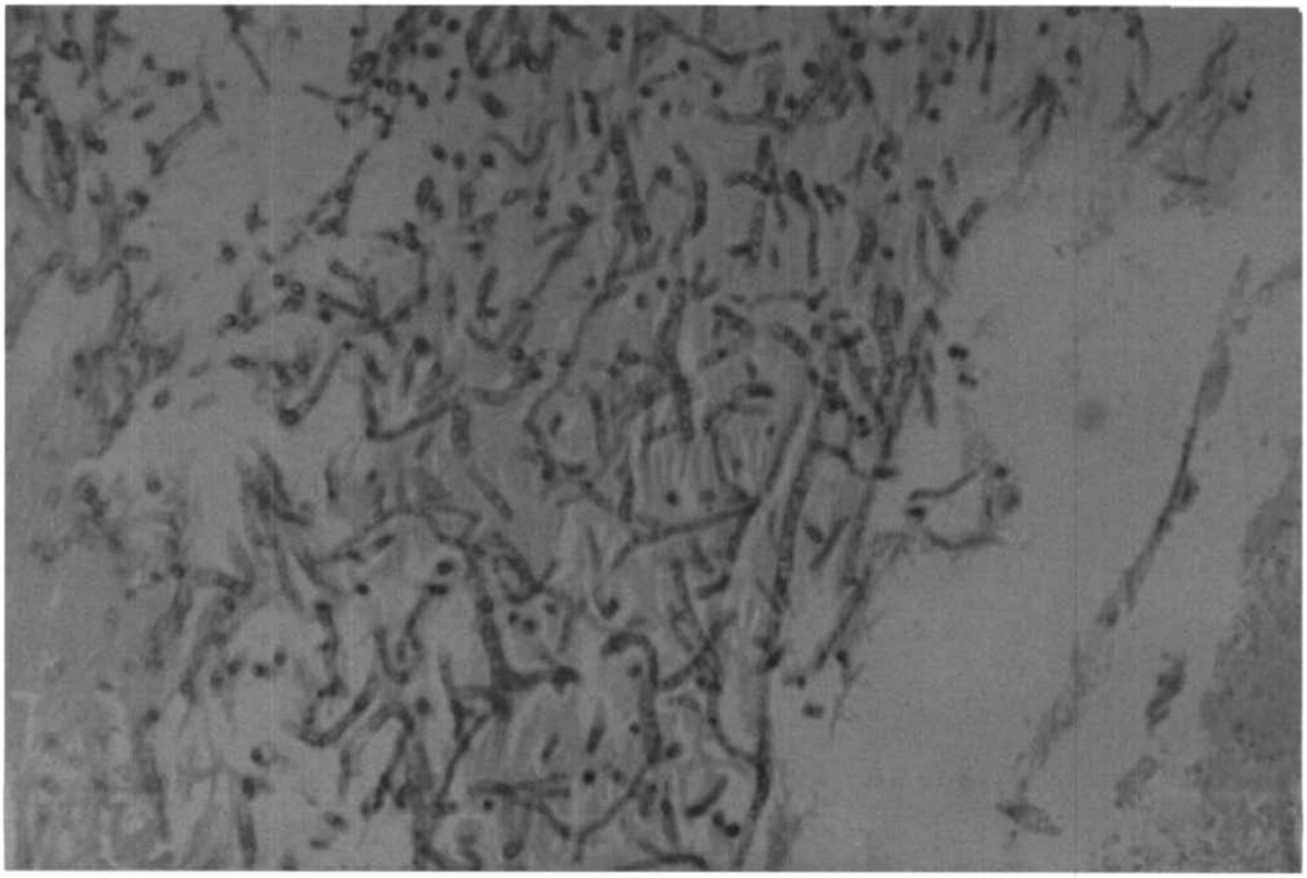

Figure 1. *Hematoxylin and eosin stain from ischemic middle turbinate. Multiple fungal hyphae are seen in this necrotic tissue, consistent with acute fungal sinusitis.*

terial. Polyposis may be massive (Fig. 5) and strikingly unilateral. Intraoperative findings include pockets of greenish-brown fungal concretions buried within polyps and allergic mucus. Often the allergic mucus and fungal debris become intermixed, resulting in a material often referred to as "machine oil," "pistachio pudding," or "peanut butter paste" (Fig. 6).

Pathogenesis and Pathology

Histologic observation of the surgical specimen reveals a triad of eosinophilia, Charcot-Leyden crystals, and extramucosal hyphae. Charcot-Leyden crystals are simply a byproduct of necrotic eosinophils. (Fig. 7) Hyphae can usually be seen with hematoxylin-eosin or potassium-hydroxide stains, and if necessary, special stains such as Gomori methenamine silver (GMS). The pathologist must examine sinus mucosa and bone to specifically exclude tissue invasion. The presence of fungi in the mucin but *not the tissue* of AFS patients differentiates AFS from chronic invasive fungal sinusitis. By definition fungal invasion *does not* occur in any case of AFS.

Prompt culturing of carefully collected fungal debris will usually reveal the etiologic organism. In our early experience with AFS, over 50% of our cases were culture negative. By selecting a specimen rich in fungal debris and rapidly placing it into culture media, yield increased to almost 100%. *Dematiaceous* fungi (phaehyphomycosis), which include *Curvularia, Bipolaris,* and *Alternaria* predominate, followed by *Aspergillus* species (Table II). These are ubiquitous organisms with no potential for contagion. The particular fungal species has no apparent effect on disease manifestation, and at present has no clinical implications.

Several retrospective studies have described an AFS-like syndrome, in which typically AFS features were seen in the absence of identifiable fungus.[14,15,22] When there is no suspicion of AFS, the surgeon will usually not submit mucus for pathologic exam or fungal culture. Therefore, retrospectively identified AFS-like syndromes probably represent AFS without preserved fungal elements, rather than a distinct syndrome. We have no experience with an AFS-like case without a positive fungal stain. However, as suggested by Schwietz and Gourley, there may be an unrecognized, nonfungal antigen capable of producing clinical manifestations equivalent to AFS.[14]

The pathogenesis of AFS is incompletely understood. Presumably, fungi become entrapped in the sinuses of allergic individuals with ostiomeatal complex obstruction, extremely thick mucus, or a mucociliary clearance disorder. The ensuing immune response exacerbates the disease. Im-

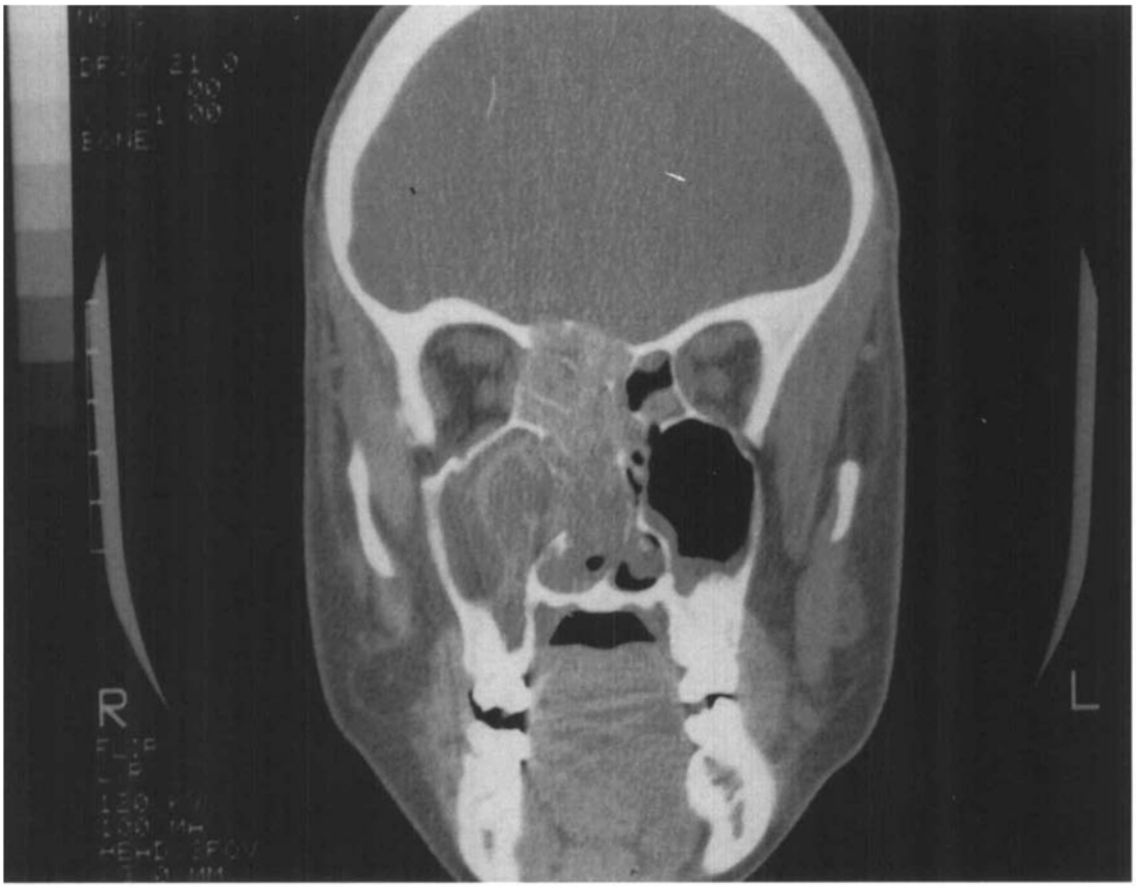

Figure 2. *CT scan demonstrating unilateral Curvularia AFS affecting multiple right ethmoid sinuses. Expanding inspissated fungal debris has eroded the medial wall of the right maxillary sinus, the lamina papyracea, and the ethmoid roof, deviating the nasal septum to the left. The opacified sinuses display a heterogenous character.*

munologists believe that both Type I (IgE mediated) and Type III (IgG mediated) immunity influence AFS, based on their proven association with ABPA. The AFS-ABPA association has been strengthened by simultaneous AFS and ABPA documented in the same patient.[24] Type I immunity has been clearly implicated in AFS based on skin testing, RAST, and total IgE elevations.[15,16] Brummund et al. demonstrated that the etiologic fungal antigen, when used in skin testing, prompted a dramatic Type I cutaneous response.[23] Manning et al. later reported nine consecutive cases of AFS with elevated IgE specific to the fungal antigen.[17] Type III immune reactions, which involve antibody binding of antigen, result in potentially harmful circulating immune complexes. These immune complexes have been shown to contribute to ABPA, and although they have been more superficially studied in AFS, initial studies indicate their involvement.[23–25]

The distinction between AFS and the other two forms of chronic fungal sinusitis (indolent/invasive and fungus ball) is often blurred. The typical features of each fungal sinusitis category are summarized in Table III. It is uncertain if these three diseases are simply stages along the same spectrum or unrelated disorders. Could all chronic fungal sinusitis begin as a fungus ball that eventually progresses to an allergic response in some and invasion in others? What permits chronic fungal sinusitis to progress to invasion in a small subset of patients? The fact that the same fungal organisms are cultured in each of the three different forms of chronic fungal sinusitis supports the notion that all the chronic fungal sinus disorders are in fact interrelated. AFS may be a continuation of fungus ball, different only by the presence or absence of an immune response to the fungal saprophyte. The immune response then generates an inflammatory reaction, resulting in nasal polyps, allergic mucus, and occasionally, bone erosion. Allphin et al. observed that in AFS "a spectrum of disease clearly exists ranging from mild allergic symptoms, polyps, and scant allergic mucin with few scattered hyphae, to an extreme atopic state with massive expansile disease that is noninvasive, but has the potential to destroy bone or cause facial deformity or eye changes."[12] We have also found this to be true, and wonder if the extension of the extremes described by Allphin might be fungus ball on the mild end and chronic invasive disease on the severe side. A report from Hawaii by Zieske et al.[19] described four patients with "allergic mucin" and fungal invasion, which perhaps represents the advanced end of the spectrum. Although no proof exists at present, it may be that unrecognized, submucosal fungal infection causes recur-

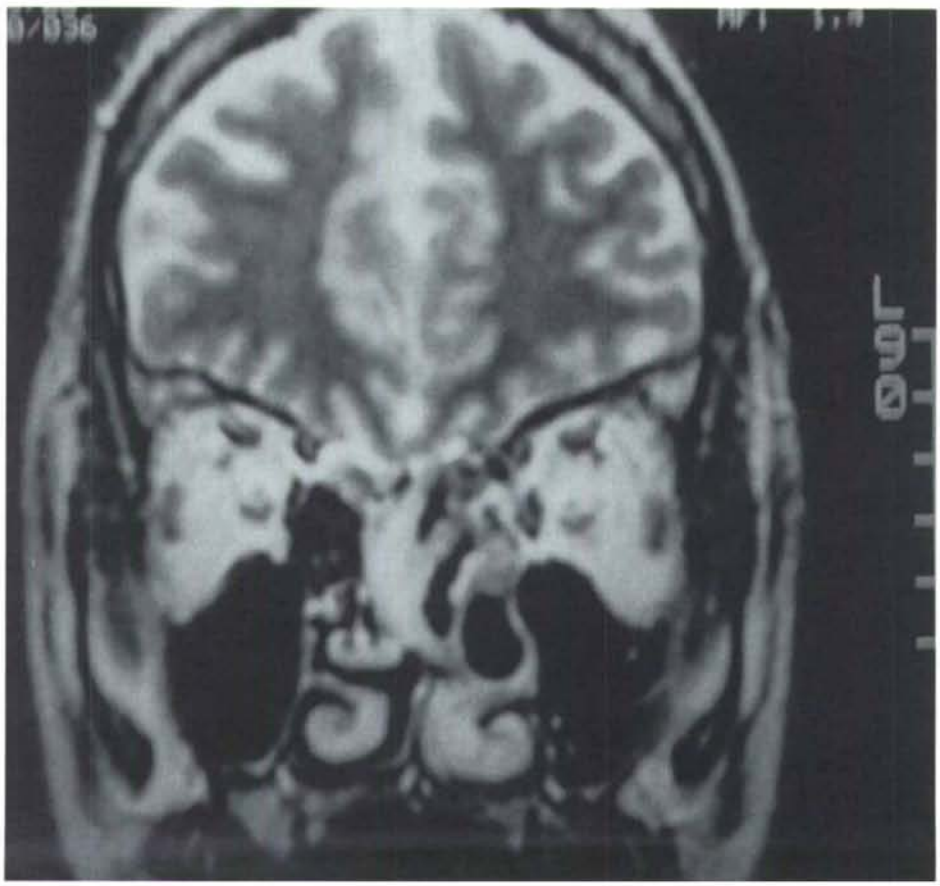

Figure 3. T2 weighed MRI of the same patient seen in Figure 4 showing the characteristic hypointense center.

rence in AFS. However, our experience leads us to believe this is purely an allergic disease. The patients do not present with fever, leukocytosis, or other signs of infection. Furthermore, the successful response to steroids cannot be explained in the face of infection.

Before 1983, AFS cases were probably diagnosed as either bacterial sinusitis or chronic invasive fungal sinusitis. It is no coincidence that case reports of chronic invasive fungal sinusitis have dropped dramatically as AFS became better understood. Many older reports of so-called "invasive" disease were considered invasive based on bone destruction or proptosis (commonly seen in AFS), not histologic tissue invasion. As recently as 1988, Washburn et al. described a young man with *Bipolaris* sinusitis, eosinophilic mucus, bone erosion, and recurrent infections, but no mucosal invasion.[8] Although the authors believed the patient had chronic invasive fungal sinusitis, he probably suffered from AFS. Most likely, chronic invasive fungal sinusitis was over-diagnosed before the description of AFS, and the current paucity of chronic invasive disease reflects its true prevalence.

Diagnosis

Physicians must maintain an index of suspicion for AFS to avoid overlooking the diagnosis. It may be easily mistaken for chronic bacterial sinusitis or nonallergic fungal sinusitis, both of which have significantly different treatments and outcomes. Without an adequate awareness, the rhinologist will miss AFS and become frustrated by unexplained recurrences among "chronic sinusitis" patients. Alternatively, the recognition of extramucosal fungal hyphae may be mistaken for the potentially lethal acute fungal sinusitis, resulting in the inappropriate use of radical surgery or toxic intravenous antifungals. To clarify the diagnosis of AFS, we prospectively evaluated 15 consecutive patients with overt AFS (Table IV).[16] Type I hypersensitivity evidenced by a strong allergic history, positive skin tests, or elevated serum IgE levels was uniformly documented. Nasal polyps were also present in all patients. CT scans reliably showed the characteristic heterogeneous opacification of the involved sinuses. The typical histology was observed in all patients, although Charcot-Leyden crystals were not seen in 9 of 15 specimens. A history of asthma and unilateral predominance of sinus disease was seen in most but not all patients. Radiographic bone erosion appeared in 12 of 15 patients, but no tissue had evidence of fungal invasion. Not all patients had a positive fungal culture or peripheral eosinophilia, and none had a history of aspirin sensitivity. Because the following features were identified in all 15 patients, we proposed that they be established as criteria for the diagnosis of AFS: 1) type I hypersensitivity, 2) nasal polyps, 3) a characteristic CT scan, 4) eosinophilic

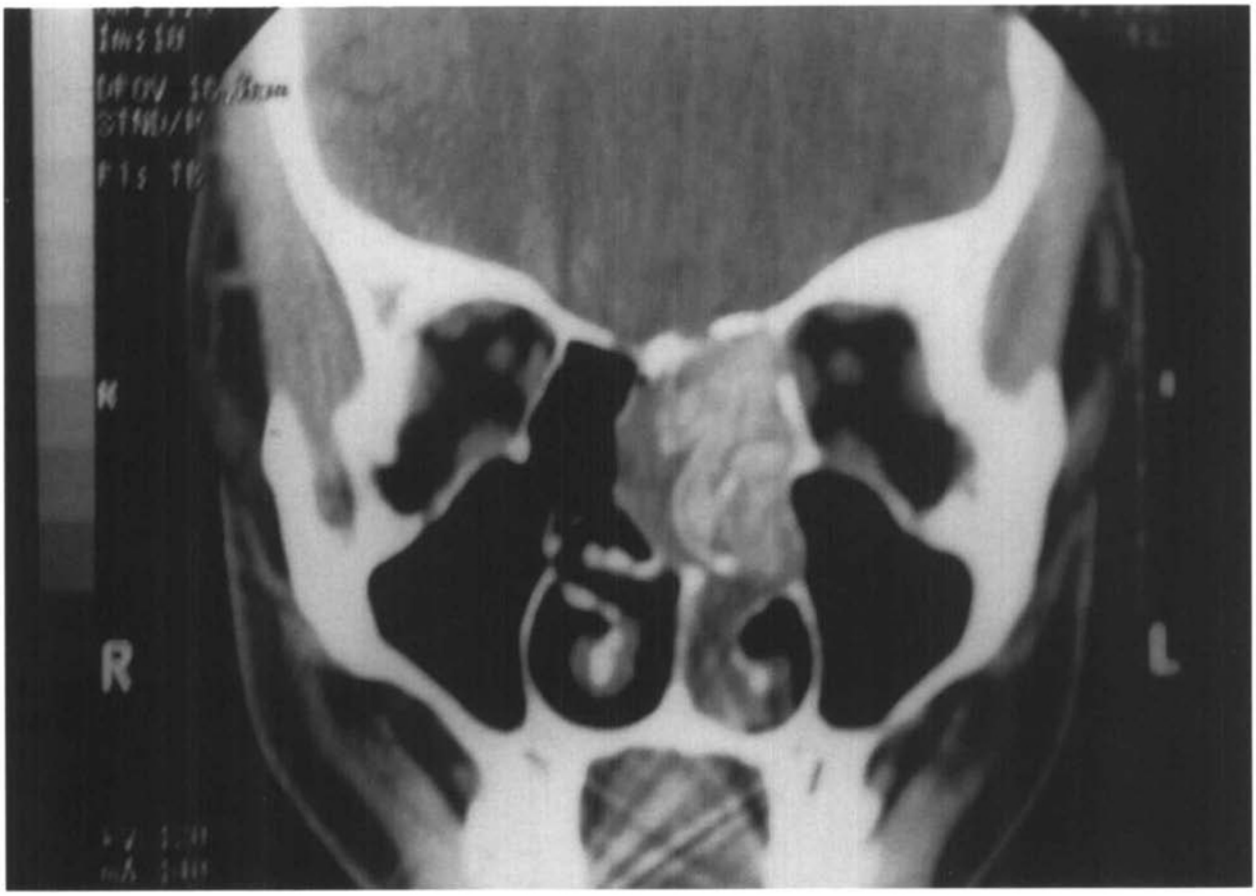

Figure 4. *CT scan of left ethmoid AFS. Expanding inspissated fungal debris has caused deviation of the adjacent lamina papyracea and nasal septum. The heterogenous opacification typical of fungal sinusitis is present.*

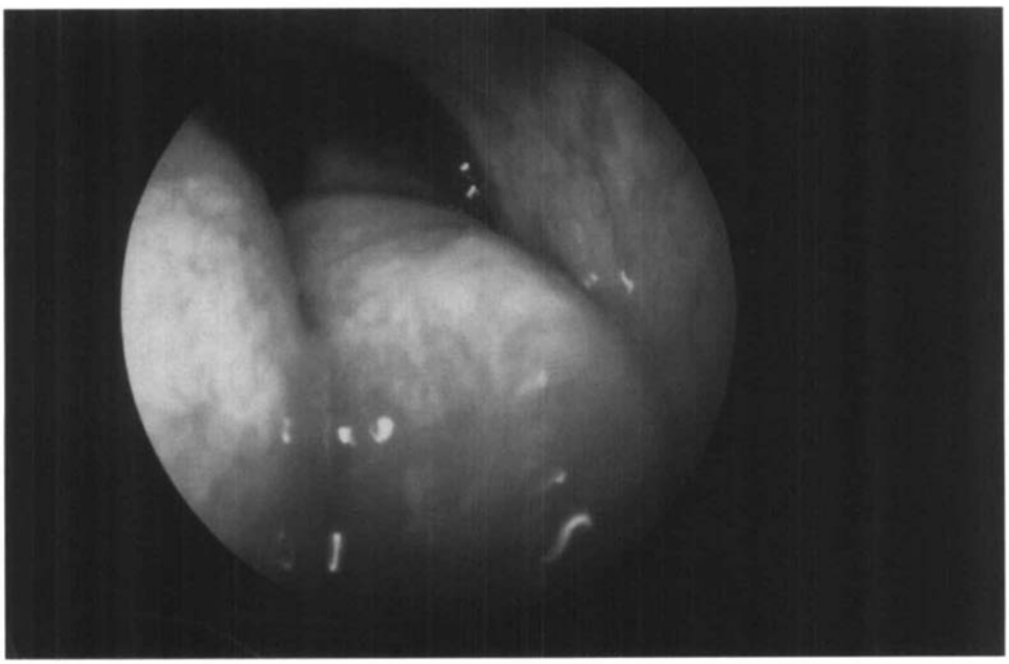

Figure 5. *A large polyp originates from the right middle meatus and extends anterior to the middle turbinate.*

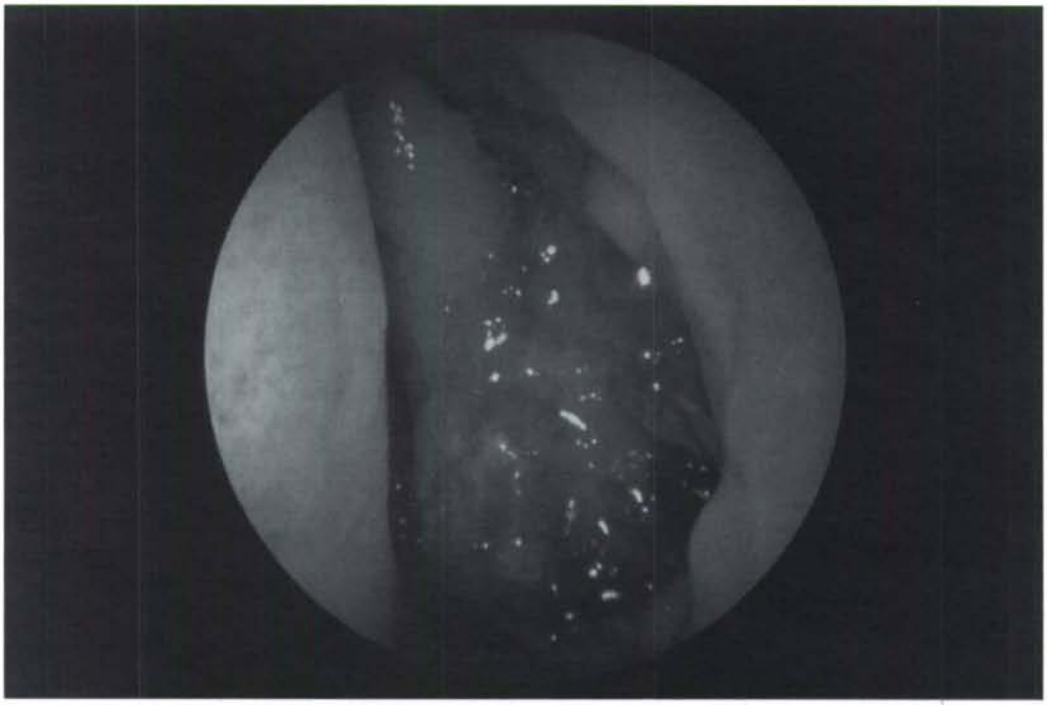

Figure 6. *Fungal and mucoid concretions in left ethmoid cavity, consistent with recurrent allergic fungal sinusitis.*

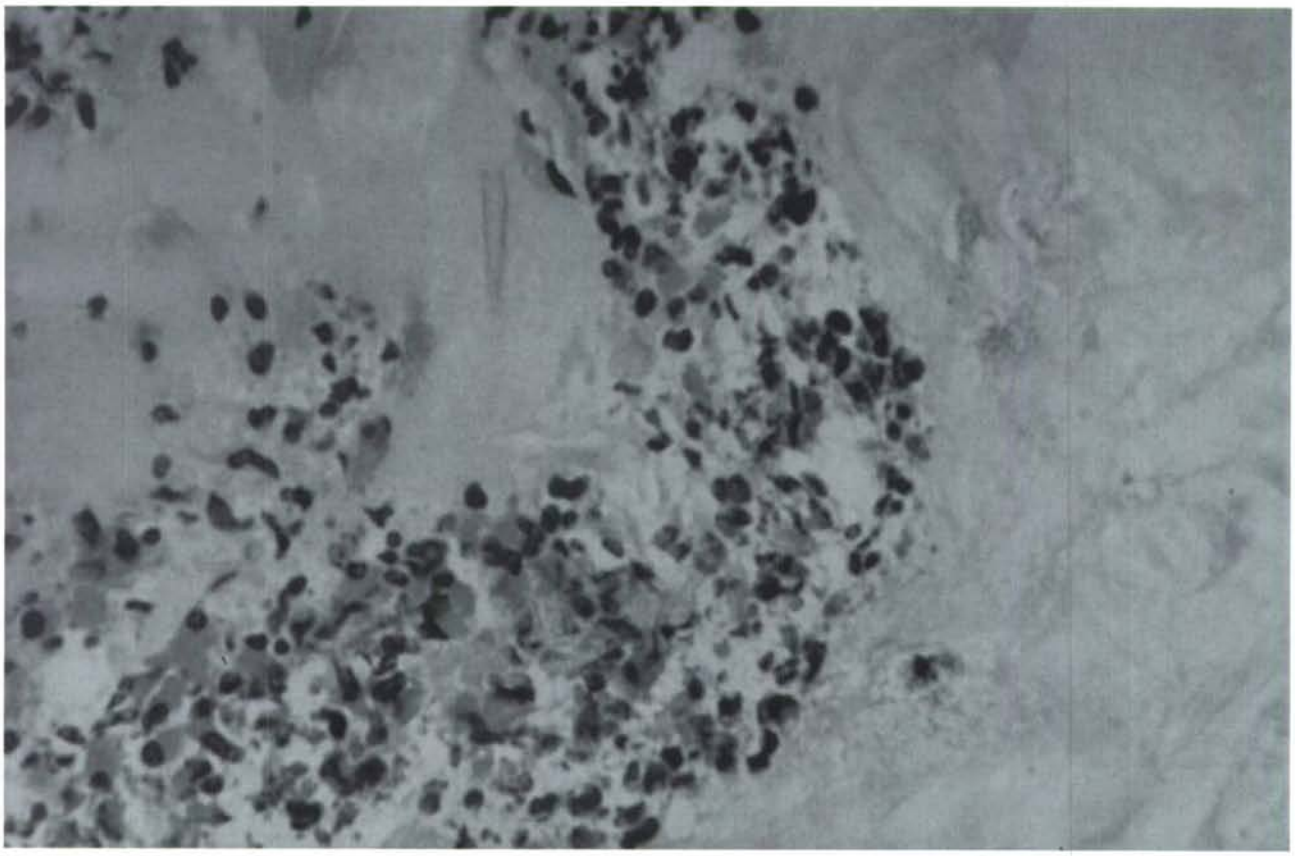

Figure 7. *Allergic mucus with sheets of eosinophils. A Charcot-Leyden crystal, released by necrotic eosinophils, is seen near the center (arrow).*

TABLE II

AFS Culture Results (n = 26)

Dematiaceous		18
Curvularia	10	
Alternaria	3	
Bipolaris	3	
Dreschlera	1	
Exserohilum	1	
Aspergillus		7
Penicillium		2
Cladosporium		1
Fusarium		1
Hyalinase		1
No growth		4
Total		34*

** Five cultures grew 2 or 3 different fungi.*

mucus without fungal invasion into sinus tissue, and 5) a positive fungal stain.[16] Postoperative patients pose a particularly challenging diagnostic dilemma, as early recurrences may lack polyps and classic CT abnormalities.

Treatment

Most otolaryngologists now understand what constitutes AFS, but this improved recognition has not translated into treatment advances. Most authorities concur that functional endoscopic sinus surgery (FESS) with complete removal of inspissated fungi and debris is indicated. The extent of surgery correlates with the amount of pathology. FESS allows preservation of all nondiseased tissue, and external or obliterative surgery is contraindicated in uncomplicated AFS. In any form of surgery, microscopic fungal contamination of the sinuses probably persists, and this may be the source of recurrent disease. Patients generally attain tremendous benefit from surgery, but unfortunately, the improvement is most often transient.

TABLE IV

Characteristics of AFS patients (n = 15)[16]

Common Traits (Present in All Patients)	Associated Traits (Number)
Type I hypersensitivity	Unilateral predominance (13)
Nasal polyps	Radiographic bone erosion (12)
CT scan	Fungal culture (11)
Eosinophilic mucus	Asthma (8)
Fungal stain	Charcot-Leyden crystals (6)
	Eosinophils (6)

Steroids decrease the abnormal immune response, and are being used with increased frequency postoperatively. Our recent retrospective analysis of 26 patients indicated that steroids effectively diminish inflammation and help maintain disease-free interval. However, disease recurred as steroids were weaned, and patients treated with steroids had no apparent outcome advantages with extended follow-up (mean follow-up = 12.5 months).[26] Despite the lack of data to support the efficacy of steroids, we still advocate their use postoperatively to prolong remissions. We recommend postoperative oral prednisone (0.4–0.6 mg/kg/day), tapering 0.1 mg/kg/d every 4 days to 0.2 mg/kg/day. Patient symptoms and objective signs guide subsequent steroid titration. The proper length of steroid treatment is unknown. Alternate day prednisone at 0.5 mg/kg for 3 months, then taper, should be considered. Some physicians reserve steroids for recurrent disease,[18] because of several well-known side effects, including premature epiphyseal closure in children, peptic ulcers, weight gain, moodiness, and immunosuppression (that could potentially lead to fungal invasion). Others argue that "understanding that AFS is a hypersensitivity reaction and not an invasive process lends support to the use of systemic steroids."[1] Our experience has been that all patients not treated with steroids will eventually recur. Preoperative use of steroids also may be considered, but the

TABLE III

Characteristics of Fungal Sinusitis

	Immune Status	Role of Fungus	Tissue Invasion	Sinuses Affected	Treatment	Polyps
Acute	compromised	pathogen	yes	one	radical debridement systemic antifungals	no
Indolent	competent	pathogen	yes	variable	complete excision systemic antifungals	maybe
Fungus ball	competent nonatopic	saprophyte	no	one	debridement aeration	no
AFS	competent atopic	allergen	no	multiple unilateral	debridement aeration steroids ? immunotherapy ? topical antifungals	yes

potential benefits must be weighed against the known risks and lack of clinical experience. Essentially, steroids act by blunting the pathologic hypersensitivity to fungal antigens, but they do not permanently reverse the disease process, leaving a great need for other forms of therapy.

Topical steroids can be used for local immune modulation without risking systemic complications. However, they have not helped noticeably, possibly due to the spray entering the nose but not the sinuses. Systemic antifungals such as amphotericin B play no role in AFS. We have had anecdotal success with using less toxic systemic antifungal, such as itraconazole or ketoconazole, but they have generally been of no benefit. In theory, systemic antifungals should be ineffective against the fungi, which are located extramucosally, outside the range of the drug circulation. Thus in order to produce an effect, a systemic antifungal must be secreted in sinus mucus, a phenomenon that has not been supported and probably does not occur. More realistically, there may be a future role for topical antifungal drugs, which could hypothetically decrease antigen load. Our initial *in vitro* analysis of fungal susceptibilities indicates that the common AFS pathogens are sensitive to several antifungals available in irrigation solution.[29]

Probably the most promising future AFS treatment is serial endpoint titration (SET), or allergy desensitization. Desensitizing patients to the fungal antigen that stimulates their abnormal Type I immune response has therapeutic potential. If fungi function as antigens and not infectious agents, then successful treatment will depend on cleansing each patient's sinuses of fungal antigens and modifying the pathological immune response. Most allergists express skepticism about desensitizing AFS patients, feeling that IgG blocking antibodies will be generated, aggravating the Type III immune contribution, and worsening the disease. We have anecdotal experience of SET producing successful results, but have not used it on a routine basis. Recent data presented by Mabry et al. exemplify that immunotherapy may be both safe and effective: prospective study of 10 AFS patients treated with immunotherapy resulted in "a marked decrease in nasal crusting, a minumum amount of recurrent polypoid mucosa, and a lessened or absent requirement for steroids (systemic or topical) in the vast majority of these patients".[30] Given this preliminary information, further study of immunotherapy can be undertaken with greater earnest and confidence.

TABLE V

AFS Objective Staging and Results (>1 month follow-up; n = 24)[26]

Stage 0: No evidence of disease	4
Stage 1: Mucosal edema/allergic mucin	1
Stage 2: Polypoid edema/allergic mucin	7
Stage 3: Polyps and fungal debris	12

Prognosis

In 1986 Waxman et al. divided postoperative AFS patients into three categories: immediate recurrence (months), delayed recurrence (years), or disease free.[18] They retrospectively studied 15 patients, of whom 2 were lost to follow-up and 5 had less than 1 year of follow-up. Most of their patients had immediate or delayed recurrence, but three individuals remained disease free for as long as 2 years postoperatively. Since they did not mention using an endoscopic exam, which often demonstrates early recurrence in the form of asymptomatic mucosal disease, their data probably portray an unrealistically optimistic prognosis. Reports from other otolaryngologists have cited recurrence rates ranging from 32% (5 of 16)[14] to 100% (3 of 3).[24]

In order to objectively classify postoperative outcome, we proposed a subjective and objective staging system. Subjectively, patients classify themselves as improved, no change, or worse. Reviewing our results, 22 of 26 patients (84.6%) were improved, and none were worse (mean follow-up = 12.5 months).[26] Objectively, endoscopic nasal examination permits staging into one of four objective categories (Table V), ranging from Stage 0 (no evidence of disease) to Stage III (polyps and fungal debris present). Results from 24 patients seen beyond 1 month follow-up are displayed in Table V.[26] Disease severity ranged from mild, asymptomatic inflammation to rapid recurrences featuring extraordinarily high serum IgE and immediate return of polyps. Physical findings tended to reflect more disease than patient's symptoms, and many patients who felt asymptomatic had endoscopic evidence of pathology. All patients followed beyond 12 months postoperatively developed objective evidence of recurrence, with the longest time to recurrence being 34 months.[28] We do not know whether recurrence results from reexposure to fungus or an immune reaction to persistent fungal antigens. With continued follow-up, we suspect that asymptomatic patients followed less than 12 months will eventually develop sinonasal complaints. Consequently, we follow patients with endoscopic exams every 1–3 months for at least 3 years.

Conclusions

A greater understanding exists regarding disease recognition and diagnosis of AFS. Although most patients can be helped tremendously with current management strategies, many questions persist about immunopathology and treatment. Hopefully, future research will deal with these issues and enable improved postoperative results.

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