

Evaluation and treatment of allergic fungal sinusitis. I. Demographics and diagnosis

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Background: Few cases of allergic fungal sinusitis have been systematically evaluated to conclusively confirm working clinical, histopathologic, and serologic diagnostic criteria.

Objectives: The objective of this study was to describe 67 consecutive cases of allergic fungal sinusitis, the largest number of cases yet published.

Methods: Cases from 1 practice over 8 years were evaluated with a consistent protocol, including skin testing, serum chemistries and serologies, and surgical specimen analysis. **Results:** All patients were atopic (100%) and had nasal polypsis (100%). They tended to be young (33.3 ± 13.1 years, mean $\pm$ SEM), immunocompetent (92%; remaining 8% with low quantitative immunoglobulin but normal function), have slight female preponderance (58%), have a history of hypertrophic rhinosinusitis (100%), report nasal cast production (75%), and have developed their disease in the southwestern United States. *Bipolaris spicifera* was the most prevalent fungus involved (67%). Total serum IgE (mean 668 IU/mL) and fungal-specific IgG were generally elevated, whereas fungal-specific precipitins and specific IgE were generally negative despite positive fungal-specific immediate hypersensitivity skin tests.

Conclusions: Patients with allergic fungal sinusitis tend to have elevated total serum IgE and fungal-specific IgG at diagnosis but not fungal-specific IgE or precipitins. Histopathologic criteria for allergic fungal sinusitis diagnosis are discussed. The southwestern United States appears to be a "hot spot" for the disease, particularly caused by *B spicifera*. (J Allergy Clin Immunol 1998;102:387-94.)

Key words: Allergic mucin; antibodies, fungal; diagnosis; Deuteromycetes, fungi; fungus diseases; hypersensitivity, type I; IgE; prednisone; serodiagnosis; spores, fungal; rhinosinusitis; sinusitis; treatment outcome

Abbreviations used

ABPA: Allergic bronchopulmonary aspergillosis
AFS: Allergic fungal sinusitis
CT: Computed tomography
ESR: Erythrocyte sedimentation rate
H&E: Hematoxylin and eosin
MRI: Magnetic resonance imaging
sIgE: Fungal-specific IgE
sIgG: Fungal-specific IgG

Fungal sinusitis is seen in 4 distinct forms: indolent, mycetoma, invasive/necrotizing, and allergic. Each can be distinguished clinicopathologically. Allergic fungal sinusitis (AFS) is characterized as an intense allergic reaction to the presence of a fungus growing in allergic mucin within the sinus cavities.¹⁻⁶ An immunopathologic analogy to allergic bronchopulmonary aspergillosis (ABPA) has been drawn, including description of fungal-specific serum IgE, IgG, and precipitins.^{2, 7-9} Consequences of this process include hypertrophic rhinosinusitis with anatomic and functional sinonasal obstruction. Concretions of peanut-buttery inspissated allergic mucin containing fungal hyphae create masses that obstruct sinus ostia and may erode through bone into the orbits, the cranium, or both.¹⁰⁻¹⁴ Clinically severe rhinosinusitis is present and often associated with a degree of reactive airways.⁶ Differentiation from the other forms of rhinosinusitis is crucial to prognosis and planning treatment because AFS has been found to be highly recurrent after surgery.^{2, 8, 13, 15} Surgery is necessary to initially debulk the sinuses of hypertrophic sinus mucosa, purulence, inspissated allergic mucin, and to recreate unobstructed sinonasal ventilation pathways. Fungal culture and careful review of the histopathologic specimens are then necessary for proper diagnosis. Fungal invasion, granuloma formation, or tissue necrosis must not be seen histologically in AFS. Silver stains may show fungal elements within the allergic mucin but not the mucosa. After surgical debulking, medical treatment consists of aggressive allergy management and close follow-up. Oral corticosteroids have been tried for refractory cases.^{6-8, 15-18} Systemic antifungal therapy has not been shown to significantly modify the clinical course of AFS.¹⁹⁻²³

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TABLE I. Criteria required for histopathologic diagnosis of AFS

1. Allergic mucin is present on gross and/or histopathologic examination.
 - a. Gross examination of allergic mucin reveals inspissated peanut-buttery dark brown to green sinus material (surgical sampling error may occasionally exclude microscopic allergic mucin on histopathology).
 - b. H&E stain reveals extramucosal mucinous exudate of allergic mucin:
 - Pale eosinophilic background
 - large pyknotic eosinophil concretions
 - Charcot-Leyden crystals
2. Either (a) methenamine silver stain of allergic mucin is positive for fungal hyphae but no fungal hyphae are seen in the mucosa (with or without positive fungal culture), or (b) silver stain is negative and fungal culture is positive.
3. Sinus mucosal H&E stain is characteristic for AFS and indistinguishable from the mucosal infiltrate in asthmatic bronchial mucosa.
 - a. Mucosal infiltrate of eosinophils, plasma cells, and small lymphocytes.
 - b. Absence of necrosis, granuloma formation, or giant cells.
 - c. Stromal edema.
 - d. Thickened respiratory epithelial basement membrane.
 - e. Partially desquamated respiratory epithelium.
 - f. Distended mucus glands.
4. Other histopathologic fungal diseases are excluded (eg, mycetoma or invasive fungal disease).

There has been a paucity of published cases of systematically evaluated and treated patients with AFS with which to draw definitive conclusions regarding working diagnostic criteria, immunologic findings, prognostic criteria, or treatment modalities. This report describes 67 cases of AFS from 1 medical practice (M.S.S.) collected over 8 years in Phoenix, Ariz. This represents the largest accumulated group of patients with AFS yet published. Clinical, histologic, immunologic, and treatment characteristics are reviewed. Part I of this 2-part series covers patient demographics and diagnostic criteria; Part II covers treatment and follow-up.

METHODS

Patients with AFS were either referred perioperatively by various otolaryngologic surgeons or were diagnosed during the course of medical management for allergic respiratory disease. All patients suspected of having AFS therefore had undergone the study—entering sinus surgery just before or early during the course of our initial evaluation. The diagnosis of AFS was made in 67 consecutive patients over 8 years from 1 Allergy and Immunology practice (M.S.S.), and each had been subsequently followed over time before entry into this retrospective case review. Before sinus surgery and referral to the allergist, all patients with AFS had had computed tomographic (CT) scans of the sinus performed by their otolaryngologic surgeons showing hypertrophic rhinosinusitis.

All patients underwent a uniform initial laboratory evaluation: (1) inhalant skin tests to Southwestern grasses, weeds, trees, dust mite, danders, and molds including *Bipolaris spicifera*; (2) delayed cutaneous hypersensitivity skin tests to T-cell recall antigens including purified protein derivative, Coccidioidin, Trichophyton, and mumps; (3) complete blood count with differential, serum chemistry screen (including glucose, electrolytes, creatinine, liver function tests, calcium, albumin, globulin, and cholesterol), erythrocyte sedimentation rate (ESR), quantitative immunoglobulins (IgG, IgM, IgA), total IgE, and urinalysis; (4) *B spicifera* serologies: precipitins, fungal-specific IgG (sIgG), and fungal-specific IgE (sIgE); (5) chest radiograph; and (6) spirometry.

Serum samples for general chemistries, immune screening, and total serum IgE

Serum specimens that were collected during clinical encounters were stored at -17°C until analyzed. Sequential serum samples were

evaluated for total IgE (IU/mL) by immunoassay at one of several accredited clinical laboratories in Phoenix, Ariz: Lab Corp, Quest, Smith Kline, or Sonora. *B spicifera* precipitins and specific immunoglobulins were performed as described below. Complete blood count, total eosinophils (%), ESR (mm/h), serum chemistries, urinalysis, and quantitative immunoglobulins (IgG, IgA, IgM) (g/L) were obtained at a patient's initial visit. Functional immune status was assessed as previously described²⁴ when required.

Preparation of *B spicifera* extract

The *B spicifera* extracts were prepared as previously described.² In short, *B spicifera* identification was confirmed by Dr Michael Rinaldi, Director, Fungal Testing Laboratory, University of Texas Health Science Center, San Antonio. Cultures were grown in stationary Erlenmeyer flasks with Czapek Dox synthetic broth media. Mats were harvested, defatted with acetone, and air dried. The defatted powder was extracted (1:10 wt/vol) at 4°C in 0.125 mol/L ammonium bicarbonate, pH 8, overnight. The crude extract was filtered serially to 0.2 μm . Skin prick test material was diluted with equal volumes of glycerin. Material for in vitro analysis was dialyzed against distilled water for 24 hours and lyophilized.

B spicifera precipitins

Gel double immunodiffusion according to the method of Ouchterlony²⁵ was accomplished with a *B spicifera* extract and 5-fold concentrated patient serum.

B spicifera fungal-specific IgG and IgE

ELISA assays for *B spicifera* sIgG and sIgE were accomplished as previously described.² ELISA results were referenced to a high-titer sera pool previously arbitrarily assigned 100 U/mL. *B spicifera* sIgG was determined by a single incubation ELISA; determinations of sIgE were accomplished with a microtiter plate transfer method to minimize the competition of IgG antibodies. All patient sera were run in duplicate.

Skin testing

Skin tests to a battery of 54 aeroallergens including Southwestern pollens (1:50 wt/vol prick, International Biologicals Inc, Piedmont, Okla; 1:20,000 wt/vol, ID, Berkeley Biologicals, Berkeley, Calif), indoor allergens (dog and cat 1:50 wt/vol, prick, International Biologicals, Inc; 1:20,000 wt/vol, ID, Berkeley Biologicals; dust

mite 10,000 AU/mL, prick, 50 AU/mL intradermal, Berkeley Biologicals), and a panel of mold spores (1:50 wt/vol, prick, International Biologicals; 1:100,000 wt/vol, ID, Berkeley Biologicals) (standard testing panel) were carried out by the percutaneous prick and intradermal methods on the arms according to a standard protocol.²⁶ *B spicifera* skin testing was performed on all patients by the prick method only. Appropriate positive and negative controls were used. Results were read at 20 minutes and rated on a scale of positivity. Patients were considered atopic if 2 or more of the standard panel skin test results were positive.

Delayed cutaneous hypersensitivity skin test reactions to PPD (5 TU), Coccidioidin (1:100; ALK, Berkeley, Calif), Trichophyton (1:100; Bayer Corp, Spokane, Wash), and mumps (40 CFU/mL) were placed and read according to a standard protocol.²⁷

Surgical specimens

Surgical specimens were cultured for bacteria and fungi in the laboratories associated with the given hospital where the patient's sinus surgery was performed. Hematoxylin and eosin (H&E) and methenamine silver stains of the surgical specimens were performed according to the standard protocols at the hospital's pathology laboratory. These stained slides were reviewed by an independent pathologist first, then by one of the authors (M.S.S.).

RESULTS

Sixty-seven patients with AFS initially were seen, as described in the Methods section. Four histopathologic criteria for the diagnosis of AFS are described in Table I; all criteria had to be met for the diagnosis of AFS. First, allergic mucin from the sinus surgery specimen was present either microscopically on the H&E stain, on gross inspection at surgery, or both. Second, either a positive silver stain for fungal hyphae was manifested in the allergic mucin and/or the surgical fungal culture was positive. Third, the sinus mucosal H&E stain met the criteria for AFS as described in Table I. Fourth, all other histopathologic fungal diseases such as mycetoma or fungal invasive disease had to have been excluded. One patient with AFS had histologic evidence for both AFS and mycetoma (fungal mat); another had evidence for both AFS and indolent fungal sinusitis (nongranulomatous, well-demarcated granulomas containing fungal hyphae) with an elevated ESR of 21 mm/h. Both patients were included in the study because of the histopathologic presence of AFS.

Fig 1 shows the characteristic sinus mucosal H&E stain from a representative case. The sinus mucosa is infiltrated by lymphocytes and eosinophils, the epithelium is denuded, and a large distended mucus gland is seen. Allergic mucin is seen extramucosally and consists of a background of pale eosinophilic mucin with large concretions of strongly staining pyknotic eosinophils. Charcot-Leyden crystals are scattered throughout the allergic mucin but cannot be seen on lower power because of their small size and birefringence. A representative silver stain of allergic mucin is shown in Fig 2, in which fungal hyphae can easily be seen. These hyphae are characteristically dispersed, not densely packed as is typically seen in a mycetoma, and they are often hard to find.

Before sinus surgery, all patients with AFS had had sinus CT scans performed by their otolaryngologic surgeons showing hypertrophic rhinosinusitis. A representa-

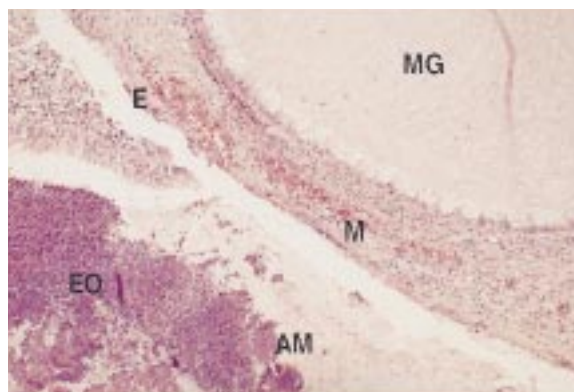


FIG 1. Surgical histopathologic specimen from representative patient with AFS. M, Sinus mucosa; MG, distended mucus gland; E, epithelium; EO, eosinophils; AM, allergic mucin (H&E stain $\times 40$).

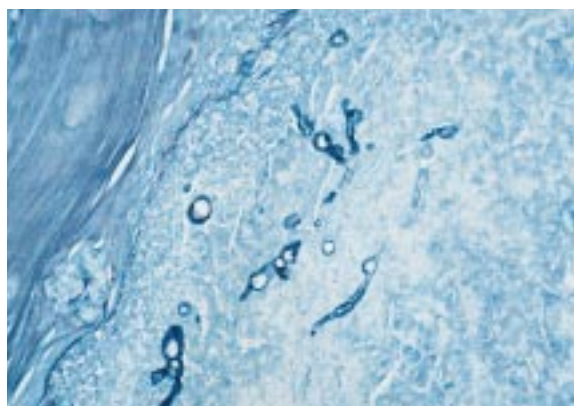


FIG 2. Methenamine silver stain of allergic mucin in AFS showing fungal hyphae ($\times 100$).



FIG 3. Representative sinus CT scan from 17-year-old male patient with AFS showing hyperattenuating masses of allergic mucin in both maxillary sinuses (arrows). *B spicifera* AFS had recurred while the patient was receiving oral itraconazole.

TABLE II. Sixty-seven patients with AFS at initial presentation

Characteristic	Mean $\pm$ SEM	Min/max	Category	No. (%)
Age (y)	33.3 $\pm$ 13.1	8/67		
Prior sinus surgeries	1.8 $\pm$ 1.7	0/7		
Sex			Male	28 (42%)
			Female	39 (58%)
Race			White	63
			Hispanic	3
			Black	1
Atopy (aeroallergens)			Yes	67 (100%)
Asthma (history and spirometry)			Yes	43 (64%)
Aspirin or nonsteroidal antiinflammatory drug hypersensitivity			Yes	9 (13%)
Immunotherapy in past			Yes	36 (54%)
Antifungal prior treatment			Yes	10 (16%)
Oral steroids at examination			Yes	3 (4%)
Chest radiograph (lobectomy for ABPB-2 cases)			Normal	57 (95%)
			Abnormal	3 (5%)
Nasal polyposis			Yes	67 (100%)
Rhinosinusitis			Severe	63 (94%)
			Moderate	4 (6%)
History of nasal casts			Yes	50 (75%)
Mold cultured at sinus surgery (2 molds cultured in 3 cases)			<i>Bipolaris</i>	45 (67%)
			<i>Aspergillus</i>	6 (9%)
			<i>Exserohilum</i>	2 (3%)
			<i>Alternaria</i>	2 (3%)
			<i>Curvularia</i>	2 (3%)
			<i>Torula</i>	1 (2%)
			None	9 (13%)
Immunologic evaluation (low Ig with normal function)			Normal	59 (92%)
			Low Ig	5 (8%)
<i>Bipolaris</i> precipitins (patients with B AFS only)			Positive	3 (8%)
IgE (IU/mL)	668 $\pm$ 834	26/4953		
Eosinophils (%)	4.51 $\pm$ 2.94	0/13		
ESR (mm/h)	11.3 $\pm$ 13.5	0/60		
<i>Bipolaris</i> sIgG (U/mL) (patients with <i>Bipolaris</i> AFS only)	50.6 $\pm$ 59.1	0/252		
<i>Bipolaris</i> sIgE (U/mL) (patients with <i>Bipolaris</i> AFS only)	5.1 $\pm$ 7.9	0.2/29		

tive coronal sinus CT is shown in Fig 3. This frame is set to bone windows, thereby accentuating the hyperattenuation of the sinus contents. Such hyperattenuating extramucosal material on CT is consistent with allergic mucin containing fungal hyphae. Several patients were seen with extrasinus AFS extension. Fig 4 shows a magnetic resonance image (MRI) of a patient with AFS who was seen with intracranial and orbital extension of AFS. Histopathologically, this material stained positive for fungal hyphae but was non-tissue invasive.

Table II shows the historic and laboratory characteristics of all the patients with AFS at entry into the retrospective case review. There was slight female preponderance (58%) and young age group (mean age, 33.3 years). On average, most patients had had several surgeries for sinus disease before the surgery diagnostic for AFS, which allowed subsequent entrance into AFS follow-up (range, 0 to 7 surgeries). On these previous surgeries several patients actually had had AFS, which was not recognized at the time;

these were diagnosed in retrospect by recutting and methenamine silver staining the stored surgical specimens.

All 67 patients had a history consistent with seasonal or perennial inhalant allergy, and all had positive skin test reactions to 2 or more aeroallergens from our standard panel. Additionally, all patients growing *B. spicifera* from AFS surgical specimens were found to have positive skin prick test reactions to the fungus. More than half had at least some degree of reversible bronchial obstruction (>10% improvement in obstructive spirometric parameters with bronchodilator) and more than half had been receiving allergen immunotherapy in the past for inhalant atopy. Aspirin or other nonsteroidal antiinflammatory drug hypersensitivity was found historically in 13%. A family history for hypertrophic rhinosinusitis was found in 17%. Two patients had previously had *Bipolaris*-allergic bronchopulmonary mycosis shown by histopathology and culture after undergoing partial lobectomy. Most patients (75%) had a history for nasal casts, described as

dark green rubbery formed elements intermittently expelled from the nose, for months and sometimes years, before the defining surgery. All patients (100%) had initially been seen with nasal polyposis.

More patients had been treated previously with antifungal agents (16%) than with oral corticosteroids (4%). No patient previously diagnosed with AFS and treated with antifungal agents by other physicians had a history suggesting significant clinical improvement with treatment. The mold cultured at surgery returned primarily *B spicifera* (67%), with other cases positive for a variety of molds, mostly dematiaceous fungi or *Aspergillus* spp. Three cases cultured 2 molds simultaneously. Fungal culture was negative in 13%, presumably reflecting surgical sampling inaccuracy. Of the total, AFS had developed in 63 patients in Arizona, as determined by historic presentation; 3 disease cases developed in Texas, and 1 each were from Alabama and Nebraska. At the time of the study-entry AFS surgery, 94% of the patients were judged to be clinically severe, and the remaining patients were judged to be moderately severe (see Part II for clinical rhinosinusitis severity rating).

Table II also shows the hematologic and serologic parameters associated with AFS. The total serum IgE was elevated (>199 IU/mL) at the time of diagnosis in 67% of patients; the mean IgE was 668 IU/mL, with a range of 26 to 4953 IU/mL. When the total serum IgE levels were compared between *B spicifera* AFS cases and all other patients with AFS, the levels were similar (data not shown). Patients did not display eosinophilia, and the ESRs were generally in the normal range. Although several patients had elevated ESR, this was believed to be secondary to bacterial infection and/or early postoperative status because no evidence for invasive fungal disease was found histopathologically (1 exception previously mentioned had mixed AFS and indolent histopathologic fungal rhinosinusitis); when these ESRs were repeated, they returned in the normal range.

The immunologic evaluation (Table II) confirmed normal immune function in all cases. Five patients (8%) had a low quantitative immunoglobulin on initial screening, but these patients had normal functional antiprotein and antipolysaccharide antibody responses to immunization and normal delayed cutaneous testing. One patient had a normal quantitative C2 protein level but low C2 functional activity; this was a child whose mother also had the same C2 abnormality and Sjögren's syndrome but no clinical immunodeficiency or sinus disease; the mother's father had the same C2 deficiency and bronchiectasis without evidence for fungus. All patients reacted normally to a panel of T-cell recall antigens on delayed cutaneous testing, consistent with gross normal T-cell function.

Among patients with *Bipolaris* AFS, *B spicifera* precipitins were generally negative, and the group mean *B spicifera* sIgE was not elevated despite positive *B spicifera* skin test results. Not unexpectedly, the skin test for immediate hypersensitivity to the mold was more sensitive for diagnosis than the in vitro test for sIgE. At initial presentation, 30 of the 45 total cases of *B spicifera* AFS

showed elevated sIgG in the range of more than 10 U/mL (mean sIgG of 50.6 U/mL).

Bipolaris spp mold spores are ubiquitous in Phoenix, Ariz, as shown in aeroallergen samples averaged from 5 counting stations placed throughout the Phoenix metropolitan area obtained twice weekly over several years (Fig 5).

DISCUSSION

AFS is increasingly being recognized as a complicating feature of hypertrophic rhinosinusitis. Although other cases of fungal sinusitis have been reported, consistent differentiation of AFS from all other forms of fungal sinusitis has only recently been scrutinized.

Our large database of 67 consecutive patients has allowed a more thorough demographic and diagnostic analysis of AFS than has previously been published. Several conclusions can be drawn from the current clinical series. Patients with AFS tend to be young, atopic, immunocompetent, and develop their disease in the southwestern United States (Table II). The most prevalent organism was *B spicifera*. Other AFS molds were equally divided among other dematiaceous fungi and *Aspergillus* spp. Nasal casts before surgery for AFS were reported so often (75% of the time) that a history for cast production should be considered strong presumptive evidence for AFS.

All patients with AFS fulfilled 4 major requirements for histopathologic diagnosis as described in Table I. Two patients were included in this study who had histologic findings for both AFS and another fungal disorder simultaneously; 1 with mycetoma, the other with indolent fungal sinusitis. Because both patients fulfilled all the other typical characteristics of patients with AFS (eg, atopic, immunocompetent, history for hypertrophic rhinosinusitis), they were included in this study. Such patients were uncommon, but their presence underscores the need to fully evaluate the histology from the surgical pathology specimens. The presence of a second form of fungal sinusitis in the same patient may have critical implications for treatment and follow-up strategies. In a patient with hypertrophic rhinosinusitis with the historic and laboratory findings of atopy and immunocompetence as described, we propose that the 4 major criteria described in Table I are sufficient for the diagnosis of AFS. Not all patients had the classic preoperative CT scan findings of hyperattenuating masses in the sinus cavities consistent with fungal-containing allergic mucin (Fig 3), but when present this finding was further strong presumptive evidence for AFS.

Whereas several other reports have described some patients with AFS to be nonatopic,^{1, 28-30} our findings support inhalant atopy as a virtual requirement for diagnosis because 100% of our patients were atopic. All patients who could be tested had positive skin test reactions to the mold involved in their AFS (generally, *B spicifera*) despite often low in vitro sIgE. AFS is a noninvasive fungal disorder, and, taken together with the universality of patient atopy, this suggests that AFS is indeed an allergic, not infectious, disorder. A number of patients

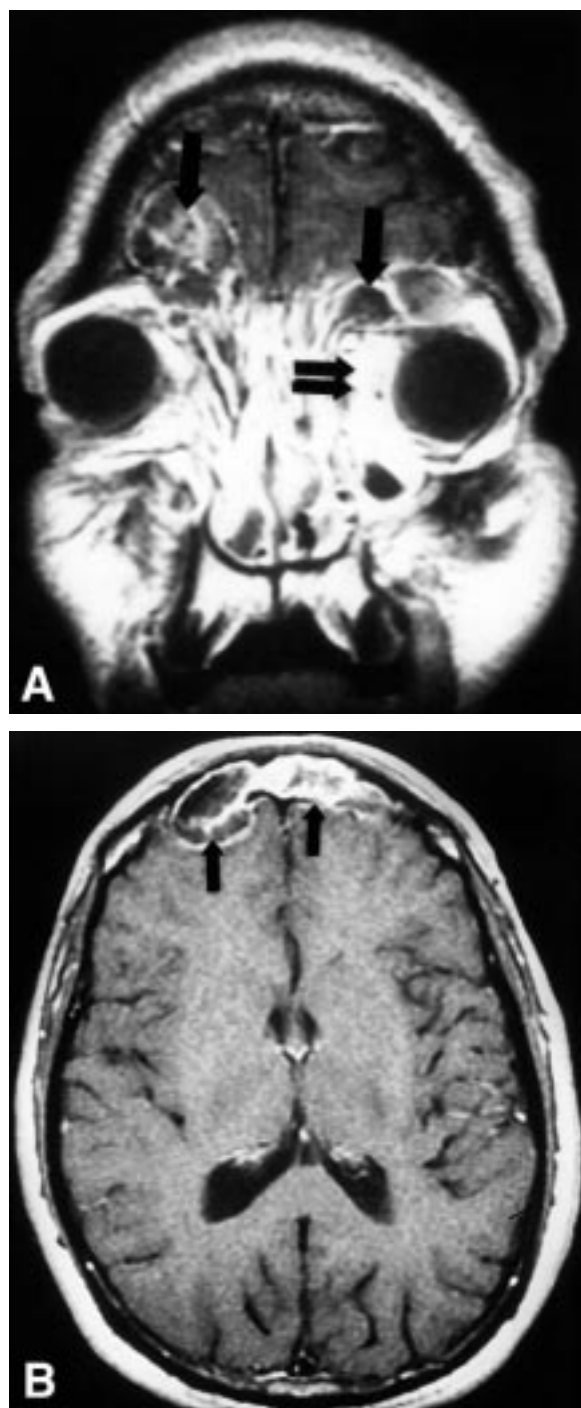


FIG 4. MRI of the head in a patient with *B. spicifera* AFS with extrasinus extension into the cranium. **A**, Cranial extension can be seen from frontal and ethmoid sinuses (arrows) and orbital extension from ethmoids (double arrows). **B**, Compression of dura can be seen over frontal lobes (arrows).

with AFS had been previously treated with systemic antifungals (Table II); none reported significant clinical improvement with antifungal treatment, consistent with the noninfectious basis for AFS.

Occasionally, patients with AFS were seen with orbital or intracranial extension of disease (Fig 4). At first glance, this would appear to be a fungal invasive process. However, in no such cases were fungal hyphae found histopathologically invading mucosa or any other tissue. It appears that rather than true invasion, the allergic mucin is capable of causing juxtaposed bone resorption, thus allowing extrasinus extension. Such bone resorption is likely to be caused by the influence of cytokines and eosinophil products produced by the intense local allergic inflammation.

AFS is analogous to ABPA in several ways. Total serum IgE levels were generally elevated, although less so than with ABPA, in which IgE levels are often between 4000 and 10,000 IU/mL.³¹ In ABPA, the inspissated *Aspergillus*-containing allergic mucin is an integral part of the clinical presentation, identical to the allergic mucin from AFS. Both ABPA and patients with AFS have sIgG to the in situ mold. However, a peripheral eosinophilia, precipitins, and sIgE are generally present in ABPA³² but not in AFS (Table II). A further pathophysiologic relation between AFS and ABPA can be inferred by the reports of several cases of ABPA with concomitant AFS.³³⁻³⁵ In our study, concomitant AFS and *Bipolaris*-allergic bronchopulmonary mycosis were seen in 2 patients. However, with the lower total serum IgE and lack of peripheral eosinophilia in AFS as compared with ABPA, we speculate that the overall level of mold hypersensitivity in AFS is lower than that of ABPA as the result of the smaller mucosal surface area for sensitization in the sinus cavities as opposed to the bronchopulmonary circuit.

We had 1 patient who had both AFS and indolent fungal sinusitis. Occasionally, ABPA can be associated with an indolent form of mucosal granulomatous invasive fungal disease, bronchocentric granulomatosis. By analogy, we speculate that the indolent form of fungal sinus disease is the sinus equivalent of bronchocentric granulomatosis.

Our data show the Southwest to be a "hot spot" for AFS, particularly that caused by *B. spicifera*. We surmise that the combination of severe atopic disease together with the respiratory exposure to the dematiaceous fungus *B. spicifera* for significant periods of the year (Fig 5) predisposes to hypertrophic rhinosinusitis with the complication of AFS. The predominance of *B. spicifera* causing AFS suggests this mold is "nasophilic," presumably for physicochemical reasons. The presence of allergically inflamed, hypertrophic, partially obstructed sinus ostia and the impaired functional mucociliary sweep mechanism described under these conditions^{36, 37} may then allow trapping of mold spores in the sinus. The allergic reaction to the presence of the fungus may then heighten the overall sinus mucosal allergic inflammation, leading to mucosal hypertrophy, functional ciliary impairment, and the entrapment and sequestration of an expanding allergic mucin mass, an AFS "sinusitis cycle."³⁸ An element of bacterial sinusitis usually accompanied this process, as surgical sinus cultures often returned positive

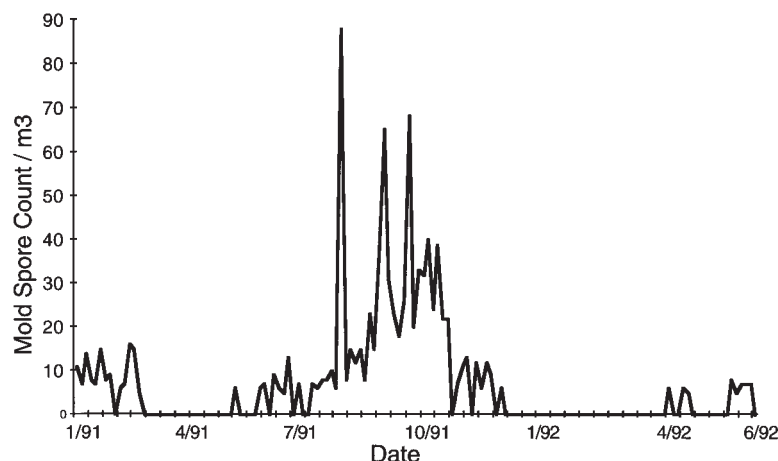


FIG 5. *Bipolaris* spp mold spore counts from the Phoenix, Ariz, metropolitan area. Data courtesy of Chester Leathers, PhD, Hi Health Research Dept, Phoenix, Ariz, by permission.

for *Staphylococcus aureus* (data not shown). Bacterial infection appeared not to be of primary importance, however, because allergic inflammation predominated in all AFS mucosal H&E stains, and the entire clinical and laboratory picture was that of severe allergic reactivity. Furthermore, virtually all patients with AFS had had significant amounts of oral antistaphylococcal antibiotic treatment before their study-entering AFS surgery historically (data not shown). Hypertrophic rhinosinusitis occurred throughout multiple sinuses in our patients with AFS. This implied that the entire sinus network was involved with AFS to a variable degree either entering multiple sinuses simultaneously from the nose or through sinus-to-sinus spread of fungal spores from an AFS-involved sinus or some combination of both. This was supported by the fact that surgery for recurrent disease often found AFS from different or additional sinuses on subsequent surgeries.

Differentiation of AFS from the other forms of fungal sinusitis is possible. The history, physical, laboratory, histopathology, microbiology, and radiology findings consistent with the diagnosis of AFS are now known. The southwestern United States as a "hot spot" for AFS (particularly with *B spicifera*) has now been described. It is likely that as an overall awareness of the disorder increases, many more cases will be reported. Distinguishing AFS from the other forms of rhinosinusitis may have important implications for the treatment and follow-up of patients with AFS, as described in Part II of this 2-part series.

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