

Diagnostic criteria for allergic fungal sinusitis

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*Diagnostic criteria for allergic fungal sinusitis have not been established, and clinical information consists primarily of isolated case reports. We proposed five diagnostic criteria for allergic fungal sinusitis including: (1) the demonstration of the characteristic eosinophil-rich allergic mucin visually or histopathologically, (2) a positive fungal stain or culture from the sinus at surgery, and (3) the absence of immunodeficiency or diabetes. With these criteria, seven patients in our metropolitan area with allergic fungal sinusitis were identified in a short period. Initial symptoms in our seven patients reflected those in 99 case reports in that two children were first seen with proptosis, one child and three adults with nasal congestion, and one adult with symptoms of chronic sinusitis. All had pansinusitis as shown on x-ray films. Six patients were atopic, five had nasal polyposis, and five had *Curvularia* species cultured from the sinuses. Infections with *Bipolaris* species, asthma, and chronic sinusitis were less common in our patients than in those previously reported. Recurrent symptoms and additional surgery sometimes resulted when the diagnosis was delayed by failure to obtain silver stains for fungus on surgical material sent for histopathologic review. Sinus tomography showed that the fungal material in the sinuses was of high density, which distinguished it from polyps or bacterial exudate. Bony compression, erosion, and rupture of the sinus walls were common. Results of IgE levels, precipitin determinations, and eosinophil counts were variable in both our patients and those in the literature. On the basis of our review, we believe that the simple diagnostic criteria proposed are appropriate for both research and clinical purposes. (J ALLERGY CLIN IMMUNOL 1995;96:24-35.)*

Key words: Sinusitis, fungus, allergic mucin

Over the last 20 years, case reports on a previously undescribed and unique form of sinusitis have accumulated in the literature of several medical specialties. In 1971, McCarthy and Pepys¹ observed that 10% of patients with allergic bronchopulmonary aspergillosis (ABPA) complained of producing nasal plugs similar to those expectorated from the bronchi. Forty-six of the 111 patients (41.4%) in that study had maxillary sinusitis as shown on x-ray films. Cultures of the nasal plugs and sinus lavages grew *Aspergillus fumigatus*. In 1976, Safirstein² reported that symptoms of nasal obstruction produced by nasal casts improved when a patient with ABPA was treated with oral corticosteroids. In the same year, Young et al.³ reported the case of an otherwise healthy 15-year-old swimmer who was first seen with ethmoidal and

TABLE I. Criteria for the diagnosis of AFS in this study

1. Sinusitis of one or more paranasal sinus on x-ray film
2. Identification of allergic mucin by rhinoscopy or at the time of sinus surgery or subsequently on histopathologic evaluation of material from the sinus*
3. Demonstration of fungal elements in nasal discharge or in material obtained at the time of surgery by stain or culture
4. Absence of diabetes, previous or subsequent immunodeficiency disease, and treatment with immunosuppressive drugs
5. Absence of invasive fungal disease at the time of diagnosis or subsequently†

*A visual description was considered adequate for identification if thick, mucinous material with the consistency of peanut butter or cottage cheese was described. The material was frequently green, yellow, or brown in color. A histopathologic description was considered adequate for identification if mucin contained dense accumulations of eosinophils with Charcot-Leyden crystals and necrotic cellular debris.

†Histopathologic examination of material from sinuses showed no evidence of fungal invasion into nasal mucosa or bone.

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maxillary sinusitis, nasal polyposis, and proptosis of the left eye. The proptosis resulted from the extension of fungal material from the sinuses into the orbit. In 1983, Katzenstein et al.⁴ described the

TABLE II. Data on seven previously unreported patients with AFS from Alabama

Age (yr)	Sex	Presenting complaint	Atopy*	Surgeries before diagnosis	Nasal polypsis	Allergic mucin	Hyphae noted	Fungus cultured	Antifungal treatment	Outcome
7	M	Proptosis, right eye	+	5	+	+	—	<i>Curvularia</i>	+	Controlled with CS 8 years later
13	M	Proptosis, left eye	—	0	+	+	+	<i>Curvularia</i>	+	Ongoing chronic sinusitis despite CS 4 years later
14	F	Nasal con- gestion	+	2	+	+	—	<i>Curvularia</i>	+	Mild rhinitis 10 years later
35	M	Nasal ob- struction	+	0	+	+	+	<i>Curvularia</i>	—	Controlled with immunotherapy and CS 1 year later
45	F	Headache, nasal conges- tion	+	0	—	+†	—	<i>Aspergillus</i>	—	Controlled with CS 6 months later
46	F	Chronic sinusitis	+	3	+	+	—	Not speci- fied	+	Ongoing sinusitis despite CS, oral antifungal agents, and anti- biotics 5 years later
64	F	Nasal con- gestion	+	2	—	+	—	<i>Curvularia</i>	—	Controlled with allergy shots and occasional CS 7 years later

CS, Corticosteroids.

*See text for criteria.

†Described visually but not histopathologically.

Abbreviations used

ABPA:	Allergic bronchopulmonary aspergillosis
AFS:	Allergic fungal sinusitis
CAT:	Computed axial tomography
CT:	Computed tomography

case histories of seven otherwise healthy patients with asthma, nasal polyposis, sinusitis, and a unique “allergic mucin” within their sinuses. This material contained laminated mucin, eosinophils, eosinophil Charcot-Leyden crystals, and fungal hyphae.⁴ Those investigators called the condition “allergic aspergillus sinusitis.” Subsequently, there have been a number of similar case reports of fungal sinusitis in normal hosts.

In the process of a review of the literature to find guidelines for the treatment of similar patients in

our own practice, we found that only a few attempts have been made to synthesize available data on these patients. We believed that a systematic review of the published experience on this disease in the context of our own experience might provide further insight into a number of unresolved issues. These issues include diagnostic criteria, natural history, and treatment. To assess these issues, we report seven new cases of allergic fungal sinusitis (AFS) in the context of 99 convincing cases of this disease already reported.

METHODS

Patients

Otolaryngologists, allergists, and infectious disease specialists in Mobile and Baldwin counties, Alabama, were contacted by mail and informed of our interest in identifying patients with AFS presently under their care. The 16 physicians contacted responded with the names of 13 patients. All available medical records for these patients, including pathology slides of material taken at



FIG. 1. Axial view on sinus CT scan from our 7-year-old patient showing opacification of the right ethmoid sinus and rupture of the lamina papyracea, which has produced orbital impingement and proptosis of the right eye. There is also marked mucoperiosteal thickening and a nonhomogeneous opacification of the ethmoid air cells. The foci of increased radiodensity within these cells suggests fungal infection.

surgery and computed tomography (CT) evaluations (computed axial tomography [CAT] scans of the sinuses) were obtained for review. Sinus CAT scans for possible AFS were obtained with a bone algorithm with thin sections no greater than 3 mm and a coronal technique with views for clivus to nasal tip.

Diagnostic criteria

On the basis of our understanding of allergic fungal sinusitis, we established diagnostic criteria for inclusion of patients in this study (Table I).

Patients were considered "atopic" if two or more allergic conditions including asthma, allergic rhinitis, or eczema were present; or if one of the three allergic

conditions was present, and the patient had an elevated serum IgE level. Patients who had three or more positive immediate hypersensitivity skin test responses to a panel of 60 common inhalant allergens were also considered to be atopic.

Literature review

Computer-based literature searches were used in our attempt to identify all cases of noninvasive fungal sinusitis in the medical literature published in English. These reports were carefully read, and those that met the diagnostic criteria for AFS were included in our review. Specific information was sought in 17 different categories.



FIG. 2. Axial view on sinus CT scan from our 7-year-old patient showing opacification of the right maxillary sinus. There is destruction of the medial wall of the maxillary sinus from polypoid material extending into the sinus cavity. There is a nonhomogeneous concentration of dense polypoid material in the right nasal vault and in the right maxillary antrum, demonstrating fungal material of higher radiodensity. The nasal septum is displaced to the left of midline.

RESULTS

Data on seven previously unreported patients with fungal sinusitis

Of the 13 patients believed to have AFS by the physicians participating in our study, seven met the diagnostic criteria for AFS. They ranged in age from 7 to 64 years. All but one patient were clearly atopic at the time of diagnosis (Table II). Only one of seven patients had asthma, and there was no evidence of bronchopulmonary fungal disease in that patient. Adults were more commonly first seen with nasal complaints, whereas two of three patients under the age of 16 were first seen with

proptosis. In these two patients, the overall effect of polyps and inflammation within the ethmoid sinus led to attenuation of its lateral wall, rupture of the lamina papyracea, and orbital impingement (Fig. 1). All seven patients had x-ray films showing pansinusitis as defined by involvement of three or more sinuses at the time of diagnosis. Three of the seven patients had evidence of loss of bony sinus margins on computerized tomography (CT) of the sinuses (Fig. 2). Although the walls of the sinuses appeared thinned and in some cases breached by sinus contents, histopathologic studies showed

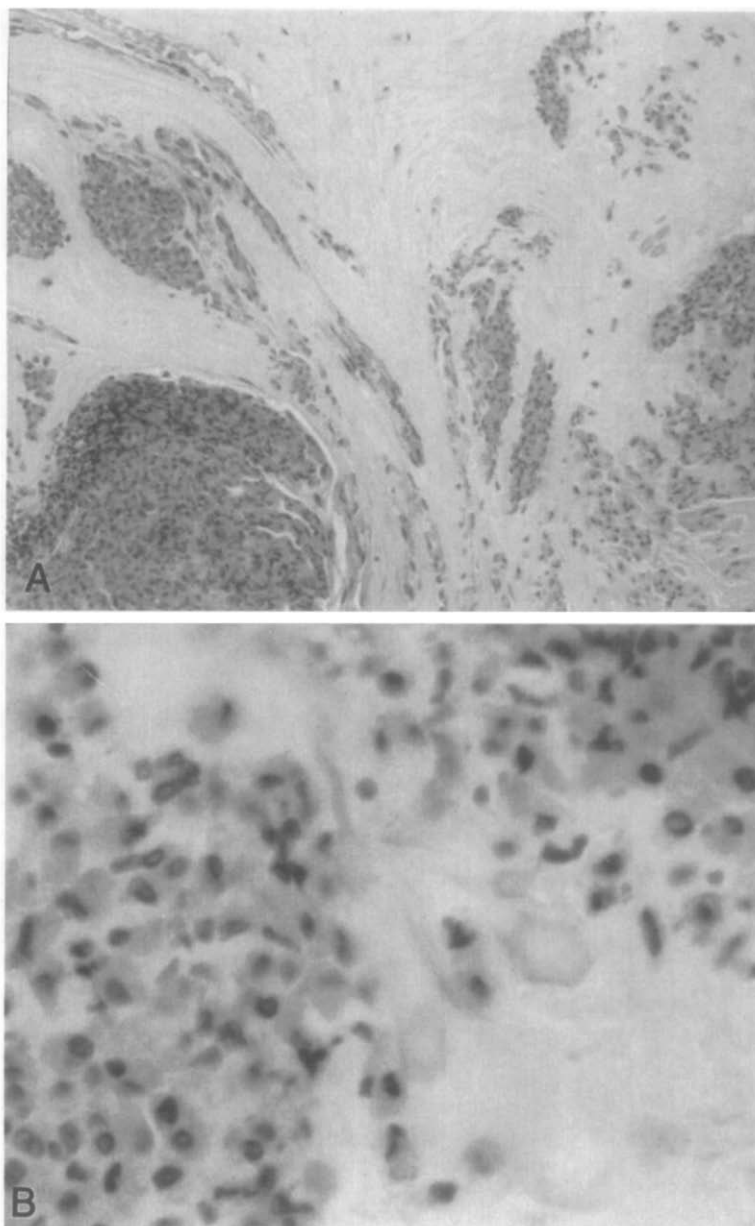


FIG. 3. **A**, Low magnification photomicrograph showing laminated mucin encompassing aggregates of necrotic eosinophils from the 14-year-old patient in our series (hematoxylin-eosin stain). **B**, High magnification view of eosinophil Charcot-Leyden crystals within allergic mucin from the 13-year-old patient in our series. Crystals that are cut in cross-section have a hexagonal appearance (hematoxylin-eosin stain).

no evidence of fungal elements in the mucosa or bone. Thus the term "erosion" used in descriptions of invasive fungal disease of the sinuses reflects a different process than that present in these cases.⁵ Nasal polyps were identified in five of seven patients. Moreover, foci of fungal material of higher radiodensity were often noted in the sinuses on CAT scans, a finding previously described^{6,7} (Fig. 2). These foci were consistently distinguishable from dense polypoid material.

Patients had varying degrees of immunologic evaluation; two underwent extensive investigation including lymphocyte subpopulation analysis and delayed hypersensitivity skin testing. None had clinical or laboratory evidence of immunodeficiency disease or diabetes. Fungal precipitins were negative in the two patients in whom these tests were performed: one for *Aspergillus* species and one for *Curvularia lunata*. IgE values were elevated above the normal range in three patients in whom

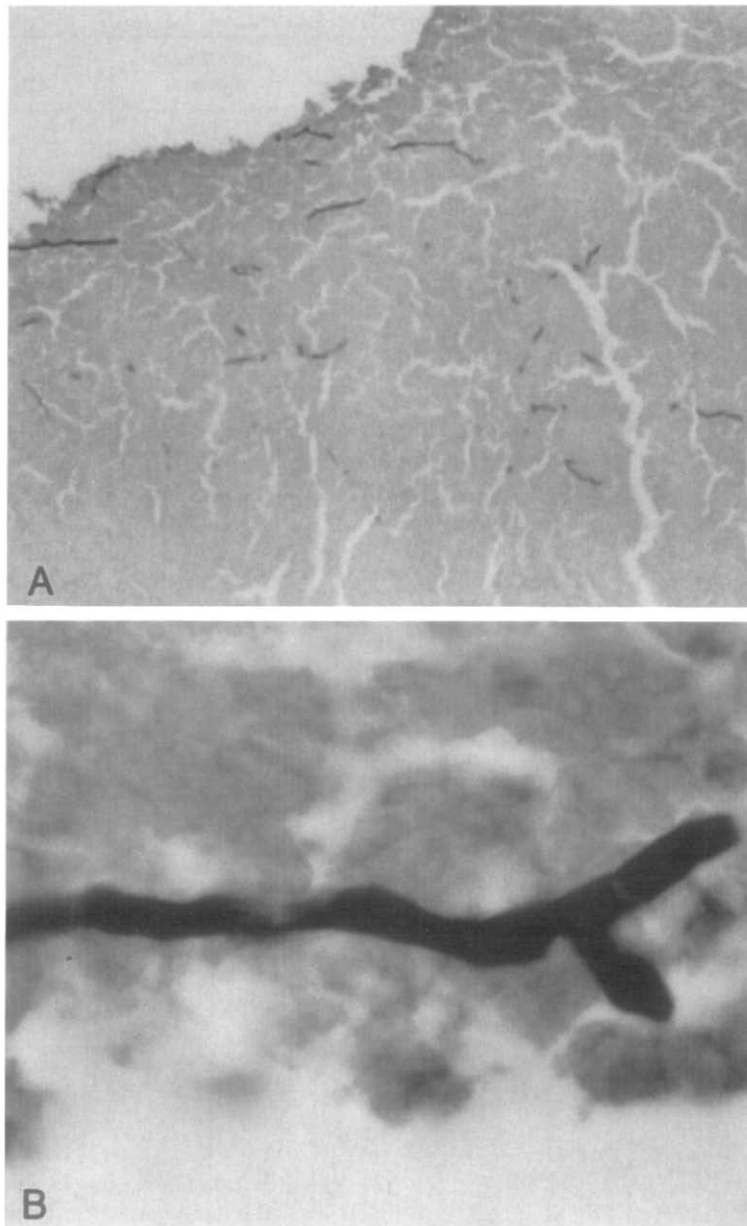


FIG. 4. **A**, Low magnification view of scattered fungal hyphae within allergic mucin from the 13-year-old patient in our series (Gomori's methenamine silver stain). **B**, High magnification view of a branching fungal hyphus within allergic mucin for the 13-year-old patient in our series. (Gomori's methenamine silver stain).

this test was performed. Peripheral blood eosinophilia ($>600/\text{mm}^3$) was present in five of the patients whose blood counts were performed contiguous with active complaints of sinus disease. Four of seven patients had the diagnosis of AFS made at the time of their first surgery for treatment of sinusitis, whereas three patients had undergone multiple surgical procedures before the diagnosis. All patients had allergic mucin described visually at surgery, and six of seven had characteristic allergic mucin as deter-

mined by histopathologic evaluation of materials obtained from the sinuses (Fig. 3, *A* and *B*). One patient had allergic mucin described at the time of surgery, but only mucosa (not mucin) was submitted for histopathologic evaluation. Hyphae were identified in the allergic mucin of three patients but were not present in mucosa or bone from any patient. Hyphae were noted diffusely distributed in mucin in the two cases in which silver stains were performed (Fig. 4, *A* and *B*). Hyphae were noted in only one of the

TABLE III. Case reports of AFS reviewed in this article

Reference	Date of report	No. of cases	Location of patients	Species of fungus
Young et al. ³	1978	1	S. Africa	<i>Drechslera</i>
DeJuan et al. ⁸	1983	2	Maryland	?
Sobol et al. ⁹	1984	3	Oklahoma	<i>Drechslera</i>
Berry et al. ¹⁰	1984	1	Virginia	<i>Curvularia</i>
Goldstein et al. ¹¹	1985	1	Pennsylvania	<i>Aspergillus</i>
Harpster et al. ¹²	1985	1	Kansas	<i>Drechslera</i>
Brummund et al. ¹³	1986	1	Wisconsin	<i>Curvularia</i>
Adam et al. ¹⁴	1986	32	Arizona	<i>Bipolaris</i> (1) <i>Exserohilum</i> (2)
MacMillan et al. ¹⁵	1987	2	Virginia	<i>Curvularia</i>
Waxman et al. ^{16*}	1987	15	Missouri	? (15)
Nishioka et al. ¹⁷	1987	1	Texas	<i>Curvularia</i>
Jackson et al. ¹⁸	1987	2	Minnesota	<i>Aspergillus</i>
Frenkel et al. ¹⁹	1987	1	California	<i>Bipolaris</i>
Sher and Schwartz ²⁰	1988	1	Ohio	<i>Aspergillus</i>
Jay et al. ²¹	1988	2	Arkansas	<i>Bipolaris</i>
Washburn et al. ²²	1988	1	S. Carolina	<i>Bipolaris</i>
Robson et al. ²³	1989	1	Australia	<i>Bipolaris</i>
Jonathan et al. ²⁴	1989	4	England	<i>Aspergillus</i> (2) ? (2)
Gourley et al. ²⁵	1990	3	Texas	<i>Bipolaris</i>
Ence et al. ²¹	1990	14	Texas	<i>Curvularia</i> (2) <i>Bipolaris</i> (6) <i>Alternaria</i> (2) <i>Aspergillus</i> and <i>Bipolaris</i> (1)
Killingsworth and Wetmore ²⁷	1990	3	Arkansas W. Virginia	<i>Curvularia</i> (2) <i>Drechslera</i> (1)
Bartynski et al. ²⁸	1990	2	Minnesota	<i>Curvularia</i> (1) <i>Alternaria</i> (1)
Shah et al. ²⁹	1990	1	India	<i>Aspergillus</i>
Scully et al. ³⁰	1991	1	Massachusetts	<i>Curvularia</i>
Friedman et al. ³¹	1991	3	Texas	<i>Exserohilum</i> (1) <i>Drechslera</i> (1) <i>Bipolaris</i> (1)
Travis et al. ³²	1991	2	Florida (1) Maryland (1)	<i>Curvularia</i> (1) <i>Curvularia</i> and <i>Drechslera</i> (1)
Manning et al. ³³	1991	22	Texas	<i>Aspergillus</i> (1) <i>Curvularia</i> (2) <i>Bipolaris</i> (10) <i>Drechslera</i> (3) <i>Alternaria</i> (1) <i>Exserohilum</i> (1) <i>Helminthosporium</i> (1)
Allphin et al. ³⁴	1991	3	Ohio	<i>Aspergillus</i> (2) <i>Curvularia</i> (1)
Bhagat et al. ³⁵	1993	1	India	?
Wickern ³⁶	1993	1	Alabama	<i>Fusarium</i>
deShazo and Swain†	1993	7	Alabama	<i>Curvularia</i> (5) <i>Aspergillus</i> (1) ? (1)

*Includes seven cases from 1983 reported by Katzenstein et al.⁴

†Not included in Table IV.

remaining five cases in which hematoxylin and eosin stains, but not silver stains, were performed.

Fungi were cultured from surgical specimens taken from all seven patients. The species of fungus was identified in all but one patient. In that case the specimen was not sent to a reference laboratory but was identified by staining of a fungal culture in a hospital laboratory. *Curvularia lunata* was identified by the Alabama State Health Department Laboratory in five cases and by the University of Texas, San Antonio, Fungus Laboratory in an additional case. An *Aspergillus* species was identified by the Alabama State Health Department Laboratory in an additional case.

Patients were treated with a variety of antifungal agents: one was treated with ketoconazole, two with intravenous amphotericin B, and one with topical nystatin. Three patients were not treated with any antifungal agent.

Information on the course of AFS was available for all patients. All patients are presently living, and no patient has been diagnosed with diabetes, an immunodeficiency disease, or invasive fungal sinusitis during follow-up evaluation from 6 months to 10 years. Five of seven patients have had their chronic sinusitis controlled with few or no symptoms but require ongoing topical and episodic oral corticosteroid treatment. Two of these patients have received allergen immunotherapy with commercial fungal extracts to the species of fungus cultured. Two of the seven patients have ongoing chronic sinusitis despite episodic oral corticosteroid therapy. One patient is presently being treated with continuous oral corticosteroid therapy.

Data on patients in 99 case reports of AFS

Ninety-eight cases from 29 published reports met the criteria for inclusion in this study^{3,8-36} (Tables III and IV). Seven cases from the 1983 report by Katzenstein et al.⁴ were included in the 1987 report by Waxman et al.¹⁶ and therefore are not listed separately. The seven new cases from Alabama discussed above were not included in the analysis to allow a comparison between our experience and that in the case reports. Patients with AFS were reported from 18 states in the United States, South Africa, Australia, England, and India (Table III). The average age at the time of diagnosis was 26 years, with a range in age of 7 to 58 years (Fig. 5). There was no male or female predominance, and three fourths of the patients met the diagnostic criteria for atopy (Table IV). The presence or absence of asthma was mentioned

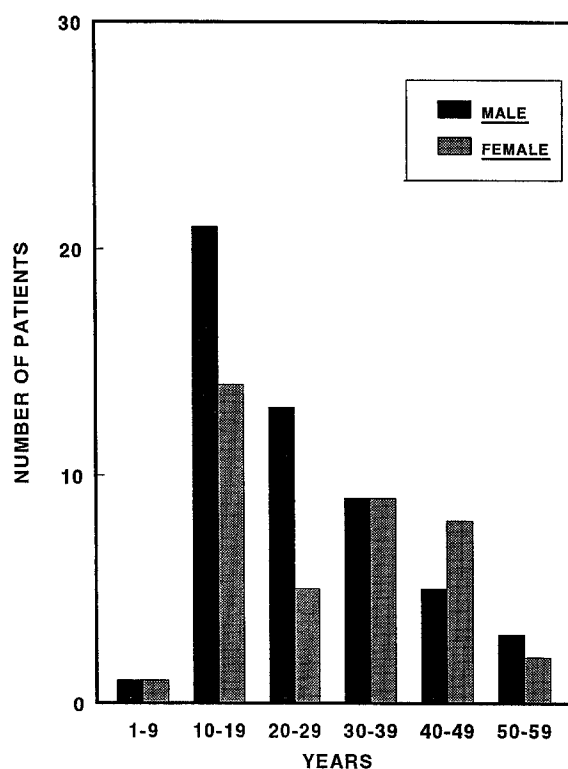


FIG. 5. Age distribution of 99 patients diagnosed with AFS.

in 76 patients, and one half of those mentioned were reported to have the condition. Three fourths of the patients had chronic sinusitis and polyps; and nasal polyps were present in these patients more often than not. Loss of bony sinus margins was noted on CT scans in approximately one third of the patients. Over half of the patients had undergone three or more surgical procedures before the diagnosis of AFS was made. Assays for serum fungal precipitins were performed in serum samples from 27 patients, and results were positive in 88%. Serum IgE levels were reported in 35 patients and were elevated in three fourths of these. Positive immediate hypersensitivity skin test responses to the fungus cultured were present in two thirds of the patients when fungal skin testing was performed. Aspirin hypersensitivity in association with nasal polyposis and AFS has been noted in only one instance.¹⁶

Fungus was cultured in 74 or three fourths of the patients (Table V). *Bipolaris* and *Curvularia* species comprised over half of the isolates, and *Aspergillus* and *Drechslera* species were about half as common as the former organisms. Much less common were *Exserohilum*, *Alternaria*, and *Helminthosporium* species. This information must be considered in the context of the previously confused

TABLE IV. Data on 99 case reports of AFS reviewed in this article

Age at diagnosis (yr)	Age range (yr)	Sex	Atopy	Asthma	History of chronic sinusitis	Polyps
26.6 ± 13.2	7-58	52% M 48% F	76.5% (38/51)	56.3% (40/76)	75.4% (49/65)	80.2% (77/96)

taxonomy among *Helminthosporium*, *Drechslera*, and *Bipolaris* species.³³ Concomitant infection with more than one species of fungus has rarely been reported in patients with AFS. Jay et al.²¹ reported a patient with *Bipolaris spicifera* and *Curvularia lunata*, Jonathan et al.²⁴ reported a patient with *Aspergillus flavus* and *Aspergillus fumigatus*, and Adam et al.¹⁴ reported a patient with *Bipolaris spicifera* and *Alternaria spicifera*.

DISCUSSION

A unique form of sinusitis

Chronic sinusitis is a common problem, which usually responds to antibiotic treatment in conjunction with management of associated anatomic or allergic problems.³⁷ Nasal polyps and polypoid sinusitis may occur in the presence of chronic sinusitis and complicate its management, probably by obstructing normal sinus drainage. Patients with chronic sinusitis unresponsive to medical therapy are candidates for sinus surgery.³⁸

AFS is a unique form of sinusitis characterized by the presence of nasal polyps and living, reproductive, but noninvasive fungal elements that exist in a characteristic amorphous, eosinophil-rich mucin within the sinuses. The fungi are primarily of the Deutromycotina (Fungi Imperfecti) subdivision of the Eumycotina, a fungal division that includes all fungi other than the slime molds.³⁹ Fungi of the Deutromycotina subdivision are common causes of allergic rhinitis.⁴⁰

The accumulation of large amounts of inflammatory "allergic mucin" and polypoid material within the sinuses not only perpetuates obstruction but may lead to erosion of bone, rupture of the sinus wall, and leakage of sinus contents into adjacent structures including the orbit and brain.³² Handley et al.⁵ reported the results of histopathologic studies of bone taken from seven patients with AFS who also had evidence of bony erosion on CT scans. Tissue and bone invasion by fungal organisms in association with granulomatous inflammation and necrosis, like that seen in invasive fungal sinusitis, were not present. To the contrary, nonspecific reactive changes with periosteal thickening, fibrosis, and greatly increased osteoblastic

activity and new bone formation were consistent findings in areas with a submucosal inflammatory infiltrate. In young patients in whom sinus structures have not fully calcified, AFS may lead to proptosis as a result of impingement of the lamina papyracea of the ethmoid bone or from compression of the roof of the maxillary sinus.^{8, 10, 11, 13} Hypertelorism has also been reported.²² Chronic sinusitis is a more common manifestation of AFS in adults.

Our own clinical experience led us to believe that AFS is not rare. This impression was supported by the fact that we were able to identify seven definite cases and six probable cases in our immediate geographic area within a month of our original mailing. We also believe that AFS may be underdiagnosed. This may be explained to some degree by confusion as to the criteria for diagnosis. This confusion may also explain the failure to diagnose the disease despite chronic symptoms and the multiple surgical procedures performed in our patients and in those in the literature. Moreover, there has been an appropriate reluctance to use corticosteroids in the treatment of this fungal disease. The information available from our patients and the case reports reviewed shed some light on these and related issues.

Diagnostic criteria for AFS

We believe that the criteria for AFS listed in Table I and used in this study are adequate for the diagnosis of patients with this condition. Fungal infections of the sinuses have traditionally been classified as invasive, indolent mycetoma and AFS.¹¹ Invasive and indolent sinusitis occur in immunocompromised hosts and are associated with invasion of fungal elements into mucosa and bone in the former and a granulomatous cellular response in the mucosa in the latter. Recently, a condition called paranasal *Aspergillus* granuloma has been reported⁴¹ in apparently normal hosts in the Sudan. Again, the histopathologic characteristics of this condition appear distinctive. Only a few patients with sinus mycetoma have been reported, a condition characterized by the presence of a ball of matted fungal hyphae within a sinus. Material

Bony erosion CT scan	Multiple surgeries before diagnosis	Fungus cultured	+ Serum fungal precipitins	Elevated serum IgE level	+ Immediate skin test to fungus cultured
35.7% (35/98)	58.9% (43/73)	75.5% (74/98)	88.9% (24/27)	74.3% (26/35)	73.3% (33/45)

with the clinical and histopathologic characteristics of allergic mucin is not present in any of these conditions other than AFS. Thus the demonstration of allergic mucin is central to the diagnosis of this condition. This material may often be obtained by means of rhinoscopy without surgery.

Nevertheless, some questions remain. For instance, Allphin et al.³⁴ reported 14 patients with the clinical features of AFS and histopathologic evidence of allergic mucin in whom fungi could not be demonstrated by histopathologic studies. These findings are explained to some degree by the fact that silver stains were performed in only five of the 11 cases with allergic mucin in that series. Fungal elements are diffusely distributed within mucin in AFS and are difficult to visualize with hematoxylin-eosin staining. In our own series fungi were frequently cultured after being overlooked on routine stains of surgical material. The findings of Allphin et al.³⁴ are in contrast to those of Ence et al.²⁶ who found allergic mucin to be very specific for AFS.

Diagnostic criteria for AFS have been suggested previously by several other investigators.^{4, 11, 25, 26, 28} These criteria have included clinical and laboratory features such as atopy, asthma, nasal polyps, elevated serum IgE levels, and serum fungal precipitins, among others. Waxman et al.¹⁶ reported that serum IgE levels were elevated and serum precipitins were present in 85% and immediate skin test responses to fungus were positive in 60% of patients with AFS. Although these are common features and support the diagnosis, our review suggests that the absence of these clinical features does not exclude the diagnosis. Passage of nasal plugs of fungus have been reported in only four cases of AFS.^{11, 14, 23, 29} Laboratory tests such as eosinophil counts, total IgE levels, or fungal precipitin tests in the setting of fungal hypersensitivity appear to be influenced by corticosteroid therapy, which is used frequently in the treatment of sinusitis, and by the activity of the disease at the time the tests are performed.⁴² The wide variations in the positivity of these tests reported in the literature may reflect these variables. Furthermore, precipitin tests for fungi are not generally available and require that the specific species of fungus

TABLE V. Species of fungus isolated from patients with previously reported AFS

Species	No. of patients
<i>Bipolaris</i>	24
<i>Curvularia</i>	20
<i>Aspergillus</i>	12
<i>Drechslera</i>	11
<i>Exserohilum</i>	4
<i>Alternaria</i>	4
<i>Helminthosporium</i>	1
<i>Fusarium</i>	1
	77*

*Three patients had more than one fungus isolated.

causing the disease be used in the assay for the results to be conclusive.⁴²

Immediate hypersensitivity skin test responses to the fungal species associated with AFS appear very useful in that they demonstrate sensitization to the fungus and identify those patients who require further scrutiny to exclude the diagnosis. Why they were positive in only two thirds of the patients tested is unclear. It is for that reason, however, that positive skin test results were not included in the criteria for the diagnosis of AFS used in this study.

One feature of fungal sinusitis may have been underutilized in the diagnosis of AFS in the past. Zinreich et al.⁶ reported that 22 of 25 patients (85%) with histopathologically proven fungal sinusitis demonstrated material of high radiodensity within the sinuses on CAT scans. Because fungal material had density comparable to that of the bony sinus walls, differential density among bacterial exudates, nasal polyps, and fungal material was readily identifiable in our series. The cause of this increased density is unclear, although it has been postulated to be due to the presence of high concentrations of iron within the fungal elements.⁶ Calcium phosphate, calcium sulfide, and other heavy metal salts may also be deposited in necrotic areas of fungal material.⁷ The increased density was not specific for *Aspergillus* species in our series but was seen with *Curvularia* species as well.

Treatment of AFS

The appropriate treatment of AFS remains to be determined. On the basis of our experience and that reported in the literature, it appears that although AFS frequently recurs with sinus surgery alone, sinus surgery with aeration of the sinuses and removal of polyps and inflammatory material, allowing permanent drainage, is important in controlling the disorder. Antifungal antibiotics have been used in a number of patients in an uncontrolled fashion. Recurrences of fungal infections are common when antifungal antibiotics are used alone or in conjunction with surgery. For instance, Frenkel et al.¹⁹ reported a patient with *Bipolaris* AFS who was treated with repeated sinus surgery and courses of amphotericin B, ketoconazole, and itraconazole over 3 years without response.

The idea that corticosteroid therapy is required for treatment of AFS has been extrapolated from clinical experience in the treatment of ABPA, a hypersensitivity disease of the bronchi clearly requiring long-term oral corticosteroid treatment for control.⁴² Inhaled topical corticosteroids more often than not fail to control ABPA. Although the experience of McCarthy and Pepys¹ suggested that ABPA and AFS may commonly occur together, we found only four convincing reports in which the two conditions coexisted.^{20, 29, 34, 35} One such patient was included in a series of three patients with AFS followed up at 6 months, 18 months, and 4 years, respectively. That patient failed to respond to surgical treatment alone, but the disease resolved with administration of oral corticosteroids, followed by administration of topical nasal steroids.³⁴

Our personal experience would suggest that surgical drainage and aeration of the sinuses, along with removal of polyps and inflammatory material, obviate the need for antifungal therapy. This should be followed by treatment with corticosteroids, administered first orally and then intranasally, in most patients. This approach has been supported by the experience of others and would most probably lead to elimination of chronic fungal colonization and the inflammatory response resulting from it.¹¹ Some patients, however, require ongoing oral corticosteroid therapy with its attendant complications. The role of newer, less toxic, antifungal agents (e.g., itraconazole) in the treatment of AFS is unclear but is under evaluation. We believe that allergen immunotherapy may well have a role in downregulating the IgE response to fungal elements in AFS so that the IgE-mediated late-phase inflammatory response,

which appears to be the source of ongoing inflammation, may be attenuated.¹¹ Validation of these approaches to management will require controlled studies yet to be done.

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