

Allergy grand rounds

Allergic *Rhizomucor* sinusitis

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Dr. Marc F. Goldstein*: Fungal sinusitis was first reported by Plaignaud¹ in 1791. Since that time few cases of fungal sinusitis have been reported compared with other sites of mycotic disease. In Europe and the United States members of the *Aspergillus* species are the most common fungi that cause sinusitis, followed by *Mucor*, *Candida*, *Penicillium*, and *Fusarium*.^{2, 3} Other isolated species, including the darkly pigmented dematiaceous fungi (*Bipolaris/Drechslera*, *Curvularia*, *Alternaria*, and *Exserohilum*), previously thought to be laboratory contaminants, have been reported to produce sinus disease in immunocompetent hosts.⁴⁻²² As discussed in a previous "Allergy Grand Rounds" in the JOURNAL, the nature of paranasal sinus fungal disease has been categorized into four distinct clinical pathologic forms: (1) chronic indolent sinusitis, (2) invasive sinusitis, (3) mycetoma, and (4) allergic fungal sinusitis (AFS).²³

The syndrome allergic *Aspergillus* sinusitis (AAS) was first described by Katzenstein et al.^{24, 25} in 1983. However, cases similar to AAS are described in the literature before this report.²⁶⁻²⁹ Allergists and otolaryngologists alike have developed a special interest in this mycotic condition because of its predilection in immunocompetent atopic individuals with or without nasal polyposis. Although most cases of AFS have been associated with *Aspergillus* species, non-*Aspergillus* fungal organisms have been identified. These fungi include: *Curvularia*,^{16, 22, 30-33} *Alternaria*,^{22, 23} *Bipolaris/Drechslera*,^{11, 14, 15, 16, 22} *Exserohilum*,¹⁵ and *Chrysosporium*.¹⁷ As a result, a broader diagnostic label, AFS, was suggested by Robson et al.¹¹ in 1989. All cases of AFS share similar clinical, radiologic,

Abbreviations used

AFS:	Allergic fungal sinusitis
AAS:	Allergic <i>Aspergillus</i> sinusitis
ARS:	Allergic <i>Rhizomucor</i> sinusitis
GMS:	Gomori methenamine-silver
ABPM:	Allergic bronchopulmonary mycosis
ABPA:	Allergic bronchopulmonary aspergillosis
CF:	Cystic fibrosis

and pathologic features that include symptomatic, multisinus disease with or without nasal polyps, radiologically opacified paranasal sinuses, and the presence of scattered fungal elements in inspissated allergic mucin. Hyphal elements are not found in the mucosa, submucosa, vasculature, and/or bone.

In this "Allergy Grand Rounds," we describe the first case of AFS caused by *Rhizomucor*. The clinical, pathologic, and mycologic features of allergic *Rhizomucor* sinusitis (ARS) are identified and a review of the pertinent literature is described. Dr. Dvorin, will you please describe the case history?

CASE PRESENTATION

Clinical findings

Dr. Donald J. Dvorin*: L.K., a 26-year-old white woman presented in January 1991 with a 5-year history of chronic nasal congestion, tenacious purulent nasal discharge, post nasal drip, anosmia, and chronic sinus pressure headaches. The patient had no history of nasal plug discharge, asthma, aspirin sensitivity, cigarette or marijuana smoking, or significant passive smoke exposure. Medical therapy with antihistamines, decongestants, intranasal steroids, and antibiotics as well as polypectomy had failed. L.K.'s past medical history was otherwise unremarkable with the exception of a multiyear history of seasonal allergic rhinitis. The family history did not identify atopic disease, aspirin sensitivity, or nasal polyposis. There was no personal history of diabetes, immunodeficiency,

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ciency, neoplasm, asthma, or any previous treatment with immunosuppressives.

On physical examination, pathologic findings were limited to the upper respiratory tract. Complete obstruction was seen in the right nasal vestibule, with polyps and partial obstruction of the left vestibule with congested turbinates. A brown-greenish mucous cast was noted in her left nasal airway. The hypopharynx revealed cobblestoning of the hypopharyngeal wall. Sinus tenderness was absent.

Cutaneous reactivity, serologic, and immunologic findings

Laboratory evaluation revealed the following: positive immediate hypersensitivity skin tests to seasonal pollens, animal danders, perennial allergens, and the following molds: *Alternaria*, *Aspergillus fumigatis*, *Candida*, *Curvularia*, *Mucor*, *Phoma*, *Pullaria*, and *Rhizopus*. Late phase skin reactions were not noted to the molds tested. C3, C4, CH₅₀, and quantitative immunoglobulins (Ig) G, A, and M, and a glucose tolerance test were within normal limits. The total eosinophil count was 2922 cells/mm³. A total serum IgE level was normal at 103 U/ml. Functional IgG and IgM class antibodies to tetanus, pneumococcus, and isohemagglutinins were present. Specific zygomyces antibodies assayed by an enzyme immunoassay (Specialty Labs, Santa Monica, Calif.) were performed immediately after endoscopic surgery. These studies revealed elevated levels of IgG antizygomyces antibodies (7.5 units) and IgA antizygomyces antibodies (4.2 units), but they revealed undetectable levels of IgM antizygomyces antibodies (<3.0 units). This assay can detect antibodies to the *Mucoraceae* species *Absidia*, *Rhizomucor*, *Mucor*, and *Rhizopus*. Phenotypic lymphocyte enumeration studies on L.K.'s circulating cells revealed normal quantitative levels of CD2, CD4, and CD8 cells, with a normal CD4:CD8 ratio of 1:3:1. T-lymphocyte mitogen stimulation studies to phytohemagglutinin, concanavalin A, and pokeweed mitogen were within normal limits.

Surgical and pathologic findings

Dr. Marc F. Goldstein: Dr. Lesser, will you please describe the surgical findings?

Dr. Raymond W. Lesser*: The patient underwent endoscopic sinus surgery in February 1991. Polyps were removed from the right middle meatus and right ethmoid sinus. Pathologic specimens with a gross

color and consistency of peanut butter were removed from the right maxillary sinus and portions of the right ethmoid sinus.

Dr. Marc F. Goldstein: Dr. Loose, will you please describe the pathologic findings?

Dr. Jeffrey H. Loose*: Microscopic examination of the surgical tissue with a hematoxylin-eosin stain revealed florid mucosal lymphoplasmacytic inflammation with numerous eosinophils. The mucin contained abundant, intact and degenerating eosinophils, cellular debris, and Charcot-Leyden crystals (Fig. 1). This mucin was identical to the allergic mucin described by Katzenstein et al.^{24, 25} Isolated fungal elements were seen in slides stained with hematoxylin-eosin (Fig. 2). There was no evidence of mucosal, bony, or vascular invasion by hyphal elements.

Gomori methenamine-silver (GMS) impregnation stains revealed numerous intact and fragmented fungal hyphae located exclusively in the mucin (Fig. 3). The hyphae were 10 to 15 μ m in diameter and were aseptate, irregularly broad, and branched at irregular angles characteristic of *Mucor* species.

Microbiologic studies

Dr. Marc F. Goldstein: Mr. Heuman, will you please describe the microbiologic findings?

Mr. Paul J. Heuman†: Aerobic and anaerobic bacterial cultures were negative. Fungal culture revealed a typical fluffy colony morphology of *Rhizomucor* with a cotton texture. The colony color was initially gray turning dark brown with age. Microscopically, irregular branching rhizoids at the base of the sporangiophores were observed. *Rhizomucor* could be identified and distinguished from *Rhizopus* by having branched sporangiophores and was differentiated from *Mucor* by branched rhizoids (Fig. 4).

Postoperative course—clinical, serologic, and immunologic findings

Dr. Marc F. Goldstein: Dr. Dvorin, will you please describe the postoperative course?

Dr. Dvorin: The patient's immediate postoperative course was characterized by significant diminution or resolution of the symptoms of rhinitis, sinus pressure headache, nasal congestion, and post nasal drip. Over time, mild to moderate relapses of her rhinitis, sinus pressure, and nasal discharge required revision endoscopic surgical intervention and/or "burst" courses of oral corticosteroids, intranasal steroids, and/or anti-

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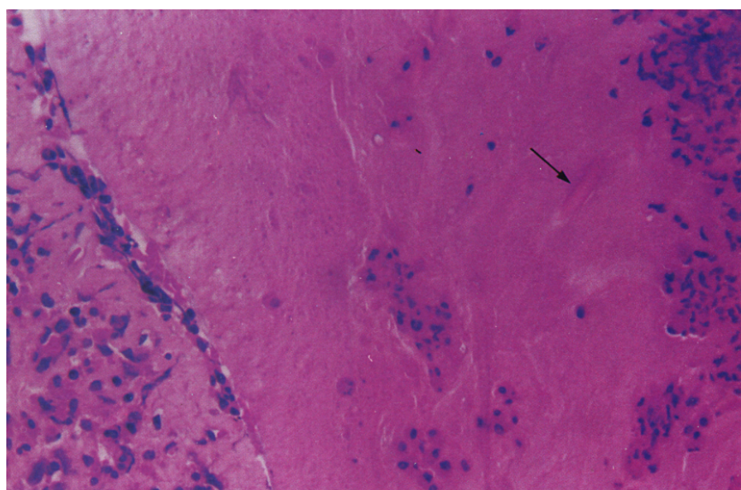


FIG. 1. Allergic mucin. Section of sinus contents shows florid mucosal lymphoplasmacytic inflammation with numerous eosinophils. The mucin contained abundant intact and degenerating eosinophils, cellular debris, and Charcot-Leyden crystals (*arrow*). Mucin identical to allergic mucin described by Katzenstein et al.²⁴ (Hematoxylin-eosin stain; original magnification $\times 400$.)

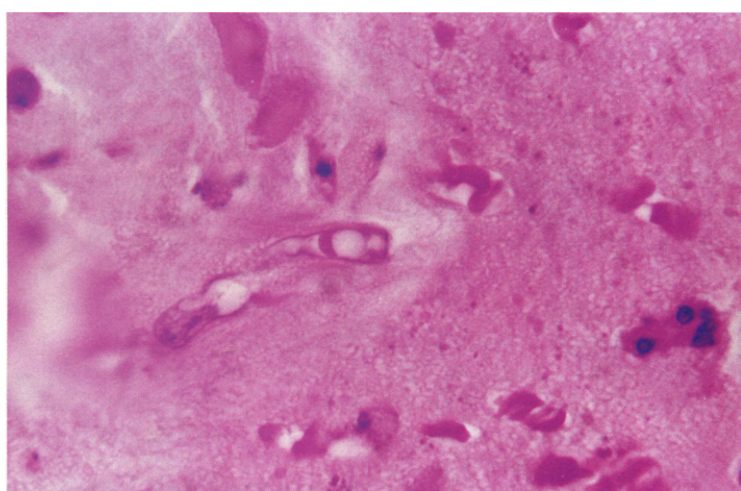


FIG. 2. Hyphal elements in mucoid matrix. Section of sinus contents reveal isolated fungal elements. (Hematoxylin-eosin stain; original magnification $\times 1000$.)

biotics. No further evidence of fungal elements have been seen on nasal or sinus specimens taken at the time of subsequent revision surgery. Repeat studies for antizygomycete antibodies performed several months after endoscopic surgery revealed decreases in IgG to an indeterminate level (3.4 units) and non-detectable IgA (<3.0 units) and IgM (<3.0 units) levels. Total eosinophil count was noted to be reduced from 2922 cells/mm³ to 410 cells/mm³.

The clinical and pathologic features described in our patient were typical of most cases of AFS reported in the literature. L.K. had a history of allergic rhinitis

and nasal polyps. Radiographs depicted opacification without bony erosion of the right ethmoid and maxillary paranasal sinuses. Sinusitis and nasal polyps were recalcitrant to standard antimicrobial therapy, oral and intranasal steroids, and surgical polypectomy. Skin testing and serologic assays to *Rhizomucor* were consistent with an immunologic hypersensitivity response to *Rhizomucor*. Marked peripheral eosinophilia was also seen. On endoscopic surgical debridement, a thick peanut butter-like material was removed from the right maxillary and ethmoid sinuses. This material was distinctly different from that typically removed

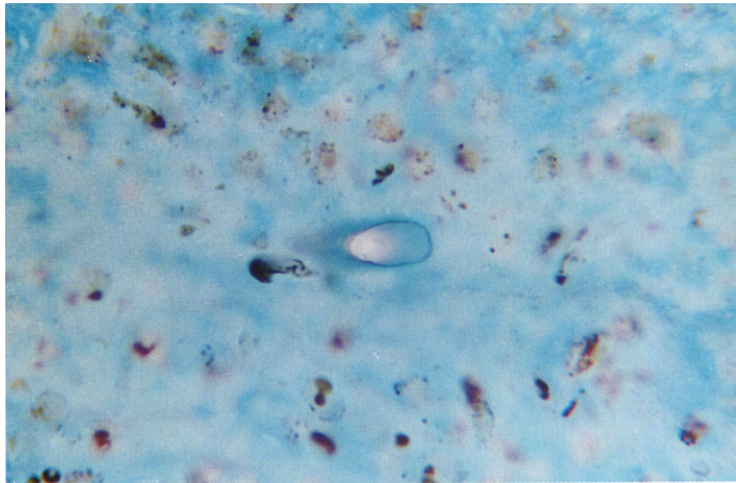


FIG. 3. *Mucor*-like fungal hyphae in mucosal matrix. Numerous intact and fragmented fungal hyphae shown to be located exclusively in the mucin. The fungal hyphae occurred singly and in loosely cohesive, scattered groups. The hyphae measured 10 to 15 μm in diameter and were aseptate, irregularly broad, and branched at irregular angles, characteristic of *Mucor* species. (GMS stain; original magnification $\times 1000$.)

from chronic bacterial sinusitis or chronic indolent fungal sinusitis, where the gross resected tissue usually has a viscous gray-green appearance.

Surgical specimens from our case revealed the unique fungal organism of *Rhizomucor*, and the microscopic findings were consistent with the characteristic allergic mucin described by Katzenstein et al.²⁴ Surgical debridement with revision endoscopic surgery, intranasal and oral steroids, and nonfungal immunotherapy have resulted in sustained remission. Antifungal therapy was not instituted. IgG and IgA antizygomycete antibodies have fallen subsequent to the initial surgery. Peripheral eosinophilia has dramatically decreased.

DISCUSSION

Pathogenesis

Dr. Marc F. Goldstein: Dr. Dunsky, will you review for us the pathogenesis of AFS and allergic bronchopulmonary mycosis (ABPM)?

Dr. Eliot H. Dunsky*: Humans have intimate and continuous exposure to fungal elements by inhalation of airborne fungal particles (indoors and outdoors), through mold contamination from ingested foods, and through symbiotic and pathogenic fungi colonizing the skin, upper and lower gastrointestinal tract, upper and lower respiratory tract, and vagina. Despite the frequency and range of exposure, humans have relatively few infectious complications caused by fungi.

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FIG. 4. Microscopic morphology of *Rhizomucor*. A few primitive, irregularly branching rhizoids (*R*) are seen at the base of a sporangiophore (*S*), differentiating the organism from *Mucor*. Dark brown branched sporangiophores are seen, which distinguish it from *Rhizopus*. The sporangia (*Sp*) are spherical-shaped spore sacs seen at the distal tip of the sporangiophores.

Fungi have long been recognized as important causes of both IgE-mediated allergic rhinitis and asthma as well as hypersensitivity pneumonitis. However, of all the important aeroallergens, mold allergy is the least understood and studied.³⁴ Although more than 80,000 species of fungi have been clinically described, only 40 to 45 different fungi are known to cause allergic pathology in sensitive human individuals.³⁵

In addition to IgE-mediated hypersensitivity, it has become increasingly recognized that immunocompetent hosts may also develop other forms of fungal-induced respiratory disease. In this regard, susceptible individuals have developed hypersensitivity responses to fungi leading to the clinical syndromes recognized as AFS and ABPM. Some have suggested that these disorders are nonpathogenic saprophytic colonization of fungi in inspissated respiratory mucus. Most authors, however, believe that AFS and ABPM are true hypersensitivity reactions. Since histologic similarities exist between ABPM and AFS, it is likely that immunopathogenic mechanisms are shared. The reasons for specific localization of allergic mucin in the upper versus lower airways or both are unknown. Immunopathogenesis of AFS and ABPM has been linked to type I, type III, and possibly type IV immune responses.^{2, 36} In addition, it has been hypothesized that fungal mycelia may also release mediators that have proinflammatory properties.³⁷ Although all patients with AFS and ABPM are thought to be immunocompetent, it is possible that unrecognized specific regulatory defects in cellular and/or humoral responses may underline these disorders.

In other respects, the pathogenic mechanisms responsible for AFS may be different from ABPM. In particular, a higher antigen load exposure to the upper versus lower airway may predispose to fungal colonization in allergic mucin within the sinuses. In addition, surgical changes in the paranasal sinuses and the presence of allergic mucin may synergistically foster an environment favorable to fungal proliferation. A French model of fungal sinusitis has also been proposed by Legent et al.³⁸ in which fungal colonization of the maxillary sinuses occurs through the iatrogenic development of sinus-oral cavity channels (e.g., after tooth extraction, periodontal destruction, root canal perforations). These cases of fungal sinusitis have been mostly unilateral sinus disease associated with aspergilloma or less frequently invasive aspergillosis. The histopathologic descriptions have not been consistent with allergic mucin. Finally, cases of AFS have not been reported in patients with oral cavity/dental surgery or trauma.

Literature review of AFS cases

Dr. Marc F. Goldstein: Dr. Dvorin, will you review the current literature on reported cases of AFS?

Dr. Dvorin: A survey of the English-language literature documents 70 well-described cases of AFS. Forty-two of these cases have been attributed to *Aspergillus* species,^{16, 23, 24, 33, 39-49} whereas 28 cases have been a result of non-*Aspergillus* species, not including this report. The latter include the following: 14 cases caused by *Bipolaris/Drechslera*,^{11, 14-16, 22} one case of *Exserohilum*,¹⁵ nine cases of *Curvularia*,^{16, 22, 30-33} three cases of *Alternaria*,^{22, 32} one case of *Chrysosporium*,¹⁷ and with this report, one case of *Rhizomucor*. With increased awareness, it is likely that other fungal species will be added to the list of non-*Aspergillus* fungi that cause AFS. Non-*Aspergillus* fungi have also been identified in ABPM.⁵⁰⁻⁵³

Demographic and clinical information regarding the 42 cases of AFS and the 29 cases of allergic non-*Aspergillus* fungal sinusitis is presented in Tables I and II, respectively. In general, most cases were reported in young adults with a mean age of 27.4 years (range, 8 to 58 years). The male to female ratio is approximately 1:1. Most patients have had an antecedent history of chronic symptomatic rhinosinusitis for months to years before actually seeking medical or surgical therapy or both. Atopy was reported in more than one third of cases as defined by either positive allergy skin tests (38%), elevated total serum IgE levels (34%), and/or history typical of allergic rhinitis (42%). All patients, where tested, displayed positive immediate hypersensitivity skin test responses to the putative fungus. The incidence of asthma was reported in 32% of cases. Concomitant allergic bronchopulmonary aspergillosis (ABPA) subsequently developed in only five cases of AFS.^{27, 29, 33, 42, 46} Approximately two thirds of cases had a history of nasal polyposis. Bony changes on CT scanning were seen in 25% of cases. Only one patient with concomitant aspirin sensitivity has been reported.⁴¹

All reported cases of AFS have been in immunocompetent individuals without underlying systemic autoimmune disease, nor did these patients receive systemic immunosuppressive therapy or radiotherapy. Presenting central nervous system and ophthalmologic complications such as visual defects,⁵⁴ proptosis,^{4, 14, 23, 31, 32, 45, 54} exophthalmus,⁴¹ telecanthus,¹⁴ intracranial extension,⁴¹ epiphora,^{14, 30-32, 39, 40} and diplopia^{11, 30} have been seen in a number of cases of AFS, especially children.⁴⁵

Allergic and serologic parameters including serum total IgE levels, total eosinophil counts, and antifungal antibodies have not shown consistent trends in re-

TABLE 1. Characteristics of reported cases of allergic *Aspergillus* sinusitis

Ref. no.	No. of cases	Age (yr)	Sex	ABPA	Asthma	AR	Polyps	Peri Eos (>3%)	Elev. total IgE	Elev. specific IgG	ST+	Abnormal radiograph
24	7	13	M		—	—	+					+
		23	F		+	—	+					
		47	F		+	—	+	+				
		18	M		+	+	+	+	+	+		
		27	F		+	+	+	+		+		
		48	M		+	+	+	+	+	+		
		17	F		+	+	+		+	+		
39	2	11	M		+	+		+			+	+
		13	F			+						+
23	1	26*	F			+	+		+	+	+	+
40	2	34	F				+					+
		41	F									+
41	8	32	F				+		+			
		56	M				+					
		37	M		+		+					
		21	M				—		+	+		
		13	F		+		+					
		28	F				+					
		44	M		+		+					
		34	F		+		+		+	+	+	
42	1	42	F	+	+	+		+	+	+	+	
43	1	26	F				+					+
44	4	45	M				+					+
		46	F		+	+	+					
		33	M									
		18	F				+					
45	6	8	F		—		+					
		13	M		+		+					+
		14	F		—		+					+
		16	F		+		+					+
		16	M		—		+					
		16	M		—		+					+
46	1	24	M	+	+	+	—	+	+	+	+	
47	1	26	M			+	+	+	+	+	+	
16	1	No data supplied										
48	4								4	4		
49	1	30‡	F				+				+	
33	2	42		+			+	+	+	+	+	
		9					+		+		+	

AR, Allergic rhinitis; *Peri Eos*, peripheral eosinophils; ST+, skin test positive.

*Asthma developed in patient 7 years after diagnosis.

†Five additional patients had positive skin tests in this series.

‡Patient had cystic fibrosis.

ported cases. Unlike the association between ABPA and very high total IgE levels, most cases of AFS have not exhibited this phenomenon. However, we have recently evaluated a patient with AFS without ABPM in whom a total serum IgE level was more than 4000 U/ml. The prognostic value of serologic testing in

identifying exacerbations of AFS, analogous to the value of following total serum IgE levels in ABPA, has not been adequately prospectively studied.

The features of fungal sinusitis seen on CT scanning have been previously reported by Zinreich et al.⁷ and include bony displacement and/or erosions with in-

TABLE II. Characteristics of reported cases of allergic *non-Aspergillus* fungal sinusitis

Ref. no.	No. of cases	Age (yr)	Sex	ABPA	Asthma	AR	Polyyps	Peri Eos (>3%)	Elev. total IgE	Elev. specific IgG	ST+	Abnormal radiograph
<i>Alternaria</i>												
22	2	14	M		+	+		+	+		+	
		50	M		+	+	+				+	
32	1	14	M			+			+		+	
<i>Bipolaris/Drechslera</i> (<i>Bipolaris</i>)												
11	1	28	M		+	+		+	+	+	+	+
14	3	16	F		+	+	+	+	+	+	+	+
		20	M		-	+	+	+	+	-	+	+
		40	F		-	+	+	+	+	+	+	+
22	5	35	F		-	+	+	+	+		+	
		45	F		-	+	+	+	+		+	
		19	M		-	+	+	+	+		+	
		58*	F		-	+	+	+	+		+	
		11	F			+	+					
15	1	43	M									+
<i>(Drechslera)</i>												
15	1	16	F			+	+					
16	3	16	M				+					
		24	M				+					
<i>Chrysosporium</i>												
17	1	17	F			+	+				+	
<i>Curvularia</i>												
30	1	21	M		+	+		+	+	+		+
31	2	18	F		+		+					
		16	F			+	+	+				
32	1	48	M			+		+				+
22	2	26	M		-	+	+					
		30	M		-		+					
16	2	29	M									
		30	M									
33	1	36					+	+	+		+	+
<i>Exserohilum</i>												
15	1		M		+							+
<i>Rhizomucor</i>												
	1	26	F		-	+	+	+		+	+	

*Also grew out *Aspergillus* on fungal culture.

tracavity areas of high attenuation.⁷ Although magnetic resonance imaging may have some added diagnostic advantage (hypointensive T₂ weighted signals of sinus content) compared with CT scans, magnetic resonance imaging has rarely been used in the diagnosis or management of AFS. Despite the benign nature of AFS, bony erosions as a result of pressure-induced atrophy or necrosis from expansion of intracavity sinus contents have been seen in a number of cases.*

*References 11, 14, 15, 22, 23, 24, 30, 32, 33, 39, 40, 43-45.

Not included in Tables I and II are other cases of dematiaceous sinusitis occurring in young atopic adults with nasal polyposis and histories of refractory sinusitis.^{2, 4-8, 10, 12, 18, 21} Sufficient histopathologic and immunologic information was not available to validate the diagnosis of AFS in these case descriptions. In retrospect, many of these cases were probably AFS.

In addition, cases of invasive dematiaceous fungal sinusitis have been reported in immunocompetent patients with nasal polyps where allergic mucin or eosinophilic exudates were histologically identified in sinus content specimens. These patients were gener-

ally not atopic.^{2, 9, 19} Unique to these cases was the finding of tissue invasion by hyphal elements either in bony trabeculas or submucosal tissue. Since all these cases occurred with dematiaceous fungi, it is unclear whether these organisms behave differently in allergic mucin than do *Aspergillus* species. These cases, therefore, may represent a malignant (invasive) variant of AFS.

Mucormycosis

Dr. Marc F. Goldstein: Dr. Dunsky, will you briefly review the clinical infections seen with *mucoraceal* fungi?

Dr. Eliot H. Dunsky: Most infections resulting from the family *Mucoraceae* (*Rhizomucor*, *Rhizopus*, *Mucor*, *Absidia*) are caused by the genus *Mucor* or the genus *Rhizopus*. These organisms are ubiquitous molds and are found frequently on decaying vegetable matter and soil. Histologically, the hyphae of *Mucoraceae* species lack septation and therefore can be distinguished from *Aspergillus* species, since both fungi exhibit 45-degree angle dichotomous branching. In addition, *Mucoraceae* species have broader hyphae of 6 to 50 μm of uneven diameter, whereas *Aspergillus* species have narrow hyphae of approximately 4 μm . As laboratory contaminants, *Mucoraceae* have been isolated from healthy individuals particularly from oral cavities and nasal passages.^{55, 56} They are not ordinarily considered pathogenic in immunocompetent hosts.

Phycomycosis, mucormycosis, and zygomycosis are general terms that refer to fungal infections caused by species of the *Mucoraceae* family. These infections can be seen in the lungs, gastrointestinal tract, paranasal sinuses, brain, or as systemic infections. Of the four clinicopathologic fungal sinusitis syndromes described in man, *Mucoraceae* species have been reported to cause chronic indolent sinusitis,⁵⁷ mycetoma,^{13, 57} and invasive sinusitis.⁵⁸⁻⁶⁰ This is the first reported case of AFS as a result of *Mucoraceae* fungus.

TREATMENT AND MANAGEMENT

Dr. Marc F. Goldstein: Optimal therapy for AFS beyond surgical debridement with restoration of mucociliary drainage and sinus ventilation has not been prospectively studied. As with treatment for ABPA, oral daily or alternate-day corticosteroids have been regarded as an essential treatment modality to limit allergic inflammation and reduce mucous secretion in the perioperative period.^{16, 22, 33, 36, 41, 61} Repeat revision endoscopic surgery, polypectomy, and antral lavage accompanied with systemic and nasal steroids have been required in some cases for recurrent disease.^{33, 41} Local treatment with intranasal steroids, cromolyn, amphotericin B suspensions, and nasal saline

irrigation has been used in conjunction with oral steroids but may be of limited value in an impacted nasal airway.¹⁶ Inhaled steroids, inhaled cromolyn, and antifungal therapy have also not been shown to be effective in the treatment of ABPA. Lack of efficacy of inhaled therapy for ABPA may be related to the inability of medications to effectively penetrate affected areas of mucoid obstruction and/or bronchiectasis.^{36, 62}

The administration of local and systemic antifungal therapy for AFS has been reported particularly during the perioperative period when invasive disease is still a diagnostic consideration. However, general consensus exists that indications for antifungal therapy are limited in the absence of mucosal infection.* This is clearly different from the treatment of invasive fungal sinusitis, where a combination of radical surgical extirpation and parenteral antifungal therapy is warranted.²

As with all allergic diseases, a reduction of antigen load is an essential therapeutic consideration. Surgical debridement is therefore the first step in limiting the presence of antigenic stimulants. Endoscopic sinus surgery has proved to be as successful as traditional surgery for AFS as seen in our case and others.^{16, 17} Reducing exposure to mold sources (exposure to decaying organic material, stored grains, musty areas) and limiting outdoor exposure during high mold spore seasons would seem prudent. Immunotherapy to the causative fungal aeroallergen has not been examined and has been avoided because of the theoretic risk of increasing circulation of fungal-specific IgG antibody. Immunotherapy to other relevant antigens, however, is helpful to reduce other sources of IgE-mediated inflammation.²³

Patients with AFS need to be prospectively evaluated for the development of recurrent polyp disease, bacterial, and/or fungal sinusitis. Careful follow-up examinations, fiberoptic rhinoscopy, and CT scans are of importance in this regard. Evaluating patients with asthma for the development of ABPM may also be important. Only five cases of ABPA after AAS have been reported.^{27, 29, 33, 42, 46} However, it should be noted that other cases of ABPA with chronic nasal or sinus symptoms have been reported, although the exact cause of the upper respiratory complaints were not well documented.⁶³⁻⁶⁵ In general, patients with AFS may have a better prognosis than those with ABPM. This may be due to the accessibility of the sinuses for surgical drainage and removal of fungal antigen stimulation, or as a result of better deposition and penetration of topical aerosol therapies into affected areas or both.

The value of following peripheral eosinophilia, to-

*References 11, 22, 31, 33, 39, 41, 43-45, 50, 61

tal serum IgE, and specific antifungal antibodies (IgE, IgG, IgA, and IgM) in patients with AFS is uncertain. Previous reports of serial IgE levels and RAST tests have not been consistent in correlating disease activity or steroid requirements or both.^{11, 23, 32, 48, 61}

It is unclear whether AFS-related pathology may recur within sinus cavities in an asymptomatic manner analogous to the fleeting asymptomatic infiltrates seen in ABPA.³⁶ Therefore the need for diligent follow-up examinations with rhinoscopy, serologies, and sinus imaging to detect new soft tissue densities, bony changes, and/or abnormal soft tissues in contiguous structures may be important. Follow-up CT scans may also show signs of new bone formation in and around sinus cavities as a function of healing.¹¹

Multidisciplinary approach to AFS

Dr. Marc F. Goldstein: Chronic sinusitis is a common clinical problem that faces primary care physicians and specialists alike. AFS is an underdiagnosed and therefore an undertreated subset of chronic sinusitis that frequently escapes diagnosis because of failure to consider this syndrome. We have found that the optimal evaluation and management of AFS requires a multidisciplinary approach with use of the skills of several physician groups, including allergists, otolaryngologists, and pathologists. Dr. Dunskey, will you describe the allergist's role?

Dr. Eliot H. Dunskey: For the allergist, any patient with refractory sinus disease, especially in the context of nasal polyps, anosmia, allergic rhinitis, history of passing brown-green gelatinous plugs, and/or peripheral eosinophilia should be prospectively evaluated for AFS. All patients with nasal polyps, sinusitis, and allergic rhinitis without a history of aspirin sensitivity should be evaluated for AFS. Only one case of aspirin sensitivity has been reported in patients with nasal polyposis and AFS.⁴¹ In this regard, AFS should also be added to the differential diagnosis of children with nasal polyposis, especially those without cystic fibrosis (CF). Although a 10% to 12% incidence of ABPA in patients with CF is reported,⁶⁶ only one case of AFS concurrent with CF has been described.⁴⁹ Nevertheless, close evaluation of patients with CF with chronic sinusitis and nasal polyps for the development of AFS is warranted.

In addition, patients with resistant sinusitis who have previously undergone sinus surgery may retrospectively be evaluated for AFS by examining recut tissue blocks of sinus and polyp specimens for the presence of allergic mucin with or without fungal elements. All cases of allergic mucin may not demonstrate fungal elements on hematoxylin-eosin stains or even on GMS stain. Sampling error, misreading on initial review or mistakenly regarding fungal pathogens as contaminants,⁵ and fragmentation and degen-

eration of fungal elements may explain the lack of fungal identification in some cases.* Alternatively, other unidentified allergens may be responsible for these pathologic changes yet yield negative fungal stains and cultures. In summary, these later cases of allergic mucin without hyphal elements may represent AFS where fungal elements have not been readily identified, or alternatively, may represent a sinus variant of mucoid impaction of the bronchus.⁶⁷⁻⁶⁹

In addition, all patients with ABPM and concurrent sinusitis should be evaluated for the presence of allergic mucin in the sinus tissue. All patients who have been diagnosed with AFS should also be evaluated and monitored for the development of asthma or ABPM or both.

Dr. Marc F. Goldstein: Dr. Lesser, will you review the otolaryngologist's role?

Dr. Raymond W. Lesser: Some patients with AFS may come to the otolaryngologist with a pseudotumor that produces mass effects leading to proptosis, visual loss, and/or facial deformities. CT scan results may also suggest the presence of tumor with bony erosions or thinning or both. CT scans, however, are not always reliable in distinguishing invasive versus noninvasive sinusitis. Many cases of AFS were presumptively diagnosed as malignancies before tissue diagnosis on the basis of clinical findings and CT scan images. At the time of surgery and on pathologic review of AFS cases, typical CT findings of bony erosions have uniformly been areas of bone thinning, bony necrosis, and/or destruction caused by pressure atrophy from expanding sinus cavity contents. Invasive fungi into bony trabeculas have not been seen except in isolated "malignant" variants of AFS.^{8, 9, 19} Radiologic bony destruction, therefore, does not necessarily imply histologic bone necrosis or tissue invasion by pathogenic fungi.

Any patient with an allergic background who has mass effects and/or a history of multiple nasal polypectomies and sinus surgery who is seeking treatment from an otolaryngologist should be evaluated for AFS. It is crucial that at the time of surgery, or revision surgery, that all surgical specimens be sent for fungal stain and culture and that the pathologist be alerted to look for allergic mucin. This is particularly true if the surgeon removes, at the time of surgery, a thick peanut butter-like debris.^{14, 31, 44, 61} Color descriptions of this material have been varied, including yellow-green,⁴⁴ muddy brown,⁴ green-black,⁴⁵ and tan-gray-brown.^{31, 63} This material may also have a foul odor. When sinus contents are removed, the underlying mucosa is often normal, hyperplastic, or polypoid.

Dr. Marc F. Goldstein: Dr. Loose, will you review the pathologist's role?

*References 16, 23, 24, 33, 39, 43, 44, 50

Dr. Jeffrey W. Loose: The diagnosis of AFS rests on pathologic and microbiologic confirmation of tissue specimens. Pathologists should be alerted to look for fungal elements, particularly if pale mucoid material with laminated layers of eosinophils, cellular debris, and Charcot-Leyden crystals in the mucoid matrix are seen. Pathologic examination of resected mucosa may show areas of submucosal edema and inflammatory infiltrates. However, fungal elements are never seen in the mucosa, submucosa, vascular structures, or bony trabeculas.^{2,23} Exclusion of invasive fungal sinus disease is an important pathologic determination. Routine hematoxylin-eosin stains may not be sufficient to reveal fungi.^{19,68,69} Silver impregnation stains or Fontana-Masson stains are required to identify fungal elements histologically.¹⁵ Dematiaceous fungi should be reported out and not automatically discarded as fungal contaminants. Species identification of fungus can best be accomplished by evaluating microscopic morphologic appearance and growth characteristics from culture colonies. This is particularly true of dematiaceous fungi that cannot be separated on the basis of histology or gross colony morphology or both alone.^{8,70}

SUMMARY

Dr. Marc F. Goldstein: In conclusion, AFS is a benign noninvasive disease of the paranasal sinuses that can be caused by a variety of fungal organisms. This report highlights the first case of AFS caused by *Rhizomucor*. Recognition of AFS as a distinct clinicopathologic entity separate from other causes of clinical and radiographic sinusitis, especially invasive fungal sinusitis and neoplasm, is important. The clinical diagnosis of AFS needs to be considered in the differential diagnosis of chronic refractory sinusitis if surgical specimens are to be properly analyzed both histologically and microbiologically. Proper diagnosis is important to ensure optimal therapy, including surgical debridement and oral corticosteroids. In addition, accurate diagnosis avoids the unnecessary use of antifungal drugs or radical surgical procedures or both.

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