

Winning Resident and Fellow Manuscript
Excellence Award, 1993

Pediatric Allergic Fungal Sinusitis: Another
"Great Masquerader"

GREGORY M. WICKERN, M.D.

ABSTRACT

Allergic fungal sinusitis (AFS) was first recognized as a distinct clinical entity in 1981. Since that time more than 70 case reports have been published. Nearly half of these cases are children under the age of 20 years. These children are immunocompetent with recalcitrant sinusitis, nasal polyposis, allergic rhinitis, and asthma. They may have epiphora, telecanthus, diplopia, and orbital proptosis. Computerized tomography (CT) scans demonstrate multisinus involvement with tumor-like expansion changes occurring frequently. They often have very elevated total serum immunoglobulin E (IgE) levels with increased specific fungal IgE and IgG levels and cutaneous hypersensitivity to the implicated fungus. The peanut butter-like mucin in their sinuses has characteristic findings both grossly and microscopically. Fungal elements are detectable within the mucin both microscopically and with culture. No evidence of fungal mucosal invasion should exist. Optimal treatment is uncertain although surgical debridement and postoperative systemic steroids are most commonly employed. Recurrence of disease is common with much still to be learned about this interesting disorder.

INTRODUCTION

Fungal organisms are ubiquitous in the human environment. Fungi are also found in and on the human body wherever they can successfully gain access. With open communication to the nasal passages, it is not surprising that the paranasal sinuses could also host fungal organisms. Four major fungal sinus disorders have been described: invasive fungal sinusitis, indolent fungal sinusitis, mycetoma ("fungal ball"), and allergic fungal sinusitis AFS.^(1,2) The first three represent true fungal infections with a nonallergic inflammatory response by the host. The last, AFS, represents a unique fungal infestation with little or no polymorphonuclear cell response and no tissue invasion.

Originally recognized as a distinct clinical entity by Katzenstein et al. in 1983,⁽³⁾ more than 70 cases of AFS have been reported with an excellent literature review recently appearing in 1992.⁽⁴⁾ The majority of AFS patients have been young adults with an average age of approximately 30 years. However, at least 34 cases

Department of Allergy-Immunology, Wilford Hall U.S.A.F. Medical Center, San Antonio, Texas.

The views expressed in this article are those of the author and do not reflect the official policy of the Department of Defense or other Departments of the U.S. Government.

have involved pediatric patients younger than 20 years of age and this probably underrepresents the true prevalence of AFS. As many as 6–7% of patients with chronic sinus disease going to the operating room may have AFS.^(3,5) This review will discuss many general aspects of AFS but will emphasize that which we have learned about children with AFS.

CASE PRESENTATIONS

To introduce you to pediatric AFS, two illustrative cases of the 34 in the literature are presented:

Case 1

A 12-year-old black male presented to our allergy clinic with a 2–3 year history of perennial nasal congestion while living in southern Alabama. Sinusitis and nasal polyps had been recently diagnosed by referring physicians. Nasal topical steroids decreased the size of his polyps but standard antibiotic therapy did not clear his sinus disease. The patient had no previously recognized history of sinusitis, pneumonia, or other major infections. No atopic disorders had previously been identified and growth and development were normal. He had experienced “bronchitis” with β -agonist responsive cough on three prior occasions. Family medical history was notable for a paternal aunt and cousin with asthma. Physical examination was normal except for a small left sided nasal polyp and nasal septal deviation. Pulmonary Function Tests (PFTs), sweat chloride test, quantitative immunoglobulins, IgG subclasses, and complete blood count (CBC) were all normal. Total IgE was markedly elevated at 4,606.5 IU/ml. The total eosinophil count was increased at $600/\text{mm}^3$. Epicutaneous skin tests were strongly positive to a histamine control and several molds: *Fusarium*, *Bipolaris*, *Curvularia*, *Alternaria*, *Helminthosporium*, and *Cladosporium*. He was negative to all other aeroallergens tested. Sinus CT scan demonstrated pansinus soft tissue opacification with areas of “speckled” hyperattenuation (Figure 2). The sphenoid sinus appeared expansile suggesting the possibility of a tumor. Marked nasal septal deviation was also noted radiographically (Fig. 1). Surgically obtained sinus specimens showed thick peanut butter-like allergic mucin with microscopically seen eosinophils and Charcot-Leyden crystals. Potassium hydroxide (KOH) preparation showed broad septated hyphae. *Fusarium* species grew in a heavy pure growth.⁶

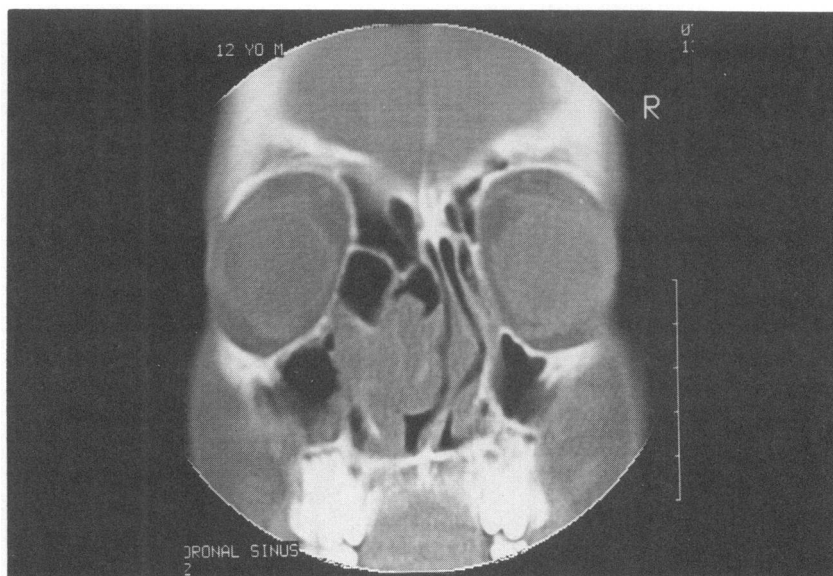


FIG. 1. Coronal CT view of Case 1 demonstrating marked nasal septal deviation, atrophic R middle turbinate, and ethmoid opacification.

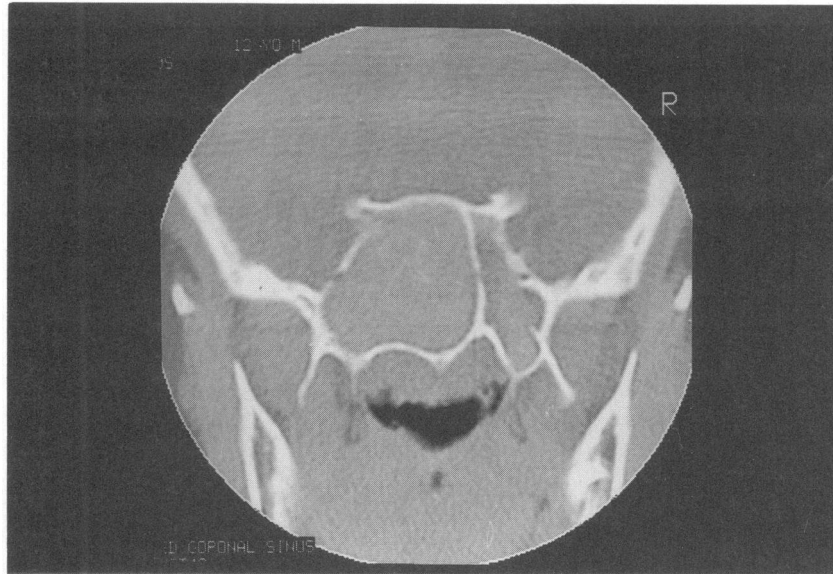


FIG. 2. Coronal CT view of Case 1 demonstrating complete opacification of the sphenoid sinus with speckled hyperattenuation and bony erosion/expansion.

Case 2

A 16-year-old white female presented to the ear, nose, and throat (ENT) and allergy clinics of our hospital in 1987 with a 12-month history of increasing nasal congestion, frontal headaches, and environmental allergies. She also had a history of mild asthma. Lateral displacement of the medial canthi, epiphora, and nasal polyposis were noted on physical examination. Immediate skin test hypersensitivity was documented to multiple trees, grasses, and molds, including *Bipolaris*. Laboratory evaluation showed total serum IgE to be 3,310 IU/ml, total eosinophil count $528/\text{mm}^3$, positive *Bipolaris* serum precipitins, elevated specific IgE and

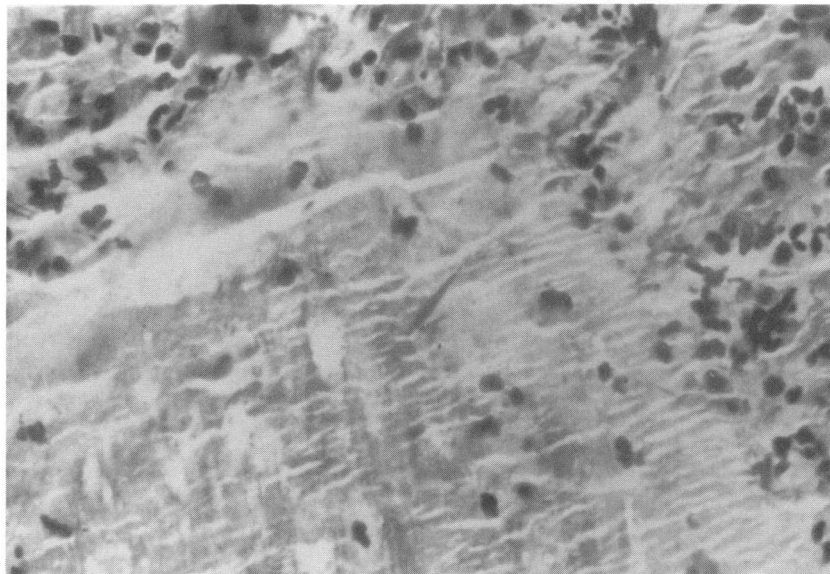


FIG. 3. Charcot-Leyden crystals and eosinophils within the allergic mucin of an AFS patient.

IgG to *Bipolaris* and immunocompetence judged by extensive laboratory and delayed-type hypersensitivity skin testing. CT scan showed pansinus soft tissue densities with areas of hyperattenuation within the soft tissue opacities and bony erosion of the medial wall of the left maxillary sinus. Expansion of the ethmoids bilaterally was also evident.

In the operating room, otolaryngologists scooped thick peanut butter-like material from her sinuses. Many eosinophils, Charcot-Leyden crystals, and fungal hyphae were present in the mucin. *Bipolaris spicifera* grew from this material. No evidence of mucosal or bony invasion by the mold was apparent. Her orbital displacement and epiphora resolved postoperatively.^(5,7)

CLINICAL PRESENTATION: ANOTHER “GREAT MASQUERADER”

Tuberculosis, sarcoidosis, syphilis, and systemic lupus erythematosus have each been referred to as “great masqueraders” in medicine because of their ability to present clinically as something suggestive of another disease. Children with AFS may provide an addition to this list.

The two case presentations demonstrate that children with AFS most frequently present with the clinical and radiographic signs of persistent sinusitis. However, the slowly progressive accumulation of thick mucin within the sinuses of these patients often results in pressure remodeling or erosion of more delicate sinus cavity walls as might an intrasinus tumor. This, along with associated malar deformities, telecanthus, orbital proptosis, epiphora, and diplopia has resulted in referral of these children as suspected tumor patients. Although occasionally seen in adults, these deformities appear to be more common among pediatric AFS patients.^(3,5-11)

The vast majority of AFS patients have a history of nasal polyps, a physical finding that should also suggest cystic fibrosis in children. Although AFS has been seen in a patient with cystic fibrosis,⁽¹²⁾ the majority of pediatric AFS patients do not appear to have this disease. The polyp formation is probably induced by immunologic stimulation of the respiratory mucosal lining of the sinus cavities, a mechanism suspected in other nasal polyp disorders. These polyps in children may also result in bony remodeling demonstrated by the severe septal deviation described in the first case above.

The majority of pediatric AFS patients also have a history of asthma and allergic rhinitis. Approximately 35–40% of reviewed pediatric AFS cases had histories positive for these two atopic conditions, with a higher percentage probably present but incompletely documented. The combination of asthma and nasal polyps should bring to mind triad asthma if aspirin sensitivity is also documented. Only one report discussed the issue of aspirin intolerance and found sensitivity was uncommon in this group of pediatric AFS patients.⁽¹³⁾

Many of these children complain of more common symptoms associated with nasal polyps and chronic sinusitis: hyposmia or anosmia, headaches, nasal congestion, and mouthbreathing.⁷

Of the 34 pediatric AFS cases reviewed, 17 were male, 16 female, and one was not identified by gender. The youngest patient was 8 years old⁽⁹⁾; the majority were teenagers. Cases were identified from England⁽¹⁴⁾ and many parts of the United States, including Texas,^(5,7,9,15,16) Ohio,⁽¹³⁾ Alabama,⁽¹⁷⁾ Maryland,⁽⁸⁾ and Minnesota.⁽¹⁰⁾

Radiographic features

All AFS patients will have abnormal sinus CT scans when disease activity is present. The most striking radiographic features of this disorder include: (1) multiple sinus involvement, (2) areas of speckled hyperattenuation (increased radiodensity) within the soft tissue opacities of the sinuses, and (3) remodeling and/or erosion of the involved sinus walls.

Table 1 emphasizes the multisinus involvement of this disorder. Where information was provided in the case reports, not a single patient had less than two diseased sinuses; eight cases had pansinus involvement while the remaining often had ethmoid, sphenoid, and maxillary disease. The frontal sinuses appear to be least often involved (Table 1).

Areas of increased radiodensity within the soft tissue density-filled sinuses have been described in many of the case reports and summarized in 1988 by Zinreich et al.⁽¹⁸⁾ These areas demonstrate a mean attenuation of

122.2 Hounsfield units, significantly higher than that seen with chronic bacterial sinusitis. Spectrometric analysis showed this hyperattenuation to be deposits of magnesium, manganese, and iron in the fungus-infected mucin. Unfortunately these areas are not seen on plain sinus radiographs. These areas of hyperattenuation are thought to be unique to AFS⁽²⁾ although it is still early to consider them pathognomonic.

Pathology features

The thick mucin recovered from the sinuses of these children is quite distinctive. Grossly, it has a peanut butter-like consistency with a tan, gray-brown, or green color. Microscopically, this mucin is similar to that seen in patients with allergic bronchopulmonary mycoses (ABPM): an eosinophilic background with predominantly eosinophils, sloughed respiratory epithelial cells, and cellular debris that includes eosinophilic granules and Charcot-Leyden crystals. The Charcot-Leyden crystals stain well with either hematoxylin-eosin or Brown and Brenn stains. These crystals vary between 2 to 60 microns in size and are composed of lysophospholipase produced by eosinophils. These features are unique among the fungal sinus disorders, supporting the distinctness of AFS as a separate disease entity.

Fungal elements are often, but not always, seen in the mucin. Grocott-Gomori methenamine-silver stain increases the chances of sighting responsible fungi. In those cases where the characteristics of the mucin are consistent with AFS but fungi are not seen, it has been proposed that pathology sampling errors could be involved.⁽³⁾

Many of our AFS patients have blown small rubbery plugs from their noses. Although thought to be associated with their AFS, the histology of these plugs is not completely consistent with that of the allergic mucin described above. The potential diagnostic value of these plugs is uncertain.

Immunologic features

Children with AFS are immunocompetent by humoral and cellular testing in those cases where data is available.^(5-7,10) They often have elevated total serum IgE and circulating eosinophil counts, although these are not consistent findings. The highest IgE level among pediatric AFS patients was 4606.5 IU/ml reported in the first illustrative case presentation.⁽⁶⁾ In allergic bronchopulmonary aspergillosis, serial IgE levels act as disease surveillance markers. In AFS, the use of IgE levels for this purpose is not as yet defined. However, experience in our institution suggests some potential usefulness and serial IgE levels as well as specific IgG ELISA are performed on our *Bipolaris* AFS patients.

Elevated fungus-specific IgE and IgG, as noted in Table 1, have also been documented. Serum precipitins using the Ouchterlony plate is a relatively easy serum screening method. Making a five-fold concentration of the patient serum permits more ready identification of pertinent precipitin bands. Precipitin bands often disappear postoperatively and may not be present in all patients even at the time of original diagnosis.

POTENTIAL PATHOGENESIS

The histologic, immunologic, and clinical similarities between patients with AFS and ABPM have encouraged investigators to propose the pathogenesis of AFS to be similar to that of ABPM.^(2,3,17) Pepys^(19,20) originally proposed that both Gell and Coombs types I and III reactions could be involved in ABPM. Beginning with fungal spores becoming trapped in the thick bronchial mucus of ABPM, a series of events might then lead to the characteristic findings of ABPM. This suggested pathogenesis was supported by Slavin's primate animal model.⁽²¹⁾ However, despite these efforts at defining the pathogenesis of ABPM and AFS, the complete explanation is still evolving.

The bony remodeling and erosions have been previously mentioned. Although pressure-induced remodeling seems likely, the exact mechanism of this phenomenon is still uncertain. One group of authors suggested a possible role of locally released inflammatory mediators, such as major basic protein from the numerous eosinophils, present in the mucin.⁽⁵⁾ The cytotoxic effects of many eosinophil-derived mediators are well known. A good animal model of AFS could help answer this question.

TABLE 1. FEATURES OF AFS

Age	Sex	Asthma	AR	Polyps	Problems	High eos	High IgE	Elev. Spec IgG	ST+	Abnml. Sinuses	Ref. #
<i>Aspergillus</i>											
13	Male	No	No	Yes	BE					M,E,F,S	1
18	Male	Yes	Yes	Yes		Yes (24%)	Yes	Yes	Yes	PEN	1
17	Female	Yes	Yes				Yes			M,E,S	1
11	Male	Yes	Yes		BE, EPA, OD	Yes (13%)			Yes	E	2
13	Female		Yes	Yes	OD					E,F	2
13	Female	Yes		Yes						PAN	3
18	Female	Yes		Yes						PAN	3
18	Female			Yes						PAN	4
8	Female	No		Yes	OD, MD						5
13	Male	Yes		Yes	BE, OD					E,S	5
14	Female	No		Yes	OD, BE					PAN	5
16	Female	Yes		Yes	OD, BE					M,E,S	5
16	Male	No		Yes	OD, DPA					PAN	5
16	Male	No		Yes	OD, BE					PAN	5
9		No		Yes			Yes		Yes	M,E	6
<i>Alternaria</i>											
14	Male	Yes	Yes	Yes		Yes	Yes		Yes		7
14	Male		Yes	Yes	OD, DPA, EPA BE		Yes		Yes	E,M	8
<i>Fusarium</i>											
12	Male	Yes	Yes	Yes		Yes	Yes		Yes	M,E,S	9

TABLE 1. (CONTINUED)

Age	Sex	Asthma	AR	Polyps	Problems	High eos	High IgE	Elev. Spec IgG	ST+	Abnml. Sinuses	Ref. #
<i>Bipolaris</i>											
16	Female	Yes	Yes	Yes	OD, EPA, BE	Yes	Yes			PAN	7, 10
19	Male	No	Yes	Yes	BE	Yes	Yes		Yes	PAN	7, 10
11	Female		Yes	Yes							7
9	Male										11
10	Female										11
12	Male										11
16	Male										11
16	Male										11
18	Male										11
16	Male										11
<i>Drechslera</i>											
16	Female		Yes	Yes							11
16	Male			Yes							12
<i>Exserohilum</i>											
11	Male	Yes		Yes	OD, DVA, BE					M,E,S	11
<i>Chrysosporium</i>											
17	Female		Yes	Yes					Yes		13
<i>Curvularia</i>											
18	Female	Yes		Yes						E,M,F	14
16	Female		Yes	Yes	OD, MD, BE	Yes				S,E,M,F	14

Pediatric AFS case summaries. Where blank spaces occur, no information was available.

Abbreviations: AR, allergic rhinitis; EOS, eosinophils; ST, immediate hypersensitivity skin tests; BE, bony erosions; EPA, epiphora; OD, orbital displacement; DPA, diplopia; MD, malar deformity; DVA, decreased visual acuity; PAN, pansinus; E, ethmoid; M, maxillary; S, sphenoid; F, frontal.

TABLE 2. SUMMARY OF MAJOR DIAGNOSTIC FEATURES OF AFS

<i>Clinical features</i>
Chronic sinusitis symptoms
Headaches
hyposmia
nasal congestion
cough
Atopic patient (asthma and allergic rhinitis)
Nasal polyps
Malar deformities
Orbital displacement
<i>Radiographic features</i>
Multisinus opacification
Areas of hyperattenuation
Bony expansion/thinning/erosions
<i>Pathology features</i>
Peanut butter-like mucin
Microscopy
Many eosinophils, Charcot-Leyden crystals, cellular debris, fungal elements
No mucosal invasion
Often fungal culture positive
<i>Immunologic features</i>
Immunocompetent host
Elevated total serum IgE
Peripheral eosinophilia
Elevated fungus-specific IgG and IgE
Positive fungal precipitins

INITIAL PATIENT EVALUATION

Our experience with AFS suggests that a multidisciplinary approach to these patients is needed. An informed pediatrician or family practitioner attempting treatment of refractory rhinosinusitis should consider referral to both an ENT surgeon and allergist. This is especially important with an atopic patient and a history of nasal polyps and asthma. In our hospital, when clinical and radiographic findings suggest AFS, the otolaryngologists refer the patients pre- or postoperatively to the allergy clinic. Mold extracts are used to determine the presence or absence of immediate cutaneous hypersensitivity, and blood is drawn and set aside for serum precipitins, total IgE, total eosinophil count, and specific fungal IgE and IgG. The precipitins and specific IgE and IgG are performed after surgical specimens are reviewed and fungal cultures yield a specific organism.

The ENT surgeon must inform the pathologist of the possibility of AFS to ensure proper specimen processing and culture selection. Appropriate stains were discussed in the pathology features section of this paper. Recognition of typical allergic mucin and, hopefully, growth of a specific fungus finalize the diagnosis.

TREATMENT

The optimal treatment of AFS remains under investigation. Surgical debridement is important for establishing the initial diagnosis and is probably helpful therapeutically by reducing the mucin and antigenic load for the patient. Many clinicians then follow the surgery with a course of systemic glucocorticoids as is

PEDIATRIC AFS

done for active ABPM: 0.5 mg/kg/day for two weeks followed by alternate day therapy at the same dose for 3–6 months. The steroids are then weaned over an appropriate period of time to avoid the problems associated with adrenal gland suppression.

However, whether systemic steroids are necessary postsurgery is not completely certain. Many patients have been treated with surgery alone with apparent short term disease improvement. Also, patients treated with steroids have had disease reoccurrence, implying the benefits of systemic steroids may be temporary at best. Although based presently only upon anecdotal experience, because of the similarities to ABPM, our institution treats all AFS patients postsurgically with oral and topical nasal steroids. Importantly, no systemic antifungal agents are considered necessary in this noninvasive disease.

The use of specific mold hyposensitization through injection immunotherapy in AFS patients has not yet been systematically examined. If Gell and Coombs type III reactions (immune complex) are involved in AFS pathogenesis, the injected extracts could theoretically increase antigen load and worsen the patient's condition. On the other hand, if the type I reaction (IgE mediated) is necessary for AFS to occur, a reduction in type I hypersensitivity could successfully prevent AFS in the first place or prevent a recurrence in the postoperative AFS patient. This is certainly an issue looking for research.

PROGNOSIS

The experience of clinicians working with AFS patients suggests three postoperative courses: (1) a long term disease-free period, (2) a rapid recurrence of disease within months of surgery, and (3) a more delayed recurrence, sometimes even years later.^(2,17) Our own experience suggests recurrence is common.

RESEARCH OPPORTUNITIES

Many questions remain unanswered regarding AFS. The pathogenesis could be studied through production of a suitable animal model as has been done with ABPM. Since allergic rhinitis caused by molds is relatively common, what factors cause only a few of these patients to develop AFS? Could AFS be diagnosed without requiring surgery through a combination of characteristic clinical, radiographic, and laboratory findings? Could recurrences be treated nonsurgically with systemic steroids alone? Are there specific disease progress markers that could be followed in these patients as there are in ABPM patients? Finally, what role might fungal hyposensitization play? Answering many of these questions could be difficult because the number of AFS patients followed by individual institutions is relatively small. Collaborative efforts may be necessary. The opportunities for AFS research are certainly many!

REFERENCES

1. Corey JP, Romberger CF, Shaw GY. Fungal diseases of the sinuses. *Otolaryngol Head Neck Surg* 1990;103:1012–1015.
2. Gourley DS. Allergic fungal sinusitis. *Insights in Allergy* 1989;4.
3. Katzenstein AA, Sale SR, Greenberger PA. Allergic Aspergillus sinusitis: A newly recognized form of sinusitis. *J Allergy Clin Immunol* 1983;72:89–93.
4. Goldstein MF, Dvorin DJ, Dunsky EH, et al. Allergy grand rounds: Allergic Rhizomucor sinusitis. *J Allergy Clin Immunol* 1992;90:394–404.
5. Ence BK, Gourley DS, Jorgensen NL, et al. Allergic fungal sinusitis. *Am J Rhinol* 1990;4:169–178.
6. Wickern GM. Fusarium allergic fungal sinusitis: A case report. *J Allergy Clin Immunol* (in press).
7. Gourley DS, Whisman BA, Jorgensen NL, et al. Allergic bipolaris sinusitis: Clinical and immunopathologic characteristics. *J Allergy Clin Immunol* 1990;85:583–591.
8. De Juan E, Green WR, Iliff NT. Allergic periorbital mucopyocele in children. *Am J Ophthalmol* 1983;96:299–303.

WICKERN

9. Manning SC, Vuitch F, Weinberg AG, Brown OE. Allergic aspergillosis: A newly recognized form of sinusitis in the pediatric population. *Laryngoscope* 1989;99:681–685.
10. Bartynski JM, McCaffrey TV, Frigas E. Allergic fungal sinusitis secondary to dematiaceous fungi—*Curvularia lunata* and *Alternaria*. *Otolaryngol Head Neck Surg* 1990;103:32–39.
11. Macmillan RH, Cooper PH, Body BA, Mills AS. Allergic fungal sinusitis due to *Curvularia lunata*. *Hum Pathol* 1987;18:960–964.
12. Bitner AS, Syns CA, Jorgensen NL, et al. Allergic fungal sinusitis in a patient with cystic fibrosis: The first reported case (Abstract). *J Allergy Clin Immunol* 1991;87:143.
13. Allphin AL, Strauss M, Abdul-Karim FW. Allergic fungal sinusitis: Problems in diagnosis and treatment. *Laryngoscope* 1991;101:815–820.
14. Jonathan D, Lund V, Milroy C. Allergic *Aspergillus* sinusitis: An overlooked diagnosis? *J Laryngol Otol* 1989;103:1181–1183.
15. Friedman GC, Hartwick WJ, Ro JY, et al. Allergic fungal sinusitis: Report of three cases associated with dematiaceous fungi. *Am J Clin Pathol* 1991;96:368–372.
16. Manning SC, Schaefer SD, Close LG, Vuitch F. Culture-positive allergic fungal sinusitis. *Arch Otolaryngol Head Neck Surg* 1991;117:174–182.
17. Waxman JE, Spector JG, Sale SR, Katzenstein AA. Allergic *Aspergillus* sinusitis: Concepts in diagnosis and treatment of a new clinical entity. *Laryngoscope* 1987;97:261–266.
18. Zinreich SJ, Kennedy DW, Malat J, et al. Fungal sinusitis: Diagnosis with CT and MR imaging. *Radiology* 1988;169:439–444.
19. McCarthy DS, Pepys J. Allergic bronchopulmonary aspergillosis: Clinical immunology I: Clinical features. *Clin Allergy* 1971;1:261.
20. McCarthy DS, Pepys J. Allergic bronchopulmonary aspergillosis: Clinical immunology II: Skin, nasal, and bronchial tests. *Clin Allergy* 1971;1:415.
21. Slavin RG, Fischer VW, Levin EA. A primate model of allergic bronchopulmonary aspergillosis. *Int Arch Allergy Appl Immunol* 1978;56:325.

Address reprint requests to:
Gregory M. Wickern, M.D.
WHMC/PSMA
2200 Bergquist Drive, Suite 1
Lackland AFB, TX 78236