Medical Journal of the
Islamic Republic of Iran

Volume 15
Number 3
Fall 1380
November 2001

ALLERGIC FUNGAL SINUSITIS AMONG CANDIDATES FOR FUNCTIONAL ENDOSCOPIC SINUS SURGERY (FESS) IN SARI (IRAN)

T. SHOKOHI, Ph.D., AND A. MADANI, M.D.*

*From the Departments of Medical Mycology and Parasitology and *Otorhinolaryngology, Mazandaran University of Medical Sciences, Sari, Islamic Republic of Iran.*

ABSTRACT

Allergic fungal sinusitis (AFS) has been clinicopathologically defined as a noninvasive form of fungal infection. This study was designed to distinguish AFS among patients with chronic sinusitis who failed to respond to repeated courses of antibiotics and were therefore candidates for functional endoscopic sinus surgery (FESS) in Sari.

Allergic mucin and sinus lavage was collected during FESS from 100 patients meeting the diagnostic criteria for AFS and were submitted for mycology and pathology investigations. The specimens were centrifuged and the sediment was mounted in 10% KOH and Gram's stain for direct examination. The specimens were inoculated in Sabouraud's Dextrose Agar. Multiple fragments of mucosa were removed at surgery and stained with H&E and PAS for the pathology evaluation.

In this study we report 9 proven cases of AFS (with demonstration of fungal hyphae by direct exam and culture) and 8 suspected cases (confirmed by direct exam or culture). The patient's age ranged from 12 to 62 years, with a mean age of 24.5 years with female predominance. All of the patients were immunocompetent. 47% of the patients had a history of atopy. Histopathologically, hyphae were not seen. The genera of the fungi were identifiable in all but one patient. 53% of isolated fungi were from the hyaline hyphomycete group particularly *Aspergillus* and *Penicillium* and 47% of them were members of the dematiaceous family particularly *Cladosporium* and *Nigrospora*. In eleven out of the seventeen, fungal hyphae were noted and in all of the seventeen there were positive fungal cultures.

Fungal sinusitis should be considered in all patients with chronic sinusitis that fails to repond to repeated courses of treatment. Recent advances in endoscopy and computed tomography and physician awareness will lead to improved diagnosis and treatment and will prevent multiple surgical procedures.

MJIRI, Vol. 15, No. 3, 133-138, 2001.

Keywords: Sinusitis, fungal, allergic, allergic mucin.

INTRODUCTION

Mycotic infection of the paranasal sinuses was first described in 1893 by Mackenzie.[1] In 1971, McCarthy and Pepys[2] 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 (41.1%) in that study had maxillary sinusitis as shown on x-ray films. Cultures of the nasal plug and sinus lavages grew *As-*

pergillus fumigatus. In 1976, Safirstein[3] 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.[4] reported the case of an otherwise healthy 15-year-old swimmer who was first seen with ethmoidal and 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. Allergic fungal sinusitis (AFS) was recognized initially by Miller[5] and Lamb[6] in Great Britain and subsequently by Katzenstein et al.[7] The diagnosis of fungal sinusitis has advanced markedly with the availability of computed tomography (CT) and sinus endoscopy.[8] Fungal sinusitis should be considered in all patients with chronic sinusitis that fails to respond to repeated courses of antibiotics and, unfortunately, often results in multiple operations before the diagnosis is recognized.[9] Retrospective studies suggest that at least 5-10% of patients requiring surgery for chronic sinusitis have AFS[10] but the actual incidence may be higher, particularly in warmer, more humid regions of the United States.[11] In Iran, the prevalence of AFS is unknown. In order to distinguish AFS from chronic bacterial sinusitis and other forms of fungal sinusitis, we reviewed the literature to find guidelines for diagnosis in our experiment. We elaborated a set of five diagnostic criteria: radiologically confirmed sinusitis; the presence of allergic mucin* within a sinus; the demonstration of fungal hyphae in allergic mucin by stain or culture; absence of diabetes, immunodeficiency or recent treatment with immunosuppressive drugs; and absence of invasive fungal disease at the time of diagnosis or subsequently.[12,13]

Table I. Previous history and clinical findings of patients having chronic sinusitis operated in Boo-Ali Sina Hospital in Sari during 1998-1999.

History and clinical findings	Frequency	%
Cigarette smoking	7	7
Asthma	3	3
Aspirin intolerence	3	3
Atopic eczema	7	7
Allergic rhinitis	21	21
Previous sinus surgery	51	51
Nasal polyposis	11	11
Seizure	1	1
Nasal obstruction	75	75
Fetid smell	21	21
Purulent nasal discharge	74	74
Nasal stuffiness	13	13
Rhinorrhea	44	44
Periorbital pain	27	27
Facial pain	19	19
Postnasal discharge	61	61
Anosmia	12	12
Fever	6	6
Nasal mucosal ulcer	1	1
Frontal headache	58	58

MATERIAL AND METHODS

All studied patients were evaluated at the Sari Medical School of Mazandaran University of Medical Sciences, Department of ENT and Mycology, at a Reference Laboratory of Mazandaran province between March 1998 and April 1999. A total of 100 patients with chronic sinusitis who failed to respond to repeated courses of antibiotics were candidates for FESS in Sari. Sari is located near the Caspian Sea (northern Iran) and the weather is temperate and humid [the average annual temperature is 18.1 (-2-36.2)°C and the average annual humidity is 79% (18-100)].

A questionnaire was provided which included data regarding a history of cigarette smoking, asthma, aspirin intolerance, atopic eczema, allergic rhinitis, previous sinus operations, diabetes, malignant disease, and recent treatment with immunosuppressive drugs. The presence of clinical evidence including nasal obstruction, fetid smell (cacosmia), purulent nasal discharge, nasal stuffiness, rhinorrhea, frontal headache, periorbital pain, facial pain, postnasal drip, anosmia, proptosis, fever, nasal mucosal ulcer and eschar and orbital apex syndrome were investigated by the ENT specialist. Radiological studies using plain radiographs and computed tomography scan findings consisted of involvement of paranasal sinuses and characteristic findings were recorded by the radiologist. All patients were examined visually at surgery and information recorded. Allergic mucin and sinus lavage taken at surgery was submitted promptly to the mycology laboratory and the specimens consisted of multiple fragments of involved mucosa submitted to the pathology laboratory in 10% formalin and stained with H&E and PAS. Allergic mucin and sinus lavages were centrifuged and the sediment was mounted in 10% KOH for direct examination and the smears were also stained with Gram stain. The specimens were inoculated in multiple plates containing Sabouraud's Dextrose Agar at room temperature for 30 days. The fungal mold was identified with the use of microslide culture

*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.[13]

Table II. Data on 9 patients with proven AFS and 8 patients with suspected AFS.

No.	Age(yr)	Sex	Complaint	Atopy*	Nasal polyposis	Allergic mucin	Hyphae noted	Fungus cultured	Total IgE
1	16	M	A	+	-	+	+	Penicillium	20048
2	38	F	A+C	+	-	-	+	Aspergillus	20
3	14	F	A+C	+	-	-	+	Cladosporium	15
4	19	F	B+C	+	-	-	+	Cladosporium	-
5	16	F	B+C	-	-	-	+	Cladosporium	-
6	12	M	A+B+C	-	-	-	+	Aspergillus	18
7	32	M	A+C	-	-	-	+	Drechselera	20
8	19	F	A+C	+	-	-	+	Nigrospora	141
9	62	M	A+B	-	-	-	+	Aspergillus	-
10	17	F	A+E	-	-	-	-	Aspergillus	-
11	16	F	A+C	-	-	+	+	Aspergillus, ANI	-
12	12	F	A+B+C	-	-	+	-	Curvularia	-
13	15	F	A+B+C	+	+	+	-	Aspergillus	27
14	14	F	A+B+C+F	-	-	-	+	Nigrospora and Penicillium	-
15	26	F	A+B+C	-	-	+	-	Nigrospora	-
16	29	F	A+B+G	+	+	+	-	Trichoderma	-
17	35	M	A+B	+	-	+	-	Cladosporium	47

*A: PND B: Nasal stuffiness C: Frontal headache D: Nasal mucosal ulcerated eschar
E: Rhinorrhea F: Decreased smelling G: Periorbital pain

technique. In this study, if the fungal elements were seen in direct examination and multiple pure colonies were isolated from the site of inoculation, it was considered as a proven case and if fungal elements were not seen in direct examination but multiple identical colonies were isolated it would be considered a suspect case. Patients were considered atopic based on deShazo and Swain's[13] criteria (as a following consideration: 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). A total IgE level below 10 units/mL is generally regarded as non-indicative of the presence of atopy. Levels above 100 units/mL, on the other hand, are highly likely to indicate the presence of atopy. Levels between 10 and 100 are equivocal in this regard.

RESULTS

52% (52 of 100) of the patients having chronic sinusitis were women and 48% (48 of 100) were men, aged 9 to 69. Previous histories and clinical findings of these patients are shown in Table I. 51% of patients (51 of 100) with chronic sinusitis had a history of previous multiple sinus operations and 21% (21 of 100) had allergic rhinitis and 11% (11 of 100) had nasal polyposis. Of one-hundred patients with chronic sinusitis refractory to medical therapy who underwent sinus surgery, the diagnosis of AFS was made in 9 patients and in 8 patients the diagnosis of AFS was suspected. Five patients were men and twelve were women, aged 12 to 62 (Table II). Eight out of the seventeen patients (47%) were atopic as defined by deShazo and Swain.[13] Two out of the seventeen patients (11.8%) had nasal polyp disease, fifteen out of the seventeen patients (88.2%) had postnasal drip (PND), twelve of them (70.6%) had frontal headache, ten of them (58.8%) nasal stuffiness, twelve of them (70.6%) had nasal obstruction, eleven (64.7%) had a history of previous sinus surgery, two (11.8%) had atopic eczema and four of them (23.5%) had allergic rhinitis. In none of the

patients was there CT scan evidence of bone erosion in any of involved paranasal sinuses. In none of the patients was there tissue invasion evidence in histologic specimens and hyphae were not seen in the specimens in which H&E and PAS staining was performed. In two patients histology revealed allergic mucin but fungal elements were not seen. Fungi were cultured from surgical specimens taken from the patients. (Table III). The species of fungus was identified in all but one patient.

Fifty-three percent of isolated fungal species were members of hyaline hyphomycete and forty-seven percent of them were members of the dematiaceous family. More than one species of fungus was isolated from two patients with AFS. *Nigrospora* and *Penicillium* were isolated from one of them and *Aspergillus* and an unidentifiable fungus from the other.

Table III. Species of fungus isolated from patients with proven or suspected AFS.

Species	No. of patients	Hyaline hyphomycete	Dematiaceous
Aspergillus	6	*	
Penicillium	2	*	
Trichoderma	1	*	
Cladosporium	4		*
Curvularia	1		*
Drechselera	1		*
Nigrospora	2		*
Total	17	9	8

DISCUSSION

Fungal sinusitis should always be considered in the differential diagnosis of chronic or recurring sinusitis resistant to adequate medical treatment. The diagnosis of fungal sinusitis has advanced markedly with the availability of computed tomography (CT) and sinus endoscopy. Fungal sinusitis can be divided into four primary categories: (1) acute/fulminant (invasive), (2) chronic/indolent (invasive), (3) fungus ball, and (4) allergic fungal sinusitis. Each subtype has unique immunologic, pathologic and clinical features. Allergic fungal sinusitis is most recently described and is the most common form.[10,17-20] Eighty-one percent of cultured fungal species reported in the literature are members of the dematiaceous family, particularly *Bipolaris*, *Curvularia, Exerohilum, Alternaria* and *Cladosporium* species.[22] Recently, other non-Aspergillus, nondematiaceous fungi such as *Fusarium*,[23] *Chrysosporium*[24] and *Rhizomucor*[25] have been documented. Jay et al.[14] reported a patient with *Bipolaris spicifera* and *Curvularia lanata*. Jonathan et al.[15] reported a patient with *Aspergillus flavus* and *Aspergillus fumigatus*, and Adam et al.[16] reported a patient with *Bipolaris spicifera* and *Alternaria specifera*. The prevalence of AFS is unknown. Gourley et al.[26] reviewed 2000 consecutive cases of chronic sinusitis requiring surgery and found 14 cases (7%) of AFS. Clinically, AFS occurs in young immunocompetent individuals with equal frequency in male and female patients. A history of atopy has been documented in most cases. Patients typically present with clinical features of AFS and histopathologic evidence of allergic mucin in whom fungi can not be demonstrated by histopathologic sutdies. 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 H&E staining. in deShazo and Swain's[13] case series, fungi were frequently cultured after being overlooked on routine stains of surgical material. The findings of Allphin et al.[17] are in contrast to those of Ence et al.[10] who found allergic mucin to be very specific for AFS. Diagnosis criteria for AFS have been suggested previously by several other investigators.[7,19,26,10,30] These criteria have included clinical and laboratory features such as atopy, asthma, nasal polyps, elevated serum IgE levels, and serum fungal precipitins. Although these are common features and support the diagnosis, deShazo and Swain's[13] review suggests that the absence of these clinical features does not exclude the diagnosis. AFS occurs in young immunocompetent individuals. Morpeth et al.[8] in a review of 95 patients from the literature with AFS reported a mean age of 27.5 years (range 8-72) and Torres et al.[22] in a clinicopathologic study of 10 cases of AFS reported an age range of 8 to 71 years, with a mean age of 25 years. In our study the mean age was 24.5 years (range 12-62) with a female predominance. In our study based on deShazo and Swain's[13] criteria, 47% of AFS patients (proven or suspected) were considered to be atopic. In AFS, cultures are often negative, which may be attributed to several factors. Ence et al.[10] suggested that eosinophils present within the sinus mucin release major basic protein, which may be toxic to fungi, leading to the sparse number of fungi often found within the allergic mucin. The fungi then become fragile and may deteriorate *in vitro* or may not survive the culture process.[18] It can also be postulated that the number of fungal organisms needed to cause an allergic reaction in an atopic host may be so small that a sampling error may lead to false-negative results.

A major dilemma occurs when histology shows fungal hyphae but cultures are negative.[28] Stainable hyphae are not present in the mucosa of patients with chronic bacterial sinusitis; they are present solely in mucopurulent material within the sinus in noninvasive disease.[29]

In our histopathologic study no fungal elements were seen. As described by deShazo and Swain,[13] in our study only mucosa (not mucin) was submitted for histopathologic evaluation. Hyphae were identified in allergic mucin and sinus lavage but were not present in mucosa or bone in any of the patients. DeShazo and Swain[13] reported one patient with hyphae present in allergic mucin but not in mucosa or bone. Allphin et al.[17] reported 11 patients with classic features of allergic fungal sinusitis but with negative fungal stains or cultures. In our study we endoscopically removed polyps and inflammatory material to establish aeration and drainage of involved sinuses as an essential first step in treatment. Daily sinus irrigation with warm isotonic saline and corticosteroid therapy (prednisone in a dose of 10 to 20 mg per day) was performed and prescribed postoperatively. We didn't use any antifungal therapy postoperatively. We identified recurrences in 2 patients clinically but without any microscopic or culture evidence. The reasons for recurrence of AFS are unknown. It may be due to exposure to fungi, persistent fungal colonization at a microscopic level or perhaps unrecognized fungal infection of the mucus membrane or bone of the sinus cavity. Bent and Kuhn[12] suggested antifungal irrigation to combat recurrent disease by reducing fungal recidivism, and notified that since the topical antifungals would not change the underlying AFS immunopathology, they should not be regarded as potentially curative.[12] Today there are no long-term clinical trials supporting the use of systemic steroids in the treatment of allergic fungal sinusitis.[8] There remains controversy as to which patients should receive steroids and for how long they should be treated. Waxman and coworkers[27] reserved systemic steroid treatment postoperatively for those patients with tendencies to recurrence.

ACKNOWLEDGEMENT

We appreciate the technical assistance of Dr. Abedian, Dr. Jafarpour, Miss Afshar, Mr. Saadatjoo, Mr. Gholizadeh, Mrs. Ebrahimi, Mrs. Mohammadi and Mr. Rahbar.

REFERENCES

1. Mackenzie JJ: Preliminary report on Aspergillus mycosis of the antrum maxillare. John Hopkins Hospital Bulletin 4: 9-10, 1893.
2. McCarthy DS, Pepsy J: Allergic broncho-pulmonary aspergillosis. Clin Allergy 1: 261-86, 1971.
3. Safirstein B: Allergic broncho-pulmonary aspergillosis with obstruction of the respiratory tract [Abstract]. Chest 70: 788, 1976.
4. Young CN, Swart JG, Ackermann D, Davidage-Pitts D: Nasal obstruction and bone erosion caused by *Drechslera hawaiiensis*. J Laryngol Otolo 92: 137-43, 1978.
5. Miller JW, Johnston A, Lamb D: Allergic aspergillosis of the maxillary sinuses [abstract]. Throat 36: 710, 1981.
6. Lamb D, Millar JW, Johnston A: Allergic aspergillosis of the paranasal sinuses. Abstracts of the Proceedings of the 143rd Meeting of the Pathological Society of Great Britain and Ireland. J Pathol 137: 56, 1982.
7. Katzenstien AL, Sale SR, Greenberger PA: Allergic *Aspergillus* sinusitis: a newly recognized form of sinusitis. J Allergy Clin Immunol 72: 89-93, 1983.
8. Morpeth JF, Rupp NT. Dolen WK, Bent JP, Kuhn FA: Fungal sinusitis. an update. Ann Allergy Asthma Immunol 76: 128-40, 1996.
9. DeShazo RD, O' Brien M, Chapin R, et al: Criteria for diagnosis of sinus mycetoma. J Allergy Immunol 99: 475-485, 1997.
10. Ence BK, Gourley DS, Jorgenson NL, et al: Allergic fungal sinusitis. Am J Rhin 4: 169-178, 1990.
11. Schweitz LA, Gourley DS: Allergic fungal sinusitis. Allergy Pro 13: 3-6, 1992.
12. Bent JP, Kuhn FA: Antifungal activity against allergic fungal sinusitis organisms. Laryngoscope 106: 1331-1334, 1996.
13. DeShazo RD, Swain RE: Diagnostic criteria for allergic fungal sinusits. J Allergy Clin Immunol 96: 24-35, 1995.
14. Jay WM, Bradsher RW, LeMay B, Synderman N, Angtuaco EJ: Ocular involvement in mycotic sinusitis caused by *Bipolaris*. Am J Ophthalmol 105: 366-70, 1988.
15. Jonathan D, Lund V, Milroy C: Allergic *Aspergillus* sinusitis: an overlooked diagnosis? Laryngol Otol 103: 1181-3, 1989.
16. Adam RD, Paquin ML, Peterson EA, et al: Phaeohyphomycosis caused by the fungal genera *Bipolaris* and *Exerohilium*. Medicine (Baltimore) 65: 203-17, 1986.
17. Allphin AL, Strauss M, Abdul-Karim FW: Allergic fungal sinusitis: problems in diagnosis and treatment. Laryngoscope 101: 15-20, 1991.
18. Bent JP, Kuhn FA: Diagnosis of allergic fungal sinusitis. Otolaryngol Head Neck Surg 111: 580-8, 1994.
19. Goldstein MF, Atkins PC, Cogen FC, et al: Allergic *Aspergillus* sinusitis. J Allergy Clin Immunol 76: 515-24. 1985.
20. Gourley DS: Allergic fungal sinusitis. Insights Allergy 4: 1-4, 1989.
21. McMillan RH, Cooper PH, Body BA, Mills AS: Allergic fungal sinusitis due to *Curvularia lunata*. Hum Pathol 18: 960-964, 1987.
22. Torres C, Ro YJ, EL-Naggar AK, Sim SJ, Weber RS, et al Allergic fungal sinusitis: a clinicopathologic study of 16 cases. Hum Pathol 27: 793-799, 1996.
23. Wickern G: Fusarium allergic fungal sinusitis. J Allergy Clin Immunol 92: 624-625, 1993.
24. Sheer L, Shatz G: Allergic fungal sinusitis due to *Chrysosporium* species [Abstract]. Ann Allergy 68: 1183,

1992.
25. Goldstein MF, Drorin DJ, Dunsky EH, et al: Allergic *Rhizomucor* sinusitis. J Allergy Clin Immunol 90: 394-404, 1992.
26. Gourley DS, Whisman BA, Jorgensen NJ, et al: Allergic *Biopolaris* sinusitis: clinical and immunopathologic characteristics. J Allergy Clin Immunol 85: 583-591, 1990.
27. Waxman JE, Spector JG, Sale SR, Katzenstein AA: Allergic *Aspergillus* sinusitis: concepts in diagnosis and treatment of a new clinical entity. Laryngoscope 97: 261-266, 1987.
28. Perez-Jaffe LA, Lanza DC, Loevner LA, Kennedy DW, Montone KT: In situ hybridization for *Aspergillus* and *Penicillium* in allergic fungal sinusits: A rapid means of speciating fungal pathogen in tissue. Laryngoscope 107: 233-240, 1997.
29. Soto-Aguilar MC, deShazo RD, O'Brien M, Chapin K, Gardner L, Swain R: Classification and criteria for the diagnosis of invasive fungal sinusitis [Abstract]. J Invest Med 45: 3A, 1997.
30. Bartynski JM, McCaffrey TV, Frigas E: Allergic fungal sinusitis to dematiaceous fungi *Curvularia lunata* and *Alternaria*. Otolaryngol Head Neck Surgery 103: 32-9, 1990.