

Fungal sinusitis: a spectrum of disease

Connie Ma, BA, Matthew W. Ryan, MD, Bradley F. Marple, MD and Ashleigh A. Halderman, MD

© 2020 ARS-AAOA, LLC.

Key Words:

Allergic Fungal Sinusitis; Chronic Rhinosinusitis; Invasive Fungal Sinusitis

How to Cite this Article:

Ma C, Ryan MW, Marple BF, Halderman AA. Fungal sinusitis: a spectrum of disease? *Int Forum Allergy Rhinol.* 2020;00:00-00.

Fungal rhinosinusitis (FR) describes a diverse group of inflammatory and infectious diseases of the sinuses caused by environmental fungi.¹ The most widely accepted classification scheme broadly categorizes FR into noninvasive and invasive forms based on histopathologic evidence of fungal invasion.² Further categorization into distinct processes based on the host's immune response can be made.

Allergic fungal sinusitis (AFS) is a noninvasive form occurring most commonly in patients with a history of atopy.³ Acute invasive fungal sinusitis (AIFS) is an invasive form with high mortality described almost exclusively in immunocompromised patients. Finally, chronic granulomatous fungal sinusitis (CGIFS), hallmarked by its indolent course and granulomatous immunologic response of the host, is not associated with immune abnormalities.^{4,5}

The distinction between noninvasive and invasive disease is recognized as an important prognostic factor and guides treatment.⁵ Rare cases of conversion or progression from noninvasive AFS to IFS have been reported in the literature and observed at our institution. The purpose of this study was to detail cases of disease conversion/progression to potentially identify patterns in presentation and associated factors.

Patients and methods

This study was approved by the institutional review board of the University of Texas Southwestern Medical Center (UTSW; STU-2019-1652). A retrospective chart review was conducted of patients at UTSW diagnosed initially with AFS who later converted/progressed to IFS. A review of Ovid Embase was also conducted to identify previously reported cases of disease conversion/progression.

A literature search to identify additional cases was performed on February 5, 2020. Information including patient demographics, medical history, symptoms, treatment, imaging, pathology, culture, follow-up, and outcomes was obtained.

Statistical analysis was performed using GraphPad software (GraphPad, San Diego, CA). For continuous data, the Student *t* test was applied. Descriptive statistics were utilized for the remaining data.

Results

Seven patients were included, 4 from UTSW and 3 from the literature.⁶⁻⁸ Demographic and clinical information is presented in Table 1. All patients were male. Five patients were African American (AA) and 2 were Caucasian (CA). Average age at time of disease conversion/progression was 29.7 (range, 21-46) years. The average age at diagnosis for AA patients was significantly younger than CA patients (25.4 vs 40.5 years; $p = 0.0165$; 95% confidence interval, -26.05 to -4.15).

No patients had documented immune compromise or concurrent steroid use at the time diagnosis of invasive sinusitis was made. The only significant coexisting medical diagnoses noted were asthma (43%, 3 of 7) and allergic rhinitis (29%, 2 of 7). Five patients converted from AFS to CGIFS (AFS/CGIFS) and 2 converted from AFS to AIFS (AFS/AIFS). Interestingly, all patients with AFS/CGIFS were AA, whereas both patients with AFS/AIFS were CA. In addition, both patients who developed AIFS did so after surgery. One patient with AFS developed AIFS after surgical repair

Department of Otolaryngology Head and Neck Surgery, University of Texas Southwestern, Dallas, TX

Correspondence to: Ashleigh A. Halderman, MD, Department of Otolaryngology Head and Neck Surgery, University of Texas Southwestern, 2001 Inwood Road, Dallas, TX 75390; e-mail: ashleigh.halderman@utsouthwestern.edu

Potential conflict of interest: None provided.

Presented as a poster at the virtual meeting of the American Rhinologic Society, on September 12, 2020.

View this article online at wileyonlinelibrary.com.

Received: 16 September 2020; Revised: 27 October 2020; Accepted: 28 October 2020

DOI: 10.1002/alr.22736

View this article online at wileyonlinelibrary.com.

TABLE 1. . Case series demographic and clinical data

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7
Institution/study	UTSW	UTSW	UTSW	UTSW	Edelmayer et al ⁷	Walter et al ⁸	Chaaban et al ⁶
Age at diagnosis, years	21	22	31	25	28	35	46
Diagnosis	CGIFS	CGIFS	CGIFS	CGIFS	CGIFS	AIFS	AIFS
Race/sex	AA/M	AA/M	AA/M	AA/M	AA/M	CA/M	CA/M
Geographic region	South-central US	South-central US	South-central US	South-central US	Southeastern US	Midwestern US	Southern US
Medical history	None	Asthma	None	Asthma, AR	Asthma	AR	None
Sinus disease history	AFS	AFS: ESS × 1	Nasal congestion while in Kuwait	AFS: ESS × 1	AFS: ESS × 2	AFS: ESS × 1	AFS: ESS × 3
Presenting symptoms	L proptosis, HA, congestion	R HA, congestion, hyposmia	None (incidental)	R HA, congestion, hyposmia	HA, R eye pressure and facial paresthesia, trismus	HA, dysarthria, UE/LE weakness	Severe L periorbital pain
Fungal culture	<i>Aspergillus flavus</i>	<i>Curvularia</i>	<i>Aspergillus flavus</i>	<i>Fusarium</i>	<i>Curvularia</i>	<i>Aspergillus</i>	<i>Rhizopus</i>
Antifungal treatment	Oral itraconazole, transitioned to oral voriconazole	Oral itraconazole, transitioned to oral posaconazole	Oral itraconazole, transitioned to oral voriconazole	IV amphotericin B, transitioned to oral itraconazole	IV amphotericin B, transitioned to oral voriconazole	IV voriconazole	IV amphotericin B and oral posaconazole, continued on oral posaconazole
Antifungal treatment, total length	2 weeks	10 years ^a with poor adherence	3 months ^a	15 months	9 months ^a	1 week	3 months
Follow-up period	Lost to follow-up	10 years ^a	3 months ^a	20 years ^a	9 months ^a	Deceased	6 months
Outcome	Lost to follow-up; unknown	Slow progression, growth of soft tissue mass in R anterior ethmoid and frontal sinuses resulting in R proptosis; continued follow-up	Resolved symptoms; continued follow-up	Resolved symptoms; continued follow-up	Continued follow-up	Deceased due to MCA stroke	Free of disease at last follow-up

^a Ongoing antifungal treatment or clinic follow-up.

AA = African American; AIFS = acute invasive fungal sinusitis; AR = allergic rhinitis; CA = Caucasian; CGIFS = chronic granulomatous invasive fungal sinusitis; ESS = endoscopic sinus surgery; HA = headache; IV, intravenous; L = left; LE, lower extremity; M = male; MCA = middle cerebral artery; R = right; UE = upper extremity; UTSW = University of Texas Southwestern.

of a traumatic basilar skull fracture, and the other did so in the setting of recent endoscopic sinus surgery for management of newly diagnosed AFS.^{6,8} In contrast, all patients who developed CGIFS followed a more indolent course of conversion without acute precipitating factors and were diagnosed either incidentally or on postoperative pathology.

Overall, *Aspergillus* was the most commonly identified fungus (43%). Patients were treated with an assortment of antifungal agents and the median length of antifungal therapy was 9 months.

Four of the 5 AFS/CGIFS patients were doing well with continued follow-up for disease monitoring/medical management, and 1 was lost to follow-up. One AFS/AIFS patient was free of disease at 6 months, and the other died from the disease.

Discussion

Traditionally, forms of fungal sinusitis have been considered distinct clinical entities. However, growing reports suggest that CGIFS may represent a more advanced form of AFS. Histologic evaluations of tissue from AFS cases has shown evidence of granulomatous inflammation and mucosal invasion in up to 21% of cases.^{9,10} This suggests conversion/progression between AFS and CGIFS may be more common than previously identified.

Interestingly, all patients described in this study who converted from AFS to CGIFS were young AA men. In the United States, AA race and low socioeconomic status have been implicated as risk factors for development of more

severe forms of AFS.⁹ The tendency for young AA men to have more advanced AFS may predispose this population to developing CGIFS.

The 2 patients who developed AIFS were immunocompetent but had trauma or surgical procedures immediately preceding disease development. We hypothesize that disease conversion/progression in these cases could have been secondary to skull-base trauma/injury, resulting in fungal spread through a direct communication between the sinonasal passages and intracranial cavity. This in contrast to AIFS in immunosuppressed individuals where intracranial spread occurs through angioinvasion. This is merely a hypothesis and cannot be proven from the available information.

Although the small sample size prevents the establishment of definitive associations, the observations made from this case series are intriguing and worthy of note. Limitations to the current study include the small sample size and the retrospective and observational nature.

Conversion/progression from noninvasive AFS to IFS is infrequently reported. However, evidence is mounting that patients with AFS may convert/progress to CGIFS more commonly than previously recognized. Although this series is too small to establish definitive associations, it appears skull-base trauma in the setting of AFS may be a risk for the development of AIFS and AA race may be a risk factor for conversion/progression from AFS to CGIFS. Further research is necessary to fully understand the process by which CGIFS arises from AFS and which patients may be at greatest risk.

References

1. Callejas C, Douglas RG. Fungal rhinosinusitis: what every allergist should know. *Clin Exp Allergy*. 2013;43:835-849.
2. Chakrabarti A, Denning DW, Ferguson BJ, et al. Fungal rhinosinusitis: a categorization and definitional schema addressing current controversies. *Laryngoscope*. 2009;119:1809-1818.
3. Schubert MS. Allergic fungal sinusitis: pathophysiology, diagnosis and management. *Med Mycol*. 2009;47(Suppl 1):S324-S330.
4. Thompson GR 3rd, Patterson TF. Fungal disease of the nose and paranasal sinuses. *J Allergy Clin Immunol*. 2012;129:321-6.
5. Singh V. Fungal rhinosinusitis: unravelling the disease spectrum. *J Maxillofac Oral Surg*. 2019;18:164-179.
6. Chaaban MR, Bell W, Woodworth BA. Invasive mucormycosis in an immunocompetent patient with allergic fungal rhinosinusitis. *Otolaryngol Head Neck Surg*. 2013;148:174-175.
7. Edelmayer L, Ito C, Lee WS, Kimbrough J, Kountakis SE, Byrd JK. Conversion to chronic invasive fungal sinusitis from allergic fungal sinusitis in immunocompetence. *Laryngoscope*. 2019;129:2447-2450.
8. Walter E, McKean EL, Camelo-Piragua SI, Parmar HA, Trobe JD. Catastrophic allergic fungal sinusitis: a report of two cases. *J Neuroophthalmol*. 2019 Oct 8. <https://doi.org/10.1097/WNO.0000000000000833> (Online ahead of print).
9. Wise SK, Ghegan MD, Gorham E, Schlosser RJ. Socioeconomic factors in the diagnosis of allergic fungal rhinosinusitis. *Otolaryngol Head Neck Surg*. 2008;138:38-42.
10. Thakar A, Sarkar C, Dhiwakar M, Bahadur S, Dahiya S. Allergic fungal sinusitis: expanding the clinicopathologic spectrum. *Otolaryngol Head Neck Surg*. 2004;130:209-216.