

Chronic invasive fungal sinusitis: characterization and shift in management of a rare disease

Brian D'Anza, MD¹, Janalee Stokken, MD², J. Scott Greene, MD³, Thomas Kennedy, MD³,
Troy D. Woodard, MD¹ and Raj Sindwani, MD¹

Background: Chronic invasive fungal sinusitis (CIFS) is a rare subtype of mycotic diseases involving the paranasal sinuses. It is characterized by a slow onset and invasive organisms with non-granulomatous inflammation seen on histopathology. Historically, treatment has involved radical surgical resection. The purpose of this study was to describe the presentation, comorbidities, and role of more conservative treatment options.

Methods: This is a multi-institutional retrospective case series of 6 patients with CIFS over 15 years. Patients' medical comorbidities, imaging results, operative procedures, pathological findings including organisms identified, antimicrobial medications used, and outcomes were reviewed.

Results: The mean time from onset of symptoms to diagnosis was 6 months. Cultures and fungal PCR identified *Aspergillus* species in every case. All 6 patients were found to have systemic comorbidities, with many being diabetic. Imaging findings ranged from thickening of sinus mucosa to invasion of the orbit and skull base. Treatment included long-term antifungal therapy and conservative endoscopic surgery in all but 1 patient, who had an open approach.

Every patient was free of invasive fungal disease at last follow-up, with a range of 1 to 27 months.

Conclusion: CIFS is an insidious disease often with months between symptom onset and diagnosis. It is differentiated from chronic granulomatous invasive fungal sinusitis (CGIFS) by a lack of granulomas on histopathology and an association with diabetes mellitus. Endoscopic debridement combined with long-term oral voriconazole was an effective treatment strategy in this series. © 2016 ARS-AAOA, LLC.

Key Words:

invasive fungal sinusitis; fungal sinusitis; FESS; medical therapy of chronic rhinosinusitis; paranasal sinus diseases; sinus surgery

How to Cite this Article:

D'Anza B, Stokken J, Greene JS, Kennedy T, Woodard TD, Sindwani R. Chronic invasive fungal sinusitis: characterization and shift in management of a rare disease. *Int Forum Allergy Rhinol.* 2016;XX:1-7.

Throughout much of the 20th century invasive fungal disease was poorly understood. Classification schemes focused on the immune status of the patient rather than pathologic, microbiologic, or epidemiologic factors.^{1,2} It was not until the 1980s that invasive fungal sinusitis

became more widely known as a distinctive clinical entity from the noninvasive forms.²

Chronic invasive fungal sinusitis (CIFS) is part of a spectrum of mycotic diseases involving the nasal cavity and paranasal sinuses. The disease is a relatively rare entity and until recently was not well characterized.^{1,3} Historically, there has been confusion regarding its distinction from chronic granulomatous invasive fungal sinusitis (CGIFS) and even acute invasive fungal sinusitis (AIFS). CIFS is not well represented in the literature with only intermittent case reports and small case series. Nevertheless, several clinical features are frequently reported, which help to differentiate it from other invasive fungal pathologies.

Previously, definition of CIFS was based primarily on the immune status of the patient.^{1,4-6} Recent studies reveal a proclivity for occurrence in patients who are immunocompromised, often suffering from diabetes mellitus or taking corticosteroids long term.¹ This is contrasted with CGIFS, which occurs in healthy and immune competent patients

¹Head and Neck Institute, Cleveland Clinic Foundation, Cleveland, OH;

²Department of Otolaryngology–Head and Neck Surgery, Mayo Clinic, Rochester, MN; ³Department of Otolaryngology–Head and Neck Surgery, Facial Plastic Surgery, Geisinger Medical Center, Danville, PA

Correspondence to: Raj Sindwani, MD, Head and Neck Institute, Cleveland Clinic Foundation, 9500 Euclid Ave, A-71, Cleveland, OH 44195; e-mail: sindwar@ccf.org

Potential conflict of interest: R.S. is a consultant for Meda Pharmaceuticals, Acclarent, and Olympus America, Inc. T.D.W. is a consultant for Acclarent and Medtronic.

Received: 30 March 2016; Revised: 4 June 2016; Accepted: 28 June 2016

DOI: 10.1002/alr.21828

View this article online at wileyonlinelibrary.com.

that are nearly exclusively from North Africa and India.⁷ The same geographic distribution does not hold true with CIFS or AIFS.

Patients with CIFS often undergo a protracted clinical course. The insidious onset can last months before being diagnosed. Most case reports note *Aspergillus fumigatus* as the inciting organism distinctive of CIFS.^{8,9} Meanwhile, *Aspergillus flavus* species and Zygomycetes or Mucoraceae families of fungi are most closely associated with CGIFS and AIFS, respectively.^{8,9} The etiologic fungal species is characteristic and helps to define it from other invasive fungal diseases.

Despite these common clinical findings, in the contemporary literature CIFS is only definitively diagnosed by tissue biopsy samples.¹⁰ Histopathologic evidence of fungal forms in soft tissues of the host in the setting of non-granulomatous inflammation is diagnostic. It is this key finding that recent reports have noted in defining it from the other forms of invasive fungal disease.¹ In contrast, CGIFS is identified by the appearance of non-caseating granulomas in host soft tissues.^{1,11} Meanwhile, AIFS is heralded by a fast-moving necrotizing infection with extensive tissue invasion, infarcted blood vessels, and mycotic aneurysms.¹² There sometimes is a lymphocytic infiltrate, but often there is little to no inflammatory response given the speed at which the disease destroys tissues.

There is minimal discussion in the current literature regarding the treatment of CIFS. Treatment has involved radical surgical resection and intravenous amphotericin B.^{1,8,9,13} The treatment of the disease is often likened to that of AIFS, where in the past open approaches predominated and significant morbidity was expected. The morbidity of medical management via intravenous (IV) amphotericin B was just as substantial, with severe side effects such as nephrotoxicity, encephalopathy and seizures.¹⁴ Only in the last decade have some case reports described utilization of voriconazole in management of invasive forms of fungal disease.¹⁵⁻¹⁸

There is a paucity of literature regarding CIFS and uncertainty still exists regarding the classification despite the themes discussed above. Our understanding of the disease and its ideal management is based largely upon case reports and summary articles, which often lump together CIFS and other invasive fungal infections. The goal of this study was to provide an improved understanding of CIFS by characterizing this rare disease and providing recommendations for management through a multi-institutional analysis of CIFS cases.

Patients and methods

A retrospective analysis was conducted of all patients with the diagnosis of CIFS seen as part of Cleveland Clinic Foundation and Geisinger Health System over a 15-year period (1999 to 2013 inclusive). The initial search included all patients regardless of age with a sinus tissue biopsy revealing invasive fungal organisms and an indolent onset of greater

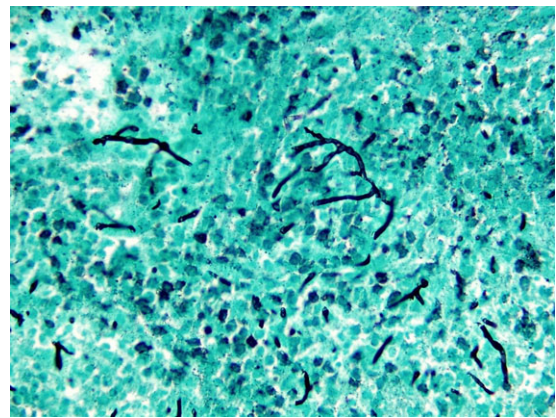


FIGURE 1. GMS stain showing a dense infiltrate of branching hyphae invasive into the surrounding tissues. GMS = Grocott's methenamine silver.

than 2 months. Histopathology was confirmed as consistent with CIFS disease when invasive fungal forms could be seen on Grocott's methenamine silver (GMS) staining. Figure 1 gives a representative pathology slide. All pathology slides were reviewed by a board-certified pathologist with further training and experience specific to head, neck, and sinus pathology. Patients with acute onset disease consistent with AIFS were excluded. A total of 8 patients were initially included in an electronic medical record chart review for the pathologic diagnosis including "invasive fungal sinusitis." We excluded 2 of these patients secondary to the diagnosis of chronic granulomatous invasive fungal disease, defined by the presence of non-caseating granulomas on review of the histopathology details.

Patients' age, gender, geographic residence and recent travel, as well as other epidemiologic characteristics were noted. Please see Table 1 for details. Patients' medical comorbidities, admission details, including diagnostic measures taken, number and manner of tissue biopsies, inpatient and outpatient treatment specifics, and imaging results were recorded. This included reviewing both computed tomography (CT) and magnetic resonance (MRI) images and reports. Additionally, operative procedures and surgical descriptions as well as medications given and the route of administration were noted. Recorded operative images, when available, were reviewed. Histopathological findings including organisms identified, culture results, and antimicrobial medications used including duration and dosing were reviewed. The offending fungal organism was determined by tissue histopathology and tissue culture in all organisms. This was confirmed by polymerase chain reaction (PCR) analysis in 2 patients. Specific attention was paid to outcomes via rates of recurrence and months of postoperative surveillance, and the rate of disease specific survival for patients at last follow-up was verified.

Results

After electronic chart review at the 2 institutions, a total of 6 patients were identified as having presentation and

TABLE 1. Patient demographics and clinical details

Age (years)	Gender	Pathology	Medical comorbidities	Surgical intervention	Disease free at last follow-up, duration (months)
33	M	<i>Aspergillus fumigatus</i>	Hepatitis C, liver cirrhosis	Endoscopic	Yes, 11
25	F	<i>Aspergillus fumigatus</i>	DM II	Endoscopic	Yes, 6
41	M	<i>Aspergillus flavus</i>	DM II	Endoscopic	Yes, 27
25	M	<i>Aspergillus fumigatus</i>	DM II	Lateral rhinotomy	Yes, 6
66	M	<i>Aspergillus fumigatus</i>	s/p Renal transplant	Endoscopic	Yes, 8
77	M	<i>Aspergillus fumigatus</i>	DM II, CHF, CKD	Endoscopic	Yes, 1

CHF = congestive heart failure; CKD = chronic kidney disease; DM II = type 2 diabetes mellitus; s/p = status post.

pathology consistent with CIFS. The mean age was 44.5 years. Demographics are shown in Table 1. The mean time from onset of symptoms to diagnosis was 6 months with a range of 2 to 9 months. The most common presenting symptom was facial pain, found in 5 patients. This was followed by odynophagia and paresthesias, found in 4 patients each.

Aspergillus was the only fungal genus isolated or determined on tissue histopathology, culture, or PCR analysis. The species *Aspergillus fumigatus* was determined to be the cause of CIFS in 83% of cases (5 patients). Please see Table 1 for complete information on each patient.

All patients were found to have systemic comorbidities with 4 of the 6 having type 2 diabetes mellitus. However, none of these diabetic patients' presenting glucose levels were elevated greater than 200, nor were they in diabetic ketoacidosis (DKA) or other hyperglycemic crisis at the time of presentation. Two patients suffered from immune compromised states: 1 patient had previously undiagnosed hepatitis C-induced liver cirrhosis, whereas the other had a kidney transplant for long-standing chronic kidney disease and was taking the requisite immune suppressing agents tacrolimus, mycophenolic acid, and prednisone. This was the only patient taking long-term corticosteroids. Table 1 lists the morbidities for each patient.

Imaging via CT and MRI showed a range of findings. The most common CT findings were a thickening of sinus mucosa and opacification of the sinuses, which was seen in all 6 patients. There was also noted erosion of bony walls of sinuses, and invasion of the orbit and skull base. As expected, MRI was much more sensitive regarding soft tissue and orbital involvement. A hypointense T1 and markedly decreased T2 signal within the orbital soft tissues was seen in 2 patients with concern for extrasinus extension of disease. Other extrasinus involvement was heralded by MRI findings of hypointense T2 signal extending to the pterygopalatine fossa soft tissues. Corresponding CT findings of intraorbital or pterygopalatine fossa involvement were either not present, nonspecific, or not present until much later in the disease course. See Figure 2 for a representative image.

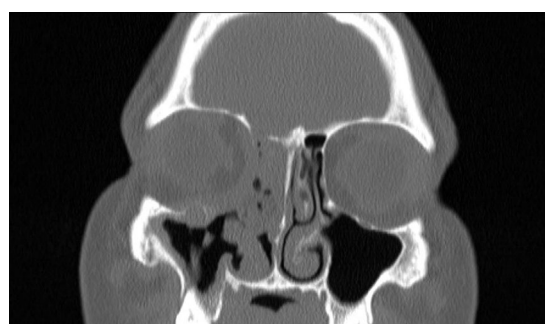


FIGURE 2. Coronal non-contrasted CT showing extensive bony destruction of lamina papyracea and orbit with skull-base erosion. CT = computed tomography.

In every patient, definitive treatment included primary surgical extirpation and long-term postoperative antifungal therapy with oral voriconazole. This is contrasted with prediagnostic empiric treatment that was highly variable. Three patients received no antimicrobials at all, whereas 2 received a 2-week course of either amoxicillin/clavulanate or levofloxacin. This was then followed by a 2-week course of fluconazole in both cases.

All 6 patients had a single definitive surgical procedure. One of the 6 patients had a preprocedure biopsy showing invasive fungal elements. This patient was the only one to have an open procedure via a lateral rhinotomy approach and extirpation of disease from involved sinuses. The procedure was performed open secondary to surgeon preference. The remaining 5 patients all underwent endoscopic endonasal sinus surgery with removal of all disease until healthy bleeding tissue was encountered. The sites of involvement for each patient can be found in Table 2. The septum, maxillary sinuses, and ethmoid sinuses were the most commonly involved sites based on intraoperative findings. In all patients, disease involved at least 3 sinonasal subsites. Bilateral nasal or sinus pathology was seen in 4 patients. In total, none of the 5 patients who underwent an endoscopic approach had disease deemed unresectable and there was no need for converting to an open approach. Additionally, all 5 of these patients had no evidence of

TABLE 2. Treatment details for each patient

Surgical approach	Sites of involvement ^a	Medical treatment	Duration of medical treatment (months)
Endoscopic	Inferior turbinates, septum, middle turbinate, maxillary sinus, nasopharynx, soft palate	Voriconazole 200–300 mg BID PO, weekly levels	6
Endoscopic	Inferior turbinates, septum, maxillary sinuses, nasopharynx, soft palate	Voriconazole PO 200 mg BID	2
Endoscopic	Maxillary, ethmoid, frontal and sphenoid sinuses, septum	Voriconazole 200–300 mg BID PO, weekly levels, amphotericin daily irrigations	12
Lateral rhinotomy	Maxillary, ethmoid, frontal and sphenoid sinuses, septum	Voriconazole PO 200 mg BID	2
Endoscopic	Sphenoid sinus, superior and middle turbinates	Voriconazole 400 mg PO BID × 2 doses, then 300 mg PO BID	1
Endoscopic	Ethmoid and sphenoid sinuses, middle turbinate, medial orbital wall	Voriconazole 200 mg PO BID	1

^aBased on intraoperative endoscopic findings and pathology.
 BID = twice per day; PO = by mouth (per os).

recurrence clinically or radiographically at last follow-up after a single operation.

Voriconazole was the postoperative antifungal medical treatment of choice in all patients. This medication was continued for an average of 4 months postoperatively, however there was a broad range (1 to 12 months) with longer durations of treatment selected for extensive disease (ie, concern for orbital or pterygopalatine fossa involvement). Duration of treatment was guided by consultation with infectious disease specialists in all cases. Dosing was titrated to weekly blood levels, typically consisting of a higher 1-week loading dose followed by a lower regular dose. All maintenance dosing fell within a range of 200 mg to 300 mg given twice daily. See Table 1 for more patient specific dosing and treatment details. In addition to medical treatment, all patients continued postoperative topical nasal saline irrigation for the duration of their follow-up. In 1 patient, this included addition of amphotericin 5 mg/mL, with 1 mL added in 50 mL of sterile saline included in a daily irrigation regimen.

Follow-up times ranged from 1 to 27 months, with an average of nearly 1 year (10 months). One patient died from pneumonia 2 months after presentation. Every patient was free of invasive fungal disease at last follow-up. Disease-specific survival was thus 100%. Table 1 lists the details for each patient.

Discussion

Despite the rarity of CIFS, the data in this study and previous literature highlight several features that help to

differentiate it from the other forms of invasive fungal sinusitis. In 1997, deShazo et al.¹ presented a contemporary classification based on a review of the literature. The scheme divided invasive fungal sinusitis into 3 categories: acute, chronic, or granulomatous. The CIFS subtype was noted to have an association with diabetes mellitus, immunocompromised patients, and a lack of granuloma formation in the tissues. The fungal species involved were nearly exclusively *Aspergillus fumigatus*. This is in contrast to CGIFS characterized by *Aspergillus flavus* species, granuloma formation, and immunocompetent patients.^{12,13} These features are consistent with the findings of our study. Using our data and a review of the literature, we have created a chart that highlights CIFS and compares the 3 forms of invasive fungal sinusitis, which can be confused (see Table 3).^{1–6,11}

AIFS is probably the best well-known invasive fungal infection. It is also the most serious and moves rapidly through tissues. It is the most common of the 3 subtypes, occurring almost exclusively in immunocompromised patients. The treatment of AIFS mirrors its presentation, as aggressive early surgery is recommended. Operative intervention is considered emergent in many cases and extensive tissue resection via multiple procedures is not uncommon. Intravenous amphotericin is often prescribed perioperatively and the patients are typically monitored in the inpatient setting.

In contrast, the treatment of both chronic invasive forms of fungal disease (CIFS and CGIFS) parallel their slow progression. This study highlights the benefits of endoscopic-directed management with limited resection of

TABLE 3. Categorization of invasive fungal sinusitis

Invasive fungal sinusitis type	Common causes	Immune-compromised state	Onset	Associated geographic areas
Acute	Zygomycetes: Mucoraceae family, <i>Aspergillus</i>	Exclusively, typically severe with ANC <1 or glucose >200	Hours to days	None
Chronic	<i>Aspergillus fumigatus</i>	DM II associated; in some cases, typically mild	Months	None
Granulomatous	<i>Aspergillus flavus</i>	No	Months to years	North Africa, Sudan, East Asia

ANC = absolute neutrophil count; DM II = type 2 diabetes mellitus.

surrounding tissues. CIFS is a less aggressive infection and preservation of tissue function should take a higher priority. The favorable postoperative outcomes in our study support this notion.

The initial presentation and onset of CIFS is not well described in the literature. The current study demonstrates a prolonged, insidious onset, as the median duration of symptoms was 6 months. This illustrates an indolent quality of the disease and helps to define it as a separate disease entity from AIFS. This is further supported by the pathology findings showing evidence of chronic inflammation and lacking the extensive thrombosis and mycotic aneurysms indicative of a fast-moving infection such as AIFS. Thus, despite both groups affecting immunocompromised patient populations, CIFS shows clinical evidence of a distinct pathogenesis.

One of the most striking associations born out in this study is that of CIFS with diabetes and immunocompromised patients. All 6 of the patients presented with a comorbid condition fitting into 1 of these categories. As well, two-thirds of the patients' had type 2 diabetes, which is consistent with previous reports.¹ This is an important association as it helps identify a likely risk factor for CIFS. Unfortunately, the nature of this relationship is unclear. Diabetics have been known to be more susceptible to infection; however, this is classically thought of in relation to uncontrolled blood glucose levels or ketoacidotic states that create a milieu for bacteria or fungi to proliferate.^{19,20} Hyperglycemia of ≥ 11.1 mmol/L (≥ 200 mg/dL) has been closely associated with reduced neutrophil activity.²¹ None of the 4 diabetic patients in this study had evidence of such condition on presentation. This does not rule out the possibility of longer-term intermittent hyperglycemia, as glycosylated hemoglobin A1c (HbA1c) levels were not collected from these patients at presentation. Further study in this area is needed.

Only one of the 6 patients in the study was taking corticosteroids long-term for therapeutic purposes secondary to kidney transplant status. Prior reports have described prevalent corticosteroid use in series with CIFS.¹ Our study did not appear to have the same proportion. Part of the

reason may be because the population largely consisted of diabetic patients, which is a relative contraindication to corticosteroid use.

Aspergillus fumigatus has been implicated as the primary pathologic fungus in prior studies involving CIFS.^{1,22,23} This study would seem to confirm this notion, as all patients but 1 had the organism positively identified in tissue biopsy cultures or PCR analysis of tissue organisms.

Two studies report their experience with a larger population of CIFS patients. Pagella et al.²⁴ describe a retrospective case series with acute and chronic invasive fungal infections. They note 8 patients with CIFS. Diagnosis is based only on length of presentation and there was no discussion regarding detailed pathology results. They identified Mucormycosis as the offending organism in the majority of cases (5), something that is not supported in our study or most of the literature.^{1-3,6,7} As well, in 4 cases there was less than a month between diagnostic and definitive procedure. These factors raise the question of whether there may be some spectrum of AIFS included in the samples.

Li et al.²⁵ reported a large sample of 28 CIFS patients that does include detailed histopathology results, including fungal hyphae within the sinus mucosa in all cases. They were able to speciate 16 cases based on histopathology, with 12 identified as *Aspergillus*. Interestingly, they report medical comorbidities in only 7 patients, with 4 of these being hypertension and only 2 having diabetes. We believe assessing the viability of the host's immune system is central to differentiating between invasive and noninvasive fungal rhinosinusitis. This is important because literature shows there can be evidence of mucosal fungal invasion in certain aggressive sinus fungal balls.²⁶⁻²⁸ As well, the study reported involvement isolated to the maxillary sinus in 50% of cases. We did not find this to be the case in our study, as the nasal cavity and ethmoids were often involved as well. Most of the literature does not specify a sinus predilection in CIFS, making the findings of this study challenging to interpret.^{1-3,6,7,22,23,29}

Surgical removal of the disease was effective with a single endoscopic procedure in all but 1 case. In the past, the gold standard for treatment of invasive fungal disease had

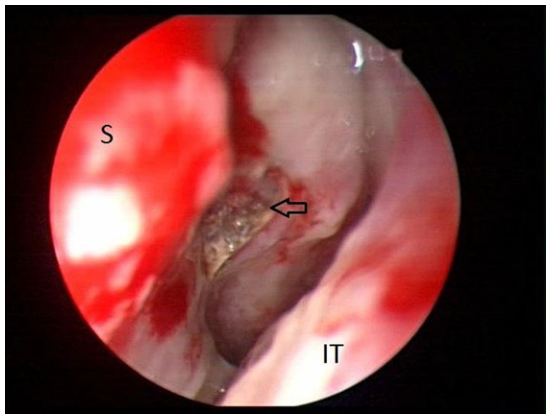


FIGURE 3. Endoscopic transnasal view of the left inferior turbinate and septum. Note the pale mucosa with an area of necrosis and ulceration along the septum designated by the arrow. IT = inferior turbinate; S = septum.

been aggressive open debridement and radical resection of all surrounding tissue. Contemporary reports of surgical management in all of the forms of invasive fungal sinusitis show a major trend toward endoscopic approaches.⁸ Endoscopy affords a better illuminated and more magnified view to give an excellent impression of the involvement, or lack thereof, in suspected tissues. Please see Figure 3 for a representative image.

The current study presents an area for discussion on the importance of MRI findings and how it relates to the extent of disease during surgical treatment. Two of our patients were noted to have evidence of intraorbital extension on MRI. Clinically, neither of these patients had visual problems, cranial neuropathies, or other evidence of orbital involvement. Meanwhile, intraoperative findings using endoscopy revealed no obvious gross disease within the areas of concern on the corresponding MRIs, namely the pterygopalatine fossa, orbit, or orbital apex. Previous reports have noted frequent orbital invasion in CIFS based on imaging findings and the subsequent removal of such tissues.^{1,22,29} In our series, conservative endoscopic resection was guided by intraoperative findings until bleeding tissue was encountered and not necessarily extended based solely on MRI findings. We believe, for CIFS, an initial conservative surgical approach sparing vital structures and preserving function (of intraorbital structures, cranial nerves, etc.) is preferred unless there is gross invasion noted intraoperatively. The lack of disease recurrence or persistence in our series (0%) supports this more conservative approach. It is our contention that although CIFS is an invasive and potentially fatal illness, complete removal of all microscopic disease may not be necessary for successful treatment when combined with long-term antifungal therapy.

Several CIFS cases noted in the literature were treated with long-term (IV) amphotericin as are many cases of AIFS.² A prior case report of a patient with CGIFS also noted a good response to long-term oral voriconazole therapy.¹¹ This medication has excellent coverage of *Aspergillus* species and penetration in the nose, sinuses,

and cerebrospinal fluid (CSF). This treatment paradigm appears to have equivalent or improved rates of cure and minimal morbidity when compared to previous treatment regimens involving more toxic antifungals. Most notably, the approach avoids the systemic toxicities associated with amphotericin use and allows for oral administration. This obviates the need for invasive procedures to place central intravenous catheters with their attendant complications and cost implications. Our approach of conservative surgical removal of disease followed by long-term oral voriconazole therapy resulted in excellent outcomes and a complete cure in all patients, and should be considered in patients diagnosed with this rare condition.

The implications of this study should be interpreted with caution. If one is faced with a situation in the operating room where invasive fungal organisms are noted on frozen section, the first thought should be to AIFS and not CIFS—simply based on the rarity of this condition. The clinical picture is of foremost importance. A prolonged time course of months and a less immunocompromised patient (eg, diabetic) may speak to CIFS. Meanwhile, a patient with severe neutropenia or a severe immunodeficiency (eg, acquired immune deficiency syndrome [AIDS]) and a shorter duration should make one think of AIFS. Regardless, if the clinical picture or imaging has any concern for AIFS we suggest treating the patient as such, with aggressive repeated debridements until either convincing pathology or a proper history reveals otherwise.

The limitations of this study are inherent in the rarity of the disease process being studied. Although 1 of the largest in the literature, the study is still small, with only 6 patients. The retrospective nature and lack of randomization or a control group are also shortcomings that limit the strength of our findings. As well, although the multi-institution pooling of data allows for a larger number of patients, there may be differences in the methods of treatment that are provider- and center-dependent, including the extent of surgery and duration of antimicrobial medication administration, for example. Nonetheless, this study does provide meaningful data on the distinctive characteristics of this disease process and suggestions for alternative, less aggressive treatment strategies.

This study is 1 of the largest series of CIFS patients reported in the literature to report detailed histopathology results and significant comorbidities, while describing long-term outcomes at a mean follow-up of nearly 1 year. All 6 of the patients were free of disease at last follow-up, resulting in a disease-specific survival of 100%. The fact that none of the 6 patients recurred or suffered significant morbidity related to the disease or treatment is a testament to the benefits of conservative initial management as well as the indolent pathology. These findings and the growing literature on this topic suggest that unlike other forms of invasive fungal infections, CIFS can be effectively managed with conservative endoscopic resection followed by long-term oral antifungal therapy. Further investigation into the host (especially immune function), organism, and

disease-related factors that differentiate CIFS from other entities in the spectrum of invasive fungal sinusitis is warranted.

Conclusion

CIFS is a rare and distinct subtype along the spectrum of invasive fungal sinusitis. It presents with a protracted

disease course, lack of granulomas on histopathology, and a tendency to affect patients with diabetes mellitus. In most cases, the fungal species involved was *Aspergillus fumigatus*. Conservative endoscopic surgical resection combined with long-term oral antifungal therapy appears to be an effective treatment strategy in these patients. ④

References

- deShazo RD, Chapin K, Soto-Aguilar M, et al. A new classification and diagnostic criteria for invasive fungal sinusitis. *Arch Otolaryngol Head Neck Surg*. 1997;123:1181–1188.
- Washburn RG, Kennedy DW, Begley MG, et al. Chronic fungal sinusitis in apparently normal hosts. *Medicine (Baltimore)*. 1988;67:231–247.
- Corey JP, Romberger CF, Shaw GY. Fungal diseases of the sinuses. *Otolaryngol Head Neck Surg*. 1990;103:1012–1015.
- Brandwein M. Histopathology of sinonasal fungal disease. *Otolaryngol Clin North Am*. 1993;26:949–981.
- Jahrsdoerfer RA, Ejecito VS, Johns ME, et al. Aspergillosis of the nose and paranasal sinuses. *Am J Otolaryngol*. 1979;1:6–14.
- Chakrabarti A, Sharma SC, Chander J. Epidemiology and pathogenesis of paranasal sinus mycoses. *Otolaryngol Head Neck Surg*. 1992;107:745–750.
- Chakrabarti A, Denning DW, Ferguson BJ, et al. Fungal rhinosinusitis: a categorization and definitional schema addressing current controversies. *Laryngoscope*. 2009;119:1809–1818.
- Parikh SL, Venkatraman G, Delgado JM. Invasive fungal sinusitis: a 15 year review from a single institution. *Am J Rhinol*. 2004;18:75–81.
- Kim TH, Jang HU, Jung YY, Kim JS. Granulomatous invasive fungal rhinosinusitis extending into the pterygopalatine fossa and orbital floor: a case report. *Med Mycol Case Rep*. 2012;1:107–111.
- Challa S, Pamidi U, Uppin SG, et al. Diagnostic accuracy of morphologic identification of filamentous fungi in paraffin embedded tissue sections: correlation of histological and culture diagnosis. *Indian J Pathol Microbiol*. 2014;57:583–587.
- Halderman A, Shrestha R, Sindwani R. Chronic granulomatous invasive fungal sinusitis: an evolving approach to management. *Int Forum Allergy Rhinol*. 2014;4:280–283.
- Hurst RW, Judkins A, Bolger W, et al. Mycotic aneurysm and cerebral infarction resulting from fungal sinusitis: imaging and pathologic correlation. *AJNR Am J Neuroradiol*. 2001;22:858–863.
- Cummings, Flint PW, Haughey BH, et al. Chapter 48: Fungal rhinosinusitis. In: Flint PW, Haughey BH, Lund VJ, et al, eds. *Cummings Otolaryngology Head and Neck Surgery*. Philadelphia: Mosby Elsevier; 2010:709–716.
- Prentice HG, Hann IM, Herbrecht R, et al. A randomized comparison of liposomal versus conventional amphotericin B for the treatment of pyrexia of unknown origin in neutropenic patients. *Br J Haematol*. 1997;98:711–718.
- Nakaya K, Oshima T, Kudo T, et al. New treatment for invasive fungal sinusitis: three cases of chronic invasive fungal sinusitis treated with surgery and voriconazole. *Auris Nasus Larynx*. 2010;37:244–249.
- Baumann A, Zimmerli S, Hausler R, Caversaccio M. Invasive sphenoidal aspergillosis: successful treatment with sphenoidotomy and voriconazole. *ORL J Otorhinolaryngol Relat Spec*. 2007;69:121–126.
- Morgand M, Rammaert B, Poirée S, et al. Chronic invasive *Aspergillus* sinusitis and otitis with meningeal extension successfully treated with voriconazole. *Antimicrob Agents Chemother*. 2015;59:7857–7861.
- Herbrecht R, Denning DW, Patterson TF, et al. Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. *N Engl J Med*. 2002;347:408–415.
- Petrikkos G, Skiada A, Lortholary O, et al. Oral epidemiology and clinical manifestations of mucormycosis. *Clin Infect Dis*. 2012;54:S23–S34.
- Vijayabala GS, Rajeshwari G, Annigeri, Sudarshan R. Mucormycosis in a diabetic ketoacidosis patient. *Asian Pac J Trop Biomed*. 2013;3:830–833.
- Kawahito S, Kitahata H, Oshita S. Problems associated with glucose toxicity: role of hyperglycemia-induced oxidative stress. *World J Gastroenterol*. 2009;15:4137–4142.
- Stringer SP, Ryan MW. Chronic invasive fungal rhinosinusitis. *Otolaryngol Clin North Am*. 2000;33:375–387.
- Aribandi M, McCoy VA, Bazan C. Imaging features of invasive and noninvasive fungal sinusitis: a review. *Radiographics*. 2007;27:1283–1296.
- Pagella F, De Bernardi F, Dalla Gasperina D, et al. Invasive fungal rhinosinusitis in adult patients: our experience in diagnosis and management. *J Craniomaxillofac Surg*. 2016;44:512–520.
- Li Y, Li Y, Li P, et al. Diagnosis and endoscopic surgery of chronic invasive fungal rhinosinusitis. *Am J Rhinol Allergy*. 2009;23:622–625.
- Robey AB, O'Brien EK, Richardson BE, et al. The changing face of paranasal sinus fungus balls. *Ann Otol Rhinol Laryngol*. 2009;118:500–505.
- Bowman J, Panizza B, Gandhi M. Sphenoid sinus fungal balls. *Ann Otol Rhinol Laryngol*. 2007;116:514–519.
- Soler ZM, Schlosser RJ. The role of fungi in diseases of the nose and sinuses. *Am J Rhinol Allergy*. 2012;26:351–358.
- deShazo RD, Chapin K, Swain RE. Fungal sinusitis. *N Engl J Med*. 1997;337:254–259.