

A multi-institutional review of outcomes in biopsy-proven chronic invasive fungal sinusitis

Ian M. Humphreys, DO¹ , Grace M. Wandell, MD, MS¹, Craig Miller, MD¹ , Aakanksha Rathor, MD², Rodney A. Schmidt, MD, PhD³, Justin H. Turner, MD, PhD⁴, Peter H. Hwang, MD² and Greg E. Davis, MD, MPH¹

Background: Chronic invasive fungal sinusitis (CIFS) is a rare, life-threatening infection of the nose and sinuses. This study aims to identify factors that impact survival in 1 of the largest cohorts to date.

Methods: Pathology records were reviewed for biopsy-proven CIFS from 3 tertiary academic institutions from 1995 to 2016. Variables were analyzed using log-rank survival analysis. Univariate Cox regression was performed at 1 and 12 months.

Results: Thirty-eight patients were included. Hematologic malignancy and diabetes were the most common underlying diseases (32% each). *Aspergillus* was the most common fungus (63%). Greater than 75% of the patients had an absolute neutrophil count (ANC) >1000 at the time of diagnosis. Overall survival at 1, 6, and 12 months was 89%, 68%, and 48%, respectively. In univariate analysis, factors associated with worse survival included: ANC <500 at 12 months (hazard ratio [HR] 4.8; $p = 0.01$), ANC <1000 at 12 months (HR 5.8; $p = 0.001$), and recent chemotherapy (HR 4; $p = 0.01$). The following factor was associated with improved

survival in univariate analysis: ANC as a linear variable in the entire cohort (HR 0.7; $p = 0.005$).

Conclusion: We present a multi-institutional case-series of CIFS and long-term follow-up. ANC <1000 at time of diagnosis and recent chemotherapy (within 1 month of diagnosis) are associated with poorer survival, whereas a rising ANC >1000 is associated with improved survival at 12 months. Further prospective studies are needed to further define factors that affect outcomes. © 2020 ARS-AAOA, LLC.

Key Words:

invasive fungal sinusitis; paranasal sinus disease; fungal sinusitis; sinusitis; chronic disease

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Chronic invasive fungal sinusitis (CIFS) is a rare infection that typically occurs in immunocompromised patients, but has a more indolent clinical course than its counterpart acute invasive fungal sinusitis (AIFS).¹⁻⁴ Similar to AIFS, in CIFS, fungi invade the mucosa of the nasal cavity or paranasal sinuses and can result in necrosis through

angioinvasion. Importantly, CIFS also differs from chronic granulomatous invasive fungal sinusitis (CGIFS) in that there are no granulomas seen on histopathology. Further, most cases of CGIFS have been described in immunocompetent patients from the Sudan, Pakistan, and India, whereas this geographic bias has not been seen in CIFS.^{2,5} However, as compared to AIFS in particular, the clinical outcomes of CIFS have been less well described.

The clinical picture of CIFS includes subtle clues of a sinus condition including complaints of nasal congestion and pain in an immunocompromised host. Historically, the most commonly reported form of immunocompromise has been poorly controlled diabetes.^{1-3,6-9} Often symptoms can be present for months before clinical deterioration (eg, fevers in immunocompromised host, worsening pain, etc.) leads to further inquiry such as referral to otolaryngology, imaging, or even hospitalization. Typically, surgical exploration occurs and pathologic specimens reveal the presence of mucosal invasion by fungal elements, with or

¹Department of Otolaryngology, University of Washington, Seattle, WA; ²Department of Otolaryngology, Stanford University, Stanford, CA; ³Department of Pathology, University of Washington, Seattle, WA; ⁴Department of Otolaryngology, Vanderbilt University, Nashville, TN

Correspondence to: Ian M. Humphreys, DO, University of Washington, Box 356515, Health Sciences Building, Suite BB1165, Seattle, WA 98195-6515; e-mail: ihumphre@uw.edu

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without angioinvasion and necrosis. The most common organism isolated has been consistently reported as *Aspergillus* species.^{1-3,6}

Previously, treatments have included external approaches with wide debridement and removal of all involved tissues, at times including the globe and orbit. However, currently, most reports have described less disruptive and function sparing endoscopic sinus surgery.^{2,3} Antifungal therapy has evolved from exclusively intravenous amphotericin to other systemic oral antifungals such as posaconazole, voriconazole, and most recently isavuconazonium. Additionally, combination therapy with antifungals as well as antifungal prophylactic therapy has become increasingly common. Most patients with CIFS receive a combination of both surgical and medical therapies.^{2,3,6,7}

Currently there is no standardized diagnostic or therapeutic pathway for CIFS. No clinical practice guideline or consensus statement exists. There is limited literature available for CIFS, of which mostly includes case reports and case series with a limited number of patients.^{2,3,6,8-12} The aim of this study was to further characterize both patient and treatment factors that affect outcomes in a multi-institutional review of CIFS from 3 tertiary academic institutions.

Patients and methods

Patient selection

This study queried CIFS cases between 1995 and 2017 from the Departments of Otolaryngology–Head and Neck Surgery at the University of Washington Medical Center, Stanford University Medical Center, and Vanderbilt University Medical Center. After institutional review board approvals were obtained, head and neck pathology records were searched for “fungus” and “hyphae.” Then, pathology reports were carefully, individually examined to confirm patients with fungal invasion of the paranasal sinus respiratory mucosa on permanent pathology. Inclusion required CIFS diagnosis, defined as period of symptom onset unto tissue diagnosis of >30 days. Additional criteria were age >18 years, histologically confirmed tissue diagnosis of CIFS, and adequate records for chart review. Radiographic data of preexisting fungal ball or allergic fungal sinusitis changes were not collected.

Data collection

The following variables were collected: demographics, presenting signs and symptoms, radiographic and endoscopic findings at the time of diagnosis, laboratory/microbiologic data, procedures performed, medical treatments (eg, immune-stimulating therapies [ISTs], antifungal therapies, etc.), and survival outcomes. Laboratory data collected included glycosylated hemoglobin A1c (HbA1c) and recent (<1 week) absolute neutrophil count (ANC). Data on patients who had recent chemotherapy (<1 month) or bone marrow transplant (BMT, <3 months) were also

collected. Orbital involvement was defined as radiologic evidence of postseptal cellulitis or intraorbital extension. Time of symptom onset was defined as sinus or nasal specific symptoms (eg, pain, congestion, pressure, etc.) occurring before pathologic diagnosis. Time of diagnosis was defined as the date of pathologic diagnosis. Survival follow-up was collected through the electronic medical record. When death records were not available, death dates were searched for and obtained from Family Search (Salt Lake City, UT; <https://www.familysearch.org/en/>).

Statistical analysis

Data were analyzed using Stata 15.1 (StataCorp, College Station, TX). The primary outcomes were survival at 1 and 12 months. These endpoints were chosen because we wanted to capture the survival risk closer to and further away from the time of diagnosis as this is a chronic disease. A *p* value of <0.05 was considered significant. Univariate survival analysis was performed using Cox regression and Kaplan-Meier curves.

Results

Study population

A total of 154 patients were identified with invasive fungal sinusitis. A total of 114 patients with AIFS were excluded and previously reported. Forty patients remained, of which 38 had complete medical records available for review. The characteristics of the population are given in Table 1. Of the patients, 47% were male with a mean age of 52 years. Facial pain (including nasal pain), nasal congestion, and facial swelling were the most common symptoms at presentation (Fig. 1). The median duration from symptom onset until time of tissue diagnosis was 82 days (mean, 157 days).

Survival data

Most patients (~92%) had follow-up data after discharge. Overall survival at 1, 6, and 12 months was 89%, 68%, and 48%, respectively. There were 17 deaths at 6 months (45% death rate) and 25 at 12 months (66% death rate).

Underlying disease

The most common immunocompromise risk factors were hematologic malignancy and diabetes (Table 2), which had an equal distribution (12/38 each). Of the 12 individuals with a hematologic malignancy, chronic lymphocytic leukemia (CLL) (*n* = 5) and acute myelogenous leukemia (AML) (*n* = 3) were most common. Other underlying causes of disease included immunosuppressive medications (*n* = 9), chronic kidney disease, human immunodeficiency virus (HIV), and primary immunodeficiency. Two individuals did not have any underlying disease or immunosuppression identified. In univariate analysis, the underlying disease did not have a statistically significant relationship with survivorship (Table 3).

TABLE 1. Study population characteristics

Characteristic	Categorical variables n (%)	Continuous variables mean (range)
Study population	38 (100)	
Patient age (years)		52 (5–83)
Male	18 (47)	
Underlying disease ^a		
Hematologic malignancy (HM)	12 (32)	
Diabetes mellitus (DM)	12 (32)	
Immunosuppressive meds (IM)	7 (18)	
Other diseases (OD) ^b	8 (21)	
No underlying disease (NUD)	2 (5)	
Other risk factors		
Recent chemotherapy ^c	7 (18)	
Recent BMT ^d	2 (5)	
Organism ^a		
<i>Aspergillus</i>	22 (63)	
<i>Mucor/Rhizopus</i>	7 (20)	
Atypical organisms ^e	8 (21)	
Mixed infection	7 (18)	
None isolated or not available ^f	5 (14)	
Extension ^a		
Orbit	7 (18)	
Cavernous sinus	12 (32)	
Intracranial	5 (13)	
Pterygopalatine fossa/masticator space	7 (18)	
Laboratory values		
HbA1c (%) ^g		6.9 (5–9)
ANC (10 ³ /μL)		4 (0–13)
ANC <500 10 ³ /μL	6 (17)	
ANC <1000 10 ³ /μL	9 (25)	
Treatment		
IV antifungals	34 (90)	
Surgery	33 (87)	
ISTs	3 (8)	
Intervals (days)		
Symptom onset to diagnosis		157 (30–799)
Symptom onset to ENT evaluation		109 (10–402)
Symptom onset to IV antifungals		277 (12–5134)
Days symptom onset to surgery		147 (13–65)

(Continues)

TABLE 1. (Continued)

Characteristic	Categorical variables n (%)	Continuous variables mean (range)
Survival ^b		
Survived 1 month	31/35 (89)	
Survived 6 months	21/31 (68)	
Survived 1 year	13/27 (48)	

^aPercentages were calculated by cases in total population with data available.

^bOD included patients with conditions included SIADH, HIV/AIDS, chronic kidney disease, genetic immunodeficiency, heart disease, and disseminated fungal infection.

^cRecent defined as chemotherapy within 1 month from CIFS diagnosis.

^dRecently defined as BMT within 3 months of CIFS diagnosis.

^eAtypical organisms included *Cunninghamella*, *Pseudallescheria*, *Candida*, *Fusarium*, *Scedosporium*, *Penicillium*, *Curvularia*.

^fThree patients did not have microbiological data available for review.

^gHbA1c was only available for 13 patients, 5 of which were diabetic.

^hSurvival data available for calculation indicated in denominators.

AIDS = acquired immune deficiency syndrome; ANC = absolute neutrophil count; BMT = bone marrow transplant; CIFS = chronic invasive fungal sinusitis; ENT = ear, nose, throat; HbA1c = glycosylated hemoglobin A1c; HIV = human immunodeficiency virus; IST = immune-stimulating therapy; IV = intravenous; OD = other diseases; SIADH = syndrome of inappropriate antidiuretic hormone hypersecretion

Recent chemotherapy

Recent chemotherapy was defined as receiving these treatments within 1 month of diagnosis of CIFS. Of the patients, 18% (7/38) had received recent chemotherapy. In univariate analysis, *recent* chemotherapy was associated with a trend toward worse survival at 1 month (hazard ratio [HR] 4.9; 95% confidence interval [CI], 0.7 to 34.6; $p = 0.1$; Table 3) and significantly worse survival at 12 months (HR 4.0; 95% CI, 1.3 to 12.2; $p = 0.01$; Table 3).

Fungal species

Tissue culture and/or polymerase chain reaction (PCR) data were available for 87% of patients. Infection with *Aspergillus* was most common (Tables 1 and 2) occurring in 22 of 38 (63%) of patients. Twenty-one percent of patients (8/38) were infected with atypical organisms including *Cunninghamella*, *Pseudallescheria*, *Candida*, *Fusarium*, *Scedosporium*, *Penicillium*, and *Curvularia*. Eighteen

percent (7/38) were infected with *Mucor/Rhizopus* species. In univariate analysis, the species of fungus did not affect survivorship at either 1 or 12 months. There was a trend toward worse 1-month survival with atypical fungal organisms (HR 4.5; 95% CI, 0.6 to 31.8; $p = 0.1$); however, this did not reach statistical significance.

Disease extension

Extension outside of the sinuses was most common into the cavernous sinus, occurring in 32% of patients, whereas extension to either the orbit (18%) or pterygopalatine fossa (18%) was less common. Although there were trends showing extrasinus extension equated with poorer prognosis, these were not statistically significant (Table 3). On univariate analysis there was worse survival at 12 months with orbital extension nearing statistical significance (HR 2.8; 95% CI, 0.9 to 8.3; $p = 0.07$) (Table 3).

ANC in all patients

ANC data were available for 95% (36/38) of the cohort. Seventy-five percent (27/36) had an ANC >1000 at the time of diagnosis, of which 26% (7/27) were diabetic and 30% (8/27) had a hematologic malignancy (Table 2). Both ANC <500 and <1000 were associated with worse survival at 12 months (Table 3); however, only 3 patients separated these groups. There was a significant linear association between ANC and survival (Table 3), with increasing ANC counts improving survival at 12 months (HR 0.7; 95% CI, 0.5 to 0.9; $p = 0.005$). When only analyzing patients with hematologic malignancy (excluding diabetics) this association was also significant (HR 0.6; 95% CI, 0.4 to 1.0; $p = 0.05$). In univariate analysis both an ANC <500 and <1000 were significant predictors of worse survival at 12 months (Table 3). In the entire cohort an ANC <1000 resulted in >5 times worse survival at 12 months (HR 5.8; 95% CI, 1.8 to 18.6; $p = 0.001$; Fig. 2). When excluding

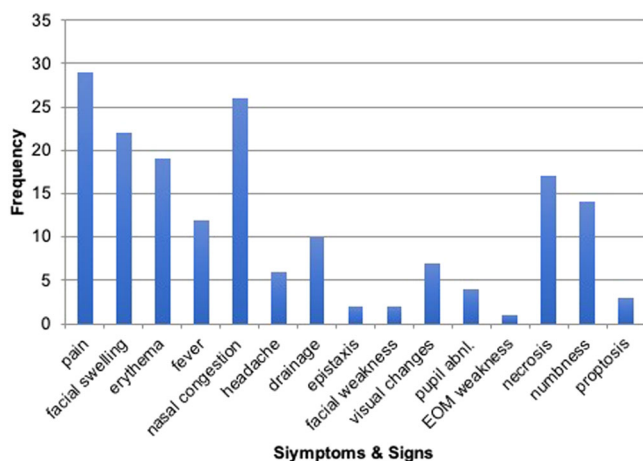


FIGURE 1. Symptoms and signs at presentation with chronic invasive fungal sinusitis. EOM = extraocular muscle.

TABLE 2. Disease characteristics, treatments, and outcomes by underlying disease*

Underlying disease ^a	HM	DM	IM	OD/NUD
Study population, n (%)	12 (32)	12 (32)	7 (24)	8 (21)
Other risk factors, n (%)				
Recent chemotherapy ^b	5 (43)	1 (8)	1 (14)	0 (0)
Recent BMT ^c	2 (17)	0 (0)	0 (0)	0 (0)
Organism, n (%)				
<i>Aspergillus</i>	7 (58)	6 (50)	3 (43)	7 (70)
<i>Mucor/Rhizopus</i>	3 (25)	2 (17)	0 (0)	2 (20)
Multiple organisms	2 (17)	1 (8)	0 (0)	4 (40)
Atypical organisms ^d	2 (17)	1 (8)	2 (29)	3 (30)
None isolated	2 (17)	4 (33)	2 (29)	1 (10)
Extension, n (%)				
Orbit	2 (17)	4 (33)	1 (14)	1 (10)
Cavernous sinus	4 (33)	4 (33)	0 (0)	5 (50)
Intracranial	2 (17)	3 (25)	0 (0)	0 (0)
Pterygopalatine fossa/masticator space	3 (25)	3 (25)	1 (14)	0 (0)
Laboratory values				
ANC (10 ³ /μL), mean (range)	3.4 (0.02–9.3)	3.4 (0.1–7.7)	5.5 (4.4–6.8)	4.0 (0–13.2)
ANC <500 10 ³ /μL, n (%)	3 (25)	2 (17)	0 (0)	1 (10)
ANC <1000 10 ³ /μL, n (%)	4 (33)	4 (33)	1 (29)	1 (10)
Treatment				
IV antifungals, n (%)	11 (92)	12 (100)	6 (86)	9 (80)
Surgery, n (%)	11 (92)	10 (83)	7 (100)	8 (80)
Days IV antifungals, mean (range)	90 (12–279)	527 (42–5134)	39 (43–146)	180 (39–518)
Days to surgery, mean (range)	83 (13–283)	193 (31–652)	142 (39–289)	181 (43–402)
ISTs, n (%)	2 (17)	1 (0)	0 (0)	1 (10)
Survival, n (%) ^e				
Survived 1 month	9/11 (82)	10/11 (91)	5/6 (83)	9/10 (90)
Survived 6 months	5/11 (45)	7/9 (78)	3/5 (60)	8/9 (89)
Survived 1 year	5/11 (45)	2/7 (29)	2/5 (40)	5/7 (71)

*Percentages determined from underlying disease.

^aRefer to results section or Table 1 for a list of underlying diseases.^bRecent chemotherapy means chemotherapy received within 1 month of CIFS diagnosis.^cRecent BMT means patient underwent BMT within 3 months of diagnosis with CIFS.^dRefer to Table 1 footnotes or Results section for a list of atypical organisms.^eSurvival data available for calculation indicated in denominators.

ANC = absolute neutrophil count; BMT = bone marrow transplant; DM = diabetes mellitus; HM = hematologic malignancy; IM = immunosuppressive medication; IST = immune-stimulating therapy; IV = intravenous; OD/NUD = other diseases and no underlying disease identified.

diabetic patients, an ANC <500 and <1000 resulted in a >6 times and >10 times worse survival at 12 months respectively (HR 6.4; 95% CI, 1.4 to 29.6; $p = 0.018$ and HR 10.4; 95% CI, 2.2 to 49.4; $p = 0.003$, respectively; Table 3).

Surgery, antifungals, and IST

Surgery was common with 87% undergoing surgical treatment (Table 1). Most patients were treated with intravenous antifungals (90%) and a small subset (8%) received ISTs. The sample size and homogeneity of the treatments

TABLE 3. Univariate prognostic factors in CIFS using Cox survival analysis

Factor	1 Month		12 Months	
	HR (95% CI)	<i>p</i>	HR (95% CI)	<i>p</i>
Underlying disease				
HM	2.3 (0.3–16.1)	0.4	2.11 (0.7–6.1)	0.2
DM	0.7 (0.1–7.0)	0.8	1.3 (0.4–3.9)	0.7
IM	1.4 (0.2–13.4)	0.8	1.3 (0.4–4.5)	0.7
Other/no underlying disease	1.2 (0.1–11.8)	0.9	0.5 (0.1–2.1)	0.3
Demographics				
Age	1.00 (1.0–1.1)	0.9	1.0 (1.0–1.0)	0.6
Male	1.2 (0.2–9.0)	0.8	1.2 (0.4–3.5)	0.7
Risk factors				
Recent chemotherapy	4.9 (0.7–34.6)	0.1	4.0 (1.3–12.2)	0.014
Recent BMT	6.5 (0.7–63)	0.1	1.6 (0.2–12.1)	0.7
Organism				
<i>Aspergillus</i>	0.2 (0.03–2.3)	0.2	0.7 (0.3–2.1)	0.5
<i>Mucor/Rhizopus</i>	1.4 (0.2–13.4)	0.8	1.7 (0.5–5.5)	0.4
Multiple organisms	1.5 (0.2–14.1)	0.7	1.3 (0.4–4.6)	0.7
Atypical organisms	4.5 (0.6–31.8)	0.1	2.1 (0.7–6.9)	0.2
None isolated	1.1 (0.1–10.8)	1.0	0.5 (0.1–2.3)	0.4
Extension				
Orbit	4.4 (0.6–31.2)	0.1	2.8 (0.9–8.3)	0.1
Cavernous sinus	0.7 (0.1–6.8)	0.8	0.9 (0.3–2.7)	0.9
Intracranial	^c		1.1 (0.3–5.0)	0.9
Pterygopalatine fossa/masticator space	1.6 (0.2–15)	0.7	1.4 (0.4–5.1)	0.6
Laboratory values				
ANC 10 ³ /μL (DM excluded) ^a	0.4 (0.1–1.3)	0.1	0.6 (0.4–0.9)	0.011
ANC <500 10 ¹ /μL (DM excluded) ^b	2.8 (0.3–30.9)	0.4	6.4 (1.4–29.6)	0.018
ANC <1000 10 ¹ /μL (DM excluded) ^b	8.3 (0.8–92.2)	0.1	10.4 (2.2–49.4)	0.003
Treatments				
IV antifungals	^c		0.6 (0.1–4.6)	0.6
Surgery	^c		^c	
Days to IV antifungal	1.0 (1.0–1.0)	0.9	1.0 (1.0–1.0)	0.049
Days to surgery	1.0 (1.0–1.0)	1.0	1.0 (1.0–1.0)	0.7

^aANC represented as a linear variable and includes all patients except those with diabetes.^bANC represented as a categorical variable and includes all patients except those with diabetes.^cUnable to calculate due to low number of events or co-linearity of variables.

ANC = absolute neutrophil count; BMT = bone marrow transplant; CI = confidence interval; CIFS = chronic invasive fungal sinusitis; DM = diabetes mellitus; HM = hematologic malignancy, HR = hazard ratio; IM = immunosuppressive medication; IV = intravenous.

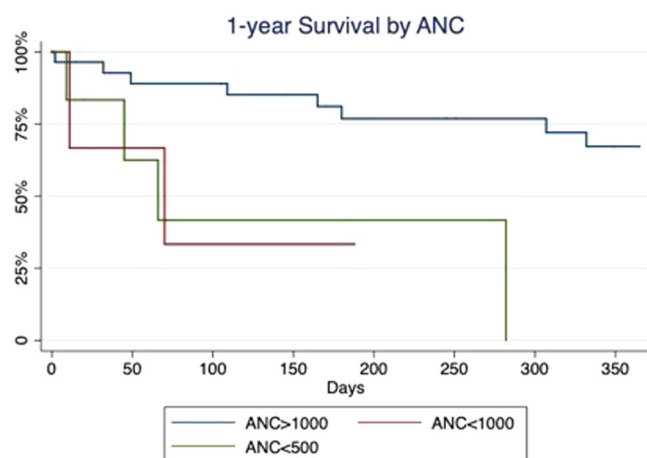


FIGURE 2. Kaplan-Meier curve of 1-year survival based on ANC in the entire cohort. ANC = absolute neutrophil count.

received in this population precluded survival analysis for these variables.

Discussion

The first reported case of CIFS was published in 1980 by McGill et al.¹¹ Subsequent investigations have since provided additional insight into CIFS as a distinct disease entity, but also characterized invasive fungal infections of the nose and sinuses more broadly.^{2,3,6,10} Specifically, in 1997, deShazo et al.¹³ proposed a new classification system including acute, chronic, and chronic granulomatous variants. It has been proposed that requirements for diagnosis include objective evidence of paranasal sinus inflammation as well as histopathologic evidence of fungal organisms within the mucosa, submucosa, blood vessels, or bone.^{1,2,7,13,14} Most studies do not require angioinvasion per se, but rather *tissue* invasion of fungus within the mucosa or submucosa (Fig. 3).^{2,3,6,15} Interestingly, necrosis has not been proposed as a diagnostic requirement because it is often a late finding in the setting of angioinvasion. Lastly,

an immunocompromised state is not required given prior case reports of invasive fungal sinusitis (IFS) in otherwise immune-competent hosts.¹⁶

Of the 3 entities AIFS is certainly the most well described, and CGIFS seems to be geographically isolated to the Sudan, Pakistan, and India.^{2,5,6} Numerous studies have described AIFS as that with an aggressive disease process and poor survivorship.¹⁷⁻²² Conversely, CIFS is less commonly described, has a seemingly indolent clinical course, and is without a known geographic pattern.^{1-3,6} Most patients are diagnosed in the fourth to fifth decade and there does not appear to be a sex predilection. In a multi-institutional study of 6 patients, D'Anza et al.² showed that CIFS was a slowly progressive disease with long symptom-to-diagnosis intervals. In 2009 a categorization and definitional scheme was proposed by Chakrabarti et al.¹ They defined CIFS as having 3 months of symptoms prior to diagnosis. Likewise, in a study of CIFS by Pagella et al.,³ inclusion criteria included symptoms for at least 3 months duration; however, in the most recent study published by D'Anza et al.,² 2 months was used. In our study we chose to include patients with at least 1 month of symptoms prior to diagnosis. Our decision to choose 1 month was based on a growing body of evidence that AIFS presents with a narrow symptom-to-diagnosis window, with most patients being diagnosed within 14 days of symptom onset; therefore, >30 days of symptoms would be unlikely to mischaracterize a patient as having AIFS. We felt that given the stakes involved in this condition, narrowing the diagnostic timeline and perhaps raising suspicion sooner would influence future studies and recommendations as well as potentially improve patient care. Lastly, in prior reports of CIFS by Stringer et al.⁷ and Li et al.,⁶ a symptom duration >30 days was used as inclusion criteria and therefore served as precedent for our study.

Interestingly, regardless of the methodologic inclusion criteria used, most studies report similar symptom to diagnosis time frames of 3 months or greater.^{2,3,7} In the study by D'Anza et al.,² the mean time from onset of symptoms to presentation was 6 months, whereas in ours we

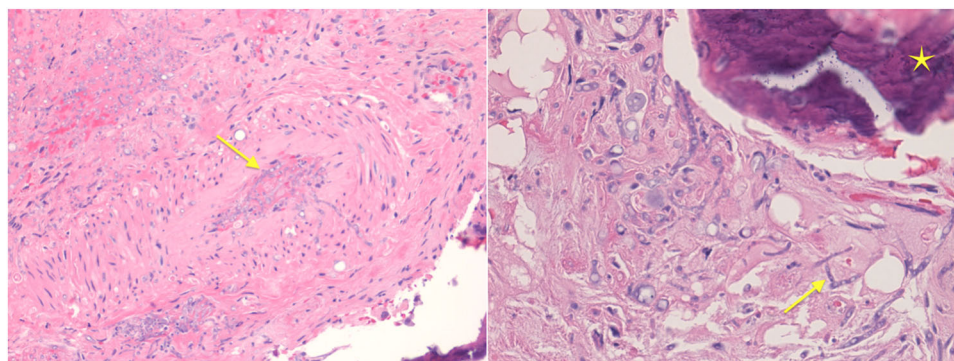


FIGURE 3. Histologic features of invasive fungal sinusitis demonstrating difference between angioinvasion and submucosal invasion without angioinvasion. (Left) H&E stain showing angioinvasion (arrow) by *Fusarium* in acute invasive fungal sinusitis. (Right) H&E stain showing submucosal invasion without angioinvasion (arrow) by *Fusarium* in chronic invasive fungal sinusitis. Note bone in top right corner (star) and connective tissue with extensive *Fusarium* invasion throughout. H&E = hematoxylin and eosin.

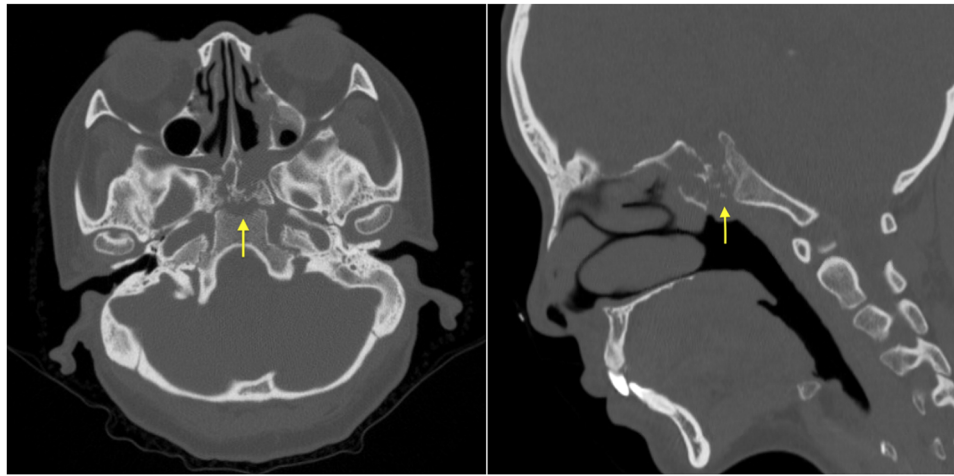


FIGURE 4. Noncontrast computed tomography images of patient with biopsy proven *Aspergillus fumigatus* CIFS. (Left) Axial view demonstrates bony destructive process through the sphenoid sinus and clivus (arrow). (Right) Sagittal view of same patient showing extension of bone destruction to floor of the sella turcica and within the clivus (arrow). CIFS = chronic invasive fungal sinusitis.

observed 5 months. These findings corroborate prior reports of a slow, indolent process and a clinical presentation that mirrors, at least initially, a low index of suspicion for the disease. Additionally, imaging findings can be nonspecific; however, radiographic changes such as bone erosion should raise concern for the diagnosis (Fig. 4). Therefore, it seems this is a diagnostic challenge for clinicians between common and probable entities (eg, viral rhinitis/sinusitis) from those of a more serious nature such as CIFS. Further, the differentiation between AIFS and CIFS is somewhat arbitrary given the use of symptom-based criteria alone and lack of objective measures to define when the disease process started. It is possible that AIFS and CIFS are the same disease process within a continuum of degrees of immune dysfunction.

Prior reports of CIFS have suggested that diabetes is more commonly implicated. In the study by D'Anza et al.,² 4 of 6 patients had diabetes and none had an underlying hematologic malignancy. Likewise, in the study by Pagella et al.,³ 7 of 8 patients had poorly controlled diabetes as the identified underlying disease. However, our study shows equal proportions of patients with CIFS who have hematologic malignancy or diabetes (12/38 each). On further examination, however, univariate analysis did not reveal a statistically significant difference in survivorship between either group. Our data suggest a trend of poorer survivorship with hematologic malignancy, and the converse with diabetes, but again this did not reach statistical significance and needs further inquiry. Furthermore, we were unable to assess for disease-specific survival and report only overall survival. However, we did identify that recent chemotherapy (<1 month from time of diagnosis) was associated with a significant 5-fold increased risk of death at 12 months. Whether this increased risk of death is specific to CIFS disease or more related to their underlying oncologic diagnosis and consequent treatment is unknown, and is a limitation of this investigation.

In both hematologic malignancy and diabetes, 1 of the most commonly proposed pathophysiologic mechanisms has been either quantitative or functional derangement in neutrophils. Classically, numerous reports have described an ANC <500 as being both a risk for development of IFS, in as much as a prognosticating and disease clearance target once diagnosed. Unfortunately, prior reports of CIFS do not provide data regarding ANC other than anecdotal evidence that it is <500. However, in this study we report, for the first time to our knowledge, that greater than 75% of patients (29/38) had an ANC >1000 at the time of diagnosis. Importantly, 8 patients were diabetic (28%), which could have resulted in a result bias (Table 3). In univariate analysis there was a statistically significant improvement in survivorship with ANC as a continuous variable, whereas with both ANC <500 and <1000 there was 5-fold to 6-fold increased risk of death. When excluding diabetic patients, similar findings were observed and an ANC <500 and <1000 resulted in a 6 times and 10 times increased risk of death at 12 months, respectively (Table 3). These findings challenge conventions held with ANC <500 as the sine qua non of any form of IFS, let alone CIFS. Future studies are needed to further define trends in ANC and perhaps ranges of risk. Alternatively, perhaps other cells of interest should be studied, such as CD4+ T cells, which seem to drive innate effector cells such as macrophages and neutrophils. Further, in our diabetic patients we observed a mean HbA1c of 6.9% (range, 5-9%), which questions the role of diabetes as an independent risk factor for CIFS.

The intersection of host immune derangement and fungal organisms is at the center of IFS. Generally, several fungal organisms have been implicated in CIFS, with *Aspergillus fumigatus* and *Mucor spp.* being most commonly reported. In the study by Li et al.,⁶ 57% (16/28) had *Aspergillus fumigatus* and 18% were infected with *Mucor spp.* Likewise, in the study by D'Anza et al.,² all

6 patients were infected with *Aspergillus fumigatus*, except 1 with *Aspergillus flavus*. Similar to others, our data showed *Aspergillus fumigatus* occurring in 63% of the patients involved and *Mucor spp.* in 20%. In this study, on univariate analysis we did not find any statistically significant associations with fungal species and outcomes. However, there was a trend toward worse survival with atypical fungal organisms and we suspect, based on our AIFS experience as well as that published in case reports, that fungal species may influence outcomes. Future investigations are needed to better clarify this observation.

Treatments for CIFS have overall been similar to that of AIFS: surgical debridement and antifungal therapy. Whereas surgical debridement in AIFS is often extensive, at times multiple, emergent, and can combine both open and endoscopic approaches; that in CIFS tends to be more targeted and less disruptive. In the published reports available nearly all patients had an endoscopic debridement procedure that was targeted to the affected tissues and rarely is an open procedure currently used. These findings are consistent with our cohort, in that 87% of patients had surgery, and all were endoscopic procedures. Nearly all of our patients (90%) received IV antifungals, with amphotericin B being most common. Most patients were subsequently switched to oral antifungals (eg, voriconazole, posaconazole, etc.) for at least several weeks to months depending on their immune function and at the discretion of infectious disease colleagues. However, the limited sample size of our study makes generalizable conclusions and statistical analyses difficult.

This study has several important limitations worth noting. This was a retrospective study with the inherent limitations in data available for collection and review. Additionally, given data collection from 3 separate institutions there could be the potential for differences in data reporting or interpretation at each participating institution. Further, there was no control group and the studied patient population was heterogeneous in their underlying disease, fungal organisms, as well as type and duration of antifungal therapy. These factors limit the strength and generalizability of our data. However, our study does

meaningfully contribute to the body of evidence surrounding this rare disease.

We present, to our knowledge, the largest multi-institutional series of 38 CIFS patients with biopsy-proven disease and microbiological data for review. A detailed analysis of both patient, disease, and treatment factors were undertaken and we were able to assess long-term outcomes. Our study is consistent with previous reports and further expands upon the growing body of knowledge in this poorly understood entity. These data suggest that CIFS is a disease distinctly different in clinical behavior to AIFS; however, future prospective investigations that specifically study host immunity and fungal pathogenicity are needed to better characterize these observations.

Conclusion

CIFS is a rare but seemingly distinct clinical phenotype of invasive fungal sinusitis with an insidious symptomatology and often a 3-month or longer delay until diagnosis. Although diabetes seems to predominate as the underlying risk factor, our data show that hematologic malignancy is implicated as well. Further, most patients in our series had an HbA1C within the normal range. Traditional conventions of ANC <500 being a key risk factor need to be reconsidered because >75% of our CIFS patients had an ANC >1000 at the time of diagnosis. However, ANC continues to be a prognostic factor, because patients with ANC >1000 had a significantly increased chance of survival. Similar to prior reports, *Aspergillus* is the most common organism. Endoscopic sinus surgery and systemic antifungals are important treatments and should be considered in every case. Future prospective studies are needed to further characterize these factors as well as investigate methods of earlier detection and standardize treatments. 4

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