

Invasive Fungal Carotiditis: A Rare Manifestation of Cranial Invasive Fungal Disease: Case Series and Systematic Review of the Literature

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Background. Rhinosinusitis, malignant otitis externa, and skull base osteomyelitis represent a spectrum of cranial invasive fungal disease (IFD). These syndromes have distinct characteristics, yet they may progress to involve similar structures, resulting in inflammation and invasion of the adjacent internal carotid artery (ICA). Invasive fungal carotiditis can have devastating consequences, including cerebral infarction, subarachnoid hemorrhage, and death.

Methods. We retrospectively studied all patients diagnosed with cranial IFD and carotid involvement at our institution from 2003 to 2018. We also searched Medline/PubMed for reports of *Aspergillus* or *Mucorales* cranial infections with ICA involvement. All cases with mycologic evidence of cranial IFD and radiographic or pathologic evidence of ICA involvement were included.

Results. We identified 78 cases of invasive fungal carotiditis between 1958 and 2018, including 4 cases at our own institution. Forty-one were caused by *Aspergillus* and 37 by *Mucorales* species. Presenting symptoms included vision changes (73%), cranial nerve palsy (69%), and headache (42%). Carotid events included occlusion, aneurysm formation, and vessel rupture. Cerebral infarcts occurred in 50% of cases. Mortality at 6 weeks, 12 weeks, and 2 years was 27%, 41%, and 71% respectively. The median time from symptom onset to death was 150 days for cases due to *Aspergillus* and 51 days for cases due to *Mucorales* species.

Conclusions. Invasive fungal carotiditis is a rare but morbid manifestation of cranial IFD. Early suspicion of IFD and administration of antifungal treatment, vascular imaging, and endovascular interventions should be considered to reduce the high mortality of this disease.

Keywords. aspergillosis; carotid artery; invasive fungal disease; mucormycosis.

Acute and subacute invasive rhinosinusitis, sino-orbital infection, malignant otitis externa (MOE), and skull base osteomyelitis (SBO) represent a spectrum of presentations of cranial invasive fungal disease (IFD) [1–6]. Although each of these syndromes exhibits distinct clinical characteristics, they all may progress to involve similar anatomical structures including the skull base and cavernous sinus (CS) [1, 7–9]. IFD of the skull base or CS results in fatal vascular complications through inflammation or invasion of the adjacent internal carotid artery (ICA), leading to intraarterial thrombosis, aneurysm formation, or rupture [10–13]. Invasive fungal carotiditis can have devastating consequences, including cerebral infarction, subarachnoid hemorrhage (SAH), and death. Despite these associations,

vascular complications are infrequently considered or screened for in patients diagnosed with cranial IFD.

The incidence of IFD, including invasive aspergillosis (IA) and invasive mucormycosis (IM), continues to rise despite the development of novel antifungal agents for treatment and prophylaxis [14–18]. Presentations of cranial IFD are usually nonspecific, making a prompt clinical and microbiological diagnosis challenging [6, 19–21]. With a growing population of immunosuppressed patients, and the high mortality rate of IFD, it is imperative to better understand the diverse clinical presentations of these invasive mycoses [14–16, 18, 22].

We present 4 cases of invasive fungal carotiditis originating from the external auditory canal or paranasal sinuses, with eventual involvement of the ICA. To further characterize this clinical syndrome, we performed a systematic review of the literature and identified an additional 74 cases, suggesting that vascular and specifically carotid complications should be considered in patients presenting with cranial IFD.

METHODS

Case Series

We conducted a retrospective study of all patients diagnosed with carotid involvement related to direct extension of IFD at

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Brigham and Women's Hospital from January 2003 to October 2018. Local databases were reviewed, and all patients diagnosed with proven or probable IFD per the European Organization for Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG) [23] were eligible for analysis. Patients were followed until January 2019 to ascertain outcomes. The study was approved by the Hospital's Office for Human Research Studies.

We collected data including demographics, medical comorbidities, clinical presentation, physical exam findings, radiographic findings, and diagnostic evaluation including laboratory values at presentation, (1→3)-β-D-glucan (BG), galactomannan (GM). Microbiological and histopathological findings were documented. Surgical intervention, antifungal therapy, disease complications, survival time from initial symptoms, and all-cause mortality were also recorded.

Systematic Review

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed [24]. We searched the Medline/PubMed database from January 1958 to December 2018 for reports of *Aspergillus* or *Mucorales* infection with related occlusion, rupture, or aneurysm of the ICA. Cases before 1958 were omitted given the lack of antifungal therapy available before the approval of amphotericin B [25, 26]. The search terms combined text words, including *Aspergillus* OR aspergillosis, *Mucorales* OR mucor OR mucormycosis, AND stroke, carotid, aneurysm, sinus OR sinusitis, orbital apex, skull base, malignant otitis externa. The search strategy for PubMed is listed in [Supplementary Figure 1](#). The searches were limited to human studies published in or translated to English. Additional studies were identified by reviewing references cited in relevant articles.

All cases of proven or probable IFD caused by *Aspergillus* or *Mucorales* species in patients aged ≥12 years with involvement of the sphenoid, ethmoid, or maxillary sinus, orbit, cavernous sinus, external auditory canal, clivus, temporal bone, or mastoid bone were considered [24]. Cases with ICA occlusion, thrombosis, aneurysm formation, rupture, mycologic evidence of cranial infection (sino-orbital, sino-nasal, skull base, carotid), and radiographic evidence of contiguous infection were included. Cases with localized sinus disease were classified as sino-nasal, those with involvement of the sinus and orbit were classified as sino-orbital, and cases with involvement of the external auditory canal and temporal bone or skull base were classified as ototemporal. Patients with IFD and vascular complications secondary to hematogenous dissemination or surgical or traumatic inoculation were excluded. Cases with unclear origin of infection or unspecified treatment and outcome were excluded. Full-text articles were reviewed, and clinical information was extracted. Study quality was not assessed, as most manuscripts described single case reports.

Potential reports were screened for inclusion, first by title and abstract, and then assessed for eligibility and quality by full-text review. Data extraction was performed with a standardized data extraction tool, and a standardized protocol was followed. Patient characteristics extracted included age, gender, medical comorbidities, presenting symptoms, origin of infection, areas of involvement within the skull base, carotid involvement, empiric steroid therapy, infectious complications, fungal species diagnosed, antifungal therapy, surgical interventions, and death. For patients who received >1 antifungal agent, the primary treatment regimen was determined to be the primary antifungal that was administered for >1 month after diagnosis of cranial IFD.

We compared baseline characteristics using the Fisher exact test or Wilcoxon test according to the nature of the covariate. The primary outcome was median survival time from onset of symptoms. We generated survival curves using the Kaplan-Meier method. Statistical analysis was performed using JMP 14.0 (SAS Institute Inc, Cary, NC). The secondary outcome was to describe the presentation and clinical evolution of patients with invasive fungal carotiditis.

RESULTS

Case Series

We identified 4 cases of invasive fungal carotiditis at our institution from 2003 to 2018. Characteristics of the cases are summarized in [Table 1](#). IFD risk factors included diabetes mellitus (DM; n = 3), glucocorticoid use (n = 3), and hematologic malignancy (HM; n = 2). All cases were caused by *Aspergillus* species. Two cases were ototemporal, 1 was sino-orbital, and 1 was sino-nasal in origin. All patients were treated with antifungals with activity against *Aspergillus* species, with initial improvement in symptoms, imaging, or decrease in BG and GM serum values. All patients subsequently presented with occlusion or aneurysm of the ICA and cerebral infarcts. Relevant imaging findings for each patient are presented in [Figure 1](#). Three patients died within 1 year of diagnosis, whereas 1 patient remained alive at last follow-up after left superficial temporal artery to middle cerebral artery bypass and long-term antifungal therapy.

Systematic Review

Demographics and Comorbidities

We identified 74 additional cases of invasive fungal carotiditis between January 1958 and December 2018. This review focused on localized cranial IFD; cases of IFD secondary to hematogenous dissemination were excluded. Forty-one cases were caused by *Aspergillus* and 37 by *Mucorales* species. Patient demographics and comorbidities are presented in [Table 2](#). Among cases, patients with IM were younger overall compared with patients with IA (IM median age, 47 years; IA median age, 70 years). The most common comorbidities were DM (58%), HM (12%), and chronic kidney disease (CKD; 10%).

Table 1. Cases of Invasive Fungal Carotiditis at Brigham and Women's Hospital, 2003–2018

Characteristic	Patient 1	Patient 2	Patient 3	Patient 4
Age, sex	66 y, male	79 y, male	66 y, male	77 y, female
Comorbidities	Follicular NHL treated with fludarabine; paraneoplastic pemphigus requiring alemtuzumab and IVIG	CLL treated with rituximab and alemtuzumab in remission; type II DM	Renal transplantation on tacrolimus, azathioprine; type II DM	End-stage renal disease; type II DM
Presenting symptoms	Headache, CN III/VI palsy	Headache, left vision loss, peri-orbital pain, CN III palsy	Headache, facial pain, otalgia, left ear drainage	Headache, facial pain, otalgia, left ear drainage
Diagnostic imaging	MRI/MRA with right parietal stroke, sphenoid and maxillary sinus disease, occlusion of right ICA	CT face with mass extending from left sphenoid sinus to orbit with dehiscence between the orbital apex and left sphenoid sinus	CT face with soft tissue density extending from left EAC to mastoid with narrowing of left ICA	CT face with opacification of left EAC and mastoid air cells with bony erosion of sphenoid sinus and narrowing of left ICA
Peak serum BG and GM index	BG >500 pg/mL ^a GM 0.26 index	BG 337 pg/mL GM 0.31 index	BG >500 pg/mL GM 1.23 index	BG 329 pg/mL GM 1.51 index
Origin	Sino-nasal	Sino-orbital	Ototemporal	Ototemporal
Diagnostic criteria	Proven: biopsy with positive pathology and culture	Proven: biopsy with positive pathology and IHC	Probable: positive BG and GM, positive clinical criteria	Proven: biopsy with positive pathology and culture
Histopathology	Right sphenoid sinus biopsy with hyphal forms	Left orbital biopsy with hyphal forms and positive <i>Aspergillus</i> immuno-stain	Left nasopharyngeal, skull base, sphenoid biopsies negative	Left mastoid and posterior ear canal with hyphal forms
Microbiology	Right sphenoid sinus culture with <i>Aspergillus fumigatus</i>	Left orbital cultures negative	Otic, skull base, clival, sinus cultures negative	Left posterior mastoid culture with <i>Aspergillus flavus</i>
Antifungal treatment, d	Isavuconazole, 104; Voriconazole, 19	Amphotericin, 16 Isavuconazole, 43	Voriconazole, 294 Recrudescence → Voriconazole, 998	Isavuconazole, 37
Surgical intervention	Sinus debridement	Orbitotomy	STA-MCA bypass	Tympano-mastoidectomy, left ICA embolization
ICA involvement	Right ICA occlusion	Left ICA occlusion	Left ICA occlusion	Left ICA ruptured aneurysm
Complications	Cerebral infarct, SAH, basilar mycotic aneurysm	Cerebral infarct, intracranial empyema	Cerebral infarct	Cerebral infarct, ruptured mycotic aneurysm
Death	Y	Y	N	Y
Time to death, ^b d	210	120	1823, alive as of 1/1/2019	150

Abbreviations: BG, (1→3)- β -D-glucan; CLL, chronic lymphocytic leukemia; CN, cranial nerve; CT, computed tomography; DM, diabetes mellitus; EAC, external auditory canal; GM, galactomannan; ICA, internal carotid artery; IHC, immunohistochemistry; IVIG, intravenous immunoglobulin; MCA, middle cerebral artery; MRI/MRA, magnetic resonance imaging/angiography; NHL, non-Hodgkin's lymphoma; SAH, subarachnoid hemorrhage; STA, superficial temporal artery.

^aAttributed to intravenous immunoglobulin at the time.

^bFrom symptom onset.

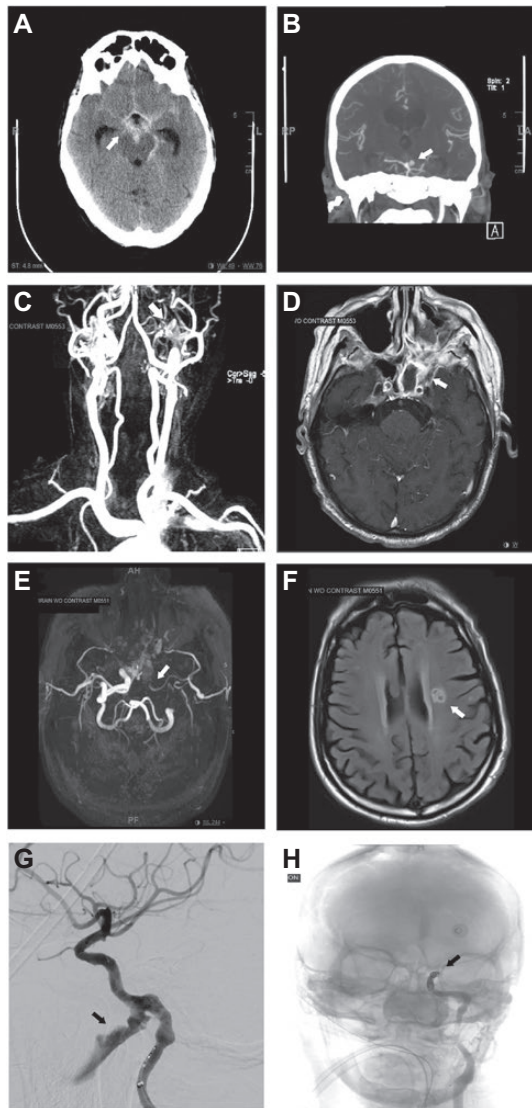


Figure 1. A and B, Patient 1 developed invasive fungal carotiditis of sino-nasal origin. He received antifungal treatment and experienced clinical improvement. He was readmitted 4 months later with acute-onset headache and syncope and was found to have diffuse subarachnoid hemorrhage (A) and basilar summit mycotic aneurysm (B). C and D, Patient 2 presented with occlusion of the left internal carotid artery (ICA) (C) and invasive fungal carotiditis of sino-orbital origin (D). The patient was treated with isavuconazole and experienced clinical improvement. He was readmitted 2 months later with acute loss of consciousness and was found to have cerebral infarcts and cranial fossa empyema. E and F, Patient 3 developed invasive fungal carotiditis of ototemporal origin complicated by occlusion of the left ICA (E) and ipsilateral cerebral infarcts (F). The patient improved with voriconazole treatment and underwent superficial temporal artery to middle cerebral artery bypass. G and H, Patient 4 developed invasive fungal carotiditis of ototemporal origin. The patient was treated with isavuconazole and experienced clinical improvement. She was readmitted one month later with acute-onset epistaxis and was found to have ruptured left ICA mycotic aneurysm (G). Despite vessel sacrifice (H), she subsequently died.

Few patients (4%) had undergone allogeneic hematopoietic cell transplantation (HCT). Sixteen patients (21%) had no apparent risk factors for cranial IFD that were identified. Fifty-one patients (65%) had 1 risk factor for IFD, and 11 (14%) had

multiple risk factors. Diabetes was the most frequent individual risk factor for IFD (44%). Patients with cases due to IM were more likely to have DM as a primary risk factor (62% vs 27%; $P = .003$), and patients with cases due to IA were more likely to have no identifiable risk factors (32% vs 8%; $P = .02$).

Clinical Features

The most common presenting symptoms were changes in vision including diplopia or vision loss (IA 73%, IM 73%), cranial nerve palsy (IA 66%, IM 73%), headache (IA 51%, IM 32%), and facial or periorbital pain (IA 37%, IM 35%) (Table 2). Patients with mucormycosis frequently had periorbital edema or proptosis (59% vs 22%; $P = .001$). Other presenting symptoms included retro-orbital pain, otalgia or otorrhea, epistaxis, and rhinorrhea or sino-nasal symptoms.

Disease Manifestations

The close proximity of anatomical structures in the sinuses and skull base as well as limitations to radiologic diagnosis make the categorization of subtypes of cranial IFD challenging. In this review, cases were divided into sino-nasal, sino-orbital, and ototemporal modes of extension to the ICA. Cases of sino-nasal origin or sino-orbital origin most commonly progress from the paranasal sinuses to involve the cavernous sinus or via the sphenoid to invade the skull base. Cases of ototemporal origin typically progress via the external auditory canal to involve the skull base via the temporal bone. Sino-nasal and sino-orbital modes of extension comprised 41% and 54% of cases, respectively. Only 4 patients developed invasive fungal carotiditis of ototemporal origin. Though almost all cases displayed involvement of the sinuses, only 14% of patients noted sino-nasal symptoms or rhinorrhea on presentation.

Diagnosis and Microbiology

Seventy-four cases were diagnosed as proven IFD by histopathology [23]. Four cases caused by *Aspergillus* species were diagnosed as probable IFD by host factors, clinical features, and mycological evidence (positive GM n = 2, nonsterile sinus culture n = 2). Seventeen patients (41%) with invasive fungal carotiditis secondary to IA were empirically treated with systemic glucocorticoids before obtaining diagnosis, and 13 (32%) were diagnosed postmortem. Six patients (16%) with IM were treated with empiric glucocorticoids, and 8 (22%) were diagnosed postmortem. Patients were misdiagnosed with giant cell arteritis, optic neuritis, inflammatory pseudotumor (IgG4 disease), and other inflammatory syndromes.

Microbiologic data are presented in Table 3. The species isolated by culture included *Aspergillus fumigatus*, *Aspergillus flavus*, *Aspergillus niger*, *Rhizopus microsporus*, and *Rhizopus arrhizus*. In 8 cases, *Rhizopus* was identified by

Table 2. Clinical Characteristics and Risk factors for Invasive Fungal Carotiditis

Clinical Presentation	<i>Aspergillus</i> sp. (n = 41)	<i>Mucorales</i> (n = 37)	Total (n = 78)	P
Demographics				
Median age [range, IQR], y	70 [15–83, 52–77]	47 [15–80, 35–61]	60 [15–83, 44–73]	<.001
Male sex, No. (%)	27 (66)	21 (57)	48 (62)	.554
Comorbidities, No. (%)^a				
Diabetes mellitus	16 (39)	29 (78)	45 (58)	.001
Hematologic malignancy	5 (12)	4 (11)	9 (12)	.999
Chronic kidney disease	3 (7)	5 (13)	8 (10)	.598
Autoimmune disease	5 (12)	2 (5)	7 (9)	.521
Solid organ transplant ^b	5 (12)	0	5 (6)	.071
Other immunodeficiency ^c	1 (2)	3 (8)	4 (5)	.539
Hematopoietic cell transplantation	1 (2)	2 (5)	3 (4)	.922
Solid organ malignancy	1 (2)	1 (3)	2 (3)	.999
No comorbidities identified	12 (24)	3 (8)	15 (19)	.034
Presenting symptoms, No. (%)				
Vision change	30 (73)	27 (73)	57 (73)	.999
Ptosis or cranial nerve palsy	27 (66)	27 (73)	54 (69)	.665
Headache	21 (51)	12 (32)	33 (42)	.147
Facial or periorbital edema	9 (22)	22 (59)	31 (40)	.001
Facial or periorbital pain	15 (37)	13 (35)	28 (36)	.999
Nasal or sinus symptoms	2 (5)	10 (27)	12 (15)	.015
Retro-orbital pain	5 (12)	3 (8)	8 (10)	.831
Epistaxis	3 (7)	4 (11)	7 (9)	.884
Otalgia or otorrhea	5 (12)	1 (3)	6 (8)	.251
Mode of extension, No. (%)				
Sino-nasal	17 (41)	15 (40)	32 (41)	.999
Sino-orbital	20 (49)	22 (60)	42 (54)	.474
Ototemporal	4 (10)	0	4 (5)	.142

Abbreviation: IQR, interquartile range.

^aOf note, patients had multiple concomitant comorbidities; percent values will not add to 100. Twenty-one percent of patients had no risk factors for invasive fungal disease (IFD); 65% had 1 risk factor for IFD, and 14% had >1 risk factor for IFD.

^bOn glucocorticoid therapy.

^cIncluding hypogammaglobulinemia, pancytopenia, and glucocorticoid therapy.

culture without identification to the species level performed. In 1 case, *Rhizomucor* was identified by culture, and in 1 case *Rhizomucor* was identified by histopathology. In 23 and 24 cases, respectively, *Aspergillus* and *Mucorales* were identified by histopathology alone.

Table 3. Microbiology of Invasive Fungal Carotiditis

Fungal Species	Frequency, No. (%)
<i>Aspergillus</i> (n = 41)	
<i>Aspergillus fumigatus</i>	14 (34)
<i>Aspergillus flavus</i>	1 (2.5)
<i>Aspergillus niger</i> (histopathology)	1 (2.5)
<i>Aspergillus</i> (histopathology) ^b	23 (56)
Probable case (galactomannan positive)	2 (5)
<i>Mucorales</i> (n = 37)	
<i>Rhizomucor</i> (culture or histopathology) ^a	2 (5)
<i>Rhizopus</i> (culture) ^b	8 (21)
<i>Rhizopus microsporus</i>	1 (3)
<i>Rhizopus arrhizus</i>	2 (5)
<i>Mucorales</i> (histopathology) ^b	24 (63)

^aSpecial immunostaining for *Rhizomucor*.

^bIdentification to the species level was not performed or reported.

Treatment

Treatment of invasive fungal carotiditis is reviewed in Table 4. Patients with IA received predominantly amphotericin-based (34%) or voriconazole-based (17%) regimens, though several (7%) received isavuconazole. Patients with IM primarily received amphotericin-based regimens (73%). Twenty-two patients overall (28%) did not receive antifungal therapy due to delayed diagnosis or poor prognosis. A majority of patients (65%) underwent surgical debridement. Other interventions included aneurysm coil embolization (n = 9), aneurysmal clipping (n = 2), carotid stenting (n = 2), and carotid bypass surgery (n = 2).

Outcomes

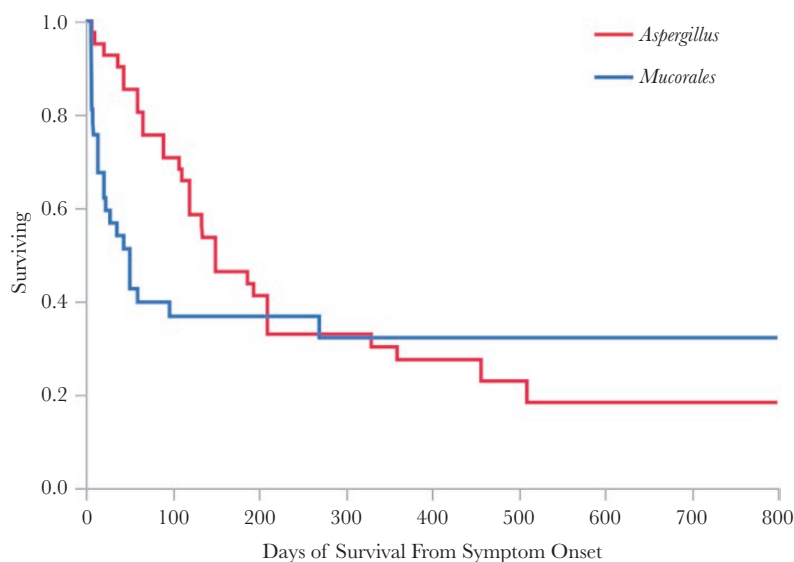
Carotid complications identified in this review included occlusion, thrombosis, aneurysm formation, and rupture. Outcomes are represented in Table 4. In cases involving *Mucorales*, occlusion or thrombosis of the ICA was more frequent (84% vs 46%; $P = .001$) compared with IA. Patients with IA were more likely to develop SAH (41% vs 5%; $P < .001$). Half of all patients experienced cerebral infarcts. All-cause mortality at 6 weeks, 12 weeks,

Table 4. Treatment and Outcomes of Invasive Fungal Carotiditis

Treatment and Outcomes	<i>Aspergillus</i> sp. (n = 41)	<i>Mucorales</i> (n = 37)	Total (n = 78)	P
Antifungal treatment, No. (%)				
Amphotericin B	14 (34)	27 (73)	41 (53)	-
Voriconazole	7 (17)	0	7 (9)	-
Isavuconazole	3 (7)	0	3 (4)	-
Echinocandin	2 (5)	0	2 (3)	-
Other antifungal	2 (5)	1 (3)	3 (4)	-
No treatment	13 (32)	9 (24)	22 (28)	-
Adjunctive therapies, No. (%)				
Hyperbaric oxygen	0	6 (16)	6 (8)	-
Surgical intervention, No. (%)				
Surgical debridement	26 (63)	25 (68)	51 (65)	.885
Coil embolization	6 (15)	3 (8)	9 (12)	.590
Aneurysm clipping	2 (5)	0	2 (3)	.546
Carotid stent	1 (2)	1 (3)	2 (3)	.942
Carotid bypass	2 (5)	0	2 (3)	.546
Outcomes, No. (%)				
Carotid involvement				
Occlusion or thrombus	19 (46)	31 (84)	50 (64)	.001
Aneurysm or rupture	22 (54)	6 (16)	28 (36)	.001
Complications				
Cerebral infarct	20 (49)	19 (51)	39 (50)	.999
Subarachnoid hemorrhage	17 (41)	2 (5)	19 (24)	.001
Cavernous sinus thrombosis	3 (7)	12 (32)	15 (19)	.012
Mortality at 6 wk (42 d)	4 (10)	17 (46)	21 (27)	.001
Mortality at 12 wk (84 d)	10 (24)	22 (59)	32 (41)	.003
Mortality at 2 y (720 d)	31 (76)	24 (65)	55 (71)	.429

and 2 years was 27%, 41%, and 71%, respectively. Mortality at 6 weeks was significantly higher for patients with invasive fungal carotiditis due to IM (46% vs 10%; $P = .001$), whereas mortality was similar for patients with IM and IA at 2 years (65% vs 76%; $P = .429$). Survival curves are presented in Figure 2.

Five patients who died quickly (4 with mucormycosis, 1 with aspergillosis) with no follow-up time specified were assigned a follow-up time of 7 days. The median time from symptom onset to death was 150 days for cases due to *Aspergillus* and 51 days for cases due to *Mucorales* species.

**Figure 2.** Survival time from symptom onset of invasive fungal carotiditis due to *Aspergillus* and *Mucorales*.

DISCUSSION

IFD is an increasingly important cause of mortality among immunosuppressed patients [15–17]. Invasive fungal carotiditis is a unique presentation of IFD that typically progresses by contiguous extension from sino-nasal, sino-orbital, or ototemporal locations to involve the carotid artery, with devastating consequences.

Major risk factors for IFD include HM, HCT, SOT, and DM. In this series, DM was a key risk factor for patients, serving as the most frequent individual primary risk factor for IFD. This was especially prevalent in cases of IM. Notably, among the cases of invasive fungal carotiditis identified, 19% of patients had no apparent risk factors for IFD. The reasons for this observation include prior bacterial or viral infections leading to disruption of the sino-nasal mucosa or ear canal epithelium, making those tissues susceptible to hyphal invasion [27], or undiagnosed immunodeficiencies in otherwise healthy hosts [28, 29]. Nonetheless, these findings indicate that early recognition of at-risk patients may be problematic.

Cranial IFD is challenging to diagnose given the nonspecific nature of the symptoms and the overlap with many autoimmune and malignant diseases involving the paranasal sinuses, orbital apex, or skull base. Patients with invasive fungal carotiditis were frequently treated with systemic glucocorticoids for misdiagnosed inflammatory syndromes. For this reason, cranial IFD should be suspected in patients with worsening symptoms or imaging findings despite antibacterial or anti-inflammatory therapy. Determining a diagnosis through biopsy ought to be considered before administration of glucocorticoids in at-risk patients.

Yet even when suspicion is high and biopsy is pursued, barriers to diagnosis remain. Involved areas of the skull base may be technically difficult to access [30, 31]. In the reviewed cases, when surgical biopsy was obtained, negative results or inadequate sampling resulted in delayed diagnosis [32]. Reinforcing these challenges, a significant group of patients (27%) were diagnosed only postmortem, suggesting that a diagnosis of invasive fungal carotiditis may be missed despite recent advances in imaging, surgery, and microbiologic testing. Novel diagnostic strategies such as polymerase chain reaction (PCR) assays should be considered to enhance diagnostic yield when suspicion for cranial IFD is high, especially with *Mucorales* species [33].

Treatment of IFD involves both medical and surgical strategies [34]. Voriconazole remains the firstline antifungal agent for the treatment of IA, though use of newer triazoles such as isavuconazole has begun to increase [35, 36], including among patients who are unable to receive voriconazole due to drug–drug interactions [37]. A majority of patients with invasive fungal carotiditis received optimal antifungal therapy and surgical intervention, yet mortality remained high. Further

investigation is essential to determine the optimal therapeutic strategies of cranial IFD with carotid involvement.

Vascular complications involving the intracranial blood vessels have not commonly been associated with IFD [1, 16, 38]. Yet, 74 cases of invasive fungal carotiditis were identified in the literature, as well as 4 cases at our own institution since 2003. Half of those patients experienced associated strokes, and many others experienced SAH or CS thrombosis. Notably, even patients who appeared to improve clinically on antifungal therapy went on to develop vascular complications, raising the question of whether more aggressive vascular screening and intervention should be undertaken in patients with cranial IFD. We would recommend in patients with disease adjacent to the ICA, with or without visible narrowing of the ICA, or involving the cavernous sinus or petrous bone, that a magnetic resonance image/magnetic resonance angiogram (MRI/MRA) be performed [39]. If the MRI/MRA reveals any vascular abnormalities, the risks and benefits of endovascular intervention should be discussed. In several cases reviewed, aggressive vascular interventions including coil embolization of aneurysms or carotid bypass have led to successful outcomes [10, 12, 40].

Although IFD with carotid involvement has previously been described [11, 12, 40], this study includes the largest number of patients to date and demonstrates the diverse spectrum of clinical syndromes that may lead to carotid involvement, as well as the varying manifestations of carotid complications, including occlusion, thrombosis, aneurysm formation, or rupture. Limitations of this study include the use of retrospective data, varying follow-up times, missing data, challenges in identifying anatomic sites of infection, and lack of clear definition between distinct manifestations of cranial IFD.

Invasive fungal carotiditis is a rare but distinct manifestation of cranial IFD. Given the nonspecific presentation, technically difficult microbiologic identification, and provider inexperience involving this syndrome, diagnosis is often delayed. Little is known about the optimal therapeutic approach to this disease, but multidisciplinary collaboration between otolaryngology, vascular, medicine, and infectious disease teams is critical. Early consideration of cranial IFD, an aggressive approach to biopsy and surgical debridement, determination of appropriate antifungal therapy, and routine vascular imaging and endovascular intervention should be considered to reduce the high mortality of this unique disease.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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References

- Petrikkos G, Skiada A, Lortholary O, et al. Epidemiology and clinical manifestations of mucormycosis. *Clin Infect Dis* **2012**; 54(suppl_1):S23–34.
- Patterson TF, Thompson GR 3rd, Denning DW, et al. Executive summary: practice guidelines for the diagnosis and management of aspergillosis: 2016 update by the Infectious Diseases Society of America. *Clin Infect Dis* **2016**; 63:433–42.
- Reischies F, Hoenigl M. The role of surgical debridement in different clinical manifestations of invasive aspergillosis. *Mycoses* **2014**; 57(Suppl 2):1–14.
- Parize P, Chandesris MO, Lanternier F, et al. Antifungal therapy of *Aspergillus* invasive otitis externa: efficacy of voriconazole and review. *Antimicrob Agents Chemother* **2009**; 53:1048–53.
- Blyth CC, Gomes L, Sorrell TC, et al. Skull-base osteomyelitis: fungal vs. bacterial infection. *Clin Microbiol Infect* **2011**; 17:306–11.
- Roden MM, Zaoutis TE, Buchanan WL, et al. Epidemiology and outcome of zygomycosis: a review of 929 reported cases. *Clin Infect Dis* **2005**; 41:634–53.
- Stodulski D, Kowalska B, Stankiewicz C. Orogenic skull base osteomyelitis caused by invasive fungal infection. Case report and literature review. *Eur Arch Otorhinolaryngol* **2006**; 263:1070–6.
- Deltomme M, Schroeven M, Lawson TM, et al. MRI and MRA features of a saccular mycotic aneurysm of the cavernous carotid artery resulting from invasive *Aspergillus* sinusitis. *J Belg Soc Radiol* **2015**; 99:76–9.
- Hurst RW, Judkins A, Bolger W, et al. Mycotic aneurysm and cerebral infarction resulting from fungal sinusitis: imaging and pathologic correlation. *Am J Neuroradiol* **2001**; 22:858–63.
- Watanabe T, Okada T, Okada C, et al. An aspergillotic aneurysm of the internal carotid artery following allogeneic bone marrow transplantation: successful management with catheter coil embolization and long-term antifungal agents. *Transpl Infect Dis* **2009**; 11:49–53.
- Bowers CA, Saad D, Clegg DO, et al. Rapidly fatal internal carotid artery mycotic aneurysm rupture in a rheumatoid patient taking a TNF- α inhibitor: case report and literature review. *J Neurol Surg A Cent Eur Neurosurg* **2015**; 76:249–54.
- Hot A, Mazighi M, Lecuit M, et al. Fungal internal carotid artery aneurysms: successful embolization of an *Aspergillus*-associated case and review. *Clin Infect Dis* **2007**; 45:e156–61.
- Patil A, Mohanty HS, Kumar S, et al. Angioinvasive rhinocerebral mucormycosis with complete unilateral thrombosis of internal carotid artery-case report and review of literature. *BJR Case Rep* **2016**; 2:20150448.
- Perfect JR, Hachem R, Wingard JR. Update on epidemiology of and preventive strategies for invasive fungal infections in cancer patients. *Clin Infect Dis* **2014**; 59(Suppl 5):S352–5.
- Hoenigl M, Zollner-Schwetz I, Sill H, et al. Epidemiology of invasive fungal infections and rationale for antifungal therapy in patients with haematological malignancies. *Mycoses* **2011**; 54:454–9.
- Marr KA, Carter RA, Crippa F, et al. Epidemiology and outcome of mould infections in hematopoietic stem cell transplant recipients. *Clin Infect Dis* **2002**; 34:909–17.
- Neofytos D, Fishman JA, Horn D, et al. Epidemiology and outcome of invasive fungal infections in solid organ transplant recipients. *Transpl Infect Dis* **2010**; 12:220–9.
- Kontoyiannis DP, Marr KA, Park BJ, et al. Prospective surveillance for invasive fungal infections in hematopoietic stem cell transplant recipients, 2001–2006: overview of the Transplant-Associated Infection Surveillance Network (TRANSNET) database. *Clin Infect Dis* **2010**; 50:1091–100.
- Johnson AK, Batra PS. Central skull base osteomyelitis: an emerging clinical entity. *Laryngoscope* **2014**; 124:1083–7.
- Candoni A, Klimko N, Busca A, et al; SEIFEM Group (Epidemiological Surveillance of Infections in Haematological Diseases). Fungal infections of the central nervous system and paranasal sinuses in onco-haematologic patients. Epidemiological study reporting the diagnostic-therapeutic approach and outcome in 89 cases. *Mycoses* **2019**; 62:252–60.
- deShazo RD, Chapin K, Swain RE. Fungal sinusitis. *N Engl J Med* **1997**; 337:254–9.
- McNeil MM, Nash SL, Hajjeh RA, et al. Trends in mortality due to invasive mycotic diseases in the United States, 1980–1997. *Clin Infect Dis* **2001**; 33:641–7.
- De Pauw B, Walsh TJ, Donnelly JP, et al; European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group; National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. *Clin Infect Dis* **2008**; 46:1813–21.
- Shamseer L, Moher D, Clarke M, et al; PRISMA-P Group. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ* **2015**; 350:g7647.
- Saravolatz LD, Ostrosky-Zeichner L, Marr KA, et al. Amphotericin B: time for a new “gold standard.” *Clin Infect Dis* **2003**; 37:415–25.
- Seabury JH, Dascomb HE. Experience with amphotericin B for the treatment of systemic mycoses. *AMA Arch Intern Med* **1958**; 102:960–76.
- Ajmal S, Mahmood M, Abu Saleh O, et al. Invasive fungal infections associated with prior respiratory viral infections in immunocompromised hosts. *Infection* **2018**; 46:555–8.
- Lilic D. Unravelling fungal immunity through primary immune deficiencies. *Curr Opin Microbiol* **2012**; 15:420–6.
- Li J, Vinh DC, Casanova JL, Puel A. Inborn errors of immunity underlying fungal diseases in otherwise healthy individuals. *Curr Opin Microbiol* **2017**; 40:46–57.
- Volsky PG, Hillman TA. Fungal skull base osteomyelitis: emerging microbial identification techniques. *Laryngoscope* **2017**; 127:E5–7.
- Kingdom TT, Delgado JM. Endoscopic approach to lesions of the sphenoid sinus, orbital apex, and clivus. *Am J Otolaryngol* **2003**; 24:317–22.
- Li W, Shafi N, Periakaruppan R, et al. Cerebral aspergillosis in a diabetic patient leading to cerebral artery occlusion and ischemic stroke: a case report and literature review. *J Stroke Cerebrovasc Dis* **2015**; 24:e39–43.
- Lass-Flörl C, Mutschlechner W, Aigner M, et al. Utility of PCR in diagnosis of invasive fungal infections: real-life data from a multicenter study. *J Clin Microbiol* **2013**; 51:863–8.
- Walsh TJ, Hier DB, Caplan LR. Aspergillosis of the central nervous system: clinicopathological analysis of 17 patients. *Ann Neurol* **1985**; 18:574–82.
- Marty FM, Ostrosky-Zeichner L, Cornely OA, et al; VITAL and FungiScope Mucormycosis Investigators. Isavuconazole treatment for mucormycosis: a single-arm open-label trial and case-control analysis. *Lancet Infect Dis* **2016**; 16:828–37.
- Maertens JA, Raad II, Marr KA, et al. Isavuconazole versus voriconazole for primary treatment of invasive mould disease caused by *Aspergillus* and other filamentous fungi (SECURE): a phase 3, randomised-controlled, non-inferiority trial. *Lancet* **2016**; 387:760–9.
- Cummins KC, Cheng MP, Kubiak DW, et al. Isavuconazole for the treatment of invasive fungal disease in patients receiving ibrutinib. *Leuk Lymphoma* **2019**; 60(2):527–30.
- Patterson JE. Epidemiology of fungal infections in solid organ transplant patients. *Transpl Infect Dis* **1999**; 1:229–36.
- Harris KG, Tran DD, Sickels WJ, et al. Diagnosing intracranial vasculitis: the roles of MR and angiography. *Am J Neuroradiol* **1994**; 15:317–30.
- Alvernia JE, Patel RN, Cai DZ, et al. A successful combined endovascular and surgical treatment of a cranial base mucormycosis with an associated internal carotid artery pseudoaneurysm. *Neurosurgery* **2009**; 65:733–40; discussion 740.