

# Invasive aspergillus sinusitis with orbitocranial extension

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## ABSTRACT

**Context:** Invasive sinonasal aspergillosis is a silently progressive disease that, left untreated, may invade the adjacent intracranial and intra-orbital compartments incurring serious morbidity.

**Aim:** To evaluate our results of a collaborative surgical management plans for patients with invasive sinonasal aspergillosis with orbitocranial extension.

**Setting and Design:** Retrospective study.

**Materials and Methods:** Between the years 2000 and 2012, 12 patients with Aspergillus sinusitis with orbitocranial extension were treated at our institution. Preoperative CT and MRI scans were done in all cases and cerebral angiography in two patients with subarachnoid hemorrhage (SAH). Surgical combined transcranial and endonasal approaches to the skull base were considered in all patients. Adjuvant antifungals were administered postoperatively with regular clinical and radiologic follow up.

**Results:** All cases had a long history of headache and nasal obstruction ( $n = 12$ ). Five presented with unilateral proptosis, one with meningitis, one with epilepsy, two with SAH, and one patient presented with trigeminal neuralgia. Craniotomy alone was chosen for the patients with isolated sphenoiditis ( $n = 2$ ) while a combined cranial and endonasal approach was elected for the other patients ( $n = 10$ ). Adjuvant antifungal therapy was used for 3-12 months. Patients were followed up clinically and radiologically for an average 36-month period (range = 12-50 months) with disease eradication achieved in eight patients (67%). Two died as consequence to SAH. Follow up also showed that three patients (25%) had sinusitis recurrence requiring evacuation through an endonasal approach.

**Conclusions:** Surgical intervention, with adjuvant antifungal therapy, aiming for safe total removal of the fungal burden, whenever feasible, has a major role in the management of invasive sinonasal aspergillosis with orbitocranial extension with minimal morbidity and good outcomes.

**Key words:** Fungal brain abscess, invasive aspergillus sinusitis, intracranial fungal granuloma, isolated sphenoiditis, mycotic fungal cerebral aneurysm

## Introduction

Since first reported by Hora and Houston in 1965, several variants of aspergillus sinusitis have been described.<sup>[1]</sup> The

spectrum is wide and encompasses non-invasive variants, in addition to indolent, and aggressively invasive forms.<sup>[2-4]</sup> Not uncommonly, invasive fungal disease may erode into the skull base or extend into the adjacent orbits, both with disastrous consequences.<sup>[4-6]</sup>

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The current management strategy calls for a timely diagnosis and a multimodal approach involving multiple disciplines.<sup>[4,7]</sup> The literature mentions varying degrees of surgical debridement ranging from simple sinus surgery to craniotomies for radical lobectomies.<sup>[4,5]</sup> This should be combined with adjunctive use of antifungal therapy.<sup>[4,5]</sup> What constitutes optimal management, however, is a matter of debate. Furthermore, it is unclear which patterns of craniocerebral invasion require an endonasal, transcranial, or combined approach.<sup>[4,5,7]</sup> We present our intermediate-term results of a collaborative surgical approach for the management of orbitocranially invasive aspergillosis of sinonasal origin. We also discuss the decision-making process employed in choosing the appropriate surgical approach.

## Materials and Methods

This retrospective study was conducted at King Abdulaziz University Hospital, Jeddah, Saudi Arabia, between January 2000 and June 2012 to review any patients treated for invasive aspergillus rhinosinusitis (IARS) with orbitocranial extension. Data were collected and analyzed for age, gender, clinical presentation, imaging features, treatment, and outcome. Histopathology slides were reviewed in all cases. Complete blood counts, liver and renal function tests, chest x-ray, human immunodeficiency virus serology, specimen cultures, and blood glucose were noted for all patients.

## Inclusion/exclusion criteria

The study included all patients of both sexes who were: (1) At least 14 years of age; (2) diagnosed by radiology as having sinonasal disease with an obvious intracranial and/or intraorbital component exerting mass effect whether cerebral or ocular respectively, note was taken regarding intradural extension; (3) not having association of any concomitant or previous chronic disease such as renal failure, cirrhosis, malignancy or had a history of intravenous drug abuse, use of immunosuppressive or corticosteroid therapy, organ transplantation, or human immunodeficiency virus infection. Diabetes was not an exclusion criterion in our series but note was taken about glycemic status; (4) having no history or evidence on chest X ray suggestive of pulmonary involvement or aspergillus disease elsewhere; (5) had been proved to have invasive aspergillosis either by histopathological analysis or by culture, coupled with the radiologic findings; as opposed to having "allergic" sinus aspergillosis; patients with the latter condition were excluded. A total of 12 patients who fulfilled these criteria were identified.

## Radiologic evaluation

Computed tomography (CT) of the brain and paranasal sinuses (PNS) was done for all patients as part of initial evaluation to assess soft tissue extension and bony erosion, and as a follow-up measure postoperatively. Magnetic resonance imaging (MRI) scans were also performed in all cases for better visualization of the extent of intracranial involvement

and to identify the relation of the fungal granuloma to important neurovascular structures, namely the optic nerves, internal carotid artery, and cavernous sinuses. In addition, magnetic resonance angiography (MRA), computed tomographic angiography (CTA), and conventional cerebral angiography were done in cases where the cavernous sinuses were involved, or there is evidence of subarachnoid hemorrhage (SAH).

## Histopathology and tissue culture

Diagnosis of IARS was confirmed with either histopathological examination of specimens revealing typical fungal hyphae branching at acute (45 degree) angles or recovery of *Aspergillus* on fungal culture media.

## Management

Treatment for these patients was planned after evaluation and discussion of the imaging findings and patient condition by the ophthalmologic, otorhinolaryngologic (ORL), and neurosurgical services. Main components of management included surgical extirpation of fungal disease and antifungal therapy. Surgical intervention consisted of various combinations of bifrontal craniotomy with subfrontal-transbasal approach, or pterional craniotomy, in addition to endonasal endoscopic approach. Whenever a combined approach was deemed appropriate, a fixed sequence was followed. Initially, the intracranial and intraorbital components of the granuloma were debrided extradurally via craniotomy with concomitant transcranial orbitotomy if needed. Second, the intradural component would be addressed. Third, the granulomas within the frontal, posterior ethmoid, and sphenoid sinuses were approached under direct vision to decompress the optic nerves, ICA, and cavernous sinus. A periosteal graft would, prepared during exposure, then be inlaid to secure the defect in the skull base. Endonasal removal of the granuloma within the anterior ethmoid and maxillary sinuses would follow. This would happen prior to closure of craniotomy incision, to allow for intervention in case of complications occurrence during the endoscopic transnasal procedure. An exclusively transcranial approach was deemed sufficient for patients with isolated sinusitis who had concurrent intracranial disease both accessible via craniotomy. Antifungal therapy consisted of liposomal amphotericin B (AT-B) followed by postoperative therapy with itraconazole (ICZ) or, once available, voriconazole (VCZ).

## Follow up

Follow-up imaging consisted of a routine CT and MRI scans to assess for residual disease immediately postoperatively, followed by a repeat scan at 3, 6, 12, 24 months postoperatively. If clear of disease, subsequent follow up would consist of symptomatic evaluation only. If relapse is noted, repeat evaluation by neurosurgery, ORL, and the infectious diseases services was deemed warranted.

## Results

### Demographics

We found 12 patients at our institution that fit our inclusion and exclusion criteria for IARS over the period spanning from January 2000 to June 2010. The male:female ratio in our series was 8:4. Ages ranged from 17 to 50 years (average  $32 \pm 8$  years, SD). Four cases were diabetic. Five cases presented with unilateral proptosis, three with a disturbed level of consciousness attributed to SAH in two and meningitis in the other, one patient with epilepsy, and one patient had a sixth nerve palsy and hypoesthesia on the left side of the face, the remaining patient presented with trigeminal neuralgia. All patients had long histories of chronic headache and nasal stuffiness. Ophthalmologic evaluation revealed that fundus examination, visual acuity, and field of vision were normal in all conscious patients ( $n = 9$ ) [Table 1].

### Radiological findings

In our series, paranasal sinus CT showed typical high attenuation of metallic quality in all cases. As illustrated by imaging study findings [Table 2], ten patients had involvement of more than one sinus and two had isolated sphenoiditis. In the fungal pansinusitis group ( $n = 10$ ), the fungal granuloma eroded the adjacent skull base (posterior wall of the frontal sinus, cribriform plate of ethmoid and/or planum sphenoidale), with seven developing orbital extension. A subfrontal granuloma was observed in eight patients and an additional suprasellar granuloma was seen in two patients.

Upon reviewing of MRI scans, the fungal disease revealed consistently low intensity on T2 sequences, with T1 sequences showing intermediate to low signals. The intracranial granuloma was intimately related to the optic nerve in seven patients, internal carotid artery (ICA) in six patients, and cavernous sinus in three patients. Two patients had temporal and one had frontal brain abscesses [Figures 1-3].

In the isolated sphenoiditis cases ( $n = 2$ ) we noted the destruction of the sphenoid body. Both patients had parasellar extension; one with an associated suprasellar granuloma and a mycotic ICA aneurysm and the other with a temporal lobe abscess. Two patients had developed SAH secondary to mycotic aneurysms. In one patient with SAH in the suprasellar cistern, MRA and cerebral angiogram confirmed the presence of a 10 mm left ICA bifurcation aneurysm. In the other, with ambient and quadrigeminal cistern SAH, a 7 mm aneurysm was apparent at the tip of the basilar artery [Figure 4].

### Histopathological findings

All specimens showed characteristic branching pattern of *Aspergillus sp.* According to the histopathological results, five patients were classified as chronic IARS where the biopsies showed fungal hyphae surrounded by inflammatory infiltrate

with predominance of neutrophils and associated with foci of necrosis [Figure 5].

On the other hand, six patients had a florid granulomatous reaction compatible with granulomatous IARS including one with isolated sphenoid sinusitis. The fungal hyphae in the biopsies of those patients were seen within giant cells of granulomas and were associated with fibrosis and inflammatory infiltrate composed predominantly of lymphocytes and eosinophils. The other patient with sphenoid IARS had fungal mass, which microscopically composed of tightly packed fungal hyphae associated dense mixed inflammatory infiltrate. Although there was no histopathological evidence of invasion, radiological assessment revealed a sellar destruction in this patient, a finding typically found in the invasive variant of the sinus fungal ball.

**Table 1: Clinical characteristics of study group ( $n=12$ )**

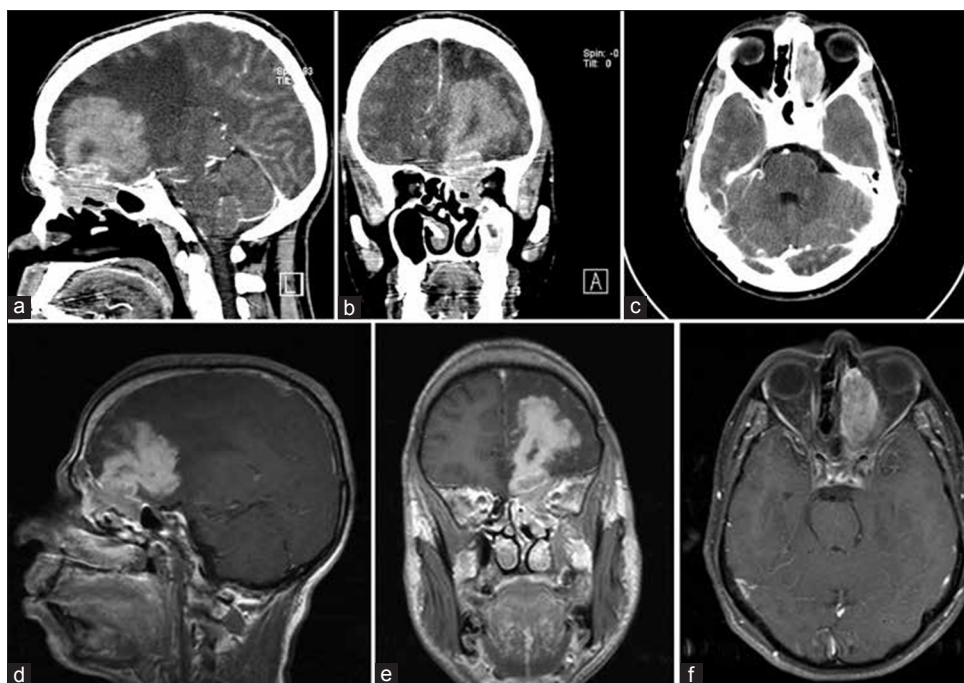
Clinical findings	Number
Age	Range, 17-50 years (average 32 years)
Gender	
Female	8
Male	4
Presentation	
Nasal stuffiness	12
Chronic headache	12
Unilateral proptosis	5
Altered LOC	3
Epilepsy	1
Trigeminal pain	1

LOC: Level of consciousness

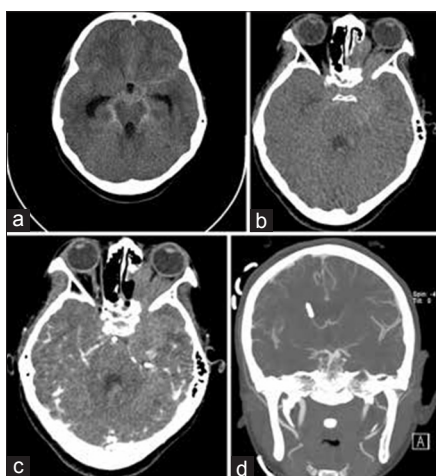
**Table 2: Summary of radiological findings in study group ( $n=12$ )**

Investigation	Findings	Number	
CT scan	Pan-sinusitis	10	
	Isolated sphenoid sinusitis	2	
	Erosion of anterior skull base	11	
	Intra-orbital granuloma	7	
	Destruction of the body of sphenoid	3	
	Subfrontal granuloma	8	
	Suprasellar granuloma	3	
	Parasellar granuloma	3	
	MRI	Granuloma not intimate to neurovascular structures	3
		Granuloma intimate to optic nerve	7
Granuloma intimate to ICA		6	
Granuloma intimate to Basilar artery and PCA		1	
Granuloma intimate to cavernous sinus		3	
Chronic brain (left temporal) abscess		2	
MRA and Catheter angiography		Left ICA bifurcation aneurysm	1
		Basilar tip aneurysm	1

CT: Computed tomography, ICA: Internal carotid artery, MRI: Magnetic resonance imaging, MRA: Magnetic resonance angiography, PCA: Posterior cerebral artery



**Figure 1:** Case illustration of 34-yr-old female with chronic IARS presented with headache and confusion. Parasagittal (a), coronal (b), and axial (c) CT images showed hyperdense lesion, enhancing homogenously after contrast involving paranasal sinuses with left orbital and cranial extension through the cribriform plate of ethmoid bone and lamina papyracea, respectively. Enhanced T1-weighted MRI study in sagittal (d), coronal (e), and axial (f) views demonstrated homogenously enhancing granuloma extending from paranasal sinuses to invade medial and apex of left orbit, cavernous sinus, and frontal lobe, with marked edema and mass effect



**Figure 2:** Case illustration of a 46-year-old female presented with sudden headache and decreased LOC. Plan axial CT image (a) showed basal SAH with acute hydrocephalus. The CT scan also demonstrated a hyperdense fungal granulomatous mass involving left ethmoid sinuses and extending the left orbit, cavernous sinus, and parasellar region (b), which mildly enhanced after IV contrast (c). The patient had EVD followed by CT angiographic study (d), which revealed ruptured left basilar aneurysm

### Antifungal therapy

The surgical intervention is summarized in Table 3.

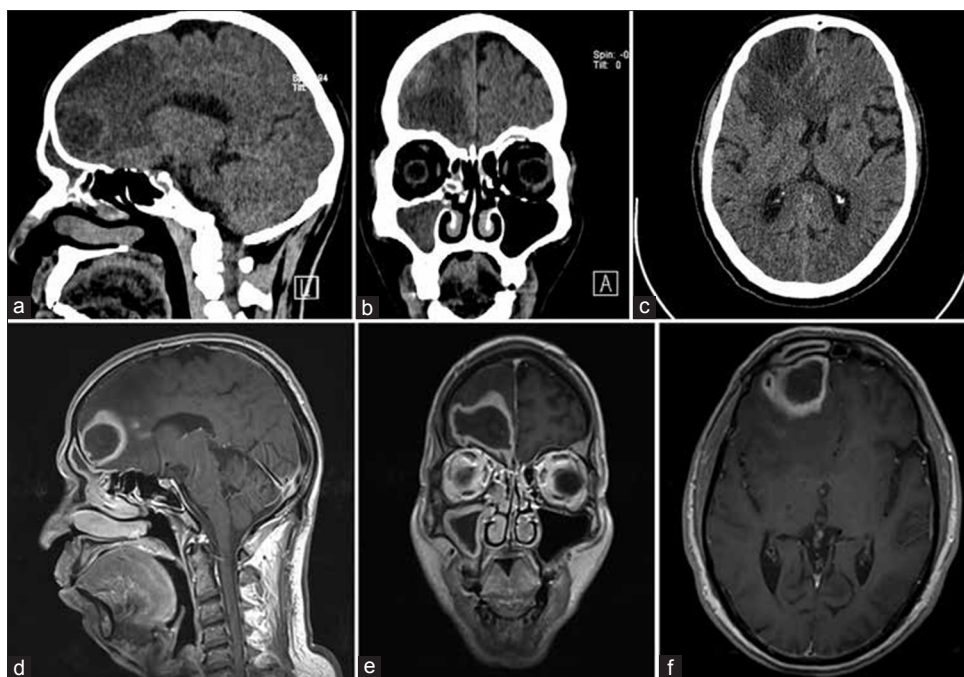
The treatment regimen consisted of intravenous AT-B (1 mg/kg/day) for 2 weeks followed by oral ICZ (400 mg/day) or VCZ (800 mg/day) for 3-12 months. All patients were put

on postoperative ICZ with only the last patient put on VCZ due to its availability. Patients were followed up clinically and radiologically for 6-50 months. The length of the treatment endpoint of oral therapy was complete radiological clearance of the disease.

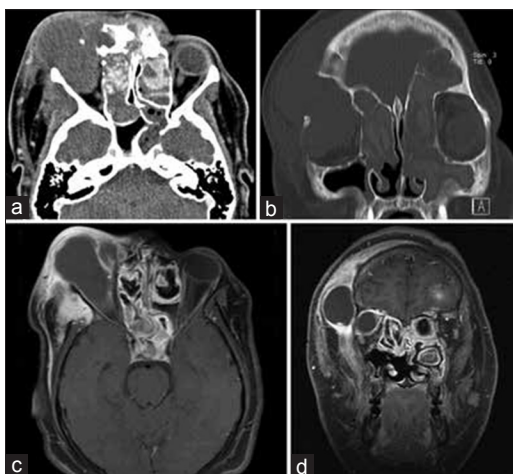
### Outcome

No morbidity or mortality directly related to the operative procedures was observed in our patients. We did, however, have two mortalities related to disease progression. One of the two patients that presented with SAH died 2 month post-operatively from aspergillus meningitis despite being on AT-B and ICZ. The other death was in the patient who presented with a ruptured basilar tip aneurysm, she had died from widespread vasospasm and brainstem infarction 2 weeks later. The patient that presented with meningitis survived and went on to improve and was discharged in good neurological condition. Proptosis was completely corrected in all five patients presenting with that complaint. Headache also improved post-operatively in all patients. Follow-up CT and MRI scans showed eradication of the fungal cranial disease in all survivors but one. He presented 6 months postoperatively with MRI evidence of satellite lesions in the basal ganglia with widespread dural enhancement indicating possible CSF dissemination despite being on ICZ. He was admitted and received intravenous VCZ for 2 weeks followed by oral VCZ for 6 months with complete remission. Evidence of recurrences in the PNS was evident in three patients (including the diabetic





**Figure 3:** Case illustration of a 27-year-old male presented with progressive headache and seizures. Parasagittal (a), coronal (b), and axial (c) plain CT images demonstrated right acute IARS of frontal/ethmoid/maxillary sinuses with intracranial extension to the right frontal lobe. Enhanced parasagittal (d), coronal (e), and axial T1-weighted MRI scan IARS with frontal lobe abscess

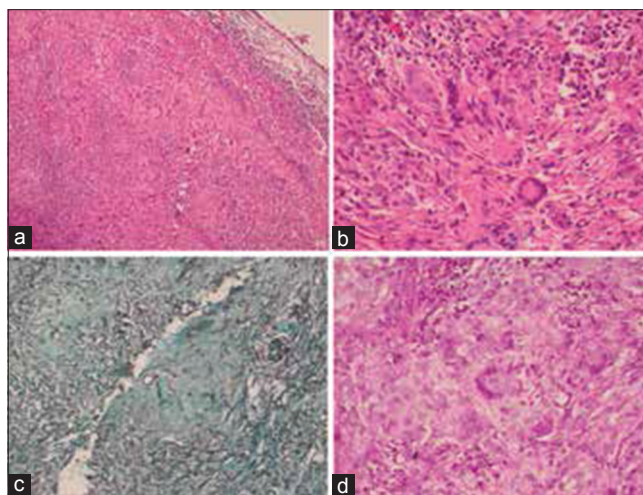


**Figure 4:** Case illustration of a 22-year-old male with progressive right exophthalmos and decreased vision due to IARS involving all the sinuses with marked intraorbital extension as demonstrated in axial (a) and coronal (b) plain CT images. Enhanced axial (c) and coronal (d) T1-weighted MRI demonstrated mixed form of IARS with intraorbital extension and abscess formation

intracranial relapse case on VCZ) during the follow-up period, which was addressed by repeat endonasal debridement in two, the remainder awaiting his appointment. Patient follow up was observed for a mean 36 months (range 12-50 m) [Table 3].

### Discussion

Orbitocranial involvement in IARS is a disease associated with unacceptably high rates of morbidity and mortality.<sup>[4,5,8]</sup>



**Figure 5:** (a) Photomicrograph at low power section reveals chronic granulomatous inflammations with numerous multinucleated giant cells (hematoxylin and eosin stain,  $\times 100$ ). (b) Higher power section reveals multinucleated giant cells (hematoxylin and eosin stain,  $\times 400$ ). (c) Gomori methenamine silver stain shows some fungal hyphae. (d) periodic acid-Schiff stain shows septated fungal hyphae with some branched at right angles identified within the multinucleated giant cells

These rates, although improving, are still disappointing when considering the advances in surgical and medical therapy. The main challenges encountered in the management of this disease include the presence of the blood brain barrier that hinders antifungal penetration intracerebrally, the morbidity of surgery and the gravity of the disease's complications on the central nervous system.

**Table 3: Summary of surgical intervention of 12 patients**

Location	Procedure	No.	Associated complication	Additional intervention	Relapse	Mortality
MSI+SICE	FESS+Craniotomy	10	IDE=2 RMA=1 IOE=7 HCP=1	Clipping=1 Orbitotomy=7 EVD insertion=1	Sinuses=3 Cerebral=1	1 Death in RMA
ISS+SICE	Craniotomy	2	RMA=1 TLA=1	Clipping=1	None	1 Death in RMA

MSI: Multiple sinus involvement, SICE: Significant intracranial extension, ISS: Isolated sphenoid sinus disease, FESS: Functional endoscopic sinus surgery, IDE: Intradural extension, RMA: Ruptured mycotic aneurysm, IOE: Introrbital extension, TLA: Temporal lobe abscess, EVD: External ventricular drain, HCP: Hydrocephalus

The exact factors underlying the pathophysiology of IARS are unclear, but the environmental load of the fungus, the specific strains, and the immune status of the host are believed to promote invasive disease.<sup>[9]</sup> A favorable microaerophilic local environment is considered the trigger that initiates the proliferation and invasion of a fungal species that is usually a harmless commensal of the upper respiratory tract.<sup>[4]</sup>

Another element central to the pathophysiology of this disease is its angioinvasiveness. Invasive aspergillosis is characterized by invasion of the organism into the vascular wall, with subsequent hemorrhage or ischemia.<sup>[10]</sup> Vascular events are poorly tolerated in the central nervous system and one of the main causes of reported mortalities in the published literature on cerebrally invasive aspergillosis.<sup>[4,5]</sup>

Imaging has a central role in the diagnosis; CT suggests the diagnosis by showing sinus opacification that appears hyperdense due to the metallic ions concentrated by the fungus.<sup>[11,12]</sup> It is also invaluable to assess for bony erosion into adjacent orbital and cranial cavities. MRI is better at defining intracranial extension, particularly cavernous sinus, orbital, and cerebral involvement. A decrease in signal intensity on T1-weighted images and a marked decrease in signal intensity on T2-weighted images is characteristic of fungal disease, especially that of caused by aspergillus.<sup>[11-13]</sup> Although CT and MRI can suggest aspergillosis, a definitive diagnosis should be made only after histological confirmation of the operative specimens.

Fungal rhinosinusitis (FRS) has been recently classified into six clinicopathologic forms based on invasion and character of the host's inflammatory response. The invasive diseases include (1) Acute invasive (fulminant) FRS, (2) granulomatous invasive FRS, and (3) chronic invasive FRS. The noninvasive diseases include (1) saprophytic fungal infestation, (2) fungal ball, and (3) fungus-related eosinophilic FRS that includes AFRS.<sup>[14]</sup>

We have encountered three variants of FRS in our series: The chronic invasive and granulomatous invasive variants in addition to the relatively rare invasive fungal ball. Our chart review noted no difference in the pattern of presentation or outcome of therapy attributable to histopathologic finding.

Siddiqui *et al.* categorized the patterns of craniocerebral invasion for IARS to three degrees that correlate with outcome: (Type 1) intradurally invasive aspergillosis that had a 66% mortality rate, (Type 2) extradural intracranially invasive aspergillosis with intermediate response and outcome, and (Type 3) invasion limited to the orbital wall and cranial base that had excellent functional outcomes with treatment. They concluded that judicious, conservative debridement is all that is necessary with preoperative orally administered ICZ further improving prognosis in patients with this disease.<sup>[4]</sup>

Applying their classification system to our cohort, we had three patients with intradural invasion in the form of temporal lobe abscesses in two and a frontal lobe granuloma in the third, with a 33% mortality ( $n = 1$  presented with ruptured aneurysm). The remaining nine patients all had intracranially invasive disease with no dural invasion, with a mortality of 11% ( $n = 1$  presented with ruptured aneurysm). Our experience showed that patients with sinocerebral disease respond well to a treatment strategy consisting of both aggressive intracranial and sinus debridement combined with adjuvant antifungal therapy. Our series differs from that of Siddiqui *et al.*, in that our patients did not receive preoperative antifungal therapy. We also followed a surgical approach that was more aggressive than theirs. The surgical approach they advocate is conservative with the aim of buying time for the antifungals to take effect by relieving only the acute emergency and aerating the sinuses. We aimed for disease eradication whenever feasible without inducing new neurologic deficit, an aim advocated by others and one we believe attainable in most cases.<sup>[5,15]</sup>

The combination of surgical debridement and antifungal therapy has been the cornerstone of treatment of IARS.<sup>[4,5,7,16]</sup> The choice of surgical approach is dependent on the site and extent of involvement, and guided by preoperative CT and MRI imaging. It should be noted that debridement in the diseased region's distorted anatomy and eroded bony structures carries the risk of inadvertent damage to local structures, which include the internal carotid arteries, the orbital contents, and dura. This can lead to visual compromise, internal carotid injury, cerebrospinal fluid leakage, and meningitis. As we have illustrated in our series, the appropriate surgical approach should allow debridement

under direct vision while avoiding unnecessary violation of uninvolved compartments and displaced critical structures to minimize complication occurrence and disease dissemination. We believe that an exclusively endonasal approach can be safely used for lesions not intimately related to the aforementioned critical structures although we did not encounter such a case in our series. A combined transcranial and endonasal approach should be utilized to eradicate craniocerebrally invasive sinusitis with resultant distortion, destruction, or encasement of any of structure necessitating careful dissection under adequate exposure. A solely transcranial approach appears sufficient to address isolated fungal frontal disease, sphenoiditis, or posterior ethmoiditis with associated intracranial complications that also need to be surgically addressed, as these sinuses can be satisfactorily accessed through craniotomy. No significant morbidity or mortality directly attributed to our surgical technique was noted in our small cohort using this surgical protocol, which is unusual considering the propensity for postoperative ischemic complications mentioned in the literature.<sup>[4,5,17]</sup>

Our series includes two cases of isolated aspergillus sphenoiditis, which is rarely encountered in practice.<sup>[18,19]</sup> Due to the disease's invasive nature and the sphenoid's proximity to critical structures of the skull base, it takes on a more aggressive clinical course requiring considerable skull base expertise. The typical clinical presentation consists of varying combinations of chronic headache, nasal symptoms, visual disturbance, and diplopia in addition to the expected sphenoid lesion with possible sellar or parasellar extension.<sup>[18,19]</sup> In our series, the two patients with isolated fungal sphenoiditis presented to the neurosurgical service, one patient as a case of pituitary apoplexy and the other as a left contiguous temporal lobe abscess. Both cases were approached transcranially, this is in contrast with the emerging trend of endoscopic approach to sphenoidal disease.<sup>[20]</sup> The arguments for this approach being the possible risk of widespread CSF dissemination with cranial approaches, though others disagree.<sup>[21-23]</sup> We attribute our choice of craniotomy in both cases to the associated cerebral invasion and lack of supporting evidence in the literature at that time of endoscopic skull base surgery for these indications at the time, as their adoption is relatively recent.<sup>[24]</sup>

We also encountered another rarity in our cohort; two patients had developed fungal cerebral aneurysms. As a result of this rarity, the ideal line of management is not yet clearly defined. Chun *et al.* proposed a systematic approach to infectious intracranial aneurysms in general.<sup>[25]</sup> They concluded that endovascular therapy would be appropriate in stable patients with ruptured aneurysms. Surgical clipping, on the other hand, should be reserved for unstable patients with ruptured aneurysms and only considered in the stable patient who fails endovascular treatment. Patients with unruptured aneurysms

should undergo medical treatment and undergo serial angiography, due to these aneurysms' tendency for resolution with treatment. We followed these guidelines in our cases with fungal mycotic aneurysms. This caused us to take both cases to the operating room for clipping with disappointing outcomes, which is not unexpected.<sup>[26]</sup> The patient with the basilar aneurysm developed severe vasospasm and subsequent brainstem infarctions after successful clipping and died 2 weeks later, while the other with ICA aneurysm eventually succumbed to aspergillus meningitis after recovering well from surgery. Ischemic complications are well known with aspergillosis due to its tendency for vascular invasion, the added vasospasm induced by SAH resulted in the uniformly abysmal outcome of these cases.<sup>[10,26]</sup>

Many antifungals have been used in the management of IARS with varying degrees of success.<sup>[16,27]</sup> Improved results have been described with the newer triazoles that have better CSF penetration and specific activity against *Aspergillus*, mainly the relatively new VCZ. This has caused its widespread adoption as the drug of choice for cerebrally invasive aspergillus disease with resultant improvement in outcomes.<sup>[16]</sup> Our treatment protocol involves initial administration of intravenous AT-B or VCZ for 2 weeks followed by oral ICZ ( $n = 10$ ) or VCZ ( $n = 1$ ) for the period of 8-12 weeks if patient displays complete response to treatment and no relapse.

Our experience with this relatively aggressive regimen compares favorably to that of the literature overall, with three cases developed sinonasal recurrence (25%) after completion of treatment necessitating reintervention to debride the sinuses. A large series of 23 immunocompetent non-diabetic patients with IARS had a relapse rate of close to 61%, despite excluding diabetics, which we have not. Only one survivor, a diabetic, developed cerebral relapse on follow up.<sup>[2]</sup> He is one of the aforementioned three cases and has relapsed while still on VCZ treatment for 6 months running due to residual sinus disease that was thought to resolve with medications but still persists. This rate of cerebral relapse also compares favorably to the literature.<sup>[4,5]</sup>

## Conclusion

We present a medium-sized cohort of IARS with orbitocranial extension that was treated with aggressive surgical debridement with good outcome. We believe that it is a morbid disease that requires the input and involvement of the multidisciplinary surgical services in the planning of surgical intervention. The goal is to choose the surgical corridor that strikes the best balance between maximal exposure and minimal morbidity. Safe eradication of this disease requires sound decision-making that considers the relation of the disease to the critical structures of the skull base, namely the optic nerves, ICA, and cavernous sinuses. In cases of extensive



disease of the skull base, a radical endonasal or transcranial approach may be replaced by a staged combined procedure with less morbidity. The importance of conducting these procedures under adequate antifungal coverage cannot be overemphasized, as displayed by our case with dissemination as a result of drug resistance.

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### Conflicts of interest

There are no conflicts of interest.

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