Invasive Aspergillosis of Anterior Skull Base in the Immunocompetent Host: Outcomes with a Combined Treatment Modality—An Institutional Experience

Saurin R. Shah¹ Amit Keshri¹ Simple Patadia¹ Rungmei S.K. Marak² Sanjay Behari¹

¹ Department of Neurosurgery, Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow, Uttar Pradesh, India

² Department of Microbiology, Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow, Uttar Pradesh, India

Address for correspondence Amit Keshri, MS, Sanjay Gandhi Post Graduate Institute of Medical Sciences, Rae Bareilly Road, Lucknow 226014, Uttar Pradesh, India (e-mail: amitkeshri2000@yahoo.com).

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Abstract

Objectives To study outcomes with voriconazole therapy in immunocompetent individuals following maximal safe endoscopic resection in invasive aspergillosis of the anterior skull base.

Design Retrospective study of patients with chronic invasive aspergillosis including symptomatology, extent of disease, and response to voriconazole following maximal safe resection in immunocompetent individuals.

Setting Tertiary care superspeciality referral center.

Participants Ten consecutive patients of invasive aspergillosis of anterior skull base managed over a period of 2 years.

Main Outcome Measures Symptom resolution with systemic voriconazole and radiologic evaluation following systemic antifungals as per predefined protocol.

Conclusions Maximal safe resection via transnasal endoscopic route followed by systemic antifungals provides excellent outcomes in invasive skull base aspergillosis. Although liver and renal functions, besides visual acuity, need serial monitoring, voriconazole is well tolerated by our patients.

Keywords

- invasive aspergillosis
- skull base
- immunocompetent
- endoscopic resection
- voriconazole
- itraconazole

Introduction

Invasive aspergillosis has been traditionally associated with immunocompromised states but its incidence in immunocompetent individuals is increasing due to widespread use of immunosuppressive treatment, steroids, and aggressive and often injudicious use of antibiotics.¹

Although acute invasive aspergillosis of the skull base is more frequent in immunosuppressed individuals, chronic invasive aspergillosis of the paranasal sinuses (defined as symptom duration over 3 months) and skull base is steadily on the rise across all age groups.²

Since the signs and symptoms resemble those of any space occupying lesion in the vicinity of the skull base, a high index of suspicion is necessary for early diagnosis and prompt initiation of treatment measures.

Chronic invasive sinonasal aspergillosis in immunocompetent individuals has been described in people inhabiting dry-air climates. Although more indolent, its propensity to involve the orbit, cranial nerves, and/or brain parenchyma and intracranial vasculature merits prompt intervention. Aggressive therapy in the form of maximal surgical debridement followed by long-term antifungal therapy is required for satisfactory outcomes.³

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Hardly any case series addressing this entity were found in published literature on PubMed when searched using the keywords “invasive aspergillosis” with “skull base.” In this study we aim to describe the spectrum of clinicoradiologic features, disease extent, and outcomes with maximal safe transnasal endoscopic resection followed by systemic antifungal therapy in 10 consecutive immunocompetent cases of aspergillosis invading the anterior skull base via paranasal sinuses. Approach to the use of antifungals in the medical management of such cases has been highlighted.

Materials and Method

A retrospective systematic review of 10 consecutive cases of aspergillosis invading the anterior skull base through the paranasal sinuses and managed by a combined treatment between July 2013 and June 2015 was done.

Inclusion Criteria

- Ten consecutive cases of invasive aspergillosis involving the anterior skull base during the said study period.
- No previous history of definitive surgery or antifungal use.
- No known immunocompromised states or history of steroid therapy.
- Informed and written consent available for maximal surgical debridement followed by systemic antifungal therapy (voriconazole/itraconazole) and use of data in scientific forums/for research purposes.
- Maximal safe resection via an endoscopic transnasal approach done by the same surgical team.
- Diagnosis of invasive aspergillosis established by histopathology and fungal culture.
- Operative procedure details with events during hospital stay available for review.
- Postoperatively on systemic antifungals as per predefined protocol.
- Serial follow-up via endoscopy and radiological evaluation (magnetic resonance imaging [MRI]) as indicated with a minimum postoperative follow-up of 6 months.

Exclusion Criteria

Allergic fungal rhinosinusitis presenting with neurological sequel due to expansion of sinus cavities were excluded from the study group.

Ten out of twelve cases of invasive sinusal aspergillosis managed during this period fulfilled these criteria.

Patients underwent a nasal endoscopy on outpatient basis and a contrast enhanced computed tomography (CT) scan of the paranasal sinuses was done to define the extent of disease, destruction of the skull base, and to form a road map for transnasal endoscopic surgery.

Patients having diminished vision, evidence of cranial nerve involvement, or intracranial extension on clinical evaluation or CT were further subjected to magnetic resonance (MR) scan with contrast.

As part of their routine preoperative evaluation, all patients were found to have hemoglobin levels above 10 g/dL, normal blood cell counts, renal and hepatic functions, and

Fig. 1 Magnetic resonance imaging of patient 3 in our series: (A) T1W axial, (B) T2W axial, (C) T1W + C axial, and (D) T1W + C coronal films showing disease extent and characteristic magnetic resonance intensities.

tested negative for viral markers for HIV and hepatitis B and C infections. Fasting and random blood sugars, radiographs of the chest, and urine examination revealed no significant anomalies.

Specific history of use of systemic steroids and recurrent episodes of skin, respiratory tract, urinary tract, and gastrointestinal infections was sought to rule out any undetected immunocompromised condition. ► **Fig. 1.**

Surgery

A maximal safe resection of the disease was done under general anesthesia via a transnasal endoscopic approach in all cases and attempt made to remove maximal disease load from areas like infratemporal fossa and orbital fissure via extended endoscopic techniques. Intracranial extension into the anterior and middle cranial fossa was not addressed surgically.

Intraoperative suspicion of a fungal infection was raised by a minimally vascular and gritty, greyish-white mass and the operative specimen were subjected to histopathology, fungal microscopy, and culture evaluations.

Systemic antifungal in the form of voriconazole was initiated in suspected cases of invasive aspergillosis based on radiology and intraoperative impression after primary fungal microscopy reports (on day of surgery). Final confirmation of the diagnosis was based on histopathology and fungal culture. ► **Fig. 2.**

Antifungal Treatment

Voriconazole was started in oral formulation in all our patients with loading dose of 400 mg, 12-hourly on day 1

Fig. 2 Features of aspergillus on mycology and histopathology evaluation (GMS [Gomori's methenamine silver]; KOH [potassium hydroxide]; PAS [periodic acid-Schiff]; SDA [Sabouraud dextrose agar]).

followed by 200 mg 12-hourly thereafter (since all patients had >40 kg body weight). It was continued for a minimum duration of 16 weeks in all cases. In patients with persistent intracranial disease, therapy was extended for a further eight weeks (3 out of 9 cases). After voriconazole regimen, for patients with only persistent sinonasal disease and complete resolution of intracranial extension, voriconazole was replaced by itraconazole 200 mg 12-hourly for 8 weeks (2 out of 9 cases). Serial liver and renal function tests and ophthalmic evaluation were advised in all patients on antifungal therapy (fortnightly in first month, monthly thereafter). **—Figs. 3 and 4 follow-up.**

Serial endoscopic evaluation and cavity debridement was done at 3 weekly intervals. Radiological evaluation (contrast enhanced MRI) was done at the end of 16 weeks of voriconazole therapy and then as indicated.

The patients with persistent contrast-enhancing soft tissue intensities in the paranasal sinuses at the end of itraconazole regimen underwent a repeat surgery for endoscopic debridement of the paranasal sinuses. **—Table 1.**

Result

Average age of the patients in our series was 40.4 years (range, 30–57) indicating the disease affects young adults frequently than the aged population.

Intracranial disease extension beyond the paranasal sinus resolved in six out of nine cases treated with 16 weeks voriconazole; three required another 8 weeks of therapy for radiologic resolution of intracranial lesion. Persistent paranasal sinus disease following voriconazole was addressed with itraconazole therapy for 8 weeks in two cases. Revision surgery following itraconazole in these did not reveal any evidence of aspergillosis on histopathology or mycology evaluation.

The operative procedure and the postoperative hospital stay were uneventful in all but one case. A patient referred to us with biopsy proven aspergillosis for further management developed supraclinoid internal carotid artery (ICA) aneurysm and unfortunately succumbed to the intracranial hemorrhage before voriconazole could be initiated (patient 5 in our series). **—Fig. 5**

Fig. 3 T1W + C magnetic resonance sequences (A, B) of patient 3 showing persistent contrast enhancing lesion involving left orbital apex, sphenoid, and ethmoid after 16 + 8 weeks voriconazole.

Fig. 4 Treatment protocol at our center.

Table 1 Summary of observations and outcomes

Sr. No.	Age/ Sex	Clinical evaluation		Radiological evaluation		Antifungal therapy		Posttherapy visual acuity	MRI after 16 wk voricon	Revised PNS surgery	Follow-up (mo)
		Spread beyond PNS	Visual acuity	PNS involved	Intracranial extent	Voricon-azole	Itracon-azole				
1	33/F	Headache, diplopia	6/6	E, S	Sella, basillar cistern	16 wk	–	6/6	NR	No	24
2	57/M	Visual loss (Lt)	6/24 (Lt)	E, S	Parasellar (& IOF)	16 + 8 wk	8 weeks	6/9	R	24 wk	24
3	30/F	Headache, total ophthalmoplegia (Lt)	6/36 (Lt)	E, S	Parasellar, temporal lobe	16 + 8 wk	8 wk	6/12	R	24 wk	15
4	40/M	Proptosis (Lt)	6/6	M, E, S	None (IOF)	16 wk	–	6/6	NR	No	12
5	37/M	Headache, vomiting, Lt III nerve palsy	6/12 (Lt)	E, S	Lt IOF, B/L cavernous sinus parasellar	Supraclinoidal ICA aneurysm with bleed; could not be salvaged		NA	NA	NA	NA
6	40/M	Headache, vomiting	6/6	S	Clivus, sella, cavernous sinus (B/L)	16 wk	–	6/6	NR	No	9
7	45/M	Total ophthalmoplegia (Lt)	6/36 (Lt)	S	Cavernous sinus (Lt)	16 wk	–	6/12	NR	No	9
8	32/M	Headache, Lt LR palsy, trismus	6/6	M, S	Subtemporal	16 wk	–	6/6	NR	No	8
9	43/M	Painful ophthalmoplegia (Rt)	6/12 (Rt)	M	None (IOF, orbital apex)	16 wk	–	6/12	NR	No	6
10	47/F	Total ophthalmoplegia (Rt)	PL +	E, S	Cavernous sinus (Rt)	16 + 8 wk	–	FC upto 1 mt	R	No	6

Abbreviations: B/L, bilateral; E, ethmoid; FC, finger counting; ICA, internal carotid artery; IOF, inferior orbital fissure; LR, lateral rectus; Lt, left; M, maxilla; NR, not required; PL, perception of light; PNS, paranasal sinus; R, required; Rt, right; S, sphenoid.

Fig. 5 Three-dimensional reconstruct computed tomography showing a saccular aneurysm involving supraclinoid internal carotid artery (encircled) in patient 5 (before antifungal therapy could be initiated).

All patients treated as per our regimen were symptom-free at the end of antifungal therapy and visual acuity improved in all cases with vision deterioration prior to treatment. Equally importantly, only two out of nine patients developed intolerance to systemic antifungals in the form of deranged liver function tests (1/9) or optic neuritis (1/9) which resolved with cessation of antifungal therapy for 3 weeks.

Discussion

Aspergillosis in the immunocompetent individual is a rare entity in spite of the widespread presence of conidia in the air.⁴ Important host factors involved in immunity against aspergillosis include macrophages for conidia and neutrophils for fungal hyphae.⁵ Although there is a paucity of published literature addressing this issue, the epidemiology of invasive aspergillosis is changing with the increasing number of immunosuppressive agents and solid organ transplantations.⁶

Once a suspicion of invasive aspergillosis arises based on clinicroadiological features, histopathology examination along with microbiological isolation is necessary to establish the diagnosis. It also helps exclude conditions such as zygomycosis which warrant separate antifungal therapy.

Aspergillus fumigatus is the species most commonly implicated in aspergillosis but *A. flavus* is more commonly associated with invasive aspergillosis of the paranasal sinus and its toxin responsible for destructive lesions. Intracranial spread has been described to result in chronic basilar meningitis. Fungal invasion causes a chronic granulomatous reaction in the involved area. Vascular invasion by the fungus is often lethal because of the potential for embolism and necrosis.^{5,7} One patient in our series developed com-

plication following supraclinoid ICA involvement and could not be salvaged.

Invasive aspergillosis of the anterior skull base presents with features of paranasal sinus involvement (nasal obstruction, epistaxis, facial pain, nasal congestion, and rhinorrhea) along with that of orbital (vision loss, proptosis, retro-orbital pain) and/or intracranial extension (headache, cranial nerve deficits, features of raised intracranial pressure).⁸

Dense concretions within a paranasal sinus mass may be pathognomonic of aspergillus granuloma but CT and MR features of invasive aspergillosis are frequently nonspecific. Hypointense lesion on both T1 and T2 MRI sequences (because of high iron and manganese content of the fungus) may be suggestive of fungal infection.⁹ The lesion is usually inhomogeneously contrast-enhancing with edema in the surrounding brain parenchyma.

Voriconazole is Food and Drug Administration approved for treatment of invasive aspergillosis³ and better than amphotericin B when used in pulmonary aspergillosis.¹⁰ Although itraconazole tends to accumulate in the brain parenchyma, its cerebrospinal fluid concentrations are undetectable and bioavailability erratic during systemic therapy. Hence we preferred to use voriconazole until the resolution of intracranial lesion and then switch over to itraconazole for persisting lesion in the peripheral nervous system (PNS) considering the cost of therapy and side effects with voriconazole. The cost of treatment is an obvious limiting factor in any developing country like ours.

Although the use of serial galactomannan assay for therapeutic monitoring is an option, the duration of treatment should be determined by resolution of clinicroadiologic features. Azole resistance of the aspergillus species may be a risk for patients chronically exposed to azole antifungals. Adverse effect profile of voriconazole includes hepatic and visual disturbances and skin rash.³ Our patients were monitored based on symptomatology, outpatient endoscopy, and MR scanning following antifungal therapy. None had any long-term sequel of antifungal therapy.

Surgery has been reported to be beneficial to restore mucociliary drainage, ventilate the sinuses, and reduce relapse.^{7,8} Three patients with persistent contrast-enhancing intensities in PNS after itraconazole did not show any evidence of fungal residue on tissue diagnosis.

Conclusion

A high index of suspicion is necessary for early detection and favorable outcomes for invasive skull base aspergillosis in this era of polypharmacy, especially since the clinical features are nonspecific in the immunocompetent host.

Endoscopic transnasal surgery allows definite diagnosis, reduction in disease burden, and restoration of sinus ventilation. A minimally vascular, greyish-white, gritty mass should arouse suspicion intraoperatively.

Voriconazole is well-tolerated by patients in our part of the world and leads to resolution of intracranial disease by 16 weeks with minimal side effects in most cases. Serial evaluation of liver function and visual acuity assessment is

imperative during voriconazole therapy. Following resolution of intracranial extension, itraconazole can be administered for disease persisting in the paranasal sinuses.

Surgery for maximal safe disease removal followed by prompt treatment with systemic antifungals in the form of voriconazole and itraconazole bring about favorable outcomes in this aggressive and challenging condition.

A longer follow-up and a larger patient database would allow us to improve outcomes and further validate the results obtained with a combined treatment modality in patients with invasive aspergillosis of the anterior skull base.

Conflict of Interest

None

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References

- 1 Clancy CJ, Nguyen MH. Invasive sinus aspergillosis in apparently immunocompetent hosts. *J Infect* 1998;37(3):229–240
- 2 Gupta AK, Ghosh S, Gupta AK. Sinonasal aspergillosis in immunocompetent Indian children: an eight-year experience. *Mycoses* 2003;46(11–12):455–461
- 3 Walsh TJ, Anaissie EJ, Denning DW, et al; Infectious Diseases Society of America. Treatment of aspergillosis: clinical practice guidelines of the Infectious Diseases Society of America. *Clin Infect Dis* 2008;46(3):327–360
- 4 Ergene U, Akcali Z, Ozbalci D, Nese N, Senol S. Disseminated aspergillosis due to *Aspergillus niger* in immunocompetent patient: A case report. *Case Rep Infect Dis* 2013;2013:385190
- 5 Karim M, Alam M, Shah AA, Ahmed R, Sheikh H. Chronic invasive aspergillosis in apparently immunocompetent hosts. *Clin Infect Dis* 1997;24(4):723–733
- 6 Centers for Disease Control and Prevention (CDC). Aspergillosis statistics. Updated November 14, 2015
- 7 Sethi P, Saluja R, Jindal N, Singh V. Invasive aspergillosis in an immunocompetent host. *J Oral Maxillofac Pathol* 2012;16(2):297–300
- 8 Kaur R, Maheshwari M, et al. Invasive *Aspergillus* sinusitis in a young immunocompetent host: call for early diagnosis and treatment. <http://www.atmph.org/text.asp?2013/6/1/120/115180>. Accessed July 7, 2016
- 9 Siddiqui AA, Bashir SH, Ali Shah A, et al. Diagnostic MR imaging features of craniocerebral Aspergillosis of sino-nasal origin in immunocompetent patients. *Acta Neurochir (Wien)* 2006;148(2):155–166, discussion 166
- 10 Herbrecht R, Denning DW, Patterson TF, et al; Invasive Fungal Infections Group of the European Organisation for Research and Treatment of Cancer and the Global Aspergillus Study Group. Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. *N Engl J Med* 2002;347(6):408–415