

Invasive fungal disease misdiagnosed as tumour in association with orbital apex syndrome

Sucheta Parija, Aparajita Banerjee

Ophthalmology, All India Institute of Medical Sciences, Bhubaneswar, Bhubaneswar, India

Correspondence to

Dr Sucheta Parija;
suchetaparija@yahoo.com

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SUMMARY

Invasive sino-orbital aspergillosis is a rare cause of orbital apex syndrome (OAS) in immunocompetent patients and often misdiagnosed as tumour because of its aggressive nature and invasive patterns. We report a 23-year-old immunocompetent man presenting with painful progressive loss of vision, ophthalmoplegia and proptosis of the right eye suggestive of OAS. MRI with gadolinium contrast showed an enhancing heterogeneous mass filling the paranasal sinuses, extraconal space and extending up to the right orbital apex. A functional endoscopic biopsy reported as invasive sino-orbital aspergillosis. He was started on intravenous voriconazole and maximal surgical debridement was done. He gradually regained his vision to 20/30 in the right eye. A review of literature reported several such cases which were managed medically or surgically but with poor visual recovery. This case highlights the need for awareness among clinicians for early diagnosis and treatment to prevent vision loss and better survival.

BACKGROUND

Invasive fungal infections in immunocompetent host are an uncommon clinical entity with diagnostic challenge and difficulty in management.¹ Fungal infections of the sinuses and the orbit can be classified into an invasive and a non-invasive form. The non-invasive form are allergic sinusitis and aspergilloma. Invasive aspergillosis can be either indolent or fulminant, and in both cases, the hyphae can invade the sinus mucosa, bone, orbital tissue, and even along the skull base leading to intracranial and intraorbital extensions.^{1 2} Sino-orbital aspergillosis is a rare, aggressive disease that develops from paranasal sinusitis and can manifest in orbit as orbital inflammation, acute glaucoma and mimic malignancy.³ Clinico-radiological findings can be misleading as the lesions are locally destructive and mimic a neoplasm. A biopsy is necessary to establish the diagnosis. However, the final diagnosis is made by histopathology, fungal mount and culture. Histopathology showing acute angled branching septate fungal hyphae with tissue invasion is specific for *Aspergillus* species.¹

Orbital apex syndrome (OAS) is a complex clinical disorder characterised by multiple cranial nerve involvement presenting as ophthalmoplegia and visual loss.³ It has varied aetiologies ranging from infectious, inflammatory, vascular and neoplastic infiltration of orbital apex.^{3 4} Infection arising from periorbital region, paranasal sinuses and central nervous system (CNS) causes OAS.

Here, we report a case of invasive aspergillosis presenting as OAS in an immunocompetent young man initially misdiagnosed as malignancy. This article points on the importance of creating awareness of such cases for early diagnosis, pathological confirmation and treatment with antifungals to reduce the risk of mortality and ocular morbidity.

CASE PRESENTATION

A 23-year-old man presented with periorbital pain, progressive loss of vision in the right eye since 5 days. He complained of intermittent headache and gradual outward protrusion of right eye for the last 3 months. He had no history of fever, sinusitis, epistaxis or trauma. He was not a diabetic, alcoholic, drug addict or on any medication. His medical records did not show any immunocompromised diseases.

On examination, visual acuity (VA) in the right eye was perception of light, and projection of rays (PR) was accurate in all quadrants and 20/20 in the left eye. There was severe abaxial proptosis in the right eye (28 mm by Leudee scale; 20 mm in the left eye) with exotropia and inferior dystopia along with partial dropping of upper eyelids (figure 1). Ocular motility was limited in all direction of gazes with severe (−3) elevation deficit in the right eye. Anterior segment features were normal in both eyes. Corneal sensation was decreased in the right eye and intact in the left eye. Pupillary examination showed relative afferent pupillary defect in the right eye and normal reaction in the left eye. Intraocular pressure was 17 mmHg and 14 mmHg in the right and left eyes, respectively. Fundus examination was normal in both eyes. Facial numbness was marked on the right side of the face.

INVESTIGATIONS

Routine blood investigations and serological tests were normal, except for raised erythrocyte sedimentation rate (ESR). MRI (MRI-coronal T1 and axial T1 post contrast) showed an enhancing expansile hyperintense lesion involving all paranasal sinuses with encroachment of bilateral medial extraconal orbital spaces with lateral displacement of medial recti muscle, extending to right orbital apex and compressing the optic nerve (figure 2A,B). A suspicion of paranasal tumour causing OAS was made and endoscopic incisional biopsy was done. Histopathological examination of the mass from orbit and paranasal sinuses revealed polypoidal fragments of tissue with infiltration of eosinophils, lymphocytes and plasma cells. Gomori methenamine silver staining demonstrated fungal hyphae



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Figure 1 Nine gaze photographs showing severe proptosis with inferior dystopia and limitation of extraocular movements in the right eye.

with 45 degrees angulated septations, suggestive of aspergillosis (figure 3A,B). The specimen was also sent for culture in Sabouraud dextrose agar, which was reported to grow *Aspergillus fumigatus* after 5 days.

DIFFERENTIAL DIAGNOSIS

As the patient presented with proptosis and external ophthalmoplegia, there were various differential diagnoses to it: idiopathic orbital inflammatory syndrome, OAS (due to aetiologies like infective, inflammatory or malignant paranasal sinus tumour), orbital cellulitis, neoplasia and cavernous sinus thrombosis. Absence of conjunctival chemosis, prominent proptosis and lack of fever ruled out the probability of orbital cellulitis. MRI further demonstrated that cavernous sinus was not involved, rather the lesion was sino-orbital in nature involving all the paranasal sinus and the orbital apex of the right eye. To confirm the aetiology, biopsy of the mass revealed septate filamentous fungi along with features of chronic granulomatous inflammation, suggesting the diagnosis to be OAS due to aspergillosis.

TREATMENT

With a working diagnosis of invasive aspergillosis, the patient was started on intravenous voriconazole 200 mg two times per day for 1 month. Endoscopic sinus debridement of the mass entailing procedures like curettage, sinus drainage and irrigation was performed by the ear, nose and throat (ENT) surgeon.

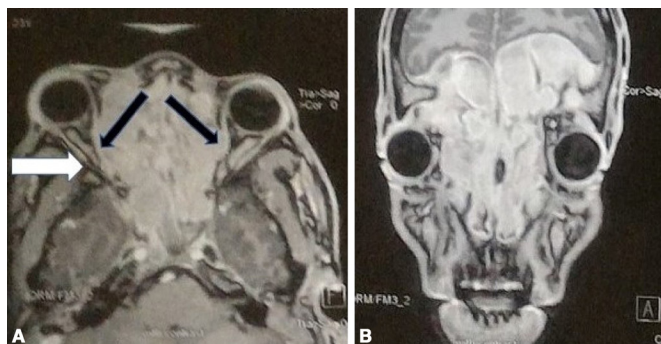


Figure 2 (A) Axial T1 post contrast MRI shows enhancing expansile lesion involving all the paranasal sinuses with encroachment of right orbital apex (white arrow), bilateral medial extraconal orbital spaces with lateral displacement of medial recti muscle (black arrow). (B) Coronal T1 post contrast MRI brain and orbit revealed all the paranasal sinuses and nasal cavity to be expanded and filled with enhancing lesion.

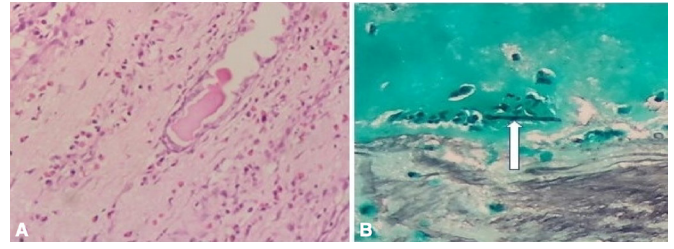


Figure 3 (A) Histopathological examination of the incisional biopsy of the mass revealing polypoidal fragments of tissue with infiltration of eosinophils, lymphocytes and plasma cells (H&E stain; $\times 40$). (B) Gomori methenamine silver stain showing septate filamentous fungi (arrow).

OUTCOME AND FOLLOW-UP

The patient's vision gradually improved in 1 week to 20/40 in the right eye. Extraocular movements gradually improved in all directions of gaze and the proptosis decreased (figure 4). At 3-month and 6-month follow-up, the patient was asymptomatic with best corrected visual acuity (BCVA) 20/30 in the right eye and 20/20 in the left eye. There were no signs of recurrence.

DISCUSSION

Invasive aspergillosis is an opportunistic infection often occurring in the immunocompromised cases, but only 17 cases have been reported among immunocompetent hosts, mostly from Sudan and India.^{5,6} Tropical climate increases the fungal growth and presence of spores in the inhaled air, which adds to the risk of invasive sino-orbital disease even in healthy hosts. Aspergillosis is a fungal disease caused by *Aspergillus*, which is a mould that usually colonise in the paranasal sinuses and the lungs.¹ *A. fumigatus* is the most frequent species isolated in human infections and commonly seen in immunocompetent hosts, followed by *Aspergillus flavus*.⁷

Invasive sino-orbital aspergillosis (ISOA) is a rare disease but lethal if associated with CNS infections or haemorrhage.⁴ Aspergillosis usually starts in the deeper tissues such as the posterior ethmoid and sphenoid sinuses, when the patient may initially complain of sinus pain, nasal discharge, intermittent fever and occasionally epistaxis. From the paranasal sinuses, it invades the orbit due to breach in the thin bony part of lamina papyracea leading to proptosis and gradual loss of vision. An intracranial extension can occur along the base of the skull and larger vessels.⁸ So, when the invasive sinusitis spreads to the orbital apex, the patient experiences loss of vision, proptosis and multiple cranial nerve palsies. OAS can mimic orbital cellulitis, optic neuritis and cavernous sinus syndrome.⁹ In our case, the patient did not have any signs of sinusitis. A high suspicion of rapidly expanding paranasal sinus malignancy was considered



Figure 4 Nine gaze photographs showing resolution of proptosis and extraocular movements after treatment.

Table 1 Review of literature

Case No	Author, year	Age/sex	Clinical features	Comorbidity	Radiological findings	Treatment	Ocular outcome
1	Chang YM <i>et al</i> , 2018 ⁴	61/F	Decreased vision, proptosis, complete ophthalmoplegia	Diabetes mellitus	MRI—2 cm low-signal nodule in the left posterior ethmoid, and sphenoid sinuses, involving the left pterygopalatine fossa, the left cavernous sinus and extraconal space	Decompression surgery with intravenous voriconazole x1 month	Proptosis resolved but vision was lost permanently
2	Huang Q <i>et al</i> , 2017 ⁸	61/M	Prosis, total ophthalmoplegia, decreased vision	Nil	Invasive inflammatory or malignancy process of sino-orbital skull base	Endonasal sinus debridement with orbital decompression along with intravenous voriconazole	On 6-month follow-up, all the symptoms resolved but blindness remained
3	Baeesa SS <i>et al</i> , 2017 ⁹	6 patients (14–53) years	Prosis, total ophthalmoplegia, decreased vision	Subarachnoid haemorrhage	6 patients had subarachnoid haemorrhage secondary to mycotic aneurysm	Antifungal therapy was used in all patients, and four underwent emergency craniotomy	5 patients died due to haemorrhage and infarction
4	Miyamoto Y <i>et al</i> , 2016 ¹³	74/M	Prosis, proptosis, total ophthalmoplegia	Colorectal cancer	MRI—small enhancing lesion in the ethmoidal sinus	Treated with intravenous voriconazole	Disease resolved after 1 month
5	Singh H <i>et al</i> , 2015 ¹⁴	64/M	Progressive decrease in vision after cataract surgery	Nil	Small mass causing destruction of ethmoid bone	Intravenous voriconazole	Successful management after switching over to voriconazole but vision did not improve
6	Rallis G <i>et al</i> , 2014 ¹⁵	37/M	Vision loss and left-sided facial nerve paresis	Diabetic	Mass in left maxillary sinus encroaching up to the left orbit	Surgical debridement of maxillary sinus, with intravenous amphotericin B and posaconazole	Other ocular symptoms resolved but vision in the left eye remained perception of light plus
7	Kim JW <i>et al</i> , 2014 ¹⁶	68/M	Vision loss	Pulmonary aspergillosis	Gross involvement of right orbital apex by mass	Intravenous antifungal therapy	Vision remained hand movement+, other symptoms resolved
8	Arakawa H <i>et al</i> , 2014 ¹⁷	86/M	Vision loss in the left eye	Nil	Involvement of left orbit and orbital apex by mass	Intravenous voriconazole	Vision in the affected eye did not improve (PL -ve), but other symptoms resolved
9	Ohlstein DH <i>et al</i> , 2012 ¹⁸	68/F	Stabbing pain behind the eye, ptosis, decreased vision	Hypertension, depression	Infiltrate reaching the right orbital apex	Intravenous Voriconazole	Symptoms resolved and vision improved to 20/40
10	Kuga A <i>et al</i> , 2007 ¹⁹	65/F	Decreased vision, ptosis, proptosis, decreased ocular movements	Peripheral T cell lymphoma	Heterogeneously enhanced mass extending from the right orbital apex to the cavernous sinus	Intravenous voriconazole	Symptoms resolved with voriconazole with no relapse, but visual acuity was not recovered
11	Yamanoi T <i>et al</i> , 2004 ²⁰	3 immunocompetent patients	Unilateral loss of vision and third cranial nerve palsy	Nil	Lesion extending from the sphenoid sinus to the orbits	Intravenous itraconazole	Favourable response with itraconazole (ocular movements improved in 2 cases and worsened in 1 case, vision remained poor)

and ENT consultation was advised for endoscopic tissue biopsy for confirmation.

Several studies have reported ISOA to occur in both immunocompetent and immunocompromised patients.^{10–11} Pushker *et al*¹¹ reported 15 immunocompetent cases of orbital invasive aspergillosis, where 3 cases did not have sinusitis or any systemic disease. Few cases had complete resolution of the mass with intravenous antifungal therapy and surgery, but visual recovery was poor. Five patients had residual mass on last imaging and one patient died during follow-up.

Kumar *et al*¹² also reported a case of an immunocompetent patient who presented with a lower lid nodular mass which was due to aspergilloma on histopathology and was completely cured with surgical excision followed by oral itraconazole.

A literature search was carried out on all English articles using the search engines such as PubMed, Medline and Embase databases. The terms such as 'invasive, fungal, aspergillosis, orbital aspergillosis, OAS, immunocompetent, visual loss' were entered in the search engine to obtain the articles. All the articles between the years 1980 up to 2019 were reviewed to study the visual outcome and management in all cases of OAS caused by invasive aspergillosis. The demographics and clinical profile along with visual outcome after treatment are described in table 1.^{4 8 9 13–20}

All the patients were elderly, except the current case who was 23 years old. Seven cases were immunocompromised and at a higher risk for infection as compared with our case who was immunocompetent. Despite treatment with either amphotericin B, itraconazole and voriconazole, visual prognosis was poor in all cases, but our case regained vision after treatment.

Radiologically, invasive aspergillosis should always be suspected in cases of painful ophthalmoplegia, if there is more than 8 mm thickening of the sinus mucosa along with optic nerve invasion and bony involvement as in our case.¹⁸ Sivak-Callott *et al*²¹ suggested that sphenoid sinus assessment on MRI scan can be helpful in early detection of lesions. However, a biopsy is essential to establish the diagnosis. Hyphae are typical and specific for each fungus. Mucor presents large, broad non-septate hyphae with right-angle branching, while aspergillus shows septate hyphae that branch at 45° angles.¹ Fungal cultures on Sabouraud dextrose agar are needed to confirm the diagnosis. Invasion of the surrounding tissues by hyphae on histopathology is the hallmark of the disease.

Anterior rhinoscopy with a biopsy, fine-needle aspiration cytology or trans-sinus orbital biopsy may be done. Apart from frozen and permanent sections, KOH mount, periodic acid-Schiff stain and Gomori methenamine stains are also advised to detect haematoxyphilic organisms with branching hyphae of 2–3 mm width.²¹ For early diagnosis, certain markers such as serum galactomannan and β -D glucan can be useful but isolation of fungus from tissue biopsy is still the gold standard for diagnosis.⁸

At times when there is delay in diagnosis because of varied spectrum of clinical features mimicking orbital pseudotumour, optic neuropathy or tumour metastasis, some cases are treated with systemic steroids, which further worsens the condition and causes rapid spread of the infection. Choi *et al*¹⁰ reported cases of invasive aspergillosis worsening with steroid therapy. We deferred the use of systemic steroids due to suspicion of fungal mass in our case.

Current protocol of management of invasive sino-orbital aspergillosis depends on case reports. The current mainstay of treatment consists of intravenous amphotericin B 5 mg/kg/day along with debridement of the focal abscess.^{12 21} In total, 40%–60% cases response is well, but when the infection reaches the orbital

apex, the mortality remains high (70%–80%).^{12 21} Due to high risk of relapse, 2 years of treatment may also be advised, but is not well tolerated due to systemic side effects like nephrotoxicity. Systemic voriconazole has emerged as a good alternative for the treatment.^{18 19 22} When compared with amphotericin B, it has fewer side effects, better penetration, better survival advantage and is a good choice for maintenance therapy.¹⁹ Repeated surgical debulking alone or along with orbital exenteration or injection of retrobulbar liposomal amphotericin B, long-term intravenous antifungal therapy and hyperbaric therapy may be considered as an alternate approach in few cases.²³

CONCLUSION

Invasive sino-orbital aspergillosis with intracranial extension often mimics inflammatory conditions but presenting as OAS is rare and fatal. Early diagnosis and treatment with voriconazole and surgical debridement can lead to visual recovery and survival. Repeated biopsies may be needed before the diagnosis is confirmed and hence use of systemic steroids must be avoided as it worsens the condition. A multidisciplinary approach is recommended in aspergillus infections for successful outcome.

Patient's perspective

I am satisfied with the investigations and treatment process for my disease. Now my vision has improved.

Learning points

- ▶ Although invasive aspergillosis commonly presents in immunocompromised patients, it can also occur in young immunocompetent patients mainly in tropical countries.
- ▶ Radio-imaging along with incisional biopsy may serve as an important diagnostic tool.
- ▶ Early diagnosis and aggressive treatment with systemic antifungal agents and surgical debridement and debulking can not only reduce the mortality but also help in recovery of vision.

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