Orbital Cellulitis: Invasive Fungal

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Introduction

Invasive fungal infections of the orbit are of two types: acute fulminant and chronic invasive. Orbital fungal infections have intracranial extensions in immunocompromised patients and are rare and difficult to diagnose; they pose challenges in the management and are often fatal. They arise from two types of fungal infections, zygomycosis and aspergillosis.

Given their poor prognoses, early detection becomes one of the key strategies to the management. This gives a better chance of local control of the infection, and along with early restoration of the immunologic or metabolic condition, it significantly influences the patient's treatment outcomes. Here, an example of each type of invasive fungal infection with orbital involvement is discussed.

Case 1: Mucormycosis

A 70-year-old woman who was diagnosed with relapsed angio-immunoblastic T-cell lymphoma had previously completed chemotherapy, and developed cytomegalovirus (CMV) infection and methicillin-resistant *Staphylococcus aureus* (MRSA) septicemia on the days following chemotherapy. While she was on tapering doses of prednisolone, antiviral and antibiotic therapy, she was hospitalized for neutropenia and fever. Prior to hospitalisation, she developed facial numbness and blurring of vision in the left eye. Examination revealed a total ophthalmoplegia with no perception of light in the left eye that progressed rapidly to involve the right side. There was increasing necrosis of the eyelids with conjunctival chemosis and proptosis (Fig. 8.1a, b).

CLOSE summary is given in Table 8.1.

Differential Diagnosis

- Fungal infection
- Non-specific orbital inflammation
- Granulomatosis with polyangiitis
- Primary neoplastic process
- Metastatic tumour
- Secondary tumour from the sinuses
- Cavernous sinus thrombosis

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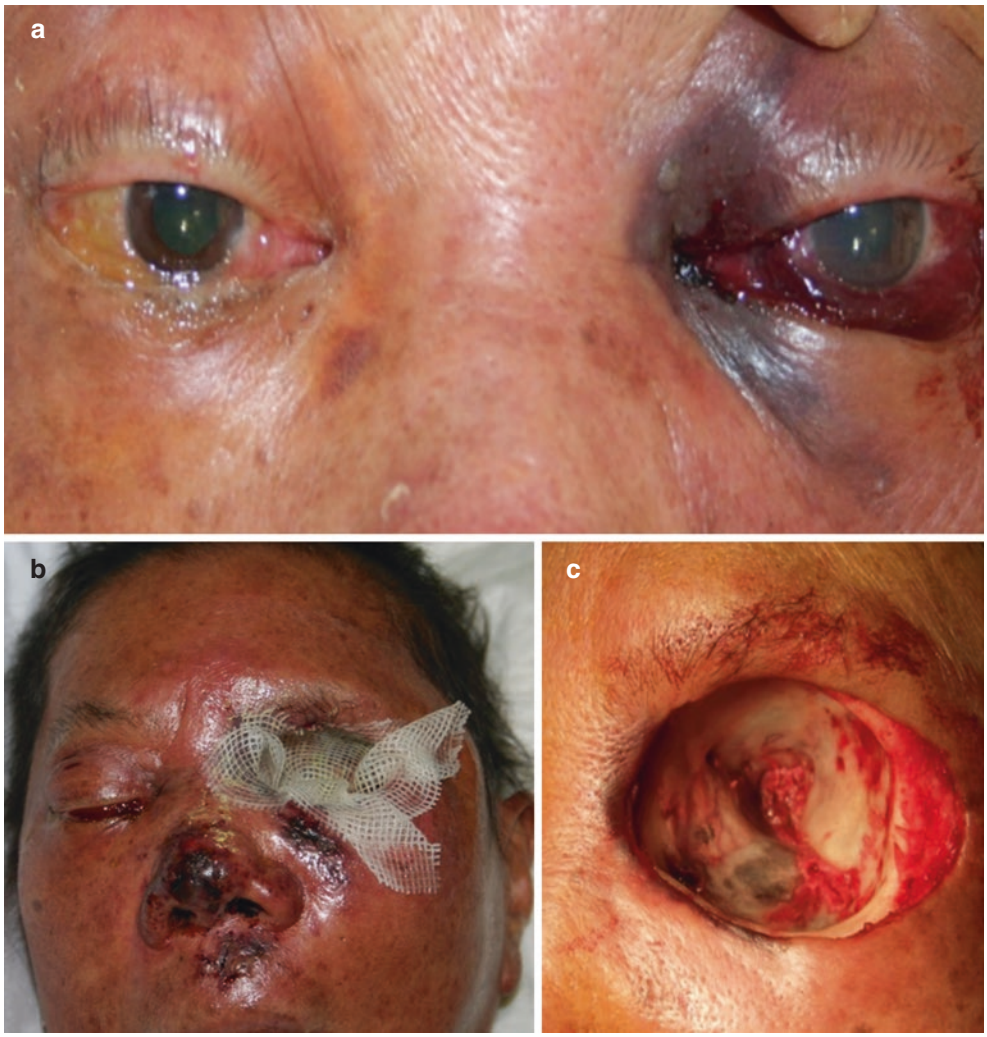

Fig. 8.1 (**a**) Clinical picture of case 1 shows left proptosis with blackening lesions in eyelids, chemosis, lustreless cornea on day 2. (**b**) Note the right-sided proptosis, ischaemic necrosis of the ala of nose and left lower lid on day 7. (**c**) The picture shows the exenterated orbit immediately after surgery. Note blackening of the bone in the floor and the absence of bleeding

Table 8.1 CLOSE summary case 1

*C*linical scenario: infiltrative
*L*ocation: bilateral orbit
*O*nset: acute fulminant
*S*igns and symptoms: loss of vision, eyelid swelling and blackening
*E*pidemiology: an immunocompromised 70-year-old Chinese female

Radiology

CT and MRI (Fig. 8.2) showed mild left-sided proptosis, associated with mucosal thickening of the ipsilateral ethmoid and maxillary sinuses. There was complete opacification of the left nasal cavity associated with septal deviation to the left. No focal mass lesion was noted in the retrobulbar space to account for proptosis. The left optic nerve appeared relatively taut compared to the contralateral side, and there was distension and enhancement of the optic nerve sheath**.** The inflammation was seen to extend to the left cavernous sinus.

Management

Nasal debridement on day 4 showed zygomycosis (mucormycosis) infection, and the patient was started on intravenous liposomal amphotericin B injections. The culture revealed the growth of *Rhizopus* species. The left orbital exenteration was performed on day 7 to reduce fungal load, but the patient progressed with no perception of light in the right eye with right orbital apex syndrome. During exenteration, there was no bleeding, indicating severe ischaemia (Fig. 8.1c). The patient's condition deteriorated when the family decided to withdraw all treatment, and she eventually succumbed to the disease.

Histopathology

The biopsy of the turbinates and the nasal mucosa showed broad hyphal fungal fragments in the blood vessels, within the lumina and vessel walls and surrounding connective tissue stroma and nerves (Fig. 8.3). These hyphae were of variable thickness,

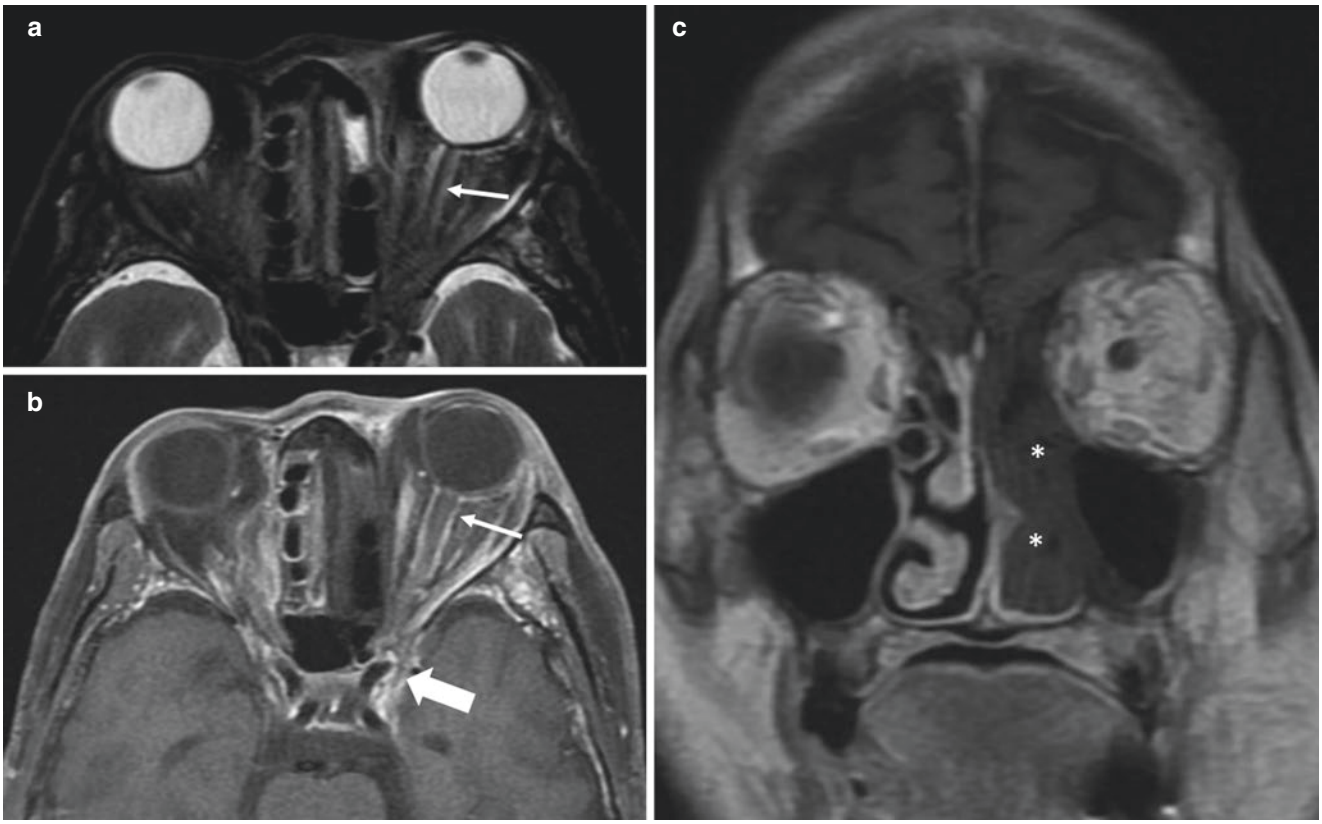

Fig. 8.2 Axial T2w FS (**a**) and axial T1w FS + C (**b**) show distension and enhancement of the optic nerve sheath (white arrow), oedema in Tenon's space and inflammation spreading to the left cavernous sinus (white block arrow) resulting in thrombophlebitis. Coronal T1w + C image (**c**) shows extensive non-enhancement of the left sinonasal mucosa and turbinates (white asterisk), indicating infarction and necrosis

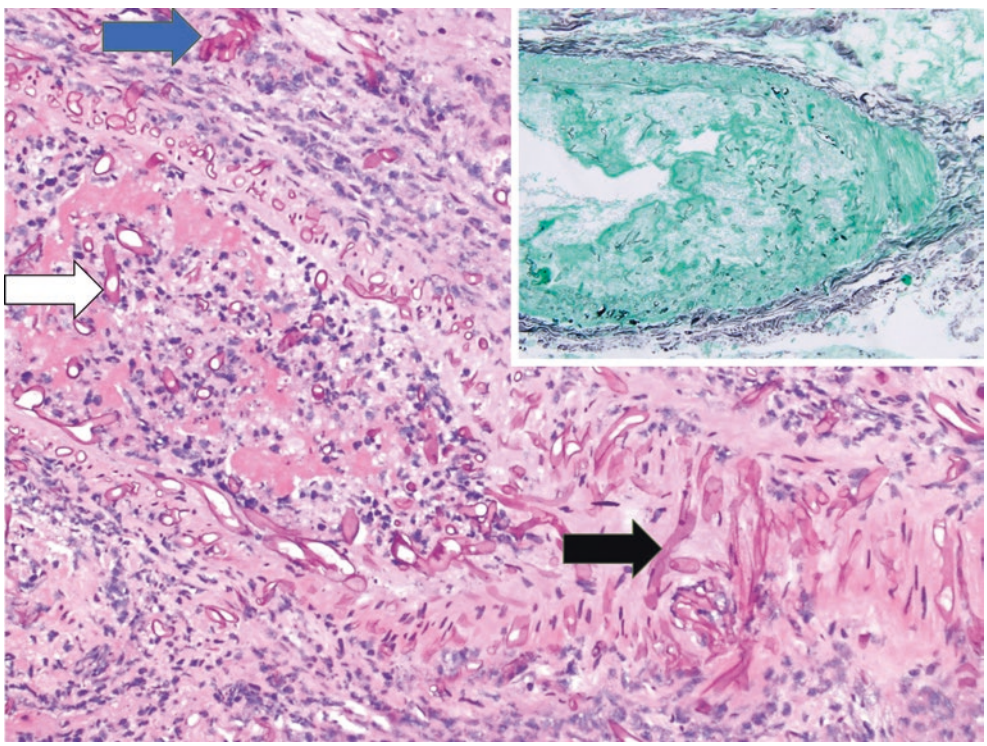

Fig. 8.3 A blood vessel is seen stretching diagonally downwards from the left upper edge of the picture to the bottom right edge. There are broad fungal hyphae within the vessel lumen (white arrow) and invading the vessel wall (black arrow), as well as in the surrounding connective tissue (blue arrow). Septa are not readily seen in this figure. HE stain; 200× magnification. GMS stain highlights the fungal hyphae in the optic nerve (inset; GMS stain; 100× magnification)

ranging from approximately 6 to 9 um in diameter. Rare septa were identified. The organisms were positive for Gomori methenamine silver (GMS) and periodic acid-Schiff (PAS) stains. This was accompanied by areas of infarction and patchy, predominantly chronic inflammation. The findings were consistent with the invasive fungal infection by zygomycosis.

The orbital contents after exenteration showed similar findings with invasive fungal infection, consistent with zygomycosis, with prominent vascular invasion and extensive ischaemic-type of necrosis. Fungal hyphae were present in all tissues including optic nerve and at all resection margins.

Case 2

A 57-year-old Chinese diabetic man with the history of nasopharyngeal carcinoma treated previously with chemoradiotherapy (completed 2 years previously), considered to be in remission, developed headache with vomiting and double vision of acute onset. On examination, his eyes were white with good vision. A right sixth nerve palsy was noted (Fig. 8.4). He was admitted to the hospital for investigations to rule out the possibility of recurrent tumour. MRI scan did not reveal any intracranial lesion but showed a sphenoidal sinusitis. The patient was discharged on systemic antibiotics but returned to the emergency department 2 weeks later with persistent headache and acute loss of vision in the right eye. He was hospitalized again, and an ophthalmic examination revealed a vision of counting fingers in the right eye with total ophthalmoplegia. A repeat MRI revealed orbital apical infiltration and fat stranding with opacification of adjacent sphenoid sinus. The PET-CT scan did not reveal any evidence of tumour recurrence. On suspicion of fungal infection, a biopsy of sphenoid sinus was carried out but was negative for fungus and tumour recurrence. Patient's eye condition worsened to no perception of light and total ophthalmoplegia in the right eye. A repeat biopsy from the apex of the orbit was advised, but the patient declined biopsy and any form of treatment and left the hospital, only to return 8 weeks later with delirium.

CLOSE summary is given in Table 8.2.

Table 8.2 CLOSE summary case 2

*C*linical scenario: infiltrative
*L*ocation: right orbit
*O*nset: subacute to chronic
*S*igns and symptoms: pain, headache, loss of vision, orbital apex syndrome
*E*pidemiology: 57-year-old diabetic Malay male

Differential Diagnosis

- Same as case 1

In addition:

- Optic neuritis
- Cranial nerve palsies

Radiology

Initial MRI showed mucosal thickening and fluid in bilateral sphenoid sinus with a bony defect in the lateral wall with marrow oedema. Persistent soft tissue thickening and enhancement at the right orbital apex and anterior cavernous sinus with suspected cranial nerve involvement and compression were seen (Fig. 8.5). The differentials included tumour recurrence as well as inflammatory/infective causes. The MRI carried out 3 weeks and 3 months later showed worsening mass lesion centred around the right orbital apex, optic nerve and cavernous sinus (Fig. 8.6) with invasion into the right middle cranial fossa, likely temporal lobe abscess formation and invasion/thrombosis of the right internal carotid artery. An invasive fungal infection was most likely from the above findings.

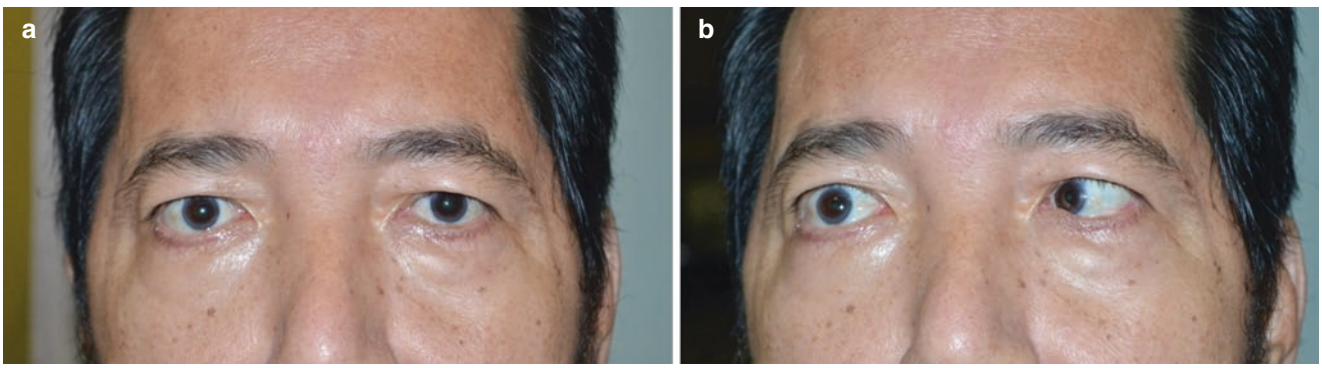

Fig. 8.4 Clinical picture of case 2 at the initial presentation (**a**) in primary position and (**b**) on right gaze. Note the right 6th nerve palsy

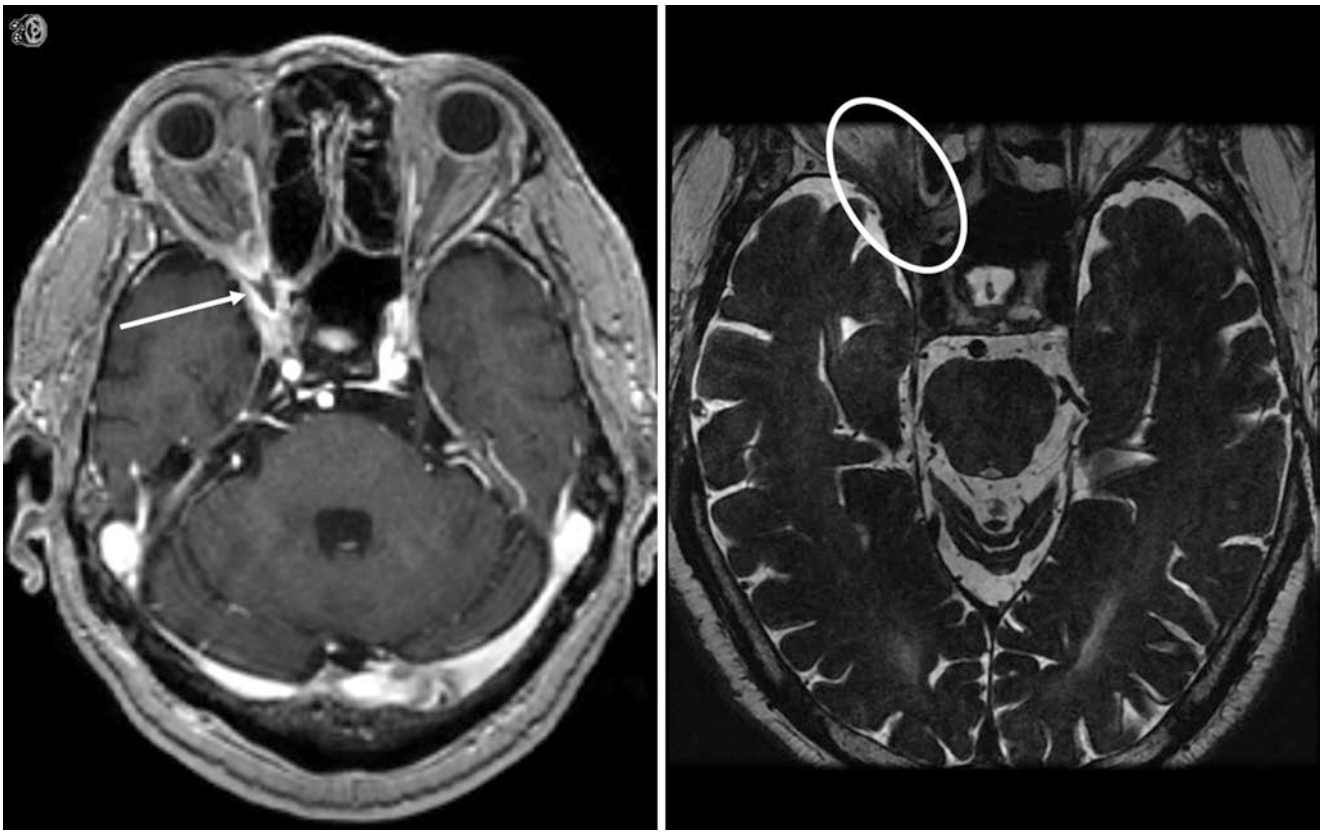

Fig. 8.5 Axial T1w + C (left) and 3D isotropic heavily T2w sequence (right), showing infiltration and enhancement of the fat at the orbital apex, with central necrosis/suppuration (white arrow and circle) at presentation

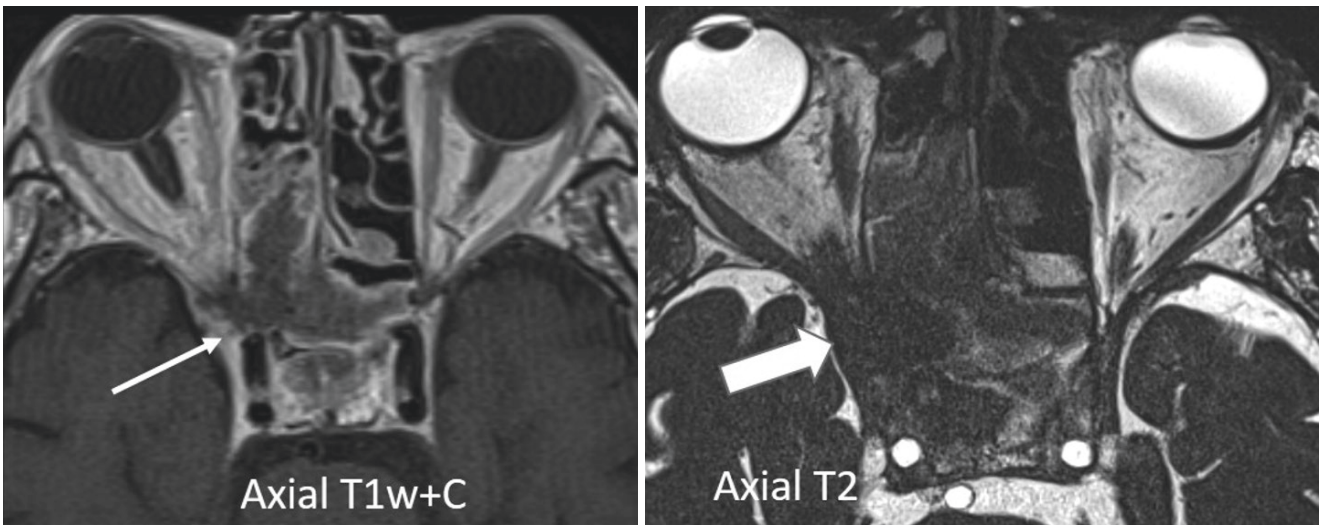

Fig. 8.6 Top: axial T1w + C and 3D isotropic heavily T2w sequences 3 weeks later showing spreading of inflammation to the anterior cavernous sinus (white arrow) and worsening necrosis (Block arrow) and enlargement of the abscess. Bottom: axial T1w FS + C and T2w FS sequences 3 months later showing worsening orbital, cavernous sinus and intracranial involvement (white arrows)

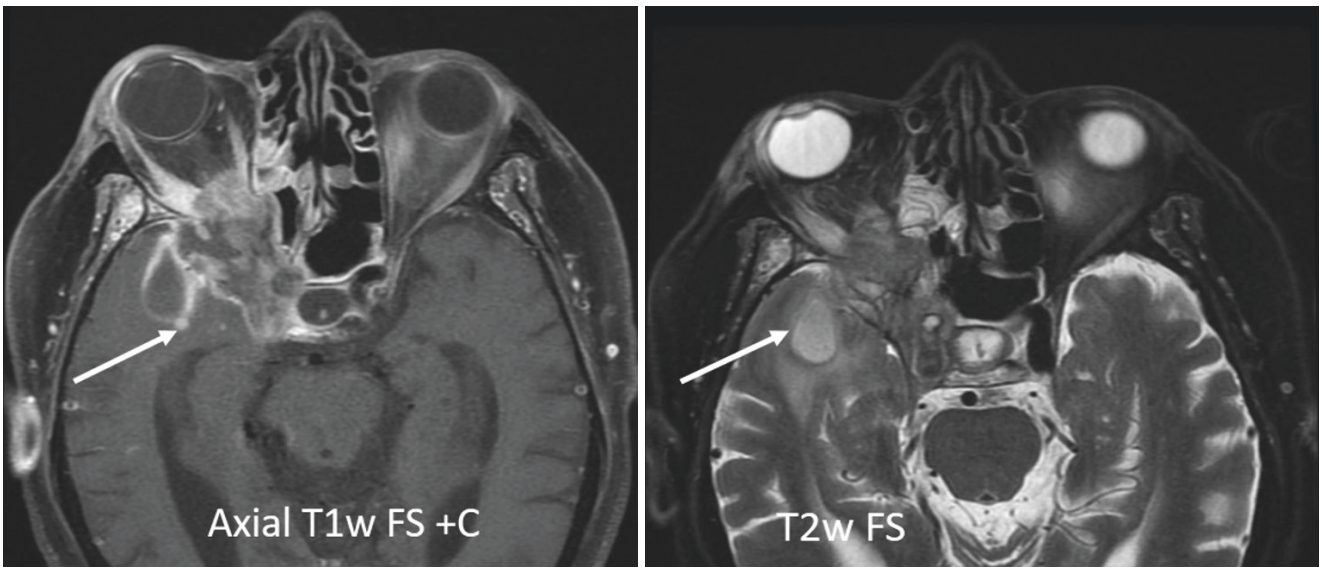

Fig. 8.6 (continued)

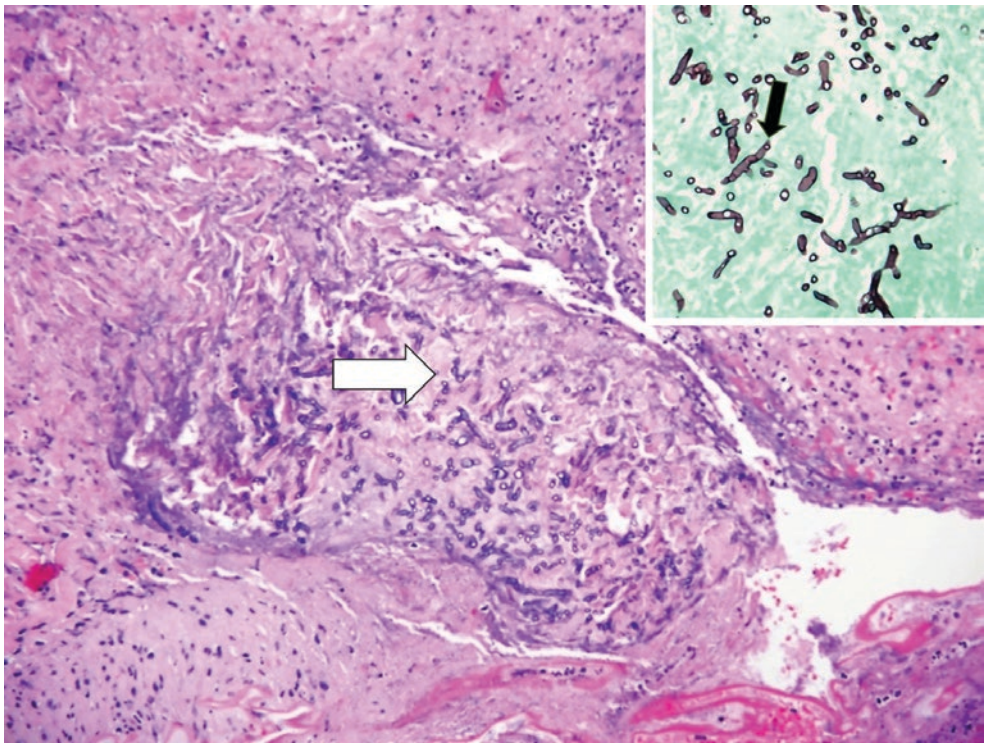

Fig. 8.7 A blood vessel is seen in the centre of the field. There is an organized thrombus within the vessel lumen within which are many fungal hyphae (white arrow). Septa are discernible (black arrow). HE stain; 200× magnification. GMS stain highlights the fungal hyphae (inset; GMS stain; 400× magnification)

Intervention

Biopsy was performed from the orbital apex by an endoscopic approach. Aspergillus PCR was positive in the tissues obtained by biopsy from the orbital apex.

Management

The patient was started on fluconazole and liposomal amphotericin B intravenously, but his condition worsened, and the patient died 5 months after the initial presentation.

Histopathology

The biopsy of the orbital apex showed a blood vessel containing an organized thrombus and adjacent to it, necrotic material. Fungal hyphae (highlighted by GMS stain) were seen within the thrombus in the vessel lumen and in the adjacent dense necrotic fibrous tissue.

Aspergillus could be recognized in histology as relatively thin fungal hyphae (approximately 3–6 um thick) which were septated and exhibited acute angle and dichotomous branching. The organisms were highlighted on special stains such as Gomori methenamine silver (GMS) (Fig. 8.7) and

periodic acid-Schiff (PAS). However, a definite diagnosis required microbiologic investigations, because other organisms could closely resemble *Aspergillus.*

Discussion

Invasive orbital fungal diseases are important causes of mortality and morbidity. Orbital fungal infections like the bacterial orbital cellulitis spread from the neighbouring sinuses, and are generally uncommon, but should be suspected in diabetics and immunocompromised patients with orbital cellulitis. Case 1 is an example of an acute invasive fungal infection that is usually caused by zygomycosis, a member of phycomycetes, in an immunocompromised individual. The condition is usually referred to as cerebro-rhino orbital mucormycosis (CROM).

Zygomycosis, also known as mucormycosis, is caused by fungus in the order Mucorales, of which *Rhizopus* species is the most common. It is an angiotropic fungus, and it is an obligate aerobe with nonseptate hyphae showing right-angled branches. The spores attach themselves to nasal mucosa and proliferate and germinate into hyphae. Patients with diabetes and ketoacidosis, accounting for 80–90%, are more prone to CROM, as the neutrophils are unable to mount a response. Mucor has a predilection for internal elastic lamina of the blood vessels, especially arteries, and forms thrombotic vascular occlusions resulting in gangrene and a haemorrhagic necrosis. The fungus also infiltrates nerves, causing loss of sensation and paralysis of extraocular muscles. There is very little inflammation, and the fungus thrives in dead organic tissue. The nonseptate hyphae are identified in all ocular tissues including the optic nerve.

Other than diabetes, patients with haematological malignancies, neutropenia (as in case 1), renal/bone marrow transplant, chronic renal failure, and iron overload are also predisposed to the development of CROM.

Clinically, there is destruction of the turbinates (seen as black turbinates in MRI), serosanguinous exudate from the nose, necrosis of the eyelids (blackening), and completely frozen orbit with ischaemic necrosis of all orbital tissues.

Diagnosis is difficult, as cultures often fail to grow mucorales. Culture can be taken from necrotic tissue. Rapid diagnosis may be possible using PCR. Early debridement, followed by local irrigation of antifungal agent, and intravenous amphotericin B, should be the treatment of choice. Rapid diagnosis and treatment seem to be the only way of reducing mortality or morbidity.

Case 2 is an example of a chronic invasive fungal infection. The predisposing causes were diabetes and previous radiotherapy with reduced local immunity. In chronic cases, the infection progresses slowly over months and, if untreated, spreads to the brain.

Aspergillus fumigatus often starts in the sphenoid sinus; the predilection for that sinus is poorly understood. As the fungus invades blood vessel walls and bone causing ischaemic necrosis and bony destruction, it spreads through the vessel walls or adjacent bony erosion into the orbit.

Invasive aspergillus infection occurs more commonly in immunocompromised patients with neutrophil deficiency and corticosteroid use. The other risk factors are diabetes, HIV infection and trauma. Rarely, there have been reports of aspergillus infection in immunocompetent patients. Aspergillus has a characteristic microscopic appearance. It has septate hyphae branching at 45°, seen well in PAS stain.

Clinically, persistent pain in the head and retrobulbar area is characteristic. Pain can precede ophthalmic symptoms. Imaging findings are subtle, and MRI may be the best modality, which shows focal enhancing lining in sphenoid sinus. Diagnosis is often delayed by months, as biopsy can yield negative results in about 50% of cases. If clinical suspicion is strong, a repeat biopsy would be necessary to clinch the diagnosis. Histologically, when fungal organisms are seen in the tissues, it is important to look for blood vessel invasion, which predicts a worse prognosis.

If treated early, the prognosis is better with a mortality rate of 25%. Intracranial extension is a significant factor in mortality of chronic invasive fungal infections. Fatality was described as 100% in two different studies. The treatment of choice is surgical debridement followed by local irrigation of amphotericin B, along with intravenous liposomal amphotericin B. The response rate is only 40–60% as the drug doesn't reach the tissues due to ischaemia. Voriconazole has been proven to be effective with less systemic effects than amphotericin B. If diagnosis is not certain, posaconazole can be used which has a wide spectrum of antifungal activity.

Learning Points

Invasive rhino-orbital fungal infections are rare, but must be considered in patients with immunocompromised status and diabetes. The diagnosis can be challenging, and it is important to obtain adequate diagnostic material for microbiological and pathological examination. Treatment should be started early and should include surgical debridement followed by irrigation of antifungal agent along with intravenous amphotericin B.

Mortality and morbidity are high in invasive fungal orbital infections.

Further Reading

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