Mucormycosis: early treatment is the key to survival

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Dot Points:

1) Mucormycosis should be considered in immunocompromised patients (including diabetics) presenting with sinonasal or orbital symptoms.
2) Any immunocompromised patient with suspected mucormycosis should receive immediate treatment with high-dose liposomal amphotericin B. Attempts to establish a diagnosis should continue, but not delay therapy.
3) Diagnosis should be made clinically; a thorough examination of the orbit and nasal cavity should be performed, and the hard palate should be checked for eschar. It should be kept in mind that clinical, nasoendoscopic, and imaging findings may be subtle. Histopathology and microbiologial investigations should confirm the diagnosis.
4) There may be a role for topical endonasal amphotericin in limiting disease spread following debridement.

Clinical record:

A 67-year-old man presented to his rural general practitioner with left facial pain. He has a background of insulin-dependent type II diabetes, psoriatic arthritis, and sarcoidosis treated with regular methotrexate and golimumab. A recent flare of sarcoidosis was treated with prednisone resulting in poor diabetic control (haemoglobin A1c =10.7%). He was initially treated for sinusitis with amoxicillin clavulanate, but hospitalised three days later for orbital cellulitis and commenced on intravenous (IV) ceftriaxone and flucloxacillin. He was transferred to our institution following further deterioration.

On day 5 since symptom onset orbital examination revealed no perception of light in the left eye, ptosis, proptosis, a non-reactive pupil, chemosis, complete ophthalmoplegia and paresthesia in the left ophthalmic and maxillary nerve distributions (Figure 1). Fundus examination demonstrated, mild diabetic retinopathy, a mildly swollen, pale optic nerve. Nasoendoscopy revealed subtle erythema of the lateral nasal wall and minor crusting on the middle turbinate which bled on contact.

Computed tomography (CT) showed inflammatory changes within the left orbit, and subtle evidence of a small collection between the globe and the lateral rectus (Figure 2). There was moderate opacification of the left ethmoid air cells and slight thickening of the maxillary sinus mucosa. Differential diagnoses included bacterial, fungal and viral infection and orbital sarcoidosis. He was commenced on daily liposomal amphotericin B (10mg/kg) IV. Repeat nasoendoscopy revealed a yellowish slough over the lateral nasal wall anteriorly, and pale mucosa over the middle turbinate which bled on contact. No pus, macroscopic fungus, eschar or dehiscence of the lateral nasal wall was evident.

We biopsied the superior orbital tissues which revealed clinical ischaemia and a necrotic medial rectus. There was fat and arterial necrosis with numerous fungal hyphae; broad and ribbon-like, suggestive of mucormycosis. Fungal polymerase chain reaction identified *Rhizopus arrhizus*. Neither swabs nor tissue cultures grew fungal species.

A left orbital exenteration with anterior and posterior ethmoidectomy, sphenoidotomy and excision of middle turbinate was performed, with aggressive debridement of necrotic mucosa to bleeding edges. Further debridement of the orbital apex was performed two days later, due to residual necrosis (Figure 3).

Medical management included withholding immunosuppressive medications and strict diabetic control. He developed acute renal toxicity so the amphotericin dose was lowered.

Magnetic resonance imaging demonstrated progression into the left cavernous sinus and cisternal portion of the trigeminal nerve. The amphotericin dose was increased, posaconazole was added, and haemodialysis commenced. Amphotericin-soaked gauze was used to pack the orbit, and hyperbaric oxygen was attempted but was poorly tolerated due to claustrophobia.

The infection gradually responded. The amphotericin was ceased after 12 weeks and dialysis ceased 2 weeks later with residual moderate renal impairment (creatinine =145, estimated glomerular filtration rate =40). Oral posaconazole was continued for 2 years. A forehead flap was used to cover the exenteration defect with good cosmetic outcome. At 3 years since presentation the patient is well.

Discussion

Mucormycosis is a rare infection caused by the Mucorales order of fungi, and characterised by rapid progression, vascular and perineural invasion, resulting in extensive tissue necrosis. (1) It typically develops in immunocompromised patients, but sometimes in otherwise healthy people.(2) Diabetes is an established risk factor, as is immune suppression from chemotherapy, immunotherapy, solid organ, and haematopoietic stem-cell transplants.(3) Mortality rates range from 40% to 80% depending on underlying conditions and sites of infection.

Rhino-orbital-cerebral infection usually originates from the paranasal sinuses, with subsequent invasion of the orbit and brain. Typical presentations include ophthalmoplegias, acute orbital apex syndrome and cavernous sinus syndrome. Diagnosis requires a high index of suspicion and delayed therapy is associated with higher mortality.(4) This case demonstrated only subtle signs on imaging and nasoendoscopy at presentation, including mucosal thickening on CT. Bone destruction involving the sinuses and orbit is often absent on CT if performed sufficiently early.(5) Diagnosis should be suspected on clinical grounds, but CT and MRI are required for excluding differential diagnoses, staging, identification of intracranial spread prior to symptom development, surgical treatment planning, prognostication and monitoring treatment effect.

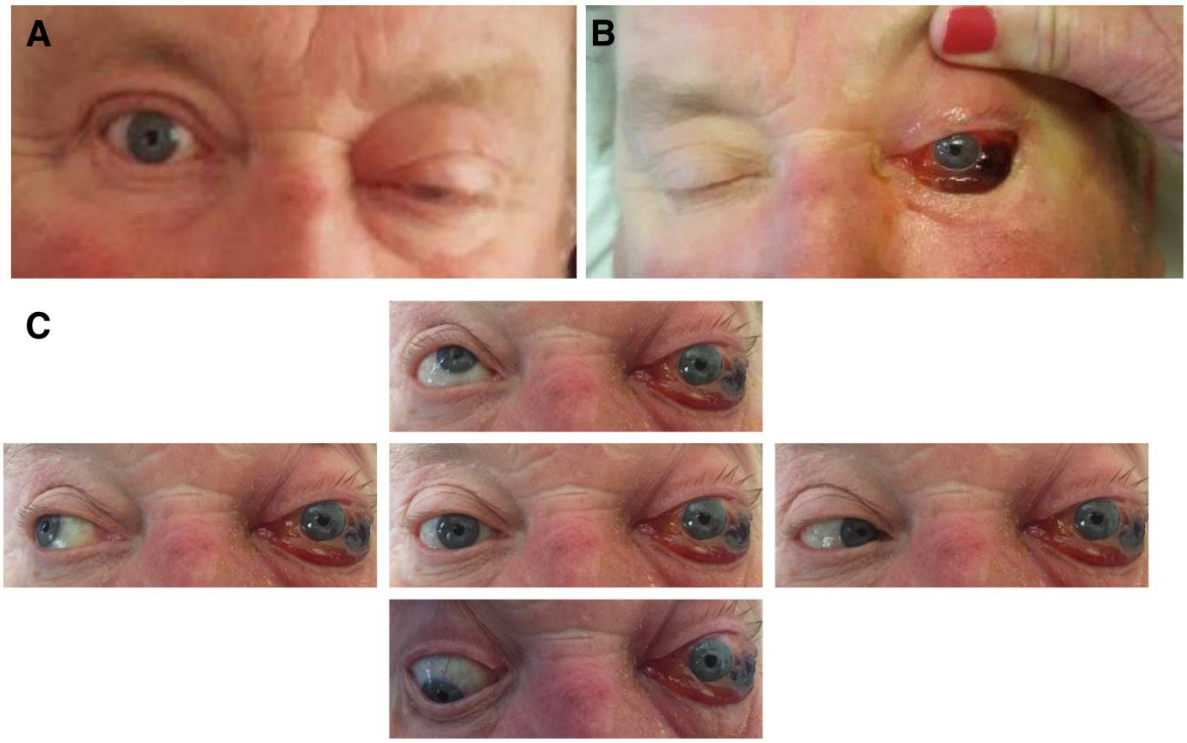
Guidelines suggest any immunocompromised patient with suspected mucormycosis receive immediate high-dose liposomal amphotericin B.(1) Continuing attempts to establish a diagnosis should not delay therapy. Prompt, aggressive surgical intervention enables disease control and histopathological and microbiological diagnosis.

Treatment should be continued until resolution of imaging findings and causes of immunosuppression are reversed.(1) Debridement should be repeated as needed. Renal toxicity from systemic amphotericin is usually reversible (6) and must be tolerated to maximize the chance of survival. We also used amphotericin-soaked gauze for topical delivery to a devascularised wound, which was easily accessible. (7)

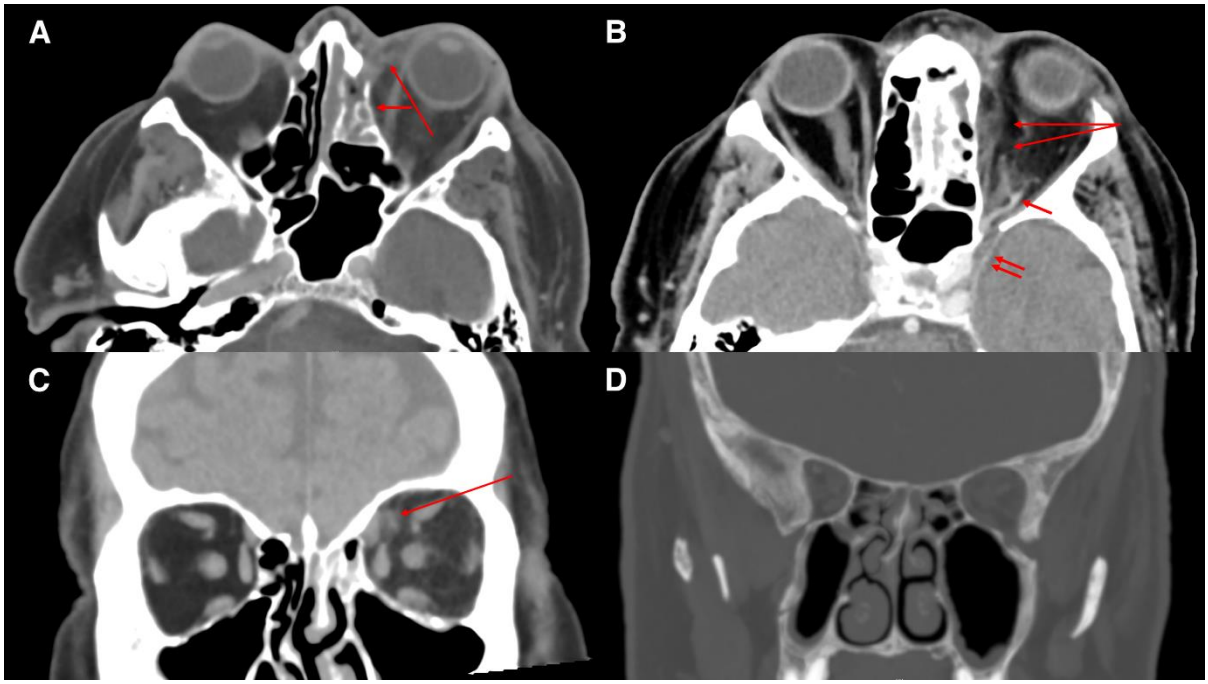
This case highlights the importance of early treatment and aggressive surgical intervention. It demonstrates the complexity of management associated with this condition, and the need for multidisciplinary care.

References:

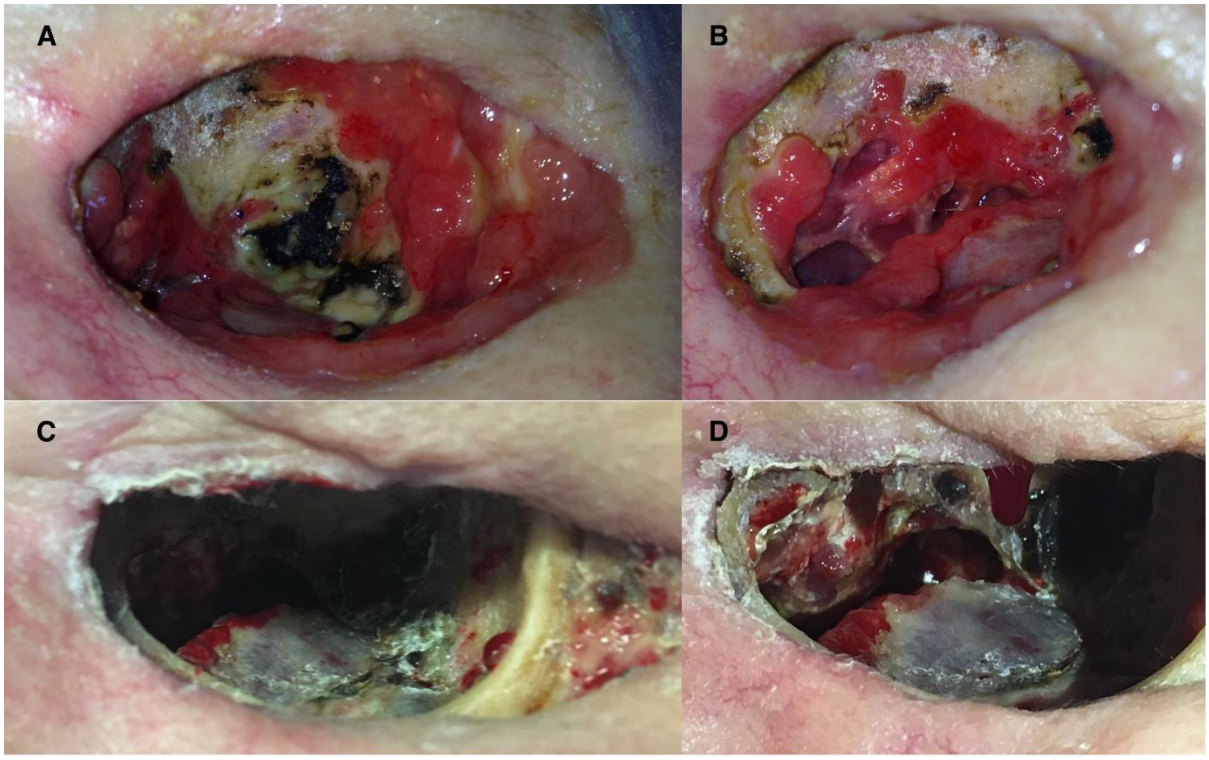
1. Cornely OA, Alastruey-Izquierdo A, Arenz D, et al. Global guideline for the diagnosis and management of mucormycosis: an initiative of the European Confederation of Medical Mycology in cooperation with the Mycoses Study Group Education and Research Consortium. Lancet Infect Dis. 2019;19: e405-e21.
2. Vaughan C, Bartolo A, Vallabh N, Leong SC. A meta-analysis of survival factors in rhino-orbital-cerebral mucormycosis-has anything changed in the past 20 years? Clin Otolaryngol. 2018; 43: 1454-64.
3. Prakash H, Ghosh AK, Rudramurthy SM, et al. A prospective multicenter study on mucormycosis in India: Epidemiology, diagnosis, and treatment. Med Mycol. 2019; 57: 395-402.
4. Chamilos G, Lewis RE, Kontoyiannis DP. Delaying amphotericin B-based frontline therapy significantly increases mortality among patients with hematologic malignancy who have zygomycosis. Clin Infect Dis. 2008; 47: 503-9.
5. Gamba JL, Woodruff WW, Djang WT, Yeates AE. Craniofacial mucormycosis: assessment with CT. Radiology. 1986; 160: 207-12.
6. Fanos V, Cataldi L. Amphotericin B-induced nephrotoxicity: a review. J Chemother. 2000; 12: 463-70.
7. Saedi B, Sadeghi M, Seilani P. Endoscopic management of rhinocerebral mucormycosis with topical and intravenous amphotericin B. J Laryngol Otol. 2011; 125: 807-10.



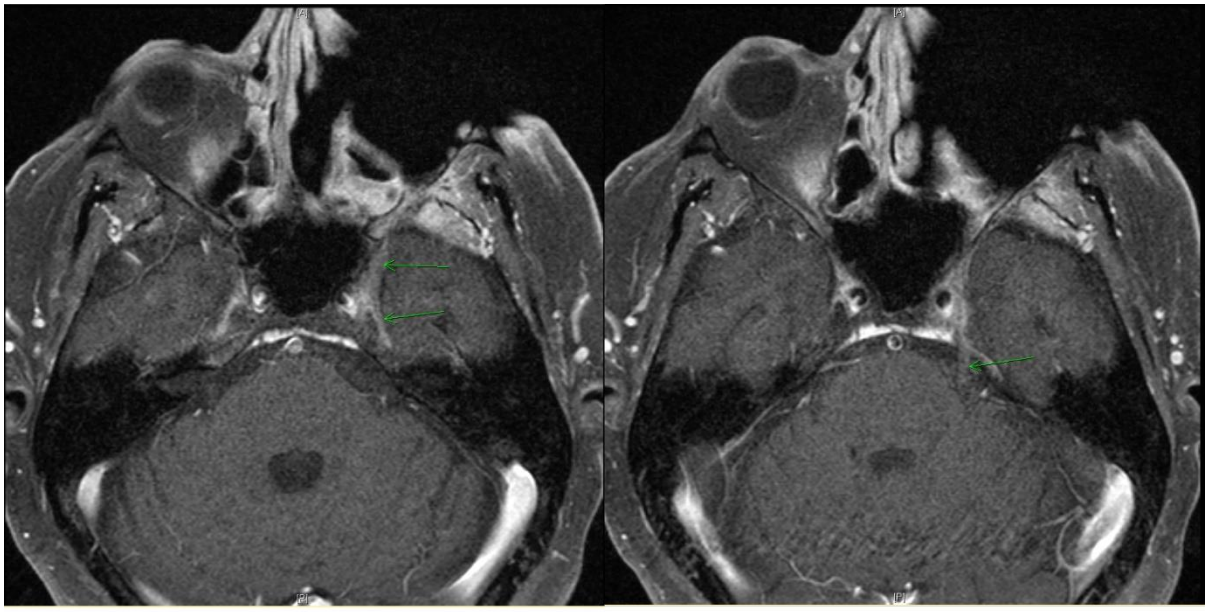
(A) The patient at time of admission to rural hospital with diagnosed orbital cellulitis; (B) after progression showing worsening proptosis and haemorrhagic chemosis; (C) At presentation to our institution showing proptosis, chemosis, miosis and complete ophthalmoplegia.



CT scan on arrival to tertiary centre: (A and B) Axial venous phase images demonstrating pre- and post-septal fat stranding medial to the globe (long arrow, A) and extensive soft tissue density material within the left ethmoid cells (short arrow, A). There is a subperiosteal / extraconal collection between the globe and medial rectus (long arrows, B). The left superior ophthalmic vein is dilated (short arrow, B) compared with the right, and there is fat stranding around a tributary suspicious for thrombophlebitis. There is subtle thickening of the dura overlying the lateral aspect of the left cavernous sinus compared to the normal appearance on the right (double arrows, B). Perivenular fat stranding is also visible in the coronal section (arrow C); (D) Coronal reconstructed image using bone window display settings demonstrating mild generalised ethmoid and maxillary sinus mucosal disease.



The exenterated left orbit: (A) early front-on post-operative image. Note the healthy granulation tissue peripherally with areas of black eschar surrounded by a necrotic slough; (B) Oblique view of medial left orbital wall. The lamina papyracea has been removed and the ethmoid air cells are visible medially; (C) Later front-on image demonstrating resolution of the eschar and necrosis; (D) Oblique view prior to discharge.



Contrast-enhanced T1-weighted axial MRI showing progression of disease: (A) enhancement within the left infratemporal fossa, and asymmetry of the cavernous sinus, and overlying dural enhancement (arrows); (B) enhancement of the trigeminal nerve.