Invasive fatal rhino-orbito-cerebral mucormycosis in diabetic ketoacidosis

George Garas • Natasha Choudhury • Roy Farrell

Department of Otorhinolaryngology and Head & Neck Surgery, Northwick Park Hospital, North West London Hospitals NHS Trust, London, UK

Correspondence to: George Garas. E-mail: garas_george@yahoo.com

DECLARATIONS

Competing interests
None declared

Funding
None

Ethical approval
Written informed consent to publication has been obtained from the patient or next of kin

Guarantor
GG

Contributorship
All authors contributed equally

Acknowledgements
None

Reviewer
James Fairley

Invasive rhino-orbito-cerebral mucormycosis, a rare opportunistic fungal infection which can rapidly lead to death is strongly associated with diabetic ketoacidosis.

Case report

A 52-year-old Indian woman presented to hospital with a one-week history of right-sided retro-orbital pain and facial swelling. She had no other significant past medical history.

On examination, she was found to be apyrexial with a pulse rate of 100 min^{-1} and confused. She also had evidence of right-sided periorbital cellulitis. Cranial nerve examination confirmed decreased visual acuity in the right eye (6/9) but with a full range of extraocular muscle movements. She was also noted to have an ipsilateral mild facial nerve weakness (House-Brackmann classification grade II).

Blood tests revealed a neutrophilic leukocytosis (31.6 x 10^9/L) with a C-reactive protein of 456 mg/L and random blood glucose of 56.1 mmol/L. Urine dipstick analysis identified the presence of ketones and blood gas analysis confirmed a metabolic acidosis. A clinical diagnosis of diabetic ketoacidosis was made and the patient was treated aggressively with intravenous fluid replacement, intravenous antibiotics (co-amoxiclav and metronidazole) and commenced on an insulin sliding scale.

An extended CT of the head including both orbits confirmed right periorbital cellulitis, with a degree of stranding of the extraconal adipose tissue consistent with Chandler classification grade II (Figure 1). There was no evidence of any intra-orbital collection or intracranial extension. However, imaging of the paranasal sinuses confirmed complete opacification of the right nasal cavity, maxillary and frontal sinuses, which were, therefore, presumed the source of sepsis.

The patient underwent an urgent endoscopic exploration under general anaesthesia. This revealed a large necrotic mass in the right nasal cavity which was excised and biopsies sent for histopathology, microscopy and sensitivity. Histopathological assessment revealed fungal invasion. The fungal hyphae were seen to be broad and distorted, branching at right angles and surrounded by extensive necrotic debris. No septae were present. The right nasal cavity and the involved paranasal sinuses were exenterated and irrigated. In view of the intraoperative findings and the histopathology report, parenteral amphotericin B was also added to the treatment regime. Despite an initial transient improvement in terms of her temperature and conscious level, the cranial neuropathies persisted and she subsequently deteriorated becoming more confused and losing vision completely from the right eye. An MRI scan of the head revealed evidence of predominantly right frontal cerebritis with early abscess formation (Figure 2). This was arising through direct extension from the nasal cavity into the frontal lobes, through the cribiform plate. Re-accumulation of fluid and thickening of the mucosa in the paranasal sinuses was evident radiologically but now with disease also affecting the sphenoid and ethmoid sinuses.

Further surgery including a right maxillectomy was performed, via a lateral rhinotomy approach. An orbital exenteration was also done as the right eye was found to be necrotic. The frontal sinus was opened and the mass seen to be extending into the dura. The dura was, therefore, also opened and

Figure 1
CT head including both orbits illustrating right periorbital cellulitis, with a degree of stranding of the extraconal adipose tissue (but no evidence of intra-orbital collection) consistent with Chandler classification grade II. Associated complete opacification of the right nasal cavity is evident

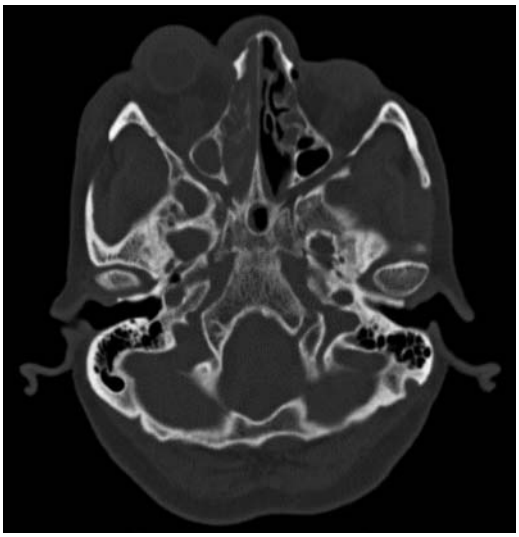
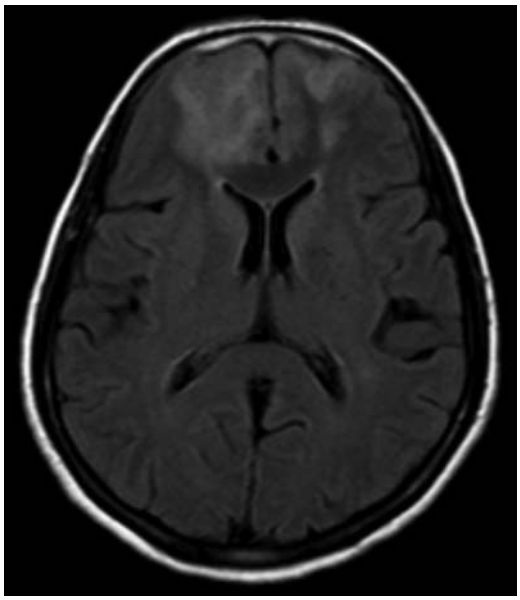


Figure 2
MRI brain revealing evidence of predominantly right frontal cerebritis with early abscess formation



necrotic cerebral parenchyma removed followed by repeated irrigation.

Postoperatively, the patient was transferred to the Intensive Care Unit (ICU) but failed to recover. She died 6 days later following a generalized seizure.

Discussion

Mucormycosis is a rare opportunistic infection caused by fungi of the class *Zygomycetes* commonly found in soil and decomposing plant materials including fruits.[1,2] Infection can be acquired via inhalation, ingestion or direct inoculation of wounds with the fungal spores.[3] Mucormycosis is a very aggressive, often fatal, disease almost exclusively affecting patients with an underlying immunosuppressive disorder, most commonly diabetes mellitus and haematological disorders.[1,4] Iron overload is also an important predisposing factor.[2] It equally affects both sexes and can present at any age. It can involve any body system.[1,3] Rhino-orbito-cerebral mucormycosis (ROCM) is the commonest form accounting for almost half of all cases.[2,3]

ROCM is thought to arise most commonly from inhalation of the fungus into the paranasal sinuses. Subsequently, upon germination, it can rapidly spread to involve neighbouring structures including the cavernous sinus, orbits and brain. In particular, the fungus has an affinity for the internal elastic lamina of arteries through which it can haematogenously disseminate to distant sites.[2] This process of cerebral angioinvasion produces extensive endothelial damage that can lead to mycotic aneurysms, dissection and/or thrombosis of the internal carotid artery with subsequent cerebral infarction.[3] It can occur rapidly accounting for the very high mortality associated with ROCM, even with aggressive treatment.[4]

As patients with ROCM may initially present with signs and symptoms mimicking bacterial rhinosinusitis and/or periorbital cellulitis and appear clinically stable (apyrexial in 50% of cases although leukocytosis is typically present – provided the bone marrow is functional - as in our case), the diagnosis is often missed until the

disease has significantly progressed, dramatically worsening the prognosis.[2,3] The additional presence of a headache, orbital inflammation, visual changes or multiple cranial nerve palsies should raise the suspicion of ROCM.[3] This is particularly true if the patient is diabetic, as 70% of ROCM cases occur in patients in diabetic ketoacidosis.[2,5]

If ROCM is suspected, prompt evaluation with radiological imaging and nasal endoscopy with biopsy of abnormal-looking tissue is mandatory to exclude the diagnosis.[2] Imaging modalities include CT and MRI. CT is useful in assessing the disease extent and typically shows mucosal thickening, opacification of the affected paranasal sinuses and periorbital tissue destruction. Moreover, it can display intracranial complications such as the presence of a cerebral abscess. CT is the optimal imaging modality to assess for bony destruction although this is often seen only late in the course of the disease.[6]

Alternatively, MRI (including MRA and MRV) is superior in visualizing and evaluating intracranial and intradural extent of the disease including thrombosis of the cavernous sinus and cavernous portion of internal carotid artery as well as soft tissue inflammation (e.g. in the orbit). The use of contrast enhancement aids the visualization of perineural spread of the disease.[3]

However, it is very important to appreciate that in early ROCM both CT and MRI may be normal as radiological findings lag behind clinical progression.[2,3] Hence, in high-risk patients, it is mandatory to progress to urgent endoscopic evaluation of the nasal cavity with biopsy of any suspicious areas.[3] Although frozen section has a role in expediting diagnosis and guiding the extent of surgical debridement,[7] the gold standard for diagnosing ROCM is histopathological examination of biopsy specimens. This typically demonstrates fungal invasion as evident by the presence of fungal hyphae branching at right angles and extensive necrotic debris surrounding the fungi, as in our case.[3,8] Fungal culture has a poor specificity and sensitivity as the organism is found in normal subjects and may be killed during specimen preparation. Serological, PCR-based and skin tests are all unreliable for ROCM.[2]

The differential diagnosis of ROCM includes sinusitis due to other opportunistic pathogens such as *Aspergillus*, as well as neoplastic disease, in particular lymphomas of the paranasal sinuses associated with HIV and AIDS.[8]

As 'time is of the essence in the management of mucormycosis',[2] treatment needs to be started as soon as clinical suspicion is present in a high-risk patient. This is to enhance survival and minimize the significant morbidity associated not only with the disease itself but also with the aggressive surgical debridement needed in the majority of cases. Treatment is multi-disciplinary and comprises of reversal of the underlying immunosuppresion (where possible), high-dose systemic anti-fungal therapy and radical surgical debridement.[1,7] Anti-fungal medications administered systemically in ROCM include intravenous liposomal amphotericin B in combination with parenteral posaconazole, a newer broad spectrum anti-fungal.[3] However, not all fungal strains are susceptible to these medications.[2] In addition, because of the angioinvasion caused by the fungi, vascular supply to affected body parts is poor, often preventing systemic medication from reaching the fungus to eradicate it.[2,3] Thus, early aggressive surgical debridement is the key to successful treatment of ROCM.[3] Indeed, in a case series of 49 patients with ROCM, the survival rate was 30% in patients treated with anti-fungal medication only while in those patients that received a combination of anti-fungal medication plus surgery survival was 86%.[9,10] Surgical treatment for ROCM often includes multiple repeat operations and may involve orbital exenteration and even removal of necrotic brain tissue, as in our case.[3]

Despite, this radical approach to treatment, the mortality associated with ROCM ranges from 50–80%, rising to >90% when disease is disseminated even without involvement of the central nervous system.[2,7]

References

1 Scheckenbach K, Cornely O, Hoffmann TK, *et al.* Emerging therapeutic options in fulminant invasive rhinocerebral mucormycosis. *Auris Nasus Larynx* 2010;**37**:322–8

2 Spellberg B, Edwards J Jr, Ibrahim A. Novel perspectives on mucormycosis: pathophysiology, presentation, and management. *Clin Microbiol Rev* 2005;**18**:556–69

3 Rapidis AD. Orbitomaxillary mucormycosis (zygomycosis) and the surgical approach to treatment: perspectives from a maxillofacial surgeon. *Clin Microbiol Infect* 2009;**15** (Suppl. 5):98–102

4 Cheema SA, Amin F. Five cases of rhinocerebral mucormycosis. *Br J Oral Maxillofac Surg* 2007;**45**:161–2
5 McNulty JS. Rhinocerebral mucormycosis: predisposing factors. *Laryngoscope* 1982;**92**:1140–3
6 Franquet T, Gimenez A, Hidalgo A. Imaging of opportunistic fungal infections in immunocompromised patient. *Eur J Radiol* 2004;**51**:130–8
7 Ghadiali MT, Deckard NA, Farooq U, Astor F, Robinson P, Casiano RR. Frozen-section biopsy analysis for acute invasive fungal rhinosinusitis. *Otolaryngol Head Neck Surg* 2007;**136**:714–19
8 Mnif N, Hmaied E, Oueslati S, *et al.* Imaging of rhinocerebral mucormycosis. *J Radiol* 2005;**86**:1017–20
9 Khor BS, Lee MH, Leu HS, Liu JW. Rhinocerebral mucormycosis in Taiwan. *J Microbiol Immunol Infect* 2003;**36**:266–9
10 Peterson KL, Wang M, Canalis RF, Abemayor E. Rhinocerebral mucormycosis: evolution of the disease and treatment options. *Laryngoscope* 1997;**107**:855–62