Rhinocerebral mucormycosis: a devastating rhinological condition

Abstract
Mucormycosis is an unusual but serious fungal infection that most commonly affects people with diabetes mellitus. A defining characteristic is the rapidity at which it develops and the devastation which it can cause. Copyright © 2014 John Wiley & Sons.

Practical Diabetes 2014; 31(1): 37–39

Key words
diabetes; glycaemic control; fungal infections; rhinocerebral mucormycosis

Introduction
Mucormycosis is a serious fungal infection that most commonly affects people with diabetes. A defining characteristic is the pugnacious rapidity at which it develops and attacks. Saprophytic aerobic fungi of the Phycomycetes class, which are common in the environment, can be transmitted through the inhalation of airborne spores, colonising the oral and nasal mucosa, paranasal sinuses and throat. In the normal host, there is a phagocytic response that destroys fungal reproduction, halting the infectious process.

However, in those with impaired immunity the response to this type of fungal attack is weakened. The majority of patients who contract mucormycosis have diabetes, often poorly controlled. Where there is a glucose rich, acidic, ketogenic environment together with weakened cellular immunity, the circumstances are ripe for the proliferation and spread of fungi throughout the nose. Other immunocompromised individuals are also susceptible; including those with haematological malignancies and patients undergoing chemotherapy or on other immunosuppressive therapies.1,2 Phycomycetes can grow extremely quickly when provided with the right conditions and fewer than 4% of cases occur without a recognised underlying cause.3,4

To aid its advance in vivo, the Mucor fungus has a predilection for lymphatics, arteries and nerves, the invasion of which causes the most serious consequences. Damage to cartilage, erosion of bone through the walls of the sinuses, spread into the orbit, retro-orbital area, along cranial nerves and via the meninges enable intracranial extension of disease. Occasionally, cerebral vascular infringement may lead to haematogenous dissemination of the infection, with or without development of mycotic aneurysms throughout the body.5

Vascular penetration produces a mucor thrombus, which occludes the fine blood vessels supplying the nose and sinuses. Blockage results in ischaemia and infarction and this directly produces the characteristic black necrotic eschars seen in this condition. There may be a purulent nasal discharge with dark necrotic material. This damage subsequently generates a more acidic micro-environment perfect for further fungal growth. This cycle of tissue degeneration, combined with high glucose and fungal entrenchment, fuels the rapid propagation of the disease.6

Incidence and disease presentation
Mucormycosis is a rare infection and as such it is hard to calculate the incidence of the infection. However, one American oncology centre revealed that mucormycosis was found in 0.7% of autopsies and roughly 20 patients per every 100 000 admissions. It is fortunate that it is a rare occurrence but it is crucial that it is not missed. Clinically, the signs and symptoms are non-specific and the extent of disease at the time of presentation can vary significantly. Like a great deal of rhinological disease, the nose has a limited repertoire of signs to display, making early diagnosis very difficult.
However, once the disease takes hold there is seldom any doubt in the mind of an experienced rhinologist. A patient may present with a short history of any of the following: headache, rhinorrhea, congestion, fever, facial pain, lethargy, epistaxis, eye irritation and lacrimation. On examination the nasal turbinates may appear grey or erythematous and may progress to black necrotic masses or ulceration. Infection can sometimes extend from the sinuses into the mouth and produce painful ulcerations of the hard palate. These patients may also have orbital findings and present with periorbital oedema and cellulitis. Invasion of the orbit results in proptosis and chemosis, and with advancing disease complete ophthalmoplegia and subsequent blindness.

At this point, the most important thing is to suspect the diagnosis of rhinocerebral mucormycosis (see Figure 1). A delay of even 12 hours in diagnosis may be fatal, as evidenced by the fact that autopsy series have found up to half of cases are diagnosed post-mortem.

Differential diagnoses are listed in Box 1.

Imaging (Figure 2) is extremely useful in evaluating the extent of disease. CT demonstrates thickened mucosa and sinus opacification but, unlike non-invasive sinilitis, there is no respect shown for the normal bony anatomy, and often extensive destruction of the bony boundaries of the nose and sinuses occurs. In these instances, MRI scanning evaluates the extent of orbital or intracranial involvement. Mucormycosis progresses rapidly, resulting in cavernous sinus thrombosis, carotid artery occlusion, and central nervous system infarction secondary to fungal thrombosis leading to hemiparesis, hemiplegia, coma, and death.

Whenever there is a clinical suspicion of mucormycosis, sufficient biopsy material should be obtained from the affected area and examined for the characteristic fungal appearance and specifically for the presence of fungal hyphae demonstrating vascular invasion, which clinches the diagnosis. Nasal scrapings and fine-needle aspiration cytology of parasanal masses can show fungal hyphae morphologically resembling *Mucor* giving a conclusive diagnosis of mucormycosis. Histological examination is considered more sensitive than cultures.

### Treatment

There are four main approaches to the treatment of rhinocerebral mucormycosis.

- Reversing the underlying physiological predisposition. This involves the management of hyperglycaemia, electrolyte disturbance and acidosis. Discontinuing any immunosuppressant therapy and the use of growth colony-stimulating factor (GC-SF) which helps to reconstitute host defences.
- Systemic anti-fungal therapy with amphotericin B. The dose should be rapidly increased to achieve the highest possible tissue levels. Its use can be limited by its toxic effects on renal, cardiac and marrow tissues.
- Use of adjunctive therapies such as hyperbaric oxygen which helps to reduce tissue hypoxia and inhibits the growth of Phycomycetes and has been shown to give significant improvement in patients with low survival rates.
- Medical treatment alone does not favour a good prognosis. The mainstay of treatment is immediate aggressive surgical resection of the whole lesion – this should be performed without delay.

The principle of effective surgical management is to debride thoroughly until one meets normal bleeding tissue. Patients may need repeated debridements. Both endoscopic and open techniques may need to be employed. Modalities include Caldwell-Luc, medial maxillectomy, ethmoidectomies, sphenoidectomies and even radical maxillectomy with orbital exenteration.

Wide excision should ideally occur before central nervous system encroachment. Owing to the rarity of mucormycosis, few substantial studies exist and there is understandably limited scope to enable a direct randomised comparison of different treatment modalities.

### Prognosis

If the patient survives the initial presentation, the extent of the disease dictates additional inpatient care. Further surgical debridement, surgical repair, and wound care may be required. Post surgical disfigurement and visual impairment are both highly likely and provision of reconstructive surgery is required once it is clear the disease has been
completely treated. Medical therapy needs to continue with tight glycaemic control, close monitoring for drug toxicity or recurrence of disease. Patients with hemiplegia, bilateral sinus involvement, facial necrosis, nasal deformity, associated renal disease and treatment with deferoxamine\textsuperscript{19} have a much poorer prognosis. Mortality with medical management alone is 58\%, while combined with surgical intervention it is substantially reduced to 17\%.

Since the introduction of combined therapy with amphotericin B and surgery, more than 80\% of the patients can be expected to survive a disease that was once universally fatal.\textsuperscript{20} Indeed, prior to 1955 there are no reported survivors of this hostile fulminating infection. Of note, the prognosis is much better if the disease has not penetrated beyond the sinus prior to surgical debridement; in local sino-nasal disease, the mortality has been reported to be <10\%. The nature of the underlying disease and the reversibility of the immune dysfunction are also important determinants of survival.

Because of the drastic nature of this devastating condition, the care of those that survive should be multidisciplinary. The infectious diseases team should be at the centre, managing antifungal therapy and coordinating other medical care. Other specialties’ involvement depends upon the extent of disease and could include neurosurgery, ophthalmology and plastic surgery, especially as there is often quite significant disfigurement following repeated debridements. Medical input may also include haematology, oncology, ITU and endocrinology for the management of unstable diabetes.

**Conclusions**

Rhinocerebral mucormycosis is a rare, deadly disease. Because the fungi that cause mucormycosis are widespread, the most appropriate preventive measures involve improved control of the associated underlying illnesses. It is important to educate at-risk patients about the signs of disease, such as facial swelling and black nasal discharge, and instruct patients to present promptly for evaluation if these signs occur.\textsuperscript{21} In the main, early recognition, suspicion and skilful ENT surgery make the greatest difference.

**Declaration of interests**

There are no conflicts of interest declared.

**References**


**Key points**

- Rhinocerebral mucormycosis is a severe fungal infection which, although rare, most commonly affects people with diabetes, hyperglycaemia being a wonderful substrate
- It is characterised by rapidity of onset, localised spread and destruction, and is associated with significant morbidity and mortality
- Imaging, biopsy and histological examination are important in helping to establish the diagnosis
- Metabolic control, antifungal therapy, hyperbaric oxygen and surgical resection (often removing large bits of the face) are the main approaches to treatment

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