Rhinocerebral mucormycosis

Introduction

This article discusses the management of a patient who posed diagnostic difficulties and reviews rhinocerebral mucormycosis.

Discussion

Mucormycosis is an angio-invasive infection caused by fungi of the order Mucorales.

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This includes species such as *Rhizopus*, *Rhizomucor*, *Cunninghamella*, *Apophysomyces*, *Saksenaea*, *Absidia*, *Mucor*, *Syncephalastrum*, *Cokeromyces* and *Mortierella*. These are normally saprophytic moulds in decaying matter and soil. It is a rare infection in humans, almost invariably being related to the presence of risk factors.

The risk factors for infection include immunosuppression states such as haematological malignancy, bone marrow or peripheral stem cell transplantation, solid organ transplantation, neutropenia, diabetes mellitus (with or without ketoacidosis), corticosteroids, and desferroxamine therapy for iron overload.

The mechanism of susceptibility in diabetes mellitus involves the combined effects of hyperglycaemia, ketosis and acidosis. Serum normally has a fungistatic activity, because transferrin reduces the free iron available to fungi (required for vital intracellular processes and growth). Acidosis temporarily disrupts the binding of transferrin to iron in the serum, increasing the availability of free iron for fungal growth. Furthermore, the presence of ketoreductase in the fungi is thought to allow them to use ketone bodies in their metabolism (Yeung et al, 2001). Diabetes is also associated with reduced neutrophil chemotaxis and poor adhesion to hyphae, again thought to be important in predisposing to infection.

The mode of presentation is usually related to the route of infection.

Case Report

A 77-year-old woman presented to the emergency department with worsening unsteadiness on her feet over the preceding 2 months. She had sustained a mechanical fall leading to head injury 3 weeks before presentation, followed by increasing confusion (as reported by her husband). She also gave a 2-day history of numbness overlying the left cheek bone. Her past medical history included type 2 diabetes mellitus (for which she was on metformin), hypothyroidism (for which she was on thyroxine replacement), and hypercholesterolaemia. Two months before presentation, she had been diagnosed with idiopathic thrombocytopaenic purpura, for which she was on high-dose prednisolone. The remainder of the history and review of systems were non-contributory.

At the time of admission, she was alert and oriented. She was pyrexial (temperature 37.7°C), other vital signs being within normal limits. On physical examination, she had a Glasgow Coma Score of 15/15 and mini-mental state exam of 7/10. There was mild sensory loss in the left maxillary area to light touch, with preserved sensation in the other divisions of the trigeminal nerve. Otherwise cranial and peripheral nervous system exam was unremarkable. No abnormalities were detected on intra-oral or on systemic examination.

Initial investigations demonstrated poor glycaemic control with a haemoglobin A_{1c} concentration of 12.8%. She also had a neutrophilic leukocytosis and elevated acute phase reactants. She underwent a computed tomography (CT) scan of her head (in view of the history of mechanical fall, confusion and unsteadiness on her feet), which was normal. Initial management involved intravenous rehydration, commencement of an insulin sliding scale and antibiotics for urinary tract sepsis. She was weaned off steroid therapy and her diabetes control subsequently improved. During the first week in hospital, she developed progressive numbness and swelling of the left side of her face. Examination showed erythema around the left cheek, soft tissue proliferation on the left nasolabial fold with some serous discharge from the left nostril, and a pigmented necrotic area on the hard palate with clearly defined margins (*Figure 1*). There was surrounding whitish exudate associated with the palatal lesion. CT scan of the paranasal sinuses indicated radio-opacity in the left maxillary sinus compatible with unilateral sinusitis, with intact palatal and antral walls. Initial biopsy of the palatal lesion demonstrated severe necrotizing active inflammation with microabscess formation, fat necrosis and vasculitis. Stains for fungi were negative and no viral inclusions were seen.

A rheumatology opinion was sought to consider a possible diagnosis of Wegener's granulomatosis. This was deemed unlikely, as she had no underlying rheumatological disease, and despite a vasculitis screen revealing a positive peri-nuclear anti-neutrophil cytoplasmic antibody, her anti-proteinase3 and anti-myeloperoxidase antibodies were within normal limits.

The palatal necrosis continued to progress despite intravenous antibiotics, so she underwent surgical debridement of the necrotic palatal mucosa. She continued to deteriorate, with left facial palsy and left sensori-neural deafness. Further CT imaging of her temporal bones showed a 'moth-eaten' appearance with lytic bony changes of her petrous temporal bones (*Figure 2*). Histological examination of specimens from the palatal debridement demonstrated ulceration, necrotizing sialometaplasia, extensive necrosis, and numerous large non-septate hyphae and spores.

The radiological and histological features thus confirmed rhinocerebral mucormycosis with skull base osteomyelitis. She underwent further urgent debridement involving the palatine bone, lateral nasal wall and all visible necrotic tissue. Eight weeks after admission, at the time of definitive diagnosis, intravenous AmBisome (liposomal amphotericin) was commenced at 1 mg/kg/day, increasing at a dose of 1 mg/kg over 5 days to 5 mg/kg/day. She failed to respond significantly to this treatment, and posoconazole was subsequently added on microbiological advice. She continued to deteriorate, becoming increasingly breathless and hypoxic. A chest X-ray demonstrated a granular appearance of both lungs fields, thought to be in keeping with a pulmonary invasion of the infection. A few days later, she went into respiratory arrest from which she could not be resuscitated.

Rhinocerebral mucormycosis occurs when fungal spores are deposited in the nasal turbinates. Other forms of presentation include pulmonary mucormycosis, with inhalation of spores into the lung; cutaneous mucormycosis (usually in those with previous skin trauma); gastrointestinal mucormycosis (secondary to ingestion of the spores, usually in malnourished immunocompromised individuals); and disseminated mucormycosis (affecting multiple organ systems).

Rhinocerebral mucormycosis is most common, and is usually seen in patients with poorly controlled diabetes, especially with ketoacidosis (Virally et al, 2002). It is a fulminant infection of the nasal cavity, paranasal sinuses and soft tissues of the orbit. Presentation may involve retro-orbital headache, facial pain, fevers, nasal stuffiness and black nasal discharge. Mucormycosis should be suspected in patients with a vasculitic illness associated with signs of tissue necrosis, as in black necrotic eschar formation in the nose or palate (*Figure 1*). Involvement of the hard palate is associated with a progressive refractory disease, leading to a poorer prognosis (Scheinfeld, 2007). Advanced disease may involve visual symptoms, e.g. diplopia or visual loss, indicating involvement of orbital nerves or vessels. The clinical differential diagnosis includes cavernous sinus thrombosis and aggressive orbital tumours.

Figure 1. Black necrotic eschar on hard palate.

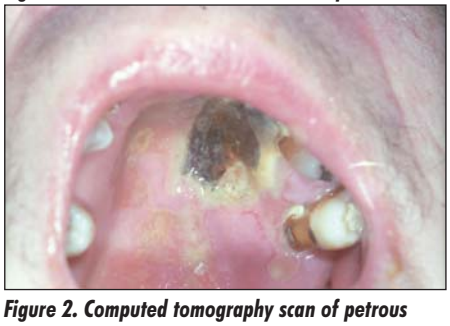
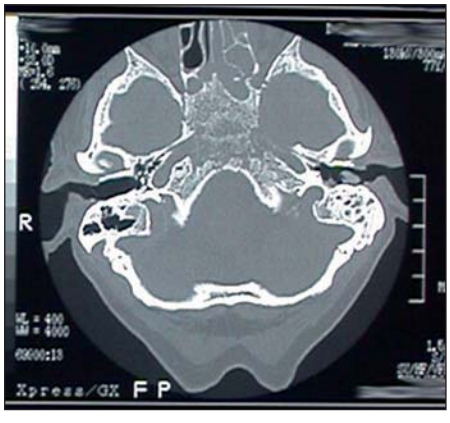


Figure 2. Computed tomography scan of petrous temporal bones demonstrating lytic bony changes.



A definitive diagnosis requires tissue biopsy, which identifies the characteristic hyphae. These are large (6–30μm) and non-septate, and demonstrate a pattern of branching that tends to occur at right angles to the parent hyphae. Radiological investigations including computed tomography scanning and magnetic resonance imaging are helpful in planning surgical intervention and assessing different stages of the disease rather than making definitive diagnosis, as the initial image findings may be indistinguishable from those of uncomplicated rhino-sinusitis. Advanced disease may further demonstrate bony erosion of walls of the paranasal sinuses and disease spread into brain matter or orbits. Demonstration of lesions surrounding blood vessels without producing a mass effect may be seen on imaging.

Treatment involves aggressive surgical debridement of necrotic tissue, systemic antifungal therapy and control of any underlying disease process. Improving control of the underlying predisposing condition (especially glycaemic control in diabetes) is associated with improved outcome (Yeung et al, 2001). Surgery should be undertaken without delay once the diagnosis is confirmed, and repeat surgical debridements may be required for local control of the condition. The mainstay of antifungal therapy is intravenous amphotericin B. High doses are required, i.e. 1–1.5 mg/kg/day, and nephrotoxicity may result. Less toxic forms such as liposomal amphotericin (AmBisome), colloidal dispersion (Amphotec) and amphotericin B complex are thought to allow higher doses to be used with less toxicity. Posaconazole (a triazole antifungal) has been approved for use in America, thereby adding to the therapeutic armamentarium (Barrak, 2007).

The prognosis in poorly controlled diabetic patients with rhinocerebral disease is generally poor (Tugsel et al, 2004) and timely medical and/or surgical intervention significantly improves the survival rate (Hilal et al, 2004). Thus, a high index of suspicion is needed in appropriate clinical settings, so as to diagnose and aggressively treat this infection, in view of the high mortality rate for susceptible patients. It should be included in the differential diagnosis when patients with diabetes mellitus present with or develop unusual and refractory infections. A concerted effort involving the clinician, microbiologist and radiologist is necessary to counter the potential threat from fulminant and invasive disease. **BJHM**

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