

A case of rhino-orbital mucormycosis in diabetes with haematogenous cerebral spread



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ABSTRACT

We document the first case of haematogenous cerebral spread in *Rhizopus arrhizus* rhino-orbital mucormycosis, and of posaconazole related adrenal insufficiency. A patient presenting with diabetic ketoacidosis and sinusitis was treated with right medial maxillectomy, ethmoidectomy and IV liposomal amphotericin. Orbital exenteration was performed after intraorbital spread of infection. IV caspofungin and posaconazole was added but complicated by adrenal insufficiency. MRI revealed a new left lentiform nucleus and thalamus rim-enhancing lesion indicating haematogenous cerebral spread.

1. Introduction

The management of people with type 1 diabetes mellitus largely focuses on the prevention and management of acute complications such as ketoacidosis, and long-term complications of retinopathy, nephropathy, and diabetic foot disease. It is also well known that there is a higher risk of infections in diabetes, but there is a lower level of awareness of rare infections such as mucormycosis, a rapidly progressive and invasive fungal infection with significant mortality rates.

The following case highlights an example of mucormycosis in diabetes that challenges our understanding of the mechanism of its spread. We also explore posaconazole treatment associated complications.

2. Case

A 44-year-old Chinese female with type 1 diabetes mellitus (T1DM) was hospitalised with diabetic ketoacidosis (DKA) (day 0). She had a history of recurrent DKA, foot ulcers with osteomyelitis, retinopathy and albuminuria.

Her serum glucose was 30.8 mmol/L, ketones 5.8 mmol/L, pH 6.90, HCO₃ 5 mmol/L, creatinine 65 μmol/L, and haemoglobin A1c 10.0%. There was leukocytosis (15.4×10⁹) and a C-reactive protein (CRP) of 234 mg/L. At presentation she was afebrile though tachycardic (HR 125bpm) with a blood pressure of 140/95 mmHg. Respiratory rate was 25/min and oxygen saturation was normal on room air (100%). Examination revealed foot ulcers on the plantar aspect of the first and third metatarsal phalangeal joints. She was treated with

clindamycin 450 mg 8 hourly.

Three months prior, her serum HbA1c had measured > 16% (> 151 mmol/mol). Her history was also notable for recent hospital admission six weeks prior with osteomyelitis of the foot due to methicillin resistant *Staphylococcus aureus* (MRSA) and Group B Streptococcus and concurrent bilateral pneumonia. At the time of this presentation there was no evidence of rhinorrhoea, facial swelling, headache or fever.

On day 3, the patient developed a tender right-sided facial swelling. Her vision and extra-ocular movements were unaffected. She was afebrile. Computerised tomography (CT) of the skull and orbits showed right-sided pansinusitis with evidence of preseptal orbital cellulitis and soft tissue inflammatory changes in the malar region of the face (Fig. 1). Bedside nasoendoscopy revealed only clear discharge and mucosal inflammation. She was commenced on nasal decongestant xylometazoline. Clindamycin was continued for presumed bacterial sinusitis. Ciprofloxacin was also commenced as *Pseudomonas aeruginosa* was grown in sputum cultures.

On day 5, as there had been no improvement, an exploration under anaesthesia was performed with discovery of necrotic eschar in the right maxillary sinus. There was macroscopic appearance of invasion of the right orbital floor. A right medial maxillectomy and anterior ethmoidectomy was performed and intravenous (IV) liposomal amphotericin (L-AMB) 5 mg/kg/day was commenced.

Ribbon-like non-septate fungal hyphae were seen on microscopy of debrided tissue. Culture of tissue specimens grew floccose grey colonies within 24 h of incubation at 30 °C which were identified as *Rhizopus arrhizus* by conventional morphology [1]. The species identity was

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Fig. 1. Computerised tomography (CT) of the skull and orbits - right-sided pansinusitis with evidence of preseptal orbital cellulitis and soft tissue inflammatory changes in the malar region of the face.

confirmed by DNA sequence analysis of the internal transcribed spacer (ITS) 1, 5.8S and ITS2 regions, and the D1/D2 region of the 28S (large subunit) ribosomal DNA gene cluster, using published primers and standard sequencing methodologies [2]. Blood cultures were negative.

On day 6, the patient developed a right-sided proptosis, visual loss (visual acuity 3/24), a non-reactive pupil, and restricted eye movements in the right eye in addition to sensory loss in the region of V1 and V2 of the trigeminal nerve. There was no evidence of cavernous sinus thrombosis on CT angiography. A magnetic resonance imaging (MRI) scan of the head demonstrated evidence of perineural spread of infection with enhancement of the right trigeminal nerve and Meckel's cave and enlargement of right infra-orbital nerve. Right inferior rectus muscle appeared enlarged. Oral posaconazole 200 mg 8 hourly was added to her antifungal regimen.

A right orbital exenteration and maxillary sinus debridement was performed. On microscopy, fungi were seen within the infraorbital nerve and within the walls and lumen of numerous infarcted vessels. Amphotericin soaked gauze was used for topical antifungal delivery to the orbit and IV caspofungin 50 mg daily was added.

A progress MRI on day 10 exhibited a right cavernous sinus filling defect and a new left lentiform nucleus and thalamus rim enhancing lesion (Fig. 2). A heparin infusion was commenced. Neurosurgical intervention was not undertaken. Posaconazole was changed from oral to 300 mg IV daily.

On day 15, the patient underwent further right orbital debridement after macroscopic orbital bone necrosis was noted on examination (Fig. 3). Caspofungin was ceased day 18.

On day 40, IV posaconazole was changed to oral posaconazole in tablet formulation 300 mg daily route and L-AMB ceased. She was discharged on day 55. As an outpatient she continued to be managed with the combination of oral posaconazole (serum level 1094 ng/mL) and amphotericin soaked gauze dressings for the orbit wounds.

Falling insulin requirements with episodic hypoglycaemia prompted testing for adrenal insufficiency. A short synacthen test confirmed inadequate adrenal response at 60 min (cortisol 422 nmol/L). Posaconazole was considered a probable cause for primary adrenal insufficiency given the known association between azole antifungals and impaired cortisol synthesis, and negative anti-adrenal antibody testing (indicating low likelihood that the adrenal insufficiency was autoimmune in nature). Due to progressive hypotension she was commenced on hydrocortisone replacement.

3. Discussion

Mucormycosis infection is considered a fungal emergency owing to its rapidly aggressive and invasive nature [3]. Infection can occur in various anatomical areas depending on the portal site of entry of spores, with predilection for certain sites based on comorbidities or risk factors. These include rhino-orbital-cerebral (ROC), pulmonary, cutaneous, gastrointestinal or disseminated forms (defined as two or more non-contiguous sites [4]). ROC infection follows inhalation of fungal spores into the sinuses and is the most common form in diabetes [4,5]. It sequentially invades sinus, orbital and cerebral tissue and morbidity relates to vascular invasion, thrombosis and necrosis, the hallmarks of the disease [3,6]. Reported mortality rates are high and range from 32% to 57% [5]. Delay in diagnosis and subsequent commencement of antifungal therapy are implicated in poor outcomes [3].

The environment created by diabetic ketoacidosis is particularly promotive of the growth of Mucorales due to their unique virulence traits [7]. Mucorales have an affinity for acidic environments and possess ketone reductase, an enzyme that allows them to thrive in states of diabetic ketoacidosis (DKA) [7]. In the largest case series to date, most infections in diabetic patients occurred in DKA (48% of T1DM and 34% of T2DM) [4]. Furthermore, these organisms survive through acquisition of iron from their hosts [3]. In acidic environments such as DKA, serum iron levels are elevated due to disruption of iron binding to transferrin [3,7,8].

Amongst people with diabetes, fungal acute sinusitis infection almost exclusively spreads via direct extension to surrounding structures [9]. Contiguous spread to cerebral tissue occurs through bony erosion or invasion of blood vessels, nerves and lymphatics [10]. If cavernous sinus involvement occurs, direct cerebral seeding may occur via the ethmoidal and orbital veins draining this area [11]. Haematogenous spread has mainly been reported in patients with a history of intravenous drug use. In these patients, spores are directly inoculated into the circulation then present as cerebral infection, usually in isolation, with preference for involvement of the basal ganglia [10,12,13]. There are higher levels of iron in these regions owing to increased expression of divalent metal transporter type 1, hence the basal ganglia environment may be particularly conducive to growth [13,14]. It is also thought that there is a relationship between the size of the Mucorales spore relative to the luminal size of the striatal

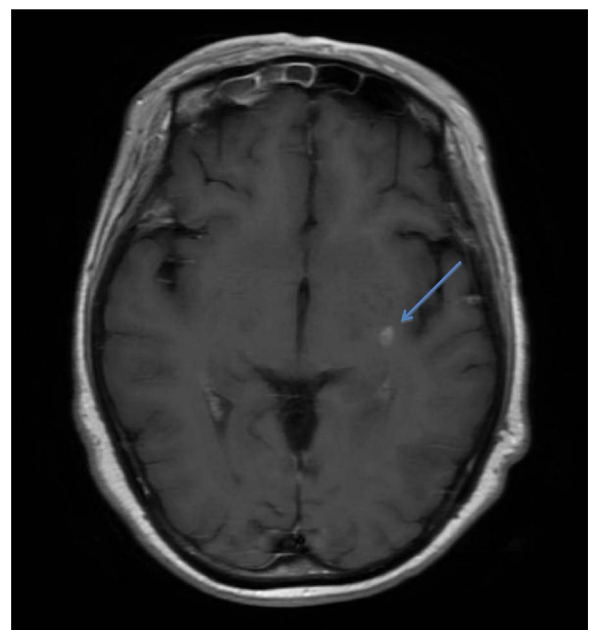


Fig. 2. MRI - new left basal ganglia (lentiform nucleus and thalamus) rim enhancing lesion.



Fig. 3. Macroscopic orbital bone necrosis.

arteries supplying the basal ganglia [4].

In the presented case, the appearance of a non-contiguous cerebral lesion in the basal ganglia is highly atypical of traditional ROC mucormycosis. Haematogenous spread following ROC mucor infection has not been previously reported. In fact, dissemination of any form in diabetes is rare with the largest case series reporting an odds ratio of 0.29 for disseminated infection in this population [4]. We infer that dissemination would have followed from significant fungal angioinvasion with development of fungaemia and subsequent cerebral seeding. The contralateral basal ganglia involvement supports this hypothesis, given the non-contiguous disease pattern. Often blood cultures are negative for fungus as they were for the presented patient [5].

The other novel aspect of this case is the development of mild adrenal insufficiency arising from posaconazole therapy. Other antifungals such as ketoconazole are known to cause adrenal insufficiency due to their effect on steroidogenesis. Fluconazole has a lower affinity for steroid metabolism enzymes and has also been associated with adrenal insufficiency albeit only in case reports and in critically ill patients [15,16]. Posaconazole is a relatively new extended spectrum azole that is being used with increasing success in mucormycosis infection. It inhibits fungal growth by inhibiting the enzyme lanosterol 14 α -methylase which is essential in ergosterol synthesis. Adrenal insufficiency with posaconazole has been reported in phase III clinical trials in patients treated for more than 6 months [17]. There have been no case reports in the post-marketing arena and it is considered an otherwise generally well tolerated drug [17,18].

Conflict of interest

Associate Professor Sharon Chen is a member of the Antifungal Advisory Board for MSD Australia, Pfizer Australia and Gilead Sciences, Inc. She has also received untied educational grants from the above.

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