Case Reports

Palatal mucormycosis in an immuno-competent infant following dengue haemorrhagic fever

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Background
Palatal mucormycosis is a rare, serious, fungal infection caused by fungi belonging to the order Mucorales, most commonly *Rhizopus* species and less commonly *Mucor, Rhizomucor*, and *Absidia* species[1]. While predominantly affecting adults with underlying medical conditions, it can occur less frequently in children[2]. The predisposing factors for mucormycosis in children are similar to those in adults, such as uncontrolled diabetes, immuno-compromised states, prolonged corticosteroid use, malnutrition or invasive medical interventions like insertion of nasogastric or endotracheal tubes[2]. Early diagnosis and prompt initiation of treatment are crucial for improving outcomes in children with palatal mucormycosis. Diagnosis is made through the microscopic identification of fungal hyphae in the tissue biopsy[3]. We present an infant with palatal mucormycosis with no underlying immunodeficiency or metabolic disease who received the longest duration of intravenous (IV) amphotericin B reported in Sri Lanka.

Case report
A Sri Lankan Muslim male infant was transferred to a medical unit after noting a blackish necrotic patch on the palate. He is the only child born to healthy, non-consanguineous parents. The antenatal period was uneventful. He was born at term with a birth weight of 2.6kg. There was no family history of early infantile deaths. At 4 months of age, he had a febrile illness, which was diagnosed as dengue haemorrhagic fever. He subsequently developed dengue shock syndrome and was transferred to the medical intensive care unit. Despite optimal management, he developed multi-organ failure with acute kidney and liver injuries, with tissue hypoxia leading to elevated lactate levels. He was intubated for 5 days. After extubating, he was noted to have a black, necrotic, foul-smelling patch on the palate on day 8 of his illness and he continued to have fever.

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Once haemodynamically stable, he was re-transferred to the medical ward for further care and evaluation. He received IV piperacillin, tazobactam, and flucloxacillin while he was managed for multi-organ dysfunction syndrome in dengue at the intensive care unit. The child initially received cephalosporin at the local hospital. Then, he was given 14 days of IV meropenem and 7 days of IV fluconazole due to continuing fever, thinking of ventilator or line-associated sepsis. Oral metronidazole was added to provide anaerobic cover due to the necrotic patch in the palate. Despite resolution of fever, the palatal necrotic patch persisted, along with the foul smell. He was referred to the Ear-Nose-Throat and Oro-Maxillo-Facial teams. Histological examination of the necrotic patch revealed aseptate broad fungal hyphae with branching, and a diagnosis of palatal mucormycosis was made (Figure 1). Although similar fungal hyphae were seen in the potassium hydroxide mount of the biopsy specimen, the infecting organism could not be recovered by culture.

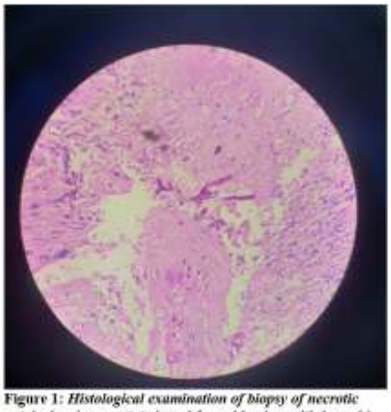

Figure 1: *Histological examination of biopsy of necrotic patch showing aseptate broad fungal hyphae with branching characteristic features of mucormycosis*

His lowest haemoglobin during the acute illness was 7.2 g/dL, and he received a blood transfusion. The mean haemoglobin thereafter was 9.8 g/dL. The mean total white cell count was 10,100 cells/cu mm, with 65% neutrophils. The mean platelet count was 212,000/cu mm. The highest C-reactive protein level was 58mg/L and the highest erythrocyte sedimentation rate was 30mm in the first hour. He had elevated blood lactate levels, the highest being 4.4 mmol/L. His blood culture was initially positive for *Staphylococcus* bacteria. No fungal growth was found. His liver and renal functions normalized after recovering from multi-organ failure. Immunological investigations showed no immunodeficiency, including flow cytometry, immunoglobulin levels, and the nitroblue tetrazolium test (NBT). HIV and hepatitis B/C screenings were negative. Metabolic screening did not suggest any metabolic disease.

After the histological diagnosis, the child was initiated on IV liposomal amphotericin B with the liaison of the mycology team. At the time of the tissue biopsy, debridement of the necrotic tissue was done. Necrosis was noted up to the left greater and lesser palatal vessels and loss of bone tissue, resulting in the loss of medial incisor teeth. Excision of mobile teeth under general anaesthesia was performed.

At 3 weeks of amphotericin B treatment, the first imaging was done. The contrast-enhanced computer tomography (CECT) of the palate showed bone changes that were suggestive of osteomyelitis (Figure 2). There was no abscess formation.

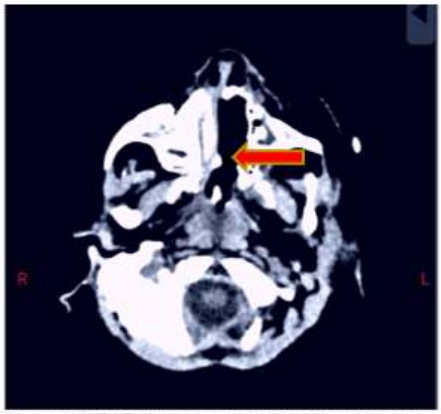

Figure 2: ***CECT of palate and skull showing destruction of palate and nasal septum due to palatal mucormycosis***

Magnetic resonance imaging (MRI) of the brain at 4 weeks of treatment showed no involvement of the brain or orbits (Figure 3). However, pan-sinusitis with bilateral mastoiditis was noted.

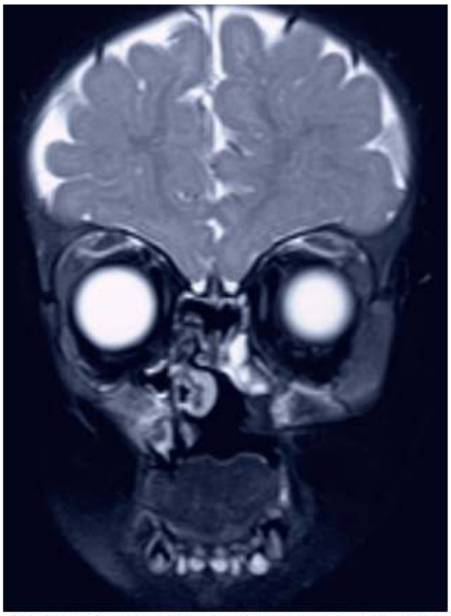

Figure 3*: MRI of face, palate and skull showing necrotic and eroded palate and nasal septum. Hyper intensities in the surrounding bones show evidence of active osteomyelitis. No involvement of orbit and cerebral structures*

A multi-disciplinary team decision was made to continue IV amphotericin B until clinical, mycological and radiological evidence of bone cure is achieved. Repeat imaging was done at 2 and 3 months of treatment, showing bone erosion with interval progression. At 5 months of treatment (day 156 of IV amphotericin), wound exploration was done under general anaesthesia. There was no clinical evidence of active bone lesions, and biopsy specimens showed no fungal hyphae.

However, IV amphotericin B was given for a total of 275 days, as repeated CECT and MRIs of the head and neck showed active bone lesions. Treatment was stopped after the last imaging showed no active lesions, and oral posaconazole was given for another 3 months. The course of IV amphotericin B was challenging as it was given through central lines and peripherally inserted central lines, which were complicated with thrombus formation and abscess formation. Serum creatinine was regularly monitored and was within normal limits. However, a successful, prolonged course was completed with complete recovery of the child. Five months after completion of antifungal therapy, the child is thriving well and remains asymptomatic. A prosthesis was inserted into the palatal defect and palatal closure is planned in due course by the plastic surgery team.

Discussion

Invasive mucormycosis has significant morbidity and mortality, especially in immunosuppressed children[1,2]. Mucormycosis cases are grouped into six main clinical entities: rhino-cerebral (ROCM), pulmonary, cutaneous gastrointestinal, disseminated and unusual presentations[3]. Rhino-cerebral disease can later spread to the hard palate and other facial structures, and it is the most common and serious entity. ROCM will gradually involve the nasal septum, epithelium, cavernous sinus, orbit, and brain. Hence, it is associated with high morbidity and mortality[4]. Palatal mucormycosis has less morbidity and mortality[5]. However, it is rare for palatal mucormycosis to occur in isolation; it usually spreads to involve the surrounding structures and, later, the orbit and brain[6]. We believe that the prompt and prolonged course of IV amphotericin B must have prevented the disease progression in our patient, thereby minimizing the morbidity.

The evaluation of our patient suggested that he is immuno-competent, and there is no evidence of metabolic disease. However, multi-organ failure and skin breach due to endotracheal intubation must have resulted in acquiring the disease. Our patient exhibited lactate levels as high as 4.4 mmol/L due to tissue hypoxia following multi-organ failure in dengue haemorrhagic fever. This highlights the fact that such rare but serious infections can occur in otherwise healthy children after a critical illness[6].

Causative organisms of mucormycosis are ubiquitous fungi commonly detected in the environment, particularly in decaying organic matter[1]. In tissue, Mucorales hyphae can often be distinguished from other common molds by their broad (3-25µm diameter), thin-walled, mostly aseptate hyphae. These hyphae have focal bulbous dilatation and non-dichotomous branching at occasional right angles[3]. Identification of Mucorales at the genus and species levels requires the cultivation of the fungus in a suitable culture medium to examine its morphological structures. Unfortunately, culture recovery of Mucorales

from tissue is inherently poor owing to the friability of the non-septate hyphae, making them more susceptible to damage during tissue manipulation[7]. This may be why our biopsy specimen did not yield a growth of the infecting fungus.

Surgical debridement is an important management aspect for histological diagnosis and clearing infected tissues. Surgical intervention may be difficult because of the surrounding delicate structures, the depth of the infection, and the difficulty in assessing the involved areas. Radical surgical debridement is usually necessary to get a cure[8]. Most children will require multiple surgeries. It is important to involve multiple surgical disciplines as the infection involves the head and neck region. The surgical debridement of our patient was done as a team effort by the ear-nose-throat surgery, plastic and reconstructive surgery, and oro-maxillary-facial surgery disciplines. Surgical input is later important in palatal reconstruction once the bone healing has been completed. Our patient is also scheduled for palatal reconstruction in due course.

Mucorales are inherently resistant to many antifungal drugs used to treat systemic mycoses. Amphotericin B is active against most agents of mucormycosis with a minimal inhibitory concentration (MIC) 90 of 1µg/ml. Posaconazole is the only currently available triazole with activity against several agents of mucormycosis with a MIC 90 of 0.25µg/ml[8]. In this patient, IV liposomal amphotericin B was initiated at 3mg/kg/day and later increased to 5mg/kg/day due to inadequate response.

The duration of treatment for mucormycosis is highly individualized[9]. The key deciding factors for the duration are near normalization of radiographic imaging, negative biopsy specimens and cultures from the affected side, and recovery from immune suppression. It was crucial to continue IV amphotericin B until radiological evidence of clearance was achieved[9]. Despite being a challenging course, we were able to continue treatment for our patient, which ended up being the longest duration of treatment for mucormycosis in both adult and child populations in Sri Lanka.

Here, we have reported a rare case of isolated palatal mucormycosis in an immuno-competent child who was successfully treated. As authors, we highlight the possibility of such rare clinical entities in children after critical illnesses.

Declaration of parental consent for publication

Informed written consent was obtained from the child's parents to publish the information and accompanying images about the child's illness.

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