Rhinocerebral mucormycosis with therapeutic challenges encountered in a rural resource constrained setting

J Sangwan1*, D Juyal1, V Negi1, M Singh2, N Sharma1

Abstract
Introduction
Rhinocerebral mucormycosis is the most serious, rapidly progressive, fatal form of the disease with a mortality rate of 70%–100% if not treated adequately and most commonly manifests itself in the setting of poorly controlled diabetes mellitus especially with ketoacidosis. Rapid progression and high mortality necessitate prompt recognition and aggressive treatment to increase survival rate.

We present a case of rapidly progressive rhinocerebral mucormycosis in a 17-year-old girl with ketoacidotic type 1 diabetes mellitus. The case exemplifies the therapeutic challenges encountered in a rural resource constrained setting.

Case report
A 17-year-old girl was brought to the emergency department of our hospital with the complaint of breathing difficulty for the last three days. On admission, she was febrile (39.1°C), had facial puffiness, marked left-sided hemifacial oedema, periorbital oedema, unilateral mucopurulent rhinorrhea, had acidic breath and difficulty in breathing. On physical examination, nasal wall and the upper lip showed necrotic lesions (more so) on the left side, also necrotic mucosal lesions in the oral and nasal cavity were evident.

Figure 1: Patient’s picture showing marked hemifacial and periorbital oedema on the left side (note the presence of black necrotised nasal wall and upper lip).

Figure 1: Patient’s picture showing marked hemifacial and periorbital oedema on the left side (note the presence of black necrotised nasal wall and upper lip).

Conclusion
Rhinocerebral mucormycosis is an acute opportunistic fungal infection, which follows an invariably fulminant course in diabetic patients. A rhinosinusal symptomatology in a patient with diabetic ketoacidosis should raise a high index of suspicion for possible rhinocerebral or rhinomaxillary mucormycosis.

Mucormycosis is an opportunistic and frequently fulminating fungal infection caused by members of the family Mucoraceae, order Mucorales and class Zygomycetes. Common genera involved are Rhizopus, Mucor and Absidia which are ubiquitous fungi surviving on decaying vegetation and diverse organic matter. The major predisposing factors for acquisition of mucormycosis are uncontrolled diabetes mellitus (DM), metabolic acidosis, haematological malignancies and immunosuppression. Depending on the patient’s immunological status disease may manifest as rhinocerebral, pulmonary, cutaneous, gastrointestinal or haematogenous form.

Rhinocerebral mucormycosis (RCM) is the most serious, rapidly progressive, fatal form of the disease with a mortality rate of 70%–100% if not treated adequately and most commonly manifests itself in the setting of poorly controlled DM especially with ketoacidosis (KA). Rapid progression and high mortality necessitate prompt recognition and aggressive treatment to increase survival rate.

We present a case of rapidly progressive RCM in a 17-year-old girl with ketoacidotic type 1 DM. The case exemplifies the therapeutic challenges encountered in a rural resource constrained setting.

Case report
A 17-year-old girl was brought to the emergency department of our hospital with the complaint of breathing difficulty for the last three days. The patient’s medical history included type 1 DM, with poor drug compliance. Her parents gave a history of odontalgia which she developed after using a match stick as a tooth pick. She took prescription from Vaidh (unauthorised medical practitioner in the village) and used clove oil and some local herbs for the treatment. After two to three days she developed low-grade fever, lethargy, purulent blood tinge nasal discharge from the left nostril.

On admission, she was febrile (39.1°C), had facial puffiness, marked left-sided hemifacial oedema, periorbital oedema, unilateral mucopurulent rhinorrhea, had acidic breath and difficulty in breathing. On physical examination, the nasal wall and the upper lip showed necrotic lesions (more so) on the left side (Figure 1), also necrotic mucosal lesions in the...
oral and nasal cavity were evident. Blood work-up revealed haemoglobin: 10.8 gm/dl; total leukocyte count: 17,000 cells/mm³ and differential leukocyte count: 83% polymorphs, 13% lymphocytes, 4% monocytes and 1% eosinophils. Erythrocyte sedimentation rate was 55 mm in the first hour and C-reactive protein levels were raised (2.4 mg/dl). Random blood sugar was 490 mg/dl and kidney function tests were slightly impaired. On urinalysis glucosuria and ketonuria were detected. Computed tomography (CT) of the paranasal sinuses (PNS) showed diffuse soft tissue inflammation and oedema involving mainly the left side of the face (maxillary region, preseptal region of left orbit, left temporal and frontal soft tissue). Bilateral maxillary and ethmoidal sinus fluid levels were consistent with acute maxillary and ethmoidal sinusitis with involvement of nasal cavity. No cerebral or post sepal orbital (apart from the eyelids) extension and bony destruction was seen. CT findings were not very conclusive and were suggestive of maxillofacial cellulitis and rhinosinusitis.

Considering the clinical manifestations and CT scan findings, a provisional diagnosis of bacterial sinusitis/fungal sinusitis was made. The patient was put on intravenous fluconazole, amikacin and amoxicillin-clavulanate and was transferred to the medical intensive care unit where she was put on ventilator support. In addition, the patient received insulin therapy for correction of hyperglycaemia and KA.

Purulent nasal discharge and scraped material from the necrotic lesion on the palate were received in the microbiology laboratory for gram staining, Giemsa staining, potassium hydroxide (KOH) mount, fungal culture and bacterial culture. For bacterial culture, the samples were inoculated on 5% sheep blood agar, MacConkey agar and incubated at 37°C. For fungal culture, samples were inoculated on Sabouraud’s dextrose agar (SDA) slants with 0.05 mg/ml of chloramphenicol and were incubated at 25°C. Analysis of 10% KOH mounts and Giemsa-stained smears of both the specimens showed the presence of broad hyaline aseptate hyphae with irregular branching morphologically suggestive of Zygomycetes (Figure 2a and b). With a diagnosis of RCM, amphotericin B 1 mg/kg/day was added to the regime and fluconazole was omitted. The random blood sugar level was brought down to 320 mg/dl but was still well above the normal range. Otorhinolaryngology was consulted urgently, maxillectomy with extensive surgical debridement of necrotic tissues of nasal wall and palate was suggested but high blood glucose levels and the unstable condition of the patient did not allow this.

A rapidly growing white fluffy, tube-filling growth was observed after 48 hours on SDA without cyclohexamide, and turned grey with time (Figure 3a). Similar growth was seen on blood agar plate too. Lactophenol cotton blue tease mount from SDA (Figure 3b and c) showed wide aseptate mycelia, with rhizoids coming off directly from the stolon and sporangiophore. The sporangia were round and filled with numerous figures.
Case report

Discussion

Mucormycosis is an increasingly emerging life-threatening infection. Out of all the clinical forms RCM is the most common and fatal form of the disease and represents 35%–50% of all the cases of mucormycosis. RCM is further divided into two subtypes: rhino-orbito-cerebral (involving orbit and CNS) and rhinomaxillary form (involving PNS).

While mucormycosis has been reported in otherwise healthy individuals; a predisposing medical condition is virtually always present. The most important predisposing factors are haematological disorders and poorly controlled DM particularly if associated with KA. Jung et al. in their case series reported 100% mortality with diabetic KA (DKA) and hence proved it to be the single determinant factor. Acidosis decreases neutrophil chemotaxis and phagocytosis, inhibits iron binding of the transferrin resulting in an increased proportion of unbound iron, which promotes the fungal growth. RCM usually begins in the nasal mucosa or palate and extends to the PNS and retro orbital region. Once the fungal hyphae enter into the bloodstream, they can disseminate to other organs such as the lung or cerebrum. Deteriorating mental state is an ominous sign, often heralding intracerebral extensions of the disease process. Typical clinical presentation includes fever, headache, lethargy, facial pain, facial cellulitis, presence of black eschar on palatal or nasal mucosa and drainage of pus from eye or/and nose. Initial radiological findings may be indistinguishable from those of simple rhinosinusitis and are helpful in assessing the stages of disease rather than making definitive diagnosis. Bony erosion is only the late feature of the disease. Definitive diagnosis requires histological identification of the fungus in tissue specimens or isolation of the fungus in culture. It has been suggested that any patient with DKA who presents with clinical and radiological findings of rhinosinusitis should be suspected as having RCM until proven otherwise.

All these findings (except for orbital discharge) were consistent in our patient. On the basis of clinical presentation, CT scan picture (suggestive of rhinosinusitis) and preliminary microbiological findings (KOH mount and Giemsa staining), rhinomaxillary mucormycosis was the most acceptable terminology. Fungal culture reports later revealed Rhizopus spp. to be the causative agent. The organism is known to disproportionately affect the patients with DKA. Rhizopus spp. has an active ketone reductase system and thrives in high glucose and acidic condition. The decreased phagocytic activity due to impaired glutathione pathway (as seen in patients with DKA) further facilitates the growth of this organism. Rhizopus spp. alone is responsible for 60% of the total mucormycosis and 90% of the RCM cases.

The successful management of mucormycosis depends on four major elements: early diagnosis, appropriate aggressive antifungal therapy, surgical debridement and resolution of the underlying condition. The mainstay of treatment is systemic amphotericin B and the highest possible tissue levels should be achieved. As the drug is nephrotoxic so careful monitoring of the renal functions is the essential part of the therapy. Liposomal amphotericin B has better results and is less toxic but is beyond the reach of most of the patients as it is quite expensive.

Despite aggressive therapy with amphotericin B the unfortunate outcome of our patient was multifactorial. Persistent high blood glucose levels may have contributed to the rapid proliferation and dissemination of fungi as it receives nourishment from sugars. Also the surgical debridement could not be performed and poor vascular supply may have prevented the drug to reach the infected site which possibly deteriorated the condition further and the patient could not recover. Studies have proved that the antifungal therapy combined with surgical debridement is more effective than antifungal therapy alone. Other therapeutic modalities such as adjunctive hyperbaric oxygen therapy, nasally nebulised amphotericin B and granulocyte–macrophage colony stimulating factor can improve the patient outcome, but due to our limited resources and economic constrains of the patient’s family these adjunctive therapies could not be started.

Conclusion

RCM is an acute opportunistic fungal infection, which follows an invariably fulminating course in diabetic patients. A rhinosinusal symptomatology in a patient with DKA should raise a high index of suspicion for possible rhinocerebral or rhinomaxillary mucormycosis. Although absence of intracranial or orbital extensions are...
indicator of good prognosis but DKA at present is the single most important detrimental factor for morbidity and mortality associated with this disease.

Consent
Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Acknowledgements
The authors would like to acknowledge Dr Prakash P Yagneshwaran (Department of Microbiology–Mycology division) and Dr Anurag Ayachit (Department of Radiodiagnostics and imaging), Kasturba Medical College, Manipal for their advice and guidance in preparation of this manuscript.

References