

## **Rhinocerebral Mucormycosis**

Tariq Ghafoor ( Department of Paediatrics and Otolaryngology, PNS Shifa, Karachi. )  
Amer Majeed ( Department of Paediatrics and Otolaryngology, PNS Shifa, Karachi. )  
Sher Muhammad ( Department of Paediatrics and Otolaryngology, PNS Shifa, Karachi. )  
Shahid Mahmud ( Department of Paediatrics and Otolaryngology, PNS Shifa, Karachi. )  
Arshad Mahmood ( Department of Paediatrics and Otolaryngology, PNS Shifa, Karachi. )

### **Introduction**

Mucormycosis is a rare but aggressive opportunistic fungal infection. The genera most commonly responsible are *Mucor* or *Rhizopus*.<sup>1</sup> These fungi are ubiquitous, surviving on decaying vegetation and diverse organic material. Because rhinocerebral mucormycosis (RCM) occurs infrequently it may pose a diagnostic and therapeutic dilemma for those who are not familiar with its clinical presentation.<sup>2</sup> Early clinical recognition of this potentially fatal disease followed by aggressive debridement, systemic antifungal therapy, and control of underlying co-morbid factors is the mainstay of therapy. Survival has improved dramatically, yet deaths still occur if the infection is not recognized and treated early in its course or if the source of immunocompromise is not reversible.<sup>3</sup>

We report a case of RCM involving the left orbit and ethmoidal paranasal sinus in a ten years old girl having diabetic ketoacidosis and renal impairment. It was successfully treated with control of hyperglycemia, aggressive surgical debridement and systemic Amphotericin B. To our knowledge no case of RCM associated with diabetes mellitus and renal impairment in paediatric age group has been reported so far in our country. The need for a high index of suspicion, early diagnosis and prompt therapy is emphasized.

### **Case Report**

A ten years old girl was admitted in the paediatric ward of PNS SHIFA Hospital Karachi, with the complaint of breathing difficulty for last 3 days. She had no history of fever, cough, vomiting, increased frequency of micturition, dysuria or any other systemic disorder. There was no past history of bronchial asthma, respiratory illnesses, medications or hospitalization. Her birth, developmental and family history were unremarkable. On examination her anthropometric data was below the 3rd centile for age. She had acidotic breathing, tachycardia and

normal temperature and blood pressure. Systemic examination was normal except few crepitations on chest auscultation. Investigations showed raised blood glucose (591mg/dl = 32.8 mmol/L), increased total leukocyte count (20.7x10<sup>9</sup>/L) normal haemoglobin (12.4g/dl) and platelet count (395x10<sup>9</sup>/L). She had mild renal impairment (serum urea 26.3mg/dl (9.4 mmol/L), serum creatinine 1.66mg/dl (147 umol/L), serum sodium 136 mmol/L, serum potassium 4.4 mmol/L. Urine examination was positive for ketone bodies and serum bicarbonate level was decreased to 15mmol/L.

Considering the clinical picture and investigations, a diagnosis of diabetic ketoacidosis (DKA) was made and her management was started with insulin therapy in conjunction with antibiotics and fluid replacement. Unexpectedly despite the appropriate management her condition deteriorated; she became unconscious, febrile and oliguric. Her renal function tests showed further aggravation in renal impairment. Serum urea increased to 99.4 mg/dl (35.5 mmol/L), serum creatinine was raised to 5.69 mg/dl (503 umol/L), serum sodium 136 mmol/L, and serum potassium increased to 4.9 mmol/L. However, with conservative management of renal impairment, intensive insulin therapy and antibiotics her general condition gradually improved and she became conscious and orientated on 6th day of hospitalisation. Her serum glucose, urea and creatinine values improved somewhat but still remained deranged.

Within the next two days she developed yellow coloured discharge from left eye along with proptosis, restricted ocular movements and deterioration of vision.

Immediate consultation of ophthalmologist was asked, who made a diagnosis of left 3rd nerve palsy with central retinal artery occlusion most probably due to orbital cellulitis. However, computerized tomography (CT) scan of orbit and brain was ordered to rule out any space occupying lesion. She had mucoid discharge from the

nose and examination by otolaryngologist documented a black membrane sticking to middle portion of the nasal septum and black slough over the left side of hard palate. These findings were suggestive of fungal sinusitis. The CT scan showed a mass in left ethmoidal sinus extending into retrobulbar area of left eye. No intracranial extension of the mass was documented on CT scan (Figure 1).

External ethmoidectomy and surgical debridement for orbital decompression was performed on 12th day of hospitalization (Figure 2). Amphotericin B infusion at 1 mg/kg (20 mg) daily was started along with broad spectrum antibiotics. The biopsy specimen was sent for histopathology and culture. The culture yielded the growth of mucor species after 5 days incubation at 28°C. Serum urea and electrolytes were monitored daily and renal impairment did not deteriorate during Amphotericin B therapy and she required only conservative management. At discharge after 48 days of hospital stay, she had ptosis and finger counting vision of left eye. Her renal function tests, liver function tests, blood glucose and blood counts were within normal range. She was advised to continue insulin therapy for life and visit the paediatric out patient department fortnightly. No clinical evidence of relapse of mucormycosis was observed during follow up visits within next six months.

## Discussion

Mucormycosis is primarily a disease of subjects with altered host defences associated with underlying conditions and predisposing factors such as diabetes mellitus, haematologic malignancies, chemotherapy, radiotherapy, neutropenic states, persistent acidosis, iron or aluminium overload, protein energy malnutrition, diarrhoea, dehydration, metabolic acidosis in small children, renal failure specially chronic cases on haemodialysis, corticosteroid therapy, organ transplantation, and less frequently, AIDS.<sup>4,5</sup> In addition to immunosuppressed children, mucormycosis also has been observed in neonates (especially premature), and children with a history of incidental trauma.<sup>6</sup> The mechanism by which uremic patients are predisposed to mucormycosis is not clear. Probably, the altered immunologic state, acidosis and neutropenia, all play a role in the pathogenesis.<sup>5</sup> Diabetic patients are predisposed to mucormycosis because of the decreased ability of their neutrophils to phagocytize and adhere to endothelial walls. Furthermore, the acidosis and hyperglycemia provide an excellent environment for the fungus to grow.<sup>6</sup>

The disease may affect as any of the following seven systems: (i) rhino-cerebral, (ii) pulmonary, (iii)

gastrointestinal, (iv) CNS, (v) utaneous, (vi) disseminated, and (vii) miscellaneous (bones, joints, heart, kidney, mediastinum). RCM is the commonest form of phycomycosis.<sup>5</sup> The cephalic phycomycosis has two forms: 1) rhino-orbital cerebral, which may be fatal, and 2) rhino-paranasal sinuses, which usually has a benign clinical course.<sup>7</sup> Spores enter the body by inhalation, ingestion or penetrating trauma and attach to the nasal or oral mucosa. Their germination is favoured by low oxygen, high glucose, acidic medium and high iron levels. Characteristic feature of pathogenesis is angioinvasion and consists of thrombosis of vessels resulting in tissue necrosis and formation of black eschars and gangrenous masses which have low tendency to bleed during surgery.<sup>8</sup>

The common symptoms of RCM include orbital and facial pain, nasal discharge or stuffiness, sinusitis, fever and alteration in vision and mental status. Physical examination may reveal the periorbital and facial oedema, proptosis, decreased vision, afferent pupillary defect, conjunctival chemosis, partial or total ophthalmoplegia and orbital apex syndrome. Black eschar like necrotic tissue can be seen on the nasal turbinates, septum, and palate. Cranial CT scan is a useful imaging tool in the diagnosis of rhinosinal invasive fungal disease and MRI offers excellent aid in the detection of intracranial extension. Definitive diagnosis requires identification of the fungus histologically in tissue specimens or recovery of the fungus by culture.<sup>4</sup>

The optimal therapy for mucormycosis in children has not been established.<sup>4</sup> The principals of management are complete treatment of underlying medical disease, correction of hypoxia, acidosis, hyperglycemia, and electrolyte abnormalities.<sup>6</sup> The mainstay of treatment is systemic amphotericin B. The highest possible tissue levels should be achieved. Renal functions are monitored to document amphotericin B induced nephrotoxicity. Because poor vascular supply may prevent systemic therapy from reaching the fungus, local irrigation of infected tissue and packing of the areas has been reported as an important adjunct to treatment and may even prevent disfiguring

surgery. Liposomal amphotericin B is recommended for persons with compromised renal function, those who are receiving other nephrotoxic therapy, or those who are otherwise intolerant to amphotericin B; it is less toxic, allowing higher doses of the medication to be given.<sup>9</sup> Adjunctive hyperbaric oxygen (HBO) is another treatment modality that appears to be promising; oxygen in sufficient concentrations is fungicidal and decreases acidosis thereby increasing tissue survival.<sup>10</sup> Additional therapies include Rifampicin and flucytosine in combination with amphotericin B and granulocyte-macrophage colony-stimulating factor as adjunctive therapies.<sup>4</sup> Aggressive surgical debridement of all necrotic tissue until normal well-perfused bleeding tissue is encountered is ideal

because of the vasoocclusive effect of mucormycosis the involved tissue rarely bleeds. Sometimes multiple debridements are required. Orbital exenteration is advised if ophthalmoplegia and loss of vision has occurred.<sup>1</sup>

Prognosis is guarded in the cases of mucormycosis. Factors related to a lower survival rate include: 1) delayed diagnosis and treatment; 2) hemiparesis or hemiplegia; 3) bilateral sinus involvement; 4) leukaemia; 5) renal disease; and 6) treatment with desferoxamine.<sup>8</sup>

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