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CASE REPORT (RHINOCEREBRAL MUCORMYCOSIS)

Om Shankar Chaurasiya[1*], Surendra Godara[2], Karnika Agarwal[2]

[1]Assistant Professor & Head, Department of Paediatrics, [2]Post Graduate Resident Department of Paediatrics, M.L.B. Medical College, Jhansi, Uttar Pradesh 284128, India.

Corresponding Author:- **Om Shankar Chaurasiya**
E-mail: chauraisyaom@yahoo.co.in

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ABSTRACT
Rhinocerebral mucormycosis is a rare opportunistic infection in diabetics and immunocompromised patients involving the nasal cavity and sinuses that can spread to the orbit and cranium within days. It can be confused with sinusitis, viral infections, diabetic ketoacidosis and carotid sinus thrombosis and often missed at early presentation. We are presenting two cases of Rhinocerebral mucormycosis and discuss its early signs, symptoms, pathophysiology, and treatment.

INTRODUCTION

Mucormycosis is a fatal invasive fungal infection caused by a fungus of order mucorales which is a member of the class zygomycetes. It involves the orbit, nose and orbit(rhino-orbital), nose orbit and brain(rhino-orbital-cerebral);may also be confined to the lung, gastoinestinal tract, skin or may disseminated. Most cases are associated with diabetes mellitus. Rhino-orbital-cerebral mucormycosis is the most common form in diabetics Goswami R et al [1].

CASE REPORT 1

A 11 year old girl, previously diagnosed with type 1 Diabetes mellitus on s.c. insulin presented to MLB Medical College, Jhansi, with RBS 360mg%, mild to moderate grade fever of one month duration, diffuse non specific abdominal pain of 20 days duration, and polyuria and polydipsia of one month duration. She also reported 20 days of increased rate and depth of respiration suggestive of Kussmaul's breathing, proptosis of the right eyeball and right sided mild to moderate headache with altered sensorium. She was started on i.v. fluids and insulin and glycemia decreased to 180 mg/dl in 24 hr and ketoacidotic coma resolved after 48 hr of therapy. On the second day the patient was fully conscious. The fourth day, she developed ptosis of the right eye, and weakness affecting left side of the body with deviation of the angle of mouth to the right indicating left facial nerve palsy. The patient did not report any history of vomiting, seizures or loss of consciousness during the course of illness.

She reported no history of trauma, or upper respiratory infectious symptoms. The patient did not report any history of vomiting, seizures or loss of consciousness during the course of illness**.** The patient had been previously admitted thrice for similar recurrent complaints.

On examination, the patient was mildly tachycardic (124 beats/min), and tachypneic (38/min) with increased depth of respiration, with a normal blood pressure and a temperature of 100.4 F.

The physical examination was significant for mild right sided periorbital swelling, ptosis and proptosis of the right eye and tenderness on palpation. She had decreased vision of 20/160 in her right eye. Fundoscopic examination of the right eye showed multiple retinal haemorrhages and disc pallor with some blurring of margins. The neurological examination was significant for left sided hemiparesis, left facial nerve palsy and right sided third and sixth cranial nerve palsies. Laboratory examination showed a WBC count of 20,000/ul, hematocrit of 40%,

blood glucose of 360 mg/dl, blood pH of 7.0 and urinalysis positive for ketones. A cranial CT scan showed bilateral sinusitis and oedema of the right orbital musculature. Biopsy of the nasal mucosa and sinuses showed hyphae characteristic of Mucor spp.

On the basis of this, patient was started on Amphotericin B and metronidazole. She was maintained on an insulin drip with blood glucose targets of 100-150 mg/dl. Further follow up could not be accomplished since the patient discontinued the treatment and took leave against medical advise.

CASE REPORT 2

A similar case was reported in MLB Medical college which was a 13 year old girl with no significant past history admitted with complaints of fever, on and off since 15 days, moderate in grade and intermittent, generalized bodyache and headache and increased rate and depth of respiration typical of Kussmaul's breathing since 2 days. Blood sugar was done on admission which was 371 mg%. Blood counts revealed leucocytosis (TLC 27,300 with 84% polymorphs). Blood urea was 42 mg/dl on presentation and Sr.creatinine was within normal limits. Urine was positive for ketones and sugar (+4). Arterial blood gas analysis revealed metabolic acidosis (pH 6.856 and bicarbonate 2.4 meq/l). The patient was started on i.v. fluids, i.v. insulin and symptomatic treatment. Glycemia was controlled after 2 days of i.v. insulin and then the patient was maintained on s.c. insulin. Few days after admission the patient developed mild puffiness of face which developed into frank proptosis and swelling around the right eye on day 7 of admission. The patient also developed progressive loss of vision of the right eye.

There was no history of trauma, respiratory tract infection, vomiting, seizures and loss of consciousness.

The physical examination on presentation was significant only for tachypnoea and increased depth of respiration. Later on the patient developed ptosis and proptosis of the right eye, periorbital oedema around right eye, and loss of vision in the right eye. The ophthalmological examination revealed exposure keratitis of bilateral eyes with retinitis of the right eye with right disc oedema and right occulomotor palsy. The neurological examination revealed right sided third and sixth nerve palsies. On anterior rhinoscopy, black crusts were visible. Oral examination revealed ulceration and impending erosion of the hard palate. Mastoid tenderness was present.

MRI brain showed right maxillary sinusitis and orbital cellulitis, and frontal lobe cerebritis. Biopsy of the nasal mass revealed hyphae characteristic of Mucor spp.

The patient was started on amphotericin B and referred to higher centre for further management.

CASE REPORT 1

Figure 1. Proptosis Rt Eye

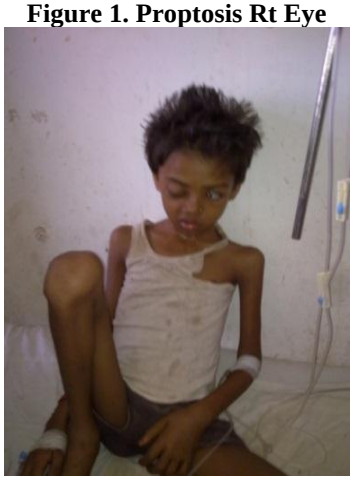


Figure 2. Palatal Necrosis

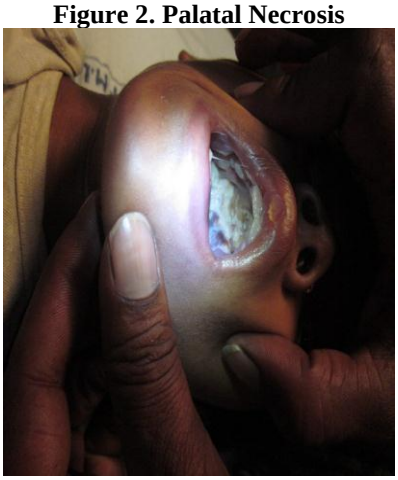
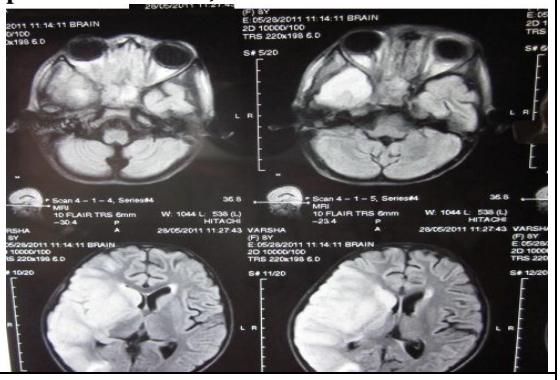


Figure 3. Cranial MRI: Righ frontal and parietal lobe of the brain, maxillary and ethmoidal sinuses, the right eye and periorbital tissues, are infected.



CASE REPORT 2

Figure 4. Proptosis Rt eye

Figure 5. nasal involvement in rhinocerebral mucormycosis

DISCUSSION

Rhinocerebral mucormycosis is a rare opportunistic infection of the sinuses, nasal passages, oral cavity, and brain caused by saprophytic fungi. The infection can rapidly result in death. Rhinocerebral mucormycosis commonly affects individuals with diabetes and those in immunocompromised states by Goswami R et al [1], Alleyne C et al [2]. Mucor are ubiquitous in nature, being commonly found in decaying vegetation, soil, and bread mold. They grow rapidly and can release large numbers of airborne spores. Thus, they are frequently found colonizing the oral mucosa, nose, paranasal sinuses, and throat. Phycomycetes do not generally cause disease in immunocompetent individuals who are able to generate phagocytic containment of the organisms. Persons at risk for infection (ie, immunocompromised individuals) typically also have decreased phagocytic activity because of an impaired glutathione pathway by Hamilton J et al [3].

In individuals who are immunocompromised, germination and hyphae formation occur, and this allows the organism to invade the patient's blood vessels. Mucormycosis is described almost exclusively in patients with compromised immune systems or metabolic abnormalities. Oyesiku NM et al [4].

Seventy percent of mucormycosis cases occur in patients with diabetes mellitus, although this percentage is declining with the use of chemotherapy and with increasing frequency of various types of immunocompromised states. An underlying risk factor is recognized in more than 96% of mucormycosis cases. Risk factors for rhinocerebral mucormycosis include the following by Stem LE et al [6], Apaydin S et al [7]:

- Iron overload
- Burns
- Acquired immunodeficiency syndrome (AIDS)
- Blood dyscrasias
- Transplantation
- Chemotherapy
- Intravenous drug use - Embolic to brain
- Immunosuppression eg. high-dose steroids

This condition is a risk factor, particularly in association with poor glycemic control and acidosis, as it relates to cellular immune dysfunction. Patients with diabetes 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.

Rhinocerebral mucormycosis generally occurs in three stage. First, inhaled spore infect paranasal sinuses and necrotic lesion of nasal mucosa, turbinates, and hard palate appear. Secondly orbital infection occurs either by direct extension through ethmoid sinus or through blood vessels. Pain, proptosis, periorbital cellulitis and ophthalmoplegia may occur. Occlusion of central retinal artery can cause visual loss. Finally, the infection spreads intracranially via cribriform plate or orbital apex Oyesiku NM et al [4].

Meningeal involvement can occur and spores invade the vasculature and proliferate within elastic lamina of arteries. The hyphae can then erode the endothelium of blood vessels and lead to thrombosis, infarction and necrosis. This can produce thrombosis of cavernous sinus and carotid artery. The classical syndrome of Rhinocerebral mucormycosis is uncontrolled diabetes, unilateral blindness, ophthalmoplegia and proptosis. Other features are headache, fever, black nasal discharge, orbito facial cellulitis, cranial nerve palsy, altered sensorium and hemiparesis Goswami R et al [1].

Mucormycosis is a rapidly progressive disease in which morbidity and mortality are directly related to the length of time before diagnosis and treatment. Recognition of early signs and symptoms of disease are important. Fever, decreased vision, and facial swelling are most common complaint in first 72 hrs. of the disease. Other common complaints include facial pain, headache and nasal congestion or discharge Hamilton J et al [3]

The two most common early physical signs are edema and multiple cranial nerve palsies consistent with orbital apex syndrome (unilateral ptosis, proptosis, visual loss, complete ophthalmoplegia, and ophthalmic and maxillary nerve anaesthesia and anhidrosis). Rogers WD et al [9]. In a study conducted by Bodenstein NP et al [8], Ferry AP et al [10] concluded that the facial edema may be confused with periorbital cellulitis but in this the edema is soft, cool and non-tender in contrast to the warm, tender and taut edema of cellulitis. The other distinguishing feature is the character of ptosis, if present; in RCM there is paralytic ptosis in which the eyelid can be raised easily by the examiner while in cellulitis it is edematous ptosis, resistant to opening. Altered mental status may be the only finding in some patients. Patients may present with fever, and are usually drowsy or obtunded at presentation by Bodenstein NP et al [8]. Fundoscopic examination may be normal in the early stages, but haemorrhages or central retinal artery occlusion may occur as late signs by Ferry AP et al [10]. Orofacial lesions such as black, necrotic oral or facial scars are late but characteristic signs.

Laboratory investigations are usually consistent with hyperglycem ia and ketoacidosis. Blood counts may show neutrophilic leukocytosis. Rogers WD et al [9]. CSF examination may show pleocytosis with increased glucose and protein. Sugar AM et al [11]. Ferry AP et al [10] showed that CSF culture and blood culture are rarely positive.

The radiograph and CT scan may show opacification of sinuses and thickening of extra ocular muscle, increased density of orbital apex, swelling of optic nerve and proptosis. Rogers WD et al [9]. MRI may show sinus and orbital involvement and can better visualize carotid artery and cavernous sinus thrombosis. Yousem DM et al [12]. The diagnosis is made by observing characteristic hyphae on biopsy of necrotic ulcer in the

nasal and oral cavity. Sampling of nasal discharge or blood is not sufficient for diagnosis because invasion of the tissue must be demonstrated. Debiscop J et al [13]. The biopsy site should be non bloody and the thick walled, broad, non-septate hyphae with right angle branching can be seen. Rogers WD et al [9]. Treatment of RCM includes early diagnosis and correction of the underlying cause. Most cases of mucormycosis are acute surgical emergencies; however, several cases of a more chronic, indolent form have been reported, with signs and symptoms developing over several weeks. The mainstay of treatment is surgical debridement and i.v. antifungal drugs. Radical resection of Rhinocerebral mucormycosis have improved survival rate. Blitzer A et al [5]. Amphotericin B is the drug of choice and in doses usually ranges 1 to 1.5mg/kg/day. Liposomal Amphotericin B is as active as Amphotericin B deoxycholate and less toxic. Liposomal Amphotericin B can often be administered at doses of10-15mg/kg/day orally. Voriconazole was a major advance in invasive aspergillus but has no effect against Zygomycetes. Sun QN et al [14]. A new drug posaconazole with broad spectrum introduced for its efficacy against filamentous fungi including aspergillus and zygomycetes Sun QN et al[14]. The efficacy of POS in pediatric mucormycosis is demonstrated in many reports and strongly suggest long term safe and beneficial in treatment and prevention of relapses Sun QN et al [14]. Reversal of underlying condition is also important. Correcting hypoxia, acidosis, hyperglycemia, and electrolyte abnormalities is critical to the successful management of this condition. Blitzer A et al [5]. Reversal of underlying immunosuppression is also significant. The oxidative metabolism and killing by phagocytosis can be impaired by diabetes. Granulocyte colony stimulating factor have been utilized to improve neutrophil number and function. Y-interferon has been used in some case reports as it is thought to improve function of monocytes, macrophage, and neutrophils. Alleyne C et al [2]. Discontinuation of immune suppressing medication if possible is recommended to improve phagocytic activity. Hyperbaric oxygen therapy has been used as an adjunctive to oxygenate salvageable tissue and to promote the generation of oxygen based free radicals, which then damage fungal membranes and inactivate antioxidant enzyme. Additionally, it may enhance oxidative metabolism of phagocytes. Alleyne C et al [2]. Rhinocerebral mucormycosis progresses rapidly and can result in carotid artery occlusion, cavernous sinus thrombosis, and CNS infarction secondary to fungal thrombosis, leading to hemiparesis, hemiplegia, coma, and death. Other complications of rhinocerebral mucormycosis include CNS hemorrhage, abscess, and cerebritis, as well as blindness and airway obstruction from head and neck infections. Permanent residual effects of the disease occur up to 70% of the time.

Neurologic function can be recovered if no irreversible damage has occurred, but morbidity is very common. Postsurgical disfigurement is likely.

Survival and morbidity depends on proper early diagnosis and definitive treatment. The cause of death in many patients is mucormycosis itself rather than the progression of the underlying disease. Yohai RA et al [15].

The mortality rate in diabetic patients appears to be lower than in nondiabetic patients and in patients with intracerebral involvement. Patients who have been treated with amphotericin B and who have had orbital exenterations are more likely to survive. Patients with frontal sinus involvement and older patients have lower rates of survival.

CONCLUSION

Mucormycosis is a devastating fungal infection that is most commonly associated with diabetes and presents with facial swelling, fever, nasal congestion or discharge. The prognosis of mucormycosis may improve with rapid diagnosis; early management, including combined antifungal and surgical interventions; and reversal of underlying risk factors.

RCM should be considered in patient with orbitofacial complaint having diabetes, renal disease or immunocompromised state.

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