Indian Journal of Medical Case Reports ISSN: 2319–3832(Online)
An Open Access, Online International Journal Available at http://www.cibtech.org/jcr.htm
2020 Vol.9 (1) January-June, pp. 8-13/Bhat et al.
Case Report

RHINOCEREBRAL MUCORMYCOSIS IN A DIABETIC PATIENT: A CASE REPORT

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ABSTRACT
Rhinocerebral mucormycosis is a fulminent and rare life-threatening infection caused by fungi from the order Mucorales. The disease occurs mostly in association with diabetic ketoacidosis and immunosuppression. It has a rapid progression and high mortality; therefore, early recognition and aggressive treatment are the only possible ways to increase the survival rate. A case of rhinocerebral mucormycosis in a diabetic male patient presenting as fever, left periorbital pain, chemosis and nasal eschar is reported. The clinical manifestations, diagnosis, and treatment of rhino cerebral mucormycosis are discussed.

Keywords: *Mucormycosis, Diabetes Mellitus*

INTRODUCTION
Mucormycosis is a fulminent and rare opportunistic fungal infection caused by members of the family Mucoraceae, order Mucorales and class Zygomycetes (Khan *et al.,* 2002). These fungi are ubiquitous in nature and survive on decaying vegetation and diverse organic matter. (Onyango2002 etal) Depending on the immunological status of the patient different anatomical sites may be involved and if untreated the course is aggressive and outcome fatal. It is commonly reported in immunocompromised patients such as poorly controlled diabetes mellitus, blood dyscrasias, malnutrition, neutropenia, iron overload on desferoximine therapy, organ transplant, and immunosuppressive therapy. Diagnosis is confirmed by histopathological demonstration of the organism in the affected tissue. Early diagnosis and treatment of mucormycosis is extremely important due to the aggressive nature of the disease. (Ferguson BJ etal, 2000) Because rhino cerebral mucormycosis (RCM) occurs infrequently, it may pose a diagnostic and therapeutic dilemma for those who are not familiar with its clinical presentation. 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 immunocompromised state is not reversible (Ferguson *et al.,* 2000). The aim of this case report is to present a patient with rhino cerebral mucormycosis in order to draw attention to its existence in our environment and to emphasize the need for high index of suspicion and institution of early therapy.

CASE
A 57-year-old male patient suffering from diabetic mellitus, nephropathy and hypertension was on oral hypoglycemic drugs and antihypertensive like glipzide, metformin and enalapil, but the blood sugar control was poor (HbA1c 10.9%). He was referred to our hospital with history of low-grade fever, lethargy, left per orbital pain, swelling, and black patch on the left side of nose. He had received oral antibiotics (Levofloxicin) fort five days. He was transferred to emergency medicine department of our hospital. On reception in the emergency he was delirious, febrile (39.1C) and physical examination revealed left periorbital swelling, and small black necrotic spot over his nose on left side. His pulse was 90/ minute and blood pressure 110/70 Chest, cardiovascular, abdominal and neurological examination was normal. A complete blood count showed leukocytosis (WBC 19,000/mm3 with neutrophil 91%). The

patient's blood sugar level was high (535 mg/dl) and had metabolic acidosis (pH 7.25). Urine for ketones was negative. A diagnosis of diabetes mellitus with facial cellulitis and possible mucormycosis was made. Patient was started with parentral vancomycin, pipercillin+salbectum and insulin. Despite two days of treatment with intravenous antibiotics and intensive insulin therapy, intermittent spiking fever persisted and the left periorbital swelling progressively extended to the right side. He also developed an obvious left sided ptosis accompanied by ocular palsy, blindness and absence of pupillary response. A black Escher involving almost entire left side of nose with extension to glabella of forehead (Fig. 1 & 2). A computed tomographic (CT) scan head and Para nasal sinuses (Fig. 3) revealed obliteration of left maxillary, ethmoid, frontal and sphenoid sinuses. An ENT consultation was done and debridement of the necrotic tissue and cleaning of the maxillary sinus was performed. Small biopsy samples obtained from the nasal eschar showed the picture of mucormycosis with some foci of non-sepatate fungal hyphae (10 to 25 micrometers in diameter), and hyphal branches typically at right angles (Fig.4). There was formation of thick-walled chlamydoconcidia at the ends of the hyphae (Fig. 4). Maxillary Sinus fluid culture and blood culture reports were sterile. An antifungal regimen including amphotericin B 1mg/Kg/day was initiated. The patient continued to receive treatment with intravenous amphotericin B and strong antibiotics. However, his consciousness continued to decline and clinical condition showed progressive deterioration. The patient finally expired five days after admission.

Figure 1: Photograph of patient showing chemosis & black eschar on glabella

Figure 2: Photo graph of patient showing chemosis, periorbital edema & black eschar on glabella

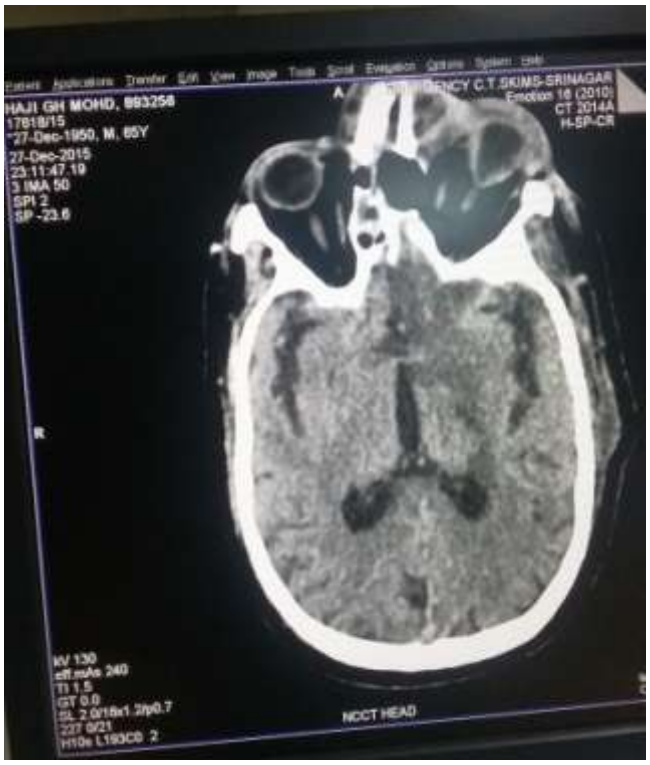

Figure 3: CT showing destruction of nasal bone & medial orbital wall and hypodense lesion in the base of right frontal lobe

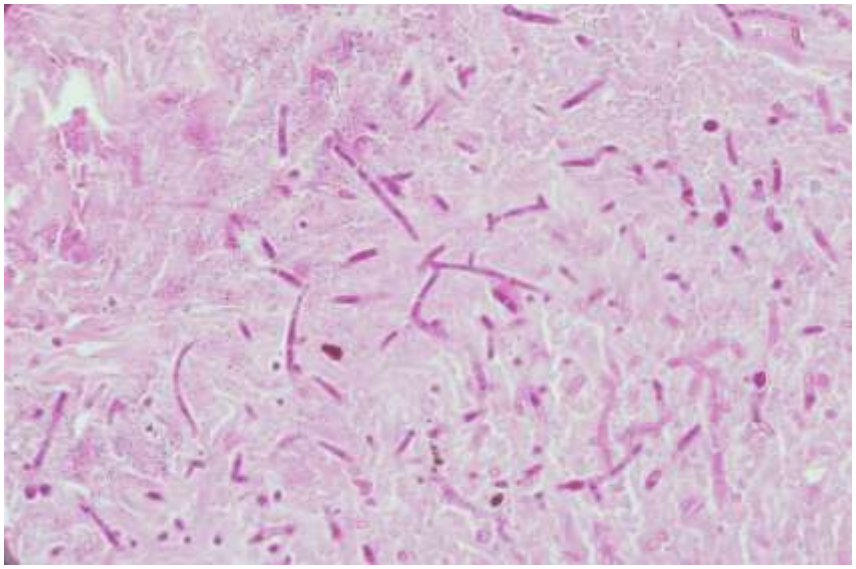

Figure 4: Swab from local lesion showing hyphae of mucor.

DISCUSSION

Mucormycosis is a fungal infection ubiquitous in nature and seldom effects immunologically competent patients. Rhizopus, Mucor, Absidia are the most common isolated from patients with mucormycosis. Mucormycosis is primarily a disease of immunocompromised host; like patients with diabetes mellitus,

hematologic malignancies, patients on chemotherapy & radiotherapy, neutropenic states, persistent acidosis, iron or aluminum overload, protein energy malnutrition, diarrhea, dehydration, metabolic acidosis in small children, renal failure especially chronic cases on haemodialysis, corticosteroid therapy, organ transplantation, and less frequently AIDS. Rhizopus is responsible for 60% of all cases of mucormycosis, and 90% of rhino cerebral mucormycosis (Brown 1986). Diabetic patients are predisposed to mucormycosis due to 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. The disease may involve the fallowing systems as rhino cerebral, pulmonary, gastrointestinal, disseminated, coetaneous and miscellaneous (bone, joints, heart, and kidney. (Galetta *et al.*, 1990) Rhino cerebral mucormycosis (RCM) is the commonest form of phycomycosis with fatal outcome (Ray *et al.,* 2002). 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 angio invasion 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 (Yohai *et al.*, 1994). About 70% to 80% of these patients have diabetes mellitus. As is reported in our case, most diabetics who develop rhino cerebral mucormycosis (RCM) are in poor metabolic control with complicating ketoacidosis (Ricardo *et al.*, 1996) It is suggested that fungal organism grows in ketotic patients because acidosis disrupts iron binding and the result increases in free iron which promotes growth of the fungus. At the same time, high blood sugar level may also alter the immunologic capability to resist mucormycosis through reduction of WBC chemotaxis and the ability of macrophages (Kenton & James, 1995). The common symptoms of RCM include orbital and facial pain, nasal discharge or stuffiness, sinusitis, fever and alteration in vision, proptosis, ophthalmoplegia, orbital apex syndrome and altered mental status. Occasionally dark, blood-tinged rhinorrhea and black eschar like necrotic tissue can be seen on the nasal turbinates, septum, and palate. As seen in our case, diabetic patients with poor controlled blood sugar who develop rhino cerebral mucormycosis typically presented with malaise, retro-orbital headache, fever, and black eschar on left lateral of nose. Because the disease provokes diffuse tissue necrosis, the fungi can therefore, easily invade the wall of blood vessels, leading to thrombosis and tissue ischemia; it is not uncommon to find the infection spreading to the cavernous sinus or the central nervous system (Nussbaum, 1994). The deterioration in mental status is an ominous sign, often heralding intracerebral extension of the disease process. All of these symptoms may develop over a period of several days or may occur as a fulminating process within hours (Nassbaum, 1994).

Imaging studies are important to evaluate the extent of the disease. 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. CT of patients with rhino cerebral mucormycosis shows pacification of the paranasal sinus and thickening of the sinus mucosa and bone destruction without an air-fluid level. In addition, when the orbit is invaded, increased density of the orbital fat and venous engorgement may be seen (Greenburg *et al.,* 1985). Magnetic resonance imaging (MRI) can demonstrate soft tissue lesions better, especially in diagnosis of cavernous sinus thrombosis. Definitive diagnosis requires identification of the fungus histologically in tissue specimens or recovery of the fungus by culture (Greenburg *et al.*, 1985). On histologic section, these organisms are characterized by wide, non-sepatate hyphae with right-angled branching (Parfrey *et al.*, 1986). Cultures are still the standard means of diagnosis. But even positive histologic findings, routine sinus cultures and blood cultures are rarely positive. Treatment of rhino cerebral mucormycosis should consist of prompt control of hyperglycemia and ketoacidosis, aggressive surgical debridement of involved tissue. The mainstay of treatment is administration of parentenal amphotericin B. Renal functions are monitored to document amphotericin B induced nephrotoxicity. A total Cumulative dosage of 2 to 4g is generally advocated. 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. (Kajs-wyllie, 1995)

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 which is less toxic and allows higher doses to be utilised is recommended for persons with compromised renal function, receiving other nephrotoxic therapy, and those who do not tolerate amphotericin B (Kofleridis *et al.*, 2003).

Additional therapies include Rifampicin and flucytosine in combination with amphotericin B and granulocytemacrophage colony-stimulating factor as adjunctive therapies. Aggressive surgical debridement of all necrotic tissue until normal well perfused bleeding tissue is encountered isideal because of the vasoocclusive effect of mucormycosis the involved tissue rarely bleeds. Sometimes multiple debridements are required. Prognosis is guarded in the cases of mucormycosis. In most cases, the prognosis of mucormycosis is poor and has varied mortality rates depending on its form and severity. In the rhino cerebral form, the mortality rate is between 30% and 70%, whereas disseminated mucormycosis presents with the highest mortality rate in an otherwise healthy patient, with a mortality rate of up to 90%.

CONCLUSION

Rhino cerebral mucormycosis is an acute opportunistic mycotic infection that predominantly affects patients with diabetes mellitus. The patients with RCM in its earliest stages masquerade as other less serious diseases. Hence, early suspicion is needed. Early diagnosis, aggressive surgical debridement, high dose amphotericin B and good control of blood sugar are the most important factors to decrease the morbidity and mortality from this fungal disease.

Conflict of interest: *Nil*
Financial assistance: *Nil*

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