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CASE REPORT

RHINOCEREBRAL MUCORMYCOSIS: A CASE REPORT

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ABSTRACT

Rhinocerebral mucormycosis is an uncommon and deadly acute necrotizing fungal infection. It usually affects individuals with underlying immunosuppression with uncontrolled diabetes and diabetic ketoacidosis being the most commonly identified condition. A high index of suspicion is crucial for early diagnosis and management as it is a rapidly progressive infection with a high rate of fatality. In this case report, we present an 18 year old female patient with type 1 diabetes mellitus, diabetic ketoacidosis and confirmed rhinocerebral mucormycosis from University of Gondar Hospital. The clinical presentation, diagnostics and hospital course is discussed.

Key words: *Rhinocerebral mucormycosis, Diabetic Ketoacidosis, fungal infection, Diabetes Mellitus*

INTRODUCTION

Mucormycosis is an uncommon and deadly acute necrotizing fungal infection caused by the filamentous fungi of the order Mucorales. It was first described as a disease of humans in 1885. It usually affects individuals with underlying immunosuppression with uncontrolled diabetes and diabetic ketoacidosis being the most commonly identified condition. A high index of suspicion is crucial for early diagnosis and management as it is a rapidly progressive infection with high rate of fatality. Advances in early diagnosis and treatment options in recent years have resulted in increased survival from the disease (1, 2). We describe an 18 year old female patient with confirmed diagnosis of rhinocerebral mucormycosis.

CASE REPORT

An 18 year old female daily laborer from Humera, North West Ethiopia presented to University of Gondar Hospital with new onset polyuria and polydipsia of 08 days duration on May 20, 2013. In addition, she had high grade fever, dry cough, fast breathing and difficulty of swallowing. Her past medical history was not significant except for malarial attacks. The physical exam at presentation to the Emergency Out Patient Department revealed an acutely sick patient with deep and labored breathing, tachycardia and tachypnea but afebrile with signs of dehydration. There were whitish patches on the tongue and a dark crusted lesion on the palate. Findings in other organ systems were non remarkable. Initial laboratory tests showed: random blood sugar 314 mg/dl, ketone 3+ on urinalysis, serum potassium 2.4 meq/L, creatinine 1.4 mg/dl, blood urea nitrogen 58 mg/dl, WBC 21,100/μL with neutrophil percentage of 76.4%, ESR 94 mm/hr and negative for HIV test.

With the diagnosis of Type 1 DM with diabetic ketoadicosis (DKA) and oropharyngeal candidiasis, the patient was started on treatment according to the DKA protocol and was put on oral fluconazole. However, the DKA could not resolve after 48 hours and intravenous ceftriaxone was started for presumed occult sepsis and patient was transferred to the intensive care unit (ICU). On the 6th day of admission the DKA resolved but the patient developed a foul smelling nasal discharge. It was also noted that she had an asymmetrical facial and periorbital edema more on the right side, a dark necrotic eschar on the right side of the hard palate and a perforated nasal septum. With this evidence, a presumptive diagnosis of rhinocerebral mucormycosis with bacterial superinfection was made. Nasal discharge analysis revealed many gram negative rods on staining and lactose fermenter gram negative rods on culture but no fungal elements were seen on KOH examination. Patient was started on Ambisome 5mg/kg/day for the mucormycosis and Intravenous Augementin and Clindamycin for the superinfection. On the 8th day, surgical consultation was made after progressive tissue destruction was noted. Surgical debridement of necrotic

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tissue, abscess drainage and tracheostomy was done.

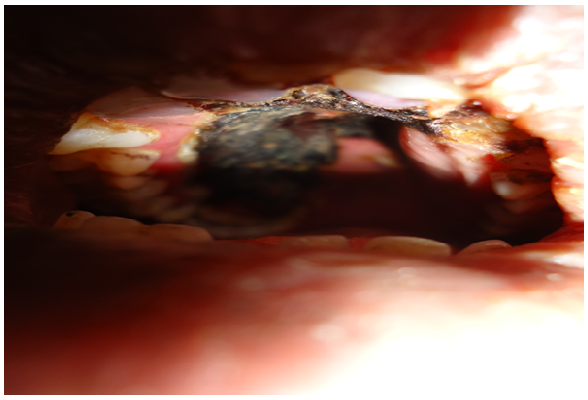

Figure 1. Dark necrotic eschar the hard palate

The hard palate was found to be perforated and the nasal septum was completely destroyed. Specimens were obtained for fungal culture and biopsy was taken for pathologic examination.

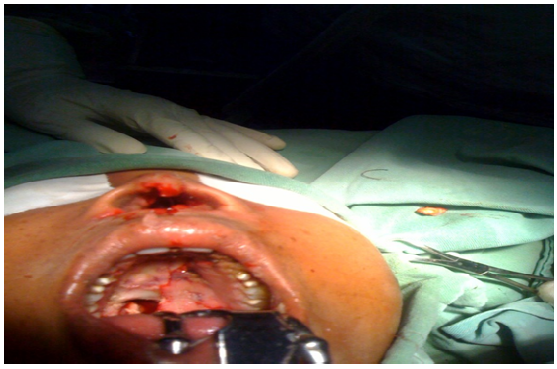

Figure 2. Perforated hard palate with complete destruction of the nasal septum after removal of the necrotic tissue

Patient continued treatment with ambisome, antibiotics, standing dose of NPH insulin with correction and wound and tracheostomy care. Despite this, the periorbital swelling progressed and patient reported decreased vision of the right eye. Ophthalmologist evaluation on the 12th day concluded that patient had right central artery occlusion and an absolutely blind right eye. Fungal culture on Sabouraud agar grew profuse black cottony colony which on microscopy was fungal mold with aseptate hyphae, long sporangiophores, multiple rhizoid with sporangium filled with spore at the tip of the sporangiospore. The biopsy section revealed sheets of neutrophils and non-septated broad gray blue hyphal elements invading the vessels accompanied by fibrinoid necrosis.

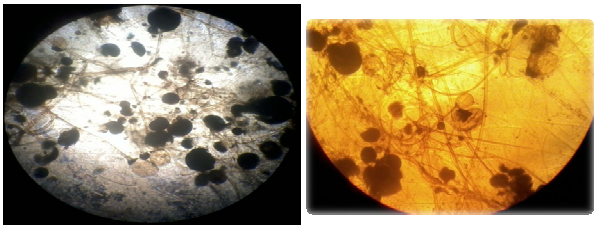

Figure 3. Fungal culture on Sabouraud media showing black cottony colonies (left) and microscopy showing aseptate hyphae with long sporangiosphore

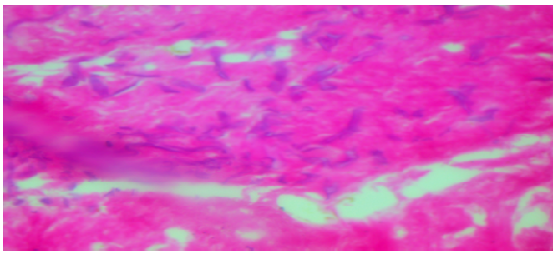

Figure 4. Biopsy section showing non septated broad gray blue hyphal elements invading the vessels accompanied by fibrinoid necrosis.

The condition of the patient progressively deteriorated with progressive destruction of involved structures. On the 17th day the patient complained of a severe throbbing headache which did not respond to analgesics and was ascribed to a possible invasion of the brain. CT scan of the brain was not obtained as the machine was out of order at the time. With the worsening conditions the patient and the attendants lost hope and left against medical advice on the 21st day of admission.

DISCUSSION

Mucormycosis, also called Zygomycosis, is an uncommon deadly angioinvasive fungal infection caused by the filamentous fungi of the order mucorales. Even though a number of species are associated with this infection, by far the most common causes are species of the Rhizopus genus. They are saprophytic aerobic fungi found widespread in the environment, especially in soil, manure, bread molds and decaying fruits and vegetables. They also frequently colonize the nasopharyngeal mucosa of asymptomatic individuals (2). The infection usually affects individuals with underlying immunosuppression. High risk groups include patients with uncontrolled diabetes, immunosuppressive drugs, neutropenia, dialysis patients on deferoxamine, and organ

transplant recipients (3). Its occurrence in the absence of these underlying risk factors is quite rare. Different clinical patterns of the infection has been recognized and they can be classified in to six groups based on the sites of involvement: rhinocerebral, pulmonary, gastrointestinal, cutaneous, disseminated and localized not belonging to the previous classes (1).

Although there are no comprehensive data, estimated annual incidences vary from 0.9-1.7 cases per million (1). The incidence has increased in the last two decades together with the increase in susceptible population with immunosuppression due to cancer therapy and organ transplantation (4). The mode of transmission is thought to be through inhalation, ingestion or possibly entry through a skin laceration (2). Human to human transmission has not been documented so far (1).

Rhinocerebral mucormycosis, which is the case in our patient, is the most commonly identified clinical pattern accounting for 30-50% of the cases. When it occurs it is usually associated with poorly controlled diabetes especially in those with diabetic ketoacidosis (1, 2, 5). The pathogenesis is usually associated with poor neutrophil chemotactic and phagocytic response and increased available serum iron. It has been proven that both can result from DKA (6). The fact that increased available serum iron facilitates the growth of this fungi is corroborated by studies showing that the use of deferoxamine in iron overloaded patients induces the infection as the fungi utilize the drug as a siderophore (6).

It can affect any age group with average age being middle adulthood and different male to female ratios have been reported in different studies (5, 6). The first site of involvement is usually the palate from which it extends to involve adjacent structures either through direct extension or by invasion of blood vessels and lymphatics (2). In fact, what is considered vital to its ability to cause progressive tissue necrosis is its capacity for angioinvasion. This acute infection can rapidly progress to involve the orbits and the CNS. It can lead to carotid artery occlusion, cavernous sinus thrombosis and cerebral infarction due to fungal thrombosis.

Patients usually present with signs and symptoms that mimic sinusitis or periorbital cellulitis. Facial pain, swelling and paralysis, bloody nasal discharge and headache with variable fever can also occur. A blackish necrotic ulcer with eschar and raised edges usually occurring on the palate or nasal mucosa is usually reported. The finding of unilateral ophtalmoplegia and visual disturbance indicates progression to the orbit. Brain involvement is usually heralded by the occurrence of alteration of consciousness and focal neurologic deficits (1, 2, 6).

Diagnosis is usually made by histopathologic identification of broad right angled branching aseptate hyphae with evidence of angioinvasion and tissue necrosis on biopsy specimen. This finding is fairly specific for the fungal species that cause mucormycosis. Even though fungal cultures can be used to confirm the diagnosis, there is a high rate of false negativity especially if only swab culture is taken. The culture media used is Sabouraud agar and sporulating hyphae can be observed over the surface within 24-48 hours. Routine species identification and susceptibility testing is not necessary for the clinical management of the patients unless it is needed for scientific or epidemiologic reasons. Molecular techniques have been tried as a means of diagnosis but the outcome is dismal so far. Imaging modalities including CT scan and MRI are helpful to assess the degree of invasion and plan surgical management accordingly. The earliest findings on imaging are opacification of the paranasal sinuses and thickening of the mucosa which are actually not specific. But with the rapid progression of the disease, involvement of bony structures including the orbits, vascular and CNS invasion are visualized (1, 2).

The standard treatment of mucormycosis has three prongs; control of the underlying risk factor, surgical debridement and systemic antifungal therapy (1). In diabetic patients, reversal of DKA and restitution of euglycemia is mandatory. Even though there are no guidelines when and to what extent it has to be done, surgical intervention has been associated with improved outcomes in different reports. Surgical removal of necrotic tissue limits the progression and allows better penetration of the antifungal agents to ischemic areas (1,2). The choice of surgical approach depends on the extent of the disease and it can include debridement and drainage of paranasal sinuses, orbital exentration, palaetectomy and craniotomy. Site should be inspected for recurrence of necrosis and repeated surgical intervention may be necessary (6,7).

The first antifungal that was used to successfully treat mucormycosis in 1955 was amphotericin B and it is still the first line antifungal therapy (2). The dose should be adjusted between 0.5-1 mg/kg/day depending on weight and renal function (2,3). The lipid formulations of amphotericin B are safe and effective

alternatives. The recommended doses are Ambisome 5-7.5mg/kg/day with higher dosages in CNS involvement (10mg/kg/day) (2, 6-8). The duration of treatment depends on the resolution of immunosuppression, clinical symptoms and radiologic signs (8). Most azole antifungals are ineffective against this infection. But posaconazole has been used as a salvage therapy or as a step down oral therapy from parenteral amphotericin B (8).

Although not confirmed, few case reports and animal studies suggest the benefit of adjunctive therapies like iron chelation therapy and hyperbaric oxygen therapy (9-11). Hyperbaric oxygen therapy (HBO) is based on the thought that high concentration of oxygen is fungicidal, improve neutrophil activity and facilitates wound healing (11). Iron chelators like deferasirox inhibit absorption of iron by the fungus and thus inhibit its proliferation. This are new areas in the treatment of mucormycosis which needs to be explored more.

Untreated mucormycosis is a grave disease with survival rate of only around 3% (4). With recent advances in early diagnosis and management options survival has increased significantly, from 84% to 47% since 1950 according to one report (5). The case fatality rate of treated rhinocerebral mucor mycosis in diabetic patients is reported to be 20-40% (2,7). The mortality increases once the brain is involved. In one study, the mortality rate for rhinoorbital cases was 24% compared to 62% for those with rhinocerebral cases (3). Treatment with combination of antifungal and surgery increased survival to 70% compared to less than 60% when treated with each alone (5).

Conclusion: Even though rhinocerebral mucormycosis is a rare infection, this case demonstrated that it has to be suspected in diabetic patients, especially with DKA, who complain symptoms pertaining to nasopharyngeal and oral problems. Early diagnosis is of vital importance for successful treatment of this deadly infection. The benefit of simple evaluation of the oropharygeal and nasal area cannot be overemphasized for the diagnosis. We can understand from the literature review that with early diagnosis, institution of antifungals and surgical intervention, these patients can be salvaged.

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