MUCORMYCOSIS; DEADLIER INFECTION: AN OVERVIEW

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ABSTRACT
Mucormycosis is an invasive and potentially lethal infection caused by fungi of the order mucorales. The microbiology, clinical forms and pathology of mucormycosis are well established but the rarity of the disease leads to difficulties in diagnosis and delays can result in a poor prognosis. The main risk factors for this disease are diabetes mellitus, renal insufficiency, organ transplantation and chronic use of iron-chelating agents and immunocompromised patients. Early recognition and aggressive treatment are of paramount importance to have reduced the mortality and morbidity.

INTRODUCTION
Mucormycosis, also known as zygomycosis and phycomycosis. It is an acute opportunistic fungal infection with a high mortality rate that predominantly occurs in dehydrated and acidotic patients caused by a group of distinctive mycoses; all of which are ubiquitous, saprophytic fungi of the class. Paltauf in 1885 described the first case of this uncommon infection in human beings. He coined the term mucosis mucorina which subsequently became mucormycosis [1]. Disease received less recognition until 1942, when Gregory et al. reported three fatal cases of central nervous mucormycosis [2]. The disease may present with various manifestations, but there is a predilection for the paranasal sinuses. It is one of the most rapidly progressing and lethal form of fungal infection in humans which usually begins in the nose and paranasal sinuses. This fungus invades the arteries, forms thrombi within the blood vessels that reduce blood supply and cause necrosis of hard and soft tissues. Once entered into the arteries, the fungus can spread to orbital and intracranial structures. Medically compromised patients are increasing day by day, but life span of patients is increasing due to improved access to medical care. Today there is alarming need to identify patients whose overall health status may not allow to tolerate surgical or dental procedures. The incidence of fungal infections of head and neck region is rising. Among the various classes of fungi which are pathogenic to human, Zygomycetes form an important group. It is divided in to 2 classes – Mucorales and Entomophthorales. Among the Mucorales, Rhizopus and Mucor are common cause of human infections. Mucormycosis is a well-established clinical entity with over 200 cases published in literature [3].

Organism: Mucormycosis are a saprophytic aerobic fungus commonly found in our environment. These organisms frequently found to colonize the oral mucosa, nasal mucosa, paranasal sinus and pharyngeal mucosa of asymptomatic patients. It can survive in vitro for 2-5 days. It is usually found in soil, dust, bread moulds, decayed fruits, vegetables & manure. Organism belongs to Phycomycetes, order mucorales, family mucoraceae [4]. The most common genera isolated are Rhizopus, Rhizomucor and Absidia. Rhizopus is the predominant pathogen, accounting for 90% of the cases of rhinocerebral mucormycosis. Although infection usually occurs after inhalation through the nose or mouth, a skin laceration can
also become an opening for mycotic entry. These fungi are ubiquitous, subsisting on decaying vegetation and diverse organic material. These fungi show minimal intensive pathogen city towards normal person but they can initiate aggressive and fulminant infections in immune compromised host [5].

Number of diseases can be predisposing to the development of invasive fungal diseases. These include diabetes mellitus, DKA, neutropenia, desferoxamine use associated with dialysis, malnutrition, leukemia, lymphoma and renal failure, IV drug abusers, malnutritional states, cirrhosis, burns, Acquired Immune Deficiency Syndrome, organ transplant, as well as immune suppression and steroid therapy. Invasive fungal diseases that are not recognized early or are treated inadequately are among the most acutely fatal infections known [6].

**Clinical manifestations [7]:**

**Age:** Any age group.

**Sex:** Both the sexes are equally affected.

**Site of Invasion:** Paranasal sinuses, lungs, kidneys etc.

**Mode of Spread:** Either through direct extension or through blood vessels/lymph vessels.

**Sites Involved:** Palate being the most common site followed by buccal mucosa, maxillary & mandibular lip and mandible. Intraorally, ulcer with raised erythematous borders with surface of the ulcer appearing black and necrotic with areas of denudation is seen (Fig 1). Other associated signs and symptoms include nasal obstruction, bloody nasal discharge, facial pain and headache, visual disturbances & facial paralysis.

**Complications:** 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. If the infection extends to the nasal turbinates, the orbit can become involved. Infection can lead to proptosis, periorbital oedema, chemosis, ophthalmoplegia, and loss of vision if the orbital apex becomes involved [8].

**DISCUSSION**

There are at least six clinical entities of mucormycosis: rhinocerebral, pulmonary, cutaneous, gastrointestinal, central nervous system, disseminated and miscellaneous like bone or kidney. The term rhinocerebral mucormycosis (RCM) should only be used if the facial, palatal, orbital, paranasal sinus or cerebral regions are involved and the patients generally present with signs and symptoms that may be primarily located in these regions [9]. Up to 40% to 50% of patients who present with mucormycosis have Diabetes Mellitus.

The RCM is the most common form in patients with diabetic ketoacidosis (DKA), involving 70% of reported cases. Even though mucormycosis is ubiquitous and grows rapidly, it seldom causes an infection in immunologically competent patients. Therefore, if an infection with mucormycosis does occur, it usually indicates a serious underlying medical condition. Mucormycosis will commonly strike debilitated patients with conditions such as opportunistic fungal infections & can infect healthy individuals as well. Uncontrolled diabetes mellitus can alter the normal immunologic response of patients to infections [10].

Such patients have decreased granulocyte phagocytic ability with altered polymorphonuclear leukocyte response & abnormal polymorphonuclear chemotaxis. Reports have suggested that the ability of serum of immunocompromised patients to inhibit Rhizopus invivo is reduced, which makes them suitable hosts to opportunistic fungal infections. This fungal infection usually originates from the paranasal sinuses. The fungus invades the blood vessels and subsequently spreads through them. Once fungal hyphae enter into the blood stream they can disseminate to other organs such as cerebrum or lungs which can be fatal for the patient. Mucor hyphae form thrombi within the blood vessels that reduce vascularity to the tissues and cause necrosis. Peripheral vascular disease (due to microangiopathy & atherosclerosis) in diabetic patients also causes local tissue ischemia and increased susceptibility to infections. Therefore thrombosis of the internal maxillary artery or descending palatine artery caused by mucormycotic infection as well as chronic diabetes in this patient had resulted in necrosis of the maxilla [11].

Disseminated involvement of mucormycosis is observed in diabetics with ketoacidosis, which favors rapid proliferation of fungus and its invasion into the orbit and cerebrum. Mucormycosis is aggressive and potentially fatal in diabetic patients because of impaired host defense mechanism and increased availability of micronutrients such as iron. Therefore, dissemination leads to rhinocerebral form of mucormycosis. The infection may also spread to involve the cranium, orbit and other organs. Therefore, a team of specialists including a dentist, ophthalmologist, neurosurgeon and maxillofacial surgeon are required for management of such patients. In the early stages of the disease, patients exhibit facial cellulitis, anesthesia, nasal discharge, necrotic turbinates, fever, headache and lethargy [12].

**Rhinocerebral Mucormycosis is often associated With Triad of Symptoms:**

- Uncontrolled diabetes mellitus
- Periorbital infection
- Meningoencephalitis
The 25% cases of the rhinocerebral mucormycosis form shows facial gangrene (Limongelli et al. 1975), the disease is known to present oral manifestations [13]. Mucormycosis of the oral cavity can be of two origins. One is from disseminating infection where the portal of entry is by inhalation (usually through the nose); the other is from direct wound contamination with dissemination to other viscera as a common complication. When arising from the nose and paranasal sinuses, the infection may cause palatal ulceration progressing to necrosis. The area appears black in the large majority of the cases. When the infection spreads from direct wound contamination, the clinical findings may appear anywhere in the oral cavity, including the mandible [14].

An important prognostic difference between infection involving the maxilla and infection of the mandible is cavernous sinus thrombosis, a serious complication of maxillary infections. Another difference is the rarity of the mandibular infections as compared to the maxillary. More than 60 reports of jaw infection have been found in the English literature; all but four with maxillary involvement [15]. In 1977, Eisenber et al. reported the first case of mandible mucormycosis [16]. In 1986, Brown and Finn reported the second case of mandible mucormycosis. The rhinocerebral form of mucormycosis is more common and is associated with homolateral facial palsy, anesthesia of the areas supplied by first and second division of trigeminal nerve. If there is cranial vault involvement, it can lead to blindness, lethargy, seizures or can even lead to death [17].

Differential Diagnosis: Among the clinical differential diagnosis squamous cell carcinoma of maxillary sinus is being considered. Such cases present as chronic ulcers with raised margins causing exposure of underlying bone. A malignant salivary gland tumor arising from the accessory glands of the palate can also be considered in the differential diagnosis. Other features seen in cases of antral carcinoma are local pain, swelling, epistaxis, nasal discharge, epiphora, diplopia or numbness. Extranodal NK T-cell lymphoma (nasal type angiocentric lymphoma or midline lethal granuloma) characteristically occurs in midline, affecting the oronasal region. In the initial stages patients may report nasal stuffiness, pain and palatal swelling [18]. Later, patients develop progressive areas of ulceration that can lead to bone necrosis and perforation. Wegener’s granulomatosis is an uncommon condition characterized by a necrotizing granulomatous condition of respiratory tract, widespread vasculitis and necrotizing glomerulonephritis. Common presenting signs and symptoms include sinusitis, rhinorrhea, nasal stuffiness and epistaxis with or without complain of fever, arthralgia and weight loss.

Gingiva has a peculiar erythematous hyperplasia and is termed strawberry gingivitis. There may be destruction of underlying palatal and alveolar bone causing oral-antral fistula. Bone necrosis can also occur due to extension of infections such as acute necrotizing ulcerative gingivitis (ANUG) from the gingiva to bone. Among histopathologic differential diagnosis includes aspergillosis. There is a close histopathological resemblance between mucormycosis and aspergillosis. Microscopically, aspergillosis has septate branching hyphae, which can be distinguished from mucormycotic hyphae by a smaller width and prominent acute angulations of branching hyphae. Moreover, the organism produces conidiophores [19].

Radiological Features In Case Of Involvement of Paranasal Sinuses: Nodular thickening of sinus mucosa, cloudy sinusitis without fluid levels, spotty destruction of bony walls of paranasal sinuses are seen. CT findings show opacification of paranasal sinuses, thickening of sinus mucosa and erosions of the bony walls [20].

Diagnosis: Culture and histological examination are imperative for the correct diagnosis of mucormycosis. Culture examination from the swab specimen can be negative for mucormycosis as it tends to invade deeply in the tissues. Therefore, it is mandatory to obtain the histological specimen as well culture specimen from the necrotic wound surface [21]. A definitive diagnosis of mucormycosis can be made by tissue biopsy that identifies the characteristic hyphae, by positive culture or both. Initial culture of diseased tissue may be negative and histopathologic examination is essential for early diagnosis. Culture media used are Sabourd’s glucose agar. Sporulation of fungal hyphae speciates for mucormycosis. Within 24-48 h of plating spores come to the surface of petridish.

The fungus can be identified by hematoxylin and eosin stain, Periodic acid Schiff stain, Gridley’s modification, Gomori’s methenamine silver nitrate and confirmed by Grocott’s silver methenamine special staining technique. Histopathological examination with hematoxylin and eosin stain readily identified non-septate mucormycotic hyphae. Grocott’s modified silver methenamine special staining technique further identified these non-septate branching hyphae of mucormycosis [22].

Management: In 1955, first cure of mucormycosis was reported by Harris. It was long regarded as a fatal infection with poor prognosis. However with early medical and surgical management survival rates are now thought to exceed 80%. This patient survived because of an early diagnosis and prompt treatment. Overall aggressive medical support of these critically ill patients also improves chances for survival. Amphotericin B was developed in the 1950s. Before that, invasive fungal infection was a uniformly fatal disease. Three principles in the patient management were followed. Firstly,
management of systemic disease like diabetes mellitus for which the patient is usually advised insulin therapy and dietary restrictions.

Secondly, removal of the necrotic bone, which acted as a nidus of infection and prevented action of systemically administered antifungal drugs (due to thrombosis of blood vessels). Thirdly Amphotericin B is administered parenterally as it is the drug of choice in treatment of mucormycotic infection. Amphotericin B 50 mg of vial of AMB suspended in 10 ml of sterile water and diluted to 500 ml of glucose solution. Nebulisation of 4 ml in each nostril 4-6 times a day is done. Amphotericin B 1.0-1.5 mg/kg/day. Liposomal Amphotericin B is the lipid formulations that can be prescribed safely to the patients with renal failure. Blood urea & creatinine levels need to be monitored.

Post-operatively patient is advised an obturator to prevent oronasal regurgitation in cases of palatal & sinus involvement [23]. Hyperbaric oxygen therapy has also been used to treat mucormycosis. The high oxygen concentrations achieved in infected tissue may decrease tissue hypoxia and acidosis, thereby reducing the ability of the fungus to proliferate. Hyperbaric oxygen therapy is administered 2 atm 1 h for 30 days. Surgical treatment options include Caldwell Lu operation, external ethmoidectomy & local debridement [24].

Figure 1. Mucormycosis Ulcer

CONCLUSION
Mucormycosis is an opportunistic fulminant fungal infection caused by zygomycetes. This fungus can cause a variety of infections in human beings, particularly in the uncontrolled diabetes mellitus. Zygomycetes impinge into the vascular network, resulting in thrombosis and necrosis of the surrounding hard and soft tissues. The infection begins in the nose and paranasal sinuses due to inhalation of fungal spores and spread to orbital and intracranial structures either by direct invasion or through the blood vessels. Sinus mucormycosis is often accompanied by a poor prognosis and a high mortality rate. Hence, aggressive surgical intervention with antifungal therapy is usually necessary. Early diagnosis and prompt treatment can reduce the mortality and morbidity of this lethal fungal infection. A non-specific palatal ulcer could well be the presenting sign of mucormycosis and it is therefore essential for dental practitioner be alert to early signs and symptoms of this disease, especially when evaluating the patients with the high-risk group.

REFERENCES