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CASE REPORT

Oral Mucormycosis in an Immunocompetent Patient: A Case Report and Literature Review

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ABSTRACT

Introduction: Mucormycosis is a life-threatening, opportunistic invasive fungal infection caused by the saprophytic fungi of the order Mucorales, belonging to the class Zygomycetes. These organisms most frequently infect immunocompromised hosts. Rhinocerebral mucormycosis is the most common clinical form of the disease, usually extending to the orbit and brain, while palatal involvement is a late occurrence. Isolated palatal ulcer without rhinocerebral involvement is a rare phenomenon, especially in immunocompetent patients.

Case report: We report a case of palatal mucormycosis in an immunocompetent patient with a review on the pathogenesis and morphological characteristics of the organism.

Discussion: As mucormycosis is usually seen in patients having a compromised immune system, treatment of the underlying cause along with prompt institution of liposomal amphotericin B therapy and surgical resection are critical.

Conclusion: Early detection and treatment is vital due to the fulminant course of the infection. Histopathology remains the most reliable technique for diagnosing mucormycosis, and hence, thorough knowledge of the morphology of the organism is essential to pick up the strains from routine staining.

Keywords: Immunocompetent, Mucormycosis, Oral, Palate.

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INTRODUCTION

Mucormycosis, also known as zygomycosis, is an uncommon opportunistic, frequently fulminant fungal infection caused by Mucorales, belonging to the class of Zygomycota. This ubiquitous fungi is present in soil, air, and as bread mold fungi. Patients with compromised host defenses are susceptible to infection, although it has been reported infrequently in immunocompetent hosts. Diagnosis is confirmed by histopathologic demonstration of fungal invasion in infected tissue. Because of the severity of the underlying disease and the often fulminant course that the infection may take, diagnosis of mucormycosis may not be made until after death.[1]

Mucormycosis infection in humans is usually acquired through inhalation of airborne fungal spores, ingestion, or by contamination of traumatized tissue. The primary infection occurs usually in the upper respiratory tract, where the spores germinate and the hyphae invade into the adjacent tissues of the sinuses, orbit, and brain.[2] Isolated involvement of the palatal mucosa without rhinocerebral involvement is a rare finding. The fungi are angiotropic and invade blood vessels causing thrombosis, resulting in extensive coagulative necrosis.[3] Here we report a case of mucormycosis in the palatal mucosa of an immunocompetent patient without rhinocerebral extension.

CASE REPORT

A 42-year-old male patient reported to the department with the complaint of black discoloration of the palate since 2 weeks. History revealed that patient had a fracture of maxilla in a road traffic accident 4 months earlier. On examination, the patient appeared debilitated, anemic, and lethargic. Intraoral examination revealed a black necrotic, ulcerated lesion of size 3 × 2 cm, extending from the right side posterior hard palate to the right buccal vestibule. The lesion emanated a foul odor. Submandibular lymph nodes were palpable bilaterally. Hematological investigations indicated leukopenia, low hemoglobin concentration, raised erythrocyte sedimentation rate, and blood glucose levels within normal limits. Based on the history and clinical examination, a provisional diagnosis of osteomyelitis was considered. Occlusal radiograph and orthopantamogram were taken, which did not reveal any abnormality.

An incisional biopsy was carried out and the tissue was submitted for histopathological examination. Microscopic examination revealed connective tissue exhibiting areas of necrosis with a minimal chronic

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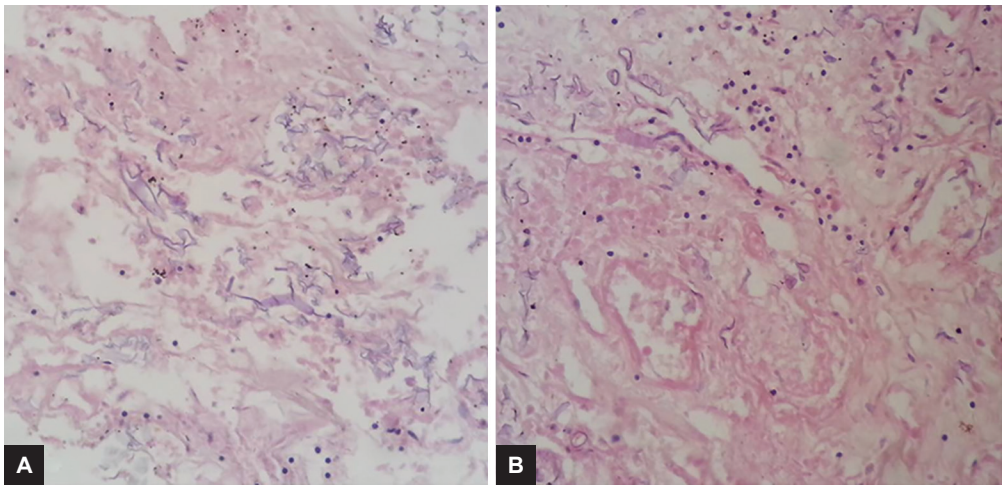
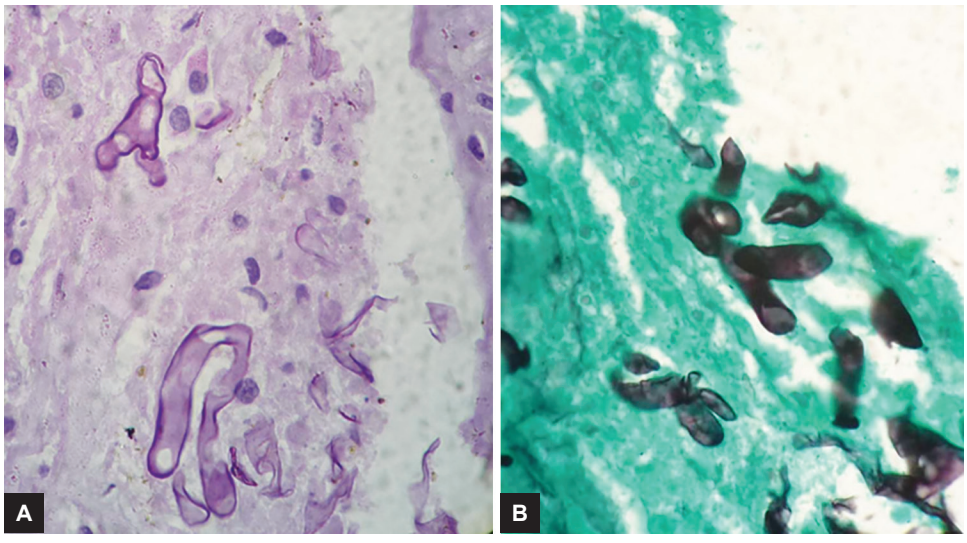


Figs 1A and B: (A) Histopathology showing eosinophilic ribbon-like structures suggestive of fungal hyphae (H&E, 10×). (B) Histopathology showing fungal hyphae invading the blood vessels (H&E, 40×)



Figs 2A and B: (A) Periodic acid Schiff stain demonstrating the fungal hyphae; and (B) Methenamine silver stain showing the branched fungal hyphae suggestive of mucormycosis

inflammatory cell infiltrate and numerous blood vessels. Numerous eosinophilic, fragmented ribbon-like structures suggestive of fungal hyphae were seen scattered throughout the connective tissue (Fig. 1A). Few fungal hyphae were seen within the blood vessels (Fig. 1B). Special stains for fungi including Periodic acid Schiff and methenamine silver staining were performed, which revealed broad, nonseptate fungal hyphae, many of which appeared distorted. A few of the hyphae showed branching (Fig. 2). Based on the fungal morphology demonstrated using special stains, a final diagnosis of mucormycosis of the palate was made. The lesion was treated by local debridement of the necrotic tissue and intravenous infusion of amphotericin B.

DISCUSSION

Human disease caused by members of Mucorales was first reported in 1885 by the German pathologist Paltauf who described it as "Mycosis mucorina".[4] Mucormycosis is reported to have an increasing incidence in several countries over the past few years.[5,6] In India, the frequency has risen and the highest risk group is patients with uncontrolled diabetes.[6,7] In immunocompromised patients, *Rhizopus oryzae* is considered the most common cause of infection causing approximately 70% of all cases, followed by *Mucor* spp. and *Lichteimia* spp.[8-11] The major risk factors for mucormycosis include uncontrolled diabetes mellitus in ketoacidosis, other forms of metabolic acidosis, neutropenia, treatment with corticosteroids, organ or bone marrow transplantation, trauma and burns, malignant hematologic disorders, and deferoxamine therapy in patients receiving hemodialysis.[8,10,12] In immunocompetent patients, *Apophysomyces elegans* is an important pathogen.[5,13] In our case, the patient did not have any immunocompromised condition, but a recent history of trauma could be a predisposing factor.

Invasive mucormycosis may manifest as rhinocerebral, pulmonary, cutaneous, gastrointestinal, or disseminated forms. Characteristic of all forms is vascular invasion, resulting in thrombosis, hemorrhagic necrosis, and a fulminant disease course. The nature of the underlying disease is an important determinant of the primary site of infection.[5,10]

Mucormycosis of the head and neck region presents as rhinocerebral mucormycosis, and is the most common form of the disease, often associated with diabetic ketoacidosis.[10] It usually originates in the paranasal sinuses following inhalation of fungal spores. Involved tissues become red, then violaceous, and finally black as vessels are thrombosed and the tissues undergo necrosis. Disease extends from sinuses into the periorbital region and oral cavity. Infection can also spread posteriorly from either the orbit or sinuses to the central nervous system.[1,9,10] In our case, the lesion was restricted to the palatal soft tissue and buccal vestibule without any extension into the sinuses, orbit, or the brain.

The pathogenesis of mucormycosis involves failure to suppress the germination of spores and subsequent failure to kill proliferating hyphal elements. Macrophages and neutrophils play a major role in normal host defense mechanism against mucormycosis.[10,11,14] In normal hosts, macrophages prevent the initiation of infection by phagocytosis and oxidative killing of the spores, thereby suppressing the spore germination process.[1] Once infection is established, neutrophils play a pivotal role in mediating fungal killing in the normal host. Neutrophils are chemotactically attracted to the hyphae on which they attach, spread, and use their oxidative cytotoxic system and cationic peptides, defensins, to damage and kill the fungal hyphae.[8] In diabetes, neutrophil function is impaired, and prolonged neutropenia is thus the main risk factor for development of the disease.[11]

Another important pathogenic factor for infection is the presence of elevated available serum iron. Iron is a requisite nutrient for Mucorales, promoting their growth and hyphal development. Many of the underlying predisposing diseases of mucormycosis share a plasma iron overload.[10] Dialysis patients under treatment with deferoxamine, an iron chelator, are particularly at risk for mucormycosis. *Rhizopus* spp. utilizes deferoxamine as a siderophore and is able to detach iron from deferoxamine. More recently, studies involving expression of the *FTR1* (high-affinity iron permease of *R. oryzae*) gene and its products have confirmed the importance of iron in the pathogenecity of Mucorales.[10,11] *Rhizopus* spp. reportedly has an active ketone reductase system. This may act as an additional virulence factor that enables Mucorales to grow well in the acidic and glucose-rich environment seen in ketoacidotic states.[1]

Angioinvasion with resultant vessel thrombosis and tissue necrosis is characteristic of mucormycotic infection. Angiotropism is also associated with hematogeneous spread to other target organs.[8,10] Hence, adhesion to endothelial cells, their penetration, and damage are important for the pathogenic mechanism of Mucorales. *In vitro* studies have shown that *R. oryzae* adheres to the subendothelial matrix protein laminin and type IV collagen. Glucose-regulated protein (GRP78) was recently identified as a host receptor that facilitates the penetration through and damage of endothelial cells by *R. oryzae*. Elevated concentrations of glucose and iron will increase the expression of GRP78 resulting in a concomitant damage to host endothelial cells.[8,11] A lesser known aspect of Mucorales is its neurotropism, which may facilitate a retrograde extension of fungi into the central nervous system by neural invasion.[15]

Other putative virulence factors of Mucorales postulated are proteolytic, lipolytic, and glycosidic enzymes, as well as metabolites like alkaloids or mycotoxins, although their role in human disease is unclear.[8,11]

The morphology of the organism in histopathology appears as broad, ribbon-like, predominantly aseptate hyphae with wide-angle (45–90°) branching.[1,15] The hyphae are thin walled compared with other fungal hyphae and may become crinkled or gnarled in tissue sections, often referred to as a "crinkled cellophane" appearance of the hyphal elements. The hyphae stain poorly or inconsistently with hematoxylin and eosin (H&E) and appear eosinophilic with empty or clear lumina, causing the infected tissue to appear frothy due to these clear spaces.[1]

Extensive necrosis, areas of hemorrhage, and a neutrophilic infiltrate are often seen within the tissues, although the host inflammatory response to the infection may be minimal in an immunosuppressed patient. Invasion of blood vessels by hyphae is present. In addition, perineural invasion by the organism is a frequently observed, although lesser known aspect of its histopathology, and has been suggested as an additional mode of invasion and spread of disease.[15] Fungus-specific tissue stains, such as methenamine silver or Periodic acid Schiff, will clearly demonstrate the organism.[1]

Successful treatment of mucormycosis requires early diagnosis, reversal of the underlying predisposing factors, surgical debridement of the infected tissues, and appropriate antifungal therapy. The mainstay of antifungal therapy is amphotericin B. Adjunctive therapy includes the use of itraconazole, posaconazole, hyperbaric oxygen, and cytokine therapy.[5,10]

CONCLUSION

Mucormycosis is a rapidly progressive opportunistic fungal infection. Rhinocerebral form with extension into sinuses, orbit, and brain is the common presentation of mucormycosis. Isolated palatal involvement is uncommon, while isolated palatal lesion in immunocompetent patients is rare. Histopathology remains the most reliable technique for diagnosing mucormycosis. Early diagnosis and management are of extreme importance for successful treatment and patient survival. It is often difficult to detect the organism under routine H&E stain. Hence, apart from routine H&E, we should consider special stains, such as methenamine silver or Periodic acid Schiff, for detecting fungal hyphae as a part of routine diagnostic aid to avoid diagnostic dilemma.

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