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Case Report

Rhino-orbital mucormycosis with cutaneous involvement in an HBV-positive patient: a case report and review of the literature

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ABSTRACT

Mucormycosis is a rare fungal angioinvasive disease characterized by infarction and tissue necrosis. It is an opportunistic infection mainly affecting patients with impaired immunity, as seen in patients with diabetes mellitus with or without ketoacidosis, injudicious use of steroid therapy, hematological malignancy, bone marrow transplant, chemotherapy, neutropenia, as well with deferoxamine therapy. The various clinical variants of mucormycosis include rhino-orbitocerebral, pulmonary, cutaneous, and disseminated forms, among which the rhino-orbital-cerebral type is the most common. A notable rise in mucormycosis cases has been observed among patients with history of COVID-19. Contributing factors may consist of thromboembolic events linked to substandard oxygen administration practices, altered cardiopulmonary dynamics, and the injudicious use of steroids and antibiotics during COVID-19 treatment. Early diagnosis and urgent surgical and medical intervention form the cornerstone of a successful outcome. In our case report, we present a 55-year-old hepatitis B-positive patient with rhino-orbital mucormycosis with cutaneous involvement. This report emphasizes on the challenges faced in the management of patients with Hepatitis B-associated mucormycosis.

We report a rare rhino-orbital mucormycosis (ROCM) case with cutaneous involvement in a patient with active Hepatitis B virus (HBV) infection and no other risk factors. The study emphasizes on early surgical and medical intervention and adequate control of comorbidity contributing to impaired immunity for a favorable prognosis.

Keywords: Cutaneous, Hepatitis B, Immunocompetent, Mucormycosis, Rhino-cerebral

INTRODUCTION

Mucormycosis is a fatal angio-invasive fungal infection mainly affecting patients with impaired immunity characterized by tissue infarction and necrosis. Clinically, mucormycosis can be rhino-orbito-cerebral, disseminated, cutaneous, gastrointestinal, and pulmonary. The fungus may cause severe systemic infection with 45-80% fatality, predominantly in patients with diabetes mellitus.1 Mucormycosis usually begins in the nose and/or paranasal sinuses and may involve the orbit, brain, and lungs.2 Urgent intervention in the form of intravenous liposomal Amphotericin B and early surgical debridement is strongly recommended.3 The most prevalent variant is rhino-orbital, which can spread from the sinuses to the oral mucosa, brain, bones, and orbit. The presenting symptoms are nasal congestion, headache, fever, facial pain, orbital swelling, and dark lesions.4,5 Orbital invasion may cause cellulitis, proptosis, and blurred vision, while brain involvement can lead to rapid progression and high mortality.6

Rhino-orbital mucormycosis is rare in patients with liver cirrhosis. A systematic literature review was conducted on studies and case reports published between August 1969 and August 2024, using search terms including liver cirrhosis, mucormycosis, HBV, and HCV. A manual review of some reference lists from the identified case

reports was also performed. The literature review revealed a total of 20 cases, with the majority resulting in a fatal outcome. Here, we report a case of mucormycosis with HBV infection with cutaneous extension. To our knowledge, our case might be the first case of rhino-orbital mucormycosis in a patient with liver cirrhosis with no other risk factors treated effectively with surgical debridement and antifungal (Liposomal Amphotericin B 5 mg/kg) and antiviral medication (Tenofovir 300 mg once a day).

CASE REPORT

A non-alcoholic 55-year-old male presented to ENT OPD of PGIMS Rohtak with complaints of right cheek swelling, pain, nasal obstruction, and intermittent fever for seven days. He also had blackening of skin (3×4 cm) over the right cheek for four days (Figure 1). The patient had no ocular or neurological symptoms. There was no history of diabetes mellitus, tuberculosis, Human Immunodeficiency Virus (HIV), COVID-19 infection, or any other chronic medical illness. The patient had never had a blood transfusion, steroid, or immunosuppressive therapy. He had no history of tooth extraction or any other dental intervention.

Diagnostic nasal endoscopy revealed black dry crusting in both nasal cavities. Oral cavity examination showed mucosal discoloration on the right side of the hard palate, with an area of exposed underlying palatine bone that smelled foul and had purulent discharge. Ophthalmological examination, including ocular mobility and visual acuity, was normal.

Potassium Hydroxide (KOH) smear of nasal discharge was positive for fungal hyphae, which were aseptate and branching at right angles. All other routine investigations were normal except for Hepatitis B serology. Quantitative HBV DNA was 3.45×105IU/ml. The liver function test showed a mild increase in Aspartate Aminotransferase (42 U/l) and Alkaline phosphatase (135 U/l). A Fibro scan of the liver showed severe scarring (12.8 kPa).

Non-contrast computed tomography (NCCT) of the nose and paranasal sinuses (Figure 2) showed thickening of the skin and subcutaneous tissue on the right nasolabial region with stranding of subcutaneous fat. Mucosal hypertrophy was also noted in bilateral maxillary and ethmoid sinuses. Contrast-enhanced magnetic resonance imaging (CEMRI) brain and orbit suggested heterogeneously enhancing the ill-defined areas with non-enhancement in right premaxillary soft tissue.

A sinus tract was also seen extending from the skin to the right alveolar surface of the maxillary bone. The patient underwent bilateral inferior maxillectomy and endoscopic sinus debridement. The excised specimen was sent for histopathological examination and showed broad aseptate ribbon-like hyphae, which was suggestive of invasive mucormycosis (Figure 3).

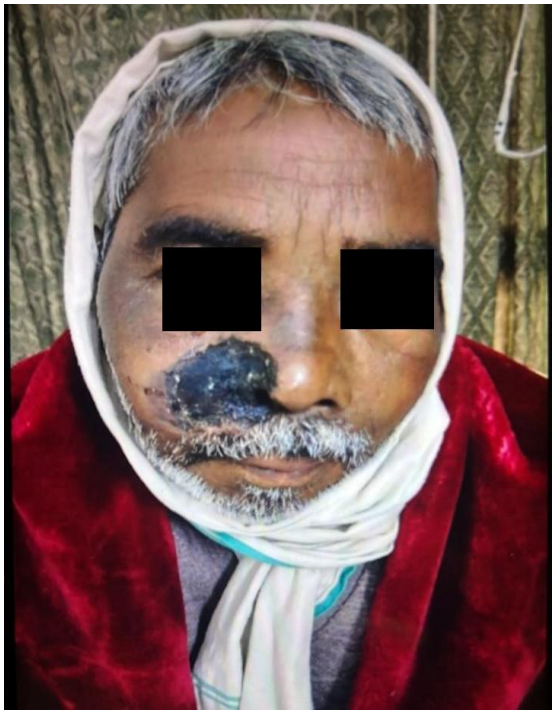

Figure 1: Blackening of skin over right cheek region.

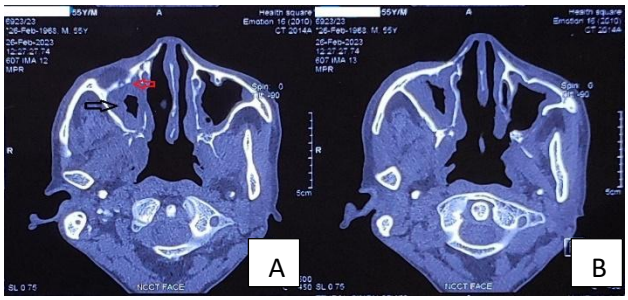

Figure 2 (A and B): Non-contrast computed tomography (NCCT) of nose and paranasal sinuses. Mucosal thickening (black arrow) in bilateral maxillary sinuses with erosion of right anterior maxillary wall (red arrow) and subcutaneous edema of right premaxillary region.

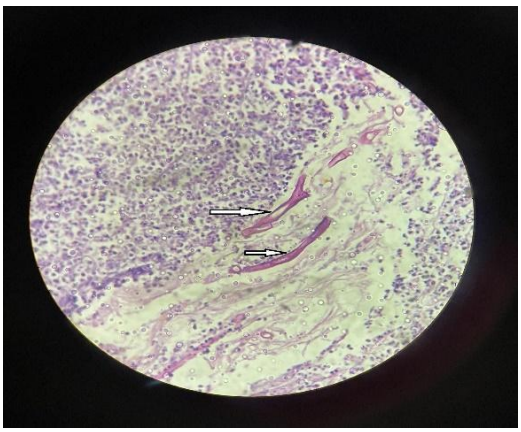

Figure 3: Mucor (white arrow) stained with H&E at 40X.

Figure 4: Intraoperative picture of patient after debridement.

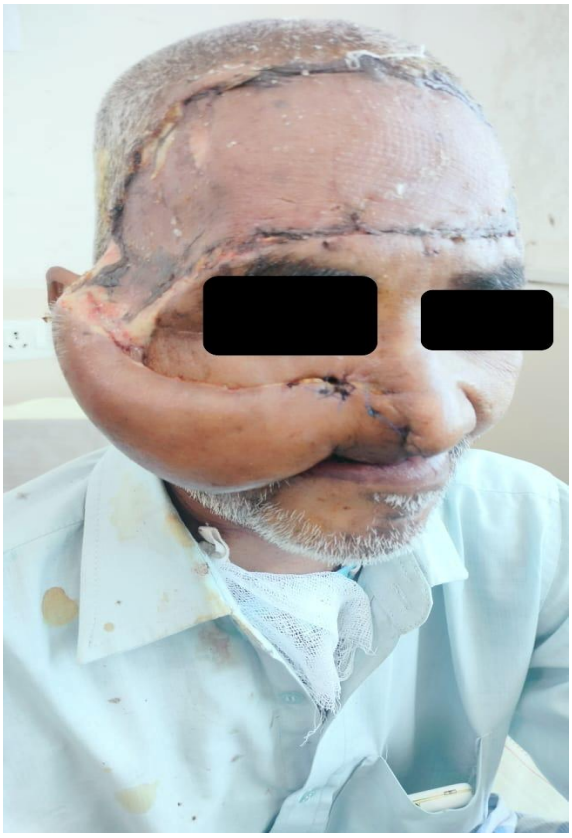

Figure 5: Postoperative picture of patient after closure of facial defect with supratrochlear artery-based graft.

Medical management consisted of antifungal (intravenous Liposomal Amphotericin B 5 mg/kg), antiviral medication (Tenofovir 300 mg once a day), and broad-spectrum antibiotic coverage. The patient was periodically monitored for electrolyte disturbances, kidney function tests, and cardiotoxicity. He underwent endoscopic debridement thrice until the biopsy was negative for mucormycosis (Figure 4). Later, the facial defect was closed with a supratrochlear artery-based forehead flap (Figure 5). He was discharged with stable vitals and fair general condition. The patient was followed up serially every three months using diagnostic nasal endoscopy for two years, and there was no evidence of recurrence of mucormycosis.

DISCUSSION

Mucormycosis represents a group of infections caused by fungi belonging to the order Mucorales within the family Mucoraceae. The most common causative organisms are Rhizopus and Mucor.[7] More than 900 cases of mucormycosis have been reported in the literature.8 Mucor fungal spores are ubiquitous in the environment and typically enter the body through the respiratory tract, affecting the paranasal sinuses and lungs.

Rhino-orbito-cerebral mucormycosis (ROCM) accounts for approximately half of the reported cases in India.[9] Rhino-orbital mucormycosis specifically involves fungal infections of the orbit, leading to inflammation, thickening of the orbital wall, and expansion affecting orbital fat and extraocular muscles.[10] Common clinical manifestations include eye swelling and facial numbness. The infection generally originates in the nose and paranasal sinuses as the primary entry point, with secondary spread to the orbit and, in some cases, invasion into intracranial structures via the orbital apex or blood vessels.[11]

Poorly controlled diabetes mellitus and compromised immunity are the most prevalent risk factors for mucormycosis. Other contributing factors include corticosteroid use, chronic kidney disease, organ transplantation, intravenous drug use, hematological malignancies, neutropenia, iron overload states, and COVID-19 infection. Diabetes mellitus remains the most frequently reported risk factor.[12] In the post-COVID-19 era, an increase in mucormycosis cases has been observed, primarily attributed to cytokine-induced immunosuppression associated with COVID-19 and its management.[13]

Fungal infections remain relatively uncommon in individuals with liver cirrhosis compared to bacterial infections. However, documented cases in cirrhotic patients include infections caused by Candida, Cryptococcus, Aspergillus, and Coccidioidomycosis.14 Reports of invasive mucormycosis in this population are scarce. Neutropenia and thrombocytopenia, frequently observed in patients with cirrhosis, may serve as predisposing factors for fungal infections, contributing to their susceptibility.[15] This highlights the importance of considering fungal pathogens, including mucormycosis, in the differential diagnosis of infections in cirrhotic patients, particularly in those presenting with hematological abnormalities.

Hepatitis B infection is a significant public health problem globally; around 30% of the population is seropositive.[16] The exact pathophysiology of the

association between mucormycosis and HBV infection is unknown. Mucormycosis, a severe invasive fungal infection, is associated with a high mortality rate, particularly in immunocompromised individuals. Immunosuppression can arise from various conditions, including active hepatitis B virus (HBV) infection, which has been implicated in the development of liver cirrhosis. Gao et al. highlighted that in HBV infection, CCR4+ T regulatory cells are the predominant subset of T regulatory cells.

These cells exhibit cytokine-driven PD-1+TCF1+ stem-like properties, contributing to significant immunosuppression. This compromised immune state in HBV-induced liver cirrhosis increases the susceptibility to opportunistic infections like mucormycosis, underscoring the interplay between viral infections, immune dysfunction, and invasive fungal diseases.[17] A case of mucormycosis with underlying liver cirrhosis, as reported by Lin et al., in which the patient suffered from maxillary sinusitis and osteomyelitis. The infection was successfully treated with antifungal agents, surgical debridement, and hyperbaric oxygen therapy. It was the first report of the safe and effective use of posaconazole to treat mucormycosis in a cirrhotic patient.[18]

Elsiesy et al, conducted a literature review in 2013 on patients with cirrhosis and mucormycosis, identifying 17 reported cases.19-31 Among these, nine were male, and eight were female. The underlying causes of cirrhosis included Hepatitis C virus (HCV) in 8 patients, Hepatitis B virus (HBV) in 2, autoimmune hepatitis in 2, alcoholic liver disease in 3, and an unknown etiology in 2 cases. Out of 17, eight cases had diabetes mellitus as co-morbidity, while three patients were on steroid therapy.[31]

Most of these cases are rhino-orbital. Four cases were associated with involvement of the upper extremity, while one case demonstrated gastric involvement by Naqvi et al. They reported a case of acute gastric mucormycosis in a patient with poorly controlled diabetes and chronic renal disease, presenting with sudden abdominal pain.[29] After an extensive search of published literature, we found only six other cases of mucormycosis in patients with cirrhosis from 2018 to 2022. The causes of liver cirrhosis were ethanol poisoning, chronic HCV infection, alcoholic liver disease, and unreported etiology.[32-35] In 2021, Vijapur et al reported a case of a 56-year-old patient, positive for Hepatitis B and diagnosed with grade 3 oral submucosal fibrosis, who had recovered from a SARS-CoV-2 infection. The patient presented with swelling around the left periorbital region and was diagnosed with rhinomaxillary mucormycosis.36 In 2022, another case of acute lymphoblastic leukemia (ALL) with hyperglycemia complicated by mucormycosis was reported by Khatun et al, in which a liver abscess ruptured, leading to empyema thoracic. The condition was successfully treated with antifungal therapy.[37]

Invasive mucormycosis was diagnosed in a 56-year-old female with ESRD and hepatitis C cirrhosis, after nasal discoloration was noted by Rihawi et al. Antifungal treatment and rhinectomy were administered, but her condition deteriorated, and death occurred.[38] In 2024, Ansari et al. reported the first case of pulmonary mucormycosis in a patient with decompensated liver cirrhosis, which was successfully treated with oral posaconazole. The treatment was well-tolerated, with no side effects, and the patient survived beyond the course of treatment.[39]

Another report in 2024 presents a case of mucormycosis-related gastric ulcer in a patient with liver cirrhosis who developed upper gastrointestinal bleeding (UGIB) following splenectomy for traumatic splenic rupture. While UGIB in cirrhotic patients is commonly attributed to portal hypertension, other causes, such as infectious ulcers due to immunosuppression, should be considered. This case highlights the need to rule out fungal-induced ulcer bleeding before attributing UGIB to portal hypertension-related variceal hemorrhage in a liver cirrhosis patient.[40]

The association between isolated Hepatitis B infection and mucormycosis has not been previously documented in the literature. This case is likely the first reported instance of rhino-orbital mucormycosis with cutaneous extent in a patient with HBV infection. Notably, the patient did not exhibit any conventional risk factors typically associated with invasive fungal infections.[1,31]

CONCLUSION

Mucormycosis is a rare and often fatal opportunistic infection. While several risk factors for mucormycosis have been well-documented in the literature, limited data regarding its association with HBV infection is available. In the case presented, HBV infection was identified as the sole risk factor for developing mucormycosis. This case report highlights the association between active HBV infection and mucormycosis. From this case and in reviewing the literature, it seems that patients with hepatitis are generally at an increased risk of developing infections. Management of these infections is particularly challenging due to hepatic dysfunction. Mucormycosis in the context of liver cirrhosis is associated with high mortality, even with aggressive treatment.

While predisposing risk factors often influence the outcome of mucormycosis, this case demonstrates that effective treatment is possible without such factors through close monitoring of liver function. Early diagnosis, imaging and histopathological evaluation, and timely and adequate treatment are critical for successfully managing and eradicating mucormycosis in these patients. Therefore, in patients with mucormycosis, hepatitis serology should not be overlooked, as it may provide valuable insights into underlying conditions that could influence management and outcomes.

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