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Short report

# Rhinoorbital mucormycosis - Unveiling the hidden menace : A case series

***Shibam Kundagrami [1*], Siddhartha Basak[1] , Uddalok Das[2]***

*1- North Bengal Medical College and Hospital, Darjeeling, India*
*2- Department of Radiodiagnosis, North Bengal Medical College and Hospital, Darjeeling, India.*

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**ABSTRACT**

**Background**: Mucormycosis is a life-threatening angioinvasive infection caused by filamentous fungi of the order Mucorales. The disease occurs commonly in immunocompromised individuals with hematological malignancies or those undergoing stem cell transplantation. Major risk factors include immunosuppression, uncontrolled diabetes, iron overload, and trauma. Diagnosis and treatment remain challenging due to inherent antifungal resistance. Depending on the host's immunological condition and route of infection, clinical and radiological symptoms differ across patients. **Case Series**: We present two cases of rhino-orbital mucormycosis in middle-aged individuals who were reported to the outpatient department of North Bengal Medical College and Hospital with varied clinical presentations. Neither patients had any history of novel coronavirus disease 2019 (COVID-19) infection. Our report demonstrates the role of radiological investigation; Magnetic Resonance Imaging (MRI) for prompt confirmation of clinical suspicion with adequate confidence. **Conclusion**: Invasive mucormycosis has been found to cause high morbidity and mortality with death rates up to 50%. Therefore, it is critical to maintain a high degree of suspicion for infection since early diagnosis and initiation of necessary treatment improves patient outcomes. MRI helps in early diagnosis of the condition and helps in quick treatment initiation thus improving patient outcome.

## Introduction

Mucormycosis is an angioinvasive infection caused by pervasive filamentous fungi of the Mucorales order of the class Zygomycetes [1]. This disease very commonly occurs in immunocompromised individuals with hematological malignancies or those undergoing hematopoietic stem cell transplantation. Immunosuppression, poorly managed diabetes, iron overload, and significant trauma are the major risk factors. High mortality rates still occur in some patient groups as a result of the challenges in diagnosis and subsequent antifungal therapy, where it shows highly inherent resistance to many of the widely used antifungal medications [2]. Mucormycosis can be categorized into one of six types based on anatomic localization: (1) rhinocerebral, (2) pulmonary, (3) cutaneous, (4) gastrointestinal, (5) disseminated, and (6) uncommon presentations, which influence clinical presentations and outcome [1]. *Rhizopus* spp., *Mucor* spp., and *Lichtheimia* spp. (previously of the genera *Absidia* and *Mycocladus*) are the most reported pathogens in mucormycosis, followed by *Rhizomucor* spp., *Cunninghamella* spp., *Apophysomyces* spp., and *Saksenaea* spp. [3]. The massive number of novel coronavirus disease 2019

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* *Corresponding author:* Shibam Kundagrami
E-mail address: shibamkundagrami@gmail.com

(COVID-19) cases in India during the second wave of the pandemic has been linked to an increasing number of reports of invasive mucormycosis following COVID-19 especially among critically ill patients undergoing corticosteroid treatment. Since mucormycosis is a fungal infection, it necessitates a comprehensive understanding of the virulence traits exhibited by the causative agents. Several factors contribute to the pathogenicity of these fungi, including size, thermotolerance, iron acquisition mechanisms, and their ability to evade the host immune system. Angioinvasion is a hallmark trait of mucormycosis and recently, the glucose-regulated protein 78 (GRP78) has been identified to enable invasion of the pathogen via an endocytotic mechanism. This endothelial cell receptor exclusively interacts with Mucorales and no other fungal pathogens [2]. Here we discuss two cases of rhino-orbital mucormycosis in middle-aged patients in the backdrop of a post-pandemic time period.

## Case reports

### Case 1

A 43-year-old female was admitted to the emergency reception of North Bengal Medical College and Hospital (NBMCH) with complaints of left-sided facial puffiness and a drowsy state for the last 2 hours. General examination was unremarkable except for a fever of 101 °C. Systemic examination revealed increased tone in all four limbs with exaggerated deep tendon reflexes. Local examination of the face revealed proptosis and soft tissue swelling over the nose and left side of the face with a black eschar near the nostril. She had no history of COVID-19 infection or COVID-19 vaccination. COVID-19 Rapid Antigen Test (RAT) was done and came as negative. A clinal suspicion of rhino-orbital mucormycosis was made. A nasal swab was taken and sent for microbiology examination and the patient was posted for a Magnetic Resonance Imaging (MRI) examination of the brain and face. MRI revealed diffuse mucosal thickening involving the left maxillary and both ethmoid sinuses. There was evidence of orbital cellulitis with proptosis of the left eye **(Figure 1)**. On diffusion-weighted images (DWI) there was diffusion restriction over basifrontal lobes, left medial temporal lobe, right centrum semiovale, and left cerebellar hemisphere suggesting infarct **(Figure 2)**, likely due to angioinvasion of vessels. The nasal swab sample was sent to the microbiology lab. Smears were made and stained with 10% potassium hydroxide (KOH) with 0.1% calcofluor white. Examination under fluorescent microscopy revealed fungal filaments with wide aseptate hyphae with irregular branching, suggestive of Mucorales. The samples were also inoculated onto chocolate agar and sabouraud dextrose agar and incubated for 1 week. On culture media, the colonies appeared cottony white, which turned brown, gray, or black with time. On slides prepared with lactophenol cotton blue (LCB), non-septate hyphae, rhizoids, and spore-filled sporangiophores were observed predominantly identified as Mucorales. The sample was sent to the National Institute of Cholera and Enteric Diseases (NICED) for antifungal susceptibility and molecular testing. The patient was planned for extensive debridement surgery and was referred to the apex center for better management.

**Figure 1.** Diffuse mucosal thickening involving the left maxillary and both ethmoid sinuses along with proptosis of the left eye

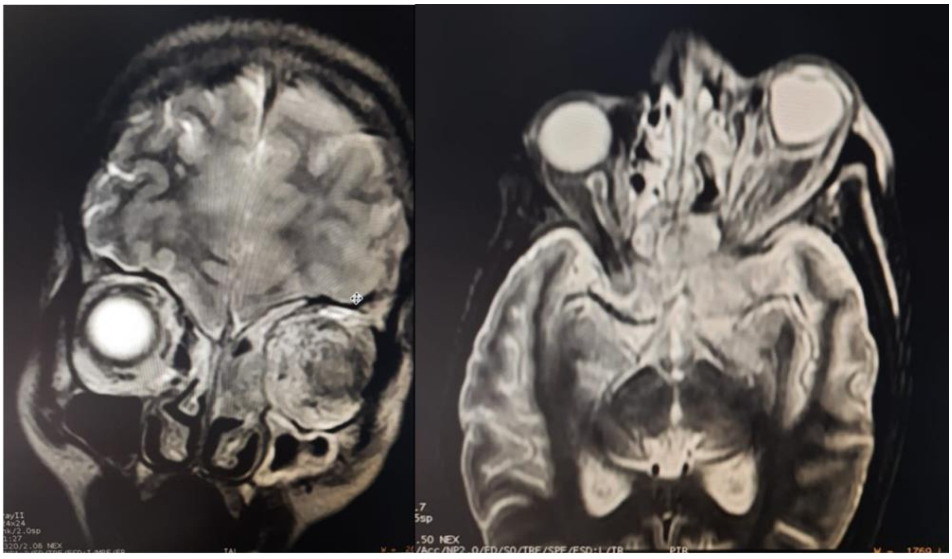
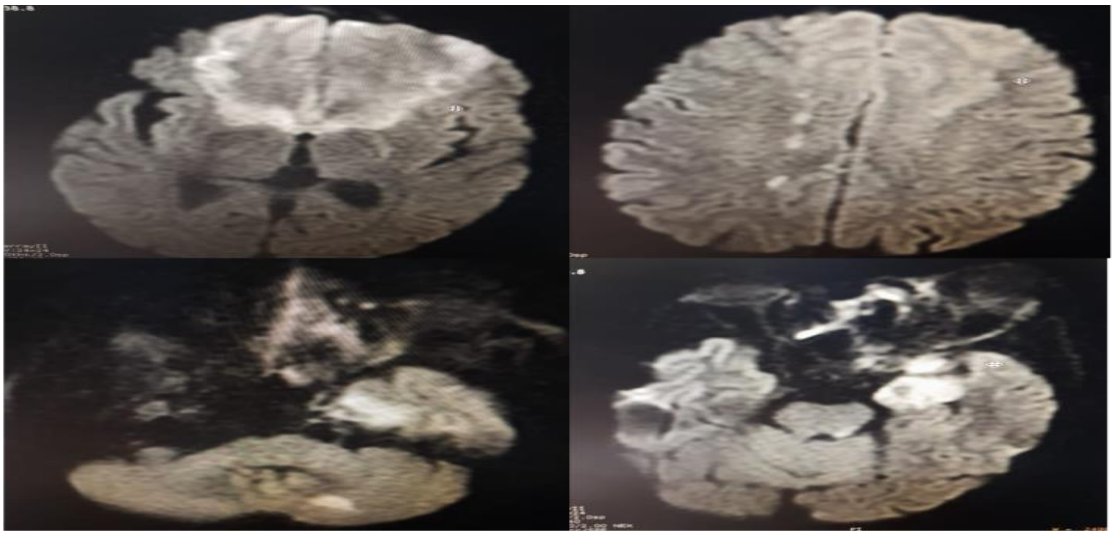


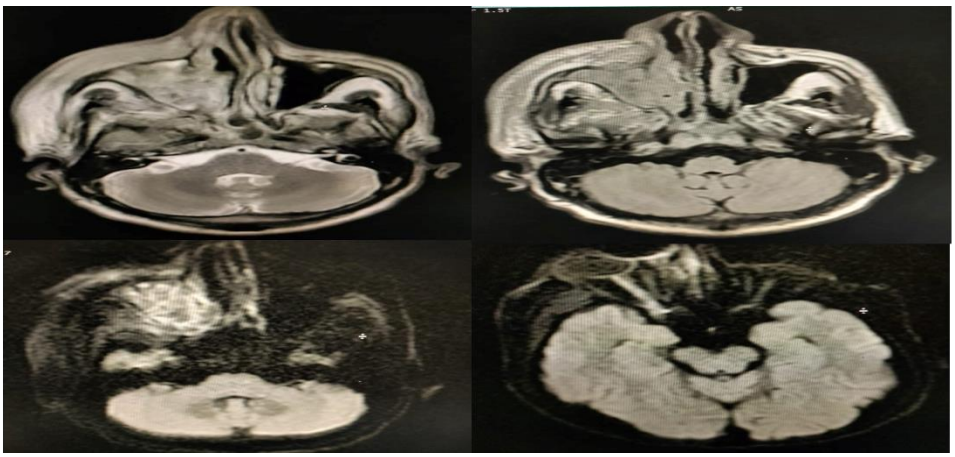
**Figure 2.** Multiple areas of diffusion restriction indicating acute infarcts



**Case 2**

A 38-year-old male presented to the outpatient department of NBMCH with complaints of sudden loss of vision in the right eye for the last few days. The patient was nondiabetic and normotensive. The ophthalmic examination was unremarkable except for proptosis on the right side and diffuse swelling of the right cheek. Also, the patient complained of purulent nasal discharge for some days duration along with black crusting of the skin near the nostril. The patient was sent for an MRI. MRI revealed diffused swelling of the right premaxillary space along with temporalis fascia. Extensive mucosal thickening involving the right maxillary and ethmoid sinuses which demonstrated restricted diffusion on DWI images. There was evidence of erosion of the medial wall of the right maxilla. On DWI images there was restricted diffusion involving the right optic nerve and left lateral temporal lobe **(Figure 3)**. A provisional diagnosis of rhino-orbital mucormycosis with right-sided optic neuritis and left lateral temporal lobe infarct was made. Nasal swabs of the patients were sent for microbiology lab. Fungal filaments with broad aseptate irregular hyphae that were indicative of Mucorales were found upon examination with fluorescence microscopy of smears prepared with 10% KOH and 0.1% calcofluor white. The samples were cultured for one week on sabouraud dextrose agar and chocolate agar. The colonies appeared cottony white. After colony growth, non-septate hyphae, rhizoids, and spore-filled sporangiophores were observed in slides prepared with LCB, indicative of Mucorales. The sample was sent to NICED for antifungal susceptibility and genetic testing. The patient neither had a history of COVID-19 infection nor COVID-19 vaccination in the past.

**Figure 3**. There is mucosal thickening involving the right maxillary and ethmoid sinuses. There is diffuse subcutaneous edema in the right cheek and premaxillary space. Restricted diffusion is seen in the right maxillary sinus, right optic nerve, and left temporal lobe



## Discussion

In immunocompromised individuals, the predominant route of infection appears to be sporangiospores inhalation, resulting in lung infection. Individuals with significant neutropenia and graft-versus-host disease are more likely to develop pulmonary mucormycosis, whereas diabetic individuals are more likely to develop rhino-orbital disease. In most cases, rhino-orbital-cerebral infection begins in the paranasal sinuses, causing decay in the bones and subsequent invasion of the orbit, eye, and brain. There may be unilateral facial edema, proptosis, and palatal or palpebral fistulas that progress into necrosis [3]. Although it might be difficult for clinicians to identify mucormycosis, clinical diagnosis is widely employed in the medical field. However, the sensitivity and specificity of it are poor. The most indicative clinical sign of mucormycosis is tissue necrosis. Contrast-enhanced MRI and Computed Tomography (CT) are preferred imaging procedures although in our cases we used Non-contrast MRI for diagnosis as per the institutional protocol with adequate confidence. This was further proved by the positive microbiology reports in both cases. Imaging is required for a variety of reasons, including early diagnosis, antifungal pharmacotherapy initiation, and treatment response monitoring. MRI is the gold standard for soft tissue and marrow abnormalities due to its better contrast resolution, but CT is frequently employed in conjunction [4]. Mucormycosis is strongly indicated by sinus opacification, isolated bone erosions, extra sinus spread, the black turbinate sign due to cavernous sinus involvement, and intracranial extension [5]. The most frequent radiographic finding in the sinuses is sinusitis, which cannot be distinguished from bacterial infection. While mucosal thickening and partial or whole sinus opacification are common, bone erosion is an uncommon and late finding. Organisms can infect the emissary veins of the ethmoid sinus to reach the cavernous sinus without destroying the lamina papyracea or the orbit. The absence of sinus involvement by CT scan, on the other hand, has a substantial negative predictive value for rhino-orbito-cerebral disorders. MRI is far more sensitive than a CT scan in detecting orbital and brain involvement; edema in the orbital muscles is the most prevalent finding of orbital disease [3]. Mucor organisms have a proclivity for angioinvasive hyphae, which leads to infarction of affected tissue (particularly nasal turbinates), giving the appearance of "dry gangrene" due to significant angioinvasion with resulting vascular thrombosis. As a result, this tissue is more prone to necrosis, devitalization, and, eventually, the formation of black eschars on endoscopic findings. This black eschar shows on Contrast-enhanced MRI as a continuous focus of non-enhancing tissue, known as the "black turbinate sign," which emerges in the early stages of nasal mucormycosis and can help with early identification [6]. Direct microscopy of clinical specimens, preferably stained with fluorescent brighteners, is frequently used in suspected mucormycosis [7]. Hyphal elements can be identified on KOH wet mounts using a fluorescent microscope and chitin-binding stains like calcofluor, Fungifluor, or blancofluor. Mucorales organisms are usually morphologically distinguishable from other filamentous fungi [8]. Non-pigmented hyphae demonstrating tissue invasion must be shown in tissue sections stained with hematoxylin-eosin (HE), periodic acid-Schiff (PAS), or Grocott-Gomori's methenamine-silver (GMS) to confirm infection [7]. The genus and species-level identification of Zygomycetes organisms continues to be dependent on their microscopic and colonial morphology. Clinical specimens are cultured at 37°C and room temperature on suitable media, such as sabouraud dextrose agar [8]. However, it is not unusual that specimens are not sent for culture or that organisms do not grow. In such cases, radiographic findings alone have to be the basis for further management. Although the diagnostic options currently are mostly restricted, more recent molecular methods like PCR have the potential to improve outcomes by yielding faster and more sensitive results in the near future. When feasible, complete surgical treatment for mucormycosis should be initiated as soon as possible, in addition to systemic antifungal therapy. As needed, resection or debridement should be repeated [3]. Across all patterns of organ involvement, first-line therapy with liposomal amphotericin B 5-10 mg/kg per day is strongly recommended. If significant renal toxicity develops, the dosage can be lowered as needed [9].

## Conclusion

Invasive mucormycosis is a rare but deadly fungal infection with substantial morbidity and mortality, particularly in individuals with underlying medical conditions or immuno-suppression. The prognosis is dismal with a case

fatality ratio reaching up to 50% [10]. Clinical and radiological manifestations might differ amongst patients depending on the host's immunological state and method of infection. However, it is critical to maintain a high degree of suspicion for infection since early identification and prompt initiation of surgical and antifungal therapy are critical to improving survival. This case report intends to highlight the importance of unenhanced MRI in early and confident diagnosis of mucormycosis which will improve patient outcomes.

**Conflicts of interest**

The authors declare that they have no conflict of interest.

**Financial disclosure**

None.

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