

# Coronavirus Disease (COVID-19) Associated Rhinocerebral Mucormycosis and Complications: A Case Report

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## Abstract

**Background:** Mucormycosis is a rare fatal infection caused by a ubiquitous fungus from the order of *Mucorales*, which can have varying clinical presentations. Immunocompromised patients are particularly susceptible to mucormycosis and can suffer fatal consequences if not treated adequately. COVID-19 infection with its immunomodulatory properties has been associated with a wide range of secondary bacterial and fungal infections. We present a case of rapidly progressive rhinocerebral mucormycosis post-COVID-19 infection with the subsequent development of several complications associated with the disease.

**Case Report:** A 62-year-old male patient with a history of hypertension and diabetes mellitus type II, presented 14 days post-COVID-19 recovery with right facial swelling, erythema, and right eye proptosis. Throughout his disease, the patient developed blindness and cranial nerve palsies. He was also found to have palatal necrotic lesions, consistent with the diagnosis of mucormycosis. The patient's disease was complicated by Garcin syndrome, meningitis, orbital apex syndrome, cavernous sinus thrombosis, brain infarction, and hemorrhage. Despite all measures and interventions, the patient died.

**Conclusion:** COVID-19 infection and its treatments are associated with an increased risk of secondary fungal infections like mucormycosis. As such, a high index of suspicion is needed amongst healthcare workers for the early diagnosis and treatment of such opportunistic infections since prompt treatment is associated with a marked improvement in outcome. Furthermore, optimal glucose control and judicious use of corticosteroids in COVID-19 patients decreases the risk of developing such life threatening superinfections.

**Keywords:** *Rhinocerebral mucormycosis; COVID-19; Diabetes mellitus; Glucocorticoids; Opportunistic infections.*

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## Introduction

The coronavirus disease 2019 (COVID-19) infection caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) continues to be a global challenge. It has been associated with multiple disease patterns, ranging from mild to life-threatening.

Opportunistic infections have also been described in COVID-19 patients and may be associated with pre-existing comorbidities, such as diabetes mellitus and lung diseases [1]. Particularly, critically ill patients admitted to the intensive care unit (ICU), patients requiring mechanical ventilation, and patients started on systemic glucocorticoid therapy were more likely to develop fungal co-infections [2]. The association of COVID-19 with significant lymphopenia compromising the immune system makes such patients more susceptible to fungal infections. While COVID-19 associated pulmonary aspergillosis is increasingly recognized, mucormycosis is still rare. Recently, multiple cases of mucormycosis have been increasingly reported worldwide, particularly in India, in people with COVID-19. Mucormycosis, formerly known as Zygomycosis, is a rare and potentially fatal disease caused by a ubiquitous fungus belonging to the class of Zygomycetes and order Mucorales, with *Rhizopus* species being the most common causative organisms. Mucorales are common in decaying vegetation, soil, and bread mold. They rapidly grow and release an enormous number of airborne spores. Thus, they frequently colonize the oral mucosa, the nose, the paranasal sinuses, and the throat. The clinical presentation depends on the disease site, with the rhinocerebral form as the most common, especially in diabetic patients. After inhalation, fungal sporangiospores colonize the paranasal sinuses, leading to acute sinusitis or periorbital cellulitis [3]. Such presentation often delays the diagnosis of mucormycosis, resulting in poor outcomes.

To date, rhinocerebral mucormycosis in the setting of COVID-19 infection has been rarely described in the literature. Here, we present the first case of COVID-19 associated rhinocerebral mucormycosis complicated by Garcin syndrome, meningitis, orbital apex syndrome, cavernous sinus thrombosis, brain infarction, and hemorrhage.

## Case Presentation

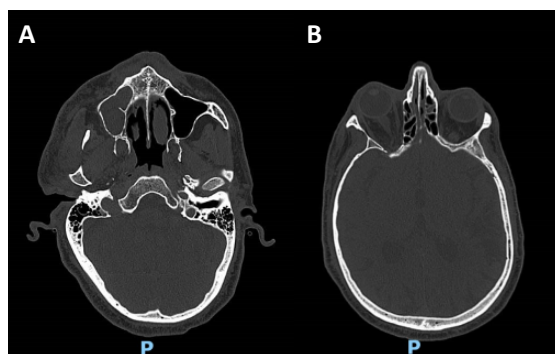
A 62-year-old male patient known to have hypertension, uncontrolled type II diabetes mellitus, and dyslipidemia was transferred to our ICU for right facial nerve palsy (Figure 1A), unremitting fever, and decreased level of consciousness.

21 days before presentation, the patient was diagnosed with COVID-19 infection, which followed a mild course in severity. The patient had a negative surgical history and no known drug or food allergies. He had quit smoking for 18 years. His history was also negative for any alcohol or illicit drug use and a review of systems was unremarkable. He was treated at home with Azithromycin 500 mg twice daily for 3 days, in addition to prednisone 20 mg once daily and Levofloxacin 500 mg twice daily for 7 days.



**Figure 1:** Figure showing (A) right-sided facial palsy and (B) Right-sided eye proptosis

On the 14th day, the patient developed right facial swelling, erythema, right eye proptosis (Figures 1A and 1B), and headache. He presented to a peripheral hospital where a maxillofacial Computed Tomography (CT) scan showed sinusitis of the right maxillary and ethmoidal sinuses (Figure 2A), along with right eye exophthalmos (Figure 2B). As a result, he was admitted for inpatient care and was started on Meropenem, Clindamycin, Acyclovir, high dose steroids (methylprednisolone 80 mg IV every 8 hours), and therapeutic anticoagulation for a possible cavernous sinus thrombosis. His clinical status deteriorated with increasing oxygen demands, and he developed generalized fatigue, blurry vision, and febrile episodes reaching 39.2 C. A lumbar puncture was consequently done on day 2 of admission and was suggestive of meningitis (white cell count of 10 cells/ $\mu$ L, red cell count of 50 cells/ $\mu$ L, proteins of 51 mg/dL, and LDH of 49 U/L). However, the Cerebrospinal Fluid culture and White Blood Count differentials were not performed because the hospital at the time was flooded with COVID-19 patients and the medical team was overwhelmed.



**Figure 2:** Maxillofacial CT scan showing (A) sinusitis of the right maxillary and ethmoidal sinuses and (B) right eye exophthalmous

One week later, after no improvement, the family decided to transfer him to our institution.

Upon arrival to our ICU, the patient's general condition was poor. He continued to have a low-grade fever of 37.9, was slightly hypertensive with a systolic blood pressure of 160mmHg, and had a blood oxygen saturation SpO<sub>2</sub> at 97% on 5L of

supplemental oxygen.

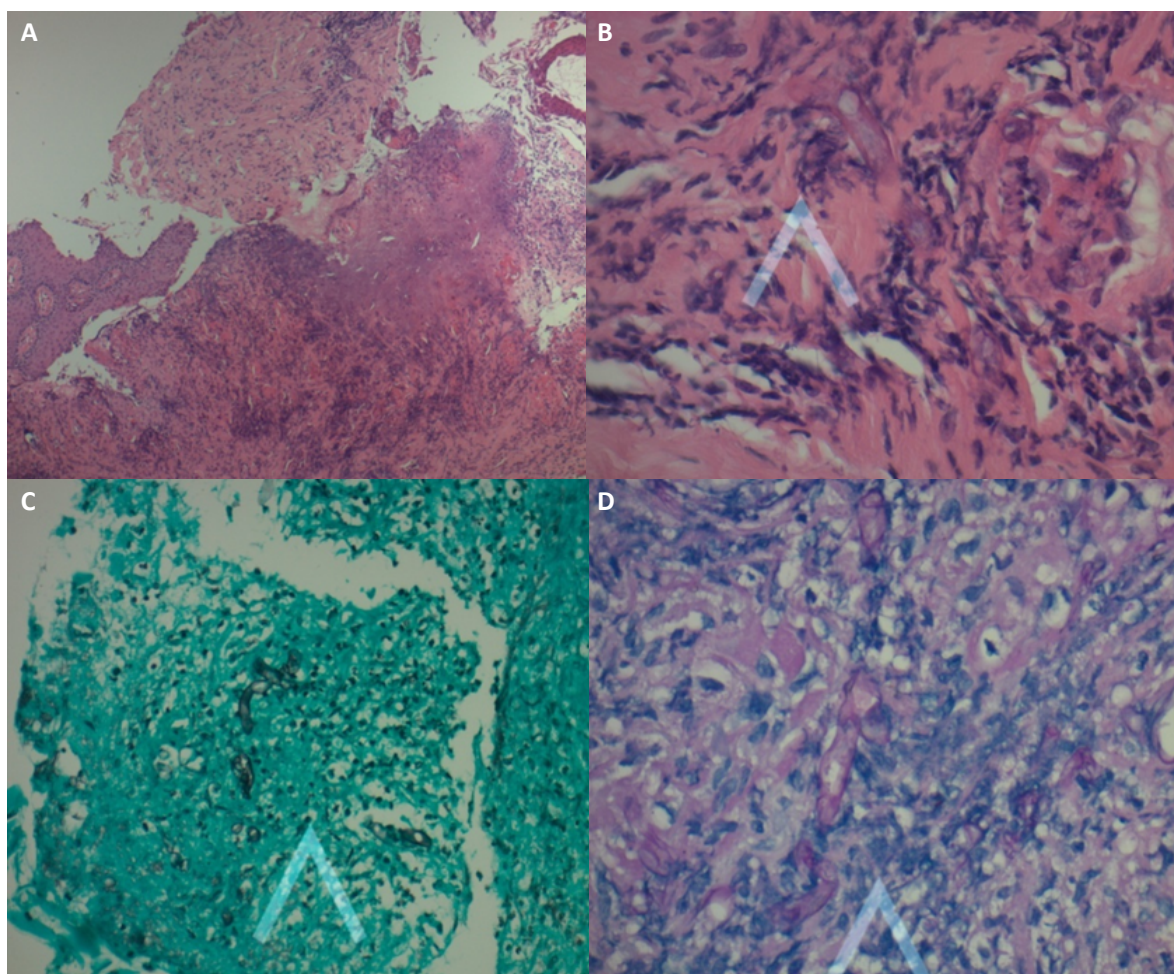
Physical examination was remarkable for decreased level of consciousness despite cooperativity and a Glasgow Coma Score of 12. The neurological examination demonstrated right-sided multiple cranial nerve involvement. He had upper and lower facial paralysis with abnormal sensation, and absent corneal, pupillary, and gag reflexes indicative of cranial nerve III, IV, V, VI, VII, IX, and XII palsies. This picture was suggestive of Garcin Syndrome, which is a rare disorder of unilateral progressive multiple cranial nerve palsies. Upon further examination, we noted a small portion of black necrotic mucosa (Figure 3) on the right side of the patient's hard palate, so we took a biopsy to confirm our high suspicion of mucormycosis.



**Figure 3:** Figure showing a black necrotic mucosa on the hard palate.

Microscopic examination of the palate biopsy with hematoxylin and eosin staining revealed squamous epithelium with a background of necrosis and focal ulceration (Figure 4A). Higher magnification showed scattered non-septated broad fungal hyphae (Figure 4B). Special stains including periodic acid-Schiff and Grocott stains highlighted the broad-based, non-septated fungal hyphae branching at 90-degree angles (Figures 4C-D).

To further exclude any other underlying infection, blood, urine, stool, and sputum cultures were taken. All came back with negative results. Furthermore, a brain Magnetic Resonance Imaging (MRI) with Gadolinium showed multiple right-sided cerebral and cerebellar acute ischemic infarcts (Figure 5A). The maxillofacial CT



**Figure 4:** (A) H and E-stained section (4x) from palate region showing squamous epithelium with necrosis and focal ulceration and a (B) (40x) magnification revealing non septated broad fungal hyphae (arrow) within a background of epithelial cells and inflammatory cells, (C) Grocott stained section (40x) showing non septated fungal hyphae branching at 90-degree angle in black (arrow), (D) periodic acid–Schiff-stained section (40x) highlighting broad non septated fungal hyphae in pink.

scan was also repeated and was consistent with the result of the previous hospital.

The collective findings along with the clinical history were consistent with the diagnosis of rhinocerebral mucormycosis.

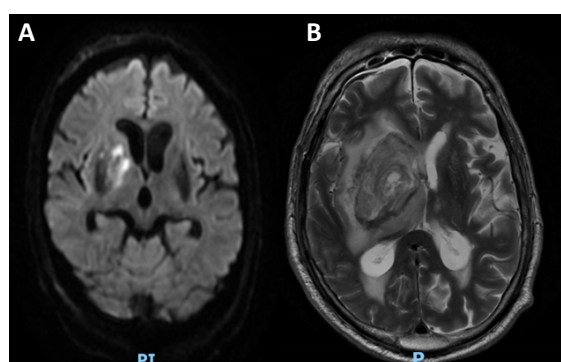
Consequently, dexamethasone was tapered, acyclovir and clindamycin were discontinued, and amphotericin B was initiated. Meropenem and vancomycin were continued due to suspected hospital-acquired pneumonia identified on a Chest X-ray. The ear, nose, and throat (ENT) surgeons were consulted for further management and suggested a surgical debridement of the necrotic lesion. However, due to the patient's poor clinical status and extent of the disease, he was not cleared for surgery.

He developed various complications during his hospital stay. Despite the initiation of subcutaneous insulin since his admission, the patient maintained irregularly elevated fasting blood glucose levels ranging from 250 mg/dL to 480 mg/dL. As a result, an intravenous syringe pump (IVSP) of insulin was initiated, and fasting glucose levels dropped to a minimum of 180 mg/dL and a maximum of 230 mg/dL. He also developed bilateral blindness. Ophthalmological examination revealed bilateral complete ophthalmoplegia, ischemia of the right orbit, and bilateral central artery occlusion, suggestive of right orbital apex syndrome.

His level of consciousness was decreasing every day, along with recurrent febrile episodes. He eventually became

comatose and was intubated.

A repeat brain MRI 16 days after admission to the ICU showed worsening enlarged acute and subacute ischemic infarcts within the right basal ganglia extending to centrum semiovale, showing hemorrhagic transformation (Figure 5B). An acute ischemic infarct was also seen on the right cerebellum extending to the pons and showing punctate foci of hemorrhagic transformation. The right temporal lobe also showed an acute intraparenchymal bleed and a right cavernous sinus thrombosis.



**Figure 5:** (A) Brain MRI showing multiple right sided cerebral acute ischemic infarcts (B) Brain MRI showing worsening enlarged acute and subacute ischemic infarcts within the right basal ganglia and extending to centrum semiovale showing hemorrhagic transformation.

Despite all measures, the patient died at day 27 after ICU admission due to refractory shock and multiple organ failure.

## Discussion

As an opportunistic fungal infection, mucormycosis is more likely to develop in patients with diabetes mellitus, especially in the diabetic ketoacidosis state, hematologic malignancies, severe burns, trauma, long term glucocorticoid use, solid organ transplantation, hematopoietic cell transplantation, hemochromatosis, HIV, malnutrition, and deferoxamine treatment [4]. However, the absence of an established risk factor does not exclude diagnosis when there is high suspicion.

Mucormycosis is primarily acquired through the inhalation of fungal sporangiospores into the nasal cavity and subsequently to the paranasal sinuses. It

takes advantage of the humid environment there to flourish and invade further [10]. It then reaches the brain through the ethmoid sinuses, the orbital apex, bone erosion, or angioinvasion. Angioinvasion occurs through the sphenopalatine and internal maxillary arteries mainly. When left untreated, it can invade the internal carotid artery and cavernous sinus by destroying the endothelium, which increases the risk of forming clots resulting in ischemia and necrosis and creating a medium that allows the organisms to thrive [1, 10, 11].

Rhinocerebral mucormycosis is associated with various complications, of which our patient developed several, including brain infarction and subsequent hemorrhage; these occur due to intravascular thrombosis and concurrent vasculitis caused by mucormycosis, which weakens the vasculature of the brain, creating aneurysms that may further rupture. Rupture leads to the formation of hematomas in the subdural, subarachnoid, and intracerebral territories [4, 18]. The disease course of our patient was also complicated by meningitis, which is thought to occur because of mucormycosis-induced vasculitis involving the meninges [19].

Another rare, yet unique complication of rhinocerebral mucormycosis is Garcin Syndrome, which is characterized by unilateral progressive multiple cranial nerves involvement with a minimum of seven nerves [4]. Garcin Syndrome is suggested to occur via the growth of mucormycosis along unilateral cranial nerves or leptomenigeal vessels [19]. In the setting of mucormycosis, as opposed to other etiologies such as bone invading malignant tumors, Garcin syndrome occurs without osteolysis in the skull base [19], and this was also seen in our patient. Furthermore, our patient also had orbital apex syndrome, yet another complication, which usually manifests as ophthalmoplegia resulting from extra-ocular motor nerve damage along with optic nerve involvement.

Diabetes Mellitus is one of the most

common predisposing factors to mucormycosis [13]. Ketone reductase enzyme in *Rhizopus* organisms allows them to survive in high glucose, low oxygen tension acidic environments [5, 12]. Moreover, uncontrolled diabetes is associated with marked depression of local inflammatory response chemotaxis of neutrophils and phagocytosis [6,7]. This makes the serum in patients with diabetes and ketoacidosis, in particular, an ideal environment for *Rhizopus* to grow and invade. Our patient had longstanding non-insulin-dependent Diabetes Mellitus type II that was poorly controlled outside the hospital due to noncompliance with oral hypoglycemic medications. Despite several attempts for glucose control at the hospital, optimal levels couldn't be achieved due to the ongoing infectious process and steroid use, putting him at an increased risk of being infected with mucormycosis.

Mucorales activate specific CD4 and CD8 T lymphocytes, which, in turn, produce cytokines such as IL-4, IL-10, IL-17, and IFN- $\gamma$  (IL: interleukin, IFN: interferon). These cytokines play a crucial role in destroying Mucorales hyphae [8]. As such, COVID-19 patients with prominent lymphopenia may fail to produce these specific T cells, which explains how COVID-19 infection can be a risk factor for mucormycosis infection in the immunocompromised setting. Nevertheless, further studies are needed to confirm that COVID-19 infection on its own is a risk factor for mucormycosis infection.

Corticosteroid use has also been associated with rhinocerebral mucormycosis infection [14, 15]. Its use depresses the immune system by causing marked lymphopenia due to the redistribution of lymphocytes, selective depletion of circulating T-lymphocytes, and suppression of lymphocytes proliferation to antigens [8, 9]. Our patient received a substantial course of steroid therapy initially for his COVID-19 infection and later for a possible cavernous sinus thrombosis. Since his admission, he had a

significantly low lymphocytic count of 160/ $\mu$ L (normal range 900 to 5200 cells/ $\mu$ L), which could be attributed to his previous COVID-19 infection, the use of high dose corticosteroids, his poorly controlled diabetes mellitus, or a combination of these. In non-hospitalized patients, there is no indication to treat these patients with corticosteroids since there is no proven benefit in patients not requiring supplemental oxygen [16]. Furthermore, the use of glucocorticoids in patients with cavernous sinus thrombosis was thought to potentially reduce cranial nerve edema and orbital inflammation. However, the evidence available suggests that they are not useful [17].

The patient described is a fatal case of rhinocerebral mucormycosis that was initially misdiagnosed in the context of COVID-19 and eventually resulted in many complications and death. Several factors contributed to this pathology. Firstly, COVID-19 infection is known to cause immune dysregulation and predispose to invasive fungal infections. In addition, the patient was given an unindicated course of steroids, which is known to directly increase the risk for rhinocerebral mucormycosis via its immunomodulatory effect [15] and indirectly via worsening his already uncontrolled diabetes mellitus [6,7].

## Conclusion

COVID-19 infection is associated with marked immune dysregulation, which predisposes to secondary fungal and bacterial infections. The overwhelming nature of the disease must not preclude the physician from considering other life-threatening illnesses such as invasive mucormycosis. A high index of suspicion is needed to detect the disease early on. Subsequently, treatment should be initiated immediately with antifungals and possible surgical intervention. Diabetes, the strongest independent risk factor for the development of mucormycosis infection, has to be adequately controlled. Finally, the overuse of medications implicated in the treatment of COVID-19,

such as antibiotics and steroids, should be avoided since they are associated with adverse immunomodulatory properties.

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