



Unprecedented Rise of Mucormycosis in COVID-19 Patients: Urgent Need for Protocol Adaptation and Awareness in India – A Review

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Abstract

Mucormycosis, a rare fungal infection, has seen a concerning surge in incidence among COVID-19 patients in India. Unlike infectious diseases, Mucormycosis spreads through fungal spores ubiquitous in the environment. COVID-19 patients with diabetes are particularly susceptible, presenting symptoms such as headache, fever, eye pain, nasal congestion, and vision loss. Early diagnosis is crucial for successful treatment. Management involves a multidisciplinary approach, including antifungal medications like liposomal amphotericin-B and posaconazole. However, treatment challenges arise due to limited availability, high cost, and prolonged administration of these drugs. Monitoring blood glucose levels during steroid therapy and raising awareness among healthcare workers and patients are essential preventive measures. Improved ventilation and hygiene practices in hospitals can reduce the risk of exposure to fungal spores. Early detection and prompt treatment are vital in preventing severe outcomes of Mucormycosis. Public education and environmental control measures are essential to mitigate the increasing incidence of this life-

threatening fungal infection.

Keywords: Mucormycosis, COVID-19, Diabetes, Steroids, Treatment

Introduction

In recent times, healthcare researchers in India have been alarmed by the alarming surge in mucormycosis (MUM), a rare fungal infection, among COVID-19 patients undergoing diagnosis and treatment. This trend has been a cause for concern, especially considering the widespread use of dexamethasone (DEX) and other medications. As oncologists accustomed to incorporating steroids into many treatment protocols and having dealt with numerous MUM cases, we understand the need for individualized treatment approaches due to the varied clinical presentations and patient responses to therapy. However, the current situation presents challenges, with healthcare providers struggling to devise personalized treatment plans amidst the overwhelming caseload. Recognizing the gravity of the situation, several states, including Tamil Nadu (TN), have classified MUM as a reportable disease under the Epidemic Disease Act. Urgent updates and adjustments to WHO guidelines and protocols are imperative to curb this escalating pandemic. The lack of surprise regarding the surge in MUM cases is highlighted in a recent study published in *Current Fungal Infection Reports*, which revealed a MUM burden of 14 cases per 100,000 individuals in India, significantly higher than in other countries. Another multicenter study conducted across various tertiary care institutions in India, published in *Microbiology and Infection Clinics*, reported an average of 40 confirmed MUM cases per center over a 21-month period.

Significance | Mucormycosis in COVID-19 patients in India necessitates urgent updates in treatment protocols and public awareness

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Mucormycosis with diabetes

Mucormycosis (MUM) cannot be transmitted from one person to another like COVID-19; this distinction is crucial. Uncontrolled diabetes (DT) is the primary cause, characterized by elevated blood sugar levels, as highlighted by Garg et al (2021), Saldanha et al (2021), Szarpak (2021), and Steinbrink and Miceli (2021). Other risk factors include the use of steroids for treating certain cancers (CA), chemotherapy or immunotherapy, and organ or stem-cell transplantation. Rhinocerebral (ROCL) and pulmonary involvement are common infection sites, as Lee et al (1999) noted. The escalation of blood sugar levels is particularly concerning due to several factors. A study published in *The Lancet* revealed that the number of people living with diabetes in India had surged to 65 million by 2016, with TN, Kerala, and Delhi exhibiting the highest prevalence rates. Additionally, the prevalence of diabetes among individuals over 20 years old increased from 5.5% in 1990 to 7.7% in 2016. Furthermore, there is a genetic predisposition to diabetes in the Indian population, and many cases may go undetected until steroid use exacerbates them, as noted by Werthman-Ehrenreich (2021), John et al (2021), and Kontoyiannis and Lewis (2011). Unfortunately, COVID-19 treatment exacerbates the condition. Laboratory research published in *Nature Metabolism* suggests that SARS-CoV-2 may promote increased blood glucose levels in COVID-19 patients. Steroids are a crucial component of COVID-19 treatment as they mitigate the cytokine storm phase, which can be detrimental in some patients. However, improper use of steroids, given too frequently or early without proper medical supervision, can be hazardous. In addition to suppressing immunity, steroids can elevate blood glucose levels, posing risks if left uncontrolled. Commonly used steroids for COVID-19 treatment include Dexamethasone (DEX), Methylprednisolone (MEDROL), or Prednisone (PREDN), as cited by Prescott and Rice (2020), Sterne et al (2020), Saad et al (2020), Ko et al (2021), Langarizadeh et al (2021), Mishra and Mulani (2021), Ranjbar et al (2021), Cano et al (2020), Draghici et al (2021), Tlayjeh et al (2020), and Lamontagne et al (2020).

Treatment approach

The association of Mucormycosis (MUM) with morbidity and mortality is significant. Effective therapy necessitates a multidisciplinary team approach, involving microbiology, pathology, radiography, infectious diseases, surgery, pediatrics, hematology, intensive care, dermatology, and pharmaceuticals. However, implementing such an approach, especially in areas with limited medical resources, is challenging, as noted by Lamontagne et al (2020), Garg et al (2021), Zurl et al (2021), Veisi et al (2021), and Singh et al (2021). MUM surgery can be debilitating, often requiring major resections. Limited availability of antifungal drugs adds to the challenge. Liposomal amphotericin-B (AMB), the gold

standard treatment, may not be accessible to many due to its cost. Although AMB deoxycholate is cheaper, its adverse toxicity profile, including kidney and electrolyte abnormalities, poses risks, as highlighted by Muthu et al (2021), Moorthy et al (2021), Mazzai et al (2021), Marques et al (2021), and Verma and Bali (2021). Posaconazole (POSANOL) and isavuconazole (ISA) are alternative treatment options, but their expense and prolonged administration periods make treatment protocols challenging to maintain on a large scale, as discussed by Stryker et al (2021), Park et al (2021), John et al (2021), Miller et al, and Panchanatheeswaran et al (2021). Recovery from COVID-19 may also present challenges, with the need for weakening operations and prolonged antifungal medication use, particularly in cases of rhinocerebral MUM where surgery is often necessary in addition to antifungal drugs. The inability to perform these surgeries effectively leads to dysfunction. It is crucial to prevent MUM infection due to the healthcare system constraints it poses, as emphasized by Singh et al (2021), Evert et al (2021), Sittig et al (2021), and Ibrahim et al (2007).

How can we reduce the number of Mucormycosis (MUM) cases and its severity?

For COVID-19 patients, the use of steroids should be closely monitored by healthcare professionals, as highlighted by Gaur et al (2021), Onder et al (2020), and Gandhi et al (2020). Monitoring blood glucose levels during steroid use to prevent MUM is crucial. Regular monitoring of blood glucose levels, especially for patients self-medicating at home, is essential. Patients should consult a doctor promptly if high blood glucose levels are detected. Implementing blood glucose surveillance for patients on steroids at home and organizing awareness campaigns about blood glucose control can help prevent MUM. Patients receiving steroids for COVID-19 treatment should promptly report MUM symptoms, such as facial swelling, eye protrusions, visual disturbances, headaches, vomiting, inflammation, ulcers, or prolonged fever. Healthcare providers and policymakers involved in COVID-19 treatment should consider training healthcare personnel to raise awareness about MUM, including community health workers and care professionals, as suggested by Ramanathan et al (2020) and Kostova et al (2021). The prolonged hospitalization of COVID-19 patients may also increase the use of multiple antibiotics to treat hospital-acquired infections. The challenge of managing patients with long-term side effects of steroids and the rising concern about the surge in multi-resistant infections also need to be addressed.

Conclusion and recommendations

Mucormycosis (MUM), commonly known as black fungal disease, poses a significant threat to individuals recovering from COVID-19. This fungal infection, primarily affecting the sinus, intraorbital, and intracranial regions, can lead to severe morbidity and mortality

if left unchecked. While MUM is typically harmless to healthy individuals, it becomes opportunistic in those with compromised immune systems, such as COVID-19 patients receiving steroid treatment. Fungi like *Mucor* and *Rhizopus*, found in soil, compost, and decaying plant matter, are the main culprits behind MUM. These fungi produce microscopic spores that, when inhaled, can lead to MUM development, particularly in hospital settings where fungal spores are prevalent. Factors such as organ transplants, congenital bone marrow diseases, and diabetes further increase susceptibility to MUM. Early diagnosis and treatment with antifungal drugs like liposomal amphotericin-B (AMB) and posaconazole (POSANOL) are crucial for effective management. Preventive measures such as raising awareness, monitoring hospital air quality, ensuring sterile oxygen therapy, and promoting rest during recovery can help mitigate the risk of MUM.

Mucormycosis, commonly referred to as black fungal disease, has emerged as a concerning complication among individuals recovering from COVID-19. This fungal infection infiltrates the sinus and can progress to affect the intraorbital and intracranial regions, potentially leading to severe consequences if not detected and treated promptly. Studies indicate that between fifty to eighty per cent of patients with untreated MUM may face fatal outcomes. Fungi, with their diverse roles in ecosystems, have been integral to Earth's processes for millions of years. While many fungi play beneficial roles in nature, some species, such as *Mucor* and *Rhizopus*, can pose risks to human health under certain conditions. The airborne spores of these fungi, which are commonly found in soil, compost, and decaying organic matter, can infiltrate hospital environments and pose a risk to individuals with compromised immune systems.

Individuals with conditions such as congenital bone marrow diseases, severe burns, cancers, and diabetes, particularly if untreated or managed irregularly, are at increased risk of developing MUM. Furthermore, COVID-19 patients receiving steroid treatment are particularly vulnerable to immune system suppression, making them more susceptible to fungal infections.

Mucor spores can germinate and invade human tissues when inhaled, leading to MUM. Symptoms of MUM can include fever, headache, facial pain, cough, and shortness of breath, among others. Diagnosis typically involves tissue biopsy and lung X-rays.

Effective treatment of MUM relies on early detection and intervention. Antifungal drugs such as liposomal amphotericin-B (AMB) and posaconazole (POSANOL) have shown efficacy in treating MUM, but early diagnosis remains challenging.

To mitigate the risk of MUM, several preventive measures can be taken. These include raising awareness about the disease, conducting regular air sampling in hospitals to monitor spore levels, ensuring the use of sterile oxygen therapy, promoting rest and recovery at home, and advising caution for individuals engaged

in activities that may expose them to fungal spores, such as farming or gardening.

In conclusion, Mucormycosis presents a significant challenge in COVID-19 recovery, particularly for individuals with compromised immune systems. Early detection, effective treatment, and preventive measures are essential in addressing this emerging health concern.

Author contribution

N.A., V.S.V., A.K.M., S.T. conceptualized, reviewed the literature, and wrote the article.

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Competing financial interests

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