

Concerning Fungal Coinfections in COVID-19: Risks, Types, and Prevention – A Review



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Abstract

The characteristics of certain fungal infections, including fever, cough, and shortness of breath, may be similar to COVID-19. Laboratory tests are needed to establish whether an individual has a COVID-19 fungal infection. Any patient can experience COVID-19 and simultaneously a fungal infection. People with serious COVID-19 are especially vulnerable to bacterial or fungal infections, such as those in intensive care units (ICUs). Aspergillosis (ASP), invasive candidiasis, is among the most frequent fungal infections in COVID-19 patients. The increased prevalence of these fungal coinfections may be linked with serious disorders and deaths. Knowledge of the potential for fungal coinfection is important to minimize delays in diagnosis and care to help avoid serious diseases and mortality due to these infections.

Keywords: COVID-19, Black fungus, White fungus, Symptoms, Preventive measures.

Introduction and cases

Mucormycosis, commonly found in soil and air, targets the respiratory tract, brain, and sinuses, leading to symptoms such as nasal congestion, eye swelling, and vision loss, among others. While this disorder is not new, healthcare providers are witnessing an unprecedented increase in cases compared to normal levels, as the World Health Organization (WHO) reported in 2021. In India, healthcare professionals are grappling with a concerning surge in cases of mucormycosis (MUM), a fungal infection primarily affecting deceased COVID-19 patients and those who recently recovered. Many of these individuals, already burdened with diabetes, received steroid treatment for COVID-19, a combination that potentially heightened their susceptibility to fungal invasion. India is currently battling the second wave of COVID-19, and amidst this crisis, there is a growing risk of mucormycosis, further compounding the challenges posed by COVID-19, according to Dr. Atul Patel, an infectious disease specialist at Sterling Hospital in Ahmedabad. "COVID-19 patients are at high risk of fungal infection, with a mortality rate of 50%, and an increasing number of COVID-19 patients have developed this infection during or after hospitalization." It is essential to be aware of the symptoms associated with this virus, including sinusitis, black nasal discharge, facial pain, headaches, and eye pain (Chohan, 2020; Toh et al., 2021; Torner, 2020; Chi et al., 2020; Das, R. C. Management of COVID-19 and Chohan, 2020).

For instance, Sion Hospital in Mumbai recorded 24 cases of MUM in the past two months, a stark contrast to the usual six cases in a year. One such case involved a 25-year-old woman who had recovered from COVID-19 three weeks earlier. Dr. Akshay Nair, a Mumbai-based eye surgeon, performed a three-hour surgery to

Significance | The article highlights the alarming rise of fungal infections like Mucormycosis among COVID-19 patients, necessitating prompt diagnosis and care to prevent fatalities.

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remove the infected tissue from her eye, highlighting the severity of the disease. Even amidst a fatal second wave of COVID-19 devastating India, healthcare professionals are now grappling with a surge in unusual infections, also known as "black fungus," among COVID-19 survivors (WHO, 2021).

Mucormycosis is an extremely rare infection resulting from exposure to *mucor*, commonly found in soil, trees, manure, and decaying organic matter. Dr. Nair explains that *mucor* is ubiquitous in soil, air, and even the nasal passages of healthy individuals. While it poses little threat to most people, it can prove life-threatening for individuals with compromised immunity, such as those with diabetes, cancer, or HIV/AIDS. The use of steroids, a life-saving treatment for severe COVID-19 cases, has been associated with mucormycosis, which has an average mortality rate of 50%. Steroids help reduce lung inflammation and mitigate the body's immune response to the virus but can also weaken immunity and elevate blood sugar levels, particularly in patients with diabetes, making them more susceptible to mucormycosis (WHO, 2021).

During the second wave of COVID-19 in April, Mumbai hospitals witnessed a surge in mucormycosis cases, with approximately 40 patients requiring treatment for fungal infections. Of these, eleven patients required surgical removal of their eyes. Similar trends were observed in other cities like Bangalore, Hyderabad, Delhi, and Pune, where hospitals reported 58 cases between December and February. Most patients developed mucormycosis within 12 to 15 days after recovering from COVID-19. Dr. Renuka Bradoo, head of the ear, nose, and throat department at Sion Hospital, highlighted the alarming increase in cases, with 24 cases reported in the past two months compared to the usual six cases per year (WHO, 2021).

Dr. Raghuraj Hegde, an eye surgeon in Bangalore, shared a similar experience, reporting 19 cases of mucormycosis in the past two weeks, predominantly among young patients. Healthcare providers expressed astonishment at the magnitude and prevalence of fungal infections during the second wave compared to the first wave last year. With over a decade of experience, Dr. Nair noted a significant increase in cases this year compared to previous years. In his extensive experience, Dr. Hegde had never witnessed more than one or two cases a year. Symptoms of mucormycosis include nasal congestion, bloody nasal discharge, facial pain, headaches, eye pain, drooping eyelids, blurred vision, and darkening of the skin around the nose. Patients often present late, already experiencing vision loss, necessitating surgical removal of the eyes to prevent further infection (WHO, 2021).

Types of Mucormycosis

Mucormycosis (MUM) is a rare but serious fungal infection caused by fungi from the *Mucorales* order. It primarily affects individuals with weakened immune systems, such as those with uncontrolled diabetes, organ transplant recipients, or individuals undergoing

immunosuppressive therapy. The infection can manifest in various forms depending on the entry route and dissemination within the body. Rhinocerebral MUM involves the sinuses and brain, with inflammation in the sinuses often leading to spread to the brain, particularly seen in untreated diabetic patients and transplant recipients (Sim et al, 2021). Pulmonary MUM, affecting the lungs, is more common in patients with cancer or those who have undergone organ or stem cell transplantation (Thompson and Kalkowska, 2021). Gastrointestinal MUM is more prevalent in young children, especially premature infants under one month old, who have received antibiotics, surgeries, or drugs that weaken their immune systems (Jamka et al, 2019). Cutaneous MUM occurs when fungal spores enter the body through skin wounds, such as after surgery or burns, and is more common in individuals with intact immune systems (Das, R. C. Management of COVID-19). Disseminated MUM occurs when the fungus spreads through the bloodstream to other body parts, including the brain, spleen, heart, and scalp (Adegbola, 2012). Understanding the different forms of MUM is crucial for accurate diagnosis and appropriate management of the infection.

Elevated MUM Risk in COVID-19

Patients with COVID-19, whether symptomatic or asymptomatic, are at risk of developing Mucormycosis (MUM). The risk is significantly higher for patients hospitalized for COVID-19, especially those requiring oxygen therapy. However, MUM cases have also been reported in patients without a diagnosed COVID-19 infection. Therefore, everyone needs to be vigilant for MUM symptoms, as highlighted by studies conducted by Garg et al (2021), Moorthy et al (2021), and Basso et al (2021).

COVID-19 and DT raise MUM risk

Even before the pandemic, individuals with untreated diabetes (DT) were already at a heightened risk due to their elevated blood sugar levels, which promote the growth and survival of fungi. During the pandemic, the risk of Mucormycosis (MUM) has increased for these patients for two main reasons if they contract the virus. Firstly, they are often prescribed corticosteroids as a treatment for COVID-19, which further elevates blood sugar levels and increases the likelihood of MUM. Dealing with this combination of untreated diabetes and COVID-19 poses a significant and potentially lethal challenge, as highlighted by studies conducted by Hassard et al (2021), Kumar et al (2021), Prestel et al (2021), and John et al (2021).

Sinus infection with MUM

MUM symptoms can seem initially non-threatening. However, patients and their families must understand these issues early and

be treated to contain the situation. If patients encounter one, they must talk to their doctor and follow up with Soin et al. (2021).

Available therapeutics

We have a host of medications and anti-allergy medicines for MUM today. These are either provided by IV or by mouth. Surgery with antimicrobial therapy is required to remove the dead tissue affected. However, the key consideration is the need for quick and timely care in order to minimise the potential for severe repercussions. "Studying the relationship between MUM and COVID-19 is currently ongoing. However, we must watch for any symptoms and get the appropriate medical attention as soon as possible. The effect of this fungal infection may be made worse by delays in diagnosis and care by Marimuthu et al (2021), Erku et al (2021) and Kanwar et al (2021).

How suspicious was (in COVID-19 patients, diabetics or immunosuppressed individuals)

Risk factors include eye and nose pressure and redness, headache, fever, coughing, shortness of breath, bloody vomiting, and mental condition changed, as noted. If there is sinusitis, facial or stubborn one-side pain, blackish discoloration on the nose or gully, toothache, blurred or double-vision, pain, skin lesion, trombosis, thoracic chest pain, deteriorating air signs in COVID-19, patients with DT and immunocompressed persons, MUM should be suspected by Mohindra et al (2021).

Fungal infection prevention

Post-COVID release should be controlled to deter this disease; steroids should be used carefully for the right time, dosage and length; pure sterile water should be used for oxygen therapy in humidifiers and antibiotics and antifungal medications should be used properly. The condition may be regulated through insulin regulation, immunomodulation cessation, steroid reduction, and thorough surgical deposition - all necrotic substances can be removed, as shown in the advisory by Sen et al (2021), Noushad and Al-Saqqaf (2021), Wang et al (2021) and Pilato et al (2021).

The guidelines recommend several strategies for preventing infection, including wearing masks in dusty environments, protective clothing when gardening, and maintaining personal hygiene. Medical care for those infected includes clinical surveillance, establishing a peripheral central catheter, ensuring hydration, and administering intravenous medication such as Amphotericin B infusion for at least six weeks. To manage infection, controlling hyperglycemia, monitoring blood glucose levels post-COVID-19, and carefully administering steroids are essential. Additionally, sterile filtered water should be used in oxygen treatment, and antibiotics should be used cautiously. Treatment involves managing diabetic ketoacidosis, discontinuing

immunomodulating treatment, and performing extensive surgical debridement to remove necrotic tissue. Medical therapy, including antifungal treatment, should be administered for at least 4-6 weeks, and disease progression should be monitored using radiographical imaging.

Pulmonary ASP associated with COVID-19

Scientists in individuals with serious COVID-19 are also taught ASP (fungal *Aspergillus* infections). Scientists have thought that ASP has almost completely arisen in individuals with extreme immune system weakness. However, in patients without compromised immune systems but with extreme respiratory infections caused by viruses, including influenza, ASP has been identified more and more. Latest studies characterise pulmonary ASP associated with COVID-19 (CAPA) by Gholipour et al (2021).

The evidence available shows the CAPA

Often happens in patients with extreme COVID-19 (for example, in ICU ventilators patients) it can be hard to diagnose because it is often not specific and diagnosis implies that a deep lung specimen may cause serious disease and death. It can be very difficult to diagnose. In patients with severe COVID-19 with deteriorating respiratory function or sepsis, clinicians should consider the potential for ASP, though they don't have classic ASP risk factors. CAPA testing generally entails taking specimens from the lower respiratory tract of patients examined for *A. galactomannan* and for fungal culture by Khurana et al (2021).

Candida auris increased in the COVID-19 pandemic

C. auris is an evolving fungus that can cause serious healthcare outbreaks. Long-term care centres for individuals with serious health problems are most widely spread in the US. However, *C. auris* outbreaks have been recorded at COVID-19 units in acute care centres since the beginning of the COVID-19 pandemic. These outbreaks can include improvements in standard infection management procedures under COVID-19, including the limited supply of or re-use of equipment, and cleaning and disinfection activities. These outbreaks are also possible. Recently, new *C. auris* cases were found in many countries, without linkages to reported cases or health services abroad, which show a rise in undetected transmission. When services from health centers and health departments are redirected to react to COVID-19, screening for *C. auris* Colonization has become an essential component of control attempt by Chen et al (2021), Salmanton-García et al (2021), and Mussini et al (2021).

Invasive applicants for COVID-19 patients

The healthcare-associated infections (HAI) of patients admitted in COVID-19, including candidemia and *Candida* bloodstream

infections, are at risk. Patients with serious COVID-19 have also been reported to have fungal antifungal-resistant infections. In patients with serious COVID-19 fungal coinfections early diagnosis of and control of Candida and antifungal resistance infection was critical to minimising mortality from COVID-19 in patients by Salmanton-García et al (2021).

Fungal pneumonia and COVID-19

Some pathogens (similar to COVID-19 and bacterial pneumonia) can be caused by fever, cough, and breath shortening, including valley fever (coccidioidomycosis), histoplasmosis, and blastomycosis. These mushrooms live on the ground. People get sick with fungal breathing in the air. Fungal pneumonia should be seen as a potential cause of respiratory disease, particularly if testing of COVID-19 was negative. It should be noted that fungal conditions can occur in conjunction with COVID-19 by Mussini et al (2021), Brissot et al (2021) and Allaw et al (2021).

Conclusion

Mucormycosis (MUM) is a rare condition that typically does not affect healthy individuals. However, if you suspect a MUM infection, it is crucial to contact your doctor promptly. Pay close attention to the signs and symptoms of MUM, especially if you or someone you know has recently recovered from COVID-19. Prompt identification, accurate diagnosis, and intensive care are essential for effective treatment of MUM. Individuals recovering from COVID-19 should prioritize personal hygiene to prevent MUM infection.

Author contribution

B.K.A., V.K.K.K., T.K.L., M.S.G.I. conceptualized, reviewed the literature, and wrote the article.

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Competing financial interests

The authors have no conflict of interest.

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