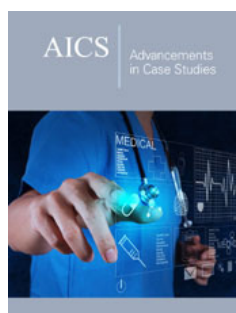


Mucormycosis and Aspergillosis have been Linked to Covid-19-Related Fungal Infections in India

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Abstract

Mucormycosis and aspergillosis have been recorded in alarmingly high numbers in India in recent decades. Even though fungal infections contribute significantly to human morbidity and mortality, the effect of these diseases on COVID-19 patients is unknown. Mucormycosis and aspergillosis were identified as two post-acute symptoms in COVID-19 patients in this study. Coronavirus 2 of the severe acute respiratory syndrome causes direct damage to the airway epithelium, allowing Mucormycosis and aspergillosis to invade. There were 8,848 infected and 219 dead cases of COVID-19-associated mucormycosis in India as of May 22, 2021. In addition, four Aspergillosis patients have been registered in Bihar, India. In India, a COVID-19-related yellow fungus case was also recorded for the first time. Both mild and moderate-to-severe illness tend to be affected by the syndrome. Despite the urgent need for efficient diagnostic tests, as well as safe and effective new drugs and vaccines, research into the pathophysiology of human fungal infections lags behind that of other pathogen-related diseases.

Keywords: Aspergillosis; Black fungus; Candidiasis; COVID-19; Mucormycosis; SARS-CoV-2; White fungus

Introduction

Infections like mucormycosis, candidiasis, and aspergillosis have become more prevalent in intensive care units and patients who have recovered from Covid. The total number of coronavirus disease 2019 (COVID-19) cases in India has now reached 2,62,89,290, with 29,23,400 active cases and 2,95,525 deaths (22 May 2021). Amid the rising number of Covid cases, India is dealing with a Black Fungus outbreak (mucormycosis). Even though mucormycosis (MCR) is becoming more common in COVID-19 patients, the epidemiological causes, presentation, diagnostic certainty, and outcome of these patients are not well understood [1].

Concerns have also been raised regarding COVID-19-associated pulmonary aspergillosis worsening the disease course and confirmed mortality. Just when the government was coping with the mucormycosis outbreak, a new fungal infection, White Fungus infection (Aspergillosis), began to spread. Azole-resistant *Aspergillus* caused the first case of COVID-19-associated pulmonary aspergillosis. Aspergillosis is a fungal infection that affects many parts of the body and spreads to the lungs. It also has serious consequences for the kidneys, mouth, skin, and brain. Infections like mucormycosis, candidiasis, and aspergillosis have become more prevalent in intensive care units and patients who have recovered from Covid. As a result, the current article focused on case reports of mucormycosis and Aspergillosis in India, as well as infections linked to COVID-19.

Mucormycosis may affect the lungs, but the nose and sinuses are the most common sites of infection for mucormycosis. It can then spread to the eyes, causing blindness, or to the

brain, causing headaches or seizures [2]. Mucormycosis can spread to the eyes and cause blindness, or it can spread to the brain and cause headaches or seizures. Mucormycosis infections occur when a person meets fungal spores in the atmosphere, and Covid-19 patients taking immunosuppressive drugs such as steroids are more susceptible to infection. While there is currently no official national count of COVID-19 related mucormycosis infections, all confirmed and suspected cases must now be reported to the national health ministry.

Infection, Symptoms, and Treatment

Mucormycosis, formerly known as zygomycosis, is a fungal disease caused by a variety of fungi in the Mucorales family. *Rhizopus oryzae* is the most common member of this family to cause infections in humans. Since inhaling fungal spores from the air, it most often affects the sinuses or lungs. It may also happen because of a cut, a burn, or some form of skin injury. Facial deformity, fever, facial pain, nasal congestion, loss of vision or pain in the eyes, altered mental state, confusion, swelling in the cheeks and eyes, toothache, loosening of teeth, and black crusts in the nose are all symptoms of Mucormycosis. While rhinocerebral (sinus and brain), pulmonary (lung), Cutaneous (skin) mucormycosis, and gastrointestinal mucormycosis are the most common types of mucormycosis, disseminated mucormycosis typically occurs in people who are already sick from other medical conditions like COVID-19, making it difficult to determine which symptoms are linked to mucormycosis. Patients with a disseminated infection in the brain can experience changes in mental status or fall into a coma [3].

Mucormycosis is a severe infection that requires antifungal medication, such as amphotericin B, posaconazole, or isavuconazole (CDC, www.cdc.gov). Patients can require antifungal medication for up to six weeks to recover. Their prognosis is contingent on how quickly the disease was identified and treated. Surgery is often required to remove dead or contaminated tissue. This can lead to the loss of the upper jaw or even the eye in some patients. Aspergillosis is a fungal infection caused by *Aspergillus*, a common mold (fungus) that can be found both indoors and out. Most people will inhale *Aspergillus* spores without being ill. People with compromised immune systems or lung disorders, on the other hand, are more likely to develop health problems because of *Aspergillus*. *Aspergillus fumigatus*, one of the causative agents of Aspergillosis, is a saprotrophic fungus that lives mainly in soil and is well-adapted to thrive in harsh conditions. This ability has allowed the fungus to withstand and survive human host defense, as well as to cause one of the most lethal lung infections in terms of morbidity and mortality [4].

Aspergillus can cause allergic reactions, lung infections, and infections in other organs, among other things. White fungus can affect not only the lungs but also the "nails, skin, stomach, kidney, brain, private parts, and mouth," according to the CDC. After testing negative for the virus, people with Aspergillosis are said to have symptoms like Covid if the infection enters the lungs. A CT scan or an X-ray may be used to diagnose the infection. While allergic

bronchopulmonary aspergillosis (ABPA), allergic *Aspergillus* sinusitis, aspergilloma, and chronic pulmonary aspergillosis are the most common forms of mucormycosis, invasive aspergillosis is more common in people who are already sick from other medical conditions such as COVID-19 [5]. From the lungs, however, Aspergillosis cannot spread between people or between people and animals. Itraconazole (for Allergic aspergillosis) and Voriconazole (for Invasive aspergillosis) are the most common antifungal medications used to treat aspergillosis (CDC, www.cdc.gov).

Case Studies

Indian Mucormycosis statistics and COVID-19-related reports: Mucormycosis is a life-threatening infection that affects many people. An analysis of published mucormycosis cases discovered a 54 percent all-cause mortality rate, with some cases only being saved by removing an eye [6]. The mortality rate differed depending on the underlying patient condition, fungus type, and affected body location. Sinus infections were associated with a 46% mortality rate, pulmonary infections with a 76% mortality rate, and disseminated mucormycosis with a 96% mortality rate [6]. Table 1 shows the clinical types of mucormycosis recorded in India between 2001 and 2020.

Table 1: Clinical types of mucormycosis that have been recorded in India, as well as the maximum mortality rate (during the period of 2001-2020).

Clinical Forms of Mucormycosis	Percentage Range	Mortality Rate (%)
(ROCM, rhino-orbital-cerebral mucormycosis)	45-75%	78.6%
Cutaneous	10-25%	57.1%
Pulmonary	5-20%	76.5%
Renal	2-7%	60%
Gastrointestinal	2-6%	94.1%
Disseminated	1-5%	78.6%
Others (oral cavity, otitis media, subglottis and bone infections)	0.5-4%	-

Source: Prakash and Chakrabarti [7]

In a previous study from March 2021, a total of 41 cases of Covid-19-associated mucormycosis were recorded worldwide, with 70% of them in India [7]. According to recent studies, the number of cases has risen dramatically, which is unsurprising considering the ongoing Covid-19 outbreak in India. In a rising outbreak of the disease, India has recorded 8,848 cases of deadly "black fungus" (as of May 22, 2021). (The Tribune, 23 May 2021). Gujarat had the most cases (2281) followed by Maharashtra (2,000), Andhra Pradesh (910), Madhya Pradesh (720), Rajasthan (700), Karnataka (500), Haryana (250), Delhi (197), Punjab (95), Chhattisgarh (87), Bihar (56), Tamil Nadu (40), Kerala (36), Jharkhand (27), Odisha (15), Goa (12), and Chandigarh (12) [8]. Four Indian doctors looked at more than 100 cases of Covid-19 patients who had developed mucormycosis in a separate report. It was discovered that 79 of them were men, and 83 of them had diabetes. In a survey of 45 black fungus patients in two Mumbai hospitals, it was discovered that all

of them were diabetics or had been diagnosed with diabetes prior to admission. Their blood sugar levels were both extremely high. Within 10 days of being admitted to a medical facility for Covid-19 care, up to 30% of patients developed mucormycosis, according to the report.

According to the CNN News reported situation, a woman from India's southern Telangana state, her father was diagnosed with black fungus on April 26, the same day he recovered from Covid-19. When he started to feel better, his face began to swell (from Covid). Doctors recommended her to have an Amphotericin B injection when the swelling did not go down. She had to apply to the state's chief minister for vials of the drug because the hospital did not have any. Once the medicine was secured, her father underwent an endoscopic sinus surgery to relieve the swelling.

COVID-19-related Indian Aspergillosis statistics: A recent research from India found a higher prevalence of *Aspergillus* sensitization (39.5%) and allergic bronchopulmonary aspergillosis (ABPA) in 564 asthma patients (27 percent). According to Nath et al. [8], the prevalence of *Aspergillus* hypersensitivity (AH) and ABPA was 35.1 percent and 21.7 percent, respectively, in a study of 350 patients. The disease is becoming more well-known, with prevalence rates for ABPA ranging from 5.9% to 20.5 percent and 38 percent to 43 percent for *Aspergillus* hypersensitivity (AH) in recent studies [9]. In this part of the world, there are few data on prevalence. At the Patna Medical College Hospital (PMCH) in India, four cases of white fungus linked to coronavirus were discovered.

The first yellow fungus case linked to COVID-19: A 45-year-old patient in Ghaziabad, Uttar Pradesh, was found infected with yellow fungus amid an increase in cases of Black Fungus infection in several Indian states, as well as white fungus cases. Yellow fungus, which causes superficial and deep mycoses in pets, captive, and wild animals, especially reptiles, is more dangerous than both Black and White fungi. The yellow fungus is a contagious fungus that affects mostly reptiles. The infected patient is currently being treated in a Ghaziabad, India hospital. Laziness, lack of appetite, or no appetite at all, and weight loss are all symptoms of yellow fungus. Yellow fungus may also cause pus leakage and slow wound healing, starvation and organ failure, and sunken eyes due to necrosis in severe cases.

CANV, yellow fungus (*Chrysosporium anamorph* of *Nannizziopsis vriesii*). Infection with the virus known as CANV had previously been identified in humans, often in immunocompromised patients [10]. However, the recent molecular characterization work has revealed these cases to be caused by species of *Nannizziopsis* that are distinct from those found in reptiles. The possibility of zoonotic transmission of *O. ophioidiicola*, *Nannizziopsis* spp., and *Paranannizziopsis* spp. from reptiles to humans is low, although it is possible in immunocompromised patients [10].

High prevalence of fungal infections among Indian COVID-19 patients

Humans may contract mucormycosis by inhaling spores, swallowing spores in food or medications, or having spores

contaminate wounds. We inhale the spores of several fungi every day. Our immune systems and lungs, on the other hand, are less likely to cause infection if they are in good condition [4]. Mucorales fungi are opportunistic, infecting people with a compromised immune system or damaged tissue [6]. Use of drugs which suppress the immune system such as corticosteroids can lead to impaired immune function, as can a range of other immunocompromising conditions.

Covid-19 drugs can deplete the body's strength and immunity. They may also cause non-diabetic Covid-19 patients' blood sugar levels to rise. Many cases of this unusual fungal infection have been discovered in Covid patients, as well as diabetics, people with kidney or heart issues, and people on high steroids. Patients can develop fungal superinfection because of the virus's extreme immunomodulation and lymphocyte depletion, as well as the subsequent administration of immune-system-targeting drugs. These spores can develop in our airways or sinuses and enter our bodies' tissues when our lungs are weakened and our immune systems are suppressed, as is the case in patients being treated for extreme Covid-19. White fungus, which affects the lungs and causes symptoms like coronavirus, is more common in COVID-19 patients. COVID patients are susceptible to Mucormycosis and Aspergillosis due to a lack of immunity caused by one or more of the following factors.

- A. using anabolic steroids for an extended period
- B. admitted to the intensive care unit
- C. on supplemental oxygen or a ventilator
- D. spent a long time in the hospital
- E. had to deal with unsanitary conditions in the hospital
- F. whether there are comorbidities
- G. take COVID19 and other medications at the same time
- H. suffer from diabetes and obesity
- I. suffer from kidney or heart disease
- J. COVID19 causes Pneumonia in the lungs.
- K. a lack of immunity

Steroids, which are used to save the lives of critically ill patients, are thought to be the cause of mucormycosis and aspergillosis, according to doctors. Steroids tend to help prevent some of the damage that can occur when the body's immune system goes into overdrive to combat the coronavirus by reducing inflammation in the lungs. However, in both diabetic and non-diabetic Covid-19 patients, they lower immunity and raise blood sugar levels. This loss of immunity is thought to be the cause of the mucormycosis outbreaks. According to India's official National Health Portal, diabetes affects 12 percent to 18 percent of the adult population, with the incidence being highest in urban areas. COVID-19 patients are at an increased risk of failing to defend themselves against species like the fungi that cause mucormycosis because of these factors.

Discussion

Mucormycosis was already much more widespread in India than in any other country prior to the pandemic [11]. In India, it affects 14 out of every 100,000 people, compared to 0.06 out of 100,000 in Australia, for example [7]. Increased serum iron levels and long-term deferoxamine consumption have recently been linked to an increased susceptibility to mucor infection [12]. *Rhizopus* species may use deferoxamine as a xenosiderophore to supplement previously inaccessible iron, allowing them to accumulate 8 to 40 times more of it [13]. COVID-19-associated mucormycosis (CAMCR) cases (total 41) were reviewed by John et al. [1] to identify risk factors, clinical characteristics, and outcomes. Patients with diabetes mellitus (DM) (94%) were more likely to have CAMCR, particularly those with poorly regulated DM (67%) and moderate or critical COVID-19 (95 percent). CAMR is the result of the collision of two storms, one DM and the other COVID-19. Doctors conclude that steroids, a life-saving therapy for serious and critically ill Covid-19 patients, could be triggering mucormycosis, which has a 54 percent overall mortality rate.

Mucormycosis is 70 times more common in India than it is worldwide [7]. There are many potential explanations, including the fact that India has a higher incidence of “uncontrolled diabetes.” Many of the patients they observed were unaware that they had diabetes before they were diagnosed with black fungus, highlighting “the absence of routine health check-ups in the Indian community.” Due to delays in finding medical treatment and diagnosing the disease, as well as difficulties in treating the advanced stage of infection, the mortality rate for mucormycosis in India is also remarkably high [7].

Covid-19 infections are more serious in people with diabetes and obesity. This increases their chances of receiving corticosteroids, which are often used to treat Covid-19 [14]. However, corticosteroids, in combination with diabetes, raise the risk of mucormycosis. Meanwhile, the virus that causes Covid-19 can damage airway tissue and blood vessels, putting people at risk of fungal infection. Harm to tissue and blood vessels caused by Covid-19 infection, corticosteroid therapy, elevated background rates of diabetes in the population most seriously affected by the coronavirus, and, most significantly, more widespread exposure to the fungus in the environment are all likely factors in India’s mucormycosis situation. It can grow anywhere as a mold, but it appears to fester in tropical countries due to the humidity.

Conclusion

Mucormycosis is more common in India than it is worldwide. Mucorales fungi are opportunistic, infecting sinus and brain, lung, skin, gastrointestinal tract of people with a compromised immune system, disseminated mucormycosis typically occurs in people who are already sick from other medical conditions like COVID-19. White fungus can affect the lungs as well as other body parts such as the nails, skin, stomach, kidneys, brain, private parts, and mouth. Yellow

fungus may cause pus leakage and slow wound healing, starvation and organ failure, and sunken eyes due to necrosis in severe cases. Controlling these fungal infections would necessitate improved vigilance, better testing to detect them early, as well as an emphasis on diabetes management, maintenance of all round hygiene during Covid infection, and the judicious use of corticosteroids. Patients will need access to surgery and antifungal care as soon as possible. A rapid rise in cases of mucormycosis has added to the challenges faced by India’s healthcare system as it deals with a massive second wave of COVID-19 infections. However, urgent research into the prevention of these infections is needed.

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