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REVIEW ARTICLE | MUCORMYCOSIS

A Narrative Review of the Pathophysiology of Mucormycosis Infection Among COVID-19 Patients in India: Epidemiology and Clinical Implications

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ABSTRACT

Background and Objective: During the second COVID-19 wave in India (April to May 2021), mucormycosis has affected the 'recovering' and the 'recovered but vulnerable' COVID-19 patients across the country. This review synthesizes information on the risk factors and pathophysiology of mucor infection among COVID-19 patients, which in turn supplements existing information from public health and clinical sciences. The study objective includes analyzing the morbidity of mucor infection and its pathophysiological mechanism, during India's second wave of the COVID-19 pandemic.

Methods: We conducted a systematic literature search of PubMed and Google Scholar databases, using the following text terms: 'COVID-19,' 'SARS-CoV-2,' 'mucormycosis,' and 'zygomycosis.' We identified 24 citations and 16 other published literature which described mucormycosis in association with COVID-19. The relevant literature was analyzed for findings on the risk factors of mucor infection and its outcome among individuals with COVID-19.

Results: The risk factors for mucor infection include diabetes mellitus, immunosuppression (for example, the administration of steroids/monoclonal antibodies/broad-spectrum antibiotics), prolonged stay in the intensive care unit, co-morbidities such as malignancy or post-transplantation, and prophylactic therapy with voriconazole (generic anti-fungal). The second wave of COVID-19 in India was more severe due to the increased occurrence of systemic inflammation and coagulopathy, which can cause direct damage to the blood vessels resulting in injuries to organs such as the liver, kidney, and heart.

Conclusion and Implications for Translation: The increased incidence of mucormycosis during the second wave of the COVID-19 pandemic in India (April to May 2021) was due to a combination of immunocompromising effects of corticosteroids, microangiopathy of diabetes, and peripheral microthrombi among COVID-19 patients. The indiscriminate usage of steroids for treating COVID-19 disease seems to be the likely cause, including the use of immunomodulatory drugs such as interleukin 6 inhibitors like tocilizumab (TCZ) for patients with severe COVID-19. Clinical practices should adopt a judicious approach towards the prescription of steroids and monitoring blood sugar for all COVID-19 patients admitted to the hospital as well as those isolated at home (even during the post-recovery period). The high mortality rate of

mucor infection demands appropriate primary prevention measures, as well as early diagnosis and treatment modalities for improving patient survival.

Keywords: • Mucormycosis • COVID-19 • Diabetes Mellitus (DM) • Immunosuppression • Steroids • Tocilizumab (TCZ) India

1. Introduction

During the third week of May 2021, India reported approximately 45% of new COVID-19 cases detected globally and approximately 34% of deaths.[1] A review of published literature from December 2019 to April 2021 shows that India reported approximately 71% of the global cases of mucormycosis, a rare fungal infection, among patients with COVID-19.[1] During the second wave of the COVID-19 pandemic in India (April to May 2021), mucor infection affected the 'recovering' and the 'recovered but vulnerable' COVID-19 patients. Mucor is an organism sometimes referred to as 'black fungus' due to its dark pigmentation. Mucor exposure potentially has fatal consequences. The incidence of fungal infection during the 2003 SARS-Co-V pandemic was 14.8-27%. It was the main etiology for patients with severe acute respiratory syndrome, which accounted for 25-73.7% of all causes of death.

Mucorales (Mucor) fungi belong to the zygomycete family and are ubiquitously present in the environment. Mucor does not cause any pathology among immuno-competent individuals. The route of infection is through inhalation of spores, which subsequently spreads to the paranasal sinuses and lungs. Mucor exposure can cause severe fungal infections among patients who are immunocompromised: for example, due to uncontrolled diabetes mellitus (DM), diabetic ketoacidosis, HIV/AIDS, lacerating wound, cancer, and organ transplantation.[2] The risk factors for mucor infection have been linked with DM in India when compared with hematological malignancies and organ transplantation in Europe and USA.[3] The various forms of mucormycosis include: gastrointestinal, which is common among young children; rhinocerebral, common among uncontrolled diabetics and kidney transplant recipients; pulmonary mucormycosis, common among cancer patients and those with organ/stem cell transplants; cutaneous and disseminated forms.[2] When compared with other fungal infections, the spread of mucor in tissues is faster, with speed in the range of 4 to 5 cm/day.[4]

The other predisposing risk factors for mucor infections include immunosuppression (for example, the administration of steroids/monoclonal antibodies/broad-spectrum antibiotics); prolonged stay in the intensive care unit (ICU); co-morbidities such as malignancy or post-transplantation; and prophylactic therapy with voriconazole.[5] The indiscriminate usage of steroids for treating COVID-19 disease is the likely cause of mucormycosis during the second COVID-19 wave in India, including the use of immunomodulatory drugs [such as Interleukin 6 inhibitors like tocilizumab (TCZ)], for patients with severe COVID-19. The infection tends to occur two to three weeks post steroid therapy.[6] The European Confederation of Medical Mycology (ECMM) study reports that among patients diagnosed with mucormycosis, 46% had received corticosteroids during the previous month.[7]

Glucocorticoids have been used in moderate and severe COVID-19 cases to reduce mortality and hospital stay.[8] Most protocols used for the treatment of COVID-19 infection (especially moderate and severe cases) include dexamethasone and methylprednisolone. Following the Randomized Evaluation of COVID-19 Therapy (RECOVERY) Collaborative Group study, the US National Institutes of Health (NIH) recommends the usage of steroids for patients on ventilator support or requiring supplemental oxygen, but not for those with mild disease.[9] A cumulative prednisone dosage of >600 mg or methylprednisone dose of 2-7 grams administered during the previous month predisposes immunocompromised patients to

develop mucormycosis. A short course of steroid therapy, even for 5 to 14 days, especially when given to patients with Type II DM, has resulted in a few cases of mucormycosis.[3]

The rationale for this review is to synthesize information from published literature on the risk factors and pathological mechanisms causing mucor infection in COVID-19 patients, including the importance of diagnosis and early treatment. Such scientific evidence on mucor infection will enable reducing its morbidity and mortality. The illustrated pathophysiology could be similar to other opportunistic fungal infections such as candidiasis, aspergillosis, pneumocystis pneumonia, and cryptococcal infections. The primary objective of this paper is to analyze the morbidity of mucor infection and its pathophysiological mechanisms during the second wave of the COVID-19 pandemic in India (April to May 2021). A secondary objective of this paper is to draw a comparison with the epidemiological characteristics from the first wave of the pandemic in India (August to October 2020), including the incidence of mucor infection during this period.

Table 1 lists the relevant reviews and case studies that have uniquely addressed some of these risk factors. However, our efforts are focused on a comprehensive analysis of many of the risk factors and an in-depth assessment of the pathophysiological mechanisms involved in the association between mucor infection and COVID-19 during the second wave of the pandemic in India.

2. Methods

In September 2021, we conducted a systematic literature search of PubMed and Google Scholar electronic databases using the following text terms: 'COVID-19/SARS-CoV-2 and mucormycosis,' 'zygomycosis and COVID-19,' 'COVID-19 and immunosuppression,' 'opportunistic fungal infections in COVID-19,' and 'complications delta COVID-19 variant.' We identified 24 citations and 16 other published literature (non-peer-reviewed reports) which describe mucormycosis infection associated with COVID-19 disease. The focus of our research was on the risk factors and pathophysiology. However, some of these articles provide information purely on clinical management. Both authors initially scrutinized the identified reviews, original articles,

Table 1: Salient features of the relevant articles

Serial No.	*Author*	*Study design*	*Outcomes*	*Implications*
1	Bhatt et al.[2]	Focused review	Severe COVID-19 patients treated in ICU are vulnerable to bacterial and fungal infections. Hospitalized COVID-19 patients are at risk for healthcare-associated infections, including candidemia and other fungal diseases.	Since lymphocytes maintain immune homeostasis, COVID-19 patients are susceptible to fungal co-infections.
2	Singh et al.[3]	Systematic review	Among 101 cases, pre-existing DM was present in 80% of cases, concomitant diabetic ketoacidosis was present in 14.9%. Corticosteroid for COVID-19 treatment was administered in 76.3% of cases. Mortality was noted in 30.7% of cases.	Trinity of diabetes, rampant use of corticosteroids in the background of COVID-19 appears to increase the occurrence of mucormycosis.
3	Garg et al.[10]	Case report and Systematic review	Of the 8 cases, DM was the common risk factor. 3 cases had been administered glucocorticoids for COVID-19. Seven cases had died.	Mucor developed 10-14 days after hospitalization.
4	Lv et al.[11]	Retrospective cohort study	Among COVID-19 & H1N1 patients, fungal mycobiota was characterized by depletion of Aspergillus and Penicillium, but Candida glabrata were enriched in H1N1-infected patients.	Dysbiosis of mycobiota occurred in both COVID-19 and H1N1 infected patients, with a higher burden of several opportunistic pathogenic fungi.
5	Pettit et al.[12]	Case-control study	Late-onset (>48 hours) infections were significantly common among recipients of TCZ. 61% of patients had a possible post-TCZ complication.	Infectious complications and drug-related toxicities are concerns associated with TCZ use.

and case studies that uniquely address some risk factors and pathophysiological mechanisms. The first author (VR) teased the relevant literature to include 21 articles from PubMed and 14 articles (as well as non-peer-reviewed reports) from Google Scholar.

The second author (RN) analyzed the screened articles for patient characteristics including the location of mucor infection, associated comorbidities, use of steroids and/or other treatment for COVID-19 management, and clinical outcomes for mucor infected COVID-19 patients. Thus, we retrieved 15 articles from PubMed and 11 articles (and reports) from Google Scholar. The flow diagram as per PRISMA guidelines that represent these activities is depicted in Figure 1. After a systematic review of the screened studies and critical interpretation of the eligible studies, both authors synthesized information regarding the association between mucor infection and COVID-19 infection, stratified by the risk factors.

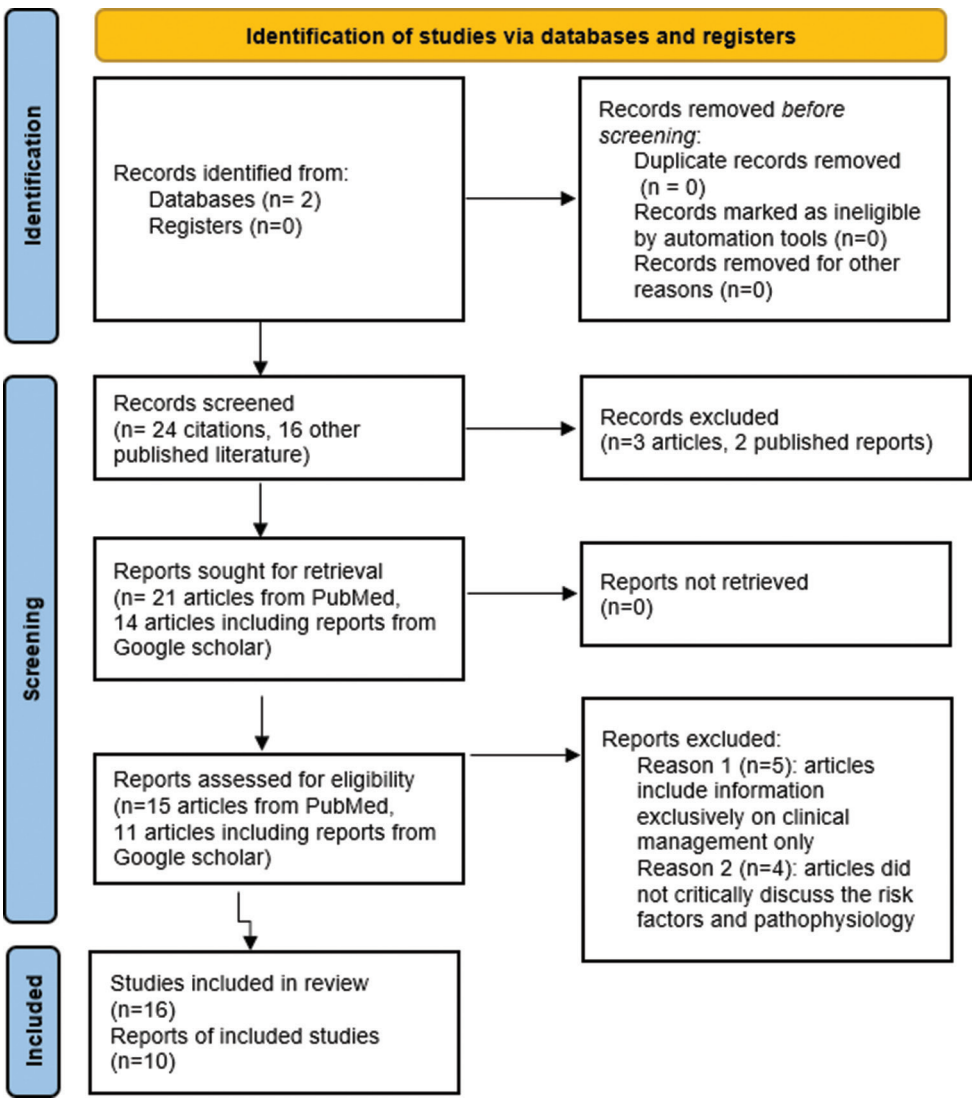

Figure 1: PRISMA Flow Diagram of Choosing Articles for Review

The Institutional Ethics Committee of Healthcare Global Enterprise Limited, India, granted an exemption for the study.

3. Results

3.1. Mucor Infection Among COVID-19 Patients

Bhatt et al.[2] report the high risk of opportunistic infections such as mucormycosis among COVID-19 patients, as the COVID-19 infection induces significant lymphopenia (as seen in >85% of patients). Such high incidence rates of opportunistic infections among COVID-19 patients justify the early detection and treatment of mucor infection and other fungal infections such as candidiasis, pneumocystis pneumonia, pulmonary aspergillosis, and cryptococcal disease. Laboratory investigations of severe COVID-19 patients show an increase in pro-inflammatory markers such as IL-1, IL-6, and tumor necrosis alpha, reduced expression of CD4 interferon-gamma and lowered count of CD4+ and CD8+ T cells.[2] Each of these markers increases the susceptibility to bacterial and fungal infections. Such airborne fungal organisms can invade the alveolo-interstitial lesions of the damaged pulmonary organ system of a severe COVID-19 patient.

Singh et al.[3] opine on the facilitating environment for germination of Mucorales spores in COVID-19 patients, which include: hypoxia, hyperglycemia (either pre-diabetes, steroid-induced, or new-onset), acidic media (metabolic acidosis, diabetic ketoacidosis), increased ferritin causing high iron levels and immunosuppression (due to co-morbidities, SARS-CoV-2 infection or steroid-induced), along with other risk factors such as prolonged hospitalization with or without mechanical ventilation.

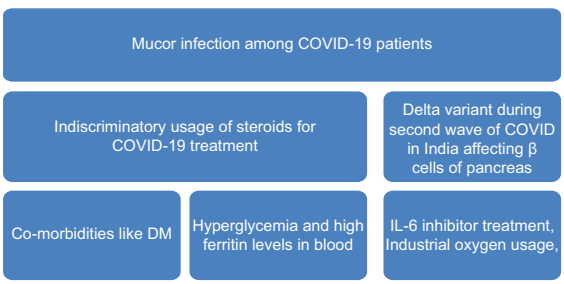

Figure 2: Factors Associated with Mucormycosis Occurrence Among COVID-19 Patients

As depicted in Figure 2, severe COVID-19 patients treated with a high dose of steroids, patients with uncontrolled diabetes, and those with a long duration of stay in the ICU are susceptible to mucor infection. The acidic nature of the patient's blood during diabetic ketoacidosis creates a fertile environment for the thriving of Mucorales fungi.[6] COVID-19 induced high ferritin levels (due to hemolysis), and lymphopenia might contribute to the steep rise in infections.

The study by Lv et al.[11] shows that the fungal load of the gut among patients with COVID-19 or H1N1 infection was significantly higher than that among healthy controls. Such fungal overgrowth in the gut is attributed to factors such as dysbiosis of bacterial microbiota, the presence of an inflammatory environment, and extensive tissue damage. The gut-lung axis plays a crucial role in the association between lung infection with SARS-CoV-2 and H1N1 and alterations of the gut mycobiota. Thus, pneumonia could be the result of the depletion of important fungi in the gut, as well as the growth of opportunistic pathogenic fungi. Pneumonia due to SARS-CoV-2 or H1N1 infection could also spawn the gastrointestinal symptoms and crucially alter the mycobiota of the gut, in addition to direct viral infection of the gastrointestinal tract.

The high mortality among mucormycosis patients is due to complications such as cavernous sinus thrombosis, osteomyelitis, and disseminated infection. The vascular invasion by fungal hyphae leads to thrombosis and tissue necrosis. Laboratory investigation involves blood analysis, biopsy, and radiological imaging. The management protocol includes the reversal of risk factors, surgical debridement, and intravenous antifungal medication such as amphotericin B.[2]

Table 1 lists the salient features of 5 studies (out of the 16 research articles reviewed), which comprehensively address the issues associated with the cause-effect relationship of interest.

3.2. Steroid Usage During the COVID-19 Pandemic: Its Implications for Mucormycosis

The immunosuppressive activity of corticosteroids along with its ability to induce hyperglycemia can

aggravate the clinical course of COVID-19 patients.[2] Balsari et al.[13] attributes the inappropriate usage of steroids to the rise in mucormycosis among patients recovering from COVID-19 in India. The authors[13] mention the ingrained culture of polypharmacy among healthcare practices in India. Such gestalt practices have resulted in the indiscriminate prescription of remdesivir, azithromycin, doxycycline, and plasma therapy, with the presumption that the organized whole (improving COVID-19 outcomes in this case) is perceived as more than the sum of its parts (indiscriminate use of drugs). The authors[13] opine that regardless of the drug efficacy or severity of the disease, more drugs such as favipiravir, baricitanib, and bevacizumab have been added to this list.

The incidence of steroid-induced hyperglycemia (SIH) is estimated in the range of 40 to 50%.[14] The known risk factors for steroid-induced hyperglycemia include increased body mass index (BMI), pre-existing DM, and older age. The 3 types include transient hyperglycemia among nondiabetics, newly discovered DM, and exacerbation of existing type 2 DM. Cortisol and other glucocorticoids tend to inhibit insulin secretion from the β cells of the pancreas and increase the glucagon secretion from α cells. This reduces the insulin sensitivity of fat tissue and skeletal muscles and stimulates the synthesis of glucose in the liver.[14] The usage of steroids also results in lowering of immunity (reduced phagocytic activity of white blood cells), and impairment of bronchoalveolar macrophage functioning (migration, ingestion, phagolysosome fusion).[3]

When the morning dose of Glucocorticoid is administered, steroid-induced hyperglycemia tends to occur during the afternoon and evening hours, followed by a gradual decline in the overnight blood glucose levels. This mandates the monitoring of diurnal variation in blood glucose levels. Higher doses of glucocorticoid and longer duration of treatment tend to increase the risk of steroid-induced hyperglycemia, irrespective of the type of glucocorticoid (considering equivalent doses). The Joint British Diabetes Societies Guidelines recommend clinical vigilance of patients during the initial phase of administration of any dose of glucocorticoid.[14]

3.3. Pathology of COVID-19 Infection – Enigmatic Association with Mucormycosis

COVID-19 infection by itself increases the levels of glucose in the blood, as the virus has the potential to infect the beta cells of the pancreas which produce insulin. Further research is indicated to determine the pathogenicity of the delta variant (which precipitated the second wave) is damaging the beta cells. The low production of insulin increases blood glucose levels. COVID-19 infection also increases the level of iron in the blood, which is a good feed for the molds of Mucor. A few microbiologists in India have opined that the samples from humidifiers (for oxygen administration) or the oxygen supply pipelines have not isolated the Mucor fungi.[4]

As depicted in Table 2, the second COVID-19 wave in India (April – May 2021) was different from the first wave (August – October 2020), in terms of symptoms, severity, and secondary infections. The characteristics of viral behavior during each wave could determine the incidence of comorbid mucor infection. Apart from black fungus (Mucor), white fungus (Candidiasis) and green fungus (Aspergillosis) were more common during the second wave. An increase in the number of deaths among the young population was also reported during the second wave.[15] Scientists used the wild-type virus strain (the Wuhan, China variant) across the globe to develop testing kits, plans of treatment, and the COVID-19 vaccines.[16] The delta variant which has been implicated for the second wave is known to possess immune escape mechanisms. Further research will determine whether the delta variant is more virulent or circulating to a greater extent among the vulnerable population and the response of health systems to the pandemic.

The activation of humoral immunity following two to three weeks of COVID-19 infection leads to the formation of antigen-antibody complexes which results in the extrapulmonary manifestations. COVID-19 induced organ damage is largely immune-mediated, quite similar to other autoimmune diseases. The debilitating symptoms for many months following COVID-19 infection

Table 2: Comparative data between first and second waves of COVID-19 in India[15,16]

Sl. No.	Second wave in India (April – May 2021)	First wave in India (August – October 2020)
1	39.4% of cases were severe	32.7% of cases were severe
2	59.7% of patients had comorbidities like diabetes, hypertension, and chronic kidney disease	54.8% of patients had comorbidities like diabetes, hypertension, and chronic kidney disease
3	Greater need for oxygen administration at admission (54.5% of cases)	Lesser need for oxygen administration at admission (41.1% of cases)
4	Average age of cases was 50 years	Average age of cases was 49 years
5	Virus (delta variant: B.1.617.2, R_0: 5.6-6.7) was 50% more infectious than the alpha variant, with entire families being affected	Virus (alpha variant: B.1.1.7, R_0: 3.6-4.2) was 50% more infectious than the wild-type variant (Wuhan strain R_0: 2.4-2.6)
6	Many asymptomatic patients and early manifestations of hypoxia led to the usage of industrial-grade oxygen along with oxygen supplied for medical use	More symptomatic patients and disease progression to hypoxia was slow, hence the demand for medical oxygen supplies was not overwhelming
7	Most common symptoms include fever, headache, sore throat, runny nose	Most common symptoms include fever, cough, loss of taste or smell
8	Long COVID-19 syndrome was prolonged even in mild to moderate cases which includes fatigue, neuro-muscular, pulmonary, and cardiac complications	Long COVID-19 syndrome was found among severe cases, and mild to moderate cases seem to have recovered completely
9	Post-COVID-19 vigilance is up to 100 days	Post-COVID-19 vigilance was two weeks
10	Secondary infections such as mucor irrespective of diabetes or steroid therapy, infarction of legs due to arterial thrombosis	Not much evidence of secondary bacterial, viral or fungal infections
11	Micro containment zones are marked for households of infected individuals, such as the entire level of an apartment complex, or an entire individual house	Containment zones were large, reducing the chances of viral transmissions, such as an entire apartment, or one community living area

could be due to the occlusive and propagative injuries, caused by the prothrombotic state which has resulted from the immune dysregulation. The etiology of long COVID-19 disease could be due to the aberrant immune response, antigen-antibody reactions, endotheliopathy, and the hypoxemic injuries.[17]

According to data from Public Health England,[16] the effectiveness of two doses of COVID-19 vaccination against related hospitalization was 96% for Pfizer's mRNA vaccine and 92% for AstraZeneca vaccine, respectively. These rates are comparable to the effectiveness against the alpha variant. Although it is imperative to receive both doses of a particular COVID-19 vaccine, the efficacy against the delta variant warrants further investigation with regard to breakthrough infections and the requirement of booster doses.[18] Such vaccine-induced immunity against COVID-19 might ward off the disease and, in turn, the possibility of co-morbid mucor infection.

3.4. Pre-Existing Diabetes as a Predisposing Factor for Mucormycosis in this Conundrum

Afroze et al.[19] study on mucor infections among diabetic patients discusses the various ways by which the body's immunological response changes among diabetics. The proliferation of fungus is stimulated by hyperglycemia, and this status also decreases the efficiency of phagocytes and the process of chemotaxis. Bhogireddy et al.[20] explain the low incidence of mucor infection among HIV/AIDS patients due to neutrophils and non-T lymphocytes playing a vital role in inhibiting the proliferation of fungal spores. Future research should determine the mechanisms by which diabetes and corticosteroid intake render the phagocytes dysfunctional. The innocuous mucor organism thrives in the acid-rich environment. In diabetic ketoacidosis, the ketone bodies in biological tissue enable the growth of Rhizopus oryzae organisms which produce the enzyme ketoreductase. This results in an increased risk of mucormycosis, as the host defense mechanism

among such patients is further compromised by the inability of transferrin in binding iron.

Garg et al.[10] report that diabetes status increases the risk of death among patients with severe COVID-19. For some of these patients, their diabetic condition may be poorly controlled resulting in renal dysfunction. The dysregulation of immunity caused by COVID-19 can aggravate the mucor infection among diabetic patients. Such co-morbid illness along with the administration of glucocorticoids and monoclonal antibodies for severe COVID-19 increases the net state of immune suppression. Mucorales have the ketone reductase enzyme and thrive in states of hyperglycemia and diabetic ketoacidosis.[8]

3.5. Hyperglycemia and High Ferritin Levels in Blood – An Unholy Mixture Predisposing the Mucor Infection

Figure 3 depicts the pathological mechanism by which hyperglycemia increases free iron in the blood through glycosylation of transferrin and ferritin, thus reducing the binding of iron. During the course of COVID-19 infection, there is an increase in the level of cytokines, especially interleukin-6. This also contributes to the increase in free iron in the blood by increasing the synthesis of ferritin and decreasing the transport of iron. Concomitant acidosis compliments these mechanisms and reduces the ability of transferrin to chelate iron.[3] These processes increase the expression of glucose-regulator protein 78 (GRP-78) of endothelium cells and fungal ligand spore coating homolog (CotH) protein. COVID-19 uses processes to increase serum iron levels, which promotes the growth of Mucorales. Mucor infection is facilitated by the described pathological change which further enables channels such as angio-invasion, hematogenous dissemination, and necrosis of tissue.[3]

3.6. Mucor Due to Treatment of COVID-19 Patients with Il-6 Inhibitors

TCZ is administered to reduce the levels of interleukin-6 (IL-6) during the cytokine release syndrome (CRS) among COVID-19 patients. It is a recombinant humanized monoclonal antibody that is used against the interleukin-6 receptor. The inflammatory effects of interleukin-6 can otherwise damage the lung tissue, and subsequent COVID-19 induced multiorgan failure. The weakened immune system due to large doses of TCZ may pave the way for opportunistic infections such as mucor infection. Suppressing interleukin-6 with TCZ will reduce the clearance of viruses and bacteria, which in turn can cause secondary infections. There are concerns regarding other toxicities associated with the use of TCZ, such as liver dysfunction, hypertension, diverticulitis, gastrointestinal perforation, neutropenia, and reactions related to the infusion.[12]

Kimmig et al.[21] studied the independent association between TCZ administration for severe adult COVID-19 patients and the presence of bacterial infections (OR: 3.960, 95% CI: 1.351-11.607, p=0.033). The logistic regression model analyzed in the study includes bacterial infections as the outcome and age, sex, and Charlson Comorbidity index as the independent variables.

Pettit et al.[12] report a 61% possible post-TCZ complication among COVID-19 patients with a hyper-inflammatory response. The study[12] reports a significantly higher proportion of late-onset (≥48 hours) infections among COVID-19 patients who received TCZ (cases) when compared with controls who did not receive it (23% vs. 8%, p=0.013). However, the overall infection rate was similar between the groups. This variation could be explained by the long half-life of TCZ: 11 days with a dosage of 4 mg/kg.[12] Additional research should explore the infectious complications and drug-related toxicities associated with the use of TCZ. A stringent selection criterion for the administration of TCZ needs to be followed, with the dosage not exceeding a single dose of 400 mg.[22]

3.7. Mucor Due to Industrial Oxygen, Primarily Used for COVID-19 Treatment

The usage of industrial oxygen (non-medical grade), was a possible route of contamination for mucor infection among COVID-19 patients during the second COVID-19 wave in India. Unlike medical oxygen, the hygiene of industrial oxygen cylinders is

likely to be compromised. Also, oxygen is given to patients through humidifier bottles attached to the cylinder, and there is a possibility of the classified water being unsterile.[23] Patients are likely to inhale the fungal spores from such contaminated humidifiers. Due to the increased demand for oxygen during the second COVID-19 wave in India, hospitalized patients sometimes had to share the same cylinder or the non-rebreather mask. However, some of the microbiological samples taken from such items did not yield mucor fungus.[15]

The oxygen which fills the cylinder, whether medical or non-medical grade, is initially passed through water which traps the fungal spores.[23] If the premise regarding contaminated ICU pipes and other equipment is considered, then a plethora of viral/bacterial secondary infections are possible, not just the risk of mucor infection. There is a possibility of fungus colonization in the nose due to the continuous usage of the same mask (>2-3 weeks). This situation is complemented by the inhaled oxygen from the cylinders which is humid and by the frequency of steam inhalation multiple times a day.

Since mucor fungus is omnipresent (mucor resides in many indoor and outdoor environments, including the ducts of air conditioners, in soil, and in decaying organic matter), any compromise in the immune status of an individual makes it invasive. Some preventive interventions include a ventilated and hygienic environment for COVID-19 patients, using sterile water for humidification in the oxygen tube, and cleaning these tubes with betadine at a frequency of 2-3 times/day. The oxygen concentrators used at home should be filled with clean distilled water.

3.8. Diagnosis of Mucormycosis and Other Fungal Infections

Other fungal infections such as invasive aspergillosis could develop into a super-infection among severe COVID-19 patients requiring care at the ICU. Across the globe, the varied incidence rates of such fungal infections could be due to the challenges in diagnosing them. Clinical symptoms, as well as the abnormalities found on chest imaging, could be non-specific. The positive sputum samples or tracheal aspirates may not profoundly differentiate colonization and infection, and the COVID-19 status of the patient dissuades invasive diagnostic procedures such as bronchoscopy/lung biopsy/bronchoalveolar lavage. Given the difficulty in isolating mucor and the lack of biomarkers such as beta-d-glucan and galactomannan for invasive aspergillosis,[10] under-diagnosis is a fallacy in the case of mucormycosis.

3.9. Treatment of Patients with Mucormycosis

The patient's current health condition precludes timely diagnosis and testing, which increases the risk of invasive mold infections. The overwhelming number of COVID-19 patients places a strain on the essential services of the hospital, including diagnostics and surgeries. Good glycemic control in the hospital and along with appropriate initiation of liposomal amphotericin B treatment will enable favorable outcomes among such patients. Systemic administration of liposomal amphotericin B is more effective and less toxic, thus facilitating prolonged administration without side effects.[8] Due to its side-effect of nephrotoxicity, the renal function needs to be regularly monitored during admission. The second line of management includes the triazole antifungals: posaconazole, and isavuconazole. Since Isavuconazole has an extended spectrum of action, it is used in the treatment of invasive mucormycosis.[24]

Due to the barrier created by vascular thrombosis and extensive ischemic necrosis, the entry of antifungal agents in adequate concentration to the infected tissue is affected. Hence, antifungal treatment alone may not be effective. To minimize the fungal load in the tissue, we need to perform a radical debridement of infected and necrotic tissue along with drainage of infected paranasal sinuses. For rhino-orbital mucor infections, the line of management includes retrobulbar antifungal therapy and intravitreal amphotericin B injection.[8]

The European Confederation of Medical Mycology and Mycoses Study Group Education and Research Consortium, provide the 2019 guidelines for the diagnosis and management of mucormycosis.[25] This includes immediate and complete surgical intervention followed by administration of systemic antifungals as the first line of management. The recommendation is to

initiate high-dose liposomal amphotericin B in association with an adequate dosage of intravenous isavuconazole and posaconazole. Posaconazole can be given as prophylaxis for high-risk individuals such as neutropenic patients with graft versus host disease.

4. Discussion

The National guidelines in India for the diagnosis of COVID-19 were revised in May 2021 to allow syndrome-based diagnosis, which countered the denial of admissions due to slow or unavailable testing.[13] The second wave of COVID-19 in India (April to May 2021) was more severe due to the increased occurrence of systemic inflammation and coagulopathy, which can cause direct damage to the blood vessels resulting in injuries to organs such as the liver, kidney, and heart. The coagulopathy observed in COVID-19 patients during the second wave of COVID-19 in India was characterized by complement-mediated thrombotic microangiopathy rather than disseminated intravascular coagulation or sepsis-induced coagulopathy.[8]

For patients with a normal immune system, mucor infection is asymptomatic. The increased incidence of mucormycosis during the second wave of the COVID-19 pandemic in India was due to a combination of immunocompromising effects of corticosteroids, microangiopathy of diabetes, and peripheral microthrombi in COVID-19 patients. This provides an ideal atmosphere for the Mucor to proliferate, given its inherent nature of angioinvasiveness.[26]

The clinical protocol for ICU patients with adult respiratory distress syndrome (ARDS) should include systematic screening for respiratory fungal infections. The onset of ARDS is likely due to colonization of fungal infections such as aspergillus, pneumocystis jirovecii, and mucormycetes. It is imperative to conduct research on estimating the median time between admission of the patient to ICU and the beginning of ARDS. The primary endpoint of such studies should not just be recovery and discharge from ICU, but should also include patient follow-up after 1 month from the primary endpoint.

It is imperative to avoid using glucocorticoids in mild COVID-19 cases (without hypoxemia) or higher doses of the drug in moderate or severe COVID-19 patients. Evidence should direct the utility of immune-modulating drugs such as TCZ. The severity of diabetes determines the prognosis of patients with opportunistic infections, thus mandating the control of glycemia and other predisposing factors. Early recognition is vital for a favorable outcome. The sequelae following immunosuppressive treatment should be followed for a few months. The healthcare system should appreciate the menace of the triad: COVID-19, diabetes, and the usage of steroids.

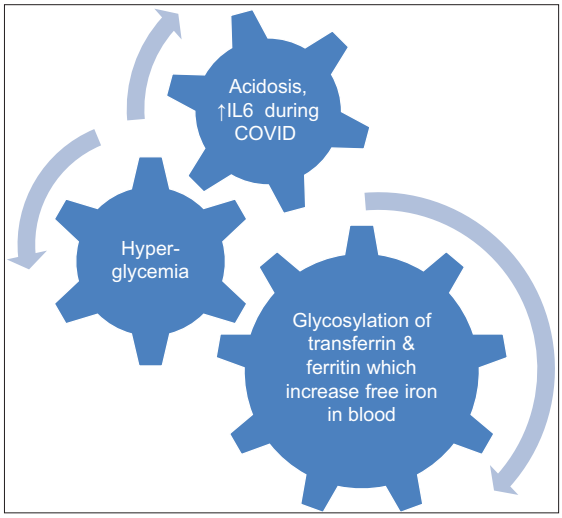

Figure 3: COVID-19 Induced Hyperglycemia and the Resulting Increase in Ferritin Levels

Mucor is an unexpected infection among COVID-19 patients who are already drained of their body's protective resources. It is important for hospitals to maintain hygiene, especially for equipment used to dispense oxygen. Clinical practices should adopt a judicious approach towards the prescription of steroids, and blood sugar monitoring of all COVID-19 patients admitted to the hospital as well as those isolated at home (even during the post-recovery period). We need to appreciate that some hypoxic patients may only need oxygenation and proning, and not all patients need ventilation (invasive or non-invasive). In the Indian context, the goal of care needs to be revised given the lack of critical care capacity as well as the strained

diagnostic capacities in rural areas. Therapeutic practices in the management of COVID-19 patients should be guided by evidence-based science. This can prevent untoward secondary infections such as mucormycosis.

5. Conclusion and Implications for Translation

The incidence of mucormycosis has risen among severe COVID-19 patients, resulting in higher mortality rates. The immune dysregulation caused by COVID-19 along with widespread use of steroids/broad-spectrum antibiotics and ventilator support are the factors that make the patient susceptible to mucor infection. It is important for hospitals to maintain hygiene, especially for equipment used to dispense oxygen. Patients admitted to the intensive care unit, and who subsequently develop ARDS should be screened for respiratory fungal infections such as aspergillus, pneumocystis jirovecii, and mucormycetes. Given the high mortality rate of mucor infection, it is imperative to primarily prevent the infection, and secondarily exercise a high index of suspicion among patients from high-risk groups, in order to diagnose the infection at an early stage, and initiate treatment modalities toward improving patient survival.

Limitations

1) Given the difficulty in microbiological/histopathological diagnosis of mucormycosis during the course of an ongoing pandemic, the morbidity of this infection could be under-represented.
2) Many studies did not associate the duration of diabetes and baseline glucose (and/or HbA1c) data for all the cases.
3) As we cannot define the at-risk individuals infected with COVID-19, the value of the denominator cannot be estimated and thus the incidence rate cannot be computed.

Compliance with Ethical Standards

Conflict of interest: *The authors declare no competing interests.* ***Financial disclosure****: Nothing to declare.* ***Funding/Support****: There was no funding for this study.* ***Ethics approval****: The Institutional Ethics Committee of Healthcare Global Enterprise Limited, India, granted an exemption for the study.* ***Acknowledgment:*** *The authors acknowledge Dr. Krishnamurthy Jayanna, Dean, Faculty of Life and Allied Health Sciences, Ramaiah University of Applied Sciences, Bangalore, India, for proof-reading the manuscript and suggesting valuable revisions.* ***Disclaimer:*** *None.*

Key Messages

- During the second wave of COVID-19 in India (April to May 2021), mucormycosis has affected the 'recovering' and the 'recovered but vulnerable' COVID-19 patients across the country.
- This review synthesizes information on the risk factors and pathophysiology of mucor infection among COVID-19 patients, which in turn supplements existing information from public health and clinical sciences.
- The increased incidence of mucormycosis during the second COVID-19 wave in India is due to a combination of immunocompromising effects of corticosteroids, microangiopathy of diabetes, and peripheral microthrombi among COVID-19 patients.

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