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Mucormycosis-The New Threat in Post-COVID 19 Infection

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Abstract
Mucormycosis is the disease caused by the filamentous fungi that belong to the fungal family Mucorales. The Mucorales are considered as opportunistic fungi which can infect people with a compromised immune system. Patients on immunosuppressants as seen with organ recipients and hematological stem cell recipients are susceptible for mucormycosis. COVID-19 infection may induce significant and persistent lymphopenia, which in turn increases the risk of opportunistic infections. Patients with severe COVID-19 have distinctly lower absolute number of T lymphocytes, CD4+T and CD8+ T cells. Since the lymphocytes play a major role in maintaining the immune homeostasis, the patients with COVID-19 are highly susceptible to fungal co-infections. Uncontrolled glycemic load in diabetic patients during COVID infection may put them in higher risk for developing mucormycosis. Corticosteroid administration during COVID 19 infection also leads to impaired immune function and alteration in glucose homeostasis. These angioinvasive fungi invade the surrounding blood vessels and cause tissue necrosis. Awareness, early diagnosis, post-covid follow up and aggressive treatment is necessary for prevention of this life-threatening disease. Glycemic control, minimizing the prescription of steroids and immunosuppressive drugs must be taken in account in diagnosed patients. As the growth of fungus is dependent on availability of iron, sequential investigation of serum ferritin level and total iron binding capacity of patients is also recommended. Till now Amphotericin B is the first line drug of choice in India, subsequently anti-mucorales drug Posaconazole and Isavuconazole are also prescribed.

Keywords
Covid, Mucorales, Fungi, Mucormycosis, Diabetes

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INTRODUCTION
The emergence of novel pathogenic SARS-coronavirus 2 (SARS Cov 2) in Wuhan, China and its subsequent rapid international spread across world is the foremost ongoing global health emergency. The infection by SARS Cov2 causes varying symptoms including fever, myalgia, diarrhoea, pneumonia, and shortness of breathing. In severe cases supportive care including oxygen and mechanical ventilation is used for infected patients. The World Health Organization (WHO) declared the outbreak of COVID 19 infection as a Public Health Emergency of International concern on 30th January 2020 and a pandemic on 11th March 2020. As of June 2021, there are more than 184 million infected cases, with 4 million confirmed deaths reported worldwide [1]. The short term and long-term catastrophe of the pandemic and its consequences are felt differently in

each country depending on the public health and economic policies of individual Government. All indications from the COVID 19 cases in India from April 2021 indicate that the country has faced the second wave of COVID 19. People experienced uncertainty, anxiety and confusion following experiences of how the number of COVID 19 cases has turned into the faces of their near and dear ones. The B.1.617 variant has become the dominant strain across India which cause severe infections in several countries like United Kingdom, Fiji, Singapore.

The novel coronavirus SARS Cov 2 utilize the human angiotensin-converting enzyme 2 (ACE2) receptors located on cells in many organs/tissues including the lung, heart, kidney, bladder, eyes, nasal and oral cavities, brain, thyroid, liver, gallbladder, stomach, pancreas, intestine, reproductive system of males and females to gain entry and employ the cellular transmembrane serine protease TMPRSS2 for S protein priming which ultimately trigger a range of clinical manifestations [2].

Infection with SARS-CoV-2 exorbitantly impacts the immune system via induction of cytokine storm, an increase in neutrophil count as well as a decrease in lymphocyte count specifically CD4+ and CD8+ T cells. Consequently, these patients are at increased susceptibility of developing opportunistic infections such as mucormycosis and other fungal diseases such as candidiasis, SARS Cov 2 associated pulmonary aspergillosis due to decreasing lymphocyte cells. CD4+ and CD8+ T cells serve a prominent role against infection with mucormycosis via recruiting cytokines, such as IL-4, IL-10, IL-17, and IFN-γ [1,3]. Symptoms of some fungal diseases can be like those of COVID-19, including fever, cough, and shortness of breath. Laboratory testing is necessary to determine if a patient is suffering from a fungal infection or COVID-19 [3].

THE PATHOGEN BEHIND MUCORMYCOSIS

Mucormycosis is an opportunistic and life-threatening mycosis caused by a number of moulds classified in the order Mucorales of the Zygomycetes. Mucorales are thermotolerant saprophytic fungi found in decaying organic matter and soil samples. These fungi are ubiquitous thermotolerant saprophytes. The leading pathogens among this group of fungi are species of the genera Rhizopus, Rhizomucor, Absidia, Cunnighamella and Mucor. These moulds enter the human body through respiratory tract or skin and less frequently through the gastrointestinal tract [4]. *Rhizopus arrhizus* is the most common agent causing this disease in India [5].

It has been shown that *Rhizopus* spores adhere to laminin and type IV collagen [6] present in tissue. *Rhizopus* adheres to and invades endothelial cells by specific recognition of the host receptor glucose-regulator protein 78 (GRP78) [7,8]. The fungal ligand which binds to GRP78 at the time of invasion of the endothelium belongs to the spore coating coat protein homologus (CotH) protein family. The most frequently isolated Mucorales from patients (*Rhizopus*, *Mucor* and *Lichtheimia*) contain 3–7 copies of *CotH*. This recognition initiates death of host cells through endothelial cell–mediated fungus endocytosis. GRP78, which was first discovered as a heat shock protein involved in stress-related responses [8] anchor to *R. delemar* as well as other Mucorales germlings but not spores [7]. Binding to germlings is consistent with the hypothesis that hyphae are the invading form of Mucorales. Incidentally, acidemic states and hyperglycemia induce the expression of endothelial receptor glucose-regulated protein (GRP 78) and the Mucorales adhesin spore coat protein homologs (CotH), which creates a quintessential storm for increased adhesion and penetration of Mucorales to the endothelium [9]. On the other hand, GRP 78 has been postulated as one of the receptors responsible for SARS-CoV-2 entry [10]. A marked increase in serum GRP78 level and seum GRP78 mRNA level are also observed in SARS-CoV-2 pneumonia [10,11,12].

CLASSIFICATION OF MUCORMYCOSIS

The presentation of mucormycosis are classified as rhino-orbital-cerebral, pulmonary, gastrointestinal, cutaneous, renal and disseminated mucormycosis. Gastrointestinal mucormycosis is less common and is thought to set in from ingestion of the organism in patients who are severely undernourished and in transplant recipients. The stomach, ileum and colon are the most frequently involved sites [5]. The symptoms are diverse and based on the site affected but non-specific abdominal pain and distention correlated with nausea and vomiting are the most common manifestations. Cutaneous mucormycosis may be primary or secondary. Primary infection is typically observed after inoculation of the fungus into disrupted skin and is most often seen in patients with burns or other forms of restricted skin lesion that turn out into an acute inflammatory response with pus, abscess formation, tissue swelling and necrosis. It occurs when a skin trauma wound is contaminated with soil. Secondary cutaneous infection is generally seen when the pathogen spreads haematogenously and more commonly from a rhinocerebral infection. Mostly affected areas of the skin are arms and legs while report exists for infections in neck, scalp, face, breast thorax and abdomen [13]. Disseminated mucormycosis may

follow any of the four forms of mucormycosis outlined above but is mostly manifested in neutropaenic patients with a pulmonary infection. The most usual site of outspread is the brain but metastatic necrotic lesions in the spleen, heart and other organs are also frequently reported. The clinical manifestations include cognitive decline with or without a sudden onset of focal neurological signs [14].

The major form is rhinocerebral mucormycosis**,** which results from germination of the sporangiospores in the nasal passages and invasion of the hyphae into the blood vessels causing thrombosis, infarction, and necrosis. It progresses very promptly with invasion of the sinuses, eyes, cranial bones, and brain. After proliferation in the nasal cavity, the mucor reaches the pterygo -palatine fossa, inferior orbital fissure and finally the retroglobal space of the orbit [15]. Blood vessels and nerve are damaged, and the patients develop edema in the involved facial area and presented with bloody nasal exudate and orbital cellulitis. Mucormycosis has recently emerged as a marked sinopulmonary infection in hematologic patients and recipients of transplantation being on antifungal prophylaxis [16]. Thoracic or pulmonary mucormycosis follows inhalation of the sporangiospores with invasion in the lung parenchyma and surrounding vasculature. In both cases ischemic necrosis is responsible for massive tissue destruction. In histopathological examination collections of aseptate hyphae infiltrating the lung parenchyma, positive Periodic Acid-Schiff (PAS) and Gomori methenamine silver stains confirm presence of pulmonary mucor. In a retrospective review of mucormycosis diabetes mellitus was found the most common risk factor as of 56% patients out of 86 cases were diabetic [17]. Various Pulmonary Mucormycosis cases have been reported from India, where this disease was presented as mimicking tuberculosis (TB), as non-resolving pneumonia and as co-infection with TB. The incidence of pulmonary mucormycosis in India was found 2.5% in a prospective study involving 38 mucormycotic patients [5]. The diagnosis of pulmonary mucormycosis is more complex than other fungal infections whether histopathology is much subtle and confirmative than cultures. Mucorales are very fast-growing fungi, but the yield of cultures is low and could be due to aggressive processing of the specimen or prior antifungal therapy. Direct microscopy of the specimens is the major and decisive diagnostic tool since it differentiates between a pathogen and contaminant [18]. Identification on H&E staining is also difficult, and many times special staining techniques are required for diagnosis. It is important to note that the key feature of mucorales is that it produces wide ribbon-like aseptate hyphae in tissues with branching at wide angles nearing 90° while *Aspergillus* spp. produce thin septate hyphae branch at acute angles of 45° [19]. Patients with post pulmonary tuberculosis and chronic kidney disease are at additional risk of developing mucormycosis in this country [5].

DIABETES - A POTENTIAL THREAT FOR MUCORMYCOSIS

The conditions that place patients at risk of Mucormycosis include acidosis especially that are associated with diabetes mellitus-leukemias, lymphoma, corticosteroid treatment, severe burns, immunodeficiencies as well as dialysis with the iron chelator deferoxamine. An upsurge in the number of diabetics has really changed the entire scenario like an epidemic in southeast Asia posing a very serious medical threat. The exact prevalence of mucormycosis in India is unknown, though the approximate prevalence is much higher than that in developed countries. Recent report brings forward that India has the highest burden of mucormycosis in the world with an estimated preponderance of 140 cases per million population. The most common risk factor associated with mucormycosis in India is diabetes mellitus [20]. The frequency of mucormycosis was reported at 0.16–1.72% in patients with diabetes mellitus from North India [21,22]. A recent widespread multicentre study in India reported a higher prevalence of diabetes mellitus as a risk factor for development of mucormycosis in North India (67%) compared to South India (22%) [23]. In this study on mucormycosis it was found that 57% of patients had uncontrolled diabetes mellitus and 18% suffers from diabetic ketoacidosis [23]. Poorly controlled type 2 diabetes is the most common risk factor for mucormycosis. Diabetes and ketoacidosis cause the phagocytic cells dysfunctional, and macrophages and neutrophils exhibit an impaired chemotaxis under this condition which predispose diabetic patients to mucormycosis [24].

Evidence suggests SARS CoV-1 induces damage of pancreatic islets resulting in acute diabetes and diabetic ketoacidosis [25]. There is also a high possibility of progression of “diabetogenic state” and imbalance of glucose homeostasis in SARS CoV-2 infection, as there is a high expression of angiotensin-converting enzyme 2 (ACE2) receptors in pancreatic islets, along with increased insulin resistance due to cytokine storm [26]. Simultaneously, β-cells also got damaged via

increased amount of inflammatory cytokines [27]. Recently, euglycemic diabetic ketoacidosis is also being reported in COVID-19 patients [28]. This is also presumed that initial damages in lungs resulting from COVID-19 might have direct or indirect impact to cause metabolic dysfunction and diabetes mellitus in particular [29]. The frequent use of corticosteroids that exacerbated glucose homeostasis, may have predisposed patients to mucormycosis [30]. There is a significant increase in the incidence of maxillofacial fungal infections in diabetic patients infected with covid 19 with a strong association with corticosteroid administration [31]. In May 2021 it was reported with scientific evidence that there is dysregulation of ACE-2 expression not only in lungs but also in esophagus, pancreas, ileum, colon, cardiovascular and renal tissues and create an opposite microenvironment for opportunistic infections like mucormycosis [32].

Ferritin and Mucormycosis

Diabetic patients suffering from ketoacidosis have an acidic serum pH with increased levels of free iron which is a major nutrient for Mucorales. Earlier it was observed that this life-threatening infection occurs in patients with diabetes with increased available serum iron (e.g. from systemic acidosis or deferoxamine therapy), and in patients immunocompromised by neutropenia or on corticosteroids medications [33,34]. During severe COVID 19 infections, in addition to imbalance of glucose homeostasis, an alteration in iron metabolism also occurs. Increased IL-6, due to severe COVID infection stimulate ferritin synthesis and down regulate iron export resulting in intracellular iron overload, further complicating the process [35]. Tissue damage occurs in consequence which leads to the release of unbound free iron into the circulation that is toxic as it could generate reactive oxygen species. Iron overload and excess free iron thus are one of the key and unique risk factors for mucormycosis [36,37]. The hypersusceptibility of patients with increased available serum iron to infection by R. oryzae, highlights the vital role of iron metabolism in the microorganism's virulence. The fungi, which is responsible for mucormycosis, are normally unable to grow in serum due to the sequestration of iron-by-iron binding proteins. However, diabetic ketoacidosis causes proton-mediated dissociation of iron from iron-sequestering proteins, and the increased levels of available iron enable enhanced growth of these fungi in serum [38].

Excessive Zinc Use and Mucormycosis

Apart from the existing causative factors like steroid medications, compromised immunity, uncontrolled diabetes and excessive use of antibiotics, researchers are now also linking the excessive use of zinc supplements to mucormycosis. Microbial studies suggest the hypothesis that Zn starvation inhibits microbial growth in tissues [39]. On the other hand, Zinc is thought to accumulate iron in body which creates a perfect birthplace for mucormycosis. During COVID 19 pandemic zinc tablets are used inadvertently as supplements along with other vitamins to boost immunity. On the other hand, while there is no proven clinical data, researchers pointing out that zinc could cause fungal infections and there is a need for more investigations. Dr Rajeev Jayadevan, scientific advisor and former president of the Indian Medical Association said that fungi feed on zinc and mammalian cells try to escape fungal invasion by 'starving' the fungus by hiding zinc. These self-defence processes against fungi are known as nutritional immunity [40].

Contaminated Medical Devices and Mucormycosis

The risk of mucormycosis contamination in hospitalized patients may increase due to contaminated humidifier bottle, cannula and unsterile oxygen mask. Sharing oxygen masks in tertiary hospital also increases the risk. Existing data suggests that the most common source of community and health acquired mucoralean outbreaks was contaminated medical devices that are responsible for 40.7% of the outbreaks followed by contaminated air (31.3%), traumatic inoculation of soil or foreign bodies (9.4%), and the contact (6.2%) or the ingestion (6.2%) of contaminated plant material. The most prevalent species were Rhizopus arrhizus and R. microsporus causing 57% of the outbreaks [41].

Available Treatment of Mucormycosis

It is extremely important to promptly diagnose the disease as it can be aggressive and life-threatening. Glycemic control, tapering of steroids and minimizing immunosuppressive drugs must be taken in account in diagnosed patients. As the growth of fungus is dependent on availability of iron, serial examinations of serum ferritin level and total iron binding capacity of patients is also recommended.

Amphotericin B is an antifungal medication which is used for major systemic fungal infections like mucormycosis, aspergillosis, candidiasis and blastomycosis. Still now it remained most useful in the treatment of invasive mucormycosis because of its broad-spectrum activity and low resistance rate. Amphotericin B comprises a 38-membrane macrocytic ring which is formed by lactonization and it has a chain of unsubstituted conjugated double bonds (Heptaene). On opposite side a polyhydroxylated chain with seven free hydroxyl groups guarantees its amphipathic nature. Lactone

rests at one end of the molecule with a free amino group forming a side chain [42]. The conventional formulation contains sodium deoxycholate and phosphate buffer. Sodium deoxycholate increases the solubility of Amphotericin B in water as the solubility of latter in water is low. Sodium deoxycholate is thought to stabilize the micellar suspension [43,44]. The hydrophobic part of Amphotericin B binds with ergosterol present in the cytoplasmic membrane of fungi. This results in activation of downstream cascade which results in formation of pores and channels in plasma membrane which allows extravasation of potassium, phosphate, ammonium, carbohydrate, and protein and thereby causing cell death [45]. The role of oxidative damage in the antifungal effect of Amphotericin B is still unknown though different studies suggest that this mechanism also participates in its anti-fungal effects**.** Studies suggest that Amphotericin B induces formation of Reactive Oxygen Species (ROS) in 44 isolates of different pathogenic yeast species. The inhibition of the mitochondrial respiratory chain by rotenone blocked the induction of ROS by Amphotericin B and provided protection from the physiological function of this antifungal drug. The formation of ROS by Amphotericin B is a universal and important mechanism of action which is correlated with the fungicidal effect and might explain the low rate of resistance to the molecule [46].

As conventional Amphotericin B is associated with more toxic effects like nephrotoxicity, liposomal Amphotericin B are used which are less toxic but provides the same pharmacological and therapeutic effect [47]. Amphotericin B is the first line drug of choice in India, subsequently anti-mucorales drug Posaconazole and Isavuconazole are also prescribed. Posaconazole and Isavuconazole are used as salvage therapy in treatment of mucormycosis. Posaconazole has been found to be a safer and effective drug of choice for the management of the invasive fungal infection in India. This drug has received approval from the Drug Controller General of India (DCGI). Posoconazole inhibits the synthesis of ergosterol by down regulating the enzyme lanosterol 14-α-demethylase which is present in all fungi except Pneumocystis and Pythium. It can also interact with additional domain of the target and thus it also blocks even mutated strains resistant to fluconazole and voriconazole [48].

Isavuconazole is a second-generation broad spectrum triazole which shows inhibitory activity against yeasts, molds and dimorphic fungi. Isavuconazole down regulates cytochrome P 450-dependent lanosterol 14-α-demethylase, that is essential for synthesis of ergosterol. Isavuconazole is proposed to be widely distributed in many tissues including brain, lung, liver, and bone. Rapid tissue penetration and distribution of Isavuconazole is confirmed in rat model for both single and daily doses of the drug [49]. Isavuconazole has many advantages over other anti-fungal medications including both oral and intravenous formulation, broad spectrum activity, predictable pharmacokinetics and lesser side effects when compared to other triazoles. In 2015, the Food and Drug Administration (FDA)approved the use of Isavuconazole for invasive mucormycosis based on the results of VITAL study [50]. The VITAL study was an open-label non-comparative study of Isavuconazole in adult patients with Invasive Aspergillosis and renal impairment or in patients with invasive fungal disease caused by other rare fungi [51]. The most reported side effects of Isavuconazole include nausea, vomiting and diarrhoea. As drug related hepatotoxicity can occur as a side effect of Isavuconazole, liver enzymes should be monitored during treatment [50].

Spreading of infection in eye (rhino-orbital-cerebral mucormycosis) may lead patients to undergo evisceration**,** a process in which the internal content of the eye is removed leaving the scleral shell and extraocular muscles intact. The surgical debridement of diseased necrotic cell mass is crucial for preventing further spreading and successful management of the disease [47].

Other important therapies may include local irrigation with Amphotericin B, administration of topical hydrogen peroxide, administration of GM-CSF, G-CSF, polyvalent immunoglobulin, and the combination of Ampotericin-B with flucytosine, rifampin or fluconazole [52]. Hyperbaric oxygen therapy aids neovascularization, promoting healing in poorly perfused acidotic and hypoxic but viable areas of tissue [47].

CONCLUSION

Mucormycosis has emerged as a challenge to India in the form of coronavirus associated disease. The present surge in the number of cases is due to COVID 19, which remain correlated with the impaired immune system of infected patient. Scientists and doctors believe mucormycosis, which has an overall mortality rate of 50%, may be being elicited using steroids and immuno-supressive medications that found to be a life-saving treatment for severe and crucially ill COVID-19 patients. Uncontrolled diabetes is the potent factor that not only increases the risk of severe COVID-19 but also endowed with conditions in which fungal infections like mucormycosis can

flourish. Early identification of the risk factors and the comorbidities is crucial to reverse the condition and reduce the mortality in infected patients. The underlying causes of impaired immunity, especially poorly managed diabetes and overzealous use of steroids must be addressed for timely management of this deadly disease.

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