Review Article

Black fungus an add on epidemic to Covid-19 Pandemic

Abstract

COVID-19 patients have lower immunosuppressive CD4+ T and CD8+ T cells and henceforth patients in intensive care units (ICU) need mechanical ventilation, henceforward they stay in hospitals. These patients have been exposed to advances in fungal co-infections. COVID-19 patients progress towards mucormycosis a black fungal infection that is deadly leading to loss of sight and hearing and eventually death. This article discusses the clinical manifestations, risk factors, and emphases on virulence traits and management of black fungus.

Keywords: Black fungus, Mucormycosis, COVID-19, Rhino-orbital Mucormycosis

Introduction

COVID-19 pandemic is an outbreak of coronavirus disease that was first acknowledged in December 2019. As the infection is asymptomatic and the severity of the disease leads to respiratory failure and death[1]. The most significant challenges increasing day by day is patient morbidity and mortality which is caused by secondary fungal or bacterial infections.[2] Candidiasis and pulmonary aspergillosis have been common fungal infections that were reported as superinfections in COVID-19 patients.[2-3] On the other hand, it has been presumed that the oral manifestations which have been reported in association with (COVID-19) have the primary pathway for infection, precisely the ones of fungal origin[1-3].

Mucormycosis or Zygomycosis, also entitled Phycomycosis, is an unusual, aggressive, invasive, speedily progressive, and life-threatening fungal infection. Triple strain coronavirus is considerably high on patients who are in need of ICU advancing them to suffer from mucormycosis. Hence fatality rate is estimated to be high[2]. The infection they cause, mucormycosis "black fungus," can infect the sinuses and bones of the face and invade the brain or cause patients to lose an eye[4]. Generally, patients reported problems to the physicians not only breathless, feverish yet had pain and pressure behind their cheekbones and around their eyes. The black fungus has painted the country red in the second wave[5].

The epidemic of mucormycosis is yet another of the unpleasant surprises produced by the COVID pandemic following MIS-C, a severe inflammatory syndrome that seems to mostly affect children, and “long COVID,” which is a complex of symptoms that continue to distress patients months after initial infection[6]. Mucormycosis is one of the violent fungal diseases that have attacked COVID patients, including a lethal yeast called “Candida Auris” and a spate of infections with Aspergillus fungi which is also known as CAPA (for COVID-associated pulmonary aspergillosis)[7]. Mucormycosis has been a center of attention all around the globe. But there seems to the difference in species and effects on the human body differing from a developed country and developing nations. [8]In developed nations this disease is less common and seen only in patients with hematological malignancies (HM). The developing countries paint a different picture, it is common in patients with uncontrolled diabetes mellitus or trauma. In India, mucormycosis is seen in 14 out of 100000 patients. In Europe and US, it is seen in 0.01 per 100000 population[6-7].

As the maxillofacial region consists of rich vascularity due to its anatomy, therefore it is more prone to opportunistic infections.[9] Mucormycosis has the potential for virulence to escape the defense mechanism.[10] The attributable risk factors comprise uncontrolled diabetes mellitus, long-term steroid therapy, Acquired Immune Deficiency Syndrome (AIDS), haematological conditions like leukemia and lymphomas, renal failure.[11] In the body the mucromycosis infection can easily invade the body through the nose, breached skin surface, and tooth extraction sockets. Primary infection spots include the skin, ears, gastrointestinal tract, and there could be disseminated forms involving multiple locations like pulmonary and rhino -orbito-cerebral.[10] Contingent on the site of infection and underlying inclining factors, mortality rates may vary from 10% to 100% [12]. Here, we review the black fungus regarding mucormycosis in immunocompromised patients and use the evidence to provide recommendations and management for black fungus treatment.

Search Strategy

Electronic databases were explored (PubMed, Embase, Scopus, Dentistry and Oral Science Source, and Google Scholar) to maximize the identification of relevant primary studies published over the last 1 year (September 2020 – July 2021). During the initial search, the following MeSH and keywords were employed: “Mucormycosis”, “Rhino-orbital mucormycosis” and

"Black fungus" is written in the English language.

Data collection process:

The necessary available information was extracted from each initially included article, through different case reports.

Microbiology

Mucormycosis is caused by fungi that belong to the order Mucorales. These ubiquitous fungi reside in the soil and organic debris. They cultivate rapidly and sporulate quickly and abundantly. The only term mucormycosis arise from the “Mucoraceae” family of the Mucorales order, which is substituted commonly from the term zygomycosis which is the prime suspect for the mucormycosis infection in human. Rhizopus arrhizus species is frequently encountered, but some other mucor species also include are Lichtheimia species (formerly known as Absidia species), and Cunninghamella species [13].

Virulence traits

Mucoromycotina is able to grow at 37^0 C known as a thermotolerant but some of them proliferate even at higher temperatures. However, in 2012 Schwartze et al [14] concluded the different virulence potential but there is no association has been observed among the growth speed at host temperature.

The second, virulence factor is iron acquisition, which acts as a vital role for development and fungal cell growth, as it has three general mechanisms for the uptake of iron and which has been identified in fungi. It encompasses the reduction of iron uptake, siderophore-sequestered iron uptake which has been facilitated by the siderophorepermease, and acquiring iron from haem in the uptake system[15].

Fungal isolates such as Rhizopus and Lichtheimia corymbifera along with Mucor species were found in children in some cases[16]. Keeping the factors of Hematological malignancies, organ transplant, surgery, diabetes mellitus, and underlying various medical conditions. The fungus targets

compromised medical conditions and attacks lungs, skin, soft tissues, sino orbital, and rhino cerebral region. The mortality rate for such cases was more than 60%. In Children, it was 15% with certain infections [13-14].

Recently, another factor has been identified i.e; glucose-regulated protein 78 (GRP78) which enables the invasion of the pathogen through the endocytotic mechanism. One more aspect contributing to the virulence of a pathogen is its ability to evade recognition and elimination by the host immune system[17].

Epidemiology

As a group, Mucoraceae represent the third most common cause of invasive fungal infection after Candida and Aspergillus species [18]. As the increasing incidence of mucormycosis has been recommended by epidemiologic studies[19]. Numerous factors contribute to the increase in, incidences including antifungal prophylaxis by agents without Mucor mycosis activity[1].

The pandemic has rapidly spread to 212 countries and caused nearly 5 million laboratory-confirmed cases and more than 310,000 deaths globally.[20]

COVID-19 patients always have immunosuppression with a decrease in CD4 +T and CD8 +T cells.[3] Critically ill patients admitted to the intensive care unit (ICU) with more extended stays were more likely to develop fungal co-infections.[4] It is crucial to notice that COVID- 19 patients can develop fungal infections.[18-19]

Risk Factors

Immune dysfunction or immunodeficiency is a primary risk factor for invasive diseases. The primary immunodeficiency form is not characteristically accompanied by mucormycosis infection[20]. The substantial risk factor is associated with the hematologic malignancy, as the presence of hematopoietic stem cell transplant or solid organ transplant recipient. Solid-organ malignancy (without transplant) is not commonly associated with mucormycosis [21].

Diabetes also is a commonly identified risk factor, with 9% to 36% of cases occurring in diabetics [7–9]. In human monocytes, elevated glucose levels directly increase SARS-CoV-2 replication, and glycolysis sustains SARS-CoV-2 replication via the production of mitochondrial reactive oxygen species and activation of hypoxia-inducible factor 1α20. Therefore, hyperglycemia might support viral proliferation. In concurrence with this assumption, hyperglycemia or a history of T1DM and T2DM were found to be independent predictors of morbidity and mortality in patients with SARS [21]. Furthermore, comorbid T2DM in mice infected with MERS-CoV resulted in a dysregulated immune response, leading to severe and extensive lung pathology [22]. Patients with diabetes mellitus typically fall into higher categories of SARS-CoV-2 infection severity than those without [23,24], and poor glycaemic control predicts an increased need for medications and hospitalizations, and increased mortality [18,25]

Pathogenesis

These organisms are spread by air-borne asexual spores and invade into the tissues in reduced host defenses via the respiratory tract, wounded skin, or via transcutaneous route[25]. Due to its high affinity towards the plasma, these fungal hyphae enter the arterial blood vessels of the internal elastic lamina and resulting in thromboembolism and causing ensuing thrombotic infarction[26]. In the blood vessels, they proliferate mainly in the lungs, paranasal sinuses and it leads to the infarction & necrosis of the blocked vessels towards the distal end of the tissue[21,22]. In medically compromised patients like in diabetic patients the free iron level increases which enhance the growth of these organisms[17].

Clinical Manifestations

This disease habitually presents with signs of acute sinusitis, fever, nasal congestion, purulent nasal discharge, and headache. Sinuses involvement with contiguous spread to adjacent structures such as the palate, orbit, brain results in clinical symptoms[27]. The disease spreads from the ethmoid sinus to the frontal lobe results in obtundation. Clinical suspicion and initial treatment with surgical debridement are vital in averting the morbidity of this often-fatal condition. [28]The clinical hallmark of mucormycosis is vascular invasion resulting in thrombosis and tissue infarction/necrosis. The most common clinical presentation of mucormycosis is a rhino- orbital cerebral infection. [20-28]It is believed to be secondary to inhalation of spores into the paranasal sinuses of a susceptible host. Predisposing mucormycosis factors are diabetes, systemic corticosteroid use, neutropenia, hematologic malignancies, stem cell transplant, and immunocompromised individuals.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection resulting in tissue hypoxia, which persuades interstitial lung damage and acute respiratory distress syndrome. [15-21]Patients with diabetes mellitus and coronavirus disease 2019 (COVID-19) exhibits dysregulation of glucose homeostasis, exacerbation of inflammation, and impairment in the function of the immune system. These conditions increase oxidative stress, cytokine production, and endothelial dysfunction leading to increased risk of thromboembolism[12] and damage to vital organs. All these factors contribute to the increased severity of COVID-19 and rapid progression to cardiorespiratory failure in patients with diabetes mellitus.

- The grown research evidence demonstrated that saprophytic zygomycetes are rarely seen in the tissue of immune-compromised patients. On the contrary, diabetes both type I and type II, tumor, and metabolic inflammation such as fungal infections these chronic diseases significantly enhance the depletion of immunity. The fungal infection caused by Rhizopus, mucor, and zygomycetes primarily enter into blood vessels and trigger thrombosis as one of the major hallmarks of chronic fungal infections. The thrombosis cases are more common in the paranasal sinus and lower respiratory tissue such as lungs causing an ischemic cascade along with self -induce tissue damage.

- Table 1: Summary of the COVID-19 associated mucormycosis (CAM) reported in the literature:

Author/country	Age in years/ sex	Comorbid illness	Clinical presentation	Organs involved by CAM	Treatment for COVID-19	Investigations	Management	Outcome
Hanley et al./ UK{33}	22/M	Hypothyroidism	COVID ARDS (mechanically ventilated) Pulmonary emboli	Lungs, Hilar lymph nodes	None mentioned	Lymphocyte count and serum creatinine, not provided	-	-
Werthman Ehrenreich / USA{34}	33/F	Hypertension, Asthma	Altered mentation, proptosis, and rhino-orbital mucormycosis	Rhino-orbitocerebral	Remdesivir, plasma therapy	Lymphopenia (5.9%) Elevated serum creatinine (2.28 mg/dL) Mri brain at -	1st- intravenous fluids, sodium bicarbonate insulin infusions. 2nd- Vancomycin ‘ piperacillin-tazobactam were administered Amphotericin B was added 3rd- MRI brain, remdesivir convalescent plasma.	26th day survival.
Mehta et al./ India{35}	60/M	Diabetes mellitus Peripheral vascular disease due to diabetes	COVID ARDS requiring mechanical ventilation	Rhino-orbital	Inj methylprednisolone 40 mg BD Dexamethasone 4 mg BD Tocilizumab 400 mg	Elevated serum creatinine (1.57 mg/dL)	1st- intravenous meropenem, oral oseltamivir, with intravenous methylprednisolone and dexamethasone. 2nd- shifted to non-invasive ventilation to maintain his oxygen saturation	6th day Survival

							3rd- received a single dose of injectable tocilizumab (400 mg) and was started on an oral combination of sitagliptin/metformin (50/500) twice daily and oral metformin (500 mg) thrice daily with subcutaneous insulin glargine (20 units) at night with regular insulin	
Monte junior ESD et al./Brazil{36}	86/M	Hypertension	COVID ARDS and diarrhea	Gastric (presentation with malena, drop in hemoglobin, and large ulcers identified on endoscopy)	Hydrocortisone	Lymphopenia (5.3%)	1st- treated with ceftriaxone, azithromycin, oseltamivir, and hydrocortisone, besides intensive care management including vasopressors and mechanical ventilation. 2nd- managed with three units of red blood cells and omeprazole. 3rd- Esophagogastroduodenoscopy (EGD) revealed two giant gastric ulcers. Antifungal agents were not	1-week survival

							administered.	
Placik et al./ USA{37}	49/M		COVID ARDS	Pulmonary mucormycosis with bronchopleural fistula and pneumothorax	Remdesivir Tocilizumab Dexamethasone	Lymphocyte count and serum creatinine, not provided	1st- empiric antibiotics with ceftriaxone and azithromycin, low-weight-molecular heparin therapy with enoxaparin, a steroid course with dexamethasone, and antiviral therapy with remdesivir. 2nd - started on a dose of tocilizumab, a humanized monoclonal antibody that suppresses the interleukin-6 receptor. 3rd- The patient was intubated for impending respiratory failure. 4th- Initial cultures were concerning for a fungal process with probable mucormycosis. The patient was started on amphotericin B.	37 days survival
Mekkonen et al./ USA{38}	60/M	Diabetes mellitus (HbA1C 14%) Asthma Hypertension	COVID ARDS (mechanically ventilated)	Rhino-orbital	Remdesivir Dexamethasone (6 mg) Plasma therapy	NA		

Pasero et al./Italy {39}	66/M	Hypertension	COVID ARDS (mechanically ventilated)	Lung Maxillary sinus thickening on computed tomography (not proven to be mucormycosis)	Hydroxychloroquine Lopinavir–ritonavir	Lymphopenia (400/lL) Renal failure requiring dialysis (creatinine not provided)	1st- A therapy with hydroxychloroquine and lopinavir-ritonavir was administered for the first 10 days. 2nd -	62 days survival

ARDS: acute respiratory distress syndrome; BMI–body mass index; COVID: coronavirus disease; E.coli: Escherichia coli; HbA1c: glycated hemoglobin, F: female, M: male.

Diagnosis

Mucormycosis in early diagnosis is critical which enables the early initiation of active antifungal therapy. The symptoms, signs, and radiographic manifestations of mucormycosis are nonspecific and a definitive diagnosis requires direct identification of the characteristic hyphae or the recovery of the organism in culture from specimens obtained from the site of infection. Specificity is also an issue because isolation from nonsterile sites is sometimes indicative of contamination rather than disease. The culture of a clinically relevant isolate enables identification and susceptibility testing of the pathogen[16].

- **Cytopathology**

The hyphae may be difficult to observe on an unenhanced Potassium hydroxide wet mount and may not stain well with conventional Gram stain. Use of chitin-binding stains, such as Calcofluor, Fungi-flour, or Blancoflour, may be used with a fluorescent microscope to identify hyphal elements on Potassium hydroxide wet mounts. [24]

- **Histopathology**

The culture still forms the basis of diagnosis in most cases, although molecular techniques are being used increasingly to complement traditional methods [17]. Molecular testing improves the accuracy of species identification compared to phenotypic identification of culture isolates [15]. Nucleic acid amplification techniques that target the ribosomal DNA gene targets 18S, 28S and Internal Transcribed Spacer (ITS) region are all used. The sensitivity and specificity of molecular diagnosis performed directly on fresh or frozen tissue depend on the DNA-extraction method used [15]. Fresh material is preferred over paraffin-embedded tissue because formalin damages DNA [16].

- **Radiography/ Imaging Techniques**

Computed tomography (CT) is useful in pre-operative procedures which defines the extent of the disease. Scan displays the edematous mucosa, fluid filling the sinuses, and destruction of the peri-

orbital tissue and bony margins, even though sinus CT is preferred in imaging modality, bony destruction is often existing in the course of the disease. Magnetic Resonance Imaging (MRI) is useful in identifying the intradural and intracranial extent of the disease, cavernous sinus thrombosis, or thrombosis of the cavernous portion of the internal carotid artery. Perineural spread of the disease can also be demonstrated with contrast-enhanced MRI scans. [26]

Treatment

A multimode approach is necessary to cure mucormycosis. Early dosage of anti-fungal agents, rapid correction of metabolic abnormalities are mandatory features. The global pandemic of COVID-19 has accelerated the race to find effective prevention and treatment for SARS-CoV-2 infection [27]. Currently, more than 1,800 clinical trials targeting viral entry and replication and immune responses to infection are ongoing; however, the efficacy of most drugs has not yet been proven (Clinical Trials. gov database of COVID-19 interventional studies). [28]Candidates for COVID-19 therapy can affect glucose metabolism pharmacologically or through the modulation of inflammation and the immune system.

Thrombosis of a blood vessel resulting in tissue necrosis during mucormycosis results in deprived penetration of antifungal agents to the site of infection. Therefore, the complete eradication of mucormycosis the debridement of necrotic tissues should be done[27]. Aggressive medical treatment with conventional antifungals and non–conventional therapeutics is the cornerstone for successful treatment[29]. Polyenes like Amphotericin-deoxycholates and lipid complex are primary therapeutic agents for mucormycosis. The dosage varies from 0.5-1.0mg/kg body weight once daily for not less than 4 weeks[37]. There should be close monitoring of serum electrolytes, as polyenes are known to cause a potassium imbalance. [29,30] Salvage therapy by Posaconazole or deferasirox is a reasonable option for patients' refractory to or intolerant to polyene therapy[31]. Non-conventional therapeutic agents like anti-diabetics, iron chelating agents, statins, granulocyte transfusions, cytokines, and hyperbaric oxygen have increased the survival rates to 94%. Prevention always remains a gold standard.[32]

Both medication and surgical management strategies are active in mucormycosis cases. Amphotericin B (liposomal) is the most frequently used drug in the management of mucormycosis. A combination of liposomal amphotericin B and Posaconazole management manifests the synergistic effects against fungal hyphae formation[28-32]. Neutropenic patients or individuals with graft-versus-host disease should be indorsed for oral Posaconazole medication as prophylactic management against mucormycosis[35], although mucormycosis cases in neutropenia or graft-versus-host disease patients managed by oral administration of fluconazole, while itraconazole and voriconazole are administered as prophylactic doses [39]

Conclusion

The COVID-19 is accompanied by a significant incidence of secondary infections, both bacterial and fungal, perhaps due to deterioration of immunity. The key fragment for the treatment of COVID-19 is the widespread use of steroids/monoclonal antibodies/broad-spectrum antibiotics which exacerbates the fungal diseases. The pre-existing factors give a perspective of invasive

secondary fungal infections in patients with COVID-19 infection. The early diagnosis and treatment of black fungus successively reduce the mortality and morbidity rates.

Data availability Not applicable.

Ethical Approval The article is a narrative review from an oral disease expert. Ethical approval is not applicable for this design of the manuscript.

Informed Consent The article is a narrative review from an oral disease expert. Informed consent is not applicable.

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