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Development of Opportunistic Fungal Infections During Recovery Phase Of COVID-19 Patients - A Narrative Review

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Abstract

Corona virus syndrome 2019 (COVID-19) spreads via direct or indirect transmission after coming in close contact with the infected person or infected animal. Throughout the course of COVID-19 widespread inflammatory action & in turn causes Immune suppression in Post-COVID-19 patients. Opportunistic fungal disease readily invades immune-compromised person. Cases secondary infection of fungal origin in COVID-19 recovered patients has been reported from various parts of the world. Mucormycosis, Aspergillosis, Candidiasis cases commonly reported in Post-COVID-19 patients. The aim of the literature review is to reveal development of opportunistic fungal infections during recovery phase of covid-19 patients, disease progression, prognosis, treatment options and preventive measures.

Introduction

Corona virus disease 2019 (COVID-19) is a recent disease entity produced by a positive strand RNA novel corona virus (SARS-CoV-2) that cause disease to human, and household and pet animals. First acknowledged in Republic of China's Wuhan city, Hubei Province on 31 December 2019 and subsequently caused a worldwide pandemic. (1)

The primary action of COVID-19 produces diffuse alveolar damage with severe inflammatory exudation. Immunosuppression with a decrease in CD4+ T and CD8+ T cells is also a common finding.

(2) Immunosuppresion susceptible individuals are Critically ill patients, especially the patients who were admitted to the intensive care unit (ICU) and required mechanical ventilation, or those who had prolonged hospital stays, sometimes as long as 50 days. These patients are more prone were for development of fungal co-infections. (3)

Co-infections with respiratory viruses (other than SARS-CoV-2), bacteria and fungi have been reported in COVID-19 patients were reported in recent literature and in COVID-19 cases, opportunistic infectious diseases were found to be one of the predictors of fatality. In severely ill individuals with COVID-19, secondary fungal infections caused by Aspergillus and Candida spp., are increasingly described in review literature from china and other countries worldwide. (4, 5) Few cases of fungus Mucorales which causes mucormycosis responsible for rhino-orbital-cerebral infection also been described in covid-19 patients.

The aim of the literature review is to reveal development of opportunistic fungal infections during recovery phase of covid-19 patients, disease progression, prognosis, treatment options and preventive measures.

Method

Literature search were made using PubMed and Google Scholar to analyze the reported cases of mucormycosis during Covid-19. Publications with relevant information based on their abstracts and, or full text are included in this article. Cases of Mucormycosis other than pandemic were excluded. Reports of cases with other fungal infections prior to the pandemic were excluded in the study.

Results

This narrative review discusses the relevant literature; reveal development of opportunistic fungal infections during recovery phase of covid-19 patients, disease progression, prognosis, treatment options and preventive measures. The search of review literature on the subject of opportunistic invasive fungal disease, mucormycosis, covid-19 done since December 2019 up to the current date.After performing a literature search using ProQuest, MEDLINE, and PUBMED, Google Scholar search engines. The search terms used were COVID-19, Corona virus, mucormycosis, “opportunistic infection”, “invasive fungal disease”, and “infection control and management”. After reading the article titles and abstracts, full text. Results included reports of cases of mucormycosis with orbital compartment syndrome, rhino orbital mucormycosis, gastrointestinal mucormycosis, pneumonia, and a middle cerebral artery infarct. 24 articles were included based on the quality of the studies.

Deepak Garg, Valliappan Muthu et.al, reported a 55-year-old man with history of fever, dry cough, and progressive breathlessness of three days duration. Case history taking revealed long-standing diabetes mellitus, hypertension, and ischemic cardiomyopathy, end-stage kidney disease. Cardiomegaly and widespread interstitial opacities were seen on a chest radiograph. A nasopharyngeal swab was positive for COVID-19 by RT–PCR. His treatment started with intravenous administration of dexamethasone & remdesivir along with Supportive care, including oxygen supplementation, thrombo prophylaxis for venous thrombosis, and maintenance hemodialysis, were continued. After two weeks of therapy, patient had clinical improvement, hypoxemia improved, and

radiological resolution. Later in third week patient complained of cough, expectoration, and burning micturition, which was diagnosed as Urinary *Escherichia coli* infection & pulmonary *Rhizopus microspores* based upon culture examination and computed tomography (CT) of the thorax. The patient received 5 g of liposomal amphotericin B and was discharged after 54 days from the hospital. (6)

Kazem Ahmadikia, Seyed Jamal Hashemi et.al, reported a 44-year- Old woman with a history of poorly controlled diabetes with a history of fever since 5-day, malaise, myalgia, dry cough and partial dyspnoea. Physical examination revealed a patient with mild breathlessness and nasal flaring. RT-PCR of upper airways swab specimens tested positive for influenza and negative for COVID-19. Computed tomography (CT) thorax demonstrated bilateral multifocal peripherally located patchy ground-glass opacities. Therefore, a diagnosis of acute pneumonia on basis of poorly controlled DM was made. Patient was treated using intravenous dexamethasone therapy & discharged after 4 days after her symptoms subsided.

3 weeks after her discharge, the patient developed toothache and headache, which was followed by earache, nasal congestion and unilateral facial swelling. She visited dental clinic & received symptomatic treatment but condition does not improved which made suspicion about mucormycosis. . The patient received IV liposomal amphotericin B & functional endoscopic sinus surgery (FESS) revealed sinusitis with some partial necrosis in the right maxillary sinus. Computed tomography (CT) of paranasal sinuses acknowledged the evidence of mucosal thickening in the right maxillary sinus. Direct and histopathological examinations showed non-septate, ribbon-like, wide hyphae with right-angle branching, suggestive of mucormycosis. liposomal amphotericin B was continued for 2 weeks & discharged after 18 days from the hospital.(7)

Amanda Werthman-Ehrenreich reported a 33-year-old female patient with known history of hypertension and asthma who showed signs of left-sided ptosis and proptosis with altered sensorium. 2 days prior to presentation patient began with symptoms of vomiting, cough, and shortness of breath. Computed tomography (CT) of face showed moderate bilateral maxillary sinus mucosal thickening as well as ethmoid sinus mucosal thickening, and mucosal opacification of the ostiomeatal units. Sinus cultures were positive Staphylococcus aureus, as well as widespread fungal elements, including hyphae, yeast, suggesting mucormycosis. The patient received IV Vancomycin and piperacillin-tazobactam later liposomal amphotericin B was added for mucormycosis. The patient expired on day 26 of her hospitalization.

The author concluded that early identification of fungal co-infections might significantly reduce morbidity and mortality. (8)

Salil Mehta, Abha Pandey reported a 60-year-old male patient with known history of diabetis who presented with symptoms of a history of severe breathlessness, fever, tachypnea, and generalized malaise since three-days prior to hospitalization. Upon physical examination revealed bilateral crept's at the lung bases. A non-healing ulcer consistent with the diabetic peripheral vascular disease was seen on his right foot. Nasopharyngeal swab was positive & later confirmed by CT scan thorax. Computed tomography (CT) thorax revealed multiple patchy ground-glass opacities in both lungs involving upper lobes, the right

middle lobe, and the lingual suggesting invasive fungal infection, probably mucormycosis. The treatment started intravenous antifungal therapy but the condition gets worsen later requiring non-invasive ventilation to maintain his oxygen saturation. Prognosis becomes poor and expired on day 6 of his hospitalization. (9)

Juergen Prattesa, Thomas Valentina reported 70-year-old male patient with known history of hypertension, diabetes with end-organ damage along with coronary heart disease and obesity. The patient also presented chronic obstructive pulmonary disease (COPD) & obstructive sleep apnea syndrome. A nasopharyngeal swab was positive for COVID-19 by RT–PCR. The patient reported productive cough, dyspnea and intermittent fever (> 38.5 °C) for one week upon case history was taken. Whilst breathing atmospheric air, the arterial pO2 was 67 mmHg. Chest examination using X-ray showed bilateral basal coarse reticular opacities. Patient was advised for hospitalization, but he refused the advice & was discharged with Cap. Doxy 200 mg four times/day. The patient returned one week later, with medical emergency due to department because of hypoxemia SpO^2 46 mmHg without any oxygen support & worsened clinical status. Computed tomography (CT) thorax demonstrated bilateral multifocal peripherally located patchy ground-glass opacities. CRP & interleukin-6 level were significantly increased. He was administered in ICU. Patient received intravenous meropenem 1 g twice/day along with azithromycin 500mg once for four consecutive day, and hydroxychloroquine 200mg twice/day. Pulmonary status was greatly deteriorated on 2nd day of ICU, thus endotracheal aspiration was acquired & sent for histopathological examination. Specimen cultured revealed *Aspergillus fumigates* growth & diagnosis of putative invasive pulmonary aspergillosis was made upon investigations. Intravenous Anti-fungal therapy using voriconazole was initiated on 4th day of ICU stay. Despite all the treatment given to the patient died 3 days after commencement of antifungal treatment due to multi organ failure. (10)

Daniela Pasero, Silvana Sanna reported 66-year-old male patient with a history of hypertension. He was diagnosed with COVID-19 after tested positive for RT-PCR of upper airways swab specimens. He was administered in ICU. Significantly deteriorated pulmonary status was reported patient was intubated after a short period of non-invasive respiratory support. . His treatment started with intravenous administration of lopinavir-ritonavir & hydroxychloroquine along with underwent protective mechanical ventilation & heavy sedation for the first 10 days. He was also had multiple organ dysfunction syndrome with sequential organ failure. The patient received IV piperacillin-tazobactam and levofloxacin later meropenam and and linezolid 600 mg twice/day was added. Surgical tracheostomy was done two weeks after ICU admission. Bronchial aspirate (BAS) showed growth of *Rhizopus* spp. Treatment started with IV liposomal Amphotericin B. *Candida glabrata* growth was revealed upon sample collected from maxillary sinus. Based upon available information provisional diagnosis of pulmonary mucormycosis was made. (11)

Antifungal treatment with liposomal Amphotericin B was replaced with Isavuconazole treatment. Despite all the treatment given to the patient died 62 days after ICU admission due to refractory shock and liver failure.

Anubhav Kanwar, Alex Jordan reported 56-year-old male patient with known history of end-stage renal disease. A nasopharyngeal swab was positive for COVID-19 by RT–PCR. He was hospitalized after complaints of fatigue and shortness of breath. The treatment started with methyl prednisone therapy for five-days and a single dose of tocilizumab, and one unit of convalescent plasma transfusion was done. He was then discharged after negative blood culture. He was re-hospitalized after worsening of pulmonary status. He was started on empiric intravenous (IV) vancomycin and piperacillin-tazobactam. Sputum culture showed fungal hyphae growth. Sputum and pleural fluid culture were repeated showed *Rhizopus azygosporus* growth. Antibacterial medications were later replaced by Anti fungal therapy using liposomal amphotericin B (5mg/kg) was started. However the status of the patient worsened as time progresses repeated blood culture showed Enterococcus spp. and Bacteroides fragilis which were found resistant to vancomycin. piperacillin-tazobactam were re instated after blood culture reports. On the very next day i.e. 17th day after hospitalization, the patient developed cardiac arrest and died. (12)

Marina Saldanha, Rashmitha Reddy, Mark Jittu Vincent reported a 32 year old female patient with known history of uncontrolled diabetes since 6 months. Rapid antigen test was performed for COVID-19 showed positive status. Case history examination revealed complete ptosis left eye along with facial pain on since 5 days. Nasal endoscopy was advised & revealed pus formation in the left middle meatal region along with deviated nasal septum. Computed tomography (CT) of nose and Paranasal sinus revealed near total opacification of the left ethmoid, maxillary and frontal sinus indicative of sinusitis due to fungal infection. MRI of Brain advised and revealed peripherally enhancing subperiosteal lesion in the superomedial extraconal portion of the left orbit which was indicative of subperiosteal abscess with optic neuritis secondary to sinusitis. The treatment plan for the patient includes endoscopic surgery with or without debridement on emergency basis. Samples obtained during endoscopic surgery were later sent for histopathological assessment and KOH mount which gave mucormycosis as a final diagnosis. The patient received Anti Fungal treatment using liposomal Amphotericin B, the treatment was discontinued because of financial constraint. 2 month follow up was done which revealed resolution in facial pain & ptosis but no improvement in vision. (13)

Mrittika Sen, Sumeet Lahane, Tatyarao P Lahane reported 46-year-old male patient with known history of diabetes mellitus. . A nasopharyngeal swab was positive for COVID-19 by RT–PCR. He was hospitalized after complaints of fatigue and shortness of breath additionally he complained initial symptoms of pain, redness, and periocular swelling. Later on drooping of eyelids, limitation of ocular movements, pain and loss of vision. MRI of Brain advised and revealed involvement right cavernous sinus & frontoparietal lobe. The treatment plan for the patient includes fiber endoscopic sinus surgery with sinus debridement on emergency basis. Samples obtained during endoscopic surgery were later sent for histopathological assessment suggestive of Mucormycosis & aspergillus as the infective fungus on microbiology culture. was found. The patient received Anti Fungal treatment using Oral posaconazole initially & later the patient was treated with IV liposomal amphotericin B with voriconazole. One week of

intraorbital irrigation using amphotericin B were performed. Postoperatively patient developed a sino-cutaneous fistula through the exenteration wound. Patient was alive and stable upon with regular follow up but loss of vision was present. (14)

Discussion

Severe viral pneumonia such as influenza, SARS-COV, COVID-19 etc. commonly progress to complication known as acute respiratory distress syndrome. This complication requires critical care including ventilator support, use of corticosteroids and other adjuvant therapies to arrest the upcoming massive airways inflammation. The drawbacks of steroid therapy for the treatment of viral pneumonia, appears to be secondary bacterial and invasive fungal infections (IFIs) which influence the morbidity and mortality of patients. (7)

Mucormycosis is an infrequent opportunistic fungal infection exemplified by host tissue infarction and necrosis produced due to vascular invasion by the fungal hyphae. Mucormycosis is a fungal urgency with a high predilection for contiguous spread and a catastrophic outcome if not diagnosed and treated early. (7, 8)

Mucormycosis invading the sinuses is a form of life-threatening invasive fungal sinusitis that typically affects immunocompromised persons with a weakened neutrophilic response. Patients can include those with uncontrolled diabetes mellitus, acquired immunodeficiency syndrome, neutropenia; especially with renal insufficiency, iatrogenic immunosuppression and haematological malignancies, and those who have undergone organ transplantation, extremes of age, broad-spectrum antibiotics, iron overload, skin trauma, intravenous drug abuse, prophylactic voriconazole for aspergillosis and malnutrition. (15, 16)

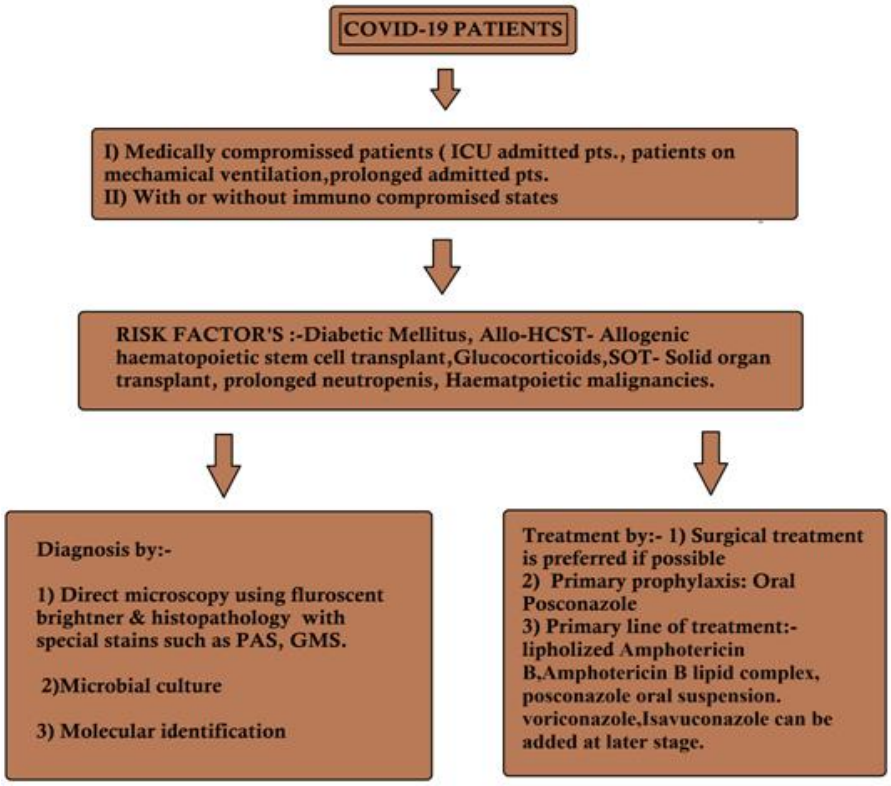

Figure 1: Guideline for diagnosis and treatment of mucormycosis in patients with COVID-19. (14)

Invasive Mucormycosis

Paltauf a pathologist from Germany gave the first scientific description of Mucormycosis in 1885 and termed as Mycosis Mucorina. Cases of Mucormycosis were increased during 1980s and 1990s among individual with immuno compromised status as per the observations. (17) The incidence of Mucormycosis varies from 0.005 to 1.7 per 100,000 populations and the global case fatality rate is as high as 46%. Prevalence of mucormycosis in Europe and the United States of America varies from 0.01 to 0.2 per 100,000 populations. Prevalence rate of mucormycosis in France reported shows amplification by 7.4% per year. In India Prevalence rate of mucormycosis reported was14 per 100,000 populations. Variation in the prevalence rate of mucormycosis can be possible due to seasonal occurrences throughout the world. Mucormycosis shows varied etiology throughout the world in developed countries, it was mostly seen in patients suffering from hematological malignancies (HM), whereas in developing countries like India, it was commonly seen in patients with uncontrolled diabetes mellitus (DM) or trauma.(18,19)

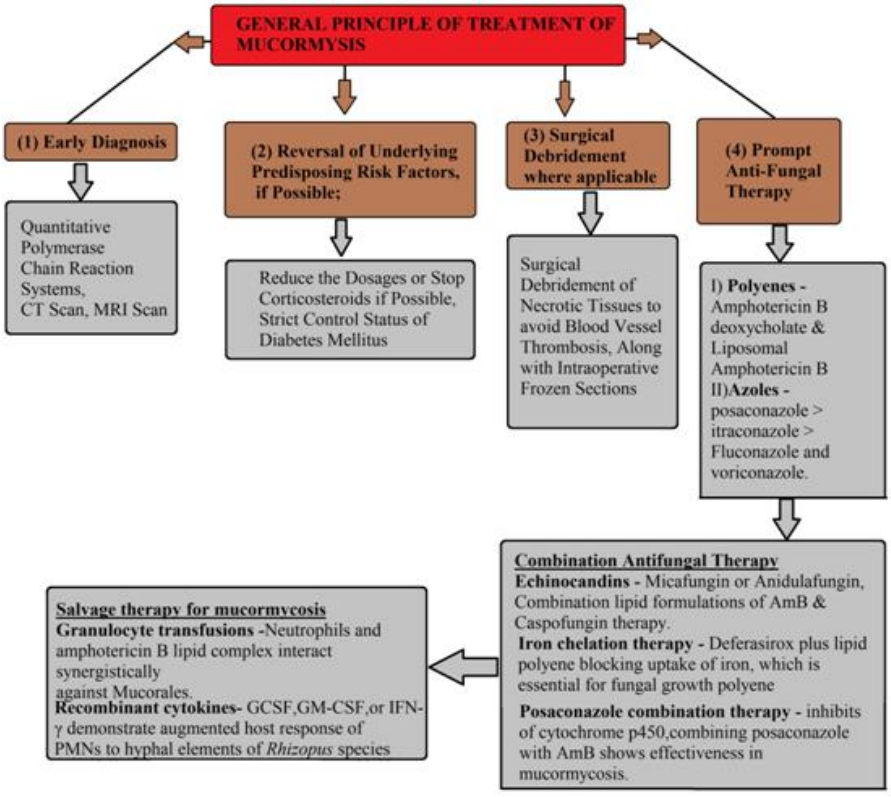

Figure 2: General Principle of Treatment of Mucormycosis.(16)

In immunocompromised patients, the main route of Mucormycosis infection seems to be due to inhalation of sporangiospores brings about pulmonary infection. Mucormycosis infection is usually presents with signs of acute sinusitis, nasal congestion, purulent nasal discharge, and headache. Prolonged fever is seen in the majority of the patients, even though some patients may be asymptomatic. Sinuses involvement

with contiguous spread to adjacent structures such as the palate, orbit, and brain results in clinical symptoms. It can spread from the ethmoid sinus to the frontal lobe results in obtundation.(20, 21)

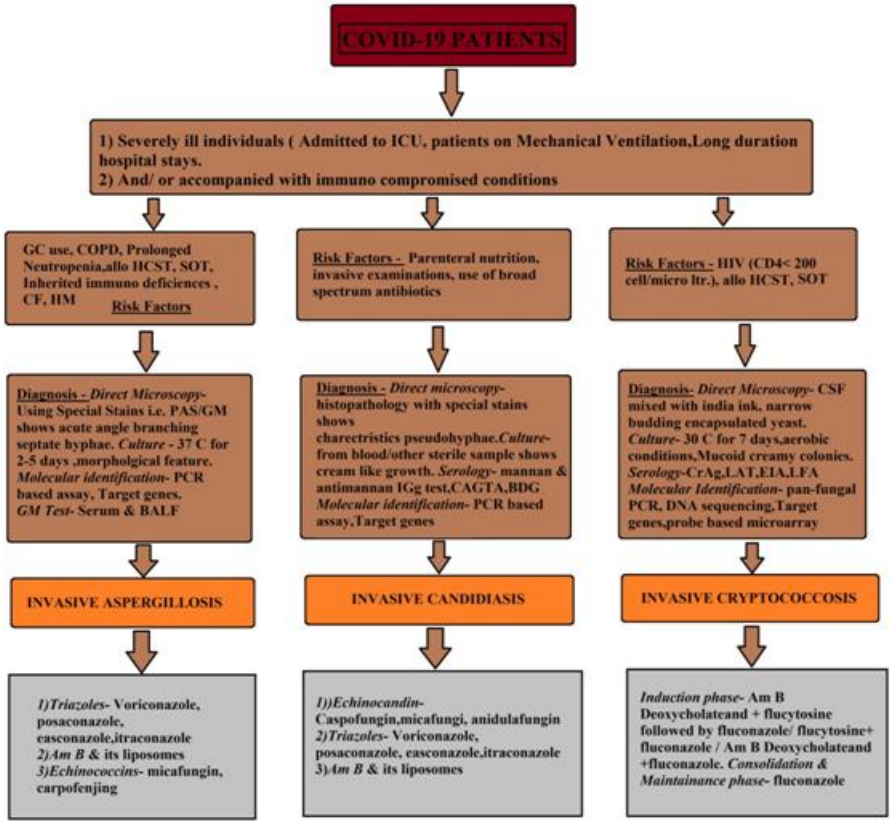

Figure 3. Diagnostic and therapeutic pathway for invasive fungal co-infection (18)

One of most common forms of mucormycosis in immunocompetent patients are cutaneous and soft-tissue mucormycosis. the lungs, are the second most frequently affected manifestation (58%) with a mortality rate up to 80% owing to its violent clinical course.(11, 21)

Rhino-orbital- cerebral infection is the most characteristic presentation of mucormycosis where there is an invasion of the fungal infection from paranasal sinuses to orbit and brain. Rhino-orbito-cerebral mucormycosis classically progresses in patients with uncontrolled diabetes (approximately 70%) as such patients seldom grow lung infection. the majority of them have diabetic ketoacidosis at the time of presentation. In a recent pan Indian multi-center case study on Mucormycosis revealed 57% of patients had uncontrolled diabetes mellitus and 18% had diabetic ketoacidosis. Mucormycosis may take a invasive course of disease. It may develop into a rare manifestation known as Orbital apex syndrome. The Orbital apex syndrome condition is frequently fatal, which progresses to complete ophthalmoplegia with rapid vision loss, involving II, III, IV, V, and VI cranial nerves. (22, 23, 25)

Rhino-cerebral disease or Rhino-orbital-cerebral infection has a survival rate of approximately

75% in patients without any systemic diseases; with other diseases survival rate becomes approximately 50%.; and in cases with pulmonary disease it is believed to be fatal and life threatening. Symptoms of rhino-orbital mucormycosis may arise as late as 30–42 days after the diagnosis of COVID-19. Delays of even six days in commencing treatment double the 30-day mortality from 35% to 66%. (14, 24)

Orbital compartment syndrome (OCS) consequences starting an expansile process within the closed compartment of the orbit leading to amplified orbital pressure. This may result in ischemia and vision loss. This requires emergency procedures that necessitate lateral canthotomy and inferior cantholysis to decompress the orbit. Delaying the treatment can cause permanent blindness. Orbital compartment syndrome trigger can be retrobulbar hemorrhage, cellulitis, orbital malignancy, or previous orbital surgery. (26)

Invasive Aspergillosis (IA)

In COVID-19 patient's development of life-threatening infection can be caused by Aspergillus species mainly *Aspergillus fumigates*. These are everywhere in the surroundings and cause a wide range of infections in humans, including invasive pulmonary aspergillosis (IPA), chronic pulmonary aspergillosis (CAPA), allergic bronchopulmonary aspergillosis (ABPA), chronic rhinosinusitis, fungal asthma, and aspergillus bronchitis. .(18,27) Several review literature of Chinese origin describes high rates of Aspergillus infections among COVID-19 patients. Prevalence rate of Aspergillus infections among COVID-19 patients ranges from 3.2–5% up to 23.3% from various studies by taking throat swab samples. An additional research from China reported that 27% of the COVID-19 patients developed fungal infections. (28, 29).

Incidences of invasive pulmonary aspergillosis in critically ill patients (e.g., patients on ICUs), rates vary substantially from 4% to as high as 35%.The diagnosis of IPA requires microbiologic and/or histopathologic evidence. By far, the most prevalent approaches have included aiming to extract Aspergillus spp. on culture media of bronchoalveolar fluid (BALF) and tracheal aspirate. While specimen gaining is demanding in numerous patients since lung biopsy may be contraindicated in patients with coagulation disorders or severe respiratory failure. Serologic biomarker testing using Galactomannan (GM) from BALF, tracheal aspirate, and serum specimens is also an alternate pathway in diagnosis of IPA. Galactomannan (GM) test from BALF was suggested as an early and precise marker using less invasive method for the diagnosis, particularly in neutropenic patients, with advantages of less injury and time-efficient.

Histopathologic examination mainly rely on finding special fungal stains on lung fluid or tissue when a fungal infection is suspected and may reveal the characteristic acute angle branching septate hyphae of *Aspergillus spp.*,and Grocott-Gomori's methenamine-silver stain (GM) and periodic acid-Schiff (PAS) stains of fixed tissue was helpful in diagnosis of IPA. Molecular techniques targeting ribosomal DNA (rDNA) sequences, particularly PCR-based tests, can also be utilized to detect *Aspergillus spp.* in tissues or BALF. and CYP51A resistance mutations in *A. fumigates*. One of most efficient diagnostic methods likely to be bronchoalveolar fluid (BALF) and tracheal aspirate culture, as well as traditional GM testing using BALF.

Still, bronchoscopy can potentially aerosolize virus [78] in patients with COVID-19 infection, thus posing a risk to patients and personnel from SARS-CoV-2 virus.(30-34)

Invasive Candidiasis (IC)

Species of yeast linked to the Candida genus, lives on various mucosal facades, such as the skin and the respiratory, digestive, and urinary tracts. The Candida genus comprising of *Candida Auris, Candida albicans, Candida glabrata, Candida parapsilosis, Candida tropicalis,* and *Candida krusei* which are the majority of ubiquitous fungal species. (35)

The high risk factors for Candida species infection in COVID-19 patients includes those treated with broad-spectrum antibacterial drugs, parenteral nutrition and invasive examinations, or the patients be associated with prolonged neutropenia and other immune impairment factors. A fungal infection frequently seen during COVID-19 is *Candida Auris.* The fungal infection caused by *Candida Auris* is particularly alarming as I) it is multi-drug resistant II) enormously difficult to recognize with standard laboratory methods and III) has capacity of causing numerous outbreaks in healthcare settings IV) increased risk poor outcomes in COVID-19 patients revealed by various studies. (36-37)

Among the intensive care unit (ICU) acquired infections, Candida genus is the most repeatedly recovered pathogen in, affecting between 6% and 10% of patients, and some studies have noted an increasing trend for candidemia. The anticipated mortality credited to invasive candidiasis is 19–40% which is even deadlier among ICU patients, reaching roughly 70%. (38-40)

A study by Amir A, Agostinho C, Frank L et. al. demonstrated that mortality amid patients with COVID-19 and *C. auris* candidemia was of 83.3% even with the use of appropriate antifungal therapy due to development of resistant to amphotericin B.(39)

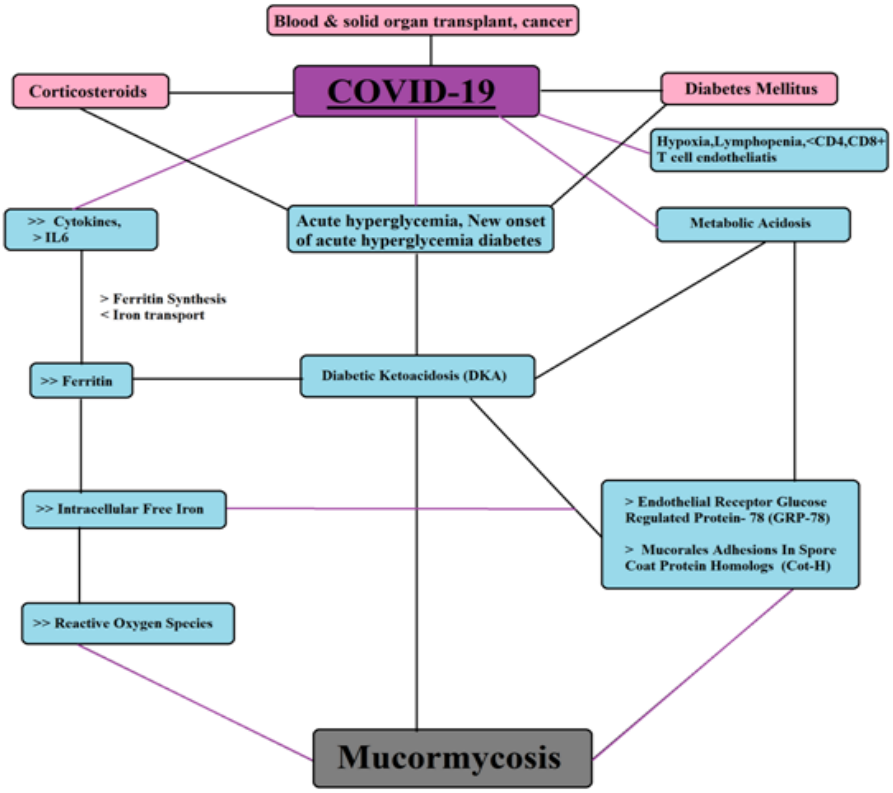

Figure 4. Hypothesizing relations of diabetes, corticosteroid, blood & organ transplant, cancer and COVID-19 with mucormycosis.

As per to current studies featuring invasive yeast infections amid gravely sick COVID-19 patients, *Candida albicans* (44.1%) was revealed to be the mainly prevalent yeast species, followed by *Candida auris* (23.2%); *Candida glabrata*, *Candida parapsilosis*, *Candida tropicalis*, and *S. cerevisiae* (4.6% each); and *Candida krusei* and *Rhodotorula spp*. (2.3% each). (37, 42) Amid Indian population, *Candida auris* was the mainly widespread Candida species found in the various study, whereas *Candida albicans* was widespread in the studies from rest of the world. Where antifungal vulnerability testing was executed, the resistance patterns varied depending on the species. for example, resistance to fluconazole, multiple azoles (fluconazole and voriconazole), and multidrug (fluconazole and AMB) was distinguished for 100%, 30%, and 40% of the *Candida auris* isolates, correspondingly, and only one *Candida glabrata* isolate was echinocandin-resistant.(37, 43)

Risk factors for the Invasive Candidiasis encompasses primarily Diabetes mellitus, renal failure necessitates hemodialysis, abdominal surgery, triple lumen catheters, parenteral nutrition, receipt of multiple antibiotics, length of ICU stay >7 days, and preceding abdominal infections. Moreover, indwelling central venous catheters are extensively utilized amid COVID-19 patients inhabiting in ICUs. (42, 44)

Diagnosis of invasive candidiasis (IC) can be made either using culture methods or using non culture methods. Culture methods comprise of blood culture or

other Samples collected under sterile conditions & it is typically believed as gold standards for IC but around 50% of the invasive candidiasis is not recognized by blood culture. Non culture diagnostic tests including mannan and antimannan IgG tests, C. albicans germ tube antibody (CAGTA), Beta-D-Glucan (BDG), T2 Candida panel combines ITS2 region amplification and T2 magnetic resonance, and thus directly detect Candida spp. in EDTA blood samples within 5 hours & PCR-based assays, are suggested to get better the diagnosis & are now emerging in clinical practice as optional extra to the cultures. While BDG function as pan fungal marker hence positive result does not always indicates invasive candidiasis. The sensitivity and specificity of Beta-D-Glucan (BDG) in diagnosis of invasive candidiasis is approximately 80%. Enzyme-linked immunosorbent assay (ELISA) can diagnose invasive candidiasis based upon detection of Candida mannan antigen. The ELISA kits are accessible commercially and are linked with high specificity and sensitivity. In a latest meta-analysis study, blood PCR was linked with a shared sensitivity and specificity for established or likely invasive candidiasis vs. at-risk controls of 95% and 92%, correspondingly. (45-48)

Treatment

Rapid accurate diagnosis, administration of drugs, accessory application of hyperbaric oxygen, recombinant cytokines or administration of granulocyte, surgical debridement, and prosthetic rehabilitation using obturator are the techniques implicated in triumphant management for mucormycosis.

The management of invasive candidiasis patients is same for both COVID-19 & non-COVID-19 patients. Echinocandins are the first drug of choice for treatment of invasive Candida infections, whereas fluconazole, liposomal amphotericin B, voriconazole, posaconazole and isavuconazole are the second drug of choice & alternative to Echinocandins.

The management of invasive pulmonary aspergillosis (IPA) involves use of voriconazole as the first-line treatment. Isavuconazole and liposomal amphotericin B is the second drug of choice & primary alternative options for treatment of IPA in the ICU. Itraconazole could be an alternate anti fungal drug for treatment of COVID-19-related IPA. (34, 49-51)

Polyene Antibiotics

Their heavily double-bonded structure gives them the term *polyene*. Amphotericin B (AMB) is a broad-spectrum antifungal antibiotic. It is effective against *Cryptococcus, Coccidioides, Candida, Aspergillus, Blastomyces, Histoplasma, Sporothrix,* fungi causing mucormycosis, etc. Polyenes have a strong affinity for ergosterol, which is found in the fungal cell membrane, and they bind with it. The polyenes are introduced into the membrane, and several molecules position themself in such a way that they create a'micropore,' causing intracellular components to diffuse & cause death of the fungi (fungicidal). (50,52-53)

For the treatment of mucormycosis, Amphotericin B deoxycholate (AmB) remains the solitary approved antifungal agent. It is also available in lipid formulations (LFABs). Liposomal amphotericin B effectively cured mucormycosis with various organ involvement patterns as per several case series, present in the review literature. The daily dosage varied from 1 mg/kg to 10 mg/kg each day. Rising doses to the recipients found to have higher response rates. The recommended dose for liposomal amphotericin B (AmB) is 5 mg/kg/day in the absence of CNS involvement.

Nephrotoxicity is the most important side effect of Amphotericin B deoxycholate (AmB). It occurs fairly

uniformly and is dose related: manifestations are—azotaemia, reduced G.F.R., acidosis, hypokalaemia and inability to concentrate urine. Liposomal amphotericin B (LFABs) hence are more preferred as it is considerably less nephrotoxic and can be unharmed dispensed at higher doses for a longer period of time than AmB. In kidney transplant recipients, Amphotericin B lipid complex can be unharmed dispensed at the rate of 10 mg/kg per day. (50, 54-56)

Azoles

Azole antifungals are largely separated into imidazoles and triazoles. They hinder the fungal cytochrome P450 enzyme lanosterol 14-demethylase and thus mess up ergosterol synthesis directing towards a cascade of membrane abnormalities in the fungus.

Fluconazole and voriconazole do not have consistent action against the agents of mucormycosis, hence Isavuconazole is suggested with reasonable strength for the first-line treatment of mucormycosis. Isavuconazole IV @ 3 × 200 mg for day 1–2, followed by 1 × 200 mg per day from day 3. In salvage therapy, Isavuconazole is used since it is successful in clinical scenarios, refractory disease, and intolerance or toxicity. Isavuconazole is still only approved for the rescue treatment of mucormycosis throughout Europe. In first line treatment the use of posaconazole oral suspension, and posaconazole delayed release tablets and infusion is well recommended. posaconazole has reported 90% minimum inhibitory concentrations (MIC90) of 1 to ≥ 4 μg/mL ,hence it can stated that it has enhanced in vitro activity against the Mucorales. The itraconazole activity is primarily limited to *Absidia* species. The recommended dose for Posaconazole is at a dosage of 400 mg orally twice daily. Posaconazole IV @ 2 × 300 mg from first day, followed by 1 × 300 mg per day from day 2. Posaconazole monotherapy cannot be suggested as primary treatment of mucormycosis because it is statistically less important than Amphotericin B deoxycholate (AmB). posaconazole is however a rational alternative for patients with mucormycosis who are noncompliant or intolerant of polyenes.(57-59)

Echinocandins

Caspofungin **A**cetate is a semi synthetic antifungal agent successful against ***C****andida* and *Aspergillus* when the patient is not responding to or intolerant to other antifungal agents. The mechanism of action of echinocandins is through prolonged / enhanced exposure of β-glucan on the fungal surface, which results in immune stimulation, & cause death of the fungi in mucormycosis.

Mono therapy or placebo therapy using **C**aspofungin **A**cetate semi synthetic antifungal agent is not better therapy for mucormycosis. Combination caspofungin plus Liposomal amphotericin B complex (ABLC) therapy markedly improved survival, compared with Combination therapy with LAmB plus either micafungin or anidulafungin also improved outcome in neutropenic and DKA mice with disseminated mucormycosis. The recommended dose of caspofungin is up to 3 mg/kg/day. (27, 33, 60-61)

Iron Chelation Therapy

deferoxamine improves the release of iron to Mucorales which in turn cause growth of the fungi in mucormycosis thus, in in vivo animal studies animals infected with *R.oryzae* that are treated with iron or deferoxamine have markedly worse survival rate / prognosis. Deferoxamine iron chelation therapy predisposes to mucormycosis.

deferasirox, is FDA approved & commercially available oral iron chelator. It is employed for the treatment of iron overload amid patients with transfusion-dependent anemia. Deferasirox is proven as

fungicidal as per in vitro study in mucormycosis, with an MIC90 of 6.25 μg/mL. The recommended dose of deferasirox is @ 20 mg/kg/day for 14 days.

Gastrointestinal symptoms (e.g., nausea and diarrhea) are the most frequent side effects of deferasirox therapy. However, the primary toxicity of concern is renal. Elevations in creatinine occurred in up to one-third of patients in deferasirox clinical trials, but they were mild and reversible upon cessation of drug use. (60, 62-64)

Adjunctive Therapies

Pro inflammatory cytokines enhance the ability of granulocytes to damage the agents of mucormycosis although its role in the primary treatment of mucormycosis is not clear till now. Pro inflammatory cytokines includes recombinant interferon-γ, recombinant granulocyte colony-stimulating factor, and granulocyte macrophage colony stimulating factor. Various case reports & studies reveal successful treatment of mucormycosis when treated with adjunctive immune therapy, in conjunction with LFAB.

Adjunctive immune therapy such as granulocyte colony-stimulating factor–mobilized granulocyte transfusions have been progressively more used for refractory mycoses, comprising mucormycosis preferably in neutropenic patients with mucormycosis as a lifesaving treatment although the data is limited. If health care centers are equipped with the proper technical expertise and facilities hyperbaric oxygen therapy can be used as adjunctive therapy in order to create a more-oxygen enriched cell environment in along with introduction of cytokines at the same time with the antifungal therapy. The usefulness of hyperbaric oxygen therapy in mucormycosis & other fungal infections is based upon limited data available from review literature. (65-68)

Surgical Management

Throughout the course of mucormycosis Blood vessel thrombosis occur which results in tissue necrosis & can cause poor penetration of antifungal agents to the site of infection. Hence, surgical treatment with debridement of necrotic tissues becomes decisive for complete obliteration of mucormycosis. Surgical treatment considered in case of soft tissues, cerebral disseminated, localized pulmonary lesion and rhino-orbital-types and should be very aggressive. Excision must not only include the necrotic tissues but also the surrounding infected healthy-looking tissues by taking account of enormous spread potential of Mucorales hyphae into the adjacent environment. The surgery can be carrying out in cases of a single localized pulmonary lesion but seems unattainable in cases of disseminated mucormycosis or when the infection reaches inaccessible areas (vicinity of brain, lung parenchyma close to great vessels) exists. Reconstructive surgery will be used to correct disfigured body areas in cases with a successful outcome.

Surgical debridement using orbital exenteration is decided by the treating physician when there is loss of vision & course of the disease is restricted to the orbit without or least extension to the cavernous sinus. Orbital exenteration becomes an imperative treatment modality particularly in patients with extensive involvement along with necrotic orbital tissue. Surgical debridement (FESS and/or orbital exenteration) not only diminish the disease burden, permit better penetration of intravenous drugs, and restricts further spread of the disease but also allows intra operative diagnosis with distinguishing necrotic tissue and supply sample for histopathological and microbiological authentication. In a logistic regression model, surgery was established to be an independent variable for encouraging outcome amid patients with

mucormycosis. In addition, in multiple case series, patients who did not go through surgical debridement of mucormycosis had a far higher mortality rate than those patients who underwent surgery. These data support the concept that surgical debridement is obligatory to optimize recovery rates. (69-73)

Conclusion

Changes in the innate immunity, widespread use of steroids, monoclonal antibodies & broad-spectrum antibiotics, uncontrolled diabetes during COVID-19 disease cause development of opportunistic fungal infections of the airways including the sinuses and the lungs. COVID-19 causes alteration in the innate immunity by means of immune deregulations differentiated by diminished T cells; consist of CD4 and CD8 cells. Physician should be attentive of the chances of opportunistic secondary fungal infections in patients with COVID-19 infection, particularly in patients with pre existing risk factors.

The pre existing risk factors for opportunistic fungal infections includes hematological malignancies (HM), uncontrolled diabetes mellitus (DM) or trauma, renal failure requiring hemodialysis, abdominal surgery, triple lumen catheters, parenteral nutrition, receipt of multiple antibiotics, length of ICU stay >7 days, and preceding abdominal infections.

Rapid accurate diagnosis, administration of drugs, accessory application of hyperbaric oxygen, recombinant cytokines or administration of granulocyte, surgical debridement, and prosthetic rehabilitation using obturator are the techniques implicated in triumphant management of opportunistic fungal infections. All efforts should be made to preserve optimal hyperglycemia and only sensible evidence-based utilization of corticosteroids in patients with COVID-19 is suggested in order to diminish the burden of fatal mucormycosis, candidiasis, aspergillosis & other fungal infections.

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