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An Overview on Mucormycosis in Covid-19 Patients

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Abstract

The devastating COVID-19 pandemic has brought the world into a new era of Public Health problems. After the first and second waves of the COVID-19 infection, the world saw a unique pattern of post-covid complications, which were even more dangerous than the alone COVID- 19 infection. The second wave brought with it the deadly Mucormycosis, which was commonly known as Black Fungus. The extreme use of steroids in managing covid infection and the covid patients with multiple comorbidities were the most affected population with the black fungus disease. The fungal strain Rhizopus oryzae was a dominantly reported etiologic pathogen for the occurrence of fungal infection called Mucormycosis in COVID patients. The baseline signs & symptoms known are characterized by Acute sinusitis, Prolonged fever, Headache, Nasal and Sinus congestion, Purulent nasal discharge, Black lesion on the upper palate & on nasal bridge, Unilateral facial edema, Numbness, Orbital swelling, Periorbital cellulitis, Blurring of vision, Conjunctival suffusion, Central retinal artery occlusion, Dry ulcers, Abscesses, Proptosis, Palatal or Palpebral fistula developing into necrosis, hyphal angioinvasion resulting into thrombosis and tissue infarction, Soft tissue necrosis and marked chemosis. The traditional treatment modes used were antifungal therapy, surgical debridement, supportive therapy and surgical/prosthetic rehabilitation the recent management of mucormycosis as released by ECMM under the —One World One Guideline initiative in 2019 provides a detailed algorithm for the successful treatment of mucormycosis. In this article, we have compiled complete information about post-COVID Mucormycosis.

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INTRODUCTION

The COVID-19, since after 31st Dec, 2019 spreading foremost in Wuhan city of China has now been a catastrophe in 220 other countries and territories around the world precipitating millions of deaths and infecting billions worldwide. Of which, WHO affirmed covid-19 as a pandemic on 11th March, 2020. SARS- CoV-2 is considered as an etiologic agent of covid-19 which is a beta coronavirus with enveloped non-segmented positive-sense RNA [1, 2] belonging to family Coronaviridae, subgenus Sarbecovirus, and OrthoCoronaviridae subfamily [2, 3] is

having 96.2% identical genome RaTG13 of bat coronavirus [1]. During 2001-2010, France and other European countries saw a slight increase in incidence of mucormycosis. India saw approximately 70 times higher incidence of mucormycosis than the rest of the world. Rhino-orbital-cerebral forms were mostly linked to diabetes mellitus which was prevailing in the country. DM remains a public threat to the world as it is estimated to affect 783 million of population by 2045 in adults (20-79 years of age) and about 125 million of Indian population by 2045. Following the COVID-19 pandemic, Mucormycosis secondary to COVID became a notifiable disease as it saw a marked rise with over 47000 cases reported during the following three months in May 2021 [4]. Though the international health authorities are focused, it brings forth growing interest in the existing therapies as well as many new researches in treating covid-19 positives. In 85% patients with Severe COVID-19 have shown serious and enduring lymphopenia, neutropenia and markedly escalated pro-inflammatory markers comprising of IL-1, IL-6, and tumor necrosis alpha, less CD4 interferon-gamma expression, and fewer CD4+ T cells and CD8 + T cells which have significant role in immune hemostasis, further disrupting the immune status increasing their susceptibility to coinfections such as bacterial and fungal infections [5, 6]. Long hospitalized patients were found to develop severe complications such as secondary systemic mycosis which may be hospital acquired or may be related to any pre-existing comorbiditie [5, 7].

Mucormycosis

Various types of fungal infections are caused by a variety of fungal strains such as Rhizopus arrhizus, Rhizopus microsporus, Apophysomyces variabilis, Rhizopus homothallicus and Rhizopus oryzae. Amongst these, Rhizopus oryzae was dominantly reported etiological pathogen for the occurrence of fungal infection called Mucormycosis in Covid patients [6, 8]. Mucormycosis is also interpreted as Zygomycosis and Phycomycosis which is an unusual, aggressive, invasive and rapidly progressive & fatal fungal infection caused by a saprophytic fungus called Mucor of order Mucorales whose spores are airborne & even present in soil, food, and decaying organic matter [5, 8]. Although having profound knowledge and numerous, therapeutic choices available for this infection, the mortality rate still ranges 40-80%, whereas, survival is observed higher in immunocompetent patients free from comorbidities [9, 10]. Patients with impaired neutrophil & T- lymphocyte count assimilates higher risk as neutrophils & lymphocytes aimed at inhibiting.

A fore mentioned that CT scan recommended for the detection of the reversed halo sign, an area of GGO surrounded by a ring of consolidation on thoracic CT, or vessel occlusion on CT pulmonary angiography. In diabetic patients with facial pain, sinusitis, Proptosis, ophthalmoplegia, or newly diagnosed amaurosis, or both. Endoscopy and MRI are then recommended to diagnose mucormycosis in case of sinusitis or disease of brain/eye respectively [9]. To prompt the antifungal treatment, AFST is done by microbroth dilution method as per the Clinical Laboratory Standards Institute fungal spore proliferation [8, 10]. Additionally, mononuclear and polymorphonuclear phagocytes kills Mucorales via generation of oxidative metabolites and cationic peptides [8]. Presentation of mucormycosis in distinct forms comprise of Cutaneous Mucormycosis, Disseminated Mucormycosis, Gastrointestinal Mucormycosis, Rhino-orbital-cerebral mucormycosis and Pulmonary Mucormycosis primarily differentiated on the basis of the site of infection. Gastrointestinal mucormycosis is the prevalent form in young children with high mortality in neonates while, Rhinocerebral Mucormycosis has marked occurrence in patients with uncontrolled diabetes as well as with renal transplant. Occurrence of Pulmonary and Disseminated Mucormycosis was noticed high among the patients treated with immunosuppressive agents for cancer along with the patients' undergone organ or stem-cell transplants [9, 11]. Extremely rare cases of renal mucormycosis have also been isolated from immunocompetent hosts across India and China. [12, 13] The baseline signs & symptoms known are characterized by Acute sinusitis, Prolonged fever, Headache, Nasal and Sinus congestion, Purulent nasal discharge, Black lesion on upper palate & on nasal bridge, Unilateral facial edema, Numbness, Orbital swelling, Periorbital cellulitis, Blurring of vision, Conjunctival suffusion, Central retinal artery occlusion, Dry ulcers, Abscesses, Proptosis, Palatal or Palpebral fistula developing into necrosis, hyphal angioinvasion resulting into thrombosis and tissue infarction, Soft tissue necrosis and marked chemosis. [14, 15] ECMM together with MSG ERC issued a guidance document to optimize the early diagnosis & ease the management, primary approaches for detection of mucormycosis includes etiological examination as direct microscopy and cultural specimens for genus & species identification. Serological tests consist of Ag-Ab tests with testing of biomarkers such as bD glucan (BDG), galactomannan (GM) in suspected patients. PCR based assays, Tissue sequencing and molecular

identification can be performed to spot out the pathogen if necessity. Whilst, respiratory samples like BALF & TA are taken avoiding its aerosol spread among the other workers and skin lesions of Mucorales hyphae that are non-septate or pauci-septate with a variable width. [16, 17] Non-pigmented hyphae showing tissue invasion is confirmed by staining tissue sections with hematoxylin–eosin (HE), PAS, or GMS. Histopathological studies when carried out for skin lesions reveals that lesions of mucormycosis are characteristic but nonspecific in which the acute lesions show hemorrhagic infarction, coagulation necrosis, angioinvasion, infiltration by neutrophils (in non-neutropenic hosts, and perineural invasion as their characteristic features. While the chronic lesions show a pyogranulomatous inflammation with the presence of giant cells, and occasionally hyphae are covered by the Splendore Hoeppli phenomenon which characterizes profound eosinophilic material enclosing the pathogen. During debridement, biopsy is sent for fungal culture/sensitivity via potassium hydroxide (KOH) wet mount method. [14] Matrix-assisted laser desorption/ionization time-of- flight mass spectrometry (MALDI-TOF/MS), metabolomics and metagenomic shotgun sequencing are other evolving technologies that are being used in the diagnosis of fungal etiology. [18] Considerable risk factors correlated/associated with mucormycosis are uncontrolled diabetes mellitus, diabetic ketoacidosis, any form of metabolic ketoacidosis, systemic corticosteroid use, neutropenia, hematologic malignancies, organ or stem cell transplant, immunocompromised individuals, trauma, burns, patients receiving deferoxamine therapy during dialysis, patients undergoing chemotherapy or cancer immunotherapy, renal failure, widespread use of broad spectrum antibiotics [19–21] and long hospitalization stays. [22, 23] Out of which, 70% of rhino-orbito-cerebral mucormycosis is linked to diabetes mellitus.

Mucormycosisin COVID-19 patients & Disease burden

Comprehensive and complex clinical presentation of mucormycosis poses burden while elevating the difficulty of the diagnosis and treatment. Mucormycosis can essentially can affect any organ (e.g., central nervous system, brain, nose, sinuses, jaw bones, skin, joints, heart, kidneys, lungs, gastrointestinal tract, and invasive mediastinum). It has been known that diagnosis is often delayed with rapid disease progression. Furthermore, laboratory diagnosis is available after a long-time frame. Sadly, all the diagnostic modalities are insensitive and time consuming. [24]

Amongst a review of 600 published articles in the literature the most common site of infection were ROC(34%), cutaneous(22%) and pulmonary mucormycosis(20%). The major risk factors for development of ROC disease are DM and ketoacidosis. Trauma remains a risk factor mainly for cutaneous mucormycosis while a few numbers of pulmonary cases have also been associated. Mainly skin locations and exceptionally primary lung involvement is linked to healthcare associated mucormycosis. Hematologic malignancies and solid organ transplantation poses major risk factor for pulmonary mucormycosis. Chest computed tomography is favoured in patients with uncertainty of pulmonary fungal infection. The presence of a reversed halo sign (RHS) is highly signifying for pulmonary mucormycosis. Persistent fevers in spite of broad-spectrum antibiotics and pulmonary symptoms are indicative of patient at risk of pulmonary fungal invasive infection. These symptoms often include cough, dyspnoea, chest pain or haemoptysis where haemoptysis has been observed commonly in some of the cases based on evidences while some patient might be asymptomatic.

Leading risk factors in Covid Associated Mucormycosis (CAM) is with extensive use of corticosteroids, monoclonal antibodies & broad-spectrum antibiotics, poorly controlled pre-existing diabetes mellitus, prolonged neutropenia, endothelialitis in serious patients, prolonged intubation/mechanical ventilation, chronic respiratory diseases, cytokine storm and Immune dysregulation in patients infected with COVID19. Also, Aggravated hyperglycemia in glucocorticoid therapy and damage of pancreatic islets along with increased insulin resistance due to cytokine storm in Covid19 patients are strong key risk factors for opportunistic mycosis including mucormycosis. Hyperferritinemia syndrome observed in severe COVID-19 patients leads to surge in intracellular iron causing generation of reactive oxygen species which results in tissue damage further releasing free iron into circulation which facilitates iron overload and excess free iron results in rising risk for mucormycosis. India has the second largest number of adults aged 20-79 years with DM which has been reported in over 50% of cases of MCM has the highest burden of MCR in the world with an estimated prevalence of 140 cases per million population. [25] A study showed that CAM is seen particularly in 94% DM patients especially with the ones with 67% of poorly controlled DM and 95% severely or critically ill with COVID-19 mostly showing rhino-orbital and rhino orbital-cerebral presentation. Chances of survival in patients with MCM remains higher if they are not

neutropenic and have lower serum concentration of iron or ferritin & whose infection were not correlated to malignancies. [26] ICMR suggests use of clean & sterile water for humidifiers during oxygen therapy along with rational and judicious use of antibiotics and antifungals. Inhalation of airborne fungal spores by high-risk individual leading to nasopharyngeal, pulmonary and gastrointestinal infection. (rc161) Pulmonary Damage, subsequent alveolo interstitial pathology and the inflammatory environment due to the infection predisposes to the invasive fungal infection of the airways including the sinuses [27–29] and the lungs [30, 31]. Rhino-orbital-cerebral infection is the most typical presentation of mucormycosis with mycotic infiltration in mucosa of nasal cavity, paranasal sinuses to the orbit of the eye and brain. [32–34] Clinical Observations have suggested the role of iron in pathogenesis of patients with DKA as elevated levels of free iron in the serum allows ground for growth in acidic pH and not at alkaline pH, concluding that acidosis obstructed the tendency of transferrin to bind iron, decreasing the iron binding capacity. [35, 36] Extensive of the organism to hematogenously disseminate from the primary site of infection to other target organs leading to damage of and penetration through endothelial cells lining blood vessels is also a probable integral step in the organism's pathogenetic approach.

Due to lack of definitive agents that detect mucormycosis in cerebrospinal fluid, delay in diagnosis is observed. Additionally, prompt and quick diagnosis of mucormycosis remains unusual when considered with literature point of view since almost half of the cases were diagnosed in the post mortem autopsy examination. A minor delay in diagnosis can increase the risk of mortality, therefore, a well-timed diagnosis upon the impression of mucormycosis followed by a proper referral to tertiary healthcare centres and quick induction of antifungal treatment especially anti-mucormycosis therapies that would evade tissue invasion and following damage in COVID-19 patients.

Management

Traditional treatment modes used were antifungal therapy, surgical debridement, supportive therapy and surgical/prosthetic rehabilitation. Isavuconazole, a triazole that has shown active invitro activity against majority of Mucorales. A single arm open label trial, VITAL study published in 2016 showed slight lower mortality rate at Day 42 among 21 patients treated by isavuconazole than to that of liposomal amphotericin in the control arm who experienced a higher mortality rate. Based upon the findings of the trial, isavuconazole has been approved for the treatment of mucormycosis. Additionally, breakthrough mucormycosis due to azole treatment failure i.e. posaconazole or isavuconazole had a higher mortality rate to the patients who were not on azole treatment. In concern to high intra and individual variability and non-linear pharmacokinetics, therapeutic drug monitoring is advised for posaconazole therapy with a target concentration of >1 μg/mL as serum levels of >1.8 μg/mL are linked to hepatotoxicity. While therapeutic drug monitoring is not indicated for isavuconazole since there is no established correlation between serum levels and efficacy or safety of the treatment.

Fosmanogepix APC001 is one of the new antifungal drugs that inhibits the fungal enzyme Gwt1 and targets glycosylphosphatidylinositol bounded protein maturation. In vivo activities of fosmanogepix is similar to that of isavuconazole when tested in a trough (0.25 μg/mL) and crest (4 μg/mL) minimum effective concentrations.

Recent management of mucormycosis as released by ECMM under the —One World One Guideline initiative in 2019 provides a detailed algorithm for the successful treatment of mucormycosis. It focuses on the radio diagnostics such as imaging studies and documenting the extent of disease which is followed by highly recommended surgical intervention. Liposomal Amphotericin B is the first line treatment along with supportive treatment using moderate strengths of intravenous isavuconazole and intravenous or delayed release formulations of Posaconazole majorly given as salvage treatments. While Amphotericin B deoxycholate can be used with caution in limited settings due to its significant toxicity. When patient is stable and responded to treatment, it is advised to switch IV therapy to oral therapy comprising isavuconazole or posaconazole delayed release tablet. Major changes related to use of isavuconazole and posaconazole have been considered in comparison to previous recommendations by the same confederation in 2013 and ECIL.

Success of the treatment relies on early diagnosis, recognizing disease patterns, control of hyperglycemia, surgical debridement and timely treatment with Liposomal Amphotericin B as it is a crucial step in management. Posaconazole can be given as prophylaxis in high-risk patients such as neutropenic patients who have graft versus host disease. Further the treatment can be tailored post identification of pathogen by selecting sensitive antifungal drugs via/ after Antifungal Susceptibility Testing (AST).

Dosing of Liposomal Amphotericin B is recom-

mended at 5-10 mg/kg and in the absence of CNS involvement 5mg/kg of dose is recommended. ICMR recommends and follows the ECMM guideline. Further, the treatment can be backed by tapering steroids, discontinuing immunosuppressant drugs, maintaining sufficient systemic hydration and continuing antifungal therapy for at least 4 to 6 weeks. Study suggested that even delaying the treatment by six days was associated with doubling of 30-day mortality. Maintenance in form of secondary prophylaxis in order to prevent any risks of relapse with oral azoles should be discussed at the time of neutropenia, chemotherapy or high-dose immunosuppressive therapy. Both intravenous and delayed release tablet formulations of posaconazole have been developed recently to aid management in the treatment of mucormycosis with a recommended dose of 300mg per day after a loading dose of 300mg twice a day on day 1. Delayed release tablets are not affected by intake of food. Thus, timely and immediate multidisciplinary involvement of medical, surgical, radiological and laboratory team can ensure effective diagnosis and treatment to enhance patient prognosis. [37] Mortality relies upon the site of involvement of mucormycosis. Pulmonary mucormycosis and disseminated forms are linked to lower survival than most of the forms. Combination therapy of either polyenes and azoles or polyenes with echinocandins can be supported rationally as long as there is no evidence on the enhanced toxicity or proven synergistic benefits to the patient. Appropriate duration of the treatment remains undefined but should be considered until the resolving of the lesions and restructuring of the host immune system. There are no specific therapeutic recommendations for pulmonary mucormycosis. Taking consideration of coinfections in covid19 patients, appropriate Stewardship interventions are required to avoid frequent prescription of broad-spectrum empirical antimicrobials in patients with Covid-19 associated respiratory infection to reduce bacterial/fungal coinfections and supporting optimal outcomes and counter unforeseen consequences of antimicrobial use on the individual and society. [38] Surveillance of co-infections with unique organisms should be carried out and clinicians should be familiar with the risk of persistent fever and hypoxemia in COVID-19 patients. [39]

Abbreviations

WHO: world health organization,

SARS CoV-2: severe acute respiratory syndrome coronavirus-2,

ECMM: The European Confederation of Medical Mycology,

FFPE: formalin-fixed paraffin-embedded,

BALF: bronchoalveolar fluid,

MSG ERC: the Mycoses Study Group Education & Research Consortium,

GGO: ground glass opacities,

MCM: mucormycosis,

AFST: antifungal susceptibility testing,

DM: diabetes mellitus,

CAM: Covid-19 associated mucormycosis,

DKA: diabetic ketoacidosis,

CNS: central nervous system,

PAS: Periodic acid–Schiff,

GMS: Grocott methenamine silver

CONCLUSION

In the times of pandemic, clinicians have been facing the difficulty of diagnosing co-infections at an early stage which has led to substantial increase in the incidence of such opportunistic infections. Possible approaches to improve outcomes in mucormycosis are early diagnosis by an expert physician can help reduce risks of opportunistic co-infection in high risk Covid19 patients and thereby improving treatment outcomes in mucormycosis. Considering predisposing factors, it can help in evaluating risks for an individual to develop mucormycosis. A lot of progress has been made in the last decade through evident understanding and knowledge of the pathophysiology, enhanced diagnosis and non-invasive diagnostic tools and various treatment modalities, regardless of the fact that mortality rate remains high. Future research must converge in the development of new antifungals, unidentified roles of combination treatments, surgical and supportive therapies. Empirical therapies for suspected invasive fungal infection should be avoided until the pathogen is distinguished, as first line treatment differs for various fungal pathogens. This will help in optimizing and initiating the early treatment and providing a better prognosis. Prompt management from the multidisciplinary team can help in early recovery from the infection. Achieving therapeutic effect at lowest doses and shorter durations. More epidemiological data would be required for better interventions.

Conflict of Interest

Authors have no conflict of Interest.

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