VOLUME - 10, ISSUE - 08, AUGUST- 2021 • PRINT ISSN No. 2277 - 8160 • DOI : 10.36106/gjra

Original Research Paper

Medical Science

MUCORMYCOSIS: A SERIOUS CONCOMITANT IN COVID-19 PATIENTS

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ABSTRACT Fungi were for a long time underdiagnosed and underestimated. The Leading International Fungal Education (LIFE) portal has estimated the burden of serious fungal infections globally. Occurrence of a deadly systemic fungal infection or mucormycosis in Covid-19 infected patients has recently noticed in India and its subcontinents. It is estimated a prevalence of 14 cases per 100,000 individuals in India. Mucormycosis usually perceived in immune-compromised patients and patients with uncontrolled diabetes. The primary sites of invasion are the paranasal sinuses, lungs, skins and gastro-intestinal tissues. Immediate correction of hypoxia, acidosis, hyperglycemia, and electrolytic imbalance are preferred. Delayed initiation of therapy is associated with increased mortality. Omission of steroids, anti-metabolites and immunosuppressive drugs are recommended. Besides surgical help, intravenous antifungal drugs, amphotericin B and isavuconazole therapy are advised.

KEYWORDS : Mucormycosis, fungal infection, immune-compromised, Covid-19, hypoxia

INTRODUCTION

Last five decades human civilizations are fights against infective contagious diseases, like AIDS, SARS, MERS, ZIKA etc. Last one and half years, more than 380 million SARS-CoV2 virus infected deaths were reported in the world. Recently, deadly fungal chest infections, commonly known as 'Black Fungus', are observed in the Indian subcontinent. In India, more than 15,000 immunocompromised patients recovering from COVID-19 were re-infected with black fungus, clinically known as mucormycosis.[1] Mucormycosis is a systemic or angioinvasive fungal infection caused by members of the class Zygomycetes, order Mucorales. This class of fungus consists of aseptate hyaline molds which are ubiquitous in the atmosphere. Mucorales comprises 261 species in 55 genera, while 5 genera namely *Rhizopus*, *Mucor*, *Lichtheimia*, *Saksenaea* and *Cunninghamella* are reported for human infections.[2-3] In medical history, mucormycosis was first described in 1876 in Germany in a cancer patient.[4] Fungal spores suspended in air, may enter through inhalation and infect lungs, sinuses, eyes, face and rarely central nervous system. It may also invade skin through cuts, scrapes, puncture wounds etc.[5] In India, the prevalence of mucormycosis is approximately 0.14 cases per 1000 population, which is about 80 times the prevalence of mucormycosis in developed countries.[6] The mortality rates for mucormycosis range from 40-80% with varying rates depending on underlying conditions and sites of infection.[7]

Mucormycosis generally attacks immune-compromised patients and patients with uncontrolled diabetes.[8] Besides that, patients suffering from acidosis, leukaemia, lymphoma, neutropenia, AIDS, chronic renal failure, liver problems, severe malnourishment, severe burns, immune suppression from long corticosteroid use, iron overload and dialysis patients on deferoxamine therapy are prone to it.[9-10] The primary sites of invasion are the paranasal sinuses, lungs, skin, and gastro-intestinal tract. These fungi show a predilection for arterial invasion, causing extensive emboli and necrosis of surrounding tissues. Vein and lymphatic invasion can occur later in the course of the infection.[11] Actually, the acidotic and hyperglycemic environment existing in patients with ketoacidotic *diabetes mellitus* favours the growth of *Rhizopus*.[5,9] Mucormycosis infections result extensive angioinvasion with resultant vessel thrombosis and tissue necrosis. It damages and penetrates endothelial cells lining of blood vessels and causes hematogenous dissemination from the original site of infection to other target organs.[12] The survival rate depends on rapid diagnostic and therapeutic intervention, including immediate involvement of a multidisciplinary medical, surgical, radiological and laboratory based team. Though mucormycosis is globally distributed, certain risk factors, clinical forms, and causative agents of the disease are prevalent in India. At present, there is lack of information in the management of mucormycosis on Covid-19 patients. In general, mucormycosis infections have been noted in Covid-19 patients after 10-15 days of their recovery. Hence, the aim of this article is to present an update on the mucormycosis and the available diagnostic methods, treatment and relation with Covid-19 for this potentially lethal disease.

DIFFERENT TYPES OF MUCORMYCOSIS

The deadly fungal disease usually spread in five forms:

(i) Rhinocerebral: The most common form, usually seen in patients with ketoacidotic *diabetes mellitus* that presents with sinusitis, facial and eye pain, proptosis, progressing to signs of orbital structure involvement. Necrotic tissues are seen on the nasal turbinates, septum, and palate. This may look like a Black Escher. Intracranial involvement develops as the fungus progresses through ophthalmic artery, superior fissure and cribiform plate.[2]

(ii) Pulmonary: Commonly seen in patients with neutropenia, such as those with leukemia or lymphoma. Symptoms are fever, dypsnea and hemoptysis.[2-3]

(iii) Gastrointestinal tract: Seen in severely malnourished patients, particularly in kwashiorkor, and in patients with amoebic colitis and typhoid. The stomach, ileum, and colon are usually involved, mimicking intra-abdominal abcess.[2,3,10]

(iv) Cutaneous: It may develop after minor trauma, insect bites, wounds, burns, and use of non-sterile dressings. Necrotic lesions occur on the epidermises that are painful and hardened, usually with a blackened central area. From epidermis lesions can progress into dermis and even to muscle.[10,11]

(v) Disseminated: Dissemination can occur, mainly from the pulmonary form, to the heart, brain, bones, kidney, and bladder. Dialysis patients on deferoxamine therapy are prone to it.[10,11]

LABORATORY INVESTIGATIONS

The following laboratory investigations are globally accepted for the detections of mucormycosis.

(i) Microscopic examination is carried out with scrapings from the upper turbinates, aspirated sinus material or sputum. The presence of thick-walled, aseptate and refractile hyphae, sometimes swollen and distorted usually indicates Mucorales fungi.[3]

(ii) Histological sections showed acute suppurative inflammation with focal areas of granulomatous. Septate hyphae invade the adjacent blood vessel walls. Grocott-Gomori methenamine silver, periodic acid-Schiff and hematoxylin-eosin (H&E) stains are commonly used. Diagnosis is frequently made from tissue sections.[2,12] It is interesting to noted that *Aspergillus* and *Candida* do not take H&E stain. *Aspergillus* has septate, narrow, acutely branching hyphae with smooth, parallel walls. *Candida* has septate, narrow hyphae in tissue, club-shaped pseudo-hyphae and presence of yeast forms.[14]

(iii) Culture is regularly done on biopsy specimens. As exudates and necrotic tissue contain few viable organisms, the inoculum from these specimens must be intense. Sabouraud's dextrose agar or brain-heart infusion agar are most commonly used for isolation. Antibacterial agents, such as chloramphenicol and polymyxin B are used to prevent bacterial overgrowth. Other media applied for inducing sporulation are potato dextrose malt agar, Czapek solution agar and hay infusion agar.[13-15] Colonies generate fluffy white, gray, or brown hyphae filling the culture within 24 hours. The hyphae are coarse and dotted with brown or black sporangia. Identification of genera is based on the presence of aseptate hyphae, the structure of the sporangiophore, and the presence and position of rhizoids relative to the sporangiophores.[2-5,14] *Rhizopus* species are the most often recovered organisms from specimens. They exhibit unbranched sporangiophores that occur singly or in groups at nodes, directly above the rhizoids. The nodes are connected by stolons. The sporangia are dark walled and spherical. Species predominantly recovered are *R. oryzae* and *R. arrhizus*.[12-15] *Mucor* species demonstrates aerial unbranched and branched sporangiophores arising randomly from mycelia without any rhizoids. The main species recovered are *M. circinelloides*, *M. ramosissimus*, and *M. javanicus*.[12-15] Moreover, branching pyreform sporangiophores arising from nodes between rhizoids are common in *Lichtheimia* sp. Species predominantly recovered are *A. ramose* and *A. corymbifera*. *Cuminghamella bertholletiae* and *Saksenaea vasiformis* have been isolated on rare occasions from clinical cases.[13-15]

(iv) Radiographical imaging is now suggestive for pulmonary mucormycosis. In patients with suspected pulmonary mucormycosis, pulmonary CT scan is recommended. In diabetic patients with facial pain, sinusitis or ophthalmoplegia cranial CT or MRI is strongly recommended. If sinusitis is diagnosed, endoscopy is strongly recommended to diagnose mucormycosis. If mucormycosis is a potential diagnosis, biopsy is strongly recommended. In view of the rapid progress of mucormycosis, weekly CT scans are strongly recommended, particularly in unstable patients.[15-16]

TREATMENT TARGETS AND OUTCOMES

The global guideline for the diagnosis and management of mucormycosis in 2019 by European Confederation of Medical Mycology (ECMM) and Mycoses Study Group Education and Research Consortium recommended an early complete surgical treatment for mucormycosis whenever possible, in addition to systemic antifungal treatment. Amphotericin B, lipid complex, liposomal Amphotericin B and posaconazole oral suspension are taken as the first-line antifungal monotherapy, while isavuconazole is strongly supported as salvage treatment.[17] The central role of iron in pathogenesis of mucormycosis has also been confirmed and uses of iron chelators, deferiprone and deferasirox in these cases may be helpful.[12] The successful treatment of mucormycosis requires early diagnosis, reversal of underlying predisposing risk factors, surgical debridement where applicable and prompts antifungal therapy. Now-a-days, the optimal time of surgery for reducing the operative risk to the patient with COVID-19 and the risk of transmission to the operating team became a challenging issue. Study noted that, reduced infectivity was noticed in moderately ill, severely ill and critically ill COVID-19-infected patients after ten, fifteen and twenty days respectively.[18] Previous studies indicated that the survival rate in patients with uncontrolled *diabetes mellitus* suffering from the rhino-cerebral form of mucormycosis is very grave.[11-13] Patients with leukemia or lymphoma suffering from the pulmonary form usually die from the infection. The GI tract infection is usually diagnosed on autopsy.[10] The overall mortality rate is high, usually 30% to 70%. Death usually results in 2 weeks if untreated or treatment remains unsuccessful. Seventy percent survivors experience permanent residual effects, including blindness, cranial nerve defects, and surgical disfigurement.[12-13]

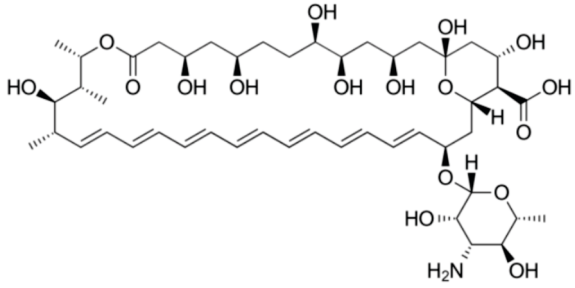

Figure 1: Chemical structure of Amphotericin B

MUCOMYCOSIS IN COVID 19 PATIENTS

Recently, several studies reported rhino-orbitary cases associated with COVID-19.[19-21] Patients with *Diabetes mellitus* alone and that with ketoacidosis are prone to rhino-orbital-cerebral mucormycosis. The most common species isolated was *Rhizopus* species, with an overall mortality of 46%.[22-24] Aggressiveness of fungal infection flares up due to decreased phagocytic activity, accessible amounts of iron due to the displacement of protons by transferrin in diabetic ketoacidosis and fungal heme-oxygenase, which promotes iron absorption for its metabolism. It is also thought that diabetic and immunocompromised patients lack normal phagocytic activity on their nasal and oral mucosal surfaces. This allows proliferation of fungus, which does not occur in people with intact phagocytic activity, and the fungus spreads via the blood vessels.[23] In a case of severe COVID-19 associated with fungal co-infection, cell counts revealed a progressive increase in white blood cell count/neutrophils and a progressive decrease in lymphocyte count.[25] SARS-CoV-2 seriously affect CD4+ and CD8+ T-cells and thereby reduced the number of lymphocytes and T-cells in severe COVID-19 cases. In invasive mucormycosis, mucorales-specific T-cells produces cytokines (IL-4, IL-10, IL-17 and IFN-) and that could be a useful surrogate diagnostic marker.[24,26] Both type 1 and type 2 diabetics are reported for alterations in cell-mediated immunity functions, such as chemotaxis, phagocytosis and cytokine secretion. Furthermore, more pro-inflammatory M1 macrophages are present in diabetic patients due to lack of natural killer cell (NK) activities. In COVID-19 disease, hyper-inflammatory response with diabetes may intensify the cytokine storm to exaggerated vascular lesions with endothelial dysfunctions.[24,27] *Diabetes mellitus* was reported in more than 70% of cases of mucormycosis.[28]

Sen *et al.* (2021) reported six cases of rhino-orbital-cerebral mucormycosis following COVID-19 infections that occurred in Indian subcontinent. They suggested that, use of glucocorticoids in mild COVID cases (without hypoxaemia), application of higher doses of glucocorticoids and drugs targeting immune pathways such as tocilizumab should be restricted.[29] Satish *et al.* (2021) encountered 25 cases of mucormycosis, out of 11 were COVID-19 positive or history of post COVID-19 disease.[30] A cluster of 10 cases of clinically diagnosed orbital mucormycosis with concurrent COVID-19 was encountered in India. All patients were treated with intravenous dexamethasone for COVID-19 disease and Liposomal Amphotericin B for mucormycosis. Four patients were expired within 1 month, 5 patients had satisfactory systemic outcomes, but with irreversible vision loss.[31] Revannavar *et al.* (2021) has experienced a rare case of a middle-aged COVID-19 positive woman with diabetes.[25] CT paranasal sinus and MRI brain revealed left-sided pansinusitis with acute infarct in the left parieto-occipital region without angioinvasion. An emergency functional endoscopic sinus procedure was done and histopathological examination revealed mucormycosis. After 1 week of conventional amphotericin B and antibiotics, repeat CT brain showed improvement in mucosal thickening and sinusitis. Interestingly, there was no angioinvasion and transient peri-arterial inflammation.[25]

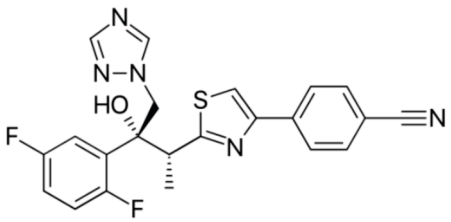

Figure 2: Chemical structure of isavuconazole

CONCLUSIONS

Mucormycosis is not only the disease of the immunocompromised patient in Covid-19 disease but a considerable number of cases are also reported in an immunocompetent host without any known underlying illness. *Diabetes mellitus* and post pulmonary tuberculosis are the most common risk factors for mucormycosis. European Confederation of Medical Mycology revised the guideline for the diagnosis and management of mucormycosis, and recently ICMR released the guidelines for the screening, diagnosis, and management of mucormycosis in patients with COVID-19. The treatment of mucormycosis involves the early detection and initiation of therapy, the surgical removal of infected tissues, antifungal therapy and managing the underlying disease. To prevent the irreversible damage of vital organs and the life of the patient, condition of hypoxia, acidosis, hyperglycemia, and electrolytic imbalance needs quick correction. Steroids, anti-metabolites and immunosuppressive drugs should be discontinued as early as possible. Surgical debridement is essential, along with antifungal drugs, amphotericin B and isavuconazole therapy until remission is achieved.

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