Original Research Article

Mucormycosis In Covid-19 Pandemic

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Abstract

Mucormycosis (Zygomycosis) is an invasive fungal infection. It typically affects immune compromised individuals with an impaired neutrophilic response. There are several case reports of Rhino-orbital-cerebral mucormycosis (ROCM) from all over the world. Recently, its alarming rise in the number amongCOVID-19 patients mostly with uncontrolled diabetes and those who received excessive administration ofsteroids for the treatment of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection hasraised interest among the scientific community to learn more about the said disease. The current reviewdescribes, its epidemiology, clinical presentation, risk factors, warning signs, diagnostic test and available preventive and treatment modalities for its effective management.

Keywords: Mucormycosis, Uncontrolled Diabetes, Severe Acute Respiratory Syndrome Coronavirus 2, COVID-19.

Introduction

Coronavirus disease 19 is caused by caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). SARS CoV-2 is an enveloped, positive stranded RNA virus, belonging to the genus Betacoronavirus of the family Coronaviridae[1]. The first case of Covid-19 infection was detected, in December 2019 in Wuhan, China. It spreads via various routes such as aerosol, respiratory droplets, and fomites[2]. The spectrum of symptoms of Covid-19 range from dry cough and fever to multisystem involvement in the form of shortness of breath, anosmia, ageusia, diarrhoea, generalised malaise, acute cardiac injury and secondary infections[3].

A large number of patients who develop coronavirus disease have an underlying co-morbidity such as obesity, hypertension, diabetes, chronic heart or kidney disease[4]. Glucocorticoids have been shown to reduce mortality in Covid-19 patients[5]. All these pre-existing conditions along with use of immunosuppressive therapy such as glucocorticoids, increase the risk of developing secondary infections[6]. There are two specific features of COVID-19 that lead to secondary fungal infections. There is extensive alveolo-interstitial pathology and immune dysregulation associated with COVID-19, leading to decrease in number of T lymphocytes, CD4+ Tcells and CD8+ T cells[7].

Mucormycosis (Zygomycosis) is an invasive fungal infection, caused by opportunist and ubiquitous fungi belonging to the class Phygomycetes, subclass Zygomycetes, order Mucorales, family Mucoraceae; usually by the following species: *Absidia corymbifera*, *Apophysomyces elegans*, *Cunninghamella bertholletiae*, *Mucor rouxii*, *Rhizomucor pussillus*, *Rhizopus arrhizus*, and by species of the genus Saksenaea spp[8]. It typically affects immunocompromised individuals with an impaired neutrophilic response.It mostly affects individuals with uncontrolled diabetes mellitus, acquired immunodeficiency syndrome, iatrogenic immunosuppression and haematological malignancies, and those who have undergone organ transplantation[9].

There are several case reports of Rhino-orbital-cerebral mucormycosis (ROCM) from all over the world. Thus, it becomes very important to study the early signs and symptoms, warning signs, diagnosis, management and prevention of ROCM for managing the cases of COVID-19 with mucormycosis more effectively.

Epidemiology of mucormycosis in India

The estimated prevalence of mucormycosis in India is nearly 70 times higher than the global data, which were estimated to be at 0.02 to 9.5 cases (with a median of 0.2 cases) per 100,000 persons[10]. Studies conducted in Southern India have shown an annual incidence of 18.4 cases per year during 2005–2015[11]. A multicentre study across India has reported an annual incidence of 22 cases per year[12]. The computational-model-based method has estimated a prevalence of 14 cases per 100,000 individuals in India. The cumulative burden ranged between 137,807 and 208,177 cases, with a mean of 171,504 (SD: 12,365.6; 95% CI: 195,777–147,688) and mean attributable mortality at 65,500 (38.2%) deaths per year[13].

Risk factors for mucormycosis in covid-19 infection

There are several factors and underlying diseases which lead to increased risk of mucormycosis in COVID-19. The most common underlying disease leading to mucormycosis is diabetes mellitus. It has been reported in 54-76% cases. Diabetic ketoacidosis is present in upto 8-22% cases[14]. Outside India, diabetes has been reported to be a major risk factor for mucormycosis in Mexico (72%), Iran (75%), and the USA (52%)[15]. Hematological malignancy is associated with mucormycosis in 1-9% cases.(15) Solid-organ transplantation (SOT)

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is another risk factor for mucormycosis in 2.6–11% of cases in India[16].

Current guidelines have recommended use of intravenous methylprednisolone 0.5-1 mg/kg/day for three days in moderate cases and 1-2 mg/kg/day in severe cases[17]. The National Institute of Health has recommended the use of dexamethasone (6 mg per day for a maximum of 10 days) in patients who are ventilated or require supplemental oxygen but not in milder cases[18]. All these lead to increased risk of developing secondary infections[19]. Moreover, injudicious use of steroids, without correct dosage and duration, particularly in mild disease also increases the risk of mucormycosis.

Other factors leading to increased risk of mucormycosis include chronic kidney disease (CKD), pulmonary tuberculosis,chronic obstructive pulmonary disease (COPD), neutropenia, trauma, burns and deferoxamine therapy in patients receiving hemodialysis[20-24]. Other risk factors for mucormycosis include intravenous drug use, autoimmune disease, HIV infection, immunosuppressant drugs, malnutrition, and ICU stay (14). A few cases of mucormycosis have been reported after treatment with voriconazole[25].

Uncontrolled diabetes, immunosuppresion due to use to corticosteroids, altered innate immunity diffuse damage to alveoli, prolonged ICU stay, use of supplemental oxygen in the setting of COVID-19, increase the risk of developing mucormycosis.

Pathogenesis of mucormycosis

Rhizopus oryzae is the most common organism causing mucormycosis and is responsible for around 70% of all cases of mucormycosis[16]. There are several factors leading to mucormycosis, which are following:

1. Host factors

Individuals having impaired phagocytic response are at higher risk for mucormycosis. Neutrophils are critical for inhibiting fungal spore proliferation by the generation of oxidative metabolites and the cationic peptides, defensins, leading to destruction of mucorales[26]. Exposure of neutrophils to *R. oryzae* hyphae results in up-regulation in Toll-like receptor 2 expression and in a robust proinflammatory gene expression with rapid induction of NF-κB pathway–related genes. In the presence of hyperglycemia and low pH, which is found in patients with diabetic ketoacidosis (DKA), phagocytes are dysfunctional and have impaired chemotaxis and defective intracellular killing by both oxidative and nonoxidative mechanisms[27,28]. Studies have shown that corticosteroid-immunosuppresed animals, are not even able to prevent germination of the sporangiospores in vitro or after intranasal infection[29]. In addition to phagocyte dysfunction, several other virulent factors also involved in pathogenesis of mucormycosis.

2. Role of iron in pathogenesis

The unbound iron in serum plays a crucial role predisposing patients with DKA to mucormycosis. Patients with DKA have elevated levels of free iron in their serum, and such serum supports growth of *R. oryzae* at acidic pH (7.3–6.88)[30]. Furthermore, adding exogenous iron to serum allowed *R. oryzae* to grow profusely at acidic conditions and simulated acidic conditions decreased the iron-binding capacity of serum, suggesting that acidosis per se disrupts the capacity of transferrin to bind iron.

Fungi obtain iron from the host by using high-affinity iron permeases called siderophores. *Rhizopus* secretes rhizoferrin, a siderophore, which supplies *Rhizopus* with iron through a receptor-mediated, energy-dependent process[31]. The high-affinity iron permeases, reduce the ferric form of iron to more soluble ferrous forms, which in turn is captured by a protein complex.

Patients receiving desferroxamine, are also susceptible to mucormycosis. Deferoxamine removes the ferric iron from bound transferrin and attaches itself on the mold through an inducible receptor, and then the iron is transported intracellularly by an active reduction of the ferric form into the more soluble ferrous form[32].

3. Angio-invasion and thrombosis

Mucormycosis is characterized by angioinvasion, resulting in vessel thrombosis and extensive tissure necrosis. The angioinvasion leads to hematogenous dissemination to other organs and ischemic necrosis leads to paucity of leukocytes and anti-fungal agents at the site of infection. The angioinvasion occurs by damage to endothelial cells and cells of extra-cellular matrix. Glucose-regulated protein (GRP78) act as a receptor to mediate the penetration of Mucorales by damage to endothelial cells. GRP78 expression is increased in patients with increased concentrations of glucose and iron[33].

Red flags of mucormycosis

Depending upon the anatomical site of involvement, the mucormycosis can have varied presentations. Rhino-orbital-cerebal mucormycosis (ROCM) is the most common form, specially in the setting of COVID-19 infection[34,35]. Other forms include cutaneous, pulmonary, renal, gastrointestinal and disseminated infections[14].

There has been an exponential rise in cases of ROCM, specially in the ongoing second wave of COVID-19 pandemic in India. There are several warning signs and symptoms of ROCM, in COVID as well as post COVID patients, which are as follows:

- Nasal stuffiness
- Foul smell
- Epistaxis
- Nasal discharge - mucoid, purulent, blood-tinged or black
- Nasal mucosal erythema, inflammation, purple or blue discoloration, white ulcer, ischemia, or eschar
- Eyelid, periocular or facial edema
- Eyelid, periocular, facial discoloration
- Regional pain – orbit, paranasal sinus or dental pain
- Facial pain
- Worsening headache
- Proptosis
- Sudden loss of vision
- Facial paresthesia, anesthesia
- Sudden ptosis
- Ocular motility restriction, diplopia.
- Facial palsy
- Fever, altered sensorium, paralysis, focal seizures.

The warning signs and symptoms of ROCM should be explained to patients and family members, during the treatment as well as following the treatment of COVID-19, so that they can seek early medical attention.

Diagnosis of mucormycosis

In presence of warning signs and symptoms, the diagnosis of ROCM requires a team approach comprising of otorhinolaryngologist, pathologist, microbiologist and radiologist. Culture and staining of endoscopy guided or deep nasal swab, provides the supportive evidence for diagnosis of ROCM. Direct microscopy of the deep or endoscopy-guided nasal swab, paranasal sinus, or orbital tissue, on KOH mount and using calcofluor white stain provides a rapid diagnosis. Non-septate or pauci-septate, irregular, ribbon-like hyphae, 6-25 um in diameter, with wide-angle of non-dichotomous branching (≥45-90 degree) and greater hyphal diameter as compared to other filamentous fungi. are seen.. Smears stained with Hematoxylin-Eosin, periodic acid-Schiff, and Grocott-Gomori's methenamine-silver stains are also helpful in rapid diagnosis. Direct microscopy has about 90% sensitivity. Obtaining the swab from clinically active lesions under endoscopy guidance helps to improve the diagnostic yield[36,37].

Culture of the deep or endoscopy guided nasal swab, paranasal sinus, or orbital tissue is done on brain heart infusion agar, potato dextrose agar or preferably Sabouraud dextrose agar with gentamicin or chloramphenicol and polymyxin-B, but without cycloheximide and incubated at 30-37°C . It helps in genus and species identification as well as antifungal susceptibility testing. On culture, rapid growth of fluffy white, gray or brown cotton candy-like colonies with Thyphae are coarse and dotted hyphae with brown or black sporangia are seen. It is difficult to distinguish the genera based upon the colony morphology and it requires a detailed microscopic evaluation. Only

about 50% of samples from cases of probable ROCM show growth of the organism on culture. Obtaining the sample from clinically active parts of the lesion may help improve the diagnostic yield[36,37].

Histopathology of Sample from the nasal mucosa, paranasal sinus mucosa and orbital tissue with Hematoxylin-Eosin, periodic acid-Schiff, and Grocott-Gomori's methenamine-silver special stain showing tissue invasion with hypahae is confirmatory of ROCM. The molecular diagnosis of endoscopy or deep nasal swab, paranasal sinus, orbital tissue, blood has about 75% sensitivity for diagnosis of ROCM. But, molecular diagnostic kits are not widely available[36,37].

CT-scan or contrast enhanced MRI scan shows nasal and paranasal mucosal thickening in early stages. The fluid level in sinuses or complete opacification of sinuses shows complete sinus involvement. Thickening of medial rectus muscle is a sign of early orbital invasion. Patchy enhancement of the orbital fat, lesion in the area of the superior and inferior orbital fissure and the orbital apex, and bone destruction at the paranasal sinus and orbit indicate advanced disease. MRI and MR angiography can help to determine the extent of cavernous sinus involvement and ischemic damage to the CNS[36,37].

Based on the warning signs and diagnostic tests, the diagnosis of ROCM can be classified into three types:

Possible ROCM

Patient having symptoms and signs of ROCM with concurrent or recently (<6 weeks) treated COVID-19, diabetes mellitus, use of systemic corticosteroids and tocilizumab, mechanical ventilation, or supplemental oxygen is considered as Possible ROCM.

Probable ROCM

When signs and symptoms are supported by diagnostic nasal endoscopy findings, or contrast-enhanced MRI or CT Scan, the patient is considered as Probable ROCM.

Proven ROCM

Microbiological confirmation on direct microscopy or culture or histopathology with special stains or molecular diagnostics classifies the patient as Proven ROCM[38].

Management of ROCM

Management of ROCM requires a team approach comprising of radiology, microbiology, pathology, infectious disease, neurology, critical care, otorhinolaryngology, ophthalmology, and neurosurgery[38]. The European Confederation of Medical Mycology (ECMM) and the Mycoses Study Group Education and Research Consortium (MSG ERC) have issued guidelines for the management of ROCM. The mainstay of treatment of ROCM involves use of anti-fungal agents, surgical debridement of infected tissue and treatment of underlying disease. Amphotericin-B is the drug of choice and early initiation of therapy is crucial in the management of disease. Other antifungal agents used in the management of ROCM are posaconazole and isavuconazole[39]. Immediate intra-venous induction therapy with liposomal Amphotericin-B 5-10 mg/kg body weight is needed. In case of financial constraints, Amphotericin-B deoxycholate can be used. In patients with impaired renal function, isovuconazole 200mg IV thrice a day for first two days followed by 200 mg once a day is used or posaconazole 300 mg twice a day on day 1 followed by 300mg once a day is used[38].

In case of predominant sinus involvement, with no or limited involvement of the orbit, aggressive debridement of involved sinus with appropriated surgical approach is used. Retro-bulbar injection of amphotericin-B 3.5 mg/ml and sinus irrigation with amphotericin-B 1mg/ml can be used[38]. Mortality rate is lower in patients treated with combination of amphotericin-B and surgical debridement of infected tissue as compared to Amphotericin-B monotherapy alone[40]. In case of extensive orbital and central nervous system involvement, orbital exentration, along with aggressive debridement of paranasal sinuses is advocated, if surgery is feasible[39].

The mortality rate of mucormycosis in India is in the range of 28–52%, with different mortality rates in ROCM (31–49%), pulmonary (61–77%), cutaneous (23–57%), gastrointestinal (67–94%), and disseminated (62–79%) forms of mucormycosis[14].

Conclusions

Rhio-orbital-cerebral mucormycosis is an rapidly progressive and lethal infection, with increasing incidence in the ongoing second wave of COVID-19 pandemic. Thus, it is very important that early warning signs and symptoms of mucormycosis are recognized so that appropriate treatment can be initiated and patient survival can be enhanced.

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