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REVIEW ARTICLE

Mucormycosis and COVID-19: A Dual Curse

Vishal R. Tandon, Akhil Mahajan[1], Annil Mahajan[1]

Abstract

Mucormycosis is a serious, but rare opportunistic, invasive and life-threatening fungal infection primarily caused by Rhizopus arrhizus with very high case fatality. Recently, its alarming rise in the number among COVID-19 patients mostly with uncontrolled diabetes and those who received excessive administration of steroids for the treatment of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection has raised interest among the scientific community to learn more about the said disease. The current review describes, its epidemiology, clinical presentation, risk factors, warning signs, diagnostic test and available preventive and treatment modalities for its effective management.

Key Words

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

Introduction

Mucormycosis is a serious, but rare opportunistic, invasive and life-threatening fungal infections primarily caused by Rhizopus arrhizus with higher case fatality rates (>50%). Mucormycosis has been established and recognized as complication of the SARS- CoV-2 infection that has shown its new face in COVID era, although not transmissible from one human to another but prompt early diagnosis and treatment are necessary to avoid high rates of mortality and morbidity particularly in COVID patients during or post COVID recovery phase. Mucormycosis is caused by the inhalation of filamentous (hyphal form) fungi especially in the patients who are immunosuppressed.

Recent alarming rise in the number of COVID-19 patients with mucormycosis infection are mostly due to uncontrolled diabetes and excessive administration of steroids for the treatment of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection (1). The triad of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), corticosteroid use and uncontrolled diabetes mellitus have been evident for significant increase in the incidence of angioinvasive maxillofacial mucormycosis (2).

Epidemiology

Invasive "black fungus" (Mucormycosis) is creating an epidemic within a global pandemic (3). Globally, the reported burden of mucormycotic cases (71% of the global cases) is highest in India. It has been estimated that the high prevalence of Mucormycosis in India is nearly 70 times that of the global norm and mean.

The prevalence of mucormycosis in India is about 80 times the prevalence in developed countries, being approximately 0.14 cases per 1000 population (4). Currently, in India diabetes mellitus is the most prevalent underlying comorbidity associated with Mucormycosis followed by haematological neoplasms or malignancy, and solid organ transplantation. It has been found that patients suffering from kidney diseases (namely chronic kidney diseases in the form of renal failure) as well as pulmonary

Departments of Pharmacology, and [1]General Medicine, Government Medical College, Jammu, Jammu and Kashmir, India

Correspondence to: Dr. Anil Mahajan, House No. 42, Sector-1, Channi Himmat, Jammu-180015 (J&K), India

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tuberculosis (namely post pulmonary tuberculosis) are at a higher risk for contracting mucormycosis infections (3).

Common Affected Sites

The most commonly reported infection sites are rhino-orbital/rhino-cerebral mucormycosis (2). Mucormycosis involving nose and sinuses (88.9%) is most common followed by rhino-orbital (56.7%). Pulmonary mucormycosis is observed in about 10% of patients (5). Cutaneous, or gastrointestinal infections can also occur.

Mortality

Infection with mucormycosis is associated with high mortality primarily due to complications such as cavernous sinus thrombosis, disseminated infection, osteomyelitis, and death. The overall mortality rate has been reported upto 50% to 66.7% in the recent studies among affected patients (6,7).

Indian Scenario

Till 15th July 2021, 432 cases of Mucormycosis have been reported and uploaded on COVID 19 portal of India. Most common types reported in India are Rhinocerebral (77.6%), cutaneous (4.3%), and pulmonary (3%). Among these 84.4% patients had the positive test for COVID 19 disease. States highest affected in the decreasing order are Maharashtra, Gujarat, Madhya Pradesh, Haryana, Delhi, Utter Pradesh, Bihar, Chhattisgarh, Karnataka and Telangana. In J&K till date 56 cases have been reported among which 46 are confirmed and 10 are suspected, 23 cured and rest are under treatment with total 23 deaths reported so far.

Pathogenesis

Fungal inoculation into the host tissues results in the activation of both innate and adaptive immune responses. However, in the presence of hyperglycemia the innate immune system is defective resulting in the inhibition of neutrophil migration, chemotaxis and decreased phagocytosis. Diabetes with ketoacidosis [DKA] is 50 percent more likely to develop mucormycosis than without DKA. Ketone bodies [beta-hydroxybutyrate] by virtue of its high pH increase the availability of free iron by inhibiting the sequestration of iron by transferrin and ferritin. This high pH and increased availability of free iron promote fungal growth in a susceptible host. Similarly, at a physiological concentration of ketone bodies, expression of GRP78 [Glucose Regulator Protein 78] in endothelium and fungal protein CotH3 is increased.

Hyperglycaemia also increases the risk of mucormycosis by the following mechanisms: (i) inhibiting the action of iron sequestrating proteins, (ii) upregulation of GRP78 and fungal protein, CotH3, (iii) impaired phagocytosis and chemotaxis by neutrophils, and (iv) by weakening the oxidative and nonoxidative pathways. Rhino-cerebral mucormycosis is almost always associated with diabetic ketoacidosis. While hematological malignancies and neutropenia cause pulmonary disease, trauma usually leads to cutaneous mucormycosis (8).

It is confirmed that the patients with ketoacidosis are at a higher risk of developing rhino-cerebral mucormycosis. The mechanisms which predispose the diabetic ketoacidosis to rhino-cerebral disease are obscure. Perhaps the acidic pH of DKA and high free iron have a role to play. Mucorales exclusively depend on the host iron for their metabolic requirements. Other observations in DKA like impaired neutrophil chemotaxis and phagocytosis cannot be consistently applied to the increased rhino-cerebral cases due to the fact that neutropenic patients frequently develop pulmonary and disseminated disease rather than rhino-cerebral disease (8).

Although the mechanism is not fully understood, evidence suggests that SARS-CoV-2 infection impairs the function of pancreatic beta cells resulting in acute DKA. It is interesting to note that the ketoacidosis in euglycemic states was also noted in many patients throughout the infection (9).

In COVID-19 patient's studies have shown that the glycemic control is not only poor but also necessitates insulin to be utilized in exceedingly high doses for their management. This transient elevation of glucose during the course of disease can be possibly linked to insulin resistance caused by increased levels of inflammatory cytokines in the body (9).

SARS-CoV-2 could possibly trigger diabetes with ketoacidosis at least in a small subset of population that may even persist several weeks or months after apparent recovery from the disease. This could possibly corroborate the late onset of mucormycosis in a few clinical series usually weeks after the recovery from COVID-19. Therefore, hyperglycemia, ketoacidosis, increased availability of free iron and impaired phagocytic action invariably leads to an environment conducive for the growth of fungi. Similarly, increased serum iron and overexpression of GRP78 in DKA cause the endothelial damage predisposing the host to fungal invasion (8).

Apart from the viral-induced hyperglycemia, systemic

steroids and antiviral agents used in the management of COVID-19 can also be considered as contributing factors in the worsening of hyperglycemia. There is an increased incidence of mucormycosis infections in diabetic patients treated for COVID-19, who received corticosteroid administration during the course of treatment. Corticosteroids and immunosuppressive agents are risk factors and prolonged high dose (>3 weeks) of corticosteroids predisposes an individual to angioinvasive mucormycosis infection (10). The propensity of corticosteroids to impair migration, ingestion and phagolysosome fusion in macrophages may explain suppressed immunity in such patients. There is a positive correlation between coronavirus and mucormycosis of the paranasal sinuses (ethmoidal sinus in particular) which must be taken into consideration.

Notwithstanding the acknowledged role of ketoacidosis, high blood sugar and iron metabolism in the pathogenesis of mucormycosis, other factors involved in SARS-CoV-2 pathophysiology which might modify or enhance the pathogenesis of Mucorales are high ferritin, increased serum iron, endothelitis, hepcidin activation and upregulation of GRP78 receptors. Arguably all these predisposing factors are primarily mediated by the SARS-CoV-2 infection implying a possible association between high incidence of mucormycosis and COVID-19 patients (11).

Clinical Presentation

Commonly reported symptoms are pain and redness around eyes and/or nose, fever, headache, coughing, shortness of breath, bloody vomitus, altered mental status, facial pain, pain over sinuses, pain in teeth and gums, paraesthesia/ decreased sensation over half of face, blackish discolouration of skin over nasolabial groove/ alae nasii , nasal crusting and nasal discharge which could be blackish or blood tinged, chemosis, periorbital swelling, blurring of vision/ diplopia, loosening of teeth/ discoloration of palate/ gangrenous inferior turbinates, worsening of respiratory symptoms, hemoptysis, chest pain, alteration of consciousness, headache (11). The median time interval between COVID-19 diagnosis and the first evidence of mucormycosis infection or CAM diagnosis is 15 days (4).

Clinical suspicion should be kept high if COVID patient present with sinusitis - nasal blockade or congestion, nasal discharge (blackish/bloody), local pain on the cheek bone, one sided facial pain, numbness or swelling, blackish discoloration over bridge of nose/palate, toothache, loosening of teeth, jaw involvement, blurred or double vision with pain, fever, skin lesion, thrombosis and necrosis (eschar), chest pain, pleural effusion, haemoptysis, worsening of respiratory symptoms (5).

Risk Factors

A systematic review of the studies and cases reported worldwide suggested that Mucormycosis was predominantly seen in males (78.9%), both in people who were active (59.4%) or recovered (40.6%) from COVID-19. Pre-existing diabetes mellitus (DM) was present in 80% of cases, while concomitant diabetic ketoacidosis (DKA) was present in 14.9%. Corticosteroid intake for the treatment of COVID-19 was recorded in 76.3% of cases (5).

Further, prolonged hospitalisation, patient on ventilator, patient on high flow mask or Bipap machines for prolonged period are also high-risk patients, presence of an open wound, HIV/AIDS, cancer, and organ transplant, mucormycosis can result in a severe invasive fungal infection. It is speculated that the indiscriminate use of steroids, antibiotics and zinc as a self-medication practice that increased during the COVID-19 epidemic may have promoted the dysbiosis of gut microbiota thereby inducing immune-suppression and making the risk group highly susceptible to this mycotic disease (11).

Diagnosis

No specific biomarkers are available to diagnose mucormycosis; imaging of the involved area and histopathological examination of the biopsied tissue are most important in diagnosis (11).

Histopathology, direct examination and culture remain essential tools, although the molecular methods are improving. The internal transcribed spacer (ITS) region is the most widely sequenced DNA region for fungi and it is recommended as a first-line method for species identification of Mucorales. New molecular platforms are being investigated and new fungal genetic targets are being explored. Molecular-based methods have gained acceptance for confirmation of the infection when applied on tissues. Methods for the detection of Mucorales DNA in blood have shown promising results for earlier and rapid diagnosis and could be used as screening tests in high- risk patients, but have to be validated in clinical studies (12).

COVID-19 infection may induce significant and persistent lymphopenia, which in turn increases the risk of opportunistic infections. It is also noted that 85% of

the COVID- 19 patients' laboratory findings showed lymphopenia. This means that patients with severe COVID-19 have markedly lower absolute number of T lymphocytes, $CD4^+$T and $CD8^+$ T cells and, since the lymphocytes play a major role in maintaining the immune homeostasis, the patients with COVID-19 are highly susceptible to fungal co-infections (7).

Based on the warning signs and diagnostic tests, the diagnosis of Rhino-orbito-cerebral mucormycosis (ROCM) can be classified into three types (13):

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.

Investigations (14)

i. NCCT PNS (to see bony erosion).
ii. HRCT chest (≥10 nodules, reverse halo sign, CT bronchus sign etc.) and CT Angiography.
iii. MRI brain for better delineation of CNS involvement.
iv. KOH staining and microscopy, histopathology of debrided tissue and culture
v. MALDI-TOF, if available
vi. Presence of Ribbon like aseptate hyphae 5-15 μ that branch at right angles.

Prevention (11)

- Control diabetes and diabetic ketoacidosis.
- Reduce steroids (if patient is still on) with aim to discontinue rapidly.
- Discontinue immunomodulation drugs.
- No antifungal prophylaxis needed.
- Extensive surgical debridement - to remove all necrotic materials.
- Rational use of antibiotics.
- Timely start of medical treatment.
- Install peripherally inserted central catheter.
- Maintain adequate systemic hydration.
- Monitor patients clinically and with radio-imaging for response and to detect disease progression.
- At present no guideline suggest the prophylactic role of anti-fungal therapy.
- High suspicion and prompt management is key to successful outcome in such patients.
- ICU and hospital disinfection protocols to be strictly followed.
- Comprehensive management teams be in place.

Management

Lipid formulations of amphotericin B (LFAB) are the mainstay of therapy, but the newer triazoles, posaconazole (POSA) and isavuconazole (ISAV) (the active component of the prodrug isavuconazonium sulfate), may be effective in patients refractory to or intolerant of LFAB.

Liposomal amphotericin B in initial dose of 5mg/kg body weight (10 mg/kg body weight in case of CNS involvement) is the treatment of choice. Each vial contains 50 mg. It should be diluted in 5% or 10% dextrose; it is incompatible with normal saline/ ringer lactate. It has to be continued till a favourable response is achieved and disease is stabilized which may take several weeks following which step down to oral posaconazole (300 mg delayed release tablets twice a day for 1 day followed by 300 mg daily) or isavuconazole (200 mg 1 tablet 3 times daily for 2 days followed by 200 mg daily) can be done (15,16).

The latest recommendations strongly recommend, as first-line therapy, the use of liposomal amphotericin B (≥5mg/kg) combined with surgery whenever possible. Isavuconazole and intravenous or delayed-release tablet forms of posaconazole have remained second-line (17,18).

Conventional amphotericin B (deoxy cholate) in the dose 1-1.5mg/kg may be used if liposomal form is not available and renal functions and serum electrolytes are within normal limits. Early surgical debridement or excision plays an important adjunctive role (18).

Conclusions

Rhino-orbital-cerebral mucormycosis is a 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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Conflicts of Interest

There are no conflicts of interest.

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