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Original Research

Mucormycosis: A New Threat in Pandemic

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ABSTRACT:
The second wave of COVID-19 has affected India substantially, with the highest number of daily reported cases being slightly more than 0.4 million on May 7, 2021, and has declined since. Even though the number of new reported cases has reduced, India still contributed to approximately 45% of the new cases detected globally and nearly 34% of the deaths globally during the third week of May, 2021. As India continues to achieve stability over the existing situation, another imminent threat has emerged as a challenge to India in the form of corona virus disease-associated mucormycosis. Mucormycosis, caused by a group of moulds called mucormycetes, is a rare but potentially fatal infection if inadequately treated. Often referred to as the so-called black fungus, the incidence of mucormycosis has risen more rapidly during the second wave compared with the first wave of COVID-19 in India, with at least 14 872 cases as of May 28, 2021. The most common causes attributed to the rise of mucormycosis in COVID-19 patients are uncontrolled diabetes, the excessive use of corticosteroids for immunosuppression, and long-term stays in the intensive care unit. The aim of present review of literature is to discuss this newer threat in detail.
Keywords: Covid-19, Mucormycosis, Black fungus

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INTRODUCTION

The corona virus disease pandemic has emerged as a community health disaster and is spreading exponentially across the globe. The first case of Covid-19 was reported in Wuhan City, China, in late December 2019. On 11th of February 2020, World Health Organization named the novel viral pneumonia as "Corona Virus Disease (COVID-19)" while the International Committee on Taxonomy of Viruses (ICTV) named this novel virus as "SARS-CoV-2" subsequent phylogenetic and taxonomic analysis.[1]

Corona virus disease 2019 (COVID-19) caused by severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) has been associated with a wide range of opportunistic bacterial and fungal infections. Both *Aspergillosis* and *Candida* have been reported as the main fungal pathogens for co-infection in people with COVID-19.[2,3]

Recently, several cases of mucormycosis in people with COVID- 19 have been increasingly reported world-wide, in particular from India. Mucormycosis is one of the rare fungal infections, which has a high rate

of morbidity and mortality. Its disease causing fungi is Mucormycetes and it belongs to the order Mucorales, subphylum Mucoromycotina.[4] Main challenge with mucormycosis is with the diagnosis and treatment of the disease, and with time there is a gradual increase in the incidence of the disease. The most common predisposing factor discovered in developed countries is Hematological malignancies, while uncontrolled diabetes seems to be the most common condition in developing countries.[5]

HISTORY

The first reported case of Mucomycosis was reported on 1885 when the German pathologist Paltauf described the first case as Mycosis Mucorina.[6] It was observed during 1980s and 1990s that cases of Mucormycosis was increasing in individual in immuno compromised conditions.[7] Rate of mucormycosis increased rapidly mostly in immunocompromised individuals consequently in 1980s and 1990s.[7] Thus a study was carried out depending upon the prevalence rate in France which showed amplification by 7.4% per year. The supposed possibility of seasonal variation of mucorales and its occurrence all over the world was also reported.[8]

ETIOPATHOGENESIS

The major risk factors for mucormycosis include uncontrolled diabetes mellitus in ketoacidosis, other forms of metabolic acidosis, treatment with corticosteroids, organ or bone marrow transplantation, neutropenia, trauma and burns, malignant hematologic disorders, AIDS, extremes of age, broad-spectrum antibiotics, iron overload, skin trauma, intravenous drug abuse, prophylactic voriconazole for aspergillosis and malnutrition., Mucormycosis acts as a destructive and potentially critical condition in diabetic patients due to increased availability of micronutrients and at same time compromised defence mechanism of the body.[9,10]

Some of the common hypotheses from literature include[11,12,,13]

- Serum inhibitory activity against Rhizopus species is low
- Decreased PH level and improved availability of iron for the pathogen
- Diminished facility to inhibit germination of Rhizopus species by pulmonary macrophages of persons suffering with diabetes mellitus

There is accelerated invasion of fungi in diabetes ketoacidosis, as acidic produces more free iron by reducing its binding to transferrin and low level of dialyzable inhibitory factor in diabetics makes it a suitable conditions for fungal duplication. Patients that are severely neutropenic and who lack phagocytic function are more prone for mucormycosis, but this is not seen patients suffering from AIDS. Thus, it implies that only the neutrophils are significant for inhibiting fungal proliferation and not the T lymphocytes.[14]

CLINICAL FINDINGS OF MUCORMYCOSIS[15, 16]

- One-sided facial pain, swelling, numbness
- Headache
- Nasal or sinus congestion
- Black lesions on nasal bridge or upper inside of mouth that quickly become more severe.
- Fever
- A bloody or blackish mucus discharge from the nose.
- Prominent aching in teeth, jawbone, degrading of tooth structures
- Sudden mobility of teeth especially in Maxillary arches.
- Hazy vision, with objects appearing blurred or in double, with eye pain
- Abnormal blood clotting or thrombosis of tissues, along with skin injury and damage or necrosis of dermal cells
- Further deterioration of respiratory functions, with chest pain, Excess fluid build-up in lungs i.e. pleural effusion and coughing up blood or hemoptysis

DIAGNOSIS OF MUCORMYCOSIS

The diagnosis of mucormycosis is challenging and treatment should start as early as possible in order to decrease mortality. No circulating antigen detection test is available for the diagnosis of mucormycosis.[17,18]

CYTOPATHOLOGY

The hyphae may be difficult to observe on an unenhanced Potassium hydroxide wet mount and may not stain well with conventional Gram stain. The use of chitin binding stains, such as Calcoflour, Fungi-flour, or Blancoflour, may be used with a fluorescent microscope to identify hyphal elements on Potassium hydroxide wet mounts.[19]

HISTOPATHOLOGY

Numerous large branching pale-staining, wide, flat non-septal hyphae with branching at right or obtuse angles are seen in the affected tissue from the lesions showing extensive necrosis, round or ovoid sporangia are also frequently seen in culture.[19] The histological detection of mucorales organisms in tissue and their interpretation may be difficult. These organisms are typically difficult to observe on hematoxylin-eosin stains. On the other hand, Periodic acid Shiff and Gomori methenamine silver stains may be used for a fully characterized appearance of the organism. Microscopic characterization of nonseptate hypae, rhizoids, columellae, sporangia and sporagiospores help to define genus and species within the order mucorales.[20]

RADIOLOGICAL INVESTIGATION

Posteroanterior view of chest shows multiple (≥10) nodules, and pleural effusion in mucormycosis. Computerized tomography (CT) scans, show a characteristic reverse halo sign (RHS) which is considered as gold standard and a strong indicator of pulmonary mucormycosis. Positron emission tomography-computed tomography (PET/CT) with [18F]- fluorodeoxyglucose (FDG) imaging technique, aids in the diagnosis and management of mucormycosis. Endobronchial ultrasound-guided fine needle aspiration is also a useful diagnostic tool when feasible. "Black turbinate sign" which refers to an area of non-enhancing mucosa on MRI is a characteristic image feature in cavernous sinus thrombophlebitis mucor infection.[19,21,22]

Management of mucormycosis

Do's	Don'ts
• Control hyperglycemia • Monitor blood glucose level post COVID-19 discharge and also in diabetics • Use steroid judiciously – correct timing, correct dose and duration • Use clean, sterile water for humidifiers during oxygen therapy • Use antibiotics/antifungals judiciously	• Do not miss warning signs and symptoms • Do not consider all the cases with blocked nose as cases of bacterial sinusitis, particularly in the context of immunosuppression and/or COVID-19 patients on immunomodulators • Do not hesitate to seek aggressive investigations, as appropriate (KOH staining & microscopy, culture, MALDITOF), for detecting fungal etiology Do not lose crucial time to initiate treatment for mucormycosis[23]

TEAM APPROACH[23]

- Microbiologist
- Internal Medicine
- Specialist Intensivist
- Neurologist
- ENT Specialist
- Ophthalmologist
- Dentist Surgeon (maxillofacial/plastic)
- Biochemist

The management of mucormycosis is based on multiple interventions occurring simultaneously, or with different timing and intensity. The basic principles of mucormycosis treatment include risk stratification for severity of the diseases, and intense attempts for early, clinical and laboratory diagnosis; timely initiation of an effective antifungal therapy (monotherapy or combination therapy) along with aggressive surgical debridement of necrotic lesions; reverse of immunosuppression (discontinuation of chemotherapy and increase of neutrophils), and when feasible control of the underlying medical condition. Early diagnosis and prompt therapeutic intervention may prevent progressive tissue invasion and its sequelae, may also reduce the need for extensive surgery and subsequent deformity, and may improve survival.[16,24]

In patients with uncontrolled diabetes rapid correction of metabolic abnormalities is mandatory also use of sodium bicarbonate (with insulin) so as to reverse ketoacidosis, even if acidosis is mild or severe it will help with a better outcome because it reduces the ability of Mucorales to invade the host tissues.[25]

Amphotericin B (AMB) and its lipid formulations, and recently isavuconazole have been studied as first-line therapy for mucormycosis. On the contrary, posaconazole has been mainly studied as salvage therapy.[26,27] The recommended dose for liposomal amphotericin B (AmB) is 5 mg/kg/day and as high as 10 mg/kg/day for infection involving the central nervous system.[27]

Isavuconazole a recently developed triazole, has shown effect against a wide spectrum of fungal infections including Mucorales. Isavuconazole is a new broad-spectrum triazole and is the biologically active agent of the prodrug isavuconazonium sulfate. It is approved in the United States for the treatment of mucormycosis, and in Europe for the treatment of mucormycosis when Amphotericin B is not feasible. It is available in both intravenous and oral formulations and it is administered with a loading dose of 200 mg three times a day for two days and 200 mg daily thereafter.[27,28]

Use of hyperbaric oxygen is another adjunctive therapy in order to make a more-oxygen enriched cell environment in combination with administration of cytokines at the same time with the antifungal therapy. in vitro and some preclinical data on granulocyte-macrophage colony stimulating factor and/or interferon-γ has shown to enhance the immune

response against certain Mucorales and thus can potentially help in treating the infection, as no clinical data is present to prove their efficacy, these therapies should be used with caution.[27,29]

Surgery management involves resection of necrotic tissues is the core of mucormycosis therapy. In pulmonary mucormycosis, surgical treatment along with appropriate systemic antifungal therapy has been shown to significantly improve survival compared to antifungal therapy alone. Bouts of hemoptysis due to cavitation of lesions near hilar vessels is an indication for urgent resection of the lesion. In certain cases of localised disease surgery might be curative. In patients with rhino-orbital mucormycosis, magnetic resonance imaging might have a role in staging the resectability of the lesions. Similarly, surgical removal of infected tissues is of paramount importance in the treatment of rhino-orbital-cerebral disease. It should be underlined however, that the effect of surgery on outcome is difficult to be defined, due to selection biases. An endoscopic approach is preferred over the open surgery in patients with early, limited disease, or with significant medical comorbidities. Open surgeries are preferred for extensive disease, and include maxillectomy, orbital exenteration and/or craniofacial resection; yet, no survival benefit has been proved for such radical approach, especially in patients with limited life expectancy.[30,31,32]

CONCLUSION

India battles a new challenge in mucormycosis, a rare fungal disease with a high mortality rate commonly referred to as 'black fungus'. Mucormycosis causes blackening or discolouration over the nose, blurred or double vision, chest pain, breathing difficulties and coughing of blood. Corona virus patients with diabetes and a weakened immune system are particularly prone to attack. Pain and redness around the eyes or nose, fever, headache, coughing, shortness of breath, bloody vomit and altered mental status are some of its symptoms. Rapid accurate diagnosis, administration of drugs, adjunctive application of hyperbaric oxygen, recombinant cytokines or transfusion of granulocyte, surgical debridement, and prosthetic obturator are the methods involved in successful management for mucormycosis.

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