Original Research Article

Mucormycosis in COVID-19- A burgeoning epidemic in the ongoing pandemic

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Abstract

Introduction: Along with COVID-19, India is also experiencing an outbreak of mucormycosis, a deadly fungal infection, which is affecting thousands of COVID-19 patients. Also known as black fungus, this disease is caused by opportunistic fungi in the Mucorales family. **Material and Method:** This is a retrospective study among mucormycosis patients, admitted to tertiary care teaching centre over a period of 3 months. These cases were admitted for the management of mucormycosis. They were assessed and treated by the relevant specialties at various time points, which included internists, infection disease specialists, intensivists and otolaryngologists. Data pertaining to demographics, clinical features, co-morbidities, laboratory investigations, histopathology, management and outcomes were collected. **Results:** In our study, 461 patients diagnosed with mucormycosis were included. Male were predominant (63.3%) and the mean age was 53 ± 9.7 years. All patients initially presented with nasal congestion with or without discharge consistent with sinusitis. The majority of patients with mucormycosis experienced a non-descript localised or generalised headache. Symptoms include diplopia, visual disturbances, facial weakness or numbness. Features of ophthalmoplegia, proptosis and long-tract signs were also observed in a proportion of patients. Imaging investigations revealed that most of the patients had features of maxillary sinusitits. Based on microbiology and/or histopathology, all subjects had features of mucormycosis. A small proportion had additional co-infection with aspergillosis and bacteria. **Conclusion:** The incidence of mucormycosis in the setting of the COVID-19 pandemic is likely to rise and result in significant morbidity and mortality. Physicians caring for severely ill patients with COVID-19 and concomitant poorly controlled diabetes should have a high index of suspicion of mucormycosis, especially if corticosteroids are used during the course of disease.

Keywords: Mucormycosis, COVID-19, Anti-fungal treatment

Introduction

India is experiencing a detrimental surge of coronavirus disease 2019 (COVID-19) cases during its second wave with a total of 28 996 949 cases and 351 344 deaths as of 7 June 2021, which is increasing with every passing day [1]. This sudden rise of COVID-19 cases has been an interplay of various factors, such as the appearance and arrival of variants of concern including B.1.617.2, B.1.1.7, B.1.351 and P.1, breach of standard public health protocols such as hand washing, wearing a mask and social distancing, and hosting of mega-events like the Kumbh Mela festival and rallies which attracted huge masses [2].

Along with COVID-19, India is also experiencing an outbreak of mucormycosis, a deadly fungal infection, which is affecting thousands of COVID-19 patients. Also known as black fungus, this disease is caused by opportunistic fungi in the Mucorales family, which is commonly found in the ecosystem and often associated with rotting organic matter. Humans can be infected by inhaling and consuming spores in food or drugs, or contaminating wounds with spores [3]. Patients with immunocompromised conditions, including those with COVID-19, are mostly affected. Immune function can be repressed by immunosuppressive medications, such as corticosteroids, and a variety of immunocompromising illnesses, such as cancer, diabetes and retroviral disease, as well as patients who have undergone transplant surgeries [4].

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With an overall case fatality rate of 50%, black fungus has emerged as a public health concern in India, especially among COVID-19 patients [5]. Due to this unfortunate scenario and possible underreporting of cases, the central government declared mucormycosis as a notifiable disease in accordance with the Epidemic Diseases Act of 1897. As of 7 June 2021, there are more than 28 200 reported cases of mucormycosis in the country [6,7].

Public health authorities and medical specialists claim that this new epidemic was exacerbated by the overdosage of corticosteroids among COVID-19 patients, as well as panic use among individuals who fear for their lives due to the increasing COVID-19-related deaths. In September 2020, the World Health Organization (WHO) recommended the use of corticosteroids to patients with severe and critical COVID-19. On the other hand, corticosteroids should not be used in treating patients with asymptomatic, mild and moderate COVID19 symptoms, unless they are taking them for another disease [8]. Following this recommendation, many Indian physicians included corticosteroids in treating severe and critical COVID-19 cases, such as patients who are on a ventilator or requiring supplemental oxygen. However, the WHO recommendation on daily dosage was not followed. The WHO suggested 32 mg of methylprednisolone per day while the Indian Directorate General of Health Services advised a daily dose of 1–2 mg/ kg, approximately 70–140 mg of methylprednisolone for a severe COVID-19 patient with an average weight of 70 kg [9]. Several COVID-19 patients became immunocompromised as a result of the high doses of corticosteroids, making them more susceptible to fungal infections. Furthermore, the general public, mostly with mild and non-severe COVID-19 symptoms, also took corticosteroids out of panic and anxiety without medical advice leading to emergence of the black fungus epidemic.

Intake of corticosteroids for COVID-19 treatment was observed in 76% of mucormycosis cases [10].

Material and Method

This is a retrospective study among patients diagnosed with mucormycosis, admitted to tertiary care teaching centre over a period of 3 months. These cases were admitted for the management of mucormycosis. They were assessed and treated by the relevant specialties at various time points, which included internists, infection disease specialists, intensivists and otolaryngologists. Data pertaining to demographics, clinical features, co-morbidities, laboratory investigations, histopathology, management and outcomes were collected.

Inclusion criteria

All age group of either gender patients with clinically and histopathologically proven cases of mucormycosis.

The diagnosis of COVID-19 was based on real-time polymerase chain reaction (RT-PCR) test from nasopharyngeal or oropharyngeal swabs. In clinically suspected patients, presence of fungal hyphae, characteristic of Mucorales fungi, by direct examination in 10% potassium hydroxide (KOH) from scrapping and biopsy was used for diagnosis. Mucormycosis was subsequently proven based on microbiological culture or specific histological features from biopsy specimen. Apart from ascertaining COVID-19 status, blood investigations and computed tomography (CT) and/or magnetic resonance imaging (MRI) of the orbit, brain and/or paranasal sinuses were performed for all cases to assess the extent of involvement from mucormycosis.

Results

In our study, 461 patients diagnosed with mucormycosis were included.

Table 1: Demographics of the patients

Gender and Mean age	Number	Percentage
Male	292	63.3
Female	169	36.6
Mean age ± SD	53 ± 9.7 years	

In table 1, male were predominant (63.3%) and the mean age was 53 ± 9.7 years.

Table 2: Clinical features of mucormycosis

Clinical features of mucormycosis	Number	Percentage
Nasal congestion	322	69.8
Headache	223	48.3
Visual disturbances	113	24.5
Diplopia	63	13.6
Proptosis	40	8.6
Ophthalmoplegia	69	14.9
Facial numbness	9	1.9
Facial weakness	7	1.5

In table 2, All patients initially presented with nasal congestion with or without discharge consistent with sinusitis. The majority of patients with mucormycosis experienced a non-descript localised or generalised headache. Symptoms include diplopia, visual disturbances, facial weakness or numbness. Features of ophthalmoplegia, proptosis and long-tract signs were also observed in a proportion of patients.

Table 3: Co-morbidities of the patients

Co-morbidities	Number	Percentage
Diabetes mellitus	299	64.8
Hypertension	213	46.2
Ischaemic heart disease	91	19.7
COPD	71	15.4
Hypothyroidism	53	11.4
Rheumatoid arthritis	37	8.0

In table 3, a maximum number of patients were history of diabetes mellitus (64.8%) while 46.2% were on medications for hypertension.

Table 4: Severity of COVID-19 pneumonia (based on CT Severity Score)

Severity	Number	Percentage
Mild (total score)	89	19.3
Moderate (total score 8-17)	305	66.1
Severe (total score ≥18)	67	14.5

In table 4, based on the CT thorax severity score, majority (66.1%) had moderate-to-severe COVID-19 pneumonia.

Table 5: Corticosteroid usage for COVID-19 treatment

Route	Number	Percentage
Intravenous (5 days)	40	11.5
Oral	307	88.5

In table 5, systemic corticosteroids were administered to 347 patients. The maximum patients received oral (88.5%) corticosteroids.

Table 6: Sinus involvement based on CT PNS or MRI findings

Sinus involvement	Number	Percentage
Frontal	322	69.8
Maxillary	411	89.1
Ethmoid	217	47.0
Sphenoid	270	58.5

In table 6, imaging investigations revealed that maximum patients had features of maxillary sinusitis (89.1%).

Table 7: Histopathological and/or microbiological diagnosis

	Number	Percentage
Mucormycosis only	222	48.1
Mucormycosis & Aspergillosis	166	36.0
Mucormycosis & bacterial infection (*K pneumoniae, E coli, P aeruginosa*)	73	15.8

In table 7, based on microbiology and/or histopathology, all subjects had features of mucormycosis. A small proportion had additional co-infection with aspergillosis and bacteria.

Table 8: Management of mucormycosis

	Number	Percentage
Anti-fungal treatment		
Amphotericin B	461	100
Type of surgery for the treatment of mucormycosis		
Not performed (due to poor prognosis)	33	7.1
Modified Denker's procedure	181	39.2
Functional endoscopic sinus surgery (FESS) debridement	221	47.9

In table 8, all individuals were treated with liposomal amphotericin B while majority of them underwent surgical treatment. Factors for not carrying out surgery were poor prognosis or death of the patients before the planned procedure.

Discussion

Another potential factor of the mucormycosis outbreak among Indian COVID-19 patients is their pre-existing diabetes. Given that India is the diabetes capital of the world, the indiscriminate usage of steroids for patients with diabetes potentially led to a surge of mucormycosis cases in the country. 94% of patients with COVID-19- associated mucormycosis have a history of poorly controlled diabetes [11]. Other pre-disposing factors include prolonged stay in intensive care units and comorbidities like malignancy or post-transplant status [12]. Clinical features of COVID-19-associated mucormycosis include symptoms like nasal blockage and discharge, pain and/or redness around eyes or nose, headache, fever, shortness of breath, coughing, hematemesis and altered mental status [13].

Mucormycosis may affect the lungs, but nose and sinuses are the most frequent infection sites. It can then spread to the eyes, causing blindness, or to the brain, causing headaches and seizures [14]. Thus, the most common form is rhino-orbito-cerebral mucormycosis, followed by pulmonary mucormycosis. Regarding the diagnosis, the mean duration between diagnosis of COVID-19 and onset of mucormycosis symptoms was 15.6 ± 9.6 days. A delay of even 6 days in initiating treatment doubles the 30-day mortality from 35% to 66% [15]. Therefore, early diagnosis and management may prevent further progression of the disease or even mortality. However, despite being one of the largest pharmaceutical hubs globally, there is a shortage of Amphotericin B, the current treatment for mucormycosis, in India due to the increasing cases of black fungus [16].

The Centers for Disease Control and Prevention and the All India Institute of Medical Sciences enumerated important factors such as control of blood sugar level, steroid monitoring and dosage variance according to the severity of COVID-19 infection. Inappropriate steroid consumption raises the blood sugar level and weakens the immune system, a condition that favours fungal infection. Medical procedures include rapid control of diabetic ketoacidosis, reduction or discontinuation of steroids and immunomodulating drugs, antifungal prophylaxis, radioimaging and clinical monitoring of fungal progression [17]. Surgical removal of necrotic tissue, debridement and enucleation of the eye, if involved, have also proved to be life-saving. Other clinical interventions include proper cleaning and sterilisation of humidifiers and ventilators, utilisation of disposable or disinfected personal protective equipment, and proper hygiene maintenance. Even though measures have been declared, a wide gap between various schemes and policy implementation still persists. The lacunae in policy execution might have galvanised the crisis of fungal outbreak. The wide disparity in doctor-to-patient ratio (8 physicians per 10000 population) often leads to poor prognosis, negligence and inadequate medical supplies [18]. Dearth of medical supplies and medicines, such as Amphotericin B, and shortage of beds in hospitals (8.5 hospital beds per 10 000 population) have caused widespread unavailability of prompt treatment leading to death of patients [19]. Another challenge with mucormycosis is the requirement of interdisciplinary management guidelines, as it does not fall under one speciality owing to its widespread involvement. The necessity to treat mucormycosis long-term with nephrotoxic drugs that can further burden the healthcare system with increasing demands of haemodialysis and hospitalisations due to renal failure should also be considered [20].

Conclusion

The incidence of mucormycosis in the setting of the COVID-19 pandemic is likely to rise and result in significant morbidity and mortality. Physicians caring for severely ill patients with COVID-19 and concomitant poorly controlled diabetes should have a high index of suspicion of mucormycosis, especially if corticosteroids are used during the course of disease. Strategies to optimise glycaemic control should be emphasised to avoid poorer outcomes. The expedient commencement of antifungal therapy together with surgical debridement may help to improve the survival of these patients.

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