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Management of Mucormycosis in patients associated with COVID-19

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Abstract: ***Introduction:*** There are increasing case reports of rhino-orbital mucormycosis in people with coronavirus disease 2019 (COVID-19), especially from India. Diabetes mellitus (DM) is an independent risk factor for both severe COVID-19 and mucormycosis. ***Material and Methods:*** This is a prospective 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 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, maximum number of patients were history of diabetes mellitus (71.5%) while 51.5% were on medications for hypertension. Based on the CT thorax severity score, majority (60.7%) had moderate-to-severe COVID-19 pneumonia. Imaging investigations revealed that maximum patients had features of maxillary sinusitis (83.8%). All individuals were treated with liposomal amphotericin B while majority of them underwent surgical treatment. ***Conclusion:*** Preventive measures may need to focus on identification and optimal management of risk factors for Coronavirus Disease Associated Mucormycosis, including aggressive glycemic control, avoidance of steroid overuse, and possibly environmental measures.

Keywords: Amphotericin B, Mucormycosis, COVID-19.

INTRODUCTION

Mucormycosis also known as black fungus, (previously called zygomycosis) is a serious but rare fungal infection caused by a group of moulds called mucormycetes. These moulds live throughout the environment. [1] Mucormycosis mainly affects people who have health problems or take medicines that lower the body's ability to fight germs and sickness. It most commonly affects the sinuses or the lungs after inhaling fungal spores from the air. It can also occur on the skin after a cut, burn, or other type of skin injury. [2]

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 14872 cases as of May 28, 2021. The state of Gujarat alone contributed to the highest number of cases, with at least 3726 cases of mucormycosis in patients with active and recovered COVID-19, followed by the state of Maharashtra. [3] Since the communication from the Health Minister of Maharashtra on May 19, 2021, there have been 90 deaths attributable to mucormycosis. Other states have also shown a steady rise in the number of mucormycosis cases and deaths related to it; with multiple states, already having declared it as an epidemic and a notifiable disease to the national health authorities. [4]

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 longterm stays in the intensive care unit. [5] Undertaken measures to ascertain control over the situation by setting up special task forces, issuing guidelines, arranging separate wards in hospitals for the management of mucormycosis cases, and procuring the drugs required for treatment. Approximately 0·1 million vials of amphotericin B, the drug used in the medical management of mucormycosis, have already been distributed to the states. [6] The Ministry also needs to step up to monitor and analyse the situation; to disseminate information, education, and communication materials for the general public; and to undertake essential measures for preventing a further rise in the number of mucormycosis cases in patients with COVID-19 and mortality.

These findings need a relook in the context of COVID-19 pandemic where corticosteroids are often being used. There has been a steep rise in case reports/series of mucormycosis in people with COVID-19 especially from India. [7] Similarly, many cases are being reported from other parts of globe. Several anecdotal cases are also being reported in grey literature such as the print and electronic media. These finding are unprecedented and carry an immense public health importance, primarily because fatality rate with mucormycosis is pretty high. Especially the intracranial involvement of mucormycosis increases the fatality rate to as high as 90%. [8] Moreover, rapidity of dissemination of mucormycosis is an extraordinary phenomenon and even a delay of 12 h in the diagnosis could be fatal, the reason 50% of cases of mucormycosis have been historically diagnosed only in the post-mortem autopsy series. [9] This prompted us to conduct a study of mucormycosis in people with COVID-19, to know its temporal associations in relation to comorbidities, association with drugs being used in COVID-19 and overall characteristics of patients with its outcome. We additionally postulated a mechanistic explanation as to why mucormycosis could be increasingly linked to COVID-19 and is being reported increasingly from India.

Materials And Methods

This is a prospective 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 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, 130 patients diagnosed with mucormycosis were included.

Table 1: Demographics of the patients

Gender and Mean age	Number	Percentage
Male	79	60.7
Female	51	39.3
Mean age ± SD	51 ± 8.6 years	

In table 1, male was predominant (60.7%) and the mean age was 51 ± 8.6 years.

Table 2: Clinical features of mucormycosis

Clinical features of mucormycosis	Number	Percentage
Nasal congestion	102	78.4
Headache	83	63.8
Visual disturbances	51	39.2
Diplopia	21	16.1
Proptosis	13	10.0
Ophthalmoplegia	22	16.9
Facial numbness	2	1.5
Facial weakness	1	0.7

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	93	71.5
Hypertension	67	51.5
Ischaemic heart disease	22	16.9
COPD	19	14.6
Hypothyroidism	12	9.2
Rheumatoid arthritis	9	6.9

In table 3, a maximum number of patients were history of diabetes mellitus (71.5%) while 51.5% were on medications for hypertension.

Table 4: Laboratory Parameters of patients

Parameters	Mean±SD
HsCRP (mg/L)	13±2.3
Ferritin (ng/mL)	139±3.7
HbA1c	7.1±0.9
Interleukin-6 (pg/mL)	17±2.1
D Dimer (µg/mL)	1.23±0.2

Table 5: Severity of COVID-19 pneumonia (based on CT Severity Score)

Severity	Number	Percentage
Mild (total score)	34	26.1
Moderate (total score 8-17)	79	60.7
Severe (total score ≥18)	17	13.0

In table 5, based on the CT thorax severity score, majority (60.7%) had moderate-to-severe COVID-19 pneumonia.

Table 6: Corticosteroid usage for COVID-19 treatment

Route	Number	Percentage
Intravenous (5 days)	17	13.0
Oral	113	86.9

In table 6, the maximum patients received oral (88.5%) corticosteroids.

Table 7: Sinus involvement based on CT PNS or MRI findings

Sinus involvement	Number	Percentage
Frontal	91	70.0
Maxillary	109	83.8
Ethmoid	51	39.2
Sphenoid	63	48.4

In table 7, imaging investigations revealed that maximum patients had features of maxillary sinusitis (83.8%).

Table 8: Histopathological and/or microbiological diagnosis

	Number	Percentage
Mucormycosis only	61	46.9
Mucormycosis & Aspergillosis	51	39.2
Mucormycosis & bacterial infection (*K pneumoniae*, *E coli*, *P aeruginosa*)	18	13.8

In table 8, based on microbiology and/or histopathology, all subjects had features of mucormycosis. A small proportion had additional co-infection with aspergillosis and bacteria.

Table 9: Management of mucormycosis

	Number	Percentage
Anti-fungal treatment		
Amphotericin B	130	100
Type of surgery for the treatment of mucormycosis		
Not performed (due to poor prognosis)	8	6.1
Modified Denker's procedure	54	41.5
Functional endoscopic sinus surgery (FESS) debridement	71	54.6

In table 9, all individuals were treated with liposomal amphotericin B while majority of them underwent surgical treatment.

Discussion

Coinfections with COVID-19 are increasingly being recognised in view of its impact on the prognosis of the disease. A recent review reported 62 of 806 (8%) secondary bacterial or fungal infections and a widespread use of broad-spectrum antibiotics (1450 of 2010, 72%) often with no underlying evidence of infection. [10] Complex interplay of multiple factors, including comorbidities, use of immunosuppressive therapy, risk of hospital-acquired infections and alteration of immune system by COVID-19, may be responsible for coinfections. [11]

There are specific pathophysiological features of COVID-19 that may predispose an individual to secondary fungal infections. First, there is immune dysregulation with reduced numbers of T lymphocytes, CD4+ T cells, CD8+ T cells, and markedly higher levels of interleukin (IL)-2 receptor, IL-6, IL-10 and tumour necrosis factor-alpha. [12] Second, there is propensity of the SARS-CoV-2 to cause extensive pulmonary disease and subsequent alveolo-interstitial pathology may enhance the risk of invasive fungal infections, specifically those with a primary pulmonary entry such as mucormycosis, pneumocystis and invasive pulmonary aspergillosis. [13]

A retrospective interventional study from India reported five cases of rhino-orbital mucormycosis in uncontrolled, diabetic, COVID-19-positive patients treated with systemic corticosteroid. [14] An observational study from Pakistan identified 15.6% fungal infection rate in patients with confirmed COVID-19 who required ICU admission. [15] A national multicentre prospective cohort study conducted in UK reported an incidence of invasive fungal infections of 26.7% with higher mortality in invasive compared with non-invasive fungal infections (53% vs 31%, respectively). [16] Corticosteroid therapy and a history of chronic pulmonary disease were associated with a higher risk of invasive fungal disease. [17-19]

The patient we reported had long-standing, uncontrolled diabetes and the signs of rhino-orbital infection were noticed only 3 days after admission for COVID-19 infection. These factors may have contributed towards the patient developing mucormycosis coinfection.

Therefore, it is important to have a high index of suspicion and low threshold for fungal coinfection in patients with COVID-19 with pre-existing medical conditions. Furthermore, suspected cases should undergo immediate imaging and specific diagnostic studies with collaborated effort from multidisciplinary teams, including infectious diseases, otorhinolaryngology, ophthalmology, neurosurgery, critical care, microbiology and pathology departments. Prompt recognition and management is necessary in cases of invasive rhino-orbital mucormycosis, as a delay of only 6 days in recognition can double the 30-day mortality from 35% to 66%. [14] There is a need to emphasise on the judicious and evidence-based use of immunomodulators to avoid triggering and flaring up of the fungal infections.

Conclusion

The unusually high number of cases of Coronavirus Disease Associated Mucormycosis seen in the context of the second surge of COVID-19 in India may be from an alignment of multiple risk factors. High background prevalence of mucormycosis in India, undiagnosed or poorly controlled diabetes, COVID-19–induced immune dysregulation, and therapies such as steroids, which cause immune suppression, in the setting of shortage of healthcare access amidst a pandemic surge created a perfect storm for this to escalate into a public health crisis. Preventive measures may need to focus on identification and optimal management of risk factors for Coronavirus Disease Associated Mucormycosis, including aggressive glycemic control, avoidance of steroid overuse, and possibly environmental measures.

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