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AN OBSERVATIONAL STUDY ON THE EPIDEMIOLOGY AND RISK FACTORS OF COVID-19 ASSOCIATED MUCORMYCOSIS

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ABSTRACT **Background:** Mucormycosis (MM) is a deadly opportunistic fungal infection and a large surge in COVID-19-associated mucormycosis (CAM) is occurring in India. **Aim:** Our aim was to delineate the clinico-epidemiological profile and identify risk factors of CAM patients presenting to the Otorhinolaryngology Department. **Study type:** This was a retrospective, single-centre, observational study. **Methods:** We included patients who presented with clinical features or diagnosed MM and who were previously treated for COVID-19 (recent COVID-19) from May 2021 to July 2021. Information regarding possible risk factors associated with Covid associated mucormycosis were obtained and analyzed. **Results:** 300 CAM patients (median age: 44.5 years, 60% males) with recent COVID-19 who presented to the Otorhinolaryngology Department in between 1st May 2021 and 31st July 2021, were included. Most common risk factors were diabetes mellitus (81.5%) and steroid use for COVID-19 disease (64.4%). Long term steam inhalation, oxygen support, hypertension and chronic kidney disease were also the risk factors associated with CAM. After clinical, microbiological and radiological workup, final diagnosis of rhino-orbital CAM was made in all patients. Systemic antifungals were started and urgent surgical debridement was planned. **Conclusion:** COVID-19 infection along with its medical management has increased patient susceptibility to MM

KEYWORDS : COVID-19, mucormycosis, diabetes mellitus, steroids, amphotericin-B.

INTRODUCTION

Mucormycosis (MM) is a type of fungal infection in humans caused by the mucorale group of fungi. These fungi are ubiquitous and present in any environment including hospitals. Inhalation of fungal spores is harmless in immunocompetent individuals but can cause life-threatening disease in those who are immunocompromised.[1] The immunocompromised states which predisposes to this fatal condition includes uncontrolled diabetes mellitus, prolonged intake of steroids or immunosuppressant medications, malignancies and other debilitating conditions like chronic liver disease and chronic malnutrition state.[2] It is notable that these conditions can also indicate risk of severe COVID-19 infection.[3] Over the past year COVID-19 pandemic has caused turbulence in the world. The second wave has been catastrophic all over the world particularly in India. During the months of April and early May 2021, millions were affected and thousands were seeking hospital care. [4] Overwhelming number of patients needed oxygen therapy which put tremendous pressure on health infrastructure.[5] Recently, an association was observed between Otorhinolaryngolgy and coronavirus, a more dangerous and potentially deadly one: that of invasive fungal sinusitis resulting from mucormycosis. MM has a high mortality even with the best of treatment.[6] Therfore, we conducted a retrospective observational study in our department with an objective to identify the possible risk factors which might be contributing to this illness in the context of the COVID-19 pandemic.

METHODOLOGY

A retrospective, single-centre, observational study was conducted in the Department of Otorhinolaryngology, at a tertiary care teaching institute of India from May 2021 to July 2021. All patients with positive covid-19 history along with positive KOH fungal staining on nasal biopsy were taken up for the study. Data was collected from the hospital records with special emphasis on the demographic profile, date of arrival, date of onset of CAM symptoms and COVID-19 symptoms, clinical features of CAM, clinical features of current COVID-19, detailed comorbidities and risk factors of CAM, steroid usage details for COVID-19, COVID-19 treatment received prior to CAM symptoms, arrival vitals, diagnostic evaluations in ENT department (radiological and microbiological), medical treatment given and final disposition with surgical plan. Details of the recent COVID-19 presentation, severity and its treatment (e.g. steroid use, oxygen supplementation) were retrieved from the available documents. Statistical analysis Counts and percentages were used to summarize categorical data.

RESULTS

Demographic Profile- A total of 300 diagnosed CAM were included for the analysis (Table 1). These patients presented to our ENT department in between May 2021 and July 2021. All patients (100%) presented with history of recent COVID-19 infection. The median age of the included patients was 44.5 years, with 79% (n=237) males. Overall, a lag period was observed between the onset of COVID-19 symptoms and the onset of CAM symptoms, with median duration being 30 days.

Risk Factors For Mm In Covid-19 Patients- Majority of patients had underlying diabetes mellitus (n =245, 81.5%), of which 135 patients were recently diagnosed during their COVID-19 illness and rest 110 were known diabetics. Of these 90 pateints (30%) had concomitant diabetic ketoacidosis. The HbA1c levels of diabetic patients ranged from 6.0% to 16.3%. Following diabetes, the second most common comorbidity was hypertension (n= 87, 28.9%). Other comorbidities like chronic kidney disease were present in 3.9% cases. (TABLE- 1)

Another important risk factor for CAM to be analysed was the indiscriminate use of steroids for COVID-19. 194 out of total 300 patients (64.4%) had received steroid treatment for COVID-19 disease prior to manifestation of CAM symptoms. 61.8% of the patients who were on steroids took oral steroids only, while the rest 38.2% had intravenous steroids followed by oral intake.(TABLE-2) Duration of steroid usage was also taken into account, and it was observed that majority (51.5%) of these patients took steroids for 7 – 14 days. (TABLE-3)

Prolonged stay on oxygen support as well as steam inhalation could also be risk factors for CAM. They were observed in 42% (n=126) and 52.6% (n=158) subjects respectively.

Table-1

COMORBIDITIES AND RISK FACTORS	No. of patients	Percentage (%)
• DIABETES • KNOWN DIABETICS • NEW ONSET	245 110 135	81.5 44.8 55.2
HYPERTENSION	87	28.9
CHRONIC KIDNEY DISEASE	12	3.9
STEROID USE DURING COVID TREATMENT	194	64.4
OXYGEN SUPPORT	126	42
STEAM INHALATION	158	52.6

Table-2

STEROIDS	ORAL	INTRAVENOUS
No. of patients	120	74
Percentage (%)	61.8	38.2

Table-3

DURATION OF STEROIDS	No. of patients	Percentage (%)
<7DAYS	64	32.9
7-14 DAYS	100	51.5
>14 DAYS	30	15.4

DISCUSSION

We conducted a single-centre, retrospective study of 300 patients with CAM who presented to the ENT Department in the setting of acute or recent COVID-19. To the best of our knowledge, this study is one of the largest case series on deadly combinations of Mucormycosis and COVID-19. As the number of CAM cases were increasing in India during the second wave of COVID-19 pandemic, we have tried to delineate the clinico-epidemiological profile of these patients.

Majority of the patients in our study were middle-aged (age: 38–55 years), of which nearly three-fourths were male. This demographic profile was similar to the population of 82 mucormycosis patients studied by Chander et al., [7] of which two-third were male and aged between the ages 31–60 years. It has been hypothesized that the effect of oestrogen might be protective in systemic fungal infection, which could have led to lower incidence in females. [8]

Many experts believe that the combination of high dose steroids and uncontrolled diabetes has led to this epidemic of mucormycosis in COVID-19 patients. [9-10] In pre-COVID era, Prakash and Chakrabarti [11] found diabetes mellitus as a predisposing factor in 17–88% cases globally and in India it was a risk factor in over 50% cases. A systematic review of 101 cases of mucormycosis in COVID-19 by Singh et al. [9] noted that more than 80% cases had either pre-existing or new onset hyperglycaemia as a risk factor. Our study has reflected their findings in that 81.5% of included patients were diabetic.

Prolonged use of corticosteroids increasing risk of mucormycosis has been reported in patients. [12] Ribes et al. [13] described that acute or chronic use of steroids in such patients predisposed them to fungal infection. Steroid use during the pandemic has been supported by the Randomized Evaluation of COVID-19 Therapy trial, only in those receiving supplemental oxygen therapy and has been endorsed by major international guidelines.[14] Subsequently the WHO guidelines recommended against the use of it in non-oxygen requiring patients.[15] In India, there were many reports suggesting indiscriminate use of steroids even in mild COVID-19 patients.[16] The underlying reasons included non-evidence-based clinical practice, availability of over the counter steroids, shortage of hospital beds, social media, homemade tutorials from unverified sources and inadequate monitoring of the patients taking steroids.[17] Other comorbid conditions identified include hypertension, coronary artery disease, chronic kidney disease, chronic liver disease, organ transplant recipients and immunosuppression.

Airway epithelial damage and immune dysfunctions are known complications of COVID-19, which may provide an opportunity for fungus to invade lung tissues. [18, 19] Additional risk factors were hypothesized for a resource-limited developing nation that deserves attention. In this pandemic, acute shortage of oxygen and hospital beds [20] led to unhygienic delivery of oxygen including use of industrial oxygen, prolonged use of humidifiers without cleaning and unmonitored use of oxygen delivery devices like nasal cannula (may lead to micro-injuries). This might have added fuel to this fire of CAM surge. [21] Some experts believed that wearing face masks over a long time without washing them [22] and multivitamins supplementation including zinc and iron might have some role in CAM pathogenesis, though extensive research is needed in this aspect.[23] Microtrauma due to multiple swab tests for diagnosis of COVID-19, steam inhalation and burn injuries may have had a role in this substantial rise of CAM.[24]

For growth and replication, Mucorales derive nutrition from the host, manipulating its environment and disseminate by escaping recognition and immune attack by the host.

a) Neutropenia and immunosuppression hamper the host defenses and allow growth of the fungus.
b) Hyperglycemia with ketoacidosis increases the risk for mucormycosis - Hyperglycemia causes glycosylation of iron sequestering proteins transferrin, ferritin, and lactoferrin, reducing their iron binding and cause proton mediated displacement of ferric iron resulting in increased free iron levels even without acidosis [13]. Hyperglycemia also causes phagocyte dysfunction with poorly characterized defects [25, 26]. The presence of ketone bodies like β-hydroxy butyrate [BHB] and the low pH in the blood vessels strongly impairs the ability of transferrin to chelate iron [27]. The increased available serum iron is transported intracellularly by the reductase-permease system [28, 29]. Glucose, iron, and BHB induce the expression of GRP78 and CotH, and this enhanced expression results in the growth of the fungus and augmented fungal invasion with subsequent injury of the endothelium [30, 31]. These host factors suppress the T lymphocyte induction, IFN-γ production, and phagocyte-mediated killing [31]. Ketoacidosis also impairs chemotaxis and phagocytosis of neutrophils and facilitates dissemination of the fungus [26,32, 13].
c) Changes in iron availability to the fungus may play an important role in the pathogenesis of mucormycosis in diabetics with ketoacidosis-Iron is considered necessary for the growth of the fungus. Strategies for iron acquisition can be generally divided into siderophore, heme, and free iron acquisition systems. Mucorales are dependent on free iron in the serum as in diabetic ketoacidosis or the action of iron reductases or hemeoxygenases for iron uptake [38].Deferoxamine, an iron chelator used in persons with increased risk of iron overload, is a xenosiderophore and it directly chelates iron from transferrin, resulting in ferroxamine (iron-deferoxamine complex). It binds to the surface of the fungus by receptors, called Fob 1 and Fob 2 b and the fungus liberates ferrous iron from ferroxamine by reduction at the cell surface [29]. The ferrous iron on the surface of the fungus is re-oxidized to ferric iron by copper oxidase and then transported intracellularly by a high affinity iron permease, called FTR1 [34,45].Hemoglobin as a Source of Iron Mucorales use hemoglobin as a source of iron, and it has access to heme due to its angioinvasive nature. The fungus transports heme intracellularly and ferric iron is obtained by the action of heme-oxygenase in the cytoplasm. Alternatively, ferric iron from heme is obtained by the action of reductase-permease system [34, 45].
d) Mucorales down regulate the genes involved in pathogen recognition, innate immune defense mechanisms, and tissue repair mechanisms, thereby facilitating fungal growth [36,37]
e) Administration of corticosteroids impairs host's ability to prevent germination of spores
f) Exposure to voriconazole makes the organism highly virulent, possibly due to an epigenetic modification [38, 39].

Patterns of mucormycosis in patients can differ based on their risk factors, e.g. sinus involvement is common among diabetics. It is noteworthy that early features of MM may be missed if not evaluated with a high level of suspicion. The presentation may be overlapping with common sinusitis. Presence of associated facial erythema, perinasal swelling, nasal ulcers or eschar should serve as early pointers.[40] Palatal necrosis is a hallmark sign which may be seen in 38% patients.[41] The red flag signs to look for are cranial nerve palsy, diplopia, periorbital swelling, proptosis, orbital apex syndrome, sinus pain and palatine ulcer.[42] Cutaneous involvement was reported in half the patients with no underlying disease.[8] In the background of COVID-19, Satish et al.[10] reported that 48% patients in their case series had rhino-orbital disease followed by rhino-orbitocerebral form. Our study too had most common features related to rhino-orbital CAM (69%) followed by rhino-orbito-cerebral CAM (24%). Mishra et al. [43] in their case series of rhino-orbitocerebral mucormycosis in COVID-19 reported sinusitis in 100% subjects. Mucormycosis with Central Nervous System involvement may present with signs and symptoms of acute ischaemic stroke to ED.[44] Microbiological diagnosis was confirmed by KOH-calcofluor mount showing aseptate hyphae and extent was assessed with contrast-enhanced computed tomography scans as per guidelines.[45] All patients in our study were started on systemic antifungals and majority received Liposomal Amphotericin -B.

The overall prognosis of MM is poor and the outcome may drastically change based on the initial treatment trajectory. Sending appropriate investigations, early administration of systemic antifungals, avoiding unnecessary antibiotics and systemic steroids, and prompting for early multidisciplinary surgical debridement.[46] It is also necessary to take strict precaution during the management of acute COVID-19 i.e. strict control of hyperglycaemia, titration of oxygen therapy only as per patient need and proper cleaning and maintenance of oxygen delivery devices within hospital settings.

Supplementary Material-none.

Conflict Of Interest:
All the authors declare that they have no conflict of Interest.

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Ethical Approval:
All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Consent:
Informed consent was obtained from all individual participants included in the study.

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