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Epidemic of Mucormycosis in India: A Covid-19 Complications

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ABSTRACT

The second wave of COVID-19 in India, was new, potentially more virulent strain of SARS-CoV-2, identified as B.1.617.2, not only led to widespread infection but also contributed to the sudden rise of COVID-19-associated mucormycosis (CAM). This condition, commonly referred to as "Black Fungus" due to the rapid necrosis and eschar formation, became a significant concern. The most prevalent form of CAM is Rhino-Orbito-Cerebral Mucormycosis (ROCM), which typically progresses from the nose and sinuses to the orbit and, ultimately, to the brain. Maharashtra was the most affected state, followed by Gujarat, with a noticeable correlation between the seasonality of mucormycosis cases and the high incidence observed in these regions during the study period. This review aims to present the patterns of mucormycosis cases across India from May to July 2021, along with demographic characteristics, such as age and gender, of the affected population.

Keywords: *COVID-19, second wave, India, Mucormycosis, ROCM, Black Fungus*

Introduction

The breaking news about the novel SARS CoV-2 reported across the globe, following that, the virus spread quickly, affecting millions of people all over the world. On March 11, 2020, it was eventually designated a pandemic [1-2]. India is one of the countries most impacted by COVID-19, with the number of cases second only to the United States of America [3-5]. Same the second COVID-19 wave in India, a new mutated potentially more virulent strain of SARS-CoV2 identified as B.1.617.2 not only directly afflicted a huge population of the country, but also resulted in the abrupt emergence of COVID-19 associated mucormycosis (CAM) [6-8]. Mucormycosis (formerly *zygomycosis*) is a rare opportunistic angio-invasive fungal infection caused by molds from the order Mucorales [9]. It was found every places of the world, including soil, air, building sites, animal faeces, decomposing wood, and food [10]. According to the research, Rhizopus and Mucor species are also the responsible for the majority of mucormycosis [11]. These fungal spores could be inhaled on a daily basis through nose or mouth by humans [12]. It's unusual for healthy people to be affected. [13].

Mucormycosis was common in India even before the Covid 19, In late 2020, an increase in the number of mucormycosis patients, but it has received more attention since Covid 1 and second wave [14-15]. Because of the quick necrosis and eschar formation, which is black in appearance, the media dubbed it “Black Fungus”. The label "black fungus" is actually a misnomer, as these fungi are greyish white in appearance. Dematiaceous fungi with melanin pigment in their cell walls are known as black fungi, commonly known as black yeasts [16-17]. When comparing the period of September–December 2020 to the same months in 2019, a 2.1-fold increase in mucormycosis cases was observed [18-19]. Although the Union Health Ministry did not release official data on mucormycosis in COVID-19 patients during the first wave, published studies indicate that India accounted for approximately 71 percent of global mucormycosis cases in COVID-19 patients from December 2019 to April 2021 [20].

The most common form of COVID-19-associated mucormycosis (CAM) is rhino-orbito-cerebral mucormycosis (ROCM), which typically progresses from the nasal and sinus regions to the orbit and then to the brain [21-22]. In India, the most frequent underlying condition linked to mucormycosis is uncontrolled diabetes mellitus, which is a significant predisposing factor for ROCM [23-24]. The sudden emergence of COVID-19 associated mucormycosis (CAM) was unprecedented in the medical world [25]. Maharashtra was the most affected state followed by Gujarat [26]. After 6 weeks of infection, the national mortality rate was 38.3 percent, and after 12 weeks, it was 45.7 percent [27-28]. The Indian Health Ministry urged all states to designate mucormycosis as a notifiable disease under the Epidemic Diseases Act, 1897, on May 20, 2021 [29]. Additionally, the Indian Council of Medical Research (ICMR) has developed comprehensive guidelines for the screening, diagnosis, and treatment of mucormycosis in COVID-19 patients [30].

Materials and Methods

Different news articles from The Hindu, TOI, Tribune India, and Livemint were searched using the keywords “Mucormycosis”, “COVID-19”, “Second wave” and “India”. The data related to mucormycosis was collected for individual states and India as a whole for a period of 3 months from May to July 2021; when mucormycosis cases were at a peak. The collected data was carefully reviewed, analyzed, and cross-checked to present the graphs. The number of cases/deaths represents only those cases that are officially reported while many cases went unreported. The electronic database of PubMed and Google Scholar was searched to retrieve published articles from 2019 to 2021 on mucormycosis to understand the disease and causes responsible for the infection. The objective of this review is to present an overview on mucormycosis cases during the given study period.

RESULTS

During the study period, we observed more cases for the mucormycosis cases across India. Maharashtra reported 9,878

cases being the highest followed by Gujarat with 6,947 cases. The mortality rate was highest in Maharashtra and Gujarat, with 1,146 and 661 deaths, respectively, by the end of July. Additionally, states such as Andhra Pradesh, Tamil Nadu, Karnataka, Rajasthan, Telangana, Uttar Pradesh, Madhya Pradesh, Delhi, and Haryana reported significantly high numbers of cases. Arunachal Pradesh remains to be the only state with no cases reported at the time of writing. Among the union territories, Chandigarh reported highest number of cases and deaths while no cases were reported from Andaman & Nicobar Islands, Lakshadweep, and Ladakh. (Fig 1).

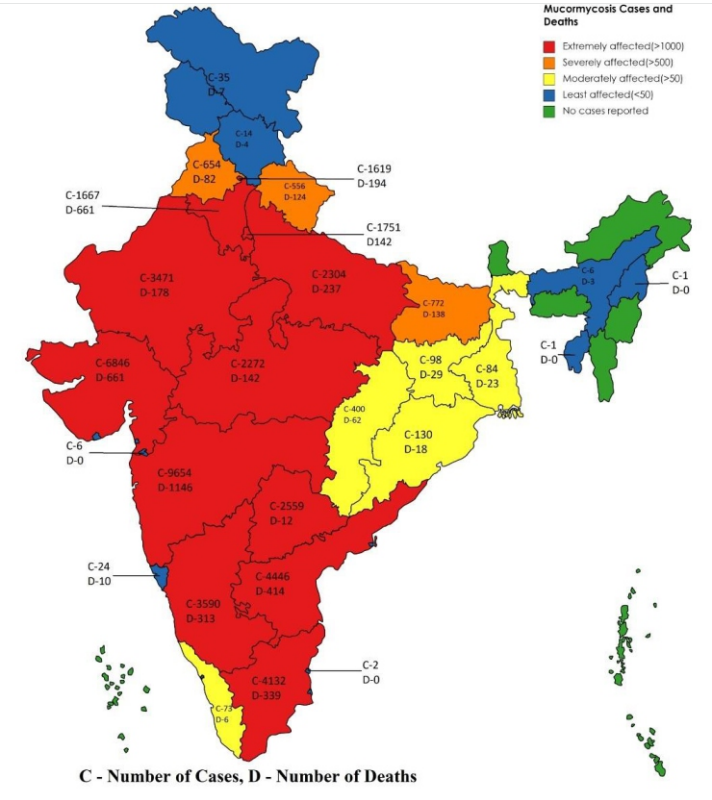


Fig. 1: Number of Mucormycosis Cases and Deaths for each state from May to July.

The total number of mucormycosis cases across India for each month was obtained for the study period. The month of June was observed to record a highest of 25,973 cases and approximately 2,669 deaths. The graph shows a decline in the total number of cases from June to July. By the end of July 47,167 cases and 4,529 deaths have been reported across India. These numbers represent only officially reported cases while the actual number of cases and deaths are likely to be much higher than this. (Fig 2).

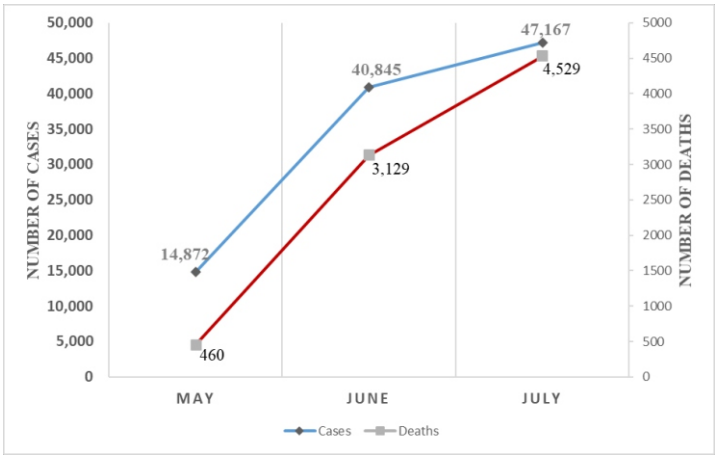
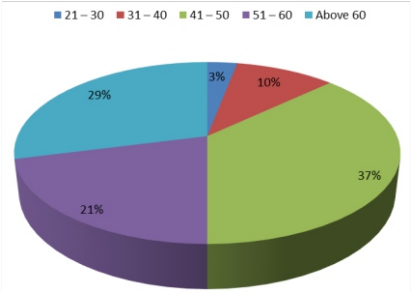


Fig. 2: Number of mucormycosis cases and deaths in India from May to July.

ROCM (Rhino-orbito-cerebral mucormycosis) type was found to be the most common clinical presentation among the patients. Pulmonary and gastrointestinal forms of mucormycosis were reported
in some places. Among ROCM patients, most of them had nose, sinuses and eye involvement. Major group of affected population belong to the middle age group and above. (Fig 3). Over the course of study, the age group of 41 to 50 years was the most commonly affected, accounting for 37%, followed by the age group above 60 years at 29%, and the age group between 51 and 60 years being 21%. (Fig 3). Gender-wise, it is observed that men are more predisposed to mucormycosis than women. (Fig 4).



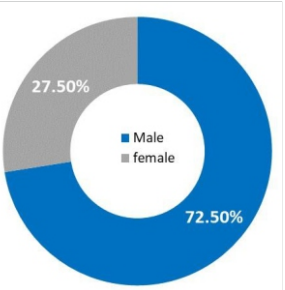


Fig. 3: Age-wise distribution of Mucormycosis (2021)
Fig. 4: Gender-wise distribution of Mucormycosis (2021)

A comparison of different studies showing the percentage of mucormycosis patients who have had COVID-19 prior, co-morbid to Diabetes Mellitus (DM) and underwent steroid therapy is shown in the table below to understand the significance of these factors in developing mucormycosis among the people. (Table. 1).

Table: Data on mucormycosis patients with COVID-19, co-morbidity to DM and steroid therapy.

Study period	COVID-19	Co-morbid to DM	Steroid therapy
September 1 – December 30, 2020	65.2%	62. 7%	78.7%
From inception until May 13, 2021	81.2%	80%	76.3%
April to June 2021	83%	79%	65%
January 3 and March 27, 2021.	100%	76.6%	

DISCUSSION

Severely ill COVID-19 patients might develop secondary fungal infections at any time during their hospitalisation or after they are discharged [31-33]. Despite the fact that it is extremely rare in healthy individuals, several compromised immune conditions predispose to mucormycosis [34-35]. The most common route of infection is through inhalation of fungal spores naturally present in the environment [36-37]. Diabetes mellitus appears to produce a vicious cycle of hyperglycemia and immunosuppression when paired with COVID-19 and steroid therapy, resulting mucormycosis [38].

Severe COVID-19 frequently causes immunological dysregulation, lymphopenia, and creates a favourable environment of low oxygen (hypoxia), thus facilitating the development of secondary fungal infections [39-40]. It has also been linked to the development of hyperglycemia in some patients [41]. The mutant Delta variant of SARS-CoV-2 (B1.617.2), initially found in India in late 2020, contributed to an abnormally high cases in India during the COVID-19 wave and elevated the risk of hospitalisation among the affected population [42-43].

The WHO has recommended corticosteroids in severe to critical patients as a life-saving therapy due to its safety profile in short-term use [44-45].

They are utilised to decrease pulmonary inflammation and lower the risk of end organ damage in Covid-19 patients. They also compromise the immunity and rise of blood sugar levels for diabetics and non-diabetic COVID-19 patients [46]. Opportunistic fungal infections can result from a loss in immunity [47]. Corticosteroid therapy also alters the ability of macrophages to block the germination of these fungal spores [48-50].

Zinc, Vitamin C, and multivitamins have been extensively recommended to COVID-19 patients across India since the outbreak began. Zinc use was found to aid fungus infection in host cells, which could be a contributing cause of mucormycosis, according to scientific literature [51]. During the COVID-19 lockdown in India, high rates of self-medication and home treatments were recorded among both infected and uninfected populations [52]. Excessive usage of steroids at this time, which was the largest ever on a global scale, resulted in a shortage and unavailability of over-the-counter medications [53]. Mucosal erosion caused by excessive steam inhalation or the use of high-flow oxygen has also been identified as a factor that promotes fungus colonisation in the predisposed population [54]. Other possible culprits include the use of industrial oxygen rather than medical oxygen in patients, the use of tap water rather than distilled water in humidifiers, a lack of hygiene in overburdened hospitals, and the use of unhygienic masks, ventilators, and oxygen systems, among others [55].

The increase in mucormycosis cases in Maharashtra, Gujarat, Andhra Pradesh, and Tamil Nadu during the study period can be linked to the seasonal conditions in these states (Fig. 1). According to a study published by [4-9], infections are most prevalent during the early phases of the hot, dry summer season, peaking toward the end of the season [56]. The study observed a rise in mucormycosis infections in May, a month characterized by dry summer conditions. States like Maharashtra and Gujarat, which experience hot and dry climates during this period, saw a significant number of cases. Thus, the seasonality of mucormycosis can be correlated with the high incidence observed in these states during the study period (Fig. 1)

Mucorales spores are more numerous in soil than in the air, and in the summer and fall than in the winter and spring [57]. It's probable that the rural population is more susceptible to these diseases due to their way of living. During the transition from summer to rainy season, tropical and subtropical regions like India are suitable for fungal growth. (Fig. 2).

The most prevalent form of mucormycosis in diabetic people is Rhinocerebral mucormycosis (ROCM) [58]. In terms of diabetes prevalence among adults aged 20 to 79 years, India ranks second in the world [59]. As a result, ROCM is the most common CAM (COVID-19 associated mucormycosis) presentation [60]. Most of the ROCM patients had nose, sinuses and eye involvement. This could be because COVID-19 affects the macrophages in the airways, reducing their ability to phagocytize the fungal spores present and allowing them to germinate into hyphae [61].

Multiple studies showed that middle age group of COVID-19 patients who were given steroid treatment were more likely to develop mucormycosis [62]. At a nationwide level, the average age of the affected population was found to be 53.4 years. It could be because old aged people are more likely to be admitted in hospitals with COVID-19. Other reports found a similar pattern [63] disussed in Fig 3.

According to a study published in the journal 'Emerging Infectious Diseases,' men made up 74.6% of those affected population [64]. Awadhesh Kumar Singh et al reported that 78.9% of the selected population were men [65]. Several other studies also showed similar results confirming the high incidence of mucormycosis in men as mentioned in the Fig. 4.

CONCLUSION

A study was conducted the second wave time of COVID-19 in India, surge of mucormycosis was observed which caused an epidemic with cases reported from every state of the country except Arunachal Pradesh. Middle-aged men were the most affected. It is observed that Rhino-orbito-cerebral mucormycosis (ROCM) is very common in COVID-19 associated mucormycosis (CAM) cases which is attributed to the uncontrolled hyperglycemia, both induced and pre-existing. Majority of the patients had nose, sinuses, and eye involvement. Delayed diagnosis, shortage of medicine, cost of treatment, and high prevalence underlying risk factors in Indian population favoured high mortality during the initial phase of the epidemic. With regard to the overwhelming population of the country, the government must strengthen the infrastructure of health care systems to treat the high case load of mucormycosis and in sight of any future outbreaks. It is also important to raise awareness among the clinicians as well as general public on epidemic diseases.

Declaration of Competing Interest

On behalf of all listed authors, the corresponding author declares that there is not any sort of financial and non-financial conflict of interest in the subject materials mentioned in this manuscript.

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