

## Reports

# Re-emergence of mucormycosis in COVID-19 recovered patients transiting from silent threat to an epidemic in India

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COVID-19 cases in India are approaching 30 million while the death has surpassed 385,167 on June 18, 2021,<sup>1</sup> with a record of 4205 deaths on Wednesday, May 14, 2021,<sup>2</sup> a few weeks after the health minister of India declared “endgame” for the COVID-19 pandemic in the country.<sup>3</sup> India is battling through the second wave with two mutant variants B.1.617.2 and B.1.1.7 challenging their healthcare system,<sup>3</sup> meanwhile, World Health Organization (WHO) has shown austerity regarding the strain B.1.617.2 and on May 09, 2021, classified it as a “variant of concern”,<sup>4</sup> which has already transmitted to 44 countries until May 13, 2021.<sup>2</sup> India with the population of 1.4 billion, experts believe that the actual COVID-19 figures will be five to ten times more than the official figure, with cases approaching nearly 400,000 a day.<sup>5</sup> The hospitals have nearly run out of beds, patients queuing up for 12 hours for the availability of a bed,<sup>6</sup> and daily oxygen supply of 50,000 tonnes needed to combat hypoxic condition of COVID-19 patients in India,<sup>7</sup> as India is reaching a “covid-hell”.<sup>3</sup>

### WHAT IS MUCORMYCOSIS AND HOW DOES IT TRANSMIT?

Amid the catastrophic situation of the COVID-19 pandemic in India, the re-emergence of a high mortality mucormycosis infection; a ‘black fungus’ among COVID-19 patients or recovered COVID-19 patients is posing a serious and unforeseen health threat in India. According to the reference to the experts, Kaul (2021) reports that Mucormycosis has become an epidemic.<sup>8</sup>

### CLINICAL FORMS OF MUCORMYCOSIS

Mucorales fungi are seen as aseptate hyphae, with some 11 genera and 27 species are known to cause human infection. Mucormycosis belongs to class Phycomycetes which is subdivided into genera *Absidia*, *Rhizopus*, and *Mucor*.<sup>9</sup> Prakash and Chakrabarti (2021) mention the presence of pathogenic species including *Rhizomucor*, *Rhizopus*, *Apophysomyces*, *Lichtheimia*, and, *Cunninghamella* in Indian soil.<sup>10</sup> Prakash et al. (2019) discussed that the global leading species to cause mucormycosis is *Rhizopus arrhizus*, while, *Apophysomyces variabilis*, is the second most common causative agent in India, along with the presence of other agents in India including *Rhizopus homothallicus*, *Thamnosylum lucknowense*, and *Mucor irregularis*.<sup>11</sup>

### TRANSMISSION OF THE DISEASE

Mucormycosis is caused by the fungus *mucor* that requires a wet surface to adhere, therefore, a humid environment is an ideal condition for it to prevail.<sup>12</sup> It could transmit through the hospital bed linen, unsterilized oxygen pipes, and hospital ventilators.<sup>12</sup> Mucormycosis infection targets immunocompromised patients, low levels of neutrophils, cancer patients, organ transplants, and patients who underwent stem cell transplants.<sup>13</sup> Steroids are used for the treatment of COVID-19 infections while heavy steroid use induces immunosuppression can potentially increase chances of opportunistic infection of which is mucormycosis.<sup>13</sup> The spores are commonly found in organic matter particularly food, soil, and plants which require humidity to grow.<sup>13</sup> The inhaled spore forms hyphae that invade the paranasal sinuses, extending further through anatomical sites within the skull causing rhino-orbital or rhino-cerebral infection. COVID-19 patients are highly susceptible to develop opportunistic mucormycosis, due to weakened immune systems by decreased levels of CD4+T and CD8+T cells.<sup>13,14</sup> Other factors that increase the vulnerability of COVID-19 patients include prolonging hospital stay, iatrogenic corticosteroid therapy with uncontrollable diabetes mellites, and diabetic ketoacidosis.<sup>13</sup> and pulmonary infections.<sup>8</sup> In India, the usual time to fumigate ICU is around 14 days, however, due to COVID-19, complete fumigation remains a challenge at large.<sup>15</sup>

### SYMPTOMS OF MUCORMYCOSIS

Indian Council of Medical Research (ICMR) has released signs and symptoms of mucormycosis that may include pain and redness around the eyes and nose, cough, fever, headache, disorientation, dyspnea, hematemesis, sinusitis, toothache, facial pain and numbness, hemoptysis, blackish discharge from nose and visual disturbances including unspecified vision loss.<sup>16</sup> ICMR has given strict instructions that any patient experiencing the mentioned symptoms must immediately seek the medical attention.

Prakash and Chakrabarti (2021) discussed the anatomical localization of mucormycosis with rhino-orbital-cerebral (ROCM) commonest area, followed by cutaneous, pulmonary, renal, gastrointestinal, disseminated, breast, ear, spine, heart, and bone.<sup>10</sup> In a study conducted by Pagano et al. (1997) through eighteen hematology departments, fever,

thoracic pain, cough, and shortness of breath were the main symptoms presented in the patient, while 89% of the patients were neutropenic at the time of onset.<sup>9</sup> Talmi et al. (2002) found bloody nasal discharge and black nasal eschar as a sign of the infection, meanwhile, malaise was seen as the most common symptom in 89% of the cases.<sup>17</sup>

## MUCORMYCOSIS IN PRE-COVID-19 AND DURING COVID-19

In the Pre-COVID-19 era, Prakash et al. (2019) discussed hematological malignancies to be the foremost global indicator for mucormycosis infection, while, diabetes mellitus was the forerunner reason the cases in India.<sup>11</sup> Other comorbid conditions involve skin trauma, human immunodeficiency virus, peritoneal dialysis, iron overload, deferoxamine therapy, illicit drug infusion, and voriconazole therapy.<sup>10</sup> Pagano et al. (1997) found the lungs to be the most affected site for the infection, followed by chronic nerve compression, sinus, liver, kidney, heart, orbital space, and large intestine.<sup>9</sup> However, currently in the mucormycosis epidemic in India, orbital space is the common site of infection followed by other organs.

## PROGNOSIS AND OUTCOMES

### OUTCOME OF INFECTION

In the study conducted by Pagano et al. (1997), the outcome of the infection resulted in thirty patients dying within 3 months of the treatment, out of which, 28 died due to mucormycosis.<sup>9</sup> Talmi et al. (2002) discussed the orbital compromise exhibits the advancement of the fungal infection into cranial fossa leading to the option of orbital exenteration, however, this may lead to mutilation and irreversible loss of vision.<sup>17</sup>

### PROGNOSTIC FACTORS

Pagano et al. (1997) found Phycomycetes to be resistant to triazoles and nystatin.<sup>9</sup> Pagano et al. (1997) found the increase in neutrophils after post-chemotherapy aplasia and amphotericin B treatment was closely associated with the prognosis from the infection.<sup>9</sup> However, oral antimycotic prophylaxis failed to prevent mucormycosis.<sup>9</sup> Controlling the environmental exposure to neutropenic patients showed positive outcomes in restricting the development of filamentous fungal infection. Isavuconazole is a new antifungal remedy for the treatment of mucormycosis, which was unavailable in India in 2018, but recently introduced in India, therefore, it lacks research on the efficacy in long-term, however, during the limited timeframe, it has shown efficacy as compared to amphotericin B.<sup>11</sup> Talmi et al. (2002) noted palatal involvement in the patients with poor prognosis. Talmi et al. (2002) discussed the use of granulocyte colony-stimulating factor (G-CSF) in neutropenic patients to hold value.<sup>17</sup>

### MORTALITY RATE

Before COVID-19 the mortality rate from mucormycosis in

India was 46.7%, where, the mortality rate in North India was higher compared to South India.<sup>11</sup> Prakash and Chakrabarti (2021) discussed that the mortality rate in the clinical presentation of mucormycosis is 64-97% in patients with gastrointestinal comorbidity, 61-77% in pulmonary, 62-79% in disseminated, 31-49% in ROCM, 23-57% in cutaneous cases.<sup>10</sup>

## INCIDENCE AND PREVALENCE OF MUCORMYCOSIS

There is a rise in mucormycosis cases globally, the rate of infection is further higher in developing countries including India.<sup>18</sup> Prakash and Chakrabarti (2021) debated on the exact incidence of mucormycosis in India due to a deficit in a population-based study, however, with the aid of the computational-model-based method, the prevalence is 14 cases per 100,000 in India.<sup>10</sup> Prakash and Chakrabarti (2021) in their research discussed that prevalence of mucormycosis is 70 times higher in India as compared to global.<sup>10</sup> It was 13 cases per year from 1990 to 1999, 36 annual cases from 2000 to 2004, 50 annual cases from 2006 to 2007, and 89 annual cases from 2013 to 2015.<sup>10</sup> One reason Prakash and Chakrabarti (2021) discussed is improvement in the diagnosis of the disease.<sup>10</sup> In other studies, discussed by Prakash and Chakrabarti (2021) the yearly incidence is 18 cases in Southern India (Tamilnadu) from 2005 to 2015, while, 9.5 cases from 2015 to 2019.<sup>10</sup> Talmi et al. (2002) mention that seasonal presence may contribute towards the incidence with the peak in fall and early winter.<sup>17</sup>

## RISE IN THE CASES OF MUCORMYCOSIS

Mucormycosis has a mortality rate of around 50 percent<sup>12</sup> and is costly to treat, which can further burden the health care infrastructure suffering from deficient and exhaustive resources. According to the report published in the Guardian, there were 300 cases of mucormycosis in Gujarat until May 13, 2021,<sup>19</sup> which exponentially increased to 2,859 cases in Gujarat until May 26, 2021,<sup>20</sup> marking over 850% increase in less than two weeks. In Gujarat 8 COVID-19 recovered patients lost their eyesight due to mucormycosis.<sup>21</sup> Similarly, 200 COVID-19 survivors are being treated for mucormycosis in Maharashtra of which 8 had died.<sup>21</sup> 58 cases from Mumbai, Pune, Delhi, Hyderabad, and Bangalore have been reported between December and February about two weeks of COVID-19 recovery.<sup>22</sup> In Mumbai, 11 out of 40 infected individuals went through enucleation due to the extensive involvement of fungus in the orbit.<sup>22</sup> whereas, some Indian states are at high risk of a surge in cases around 100-200 percent.<sup>15</sup> 2,770 cases for mucormycosis are recorded in Maharashtra, 768 in Andhra Pradesh, 752 in Madhya Pradesh, and 744 in Telangana, while a total of 11,717 cases are detected in India as of May 27, 2021<sup>20</sup>; which is three times more than found in a decade in Europe,<sup>23</sup> while there were only 29 cases of mucormycosis in March of this year in India.<sup>24</sup> The cases further rose to 28,000 according to a report,<sup>25</sup> while, cases are on the rise with 2,856 cases reported in Karnataka.<sup>26</sup> A study by Sharma et al. (2021) conducted in Jaipur, India, among 23

COVID-19 recovered patients from August to December, the rhino-orbital fungal infection mainly starts in ethmoidal sinus then proceed to the maxillary sinus, all patients received corticosteroids for COVID-19 and the majority of 21 patients were diabetic indicating a major link with diabetes mellitus.<sup>15</sup> According to WHO, around 8.7% population in India are diabetic, and with inevitability to use steroids for the treatment of COVID-19 makes them susceptible to contact with mucormycosis.<sup>27</sup>

#### WAS IT THE CASE OF AN EMERGING PATHOGEN, RISE DURING THE COVID-19?

Mucormycosis is not a new infection, neither it has been reported recently. It had its presence but the condition remained as rare.<sup>9,10,17</sup> However, the steroid treatment in COVID-19 patients is causing an immunosuppressed condition, together with the conditions in which mucormycosis infects humans.

#### COSTS, EFFORTS, AND TREATMENT OF MUCORMYCOSIS

Immediate efforts are being made by Gujrat state, by an immediate supply of 5000 doses of Amphotericin b worth Indian Rupees 3.12 crore<sup>21</sup> (approx. US\$425,000) and allocating 60 beds each in two separate wards.<sup>28</sup> The antifungal I/V treatment is the only treatment that costs around Indian Rupees 196,000 (US\$2,688) per patient.<sup>22</sup> Amphotericin b is nephrotoxic, which leads to kidney damage.<sup>8</sup> ICMR has released advisory guidelines to inhibit the spread of mucormycosis, encouraging COVID-19 patients to keep glucose level under control, usage of sterile water, and cautious usage of steroids, while, prohibiting patients to ignore symptoms of mucormycosis, and seeking medical help as appropriate.<sup>16</sup>

#### DO CASES DECLINE AS THE COVID-19 SITUATION IMPROVES?

Given the current scenario, it is difficult to suggest that whether a decline in COVID-19 cases may bring improvement in the cases of mucormycosis. According to the expert prediction, India is expected to be hit by the third COVID-19 wave by October,<sup>29</sup> and the possibility of a new mutant

variant may result in a completely unknown situation. The use of steroids, along with the comorbid conditions, may still pose a serious health risk of mucormycosis among the COVID-19 recovered patients.

#### CONCLUSIONS

The burden of COVID-19 in India has affected millions, which has been an emergency throughout the country during the second wave. The mucormycosis infection has been declared an epidemic in India due to the increased vulnerability of COVID-19 recovered patients with corticosteroid therapy and diabetes mellitus. Since the treatment is expensive, the burden of infection is increased on the health care system. The mortality rate of mucormycosis is much higher than of COVID-19 infection alone. Since the world has a greater population of diabetic patients in most regions and steroid therapy being used as a potential drug for COVID-19 infection, the warmer and humid regions where COVID-19 and diabetes are prevailing can be an immediate health hazard, especially in low-income and middle-income countries.

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Mahnoor Sukaina is the sole author.

#### COMPETING INTERESTS

The author completed the Unified Competing Interest form at [www.icmje.org/coi\\_disclosure.pdf](http://www.icmje.org/coi_disclosure.pdf) (available upon request from the corresponding author) and declare no conflicts of interest.

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