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Editorial

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

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The developing world is paralyzed by the pandemic of coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1] This pandemic has spared no communities and individuals and has resulted in large-scale morbidity and mortality.[1] To date i.e., 26^{th} May 2021 COVID-19 is diagnosed in 168,678,835 cases with 3,502,484 deaths and 150,240,883 recoveries.[2] The disease has not only affected the lives of millions but the aftereffects in the survivors are even graver.[3] There is a huge number of cases of opportunistic fungus like Mucormycosis (MCR) (previously called zygomycosis) which are being reported from the countries like India.[3] India is currently having a second wave of COVID-19 highlighted by the B.1.617 variant which has 13 mutations, two of which are similar to those seen separately in other variants.[4] The country which spends a meager amount on the health sector out of the annual budget was devastated by the second wave of COVID-19 with a shortage of testing kits, drugs, ventilators, oxygen, hospital beds, etc.[4,5] The shortage of skilled manpower i.e., healthcare workers was also evident.[5] The condition in cities was shocking and now the reports of the COVID-19 spreading into the villages are alarming.[6] The fragile health systems of villages lack appropriate and timely testing and treatment facilities.[5,6] In this present paper, the authors highlight the rapid rise of cases of opportunistic infections by fungus like MCR in the patients of the COVID-19 disease.

India has the highest burden of MCR in the world with an estimated prevalence of 140 cases per million population.[7] The group of fungi that cause MCR is called Mucormycetes and belongs to the class Phygomycetes, subclass Zygomycetes, order Mucorales, and family Mucoraceae.[8] These are ubiquitous, especially in soil and in decaying organic matter, such as leaves, compost piles, and animal excrement.[8] They are quite common in the soil as compared to air, and in seasons like summer and fall than in winter or spring.[8] Since it is present throughout the environment thus the fungal spores come in contact with the majority of the population daily.[8] It is not a new thing that these fungal spores are coming in contact with the population however the thing that is noteworthy here is that these fungi are affecting the immunologically weak COVID-19 patients.[9] As the inhalation of these spores could result in an infection in the lungs or sinuses which can spread to other parts of the body.[8] The most common types that cause MCR are Rhizopus species and Mucor species.[10] Other examples include Rhizomucor species, Syncephalastrum species, Cunninghamella bertholletiae, Apophysomyces, Lichtheimia (formerly Absidia), Saksenaea, and Rhizomucor.[11]

The rapid rise of the case of MCR, an angioinvasive disease in COVID-19 patients could be attributed to the rampant use of corticosteroids in both hospital and home

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settings.[12] The improper knowledge and over the counter availability of these drugs added up by the shortage of hospital beds and fear of death among the general public has led to a grave situation wherein the immune suppression caused by the corticosteroids resulted in an increase in the cases of opportunistic fungal infections like by MCR.[12] MCR is usually reported in those COVID-19 patients who had an already weak immune system or immunocompromised, including those with hematological malignancy, diabetes mellitus, patients on systemic corticosteroid use, neutropenia, and stem cell transplant.[13] The persistent lymphopenia in COVID-19 patients could also be an important contributor to the vulnerability of these patients to opportunistic fungal infections. These severe COVID-19 patients have a remarkably low absolute number of T lymphocytes, CD4+T, and CD8+ T cells, as a result, there is disturbed immune homeostasis, ultimately making these patients with COVID-19 highly susceptible to fungal co-infections.[14]

Moreover, India has the second-largest number of adults aged 20–79 years with diabetes mellitus (DM).[15] In fact, DM is the single most common (i.e., seen in more than fifty percent cases of MCR) risk factor for MCR in India.[15] This is supported by a recent nationwide multi-center study on MCR in India, where 57% of patients had uncontrolled DM and 18% had diabetic ketoacidosis.[15] The uncontrolled/unsupervised use of corticosteroids that compounded the glucose homeostasis, could have been a contributing factor exposing COVID-19 patients to MCR. Corticosteroid use is a key risk factor for opportunistic mycoses, including MCR.[12,15] Not only the cases who have been treated or on the treatment of COVID-19 are affected but cases of MCR in non-COVID-19 patients are also reported from India.[16,17]

In the current pandemic of COVID-19, a myriad of manifestations and complications have emerged due to MCR and are being reported every other day.[18] MCR usually developed 15.6±9.6 days after diagnosis of COVID-19.[19] The disease initially presents with blackening or discoloration over the nose or upper inside of the mouth that quickly become more severe, blurred or double vision, itchiness, redness in the eyes, chest pain, breathing difficulties and coughing blood, loosening of a tooth, one-sided facial swelling, shortness of breath, abdominal pain, nausea, vomiting, and gastrointestinal bleeding.[20] MCR affects the sinuses, the brain, and the lungs also, it can be life-threatening in people who have suppressed immunity.[20] Till 25th May 2021, there are about 11717 cases of MCR that have been reported from India with more than 200 casualties.[21] The rapid rise of cases has led to the disease being declared an epidemic in multiple states of India.

A high index of suspicion and aggressive management involving a multidisciplinary team of specialists like pulmonologist, infectious disease specialist, ENT surgeon, ophthalmologist, radiologist, neurosurgeon, pathologist, microbiologist, and a critical care physician is required to achieve the desired outcomes in these cases.[19] A delay of even six days in treatment initiation doubles the thirty-day mortality from 35% to 66%.[19] For a long, it is well known that invasive pulmonary aspergillosis can muddle the course of COVID-19.[22] This fact about COVID-19 associated pulmonary aspergillosis has received a lot of attention, however, MCR, which is the present cause of a large number of cases was until recently a nearly unrecognized entity in COVID-19 settings.[22] Invasive mold infections (invasive pulmonary aspergillosis and pulmonary MCR) share similar risk factors, clinical presentation, and radiology.[22] Thereby making the diagnosis of COVID-19 associated MCR an uphill task.[22] The situation becomes even worse when such cases are reported from isolated villages and small towns where the healthcare and testing laboratory system is weak eventually leading to underdiagnoses of the actual number of the MCR cases.[22]

Additionally, pulmonary MCR is now more and more diagnosed, and the mortality has remarkably tweaked over time.[22] Early diagnosis with the management of hyperglycemia, together with early treatment with liposomal Amphotericin B, and surgery are some of the notable things for the successful management of MCR.[22] But it is always easy to say than done as the panic and chaos associated with management of COVID-19 wherein the use of corticosteroids was imperative leading to hyperglycemia added up by the supersaturated healthcare systems where the services like diagnostics and surgeries were either lacking or were curtailed ultimately resulted in the rapid rise of a large number of cases of opportunistic infection and thus the mortality. There are reports of a shortage of essential drugs required in the MCR management and this is just adding up to the agony.[23] MCR is associated with high mortality primarily due to complications such as cavernous sinus thrombosis, periorbital destruction, palatine ulcers, disseminated infection, osteomyelitis, and death.[24]

There are certain reports of excessive use of zinc as a contributing factor for the growth of MCR.[25] Besides, the role of iron and aluminum overload as risk factors is also documented.[26] However, all such claims are not backed by large-scale epidemiological studies and till these studies provide evidence for such an association it is difficult to comment on any such links. Some other possible contributors could be widespread and over the counter use of antibiotics (like Doxycycline, Azithromycin, Ivermectin, etc.); immunomodulators (like Tocilizumab with steroids); immune suppression by the B1.617 variant of COVID-19 virus; use of tap water instead of distilled water in humidifiers; industrial oxygen use instead of medical oxygen in patients; reuse of mask and cannulas; lack of hygiene in overwhelmed hospitals; use of unhygienic masks, ventilators, oxygen systems, humidifies,

etc. Besides, the recent reports of yellow fungus and white fungus from various parts of India have alerted the health systems so that the suffering in a country devastated by COVID-19 could be avoided.[27]

To summarize, MCR is treatable with early diagnosis, and the use of antifungal drugs and surgeries. The governments should ensure an uninterrupted supply of drugs and hospital beds to the patients. It is important to have a specialized team of doctors who should be working in the anti-MCR units for the timely detection and management of this fungus. There should be a routine check-up of all current and COVID-19 recovered cases. The importance of health education and its dissemination is the need of the hour. Moreover, the importance of COVID-19 appropriate behavior along with the timely administration of anti-COVID-19 vaccines is essential and should be encouraged.

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2. Conflict of Interest

The authors declare that they have no conflict of interest.

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