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Factors predisposing for mucormycosis in COVID-19 patients: a questionnaire survey

Dr. Ashok Bhansali[1], Dr. Maya Indurkar[2], Dr. Aishwarya Khachane
1(department of periodontology, GDCH Aurangabad, MUHS Nashik, India),
2 department of periodontology, GDCH Aurangabad, MUHS Nashik, India),
3 department of periodontology, GDCH Aurangabad, MUHS Nashik, India)

Abstract
Background and aims: *Mucormycosis or as it is called, "the black fungus" has taken the headlines these days and has created a huge fury in everybody's mind. A rapid surge in cases in the post-COVID period has further complicated the pandemic scenario leading to declaring mucormycosis an epidemic in Indian states. We aim to conduct a questionnaire survey looking out for the most common predisposing factors for mucormycosis among COVID-19 patients.*
Methods: *A questionnaire survey was conducted on a sample size of 50 COVID affected patients admitted for mucormycosis in govt. Medical college and hospital, Aurangabad during 6months period from March 2021 to August 2021. Subsequently the patient demographics, associated comorbidities, type of mucormycosis, steroid use, medication history and its outcome in people with COVID-19 were analyzed.*
Results: *50 cases of mucormycosis in patients with COVID-19 have been analyzed.Mucormycosis was predominantly seen to have male predisposition (60%).Both in patients with active infection (36%) or patients recovered (64%) from COVID-19,mucormycosis was more common among elderly patients of age >55 (60%). Diabetes was the most common predisposing factor present in 86% cases,of which chronic long-standing cases accounted for 74.41% whereas 25.58% cases were recently diagnosed for diabetes. 30.23% patients had concomitant diabetes ketoacidosis. 80% patients had elevated serum ferritin levels. Corticosteroid use was reported in 58% cases.*
Conclusion: *Pre-existing systemic comorbidities, especially diabetes mellitus and exorbitant, reckless use of corticosteroids in wake of COVID-19 appears to predispose mucormycosis. Essential blood sugar control and judicious use of corticosteroids in patients with COVID-19 should be stressed.*
Key word:*mucormycosis, COVID-19, diabetes mellitus, corticosteroids*

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I. Introduction:

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-COV-2), has been spreading rapidly across the globe.[1]Coronavirus disease 2019 (COVID-19) has been associated with a wide range of opportunistic bacterial and fungal infections. *Aspergillus* and *candida* have been reported as the main fungal pathogens for co-infection in people with COVID-19.[1]

Mucormycosis is an angioinvasive fungal infection due to fungi of the order mucorales.[2]Recently,there is a rapid surge in cases of mucormycosis among COVID-19 affected people.COVID-19 patients presenting with diffuse alveolar damage with severe inflammatory exudation, almost always have immunosuppression with a decrease in CD4 + T and CD8 + T cells .[3]Critically ill patients, especially those admitted to the intensive care unit (ICU) and required mechanical ventilation, or had longer hospital stays, were more likely to develop fungal co-infections.[4]Hence, it is important to note that COVID-19 patients can develop fungal coinfections during or at latter stages of the disease, especially the critically ill ones.[5]

Secondary fungal infections are common in conditions with immunosuppression as it is conducive for the organism to establish itselfand cause infection. Clinical evidence demonstrates that phagocytes are the major host defense mechanism against mucormycosis. For example, neutropenic patients are at increased risk of developing mucormycosis. Furthermore, patients with dysfunctional phagocytes are also at higher risk for developing mucormycosis. On the contrary, incidence of mucormycosis among AIDS patients is found to be low suggesting that T lymphocytes may have meager role in inhibition of fungal spore proliferation. In hyperglycemic and acidosis condition phagocytes become dysfunctional and their ability to move toward and kill the organisms by both oxidative and non-oxidative mechanisms is impaired.[6] Additionally, corticosteroid treatment has been found to impair the ability of bronchoalveolar macrophages to prevent germination of the spores in vitro or after in vivo infection induced by intranasal inoculation.[7] Recent increase in mucormycosis

incidence among COVID affected patients may have been spurred due to multiple predisposing factors combined together. Through this study, we try to look out for the most common predisposing factors that might have contributed for the establishment of mucormycosis in COVID affected patients. Looking out for common factors among patients with mucormycosis might help us find the common factors linking the CAM (COVID associated mucormycosis) cases together.

II. Material And Method:

This was a cross-sectional study that collected data through a questionnaire survey. The study was conducted atGMCH Aurangabad. We enrolled around 50 patients who were admitted to GMCH Aurangabad for mucormycosis during or post COVID-19. A structured custom-made questionnaire composed of 15 close ended questions was designed to find out the most common predisposing factors for mucormycosis among COVIDpatients.The criterion for the study was formulated to make the study simple and clear. The sample was selected based on exclusion and inclusion criteria.

Exclusion criteria:

- Patients not willing to participate in the study
- Critically ill patients
- Patients with history of psychiatric illness

Inclusion criteria:

- Patients with history of or affected withCOVID-19
- Willingness to participate in survey
- Patients with ability to understand &/or read and respond &/or fill the questionnaire.

The eligible and willing participants received the structured questionnaire in printed form after a brief explanation about the studyand its purpose. The questionnaire was thoroughly explained to the patient in their regional language and individually supervisedfor each patient.All statistical analysis were performed using Microsoft excel windows 2007. Descriptive measures were denoted as percentages. 15 close ended questions with yes or no responses were analyzed and graded as percentage positive response.

III. Results:

Out of the 50 participants, 18 patients were active cases of mucormycosis and 32 patients had post-COVID mucormycosis,with gender distribution of 60% male and 40% female. 40% of the participants belonged to the age group of 15-55 years whereas 60% participants were over 55 years.Majority of patients suffering from CAM were diabetics (86%). Among the diabetics, chronic long-standing cases accounted for 74.41% whereas 25.58% cases were recently diagnosed for diabetes. 30.23% patients had concomitant diabetes ketoacidosis. 30 of the 50 patients either had renal dysfunction or history of dialysis therapy. About 80% of patients had elevated serum iron or ferritin levels.56% patients reported to have other longstanding medical comorbidities. 39 of the 50 patients had experienced acute respiratory distress during COVID. 58% patients had consumed steroids for more than 3 months for some medical condition or as a part of management forCOVID. 4% patients had a history of organ transplantation. 10% patients had a history of malignancy or cancer therapy procedures. Hospital stay due to COVID exceeded 2weeks for 56%patients. 15 out of 50 subjects received immunomodulatory drugs and 2% received anti-fungals as a part of management for COVID. 40% gave a history of repeated use of broad spectrum antimicrobials. 20% patients had reported history of cut/injury/burn/trauma or surgical injury before, during or post COVID. 60% patients were reportedly undernourished. About 80% patients responded positively to following COVID preventative practices like sanitation, social distancing.(Figure 1, Figure 2)

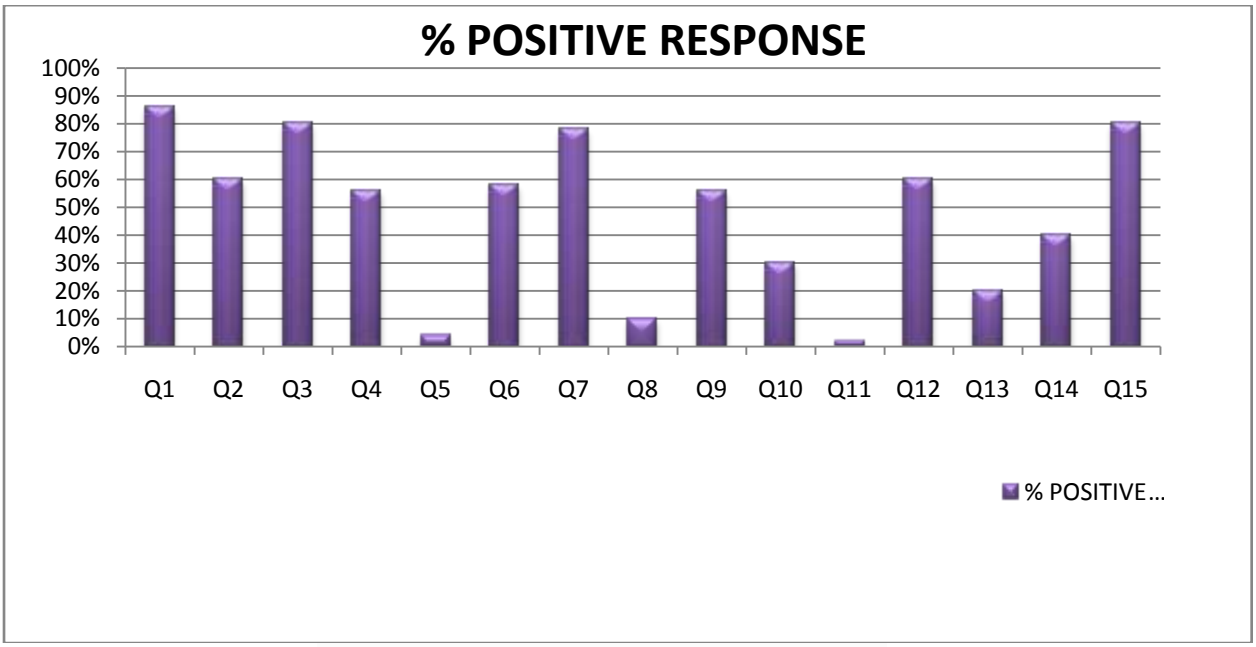

Figure 1: response of the patients to questionnaire

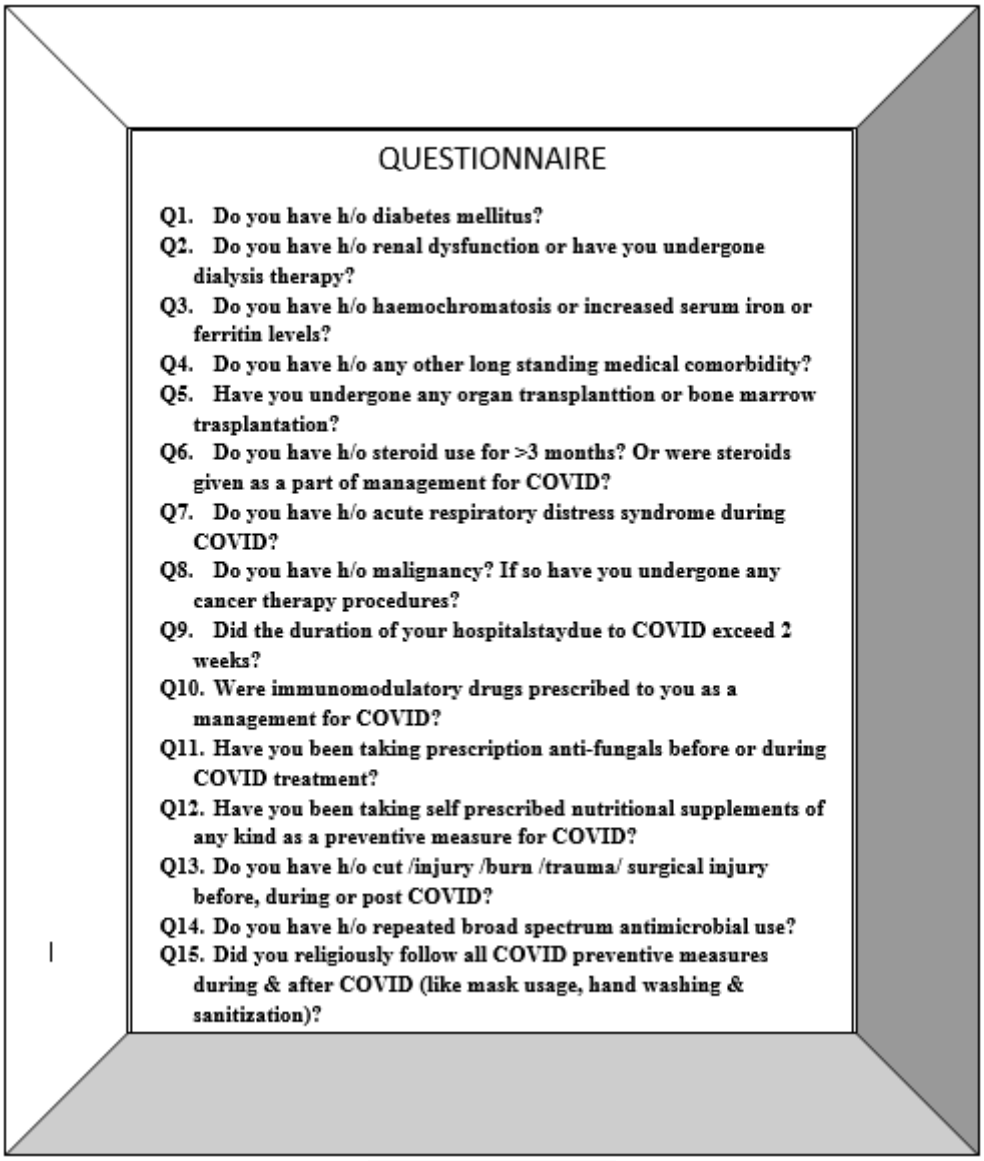

Figure 2: questionnaire

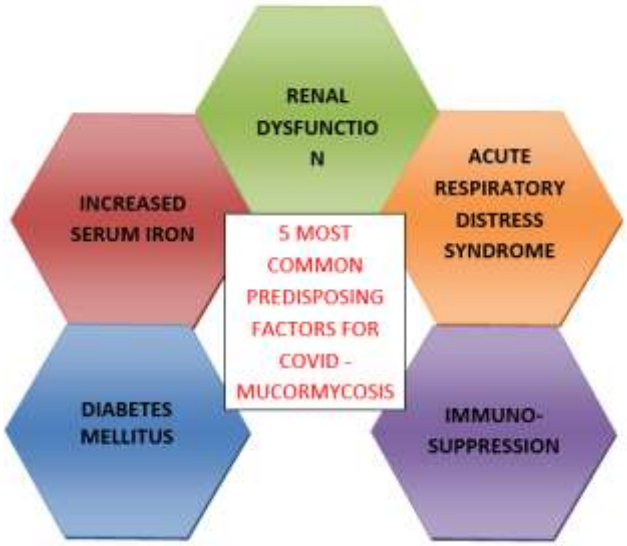

Figure 3: 5 most common factors predisposing for mucormycosis

IV. Discussion:

The second wave of COVID presented with various acute respiratory infections as well as opportunistic infections in patients with long standing chronic systemic co-morbidities. On the basis of results, we establish 5 most common predisposing factors among COVID affected mucormyosis patients: diabetes mellitus, increased serum iron, renal dysfunction, acute respiratory distress syndrome and immunosuppression. (Figure 3)Type 2 diabetes was found to be ubiquitous among post-COVID mucormycosis patients. In our study 43 out of 50 patients were diabetic, all type 2, out of which 32 were chronic long standing cases suggesting its role in etiopathogenesis. 13 patients had diabetic ketoacidosis and 11 were recently diagnosed cases for diabetes implying essential diabetic control among COVID-19 patients.

Prior to the COVID-19 pandemic, mucormycosis was most commonly reported in severely immunocompromised patients with uncontrolled diabetes. It was mostly a diabetes-defining disease. Hyperglycemia, usually with an associated metabolic acidosis, might be the major predisposing factor.[8]India is the diabetes capital of the world with around 77 million adults affected by diabetes.[9]Mucormycosis was commonly found to occur in patients with severe COVID-19 infection and the severity of COVID-19 was commonly found to correspond with the level of diabetic control. Hyperglycemia in diabetics might lead to metabolic alterations in tissues predisposing them to a chronic inflammatory state which in turn would invite a range of opportunistic infections. Also the hyperglycemia induced inflammatory state might be potentiated by the anti-viral host defense during COVID infection. Studies have reported an increased morbidity and mortality in COVID-19 patients with uncontrolled diabetes.[10] SARSCOV-2 infects the host by tropism to host angiotensin-converting enzyme-2 (ACE2) receptor. Increased ACE2 receptor expression and hyperglycemia favor SARSCOV-2 replication with the added benefit from immunocompromised condition due to steroid medications or other immunosystemic conditions. The rhizopus thrives under high glucose and acidic conditions. The spore coat protein (CotH) interacts with GRP78 (glucose-regulated protein) receptor of host cell. Increased expression of GRP78 with hyperglycemia and acidic environment due to diabetic ketoacidosis, along with the diminished defense mechanisms andwith the increased availability of iron and micronutrients for the pathogen growth make DM the most commonly prevalent risk factor for mucormycosis. Also the vascular endothelial injury due to inflammation might serve an easy entry route for rhizopus invasion.GRP78 is specifically over expressed in nasal epithelial cells, which might explain the damage to the nasal epithelium, leading to invasion of rhizopus and occurrence of rhino-orbito-cerebral mucormycosis more in patients with DM than those without.[11,12]

Singh et.al.(2021) reported that hyperglycemia at presentation was the single most important risk factor observed in 83.3% of the patients with mucormycosis and COVID-19, pre-existing DM in 80% and concomitant DKA in 15% which was similar to what we observed in our study.[13]

Compared to developed countries where hematological malignancies and solid organ transplants account for the most common underlying predisposing conditions, in developing countries like India, uncontrolled diabetes mellitus carries most of the blame. Though only 4% patients in our study had undergone organ transplants, it does not exclude its role as a risk factor. It might be overshadowed due to the highly prevalent uncontrolled DM. A prospective multicentre study conducted on mucormycosis in India conducted by Prakash H. et.al. highlights the role of uncontrolled DM in cases of mucormycosis. This was the largest cohort comprising of 388 patients and provided insights on the mucormycosis status in India establishing diabetes as the major predisposing factor among mucormyosis patients especially in north India.[14]Normal human serum does not support the in-vitro growth of many fungal species including those causing mucormycosis. This indicates that presence of some inhibitory factor in serum might be responsible for the impediment of the fungal growth. Evidence suggests transferrin, an iron binding glycoprotein, to be that factor. The observation that transferrin with a measurable iron binding capacity inhibits fungal growth and not an iron-saturated transferrin suggests that transferrin inhibits fungal growth by binding iron and making it unavailable for fungal growth. This is a form of nutritional immunity which the host exerts against fungi. But the transferrin-iron binding is affected by various local conditions one of which is pH. Acidic condition during ketoacidosis might decrease the affinity of transferrin for iron resulting in a hyperferritinemic state which in turn favors fungal growth. Severe COVID-19 infection is characterized by cytokine storm.[15,16] Elevated intracellular iron in turn leads to production of reactive oxygen species which further induce tissue damage and releases free iron into the circulation. Renal dysfunction and hypoxia can further aggravate the acidosis.[17] Evidence shows that the increased levels of serum free iron together with the low levels of dialyzable inhibitory factor in diabetics are conducive for fungal growth. Hence, the acidic milieu resulting from the amalgamation of different factors, forms an ideal environment for fungal proliferation with the availability of free iron required for cell growth and development.[18]

Acute respiratory distress syndrome was also one of the common finding among CAM patients. Pulmonary aspergillosis is the commonly associated mould-disease in COVID-19 patients with ARDS. But

post-COVID, pulmonary mucormycosis cases also surged due to the immunosuppression and increased susceptibility for opportunistic infections. Also the distinction between pulmonary aspergillosis and mucormycosis has been a challenge owing to the similar radiographic features of both the conditions and absence of serum antigenic biomarkers and lower availability of PCR testings in developing countries.[19]Metabolic alterations caused due to long-standing illness, together with the abundant availability of micronutrients from the self-prescribed and possible "immune-boosting" supplements provide a suitable nutrient rich habitat for superinfections from fungi. Zinc-binding proteins act as transcription factors for biological processes responsible for fungal growth. Studies have shown that zinc starvation induces biological stress and inhibits fungal proliferation.[18] use of nutritional supplements, including zinc as a possible immune booster has increased in the COVID-19 era with around 60% respondents in our study taking some or other nutritional supplement as a preventive measure for COVID.

Renal dysfunction was present in 60% of our study participants and also 56% participants reported to have some additional comorbity other than diabetes, mostly hypertension. The presence of these additional systemic comorbidities might be responsible for the patients increased severity of COVID infection prolonging their duration of hospital stay and making them prone to superinfections.

Excessive and irrational use of antibiotics in patients in general is underreported and this has further increased during COVID. Between 2000 and 2010, worldwide consumption of antibiotics by humans increased by 36%, with Brazil, Russia, India, China, And South Africa (BRICS) accounting for three-quarters of this increase despite collectively representing only 40% of the world's population. In BRICS countries, 23% of the increase in the retail sales volume was attributable to India where regulations to control over-the-counter sales of antibiotics are poorly enforced.[20]An interrupted time series analyses of sales volumes of antibiotics in India estimated that COVID-19 likely contributed to 216.4 million excess doses of antibiotics and 38.0 million excess doses of azithromycin until the peak of the first pandemic wave.[21] Chronic antibiotic use by itself is an independent risk factor favoring opportunistic fungal infections like mucormycosis and irrational antibiotic use can lead to emergence of antimicrobial resistance.[22] Also the use of systemic corticosteroids and antibiotics in hospitalized patients has increased the susceptibility for superinfection. A chronic systemic comorbidity like diabetes mellitus together with the immunosuppression from corticosteroids and the potential antibiotic resistance due to irrational use of antibiotics, coupled with the conducive nutritional environment for microbial growth causes a vicious cycle leading to fungal colonization. A study performed at a tertiary care center in south India compared the risk factors among CAM and non-COVID mucor patients. DM was a significant risk factor in both groups, whereas uncontrolled DM and newly detected DM were more common among cam group. Unwarranted steroid use and elevated serum ferritin levels were found to be significantly higher in cam patients.[23]

Our study showed a 3:2 male to female ratio among CAM cases showing an increased predilection of males over females. In a review by Teclegiorgis Gebremariam et. al., 78% of the mucormycosis cases occurred in males and in the mice model, female mice were more resistant to mucorale than male mice. However the gender predilection for mucormycosis needs to be studied further.[24]

One alarming observation was that 5 patients who did not have any other medical co-morbidity including diabetes presented with mucormycosis post–COVID. In all those patients hospital stay exceeded 2 weeks and 4 of them received steroids & other immunomodulating drugs suggesting need for judicial use of steroids in COVID.

Through our study we could assess the most common factors that might predispose a COVID affected patient to mucormycosis. However, our study relied on patients' knowledge of their preexisting medical condition. Also we could not assess the then prevailing hospital environment, sanitation and use of oxygen cylinders and humidifiers at the time of patients hospital stay.

V. Conclusion:

- Diabetes appears to be the most common condition associated with post COVID mucormycosis. This calls for essential blood sugar control among COVID patients.
- Also physicians caring for critically ill COVID patients must be aware of serious infections that can complicate the course of COVID-19.
- Timely lookout for predisposing factors might serve early diagnosis which is necessary to improve outcomes in mucormycosis patients.

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