A systematic review of mucormycosis cases in COVID-19: Is it an unholy trilogy of COVID-19, diabetes mellitus, and corticosteroids?

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ABSTRACT

Background: A significant surge of cases of mucormycosis is seen in individuals with COVID-19 with presence of diabetes mellitus (DM) and usage of corticosteroids. We aim to conduct a systematic analysis of the cases involving presence of mucormycosis and to find out its association with COVID-19, diabetes mellitus, and corticosteroids. Method: The electronic records of PubMed, Google Scholar, and Science Direct were searched for the case reports and case series that reported mucormycosis in association of COVID-19. The particulars of each case report and case series were retrieved, stored and analyzed. Results: In this study, 476 cases of mucormycosis were reported. In 346 cases of mucormycosis, the patients were found to be COVID-19 positive. The incidence of diabetes Mellitus (DM) was 67.01%. Corticosteroid was administered in 57.77% of the cases. Mortality was reported in 36.34% of the cases. Conclusion: An immunosuppressive environment created due to the COVID-19, diabetes mellitus, and extensive use of corticosteroid provide a suitable background for the increased incidence of mucormycosis. The COVID task force should adopt an aggressive multidisciplinary approach to optimize the use of corticosteroids and maintain glucose in the optimal range.

Keywords: Corticosteroids, COVID-19, diabetes mellitus, mucormycosis, SARS-CoV-2

Introduction

Coronavirus disease 2019 (COVID-19) is a communicable disease causing havoc all around the globe. The pandemic of COVID-19 has changed the perception of understanding the subject of medicine in countless ways. COVID-19 is highly contagious with a significant mortality rate that is often associated with changing evolution of the disease and with it bringing drastic change to the therapeutic protocols which may further lead to the development of certain morbidities which posed further challenges. In recent times, there are incidental reporting of fungal infection in post-COVID-19 patients. It is assumed that there is a strong correlation between the presence of COVID-19 history and mucormycosis as evident by the increase of reporting of mucormycosis cases in people with COVID-19 for almost a year worldwide, especially from India.
Mucormycosis is an infrequent and fatal infection seen in individuals with altered immunity. It is an opportunistic fungus whose nature of the infection is deep, acute, and aggressive. Mucormycosis is an invasive fungus caused by the inhalation of the spores of mold fungi of the genus *Rhizopus, Mucor, Rhizomucor, Absidia*, and *Cunninghamella*. *Rhizopus Oryzae* is the commonly found genus in human cases (60%) and it infects mostly the rhino-orbito-cerebral (90%). The cases of oral mycosis have unusually increased worldwide but India bears the highest burden of mucormycosis cases globally.

India is designated as the diabetes capital of the world due to the high prevalence of diabetes mellitus (DM). Notably in India, the most common risk factor for mucormycosis has been attributed to DM; although blood malignancies and transplantation are the most causative factors for mucormycosis in western countries. However, DM remains the leading risk cause of 46% mortality globally in patients with mucormycosis. The upsurge of cases of opportunistic fungal infections including aspergillosis and mucormycosis has been observed to be associated with the continuing use of corticosteroids. It is hypothesized that even a brief treatment with corticosteroids for people with DM has recently reported an increased incidence of mucormycosis. Lionakis et al. also mentioned that the patients are more prone to mucormycosis if they receive a cumulative dose of more than 600 mg of prednisone or 2-7 g of methylprednisone dose during the previous month. However, the presence of an unholy trilogy of COVID-19, diabetes, and steroids was observed to increase the cases of mucormycosis worldwide. Thus it is important for the treating physicians especially the general primary care providers and family physicians working in the COVID care center to understand the underlying pathogenesis and judiciously use corticosteroids in COVID-19 patients. This motivated us to write a systematic review of mucormycosis cases related to COVID-19 and to verify its association with comorbidities, usage of corticosteroids in COVID-19 treatment, and its general outcome in the COVID-19 patients with mucormycosis.

**Materials and Methods**

The literature was systematically reviewed using various database from PubMed, Google Scholar, and Science Direct till June 10, 2021, with the keywords or medical subject headings (MeSH): {“COVID-19"}, {“SARS CoV-2"}, AND {“Mucormycosis"}, {“Zygomycosis"}, {“Mucor"}, {“Rhizopus"}. The literature was reviewed by two authors (RK and AK) independently. A total of 762 studies were screened from various database from PubMed, Google Scholar, and Science Direct and later exclusion of other articles like systematic review and metaanalysis, review articles, original research articles, commentaries and correspondences, letter to editor, articles in language other than English and duplicates, finally 40 articles were found to report the original case(s) and series which were included for the synthesis of this review [Figure 1].

In this study, only case reports and case series were included as they were the only available literature when the incidence of mucormycosis in COVID-19 patients were at the peak. The population in this study included the cases of mucormycosis irrespective of their COVID-19 status. After initial selection of case reports and case series, the full text articles were further assessed for eligibility. The data were extracted, collated, disagreements were discussed, and any discrepancy in the article screening process was resolved with discussion and consent with the third author (BK). Microsoft Excel v. 16 was used to record the demographic and clinical data of the patient and evaluated for various conclusions. This study was conducted in agreement with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

**Results**

On analyzing the 40 selected articles, overall, 476 cases of mucormycosis were recorded including the confirmed and suspected cases with COVID-19. This study included 28 case reports and 12 case series which are mostly from India (425 cases) followed by Iran (15 cases), Turkey (11 cases), and United States (8 cases). The data for the following information was extracted from the case series and case reports such as study characteristics, including author name, country of report, number of patients, patient demographics (e.g. age and gender), COVID status, comorbidities (Diabetes mellitus, Hypertension, Others), steroid (received or not), location of mucormycosis, isolate confirmation and outcomes [Tables 1 and 2].

In [Table 3], 346 patient who reported mucormycosis were also found to be COVID-19 positive, it was found that the disease was most prevalent above 45 years old. The pooled data of the cases showed that mucormycosis was predominantly seen in males (73.94%). All the patients were diagnosed by imaging techniques like Computed Tomography (CT) scans. Standard care of treatment was given to all the positive cases of COVID as per the evolving protocol of the countries from time to time.

The most significant risk factor observed in this study was the presence of hyperglycemia in 67.01% i.e. 319 cases, followed by hypertension, chronic renal failure, and obesity. Corticosteroid was administered in 275 cases of COVID-19 patients while the others received remdesivir, tocilizumab, and Interferon-alpha. The role of other drugs in the pathogenesis were not considered as the data was sparse. The most common organ involved with mucormycosis was the rhino-orbital in 254 cases (53.36%) followed by rhino-orbito-cerebral in 151 cases (31.72%), pulmonary in 33 cases (6.93%), and nasal bone/sinus in 11 cases (2.31%). Out of 476 cases of mucormycosis, only in 179 cases (37.60%), isolates were identified. The isolates were mostly *Rhizopus microsporus, Rhizopus oryzae, Rhizopus arrhizus, and Mucorales*. Liposomal amphotericin B was the most prescribed anti-fungal for the management of mucormycosis. In most of the patients, intraorbital and intracranial exenteration was the major technique followed to extract the mucor. The number of cases that survived after...
mucormycosis was 299 (62.81%) better than the overall mortality which was noted in 173 cases (36.34%). Most of the mucormycosis patients died between 7 days to 175 days after the onset of symptoms. Most of the patients were discharged after receiving surgical treatment like extensive surgical debridement accompanied by antifungal drugs [Table 3].

**Discussion**

In the background of the second wave of this pandemic, a significant surge of cases of mucormycosis is seen. India stands with nearly three-fourth (71%) of the cases of invasive fungal infection globally with the probable prevalence of 140 cases/million people. This fungus frequently presents in the nasal mucosa as a commensal with other organisms, but it may germinate in this region due to the favorable condition provided by the immunosuppression due to diabetes mellitus or by taking immunosuppressant drugs or other medical conditions like cancer, transplant, severe burns, etc. As the fungus multiple in the cavities and sinuses of the cranio-maxillary region; it invades, infects, and causes massive destruction to the structures of the cranio-maxillary region which ultimately results in the demise of the patient. The pathogenesis of mucormycosis is trademarked by tissue necrosis which results from the invasion and thrombosis of the vasculature. The inhalation and germination of the spores into the paranasal sinuses of the vulnerable hosts causes the most common type of mucormycosis, rhino-orbito-cerebral. The disease is time-bound as the mortality rate touches 50% if not treated at the appropriate time.

As immunosuppression by diabetes mellitus is a contributing factor for the prevalence of mucormycosis. India has one of the largest burdens of DM due to the second-highest population in the world. Prakash et al. reported patients are more prone to mucormycosis if they had uncontrolled diabetes mellitus and diabetic ketoacidosis. In this study, the percentage of mucormycosis with diabetes mellitus is 67.01% which is higher than 57% reported in the study by Prakash et al. The type of mucormycosis in our systemic review is rhino-orbital which is similar to the outcomes of Farmakiotis et al. who also observed that rhino-orbital or rhino-cerebral type of mucormycosis predominates in a patient with diabetes mellitus. In our study, the finding of increased mortality of patients of mucormycosis with DM and COVID-19 positive correlates well with the study done by Singh et al. Yang et al. suggested that severe acute respiratory syndrome Coronavirus 2 (SARS CoV-1) induces acute diabetes and DKA in COVID-19 patients by damaging the pancreatic islets. Kothandaraman et al. suggested that the “diabetogenic state” is commonly seen in COVID-19 infection because of two factors namely the high concentration of ACE2 receptors in the islets of the pancreas and also cytokine storm induced increased insulin resistance. On the other hand, it is observed that corticosteroid was the most commonly used drug for the treatment of COVID-19 patients. The long-term and rampant use of corticosteroids have contributed to the rise of mucormycosis due to the disturbances of the glucose homeostasis providing a hyperglycemic state and providing a fertile ground for the opportunistic mycoses, including mucormycosis.
patients (275 cases) had a history of corticosteroid administration which correlates well with the study by Singh et al.[4] The contributing factors of diabetes mellitus and extensive usage of corticosteroid seems to have a contributory relationship to increase the incidence of mucormycosis. Mucormycosis is an invasive fungus that is provided with the ideal environment in the COVID-19 patients due to the immunocompromising effects of corticosteroids; and microangiopathy and possible peripheral microthrombi caused by diabetes mellitus.[40] Apart from the state of hyperglycemia, there are more theories that may correlate the prevalence of mucormycosis and COVID-19. There is an alteration of iron metabolism which leads to a hyper-ferritinemic syndrome in SARS CoV-2.[43] In severe COVID-19, a high level of ferritin is found which may indicate excessive storage of intracellular iron in the body. Excessive intracellular iron may produce reactive oxygen species (ROS) which may lead to tissue damage. The presence of diabetic ketoacidosis and excessive level of cytokines, mainly IL-6 in a severe case of COVID-19 may further upregulate the synthesis of ferritin and decrease the export of iron which consequence of an excessive surplus of intracellular iron.[46] These may again further aggrivate ROS resulting in tissue damage and discharging free iron into the system.[49] The surplus iron may produce an acidic environment acting as a contributory factor for mucormycosis in the COVID-19 patient.[47] The other possible theory explaining the relationship between severe SARS CoV-2 and mucormycosis is the phenomenon of “endothelialitis”. The autopsies of SARS CoV-2 patients showed fatal injury to endothelium and angiogenesis.[40,41] The pathogenesis of mucormycosis includes the critical steps of endothelial adhesion and penetration of Mucorales to the endothelium.[53] In the COVID-19 patients, the critical steps are regulated by the two proteins, namely the Mucorales adhesin spore coat protein homologs (CotH) and the endothelial receptor glucose-regulated protein (GRP 78) which are induced by the acidic states and hyperglycemia.[52]
In the study, the prevalence of Covid-19 is mostly seen in males which may be a reflection of the higher prevalence of the infection in males recorded in India. Mucormycosis is not an age or gender-dependent disease as a significant number of cases are seen in males. As per the national statistics on COVID-19, approximately 66% of Covid-19 cases with mucormycosis were observed to be males which correlate well with our systemic review with the prevalence of 73.94% in males. Arnaiz-Garcia et al. mentioned earlier that the rhino-orbito-cerebral mucormycosis is the most common type of mucormycosis seen in 44–49% of the cases followed by cutaneous, pulmonary, disseminated, and gastrointestinal. The mortality rate reaches as high as 90% if there is intracranial involvement due to mucormycosis. The most common clinical features of mucormycosis are usually headaches, fever, facial swelling (one-sided), palpebral edema, ptosis, chemosis, and ophthalmoplegia. Computed tomography (CT scan) is the investigation of choice for the involvement of the paranasal sinuses and gadolinium-enhanced magnetic resonance imaging is done for the intra-orbital or intracranial extension. Radiologically diagnosis can be made by the presence of focal bony erosions and extra sinus spread. The biopsy specimen for culture and potassium hydroxide examination of skin lesion (KOH) will provide the definitive diagnosis of mucormycosis. Mucormycosis is a time-bound disease as the rapid dissemination of fungus is an extraordinary phenomenon. The delay in diagnosis and initiation of treatment by even 12 hours could be fatal. Scheenbach et al. and Jung et al. reported that the mortality due to mucormycosis ranges from 33.3% to 80% which correlates well with the mortality of 36.34% in our study.

The above discussion can be easily integrated that the recent surge of cases of mucormycosis of the cranio-maxillary region may not include Covid-19 infection, diabetes mellitus, and corticosteroid as a contributory factor. The presence of the above trio has coexisted in this pandemic which dysregulates the immune system of the patients leading to the invasive fungal infection. The substantial numbers of COVID-19 patients with diabetes mellitus or COVID-19 induced hyperglycemia as well as administration of corticosteroid for the treatment of the inflammatory phase of COVID-19 infection prove the very hypothesis. In cases of suspected or confirmed mucormycosis, all the immunosuppressive therapy used for COVID-19 should be scaled down or discontinued as per the clinical condition of the patient. An early diagnosis and surgical debridement of the affected tissue should be a priority in cases of mucormycosis in order to reduce the high mortality rate. The survival rate of patients with mucormycosis improves drastically by an aggressive surgical approach surgery. Anti-fungal treatment...

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**Table 2: Summary of case series**[^41^-^52^]

| Author       | Country | Sample Size | Age, Range Sex | COVID Status | Comorbidities | Steroid received | Location of Mucormycosis | Isolate confirmation | Outcomes |
|--------------|---------|-------------|----------------|--------------|---------------|------------------|--------------------------|----------------------|----------|
| Moorthy et al. | India   | 18          | 35-73, M- 15, F- 3 | Positive-18  | DM 16+ HT - - | 16+              | Rhino-orbito-cerebral     | 16+                  | Alive-11 |
| Sharma et al. | India   | 23          | NM M- 15, F- 8   | Positive-23  | 21+ 14+ 1+    | 23+              | Rhino-orbito-cerebral     | NM                   | Death-6  |
| Sen et al.    | India   | 6           | 46.2-73.9 M- 6   | Positive-6   | 6+ 3+ 2+      | 5+               | Rhino-orbito-cerebral     | NM                   | Alive-6  |
| Satish et al. | India   | 25          | 30-74 M- 22, F- 3| Positive-11  | NM NM 1+      | NM               | Rhino-orbito-cerebral - 12| NM                   | Alive-23 |
| Mishra et al. | India   | 10          | 37-78 M- 15, F- 3| Positive-10  | 8+ 3+ 1+      | 6+               | Rhino-orbito-cerebral     | NM                   | Death-2  |
| Ravani et al. | India   | 31          | 56.3 (Mean) M- 15, F- 3 | Positive-19  | 30+ 17+ -     | 19+              | Rhino-orbital             | NM                   | Alive-28 |
| Sarkar et al. | India   | 10          | 32-67 M- 8, F- 2 | Positive-10  | 10+ - -       | 10+              | Orbital                  | 6+                   | Alive-6  |
| Nehara et al. | India   | 5           | 52-70 M- 4, F- 1 | Positive-5   | 5+ 2+ -       | 5+               | Rhino-Cerebra             | 5+                   | Alive-3  |
| Patel et al.  | India   | 287         | Non-CAM: 46.9*   | Positive-187 | 180+ 27+      | 152+             | Rhino-orbito-cerebral - 167| 136+                 | Death-2  |
| Bayram et al. | Turkey  | 11          | 73±7.7 M- 9, F- 2| Positive-11  | 8+ 4+ 11+     | Rhino-orbital      | 143+                     | NM                   | Alive-8  |
| Ashour et al. | Egypt   | 8           | 41-67 M- 5, F- 3 | Positive-8   | 6+ 2+ 2+      | NM               | Rhino-orbito-cerebral     | NM                   | Alive-5  |
| Pakdel et al. | Iran    | 15          | 14-71 M- 9, F- 6 | Positive-15  | 13+ - 7+      | Rhino-orbital      | NM                       | NM                   | Alive-8  |

[^41^-^52^]: M=Male, F=Female, NM=Not Mentioned, *+ = Present, *‑ = Absent, LOF=Lost of Follow-up, *Mean, *As per Patel et al, death was calculated for 286 subjects at 12 weeks, *Coronavirus disease (COVID-19)- associated mucormycosis (CAM), Non-coronavirus disease (COVID-19)- associated mucormycosis (CAM)
The radiological evidence of obliteration of the central ciliary and retinal artery may require exenteration of the eye to prevent intracranial extension. Surgical debridement may be repeated if needed to control the invasion of local tissue by the fungus. As the government of many states considered mucormycosis as an epidemic disease, it may be wise for the experts including general primary care providers and family physicians to revisit and revise the standard protocol of Covid-19 management.

Strengths and limitations

This is a comprehensive systematic review describing the data on demographic, clinical characteristics of cases of mucormycosis in cases of COVID-19. Since, COVID-19 is still an evolving disease hence there are chances that we could have missed out on case reports continuously getting published and also cases published in local languages as we only included case reports published in the English. The analysis of case reports can generate an effective hypothesis however potential of risk of bias due to lack of external validity cannot be ruled out.

Conclusion

The cases of mucormycosis reported in India might be the tip of the iceberg. As understanding of COVID-19 disease processes and their treatment is evolving continuously, it can be estimated that the one-size-fits-all approach cannot be used in the community approach for the management of COVID-19. Though corticosteroids demonstrated to be a crucial drug in the management of moderate to severe COVID-19 infection, their indiscriminate use has come with a price. In COVID-19 patients, newly onset diabetes mellitus is a common finding, and hyperglycemia induced by steroid therapy is also a common occurrence in COVID-19 patients. The presence of diabetes in COVID-19 worsens the prognosis of the disease. The COVID-19 recovered patients should be monitored for new-onset diabetes mellitus and followed for the consequence of immunosuppression due to steroid therapy.

So, can we say that COVID-19, diabetes, and steroids: An unholy trilogy? The forecast of a direct association might not be possible but the scenario leading to immunocompromised conditions of the patient with COVID-19 might give substantial evidence of the association of the unholy trilogy. It has been found that the virus itself affects the cell-mediated immunity, the altered immunity due to comorbid conditions like diabetes mellitus, and the icing on the cake is done by the immunosuppressive drugs in the treatment protocols. Thus provided a fertile ground for invasive fungal infections. The presence of this ominous trinity in any COVID-19 patient should prompt the doctors to be extra cautious and suspicious of the association of this unholy trinity and act promptly albeit judiciously. Early diagnosis, prompt surgical intervention, and intravenous anti-fungal treatment should be the pillars for the management of mucormycosis.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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