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Original Research Article

Clinical profile and risk factors associated in patients of mucormycosis in COVID-19 pandemic: a study in a tertiary centre

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ABSTRACT

Background: The objective of this study was to determine the clinical profile and risk factors associated in patients of mucormycosis in COVID-19 pandemic.
Methods: It was a prospective observational study conducted at a tertiary care centre in the month of May and June 2021. It involved all patients of mucormycosis mainly involving paranasal sinuses and orbit. The clinical profile and associated risk factors leading to mucormycosis were studied.
Results: Thirty patients of mucormycosis mean age 56.62 years out of them 25 (83.33%) male and 5 (16.66%) female were studied. Twenty-four patients (80%) had COVID-19 infection, out of them 7 (29.2%) were active and 17 (70.8%) had recovered within 4 weeks. Five (16.6%) patients were suspected as they had symptoms of COVID-19 previously but never got tested. One patient had no history of COVID infection. All the patients were diabetic at the time of presentation, out of them 26 (86.6%) of patients were known diabetic and 4 (13.3%) became diabetic after COVID-19 infection. The ethmoids were the most common sinuses affected. Intra-orbital extension was seen in 13 (43.3%) of cases while intracranial extension was seen in 4 (13.3%) patients. Twenty-eight (93.3%) patients gave history of steroids intake. Antibiotics were taken by 76.6% patients while zinc supplement was used by 83.3% patients. Oxygen was used 10 (33.3%) patients, 80% of them using face mask or canula and 4 of them requiring mechanical ventilatory support.
Conclusions: The risk factors associated with mucormycosis in COVID pandemic must be given serious consideration as there is sudden increase in the case and mortality is very high. Uncontrolled diabetes and over use of steroids in COVID management are two main aggravating factors, however other factors must also be studied thoroughly.

Keywords: Mucormycosis, COVID-19, Pandemic, Diabetes, Steroids, Oppurtunistic

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). The first case was reported in December 2019 in Wuhan, China and since then there have been a lot of changes in its diagnosis, management, sequelae and complications.[1] The COVID-19 disease spectrum now not only includes cough and high-grade fever but also various multisystem problems such as shortness of breath, anosmia, ageusia, diarrhoea, generalised malaise, acute cardiac injury and even deadly secondary opportunistic fungal infections. Early and prompt identification of these high-morbidity conditions is crucial for optimal treatment and improved outcomes.

Since the outcome of deadly second corona wave in April 2021 in India a new variant of COVID-19, B.1.617 (delta variant) was isolated. Unlike the first corona wave the second corona wave was not only characterized by varied symptoms and high mortality the aftermath of the disease was more difficult to tackle with deadly oppurtinustic

fungal infections flaring up. One of the most commonly encountered opportunistic fungal infections were black fungus or mucormycosis which due to its potentially dangerous sequale raised alarm in whole of the country medical fraternity.

Mucormycosis, a life threatening angioinvasive infection caused by common filamentous fungi, mucormycetes and constitutes the third most common invasive fungal infection following aspergillosis and candidiasis.[2] The transmission of disease is mainly by inhalation of spores or by direct inoculation of the spores into disrupted skin or mucosa. The fungi can cause infections with high mortality specially in immunocompromised patients, mainly diabetic patients.[3] Mucormycetes can be identified by the presence of broad aseptate hyphae (coenocytic mycelia) and formation of zygospores. The order Mucorales includes several species mainly involving rhino oculo cerebral, pulmonary, cutaneous, and gastrointestinal all characterized by tendency to disseminate.

Globally, the prevalence of mucormycosis varied from 0.005 to 1.7 per million population, while its prevalence is much more-higher (0.14 per 1000) in India compared to developed countries, in a recent estimate of year 2019-2020.[4-6] In other words, India has highest cases of the mucormycosis in the world. Notwithstanding, India is already having second largest population with diabetes mellitus (DM) and was the diabetes capital of the world. Importantly, DM has been the most important and consistent risk factor linked with mucormycosis in India, although hematological malignancies and organ transplant takes the lead in Europe and the USA.[6] Nevertheless, DM remains the leading risk factor associated with mucormycosis globally, with an overall very high mortality of 46%.[7]

Clinically Rhinocerebral mucormycosis is the commonest clinical presentation in most of the mucormycosis patients.[8] It can present with atypical signs and symptoms similar to complicated sinusitis, such as nasal blockade, crusting, proptosis, facial pain and swelling, ptosis, chemosis, and even ophthalmoplegia, with headache and fever and various neurological signs and symptoms if intracranial extension is present.[9,10] A black eschar is often seen in the nasal cavity or over the hard palate region, but is not characteristic.[11,12] Histological features of mucormycosis include mycotic infiltration of blood vessels, vasculitis with thrombosis, tissue infarction, haemorrhage and acute neutrophilic infiltrate.[13]

If the disease is not diagnosed early and treated aggressively, there may be rapid progression of the disease, with reported high mortality rates from intra-orbital and intracranial complications of 50-80 per cent.[14] Even with prompt diagnosis, treatment of underlying diseases, and aggressive medical and surgical intervention, the management is often not effective ultimately leading to death.[15] Recently, when the country was facing the deadly second corona wave, a huge surge in the cases of mucormycosis was observed in whole of the country. In our institute also, a tertiary care teaching hospital, we saw a large number of in cases of invasive fungal sinusitis, specifically of mucormycosis in last few months.

In the present scenario of ongoing COVID-19 pandemic, this sudden spike in number of mucormycosis was largely attributed to COVID-19 infection and cocktail of drugs used in its managment. SARS-CoV-2 infection is characterized by an increase in pro-inflammatory cytokines and a decrease in anti-inflammatory cytokines, resulting in a state of cytokine storm syndrome. Dexamethasone most widely and accepted drug used in COVID-19 management can decrease the regulation of this inflammatory state and further suppress the immunity.[16] Critically ill patients, especially those admitted to intensive care units and those who required mechanical ventilation, or patients having longer duration of hospital stays, were more likely to develop fungal co-infections.[17] Not only the corticosteroid but other drugs used like monoclonal antibody tocilizumab, rampant use of broad spectrum antibiotics, long term zinc supplement, oxygen therapy, steam inhalation etc are thought to be risk factors involved in the pathogenesis of mucormycosis. However due to novelty of the disease in recent ongoing COVID pandemic there are very few clinical studies in literature which clearly suggests the pathogenesis and risk factors associated with mucormycosis. The aim of the study was to determine the clinical profile and associated risk factors in patients of mucormycosis visiting our tertiary care centre.

METHODS

A prospective observational study was undertaken at Rajendra Institute of Medical Science, Ranchi, Jharkhand, India over a period of two months, from May to June 2021. The inclusion criteria mainly included all patients with suspected sign and symptoms of mucormycosis involving paranasal sinuses, orbit or central nervous system visiting ENT/eye/neurology department. The patients who did not give consent and had sign and symptoms of pulmonary and gastrointestinal mucormycosis were excluded (as they were treated with other speciality).

The suspected patients underwent diagnostic nasal endoscopy, fungal microscopy and culture of the swab collected from involved part, biopsy and histopathological examination of the involved part, and radiological investigations mainly contrast enhanced magnetic resonance imaging and computed tomography. The patients who were diagnosed underwent thorough history taking, their presentation details, COVID history, imaging findings, co-morbidities, management details, and follow-up information were obtained, recorded and analysed. All patients underwent proper surgical debridment along with administration of liposomal amphotericin. Proper ethical

clearance was obtained from institutional ethical clearance committee. All data were stored and analyzed using SPSS for windows, version 8.0.

RESULTS

A total of 30 patients presented; 25 (83.3%) of these were male and 5 (16.6%) were female. The mean age of presentation was 56.62 years. Twenty-four patients (80%) had COVID-19 infection, out of them 7 (29.2%) were active and 17 (70.8%) had recovered. Recovered cases were those who had COVID infection within last four weeks and had RT-PCR test negative at the time of presentation. Five (16.6%) patients were suspected. Suspected cases where those cases who had history of symptoms of COVID-19 within last four weeks but never got RT-PCR or HRCT chest done during that period and had recovered. At the time of presentation they underwent rtpcr test and all them turned out to be RTPCR negative. One of the patient had no history of COVID-19 infection but was known diabetic and had uncontrolled blood sugar level at time of presentation (Table 1).

Table 1: COVID status of patients.

COVID status	Cases N (%)
COVID positive	24 (80)
Active	7 (29.2)
Recovered	17 (70.8)
Suspected	5 (16.6)
COVID negative	1 (3.3)

All of the patients were diabetic at the time of presentation. Out of them 26 (86.6%) patients were known diabetic (pre COVID) and 4 (13.3%) of the patients were non-diabetic pre COVID but became diabetic after COVID-19 treatment. Twenty-four (80%) of them were uncontrolled diabetic with hbA1c level more than 6.5 (Table 2). Fourteen patients had hypertension; all of these were diabetic. One of the patient was a known case of multi drug resistant tuberculosis and was on treatment while another patient was in renal failure at the time of presentation.

Table 2: Diabetes status of patients.

Diabetes status	Cases N (%)
Known diabetic	26 (86.6)
COVID diabetic	4 (3.3)
Uncontrolled (hbA1c>6.5)	24 (80)
Controlled (hbA1c<6.5)	6 (20)

All patients had a primary disease involving the ethmoid group of sinus air cells. The next sinus most commonly involved was maxillary sinus followed by sphenoid and frontal sinus. Out of the 30 patients, ocular involvement was seen in 13 (43.3%) of patient, 3 out of them having no vision (no perception of light) in the involved site (Figure 1-4). Intracranial involvement was seen in 4 (13.3%) cases while palatal involvement was seen in 2 (6.6%) of cases at the time of presentation (Table 3).

Figure 1: Clinical picture showing facial and orbital involvement.

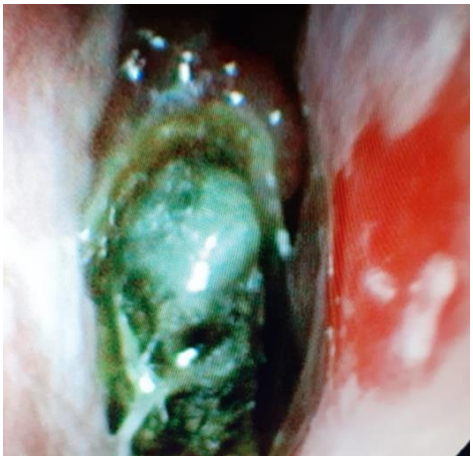

Figure 2: Endoscopic view showing necrosed middle turbinate.

Figure 3: Coronal magnetic resonance imaging showing intra orbital extension.

Figure 4: Magnetic resonance imaging showing m axillary antrum spread.

Table 3: Extra sinonasal spread of mucormycosis.

Extra sino nasal spread	Cases N (%)
Orbital involvement	13 (43.3)
CNS involvement	4 (13.3)
Platal involvement	2 (6.6)
Orbital involvement	13 (43.3)

Twenty-eight (93.3%) patients had used steroids in last weeks during the management of their coronavirus treatment or associated illness either in tablet or injectable form. Twenty-three (76.6%) patients gave history of use of antibiotics and 25 (83.3%) of the patients had used zinc supplement during the course of treatment. Ten (33.3%) received oxygen therapy for treatment for COVID/associated illness. Out of them 8 (80%) of them used by face masks/nasal canula and only 2 (20%) gave history of use of mechanical ventilation (Table 4).

Table 4: Treatment history of patients.

Treatments	Cases N (%)
Steroids	28 (93.3)
Broad spectrum antibiotics	23 (76.6)
Zinc	25 (83.3)
Oxygen usage	10 (33.3)
Mask/canula	8 (80)
Mechanical ventilation	2 (20)

DISCUSSION

Oppurtunistic fungal infections were commonly seen in recent previous pandemics. In the SARS-CoV-1 outbreak, a small series of autopsy cases described that 10% of them had a invasive infection suggestive of aspergillosis and the infected patients were treated with high-dose corticosteroids.[18] In another published autopsy cases, the authors confirmed the existence of isolation of Aspergillus sp and Mucor sp in the upper airways and lung, and a case has also been described with multiple aspergillus abscesses in different organs.[19]

The ongoing pandemic caused by novel SARS-CoV-2 has been associated with a wide range of disease spectrum, ranging from a mild cough to life-threatening ARDS.[20] SARS-CoV-2 has been associated with a wide range of opportunistic bacterial and fungal infections. Both aspergillosis and candida have been reported as the main fungal pathogens for co-infection in people with COVID-19.[21] Recently several cases of mucormycosis mostly in people recovered with COVID-19 have been increasingly reported world-wide, in particular from India. The main reason that appears to be facilitating mucorales spores to germinate in people with COVID-19 is an ideal environment of low oxygen (hypoxia), high glucose (diabetes, new-onset hyperglycemia, steroid-induced hyperglycemia), acidic medium [metabolic acidosis, diabetic ketoacidosis (DKA)], high iron levels (increased ferritins) and decreased phagocytic activity of white blood cells (WBC) due to immunosuppression (SARS-CoV-2 mediated, steroid-mediated or background comorbidities) coupled with several other shared risk factors including prolonged hospitalization with or without mechanical ventilators.

In our study we found that 80% of patients having mucormycosis had COVID infection. Out of them 7 (29.2%) of the patients were COVID-19 positive at the time of presentation and 17 (70.8%) of them had recovered. Five (16.6%) patients were suspected who had history of symptoms highly suggestive of COVID-19 in last 4 weeks but they never underwent RT-PCR or HRCT chest done during that period and now presented with RT-PCR test negative. This was mainly due to lack of awareness, fear of disease, cost involved in testing which included transportation, non-avaliability of nearby testing centres etc. However, in time of COVID pandemic and in a developing country like India we can conclude that majority of these suspected patients had COVID-19 infection in past and now presented with post COVID complications. This suspected group of people were at most risk as majority had taken self-medication or treatment by non-qualified practitioner, and were prescribed high doses of corticosteroid without any sugar monitoring.

Several cases have been reported in literature which suggests association of mucormycosis and SARS-CoV 2 along with diabetes and use of excess corticosteroids. Mehta and Pandey reported a single case of a 60-years-old male with rhino-orbital mucormycosis associated with COVID-19 in September 2020.[20] Another such case report was published by Werthman-Ehrenreich in the same month.[22]

White et al studied 135 adults with COVID-19 infection, and reported an incidence of 26.7 per cent for invasive fungal infections.[23] Song et al studied the association

between COVID-19 and invasive fungal sinusitis in April 2020, and concluded that a large number of patients affected had recovered from COVID-19.[21] In a recent review by Rawson TM et al 8 per cent of coronavirus-positive or recovered patients had secondary bacterial or fungal infections during hospital admission, and had history of widespread use of broad-spectrum antibiotics and steroids.[24]

While most of the studies conducted mainly suggests that mucormycosis was a part of post COVID complication we found that 7 (23.3%) of patients developed mucormycosis while they were still COVID-19 positive. This implies that mucormycosis is not necessarily a post COVID complication but should always be kept in mind while treating COVID patients specially while treating immunocompromised or diabetes patients having uncontrolled sugar level and patients must be thoroughly investigated for mildest of suspicion.

Diabetes along with improper use of steroid for COVID-19 treatment and immunosuppression caused by SARS-CoV 2 virus seems to be the main risk factors for sudden rise in mucormycosis cases. Presence of DM significantly increases the odds of contracting rhinocerebral mucrmycosis by 7.5-fold (Odds ratio 7.55, p=0.001) as shown in a prospective Indian study, prior to COVID-19 pandemic.[25] A 2019 nationwide multi-center study of 388 confirmed or suspected cases of mucormycosis in India prior to COVID-19, Prakash et al found that 18% had DKA and 57% of patients had uncontrolled DM.[26]

In a recent systematic review conducted until April 9, 2021 by John et al that reported the findings of 41 confirmed mucormycosis cases in people with COVID-19, diabetes mellitus was reported in 93% of cases, while 88% were receiving corticosteroids.[27] These findings were consistent with our findings in which we found that all the patients were diabetic at the time of presentation. Out of them 26 (86.6%) of patients were known (pre COVID) diabetic and 4 (13.3%) became diabetic after COVID-19 infection. Most of them (80%) had hbA1c level greater than 6.5. This was mainly due to non-judicious use of steroids as 28 (93.3%) of the patients gave history that they received steroids in any form.

A recent systemic metareview of larger case series of 101 mucormycosis cases (95 confirmed and 6 suspected) in COVID-19, where 80% cases had diabetes, and more than two-third (76.3%) received a course of corticosteroids.[28]

There are various possible reasons for this association, including the immunosuppression caused by COVID-19 infection and disease process, or the extensive use of steroids and broad-spectrum antibiotics in the management of COVID-19, leading to the development or exacerbation of a pre-existing fungal disease. The National Institute of Health, according to the Randomised evaluation of COVID-19 therapy ('Recovery') Collaborative Group, recommends steroid use only in patients who are on a ventilator or require supplemental oxygen, but not in milder cases.[29]

COVID-19 infection by itself often causes endothelialitis, endothelial damage, thrombosis, lymphopenia, and reduction in $CD4^+$ and $CD8^+$ level and thus predisposes to secondary or opportunistic fungal infection.

Free available iron is an ideal resource for mucormycosis. Increased blood sugar level causes glycosylation of transferrin and ferritin, and reduces iron binding allowing increased free iron. Moreover, increase in cytokines in patients with COVID-19 especially interleukin-6, increases free iron by increasing ferritin levels due to increased synthesis and decreased iron transport. Further, concomitant acidosis increases free iron by the same mechanism and additionally by reducing the ability of transferrin to chelate iron. High glucose, low pH, free iron, and ketones in presence of decreased phagocytic activity of WBC, enhances the growth of mucor. In addition, it enhances the expression of glucose-regulator protein 78 (GRP-78) of endothelium cells and fungal ligand spore coating homolog (CotH) protein, enabling angio-invasion, hematogenous dissemination and tissue necrosis[30].

Several other reasons like oxygen usage, specially use of industrial oxygen, use of broad-spectrum antibiotics, excess of zinc supplement have been said to be an additive risk factor for rise in mucormycosis cases. During second COVID wave in India due to scarcity of medical oxygen industrial oxygen was being diverted for use in hospitals and COVID wards. However unlike medical oxygen cylinders industrial oxygen cylinders are not regularly cleaned and disinfected, also they are more prone to microleaks. Also, non-sterile waters used in humidifiers are said to further increase the risk of opportunistic fungal infection. However, in our study only about one third 33.33% of the patients gave history of oxygen usage and mostly (80%) it was delivered by nasal mask or canula.

Excessive use of zinc and broad-spectrum antibiotics are also said to be an additive risk factor for mucor growth. Zinc is said to provide ideal environment for fungal growth.[31] Excessive use of broad-spectrum antibiotics eliminate the normal commensals which prevents opportunistic infections to flare.

When immune system is of the body is already compromised due to high dose of steroid, diabetes, COVID-19 it provides a breeding ground for opportunistic fungi. Since antibiotics and zinc are easily available over the counter drugs and many patients take without proper consultation. This may lead to their misuse and when used with high doses of corticosteroids it may lead to opportunistic infections. However, we could not find any study in literature which clearly links these factors like use of industrial oxygen, antibiotics, zinc supplement with pathogenesis of mucormycosis. Most of the studies shows

an indirect effect of use of these medicines on mucormycosis pathogenesis. Further studies and more research are required regarding this.

CONCLUSION

The sudden increase in mucormycosis in Indian context appears to be a result presence of diabetes (high prevalence genetically), dis-propotrianate use of corticosteroid (increases blood glucose and opportunistic fungal infection) and COVID-19 (cytokine storm, lymphopenia, endothelial damage). Other factors like industrial oxygen usage, rampant use of antibiotics, zinc supplementation need to be further studied. Strict monitoring of blood glucose level and judicious evidence-based use of corticosteroids, antibiotics in patients with COVID-19 is recommended to reduce the burden of deadly mucormycosis.

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