ORIGINAL ARTICLE

Covid-19 Association with Mucormycosis (CAM): An Experience from Single Hospital Based Study

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ABSTRACT

Objective: This study aimed to assess the outcomes experienced by patients diagnosed with mucormycosis linked with COVID-19 while they were hospitalized.
Study Design: Retrospective study
Place and Duration: This study was carried out at Sardar Begum Dental College from January, 2022 to June 2022.
Methods: There were 215 patients of both genders had age 18-80 years were presented in this study. Included patients had confirmed coronavirus disease with symptoms of mucormycosis. Patients were provided informed written consent for detailed demographics. Clinical and laboratory outcomes among all cases were assessed. We used SPSS 22.0 to analyze all data.
Results: There were majority males 165 (76.7%) and 50 (23.3%) females in this study. Mean age of the patients was 45.6±17.53 years and had mean BMI 26.13±8.17 kg/m^2. We found that diabetes mellitus was the most common co morbidity in 140 (65.1%) cases, followed by hypertension in 85 (39.5%) cases. Frequency of rhino orbital mucormycosis was found in 110 (51.2%) cases, sinuses in 70 (32.6%) cases and cerebral in 35 (16.3%) cases. Majority of the cases were treated by steroid. Mean hospitalization was 16.8±7.67 days. Frequency of died patients was 28 (13.02%) because of CKD, renal dysfunction and orbital involvement.
Conclusion: We concluded in this study that rhino-orbital involvement, CKD and renal dysfunction were a significantly risk factors for mortality among patients of COVID-19 with mucormycosis.
Keywords: Mucormycosis, Covid-19, Mortality, Hospitalization, Steroids

INTRODUCTION

There have been links between the coronavirus disease 2019, (COVID-19) pandemic and severe bacterial and fungal illnesses[1]. A fungal infection called mucormycosis is brought on by Mucorales fungi such Rhizopus, Mucor, Rhizomucor, Condition can potentially, and Lichtheimia[2]. The main line of defence for the host against mucormycosis is the phagocyte[3].

Mucormycosis infection is characterised by a significant angio-invasion that results in arterial thrombosis or tissue destruction[4]. Because mucormycosis spreads quickly across the bodily systems, it can damage the paranasal sinuses, orbits, lungs, gastrointestinal tract, kidneys, skin, and central nervous system. The following factors often affect mucormycosis manifestations: (a) the method of fungal spore ingestion, inhalation, or direct skin injections; and (b) the co-existing medical conditions of the affected patients[2].

In those with impaired immune systems, mucormycosis is more prevalent. The two most frequent risk factors for a mucormycosis infection are diabetic ketoacidosis and drugs. significant side effects such brain and ocular involvement[5]. Because corticosteroid therapy reduces macrophages' capacity to stop the germination of mucor fungus spores[4], Furthermore, it is thought that a low oxygen environment with high glucose from diabetes, new-onset hyperglycemia, or microtubule hyperglycemia is optimum (hypoxia).

Less is understood about COVID-19-associated mucormycosis than CAPA (CAM). Because the fungus' hyphae are angio-invasive, mucormycosis is a fungus pathogen that affects infarction and death of the host tissues [6]. The very first case series with CAM in India gathered clinical data during August and Dec 2020 and suggested that mucormycosis and COVID-19 may be related [7]. Other findings [8, 9] describing the effect of glucocorticoid treatment for COVID-19 on the ensuing mucormycosis provided more evidence for this connection. On the other hand, a number of case studies documented the concurrent diagnosis of mucormycosis and COVID-19 [10]. These instances

focused more on the effects of baseline risk variables for both illnesses that are common, such as neutropenia and diabetes (DM), than on the causative connection brought about by COVID-19 therapy with glucocorticoids.

Incidence rates of mucormycosis in the population in general range from 0.005 to 1.7 per thousand people globally. The frequency of mucormycosis is, however, 80 times higher in India than in affluent nations [11]. Patients with COVID-19 who are still ill or who are recovering may exhibit CAM. Uncontrolled diabetes, respiratory conditions including bacterial and viral infections, cancer (such as haematological cancer), and an immunocompromised state are all CAM risk factors [12,16]. In published studies of CAM, mortality rates differ significant. Studies examining the factors that predict mortality in CAM are, however, few. In this study, we sought to identify the factors that predict among-hospital mortality in CAM patients.

MATERIAL AND METHODS

This retrospective study was conducted at Sardar Begum Dental College and comprised of 215 patients of Covid-19. Patients were provided informed written consent for detailed demographics. Patients <18 years of age, pregnant females and those did not provide any written consent were excluded.

Every single one of our patients came highly recommended from another clinic. Our clinic performed the necessary diagnostic tests to confirm their identities. It was assumed to be CAM when mucormycosis was detected in COVID-19 positive patients. Nose and/or pharyngeal samples that tested positive for COVID-19 in reverse transcriptase chain reaction (RT-PCR) analyses were used to make the diagnosis. Mucormycosis was diagnosed through a combination of clinical symptoms like eye pain, cramps, and facial swelling with imaging methods like computerized imaging technology of the sinus sinus (CT-PNS) or imaging (mri of the sinus sinus (MRI-PNS), and the show of strength of fungi using techniques like testing by alkaline (KOH) mount, bacteria and fungi culture, and histology. We chose the seniors with a CAM diagnosis

who had undergone surgery or taken medication. Both sexes are welcome, and patients must be least 18 years old. All patients undergoing CAM got thorough medical care, including close monitoring of their blood sugar levels and excellent glycemic control while in the hospital.

Extracted data on patient demographics, medical history, and results was entered into a conditions-based record proforma. Comorbidities, length of hospital stay, steroid and immunosuppressant use (including tocilizumab), and other clinical details relating to COVID-19 were recorded. Furthermore, clinical signs and indications of CAM were documented. Other laboratory parameters for which information was recorded were blood creatinine, haemoglobin, total leucocyte count, haemoglobin A1c, and inflammatory markers such as C-reactive proteins (CRP), D-dimer, iron, etc. Chronic kidney disease patients were diagnosed with renal impairment (CKD).

CAM patients with rhino-orbital-cerebral mucormycosis were categorized based on MRI grade (ROCM). Mortality throughout the hospital stay was the main result. We evaluated the death rate and the predictors of mortality. We used SPSS 22.0 to analyze all data.

RESULTS

There were majority males 165 (76.7%) and 50 (23.3%) females in this study. Mean age of the patients was 45.6±17.53 years and had mean BMI 26.13±8.17 kg/m². We found that diabetes mellitus was the most common co morbidity in 140 (65.1%) cases, followed by hypertension in 85 (39.5%) cases, ischemic heart disease in 34 (15.8%) cases and chronic kidney disease in 26 (12.1%) cases.9 (4.2%) cases were smokers.(table 1)

Table-1: Patients demographically details

Variables	Frequency	Percentage
Mean age (years)	45.6±17.53	
Mean BMI (kg/m²)	26.13±8.17	
Gender		
Male	165	76.7
Female	50	23.3
Co-morbidities		
DM	140	65.1
HTN	85	39.5
IHD	34	15.8
CKD	26	12.1
Smokers		
Yes	9	4.2
No	206	95.8

Frequency of rhino orbital mucormycosis was found in 110 (51.2%) cases, sinuses in 70 (32.6%) cases and cerebral in 35 (16.3%) cases. Majority of the cases were treated by steroid, followed by remdesivir and methylprednisolone. (table-2)

Table-2: Different type of mucormycosis and treatment

Variables	Frequency	Percentage
Types of Mucormycosis		
rhino orbital	110	51.2
sinuses	70	32.6
cerebral	35	16.3
Treatment		
Steroids	180	83.7
Remdesivir	150	69.8
Methylprednisolone	130	60.5
Dexamethasone	70	32.6
Favipiravir	32	14.9
Tocilizumab	11	5.1

Mean hospitalization was 16.8±7.67 days. Frequency of died patients was 28 (13.02%).(table-3)

We conducted multivariate analysis keeping in mind the parameters found in univariate analysis. The use of tocilizumab, renal impairment brought on by hospitalization, orbital involvement, and serum creatinine concentrations were all linked to higher mortality risks in CAM patients.(table-4)

Table-3: Frequency of mortality and hospital stay

Variables	Frequency	Percentage
Mean Hospitalization (days)	16.8±7.67	
Mortality		
Yes	28	13.02
No	187	86.98

Table-4: Using multivariate analysis to identify mortality predictors

Variables	95% Confidence Interval	P value
Tocilizumab use	2.1±7.19	0.012
Renal dysfunction/failure during hospitalization	1.25±88.08	0.011
Orbital involvement	1.50 ±128.80	0.014
Serum creatinine	1.87±352.41	0.019

DISCUSSION

Mucormycosis has become a major worry during the latest wave of a COVID-19 pandemic. The high prevalence of untreated and uncontrolled diabetes is probably to blame [14]. The manifestations of mucormycosis vary. The most prevalent form of this pandemic is rhino-cerebro-orbital mucormycosis. The CT sinus sinus and MRI brains are used to make the diagnosis [15]. Singh et al. found that rhino-orbital involvement (56.7%) was the second-most prevalent mucormycosis site, behind the sinuses and nose (88.9%) [16].

In our study rhino orbital mucormycosis was found in 110 (51.2%) cases, sinuses in 70 (32.6%) cases and cerebral in 35 (16.3%) cases. Frequency of died patients was 28 (13.02%). Jiang et al. [17] reported that even among those people, only 3 out of 11 with severe rhino-orbital-cerebral mucormycosis who were not carriers of COVID-19 survived. It's crucial to get a proper diagnosis quickly so that treatment can begin. If treatment is delayed by just six days, the chance of dying within 30 days rises from 30 to 60 percent [18]. Multidisciplinary medical care, including fast and effective necrotic tissue removal (source control: 95.2%), sufficient anti - fungal medicinal (liposomal editions (>85.7%)/posaconazole (65%)), conscientious blood sugar tracking, and good measures regarding glucose control, likely contributed to the lesser mortality rate observed in our study.

High mortality was substantially correlated with a number of variables, including CKD, orbital participation, tocilizumab usage, and renal impairment throughout the hospital stay. According to Deutsch et al., the mortality rate might reach 90% when mucormycosis is present intracranially [19]. It is quite likely that COVID-19 will have mucormycosis. High ferritin levels, hypoxia, hyperglycemia, and decreased cell lysis of leucocytes can all have an influence on the formation of CAM [16]. In COVID-19 patients, the incidence of CKD is larger (4.09%) than it is in the overall population (0.46%). Mortality rises considerably when CKD is present (44.6% versus 4.7% in others without COVID-19) [20].

One of the main risk factors for mucormycosis is diabetes mellitus, particularly uncontrolled diabetes [21]. Despite the fact that 65.1% of patients had diabetes, we could find no link between the disease and death. Although having poorly managed blood sugar levels is one of the factors that can cause CAM, average HbA1c levels were similar in both survivors and non-survivors. A larger research is required to fully assess the effect of diabetes on death in patients with CAM. Age is another factor harmful to the results of CAM in addition to these.

The average period between both the COVID-19 and the occurrence of mucormycosis was 18 days, and no meaningful link was discovered. It is advised that throughout the recovery time, the practitioners should keep an eye out for the development of mucormycosis and reduce the patient's steroid dosage while closely monitoring them for DM management. [22]

CONCLUSION

We concluded in this study that rhino-orbital involvement, CKD and renal dysfunction were a significantly risk factors for mortality among patients of COVID-19 with mucormycosis.

REFERENCES

1   Kubin, C. J. et al. Open Forum Infectious Diseases. ofab201 (Oxford University Press US).
2   Skiada, A., Pavleas, I. & Drogari-Apiranthitou, M. Epidemiology and diagnosis of mucormycosis: An update. J. Fungi 6, 265 (2020).
3   Waldorf, A. R. Pulmonary defense mechanisms against opportunistic fungal pathogens. Immunol. Ser. 47, 243–271 (1989).
4   Bouchara, J. et al. Attachment of spores of the human pathogenic fungus Rhizopus oryzae to extracellular matrix components. Eur. J. Cell Biol. 70, 76–83 (1996).
5   Prakash, H. & Chakrabarti, A. Global epidemiology of mucormycosis. J. Fungi 5, 26 (2019).
6   Petrikkos G, Skiada A, Lortholary O, Roilides E, Walsh TJ, Kontoyiannis DP. Epidemiology and clinical manifestations of mucormycosis. Clin Infect Dis. 2012;54:S23-34. https://doi.org/10.1093/cid/cir866.
7   Sen M, Lahane S, Lahane TP, Parekh R, Honavar SG. Mucor in a viral land: a tale of two pathogens. Indian J Ophthalmol. 2021;69:244–52. https://doi.org/10.4103/ijo.IJO_3774_20.
8   Mehta S, Pandey A. Rhino-orbital mucormycosis associated with COVID-19. Cureus. 2020;12:e10726. https://doi.org/10.7759/cureus.10726.
9   Saidha PK, Kapoor S, Das P, Gupta A, Kakkar V, Kumar A, et al. Mucormycosis of paranasal sinuses of odontogenic origin post COVID19 infection: a case series. Indian J Otolaryngol Head Neck Surg. 2021. https://doi.org/10.1007/s12070-021-02638-1.
10 Werthman-Ehrenreich A. Mucormycosis with orbital compartment syndrome in a patient with COVID-19. Am J Emerg Med. 2021;42:264.e5-264.e8. https://doi.org/10.1016/j.ajem.2020.09.032.
11 World Health Organization. Coronavirus Disease (COVID-19). Mucormycosis. (2021). Accessed: June 30, 2021: https://www.who.int/india/emergencies/coronavirus-disease-(covid-19)/mucormycosis.
12 Singh Y, Ganesh V, Kumar S, Patel N, Aggarwala R, Soni KD, Trikha A: Coronavirus disease-associated mucormycosis from a tertiary care hospital in India: a case series. Cureus. 2021, 13:e16152. 10.7759/cureus.16152
13 Sreshta K, Dave TV, Varma DR, Nair AG, Bothra N, Naik MN, Sistla SK: Magnetic resonance imaging in rhino-orbital-cerebral mucormycosis. Indian J Ophthalmol. 2021, 69:1915-27. 10.4103/ijo.IJO_1439_21
14 Szarpak L, Chirico F, Pruc M, Szarpak L, Dzieciatkowski T, Rafique Z: Mucormycosis—a serious threat in the COVID-19 pandemic?. J Infect. 2021, 83:237-79. 10.1016/j.jinf.2021.05.015
15 Chandra S, Rawal R: The surge in Covid related mucormycosis. J Infect. 2021, 83:381-412. 10.1016/j.jinf.2021.06.008
16 Singh AK, Singh R, Joshi SR, Misra A: Mucormycosis in COVID-19: a systematic review of cases reported worldwide and in India. Diabetes Metab Syndr. 2021, 15:102146. 10.1016/j.dsx.2021.05.019
17 Jiang N, Zhao G, Yang S, et al.: A retrospective analysis of eleven cases of invasive rhino-orbito-cerebral mucormycosis presented with orbital apex syndrome initially. BMC Ophthalmol. 2016, 16:10. 10.1186/s12886-016-0189-1
18 Gibertoni D, Reno C, Rucci P, et al.: COVID-19 incidence and mortality in non-dialysis chronic kidney disease patients. PLoS One. 2021, 16:e0254525. 10.1371/journal.pone.0254525
19 Deutsch PG, Whittaker J, Prasad S: Invasive and non-invasive fungal rhinosinusitis—a review and update of the evidence. Medicina. 2019, 55:319. 10.3390/medicina55070319
20 Gibertoni D, Reno C, Rucci P, et al.: COVID-19 incidence and mortality in non-dialysis chronic kidney disease patients. PLoS One. 2021, 16:e0254525. 10.1371/journal.pone.0254525
21 Jeong W, Keighley C, Wolfe R, Lee WL, Slavin MA, Kong DC, Chen SC: The epidemiology and clinical manifestations of mucormycosis: a systematic review and meta-analysis of case reports. Clin Microbiol Infect. 2019, 25:26-34. 10.1016/j.cmi.2018.07.011
22 Sen M, Lahane S, Lahane TP, Parekh R, Honavar SG. Mucor in a viral land: A tale of two pathogens. Indian J Ophthalmol. 2021;69:244–52