



Research Paper

Mucormycosis Associated With COVID-19: A Case Series at a Tertiary Care Center in India



Charudatt Chalisgaonkar¹, Sandeep Singh², Ambrish Mishra², Gaurav Derashri^{3*}, Neera Marathe²

1. Department of Ophthalmology, Shyam Shah Medical College Associated With Sanjay Gandhi and Gandhi Memorial Hospital, Rewa, Madhya Pradesh, India.
2. Department of Community Medicine, Shyam Shah Medical College Associated With Sanjay Gandhi and Gandhi Memorial Hospital, Rewa, Madhya Pradesh, India.
3. Community Health Centre, Narwar, Ujjain, Madhya Pradesh, India.



Citation Chalisgaonkar C, Singh S, Mishra A, Derashri G, Marathe N. Research Paper: Mucormycosis Associated With COVID-19: A Case Series at a Tertiary Care Center in India. *Caspian Journal of Health Research*. 2022; 7(2):61-68. <https://doi.org/10.32598/CJHR.7.2.414.1>

Running Title COVID-19 Associated with Mucormycosis

doi <https://doi.org/10.32598/CJHR.7.2.414.1>



ABSTRACT

Background: COVID-19 patients across the globe have been reporting several post-COVID health conditions such as respiratory, vascular, cardiac and renal complications and opportunistic infections; the most common of which has been fungal infections.

Objectives: The objective of our study was to identify socio-demographic characteristics, risk factors, clinical parameters, site of involvement and outcome of patients with COVID-19 Associated Mucormycosis (CAM) at a tertiary care centre in Rewa (Madhya Pradesh, India).

Materials & Methods: This was a prospective observational study, conducted between 1st May to 30th June 2021; including 40 patients who had Mucormycosis with recent or active COVID-19. The data was collected using a structured data collection form by trained interviewers who were already working in Mucormycosis Ward.

Results: The overall mean and median age of the patients was 50.8 years and 52.5 years respectively, with majority of the males (72.5%). Of total, 47.5% patients had active COVID-19, whereas 50% had recent COVID-19 infection. Twenty-two patients (55%) had co-morbidities, among whom the majority had underlying diabetes mellitus (50%). History of Oxygen supplementation and use of steroids was found in 75% and 45% of the patients respectively. History of self-consumption of decoction (Kadha) and self-administration of inhalation drugs was found among 22 (80%) and 8 (20%) patients respectively. Twenty-one patients (52.5%) had gone through operative procedure/intervention and 11 (27.5%) patients received conservative treatment. In terms of outcome, 20 patients (50%) had been successfully discharged, followed by 14 deaths (35%), 3 referrals (7.5%) to the higher centres and 3 readmissions (7.5%).

Conclusion: Addictions and Indian traditional therapies might have played crucial role in occurrence of CAM. In addition, although Oxygen supplementation and steroid consumption have been life-saving against COVID-19, yet might be responsible for acute surge in CAM cases.

Keywords: Mucormycosis, Fungal, Opportunistic infections, COVID-19

Article info:

Received: 25 Dec 2021

Accepted: 02 Mar 2022

Published: 01 Apr 2022

* Corresponding Author:

Gaurav Derashri, MD.

Address: Community Health Centre, Narwar, Ujjain, Madhya Pradesh, India.

Tel: +91 (98) 70204240

E-mail: drgauravderashri@gmail.com

1. Introduction

CCOVID-19 has been circulating across the world for about 2 years now. India is gradually recovering from the ramifications of the second wave (May-June'21) of COVID-19 pandemic [1]. But, COVID-19 patients all over India are reporting several post-COVID health conditions like respiratory and vascular complications, cardiac and renal injury and opportunistic infections; the most common of which has been fungal infections [2].

Mucormycosis (MM) is an opportunistic angio-invasive disease caused by organisms in the Order Mucorales [3]. These fungi are cosmopolitan, inhalation of which can cause grave disease in immunocompromised individuals [4]. Till 1st September 2021, India has recorded more than 12,000 cases and 300 deaths among patients with COVID-19 Associated Mucormycosis (CAM). Auraiya district in Uttar Pradesh reported the first death caused by CAM [1]. In Rewa, first case of CAM was reported on 1st May.

Very few studies have been conducted to explore various risk factors responsible for CAM till now. In these studies, mainly co-morbidities, injudicious use of steroids, and oxygen supplementation has been attributed for occurrence and rise in cases of CAM [2-4]. In addition, it has been established that COVID-19 also leads to poorly regulated immune systems among patients and moreover exposure to rapidly expanding treatment modalities has led to extensive range of health issues among both the recovering and recovered patients [3, 4].

In India, to boost immunity against COVID-19, few herbal measures had been recommended to general population by AYUSH (Ayurveda, Yoga, Unani, Siddha & Homeopathy) department of Ministry of Health and Family Welfare of Govt. of India. Firstly, consumption of decoction (Kadha) that is a mixture of Tulsi (Basil), Dalchini (Cinnamon), Kalimirch (Black pepper), Shunthi (Dry Ginger) and Munakka (Raisin) once or twice a day and secondly, steam inhalation with fresh pudina (Mint) leaves or Ajwain (Caraway seeds) once a day had been advised. Extended use of these measures could be a reason for CAM which has not been explored yet [5]. With this background, we conducted a prospective observational study with an objective to particularize the socio-demographic characteristics, risk factors, clinical parameters, site of involvement and outcome of patients with CAM.

2. Materials and Methods

This was a prospective observational single-centre study, conducted at Shyam Shah Medical College associated with Sanjay Gandhi and Gandhi Memorial Hospital, Rewa between 1st May to 30th June 2021; including 40 patients of age 18 years and above who had Mucormycosis with recent or active COVID-19 and were willing to give consent and participate in this study.

Mucormycosis was diagnosed as positive KOH (Potassium hydroxide) that is a sign of calcofluor mount (presence of fungal hyphae) accompanied with clinical features; facial swelling, facial pain, headaches, nasal or sinus congestion or pain, serosanguinous nasal discharge, fever, ptosis, proptosis, loss of extraocular muscle function, and vision disturbance [6]. Radiological diagnostic modalities included contrast-enhanced computed tomography of brain, orbit and paranasal sinuses was used to detect site of CAM.

Active COVID-19 cases were defined as those patients who were laboratory confirmed for SARS-CoV-2 by Rapid Antigen Test (RAT) or Real Time Polymerase Chain Reaction test (RT-PCR). Patients who had suffered from COVID-19 in the past 3 months of presentation, but were currently negative for SARS-CoV-2 were considered as recent COVID-19 cases [2]. Patients who needed oxygen support during active/recent COVID-19 treatment were considered as severely ill patients [1].

Data collection

After review of literature, socio-demographic characteristics, co-morbidities, addictions, history of steroid use, history of oxygen supplementation, history of self-consumption of decoction (Kadha), self-instillation of oil/medicines into nose, steam inhalation and immunization status were collected using a structured data collection form. To make the questionnaire valid and reliable, a pilot study was performed on 5 Mucormycosis cases. Data were collected through interview by interns and junior students who were already working in Mucor Ward and were trained through induction training. The interrater agreement was assessed by calculating Kappa value=0.62. Written informed consent was obtained from all the patients. During collection of data, COVID-19 appropriate behaviour was adopted by all the interviewer and the patients.

Tobacco use included smoking, sucking, chewing or snuffing any tobacco product [7]. Smoker was defined as a person who had smoked more than 100 cigarettes/bidis during his/her lifetime [8]. A person was defined

to be an alcoholic if he/she was 15 years and older and have consumed alcoholic beverages at least 6 times in the previous 12-month period [9].

Steroid use and Oxygen supplementation during treatment of COVID-19 were assessed from patient's record. Clinical parameters taken into consideration were Random Blood Sugar (RBS) at arrival, D-dimer, Neutrophil-Lymphocyte Ratio (NLR), C-reactive protein and CT-Severity Score which were also retrieved from patient's case file.

Statistical analysis

Numbers and percentages were used to summarize categorical data. Mean±SD were used to summarize numerical data. No statistical test were applied due to lack of comparison groups and relatively small sample size.

3. Results

A total of 40 CAM patients were included for the analysis. The overall Mean±SD and median age of the patients was 50.8±13.65 years and 52.5 years respectively, with the majority of the males (73%) participants. Table 1 shows sociodemographic characteristics of the study participants.

Risk factors for Mucormycosis are depicted in Table 2. Of total, 47.5% had active COVID-19, whereas 50% had recent COVID-19 infection. Table 2 also depicts that 22 patients (55%) had co-morbidities, among whom the majority had underlying diabetes mellitus (50%) followed by either solitary hypertension (13%) or hypertension accompanied with diabetes (13%). Other co-morbidities were present in 23% of the patients. Out of total 22 patients with existing co-morbidities, 45% had uncontrolled chronic illness status during last time consultation (range: 1-24 months; mean=6.1 months).

Table 1. Socio-demographic characteristics of patients with Mucormycosis (N=40)

Demographic Variables		No.(%)
Gender	Male	29(73)
	Female	11(27)
Age groups	21-40 years	10(25)
	41-60 years	19(48)
	>60 years	11(27)
Education	Illiterate	3(7)
	Up to higher secondary	14(35)
	Higher	23(58)
Occupation	Laborers	3(8)
	Farmers	7(18)
	Govt employees	10(25)
	Private employees	8(20)
	Housewives	7(17)
	Retired	5(12)
Geographical distribution	Rural	27(67)
	Urban	10(25)
	Slum	3(8)

Table 2. Risk factor assessment of patients with Mucormycosis

	Risk Factors	No.(%)
Co-morbidities (n=22, 55%)	Diabetes mellitus	11(50)
	Hypertension	3(13)
	Diabetes with hypertension	3(13)
	Diabetes with Coronary Artery Diseases	2(9)
	Hypothyroidism	2(9)
	Chronic Obstructive Pulmonary Diseases	1(6)
	Addictions (n=25, 62.5%)	Tobacco user
Tobacco+Alcohol		9(22)
Narcotic Abusers		2(5)
History of (H/O) nasal instillation of oil/any other medication		2(5)
H/O self-consumption of decoction (Kadha)		32(80)
H/O steam Inhalation (self)		8(20)
H/O oxygenation		30(75)
H/O surgery in last 6 months		2(6)
H/O use of steroid		18(45)
Unvaccinated		29(72)

CJHR

An important risk factor for CAM was the oxygenation received during COVID-19 management. A total of 30 patients (75%) had either history of oxygenation or were receiving oxygen during concurrent COVID-19 management with average duration of 10.8±8.9 days. History of use of steroids for COVID-19 management was found in 18 (45%) patients while most commonly used steroid used was Dexamethasone (66%).

Regarding addictions and other risk factors, 20 patients (50%) had addictions out of which 11 (55%) were tobacco users followed by either alcohol alone or alcohol in combination with tobacco use (20%). Tobacco users included 5 smokers (20%) and 20 chewers (80%).

History of self-consumption of decoction (Kadha) and self-administration of inhalation was found among 32 (80%) and 8 (20%) patients respectively. Frequency of

Table 3. Clinical parameter details of patients with Mucormycosis

Parameters	Mean±SD
Random blood sugar*	253.6±115.5
D-dimer	457.0±348.3
C-Reactive Protein	56.3±38.3
Neutrophil Lymphocyte Ratio**	6.94±5.62
CT Severity Score	15.8±5.4

* On admission; **n=25

CJHR

Table 4. Distribution of patients according to site of Mucormycosis involvement

Site	Paranasal Sinus Extension, No.(%)
Maxillary*	21(52)
Ethmoidal [#]	17(42)
Sphenoidal [@]	8(20)
Frontal [^]	6(15)
Orbital Extension [§]	13(32)
Extension to Brain	6(15)

*Most common maxillary sinus: Right, [#]Ethmoidal: Right/Left, [@]Sphenoidal: Right, [^]Frontal: Left, [§]Orbit: Right



decoction (Kadha) consumption and steam inhalation was found to be 1-4 times per day (2.1 ± 0.88) and 1-3 times per day (1.9 ± 0.83). Twenty-nine patients (72%) were not vaccinated with any of the available COVID vaccine. Only 2 (5%) patients were fully vaccinated.

Clinical parameters and Site of Mucormycosis are shown in Tables 3 and 4. Random Blood Sugar (RBS) at arrival was reported to be 253.5 ± 115.5 mg/dL. The mean value of C-Reactive Protein (CRP), D-dimer and Neutrophil-lymphocyte ratio was found to be 56.3 ± 38.3 , 457 ± 348.3 and 6.94 ± 5.62 respectively. The mean CT-Severity Score (CTSS) reported was 15.8 ± 5.4 . Maxillary sinus (52.5%) was the most common site affected by Mucormycosis, followed by Ethmoidal sinus (42.5%) and Orbit (32.5%). Most common side of Maxillary sinus, Ethmoidal sinus and Orbit infected with MM was right side.

Regarding to Treatment modalities, 21 patients (52.5%) had gone through operative procedure/intervention and 11 (27.5%) patients were receiving Liposomal Amphotericin-B till formulation of this manuscript. In terms of Outcome, 20 patients (50%) had been successfully discharged, followed by 14 deaths (35%), 3 referrals (7.5%) to the higher centres and 3 readmissions (7.5%).

4. Discussion

In our study, the majority of the patients were male and belonged to 41-60 years old age group; which was also observed by the majority of previous studies [10-13, 15, 17, 19]. Besides this, in our study, patients who had co-morbidities, half of them had underlying diabetes mellitus. Following diabetes, the second most common comorbidity was either solitary hypertension or hypertension accompanied with diabetes. The same findings were observed in the majority of the studies conducted globally [10-13, 15, 17, 19].

We identified that half of the patients had addictions out of which more than half were tobacco users followed by either alcohol alone or alcohol in combination with tobacco use. Studies regarding the role of addictions in development of CAM from reliable search engines could not be found but these factors need further in-depth exploration.

The role of other traditional Indian therapies has not been ascertained by any other study conducted in India. In our study, proportion of patients having history of self-nasal instillation with oil/other ayurvedic preparation and self-consumption of decoction (Kadha), was 5% and 80% respectively.

Mucormycosis has been observed especially among those patients who needed oxygen support because of which the immune system may become weak due to inflammatory storm. In addition, use of industrial oxygen cylinders and contaminated/tap water in humidifiers also attribute to CAM. In our study, history of oxygenation during recent/concurrent COVID-19 was found in majority of the patient which has also been reported by numerous studies [10, 12, 17, 19].

Despite the commendable effect of steroids when used judiciously within appropriate regimen on improving the inflammatory condition, the unreasonable and extended use of corticosteroids; due to rapidly modified guidelines, in COVID-19 patients giving rise to immunocompromised state, can be the trigger for black fungus infection [20]. In our study, history of steroid use (mainly dexamethasone) for treatment of recent/concurrent COVID-19 was found in nearly half of the patients which is in concordance with the other studies [10, 12, 13, 14, 16]. Furthermore, various clinical parameters like Random Blood Sugar (RBS), C-Reactive Protein (CRP), D-dimer, Neutrophil Lymphocyte Ratio (NLR) and CT Severity Score (CTSS) have been reported at higher level in different studies [12, 19]

depicting severity of infection. Clinical data also suggest that the SARS-CoV-2 impairs glucose homeostasis [20, 21]. Likewise, in our study, all the above-mentioned parameters were reported to be raised.

In our study, most common site involved in Mucormycosis was right maxillary sinus followed by right ethmoidal sinus and orbit. Findings of other studies revealed the same rhino-orbital region followed by rhino-orbital-cerebral region mostly affected by Mucormycosis [10-15, 17, 19]. Considering outcomes, we observed comparatively reduced mortality as reported in different parts of the world [10, 12, 14, 16]; reason of which could be, not assessing final outcome of the referred and readmitted cases.

5. Conclusion

Findings of our study suggested that diabetic males of 41-60 years age group having severe COVID-19 were most prevalent among CAM patients. Most common site for CAM was right maxillary sinus and mortality rate was found to be more than 35%. Addictions and Indian traditional therapies might have played crucial role in occurrence of CAM. In addition, although Oxygen supplementation and steroid use have been life-saving against COVID-19 yet might be responsible for acute surge in CAM cases.

This study suffered from many limitations. Firstly, we could not assess compromised quality of Oxygen supplementation. Along with this, hygienic condition of the equipment involved in Oxygen supplementation couldn't be evaluated in view of patient's severity. So, to prove association between role of quality of Oxygen supplementation and CAM, multi-centre studies should be conducted focused on source and hygienic condition of Oxygen. Secondly, steroid use during treatment of COVID-19, as a cause of CAM needs to be explored through Case-control studies. Furthermore, role of Indian traditional therapies like decoction (kadha) and steam inhalation using herbs should be investigated as well.

Ethical Considerations

Compliance with ethical guidelines

The study was approved by the Institutional Review Board and Institutional Ethics Board of [Shyam Shah Medical college](#) associated with [Sanjay Gandhi Memorial Hospital](#), Rewa (M.P.). Standard written informed consent was obtained from all the patients with maintenance of confidentiality and anonymity. Declaration of Helsinki was followed throughout the study.

Funding

This research did not receive any grant from funding agencies in the public, commercial, or non-profit sectors.

Authors' contributions

All authors equally contributed to preparing this article.

Conflict of interest

The authors declared no conflict of interest.

Acknowledgements

We are grateful to all the study subjects, their caretakers and trained volunteers for their participation and cooperation in the study. In addition, we also acknowledge all the scientific studies providing guidance.

References

- [1] Ministry of Health and Family Welfare, Govt of India. COVID-19 Portal. Delhi: Ministry of Health and Family Welfare, Govt of India; 2022. <https://www.mohfw.gov.in>
- [2] Nalbandian A, Sehgal K, Gupta A, Madhavan MV, McGroder C, Stevens JS, et al. Post-acute COVID-19 syndrome. *Nat Med*. 2021; 27(4):601-25. [DOI:10.1038/s41591-021-01283-z] [PMID] [PMCID]
- [3] Petrikos G, Skiada A, Sambatakou H, Toskas A, Vaioopoulos G, Giannopoulou M, et al. Mucormycosis: Ten-year experience at a tertiary-care center in Greece. *Eur J Clin Microbiol Infect Dis*. 2003; 22(12):753-6. [DOI:10.1007/s10096-003-1035-y] [PMID]
- [4] Bhogireddy R, Krishnamurthy V, Jabaris S SL, Pullaiah CP, Manohar S. Is mucormycosis an inevitable complication of COVID-19 in India? *Braz J Infect Dis*. 2021; 25(3):101597. [DOI:10.1016/j.bjid.2021.101597] [PMID] [PMCID]
- [5] Ministry of Ayush. Ayurveda's immunity boosting measures for self-care during COVID-19 crisis. New Delhi: Ministry of Ayush; 2020 <https://www.mohfw.gov.in/pdf/ImmunityBoostingAYUSHAdvisory.pdf>
- [6] Honavar SG. Code mucor: Guidelines for the diagnosis, staging and management of rhino-orbito-cerebral mucormycosis in the setting of COVID-19. *Indian J Ophthalmol*. 2021; 69(6):1361-5. [DOI:10.4103/ijo.IJO_1165_21] [PMID] [PMCID]
- [7] Bhatt G, Vyas S, Trivedil K. An epidemiological study of multi drug resistant tuberculosis cases registered under Revised National Tuberculosis Control Programme of Ahmedabad City. *Indian J Tuberc*. 2012; 59(1):18-27. [PMID]
- [8] Gupta A, Mathuria JP, Singh SK, Gulati AK, Anupurba S. Antitubercular drug resistance in four healthcare facilities in North India. *J Health Popul Nutr*. 2011; 29(6):583-92. [PMID]

- [9] World Health Organization (WHO). STEPwise approach to NCD risk factor surveillance (STEPS). Geneva: WHO. <https://www.who.int/teams/noncommunicable-diseases/surveillance/systems-tools/steps>
- [10] Patel A, Agarwal R, Rudramurthy SM, Shevkani M, Xess I, Sharma R, et al. Multicenter epidemiologic study of coronavirus disease-associated Mucormycosis, India. *Emerg Infect Dis*. 2021; 27(9):2349-59. [DOI:10.3201/eid2709.210934] [PMID] [PMCID]
- [11] Satish D, Joy D, Ross A, Balasubramanya. Mucormycosis coinfection associated with global COVID-19: A case series from India. *Int J Otorhinolaryngol Head Neck Surg*. 2021; 7(5):815-20. [DOI:10.18203/issn.2454-5929.ijohns20211574]
- [12] Ramaswami A, Sahu AK, Kumar A, Suresh S, Nair A, Gupta D, et al. COVID-19-associated mucormycosis presenting to the Emergency Department-an observational study of 70 patients. *QJM*. 2021; 114(7):464-70. [PMID] [PMCID]
- [13] 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(4):102146. [DOI:10.1016/j.dsx.2021.05.019] [PMID] [PMCID]
- [14] Moorthy A, Gaikwad R, Krishna S, Hegde R, Tripathi KK, Kale PG, et al. SARS-CoV-2, uncontrolled diabetes and corticosteroids-an unholy trinity in invasive fungal infections of the Maxillofacial region? A retrospective. multi-centric analysis. *J Maxillofac Oral Surg*. 2021; 20(3):418-25. [DOI:10.1007/s12663-021-01532-1] [PMID] [PMCID]
- [15] Jeong W, Keighley C, Wolfe R, Lee WL, Slavin MA, Kong DCM, et al. The epidemiology and clinical manifestations of mucormycosis: A systematic review and meta-analysis of case reports. *Clin Microbiol Infect*. 2019; 25(1):26-34. [PMID]
- [16] Sharma S, Grover M, Bhargava S, Samdani S, Kataria T. Post coronavirus disease mucormycosis: A deadly addition to the pandemic spectrum. *J Laryngol Otol*. 2021; 135(5):442-7. [PMID]
- [17] Singh Y, Ganesh V, Kumar S, Patel N, Aggarwala R, Soni KD, et al. Coronavirus disease-associated mucormycosis from a tertiary care hospital in India: A case series. *Cureus*. 2021; 13(7):e16152. [DOI:10.7759/cureus.16152]
- [18] Rao VUS, Arakeri G, Madikeri G, Shah A, Oeppen RS, Brennan PA. COVID-19 associated mucormycosis (CAM) in India: A formidable challenge. *Br J Oral Maxillofac Surg*. 2021; 59(9):1095-8. [PMID] [PMCID]
- [19] Bhanuprasad K, Manesh A, Devasagayam E, Varghese L, Cherian LM, Kurien R, et al. Risk factors associated with the mucormycosis epidemic during the COVID-19 pandemic. *Int J Infect Dis*. 2021; 111:267-70. [DOI:10.1016/j.ijid.2021.08.037] [PMID] [PMCID]
- [20] Müller JA, Groß R, Conzelmann C, Krüger J, Merle U, Steinhart J, et al. SARS-CoV-2 infects and replicates in cells of the human endocrine and exocrine pancreas. *Nat Metab*. 2021; 3(2):149-65. [PMID]
- [21] Accili D. Can COVID-19 cause diabetes? *Nat Metab*. 2021; 3(2):123-5. [PMID]

This Page Intentionally Left Blank