

Study of mucormycosis in COVID-19 patients in a tertiary care center, Raichur Institute of Medical Sciences, Raichur

Rajkumar Chemudugunta, Channabasappa Bindu¹, K. Indrani, B. Hanumanthappa Ramesh

Department of Pathology, Raichur Institute of Medical Sciences, Raichur, ¹Department of Oral and Maxillofacial Surgery, M R Ambedkar Dental College, Bengaluru, Karnataka, India

Abstract

Context: Coronavirus disease-2019 (COVID-19), caused by severe acute respiratory syndrome (SARS-CoV-2), has become an emergency global public health issue. Disease pattern of COVID-19 ranges from mild to life-threatening pneumonia with associated bacterial and fungal coinfections. Due to associated comorbidities (e.g., diabetes mellitus and chronic obstructive pulmonary disease) and immunocompromised conditions (e.g., corticosteroid therapy), these patients are prone to develop severe opportunistic infections.

Aims: The aim of this study was to investigate the incidence of fungal coinfection of hospitalized patients with COVID-19 infection (SARS-CoV-2) in RIMS, Raichur.

Materials and Methods: Our study included 94 patients with invasive fungal infection who presented with either COVID-19 infection or had recovered from COVID-19 infection. Tissue samples from suspected sites were received in formalin for histopathological examination, and these were stained with hematoxylin and eosin and with periodic acid–Schiff/Gomori's methenamine silver wherever required.

Results: A total of 94 biopsies were received with clinical suspicion of mucormycosis. Out of these, 52 (55.3%) were positive for mucormycosis and 42 (44.7%) were negative. Out of 52 positive cases, 46 (88.4%) were males and 6 (11.6%) were females. The highest number of cases was seen in age group of 51–60 years (26.92%). Out of the 52 positive cases, KOH mount was positive for fungal elements in 8 cases and negative for fungal elements in 29 cases.

Conclusions: Uncontrolled diabetes and overzealous use of steroids are two of the main factors aggravating the incidence of mucormycosis in COVID-19 patients. Early surgical intervention, histopathological confirmation and rapid and judicious intravenous antifungal treatment should be initiated for better patient outcomes.

Keywords: Coronavirus disease-2019, diabetes, fungal sinusitis, mucormycosis, steroid

Address for correspondence: Dr. K. Indrani, Department of Pathology, Raichur Institute of Medical Sciences, Raichur-584102, Karnataka, India.

E-mail: drrajcumarchpgrims@gmail.com

Submitted: 07-Dec-2021, **Accepted:** 10-Jan-2022, **Published:** 22-Dec-2022

INTRODUCTION

The human-to-human transmitted disease, coronavirus disease-2019 (COVID-19), caused by severe acute

respiratory syndrome (SARS-CoV-2), has become an emergency global public health event. The disease pattern of COVID-19 can range from mild to life-threatening

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: WKHLRPMedknow_reprints@wolterskluwer.com

How to cite this article: Chemudugunta R, Bindu C, Indrani K, Ramesh BH. Study of mucormycosis in COVID-19 patients in a tertiary care center, Raichur Institute of Medical Sciences, Raichur. *J Oral Maxillofac Pathol* 2022;26:593-4.

Access this article online

Quick Response Code:



Website:

www.jomfp.in

DOI:

10.4103/jomfp.jomfp_425_21

pneumonia with associated bacterial and fungal coinfections. COVID-19 disease has a propensity to cause extensive pulmonary disease and subsequent alveolo-interstitial pathology.

Severe COVID-19 alters the innate immunity due to COVID-19-associated immune dysregulation characterized by decreased T cells, including CD4 and CD8 cells.^[1] Studies have shown that SARS-CoV and SARS-CoV-2 belong to the same species and have the similar prevalence, biological and clinical characteristics.

Due to the associated comorbidities (e.g., diabetes mellitus and chronic obstructive pulmonary disease) and immunocompromised conditions (e.g., corticosteroid therapy, ventilation and intensive care unit stay), these patients are prone to develop severe opportunistic infections such as mucormycosis, oropharyngeal candidiasis, pneumocystis jiroveci pneumonia, pulmonary aspergillosis and bloodstream candida infections.^[2]

Among these, mucormycosis is a serious, sporadic but cosmopolitan, rare and opportunistic fungal infection caused by a group of molds called mucormycetes. Mucormycosis mainly affects people with serious underlying diseases such as diabetic ketoacidosis, acute leukemia and in patients treated with corticosteroids or cytotoxic drugs.

Mucormycosis caused by mucormycetes molds has five forms based on site of spread being sinuses, orbital and brain (rhino-orbito-cerebral), pulmonary, gastrointestinal, cutaneous and disseminated.^[3,4]

Mucormycosis infection of the sinuses is a form of life-threatening invasive fungal sinusitis that typically affects immunocompromised individuals with an impaired neutrophilic response.^[5,6]

This by itself may predispose to invasive fungal infections of the airways including the sinuses and the lungs.^[7] It is postulated that the use of nonsterile medical supplies might be associated with spore contamination and higher exposure of patients to mucormycosis.^[8] Invasive mucormycosis can result in destruction of facial bones, loss of vision and can be fatal if it extends into brain and cranium. Without early diagnosis and treatment, there may be rapid progression of the disease, with reported mortality rates from intra-orbital and intracranial complications of 50%–80%.

Histopathological examination is one of the main investigations in early diagnosis of mucormycosis. The major morphological differentiation should be done among *Mucorales* genera, *Aspergillus* and *Candida* species. The presence of abundant septation and acute-angle branching should suggest the diagnosis of *Aspergillus*, while yeasts with pseudohyphae should suggest *Candida* species. Poor staining of hyphae with Follow Grocott's Methanamine Silver (GMS) should suggest mucormycosis.^[9]

Even with prompt diagnosis, treatment of underlying diseases and aggressive medical and surgical intervention, the management is often not effective, leading to an extension of the infection and ultimately death. Therefore, it is pertinent that a study should be undertaken to find the prevalence of mucormycosis in COVID-19 patients.

The aim of this study was to investigate the incidence of fungal coinfection of hospitalized patients with COVID-19 infection (SARSCoV-2) in a tertiary care teaching hospital.

Here, we are presenting our experience of 94 cases of clinically suspected mucormycosis during a period of 5 months in a tertiary care hospital.

MATERIALS AND METHODS

A prospective observational study was undertaken at Raichur Institute of Medical Sciences, Raichur, India, over a period of 5 months, from June to October 2021.

All the patients presenting with COVID-19 and with symptoms of fungal rhinosinusitis were included in the study.

All the patients who were included were having comorbidities like diabetes mellitus and were treated with immunosuppressive therapy and oxygen support.

The patients' presentation details, imaging findings, comorbidities, management details and follow-up information were obtained, recorded and analyzed.

The patients underwent surgical debridement, and the biopsy was received in Histopathology Laboratory, Department of Pathology, RIMS, Raichur.

Biopsies received in 10% neutral buffered formalin were processed and stained with hematoxylin and eosin (H&E) along with special stains for fungal elements such as periodic acid–Schiff and Gomori's methenamine silver.

RESULTS

A total of 94 biopsies were received with clinical suspicion of mucormycosis.

Out of these, 52 (55.3%) were reported as positive for mucormycosis and 42 (44.7%) were reported as negative for mucormycosis.

In the present study, out of 52 positive cases, 46 (88.4%) were males and 06 (11.6%) were females.

The mean age of incidence of mucormycosis was 51 years and age range of the patients was from 27 to 93 years [Graph 1].

In our study, the highest number of cases was seen in age group of 51–60 years (26.92%), followed by the age group of 41–50 years, where 23% of cases were identified [Table 1].

Out of the 52 positive cases, KOH mount was positive for fungal elements in 8 cases and negative for fungal elements in 29 cases. In remainder of 15 cases, the KOH mount was inconclusive.

The most common diagnosis in cases reported negative for mucormycosis was Chronic non specific inflammation in 18 cases.

Table 1: Age- and gender-wise distribution of mucormycosis cases

Age	Male	Female	Total	Percentage
21–30	3	-	3	5.76
31–40	10	1	11	21.15
41–50	12	-	12	23.07
51–60	12	2	14	26.92
61–70	6	3	9	17.3
71–80	2	-	2	3.84
81–90	-	-	-	0
91–100	1	-	1	1.92
Total	46	6	52	100

Table 2: Diagnoses in cases reported as negative for mucormycosis

Diagnosis	Number of cases (%)
Chronic nonspecific inflammation	18 (42.9)
Nonspecific inflammation	6 (14.3)
Acute on chronic nonspecific inflammation	4 (9.5)
Negative	4 (9.5)
Nonspecific fungal inflammatory lesion	3 (7.1)
Aspergillosis	2 (4.8)
Chronic nonspecific granulomatous inflammation	1 (2.4)
Nonspecific fungal rhinosinusitis	1 (2.4)
Acute nonspecific inflammation	1 (2.4)
Acute necrotizing inflammation	1 (2.4)
Acute necrotizing inflammation with yeast forms	1 (2.4)
Total	42 (100)

DISCUSSION

The COVID-19 pandemic has brought with it a variety of complications and secondary infections and varied manifestations. Moreover, as days pass by more new ones are emerging and being reported on, as we continue to learn more about this novel COVID-19 pandemic. COVID-19 affects more commonly individuals with comorbidities like diabetes. Mucormycosis or zygomycosis, also called phycomycosis, initially described in 1885 by Paltauf, is an uncommon and aggressive fungal infection that usually affects patients with alteration of their immunological system.^[5]

Mucormycosis is a lethal fungal disease, with rhinocerebral type being its most common presentation. Although it has a low incidence rate, ranging from 0.005 to 1.7 per million. In the wake of the ongoing coronavirus pandemic, there has been a significant increase in its incidence.

The etiologic agent of mucormycosis is ubiquitous in nature and thus may easily be acquired, and its global epidemiology has been studied by several investigators, and may pose a threat during ongoing pandemic as has been observed in India.

Most of the predisposing factors for mucormycosis are fulfilled in COVID-19. Normal host defense against the *Mucorales* is mainly by macrophages that inhibit germination of spores by nonoxidative killing. However, once the germination of spores occurs, the neutrophils take over the host defense using oxidative burst to kill proliferating hyphal elements directly. Thus, patients who have diseases affecting the function of these two cell types will be at risk for infection.^[9]

Diabetic ketoacidosis causes dysfunction of macrophages and is the most frequent risk factor for sinusitis and rhinocerebral infection with mucormycosis. In addition to hyperglycemia, an alteration of iron metabolism occurs in severe COVID-19. Severe COVID-19 is a hyperferritinemic syndrome, but whether high ferritin is a marker of a severe systemic disease versus a modulator of pathophysiology is not known. Irrespective of its role, high ferritin levels lead to excess intracellular iron that generates reactive oxygen species resulting in tissue damage. Cytokines, especially IL-6, due to severe infection and DKA, stimulate ferritin synthesis and downregulate iron export resulting in intracellular iron overload, further exacerbating the process.^[10]

In our study, a total of 94 biopsies were received with clinical suspicion of mucormycosis. Clinical presentation of

mucormycosis ranged from mild facial swelling [Figure 1a], periorbital swelling [Figure 1b], periorbital swelling with lid edema [Figure 1c], to extensive eye involvement [Figure 1d].

Out of the total 94 biopsies, 52 (55.3%) were reported as positive for mucormycosis and 42 (44.7%) were reported as negative for mucormycosis [Chart 1].

In the present study, out of 52 positive cases, 46 (88.4%) were males and 06 (11.6%) were females [Chart 2]. This is comparable to findings of studies done by Sunil Kumar *et al.* 1 in which 82% were males and 18% were females, and by Priyanka and Jignasa 6 who found that 72% were males and 28% were females.

Age-wise distribution of mucormycosis positive cases revealed highest incidence (26.9%) in the age range of 51–60 years [Table 1]. This is in concordance with Sunil Kumar *et al.* who also had highest incidence (27.6%) in the same group of 51–60 years.

Mucormycosis is frequently shows extensive angioinvasion [Figure 2a] that leads to vessel thrombosis and tissue necrosis. Histologically, mucormycosis is characterized by their broad, aseptate ribbon-like hyphae with right-angle branching. These are more pronounced in special stains for fungi such as periodic acid–Schiff [PAS, Figure 2b] and Gomori's methenamine silver [GMS, Figure 2c]. Figure 2d shows *Aspergillus* spores and thin septate hyphae. In our study, histopathological examination detected considerably more cases of mucormycosis (52 cases) than KOH mount (8 cases), considering that histopathology is the gold standard. Two cases of aspergillosis were also detected, and one case showed yeast forms. Of the 42 cases, which turned out to be negative for mucormycosis, most of the biopsies (18 cases) were reported as chronic nonspecific inflammation [Chart 3]. The various diagnoses which were reported in the cases that turned out negative for mucormycosis are enlisted in Table 2.

All cases which were positive for mucormycosis had diabetes mellitus and all had received supplemental oxygen and steroids during treatment of COVID-19. This is comparable to findings by Sharma S *et al.* 5 who found that 91.3% of mucormycosis cases had diabetes and all of their cases also had received steroids during treatment of COVID-19.

Uncontrolled diabetes and overzealous use of steroids are the main factors aggravating the illness; hence both of these must be kept in check. If infected, early surgical intervention and intravenous antifungal treatment should be sought for management; as a good prognosis and less fulminant, disease course can be achieved in cases of postcoronavirus mucormycosis.



Figure 1: Clinical presentation of mucormycosis ranged from mild facial swelling (a), Periorbital swelling (b), Periorbital swelling with lid edema (c), to extensive eye involvement (d)

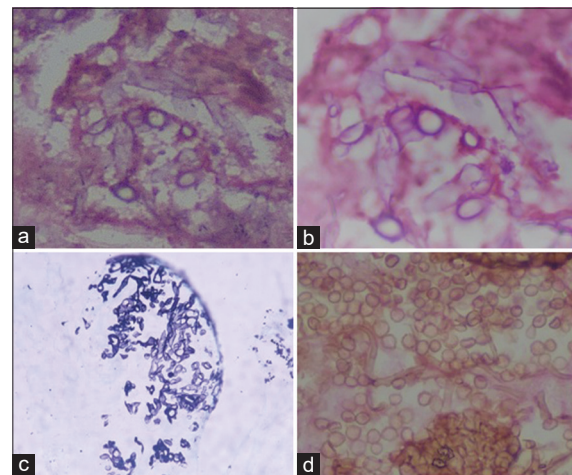


Figure 2: (a) H and E stain showing broad, aseptate hyphae (400x), (b) Periodic acid–Schiff stains the hyphae deep pink to magenta (400x) (c) GMS stains the hyphae black (100x) (d) H and E stain *Aspergillus* spores and thin septate hyphae (400x)

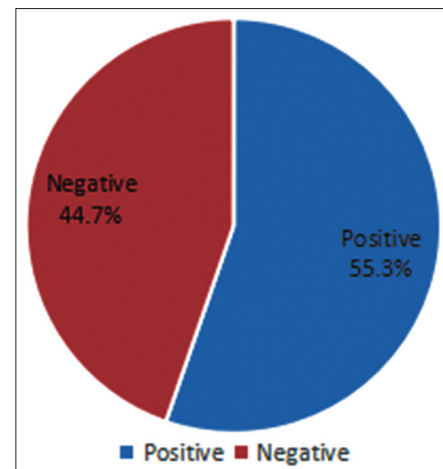


Chart 1: Proportion of mucormycosis in suspected cases

CONCLUSION

Mucormycosis is a rare and occasionally fatal opportunistic infection that affects immunocompromised patients. Most patients who develop mucormycosis are diabetics with

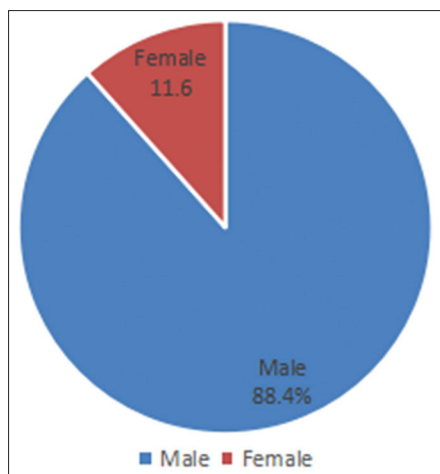


Chart 2: Gender distribution

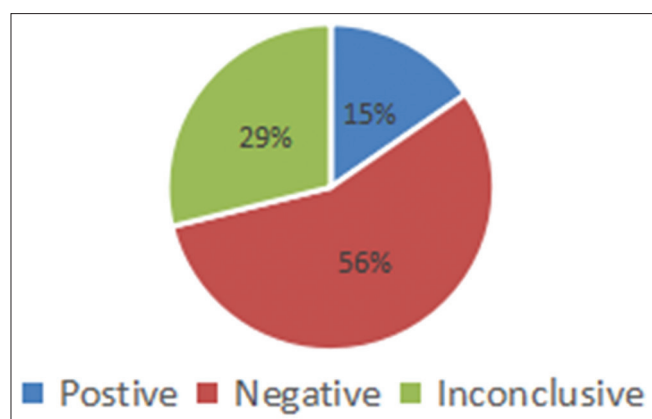
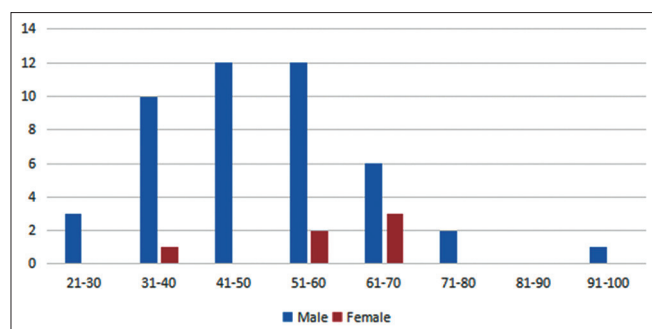


Chart 3: KOH status



Graph 1: Age distribution of mucormycosis cases

uncontrolled diabetes. In the COVID-19 era, the rate of mucormycosis seems to be increasing, and the earlier the presentation to hospitals, the better the outcome. Its

association with invasive mucormycosis sinusitis is dangerous and must be given serious consideration. Uncontrolled diabetes and overzealous use of steroids are two of the main factors aggravating the illness, and both of these must be properly checked. Histopathological examination of the debrided tissue must be given utmost importance as it is superior to KOH mount as has been in our study, considering that histopathology is the gold standard.

Acknowledgments

We would like to acknowledge the meticulous work done by our histopathology technicians Mr. Narasimhalu, Mr. Basavaraj, Mr. Raviraj, Ms. Annapurna and Mr. Mehboob and for all the support extended.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

- Katari SK, Sunkari S, Bhargavi, Khadeeja T, Aparna C, Baleswari G. Study on a deadly uninvited guest during the historical second wave at a tertiary health care center in south India. *MedPulse Int J Pathol* 2021;20:01-5.
- Salehi M, Ahmadikia K, Badali H, Khodavaisy S. Opportunistic fungal infections in the epidemic area of COVID-19: A clinical and diagnostic perspective from Iran. *Mycopathologia* 2020;185:607-11.
- Ribes JA, Vanover-Sams CL, Baker DJ. Zygomycetes in human disease. *Clin Microbiol Rev* 2000;13:236-301.
- Roushdy T, Hamid E. A case series of post COVID-19 mucormycosis – A neurological prospective. *Egypt J Neurol Psychiatr Neurosurg* 2021;57:100.
- 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;135:442-7.
- Priyanka V, Jignasa B. Post COVID fungal infection: histopathological and microbiological correlation. *IAIM* 2021;8:53-61.
- Sarkar S, Gokhale T, Choudhury SS, Deb AK. COVID-19 and orbital mucormycosis. *Indian J Ophthalmol* 2021;69:1002-4.
- Hartnett KP, Jackson BR, Perkins KM, Glowicz J, Kerins JL, Black SR, *et al.* A guide to investigating suspected outbreaks of mucormycosis in healthcare. *J Fungi (Basel)* 2019;5:69.
- Guarner J, Brandt ME. Histopathologic diagnosis of fungal infections in the 21st century. *Clin Microbiol Rev* 2011;24:247-80.
- John TM, Jacob CN, Kontoyiannis DP. When uncontrolled diabetes mellitus and severe COVID-19 converge: The perfect storm for mucormycosis. *J Fungi* 2021;7:298.