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ORIGINAL ARTICLE

Comparison of mucormycosis infection between patients with and without a history of COVID-19 infection: a retrospective cohort study

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Background: Mucormycosis infection is a complication seen in some coronavirus disease 2019 (COVID-19) patients. This study compares the characteristics of mucormycosis infection between COVID-19 and non-COVID-19 patients.

Methods: This retrospective cohort comprised 87 patients with mucormycosis divided into two groups. The first included 44 patients who had COVID-19 recently before hospitalization due to mucormycosis at Namazi Hospital, Shiraz, Iran, between February 2019 and August 2021. The second group included all 43 patients hospitalized at the same hospital due to mucormycosis between 2010 and 2019 (pre-pandemic).

Results: Mucormycosis patients with a history of recent COVID-19 infection had a higher rate of diabetes mellitus, fewer malignancies and higher blood glucose, erythrocyte sedimentation rate and C-reactive protein levels ($p<0.05$). Glucocorticoid use was common (77%) in the COVID-19 group.

Conclusions: In the pre-COVID-19 era, mucormycosis mainly affected immunodeficient patients like those receiving chemotherapy due to malignancy but now seems to affect COVID-19 patients with uncontrolled blood glucose and glucocorticoids use. Special care must be taken in prescribing glucocorticoids and controlling the blood glucose levels of COVID-19 patients.

Keywords: COVID-19, coronavirus, mucormycosis, opportunistic infections, viral disease

Introduction

The coronavirus disease 2019 (COVID-19) pandemic has caused the deaths of >5 million people to date, with various aspects of the disease yet to be uncovered.[1] Although systemic corticosteroids lead to decreased mortality in patients with severe COVID-19, they may put patients at risk of opportunistic fungal infections like mucormycosis.[2] A remarkable increase in the number of cases of mucormycosis diagnosed concurrently or in proximity with COVID-19 has given rise to concern regarding COVID-19-associated mucormycosis (CAM).[3]

Mucormycosis (previously called zygomycosis) refers to a group of fungal infections caused by various genera of the Mucorales order, the most common of which are *Rhizopus*, *Absidia*, *Mortierella* and *Mucor*. Although these saprophytic fungi are widespread, they possess minimal pathogenicity in healthy individuals. However, the fungi and their spores can give rise to aggressive infections in certain clinical conditions, particularly in immunocompromised patients.[4] The disease begins primarily in the upper or lower airways and can progress to rhinocerebral, rhino-orbital, pulmonary, cutaneous, gastrointestinal or disseminated presentations.[4] If patients do not receive aggressive surgical and medical treatment, the direct spread of the infection to nearby sites is expected.[5] As the third most common invasive fungal disease, mucormycosis has been identified in 8.3–13% of mycosis-related autopsies.[6] Risk factors for mucormycosis include haematologic malignancies, solid organ or stem cell transplantation, severe or prolonged neutropenia, uncontrolled diabetes mellitus (DM), iron overload, deferoxamine use, major trauma, prolonged corticosteroid therapy, intravenous drug abuse, prematurity and malnutrition.[6–8]

Table 1. Characteristics of mucormycosis patients with or without a history of COVID-19

Variables		COVID-19 (n=44), n (%)	Non-COVID-19 (n=43), n (%)	p-Value
Sex	Male	27 (61.4)	25 (58.1)	0.759
	Female	17 (38.6)	18 (41.9)	
DM	Yes	38 (86.4)	29 (67.4)	0.036
Hypertension	Yes	27 (61.4)	30 (69.8)	0.410
CKD	Yes	17 (38.6)	16 (38.1)	0.950
Malignancy	Yes	4 (9.1)	12 (27.9)	0.024
Other comorbidities	Yes	9 (20.5)	11 (25.6)	0.708
ICU admission	Yes	20 (44.5)	24 (55.8)	0.281
Co-infection	Yes	7 (15.9)	11 (25.6)	0.265
Surgical intervention	Yes	38 (90.5)	32 (74.4)	0.052

In the management of COVID-19, a critical window of opportunity for immunosuppressive treatment arises once the patient's condition begins to deteriorate.[9] However, corticosteroids can give rise to hyperglycaemia, which is of more significant concern in diagnosed or undiagnosed DM patients. Furthermore, patients with DM and hyperglycaemia are at risk of secondary infections, as they are prone to the pro-inflammatory state.[10,11]

It is sometimes difficult to diagnose CAM, given the non-specific clinical and radiological signs of some forms of mucormycosis, with features of dissemination and pulmonary involvement sometimes mistaken for COVID-19 manifestations. Nonetheless, more and more cases of CAM are emerging.[2,3] According to recent review studies, the predominant risk factors for CAM appear to be uncontrolled DM, male gender and corticosteroid therapy, with more than two-thirds of cases known to date having been reported from India.[3,12–15] In Iran, <20 cases of CAM (none with pulmonary involvement) have been reported so far,[16–18] meaning that further investigations are necessary. The present study aimed to shed further light on CAM by comparing mucormycosis patients with and without a history of COVID-19 infection in terms of various characteristics. We provide new information on mucormycosis by comparing these two groups: a group with a COVID-19 coinfection and steroid use and a group with features before the COVID-19 pandemic.

Methods

We used the International Classification of Diseases, Tenth Revision code for mucormycosis to find patients. We found 67 cases of mucormycosis diagnosed between February 2019 and August 2021 and 52 cases diagnosed between 2010 and 2019, before the COVID-19 pandemic. Those who had incomplete medical data, cases of mucormycosis since 2019 and those who had not had a positive COVID-19 reverse transcription polymerase chain reaction (RT-PCR) test were excluded. Finally, 87 patients with confirmed mucormycosis were selected. One group included 44 patients who had a positive COVID-19 RT-PCR test before developing mucormycosis symptoms and were diagnosis between February 2019 and August 2021 and the other group contained 43 patients who suffered from mucormycosis between 2010 and 2019, before the COVID-19 pandemic. This study complied with the ethical standards outlined in the Declaration of Helsinki and was approved by the Ethics Committee of Shiraz University of Medical Sciences (code IR.SUMS.MED.REC.1400.385).

Data including age, gender and medical history, including DM (DM diagnosis before COVID-19 treatment in COVID-19 patients and before admission for non-COVID patients), hypertension, renal disease, malignancy and other comorbidities, were obtained from the medical records of the patients. Moreover, the levels of white blood cells (WBCs), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), blood glucose (at the hospital admission due to mucormycosis), blood urea nitrogen (BUN) and creatinine upon admission were recorded. Other variables noted were the type of antifungal treatment, location of the mucor, days of hospitalization, intensive care unit (ICU) admission, surgical intervention and outcome. Among the COVID-19 patients, the types of corticosteroids received were also analysed.

Data were analysed using SPPS version 23 (IBM, Armonk, NY, USA). Continuous variables were described as mean±standard deviation, while categorical variables were described using frequency and percentage. The one-sample t-test was used to compare quantitative variables with normal distribution between groups, with the Mann–Whitney test being used when normality was not upheld. For qualitative variables, the χ^2 test was used. A significance level of $p<0.05$ was used for all statistical tests.

This study was performed in Shiraz and we used medical data from Namazi Hospital, the largest medical centre in southeast Iran.

Results

The characteristics of the study subjects are summarized in Table 1. A total of 50.5% of patients had COVID-19 before mucormycosis and 49.4% were infected by mucormycosis before the COVID-10 pandemic. The mean age was 57.49±12.86 y in the COVID-19 group and 60.8±13.4 y in the non-COVID-19 group, representing no significant difference (p=0.244). In terms of gender, 61.4% of the COVID-19 group and 58.1% of

Table 2. Comparison of quantitative variables between mucormycosis patients with and without a history of COVID-19

	COVID-19				Non-COVID-19				
Variables	Valid (n)	25th percentile	50th percentile	75th percentile	Valid (n)	25th percentile	50th percentile	75th percentile	p-Value
Blood glucose (mg/dL)	43	190	270	345	43	118	150	333	0.042
ESR	39	36	72	98	35	26	46	79	0.060
CRP (mg/L)	42	68	113	150	42	24	84	104	0.013
WBC count (per μL)	43	8000	10 900	14 400	43	6400	10 000	18 800	0.907
Hospital stay (days)	44	20	32	44.25	43	16	25	52	0.266
BUN (mg/dL)	43	13	24	36	43	13	20	38	0.95
Creatinine (mg/dL)	43	0.89	1.33	2.4	43	0.9	1.2	2	0.746

the non-COVID-19 group were male, indicating statistical similarity between the groups in gender distribution (p=0.759). We considered ICU admission as a proxy for disease severity. Although there were no significant statistical differences in the two groups regarding the need for ICU admission (p=0.281), 44.5% of COVID-19 and 55.8% of non-COVID-19 patients had ICU admission.

In terms of comorbidities, 86.4% of COVID-19 patients and 67.4% of non-COVID-19 patients had a history of DM, revealing a significant statistical difference (p=0.036). The COVID-19 group also had a significantly lower rate of malignancies than the non-COVID-19 group (p=0.024).

Coinfection (other microbiological infections during hospital admission due to mucormycosis) were reported in 15.9% of COVID-19 and 25.6% of non-COVID-10 patients.

None of the quantitative variables had a normal distribution, so they were analysed using the Mann–Whitney test. Table 2 shows the results of the Mann–Whitney test comparing quantitative variables between the groups. There were significant statistical differences between the two groups in the blood glucose levels and hospital stays.

Based on the location of the mucormycosis infection, patients were grouped into five categories: sinonasal, orbital, buccal, lower respiratory and mixed. There was no significant difference between the two groups in the site of mucormycosis infection (p=0.214). The most common site of involvement was sinonasal (37 cases in the COVID-19 group, 40 in the non-COVID-19 group); other sites included orbital (n=1 in the COVID-19 group), buccal (n=1 in the COVID-19 group), pulmonary (n=2 in the COVID-19 group and 1 in the non-COVID-19 group) and mixed (n = 3 in the COVID-19 group and 2 in the non-COVID-19 group).

In the CAM group, the interval between COVID-19 diagnosis and hospitalization for mucormycosis was 30.2±31 d (minimum 2 d, maximum 168 d). The most common corticosteroids prescribed to the COVID-19 patients were methylprednisolone, prednisolone and dexamethasone.

Among patients who had mucormycosis in the pre-COVID-19 era, five had acute myeloid leukaemia, one had acute lymphoid leukaemia, four had lymphoma, three were organ transplant recipients, two had a history of cerebrovascular accidents, one had aplastic anaemia and two had liver cirrhosis.

Surgical intervention was performed for 100% of discharged or admitted patients and for 63.4% of those who died (56% of non-COVID-19 and 75% of COVID-19). Among cases with a history of COVID-19 infection, 15 (34.1%) were discharged from the hospital and 16 (36.4%) died, with 13 remaining admitted at the time of this publication. Among non-COVID-19 mucormycosis patients, 18 (41.9%) died and 25 (58.1%) survived.

Discussion

The present study compared the characteristics of mucormycosis between patients with and without a history of COVID-19 infection. Overall we found 87 cases of mucormycosis in the referral centre in Shiraz, with roughly the same number of cases being recorded in the short duration of the pandemic as the previous 9 y. The key differences between the study groups were in the proportion of patients with DM and malignancy, as well as blood glucose, CRP, ESR and antifungal dose levels.

In terms of predisposing factors, we found DM (86.4%) and glucocorticoid use (77%) widespread among our cases of CAM. In contrast, the rate of DM was significantly lower in the historic non-COVID-19 mucormycosis group (67.4%), although data on their use of glucocorticoids were limited. Among CAM patients, other predisposing factors included hypertension (61.4%) and renal failure (38.6%), which were seen at similar rates in the non-COVID-19 group. These findings are in agreement with previous studies, where John et al.[13] reviewed 41 cases and asserted that CAM was typically seen in patients with DM (94%), especially the ones with poorly controlled DM (67%) and severe or critical COVID-19 (95%). Singh et al.[14] assessed the details of 101 patients with CAM, most of whom were males (78.9%). Notably, 80% of the patients had DM, while corticosteroids had been prescribed for COVID-19 in 76.3%. Hyperglycaemia at presentation was the outstanding risk factor observed in most cases (83.3%). Hoenigl et al.[15] analysed 80 CAM cases from 18 countries and cited uncontrolled DM and systemic corticosteroid treatment as major predisposing factors. Treatment with systemic corticosteroids was reported in 75% of the cases (60/80), mostly being initiated before the diagnosis of mucormycosis.

Our historic non-COVID-19 mucormycosis patients had a significantly higher rate of malignancies (27.9%) than the CAM

group (9.1%). Hence it seems that a different mechanism exists through which mucormycosis infection is potentiated in COVID-19 patients. Hoenigl et al.[15] suggested that the paradoxical potentiation of the hyperglycaemia-induced inflammatory state by antiviral immunity to sever acute respiratory syndrome coronavirus 2 (SARS-CoV-2) renders COVID-19 patients with uncontrolled DM vulnerable to invasive fungal diseases. They also noted that considering the augmentation of pro-inflammatory cytokine secretion by Mucorales fungi, the convergence of multiple inflammatory pathways might trigger CAM development in COVID-19 patients even when immunosuppressive therapy is not administered. Our CAM patients also had significantly higher ESR and CRP levels than the non-COVID-19 group, the significance of which is unknown, as elevations in these markers have also been detected in non-mucormycosis COVID-19 survivors compared with controls.[19,20] Given these findings, it seems essential to maintain an optimal blood glucose level and use corticosteroids judiciously when treating COVID-19 patients.

At the cellular level, the disease and the clinical management of COVID-19 may both place patients at risk of developing CAM. Mucorales infections are countered by macrophages, which limit the amount of intracellular iron available to fungi by activating a nutritional immunity program.[21] Notably, the level of free iron in the blood is higher in most COVID-19 patients,[22] meaning that iron availability may represent an important aspect of CAM pathogenesis.[23] This issue may become more profound in COVID-19 patients who develop ketoacidosis as binding proteins release iron during acidosis.[24] From another perspective, corticosteroids impair neutrophil migration, ingestion and phagolysosome fusion, all of which can increase the risk of Mucorales infections.[25] Also, extensive antibiotic therapy may give rise to dysbiosis and epithelial injuries, creating a favourable environment for developing invasive fungal infections like mucormycosis.[26,27]

In the present study, patients with CAM were mainly men (61.4%), and the mean age overall was 57.49±12.86 y. The male preponderance seen in our study agrees with the literature, where 66.0–78.9% of CAM cases to date have been men.[13–15,17] However, a male predominance (58.1%) was also established in the non-COVID-19 mucormycosis patients, indicating that this issue is likely related to the generally higher susceptibility to mucormycosis among men rather than a link with COVID-19. Furthermore, the mean age of patients was slightly higher yet statistically similar (60.8±13.4 y) in our non-COVID-19 mucormycosis patients. Hence we cannot conclude that COVID-19 predisposes individuals of a younger age to mucormycosis. However, further research on this issue is necessary, as statistical significance may have been reached if the groups were larger.

In our research, the most common sites involved were sinonasal, while pulmonary cases were less common, probably due to difficulties in establishing the diagnosis. Challenges in obtaining bronchoalveolar lavage fluid and biopsies in COVID-19 patients have also been noted in the literature,[15] and investigations from Iran have not previously reported cases of pulmonary involvement.[16–18] In the present study, two cases of pulmonary CAM were identified, both of whom were diabetic and required intensive care. A notable finding of our study was the statistically similar distribution of mucormycosis sites between the CAM group and the historic non-COVID-19 mucormycosis group. This is important because even though COVID-19 involves the lungs, a significantly higher rate of pulmonary mucormycosis was not detected in the CAM group, suggesting the lack of a direct association between SARS-CoV-2 activity in the lungs and pulmonary mucormycosis. Nonetheless, we note that underdetection of pulmonary mucormycosis is possible, meaning that further studies are required to draw concrete conclusions.

In our study, 28 of our 44 CAM patients died, representing alarmingly high mortality of roughly 36.4%. This figure is less than the proportion of deceased patients in the non-COVID-19 group (41.9%), although we note that 29.5% of our CAM cases remained admitted and were yet to have a definite outcome when this article was published, so a statistical comparison was not possible. Nonetheless, mortality is much lower in the general population of COVID-19 patients. A recent study conducted in the same setting noted 8% mortality among 113 hospitalized COVID-19 patients (mean age 53.75 y, 62.8% male) in southern Iran.[28] In comparison, 47% mortality was reported among 15 CAM cases in northern Iran, ranging from 30.7 to 49.0% in systematic reviews and analyses, with pulmonary, disseminated or cerebral involvement mainly driving this high mortality.[13–15] Furthermore, Hoenigl et al.[15] indicated that 6.3% of cases were diagnosed at autopsy. The rarity of performing autopsies on COVID-19 victims in resource-limited countries leads to underestimating the burden of CAM.[29] Even in survivors, life-changing morbidities like vision loss have been noted in up to 46% of cases.[15] What is clear is that we only see the tip of the CAM iceberg in Iran and much needs to be done to raise awareness about this condition and the ways to prevent both morbidity and mortality. Additionally, we noticed a significant increase in mucormycosis cases in the period 2010–2019 (5.2 cases per year) compared to the number of cases during the COVID-19 pandemic (since 2019). Moving forward, CAM can no longer be ignored and represents a considerable complication of severe COVID-19, particularly in men with uncontrolled diabetes.[15] Widespread awareness of this condition is necessary among physicians to facilitate early detection and management. In terms of prevention, blood glucose must be maintained at normal levels and glucocorticoids should be used judiciously and by indication in patients predisposed to mucormycosis. Nosocomial sources of infection should not be overlooked, as foods, bandages, intravascular devices, feeding solutions and drug preparations may be implicated in healthcare-associated mucormycosis.[8,30] Notably, many common food items contain Mucorales sporangiospores, with the contamination of tea, biscuits, freeze-dried soup and pepper intended for patients in haematological units having been reported.[30]

Conclusions

Mucormycosis patients with a history of COVID-19 infection had higher blood glucose, ESR and CRP levels, with a more prominent history of DM but a lower rate of malignancies than controls. In the pre-COVID-19 era, mucormycosis mainly affected immunodeficient patients such as those receiving chemotherapy due to cancer, with eventual poor outcomes. In contrast, in patients with a history of COVID-19 infection, it seems that DM and glucocorticoids were common predisposing factors for mucormycosis. Hence special care must be taken in prescribing glucocorticoids to COVID-19 patients and controlling their blood glucose levels.

Further studies should look for any dose-dependent relationship between glucocorticoids use and mucormycosis infection.

Authors' contributions: MHGS, SAH, ZK and MoM designed the study protocol. MHGS, SAH, ZK, MaM and NO gathered the data. MHGS, SAH and ZK analysed the data. MHGS, ZK, SAH and MoM interpreted the data. MHGS, SAH and MaM drafted the manuscript. MaM, MoM, MHGS, ZK, SAH and NO revised the manuscript for intellectual content. All authors read and approved the final manuscript and are guarantors of the paper.

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Data availability: The datasets used and analysed during the current study are available from the corresponding author upon reasonable request.

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