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Original Article

Fungal Rhinosinusitis in the COVID-19 Era

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ABSTRACT

Background: Mucormycosis, a rare fungal infection due to exposure to Mucor. In the era of COVID-19 pandemic, its incidence showed significant increase. The characteristic phenotype of the growth of hyphae in mucormycosis is in and around the blood vessels, leading to life-threatening scenarios, specifically in severely immune-compromised patients. The primary reason facilitating Mucorales spores to germinate in people with COVID-19 is an ideal environment of low oxygen, high glucose, high iron levels, and decreased phagocytic activity of white blood cells due to immunosuppression.

The Aim of the work: This work aimed to describe the clinical characteristics, risk factors, and prognosis of patients with mucormycosis associated with COVID-19, as well as to identify the prevalence of DM and other risk factors among COVID-19-linked fungal rhinosinusitis.

Patients and Methods: A cross-sectional study conducted at the Ear, Nose, and Throat [ENT] departments in military hospitals between September 2021 and April 2022. The study included 18 eligible cases of COVID-19-associated mucormycosis. Laboratory investigations and imaging modalities were used to determine the clinical characteristics and outcomes of the disease.

Results: The mean age of participants was 42.5 years and 67% were males. Most patients suffered from diabetes mellitus [DM] type 2 [83%], while 44% were on immunosuppressive therapy. Half of the patients developed rhino-orbital mucormycosis. Only 11% of the patients improved, while 44% died during follow-up.

Conclusion: Mucormycosis seems to be a serious complication of COVID-19 in high-risk patients. Poor control of diabetes mellitus [DM] might be an important predisposing factor for COVID-19-associated mucormycosis.

Keywords: Mucormycosis; Superinfection; Coronavirus; Fungal rhinosinusitis; Immunosuppression.

INTRODUCTION

Mucor mold is the source of the uncommon fungal infection known as Mucormycosis. It is ubiquitous in soil, manure, plants, decaying fruits, vegetables, air, and even in the mucus of healthy people. Mucormycosis can be fatal in patients with severe immunodeficiencies as well as in those with diabetes mellites, as it affects the sinuses, brain, and lungs [1].

The severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2] responsible for the coronavirus disease 2019 [COVID-19] has been associated with several opportunistic infections [bacterial and/or fungal] [2].

Mucormycosis is rare condition. Its incidence ranges from 0.005 to 1.7 cases per million people [3]. However, with recent COVID-19 epidemic, there has been a considerable uptick in its incidence [4]. Mucormycosis forms hyphae in and around the blood vessels. Infarction, necrosis and thrombosis occur with invasion of blood vessels [5].

Mucormycosis is a time sensitive condition. In most cases, delaying surgery and antifungal treatment causes the condition to quickly worsen and end in death. Mucormycosis has a 54% mortality rate that is dependent on the location of the infection. Patients with widespread mucormycosis had the highest mortality rate [96%] followed by infections of the lungs [76%], and sinuses [46%] [6]. Unfortunately, there aren't enough population-based studies to fully assemble the prevalence statistics for mucormycosis [7].

THE AIM OF THE WORK

In this study, we set out to describe the clinical characteristics, risk factors, and prognosis of patients with mucormycosis associated with COVID-19, as well as to identify the prevalence of DM and other risk factors among COVID-19-linked fungal rhinosinusitis.

PATIENTS AND METHODS

A cross-sectional descriptive study was conducted at the Ear, Nose and Throat [ENT] Departments of four affiliated military hospitals between September 2021 and April 2022. Adult mucormycosis patients [histopathologically confirmed] with a confirmed COVID-19 infection [by real-time reverse transcriptase polymerase chain reaction], of both sexes, were included in this study. Patients with a history of fungal rhinosinusitis before the era of COVID-19 [within 2 years] were excluded from the study.

Accordingly, 18 patients with COVID-19 associated fungal rhinosinusitis from the four military hospitals were enrolled in this study. Clinical assessment of these patients was performed through history taking, general examination, and a full ENT examination. Serum blood samples were obtained for laboratory investigations such as complete blood counts [CBC], C-reactive protein [CRP], marker of coagulopathy [D-Dimer], liver function tests, renal function tests, and hemoglobin A1C. To assess the clinical characteristics of mucormycosis, a computerized tomography scan and magnetic resonance imaging of the orbit and paranasal sinuses were used for all patients. The clinical characteristics of eligible participants were recorded, and their medical records were reviewed. Also, patients were followed up for three months for the clinical outcomes.

Statistical analysis: SPSS [statistical software for social science] version 26.0 was used to analyze and present the data on an IBM compatible computer [IBM® Inc., Armonk, IL, USA]. The qualitative data were presented as numbers and percentages. Mean, standard deviation, range, median, and interquartile range were used to summarize the quantitative data.

Ethical considerations: The study proposal was approved by the Armed Forces College of Medicine Ethical Review Committee [IRB: 37; meeting: September 25, 2021; serial number: 79]. Written informed consent was obtained from all participants before their recruitment. The study adhered to the requirements of the Revised Helsinki Declaration of Biomedical Ethics. The policies regarding data confidentiality were meticulously applied.

RESULTS

This study was conducted on 18 patients who met the preset criteria, 12 [67%] were males and 6 [33%] were females. The mean age of the study population was 42.5±12.25 years. The minimum duration for hospital stay was 9 days, whereas the maximum duration was 84 days with a mean of 46.5 day. The associated comorbidities were diverse. However, most of the patients [83%] reported a history of DM type 2. Medical risk factors among the study participants revealed

that, 44% and 17% of the patients were on immunosuppressive therapy and chemotherapy, respectively [Table 1].

Table 2 shows the anatomical distribution of mucormycosis among the study group and the clinical manifestations. Half of the study group [9 patients] suffered a rhino-orbital mucormycosis, while 33% [6 patients] suffered a sino-orbital mucormycosis.

Most of the patients [67%] showed ptosis, proptosis, acute vision loss, and unilateral periorbital facial pain. Cranial nerve palsy and unilateral periorbital facial pain were observed in 56% of the patients. Moreover, headache and palate necrosis were reported and observed in 33% of the patients. The results of blood investigations are summarized in **Table 3. Table [4]** shows the medical regimen given to the patients of the study group. The clinical outcomes are detailed in **Table 5**. Unfortunately, 44% of mucormycosis patients succumbed to their disease.

Table [1]: Patient demographics, length of hospital stays, associated comorbidities and potential risk factors among study population

Variables		Statistical values [n=18]
Gender [n, %]	Male	12[67.0]
	Female	6 [33.0]
Age [years]	Mean ± SD	42.5 ± 12.25
Hospital stay [days]	Mean ± SD	46.5 ± 18.75
	Median [IQR]	46.5 [33.84 - 59.16]
	Range [minimum-maximum]	75 [9 - 84]
Associated comorbid Conditions [n, %]	Diabetes Mellitus	15 [83]
	Hypertension	8 [44]
	Hematologic malignancies	2 [11]
	Asthma	2 [11]
	Cardiovascular diseases	1 [6]
	Hepatic cirrhosis	1 [6]
	Hypothyroidism	1 [6]
	Tuberculosis	1 [6]
Potential risk Factors [n, %]	Immunosuppressive therapy	8 [44]
	Chemotherapy	3 [17]
	Neutropenia	3 [17]
	Ketoacidosis	1 [6]

SD: standard deviation **IQR:** interquartile range

Table [2]: Clinical characteristics of mucormycosis among the study participants [N = 18]

Characteristic	Category	Count	Percent
Anatomical site	Rhino-orbital	9	50%
	Sino-orbital	6	33%
	Orbital	2	11%
	Sinonasal	1	6%
Clinical manifestations	Nasal blockage	2	11%
	Fever	5	28%
	Headache	6	33%
	Palate necrosis	6	33%
	Unilateral facial swelling	10	56%
	Unilateral periorbital facial pain	12	67%
	Ptosis	12	67%
	Proptosis	12	67%
	Acute vision loss	12	67%
	Cranial nerve palsy	10	56%
	Otological symptoms	2	11%

Table [3]: Serum laboratory investigations among the study participants [N = 18]

Component	Range [Min- max]	Mean ± SD	Median [IQR]
White blood cells [per mm^3]	5886 [6448- 12334]	9391 ± 1471.5	9391 [8397.7- 10384.3]
Lymphocytic count [per mm^3]	1879.2 [749.7- 2628.9]	1689.3 ± 469.8	1689.3 [1372.2- 2006.4]
Erythrocyte sedimentation rate [mm/ hour]	22.9 [70.2- 93.1]	81.6 ± 5.7	81.6 [77.7 - 85.5]
C-reactive protein [mg/L]	61.2 [51.1- 112.3]	81.7 ± 15.3	81.7 [71.4 - 92.1]
Hemoglobin A1C [%]	2.3 [8.7- 11.0]	9.9 ± 0.6	9.86 [9.5 - 10.3]

Table [4]: Prescribed medications for the study participants [N = 18]

Medication	Count	Percentage
Amphotericin B	18	100%
Posaconazole	5	28%
Caspofungin	4	22%
Combined therapy	7	39%

Table [5]: Disease outcomes among the study participants [N = 18]

Outcome	Category	Count	Percentage
Mortality	Yes	8	44%
	No	10	56%
Clinical outcome	Improved	2	11%
	Exenterated	6	33%
	Non-exenterated blind frozen eye	9	50%
	Non-exenterated seeing eye	1	6%

DISCUSSION

India has the greatest global prevalence of mucormycosis. A recent estimate for the years 2019–2020, showed the prevalence of mucormycosis to range from 0.005 to 1.7 per million people worldwide, being around 80 times more prevalent [0.14 per 1000] in India than in the Western Nations [8].

Mucormycosis cases have reportedly increased globally in patients with COVID-19. According to **Kubin *et al.*** [2], COVID-19 provides an ideal environment that favors the fulminant course of mucormycosis. This is attributed to the state of low oxygen [hypoxia], high glucose [DM], new-onset hyperglycemia, steroid-induced hyperglycemia, acidic medium [metabolic acidosis, diabetic ketoacidosis], high iron levels [increased ferritins], and decreased phagocytic activity of WBC due to immune-suppression. Noteworthy, India has the second-highest prevalence of DM and, until recently, was the disease global epicenter. Diabetes was also the leading underlying condition in the study by **Stemler *et al.*** [9] in countries of the Middle East and North Africa.

Recent research has shown a relationship between mucormycosis and even a brief course of corticosteroids, especially in people with DM. A cumulative dose of more than 600 mg of prednisone or a cumulative dose of 2–7 g of methyl prednisone given over the previous month predisposes immunocompromised individuals to mucormycosis [8].

Few cases of mucormycosis caused by even a brief course of steroid therapy [5–14 days] have been reported, especially in diabetics. As reported, 46% of patients in the European Confederation of Medical Mycology research were found to have received corticosteroids within a month after a diagnosis of mucormycosis was made [7].

Ravani *et al.* [10] also confirmed that the two primary risk factors for mucormycosis were COVID-19 positivity [61.2%] with concurrent steroid use [61.2%] and DM [96.7%].

The main aim of this study was to report the clinical features, contributing factors, and outcomes of patients with COVID-19-associated mucormycosis and to detect the prevalence of DM and other risk factors among COVID-19-associated fungal rhinosinusitis.

The mean length of hospitalization in our study population was 46.5 days with a standard deviation of 18.75 days compared to the study of **Pakdel *et al.*** [11] who reported a mean length of hospitalization of 30 days. Also, our results are in accordance with the same authors regarding

associated comorbid conditions. They reached the conclusion that DM and hypertension were the most common comorbidities seen in 13 [87%] and 7 [46%] respectively of their series of mucormycosis associated with COVID-19. Moreover, seven of their patients [46%] had received intravenous corticosteroids for the treatment of COVID-19 [either dexamethasone or methylprednisolone]. Similar results were reported by **Selarka *et al*. [12]** who reported that 27 individuals [57.4%] were taking medication for hypertension and that 36 [76.6%] had a history of DM. This was also confirmed by **Ravani *et al*. [10]** stating that the two primary risk factors for mucormycosis were COVID-19 positivity in [61.2%] with concurrent steroid use [61.2%] and DM [96.7%]. 29 [93.54%] of their study group had uncontrolled type II DM, and one patient had type I DM. When mucormycosis first manifested in six patients of their study group, DM was a recent diagnosis while in 24 patients DM was present for an average of 4.4 years.

In this study, 50% of the total number of patients suffered from rhino-orbital mucor-mycosis. Our findings were consistent with those of **Pakdel *et al*. [11],** who reported that rhino-orbital mucormycosis was the most common type of mucormycosis seen in 47% of their COVID-19 patients, sino-orbital mucor-mycosis in 33%, isolated orbital involvement in 13%, and sinonasal mucormycosis in 7%. In the study of **Selarka *et al.* [12],** Imaging revealed that nearly all their study population with COVID-19 had pansinusitis with infection spread to regions outside of the paranasal sinuses in 78.7% of cases most commonly orbital invasion in 40.4%. Similar results were observed by **Hoenigl *et al*. [14]** with CNS extension occurring in 37% of their study population.

Laboratory results in our study showed that the mean WBC count was 9391 cells per mm^3, the mean lymphocytic count was 1689.3 cells per mm^3, the mean ESR was 81.6 mm in the first hour, the mean CRP was 81.73 mg/L, and the mean hemoglobin A_1C was 9.86%. Our findings were in line with the findings of **Pakdel *et al*. [11],** who reported that during the COVID-19 course, all patients had elevated levels of ESR and CRP.

The clinical findings in our study match those of **Pakdel *et al*. [11]** and **El-Kholy *et al*. [13]** who showed that facial discomfort, facial numbness, ophthalmoplegia, and sight loss were the most frequent symptoms and indicators for the development of mucormycosis.

Amphotericin was administered to every patient in our study population. The study by **Hoenigl *et al*. [14]** showed that systemic antifungal drugs aimed against mucormycosis were effective in the majority of all but three of their patients. Posaconazole was added to amphotericin to manage six patients with rhino-orbital cerebral mycosis. Amphotericin B formulations were used in the vas tericin B patients [71 [89%] of 80]. Isavuconazole was used to treat five individuals in an effort to save them, either alone [two patients], in conjunction with amphotericin B [two patients], or in both cases [58%] [one patient]. The results after therapy were somewhat frustrating, almost half of the patients [44%] succumbed to their disease. Those who survived suffered loss of their eyesight [88%]. Only two patients [11%] recovered without comorbidity. This conformed with the results reported **Pakdel *et al*. [11], Singh *et al.* [8]** and **Selarka *et al*. [12].**

Limitations of the study: The lack of a control group for comparing clinical data, imaging studies, and therapeutic intervention factors as well as the comparison of all COVID-19 clinical and laboratory characteristics between people with and without mucormycosis were some of the study's limitations together with the small sample size, which prevented subgroup analysis. Future research will focus on the role of combination of antifungal therapy and how illness stage affects prognosis.

Conclusion: Patients infected with COVID-19 who have received steroids and have symptoms such as facial numbness, hazy vision, nasal discharge, nasofrontal headache, ocular pain, fever, diplopia, and chemosis should be suspected of having invasive fungal rhinosinusitis. Our research results suggest that there might exist probable risk factors for mucormycosis. COVID-19 itself has an immunomodulation effect on the immune system and can lead to decreased immunity as well as immunosuppressive drugs, eventually leading to infection with opportunistic infections like mucormycosis. We found that most of our study population were males with risk factors like type 2 DM, hypertension, or immunosuppressive therapy. For such, we need further studies on these probable risk factors to confirm this observation, and the attending physicians should

be aware and have a high level of suspicion towards these cases.

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Authors' contributions: Anas Ahmed: conception and design of the study. Maged Mahmoud Baher: design of the data collection tool, data collection, and revising the manuscript before submission. Ashraf lotfy: design the data collection tool, data collection, analysis and interpretation, and writing the original draft. Mohamed Fathy Elsawy: design of the study, analysis and interpretation of data, and revising the manuscript before submission. All authors have read and approved the manuscript

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