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Comparing the Characteristics of Mucormycosis Between Cases with and without COVID-19; a Cross-sectional Study

Mohammad Sistanizad[1,2], Mohammad Haji Aghajani[1], Mehrdad Haghighi[3], Hossein Amini[2], Asma Pourhoseingholi[1], Niloufar Taherpour[1], Shadi Ziaie[2], Sara Salarian[4], Omid Moradi[5]*

1. Prevention of Cardiovascular Disease Research Center, Imam Hossein Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

2. Department of Clinical Pharmacy, School of Pharmacy, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

3. Infectious Diseases and Tropical Medicine Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

4. Department of Pulmonary and Critical Care Medicine, Imam Hossein Teaching and Educational Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

5. Department of Clinical Pharmacy, Faculty of Pharmacy, Hormozgan University of Medical Sciences, Hormozgan, Iran.

Abstract: **Introduction:** Mucormycosis as a rare but life-threatening disease with 46-96% mortality, which challenged the healthcare system during the COVID-19 pandemic. This study aimed to compare the characteristics of mucormycosis between cases with and without COVID-19. **Methods:** This cross-sectional study was done in two referral hospitals, Imam Hossein and Labbafinezhad Hospitals, Tehran, Iran, between 21 March to 21 December 2021. Data related to all hospitalized adults subject with the diagnosis of mucormycosis during the study period was collected from patients' profiles and they were divided into two groups of with and without COVID-19 based on the results of real time PCR. Then demographic, clinical, and laboratory findings as well as outcomes were compared between the two groups. **Results:** 64 patients with the mean age of 53.40±10.32 (range: 33-74) years were studied (53.1% male). Forty-three (67.2%) out of the 64 subjects had a positive COVID-19 PCR test. The two groups had significant differences regarding some symptoms (cough (p < 0.001), shortness of breath (p = 0.006)), acute presentation (p = 0.027), using immunosuppressive (p = 0.013), using corticosteroid (p < 0.001), and outcomes (mortality (p = 0.018), need for intubation (p < 0.001)). 22 (34.3%) patients expired during hospital admission. Univariate analysis showed the association of in-hospital mortality with need for ventilation (p < 0.001), sinus involvement (p = 0.040), recent use of dexamethasone (p = 0.011), confirmed COVID-19 disease (p = 0.025), mean body mass index (BMI) (p =0.035), hemoglobin A1c (HbA1c) (p = 0.022), and median of blood urea nitrogen (BUN) (p =0.034). Based on the multivariate model, confirmed COVID-19 disease (OR = 5.01; 95% CI: 1.14-22.00; p = 0.033) and recent use of dexamethasone (OR= 4.08, 95% CI: 1.05-15.84, p = 0.042) were independent predictors of mortality in this series. **Conclusion:** The mucormycosis cases with concomitant COVID-19 disease had higher frequency of cough and shortness of breath, higher frequency of acute presentation, higher need for immunosuppressive, corticosteroid, and ventilator support, and higher mortality rate. The two groups were the same regarding age, gender, BMI, risk factors, underlying diseases, symptoms, and sites of involvement.

Keywords: COVID-19; Mucormycosis; Mortality; Cross-sectional studies; Risk factors; Diabetes mellitus

*Corresponding Author: Omid Moradi; Department of Clinical Pharmacy, Faculty of Pharmacy, Hormozgan University of Medical Sciences, Bandar Ab- bas, Iran. Zip code: 7919691982 Phone number: +987633710406, Email: O_moradi@outlook.com, ORCID: http://orcid.org/0000-0001-5754-535X.

1. Introduction

From late 2019 to date, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has infected many people, and more than 400 million cases of coronavirus disease 2019 (COVID-19) have been reported (1). Increasing cases of co-infections with bacterial and fungal pathogens have been reported in COVID-19 patients (2). Opportunistic infections, including aspergillosis, and mucormycosis, have been reported in patients with COVID-19 (3). Most of the reported cases are from India during the Delta variant (B.1.617.2) outbreak.

Mucormycosis is an opportunistic lethal fungal infection. This fungus could infect patients with altered immune system (4). Inhalation of the fungal spores in an immunocompromised patient results in angioinvasion (4, 5).

Many mechanisms have been proposed for the increased chance of infection by opportunistic fungi (Mucorales) in hospitalized patients due to COVID-19. Hypoxia, diabetes mellitus, metabolic acidosis, and lymphocytopenia increase the probability of mucormycosis in COVID-19 patients. Also, using immunomodulating medications such as corticosteroids and biological agents could increase the risk of infection in some COVID-19 patients (6, 7).

The mortality rate due to mucormycosis could be as high as 90 percent (7). Diagnosis and treatment of this opportunistic infection in hospitalized patients could be lifesaving, and the therapy consists of surgical and pharmacologic approaches (8). Twelve hours of delay in diagnosis of the disease could be associated with a significantly increased mortality risk (9, 10).

Based on the above-mentioned points, this study aimed to compare the characteristics of mucormycosis between cases with and without COVID-19.

2. Methods

2.1. Study design and setting

This cross-sectional study was done in two referral hospitals, Imam Hossein and Labbafinezhad Hospitals, Tehran, Iran, between 21 March to 21 December 2021. Data related to all hospitalized adult subjects with the diagnosis of mucormycosis (black fungus) during the study period was collected from patients' profiles and they were divided into two groups of with and without COVID-19, based on the results of real time PCR. Then demographic, clinical, and laboratory findings as well as outcomes were compared between the two groups. The study was in accordance with the principles of the Helsinki declaration and the ethics committee of Shahid Beheshti University of Medical Sciences approved the study protocol (IR.SBMU.RETECH.REC.1400.660).

2.2. Participants

In this study, all adults referred to the two hospitals, who were diagnosed with mucormycosis or hospitalized patients with mucormycosis complications during hospital stay were included using the census method. Diagnosis of mucormycosis as a fungal disease was made by an infectious disease specialists, based on the clinical presentation and by considering specific signs and symptoms. Acute mucormycosis was defined as the duration of clinical presentation of the disease being seven days or less, and the sub-acute form was defined as presence of symptoms for 7-21 days (12). In addition, all subjects were screened for the possibility of COVID-19 co-infection using the standard Real-Time reverse-transcriptase–Polymerase-Chain-Reaction (rt- PCR) test. Patients with incomplete information were excluded from the study.

2.3. Data gathering

Data were extracted from patients' medical records using the researcher-made checklist. The checklist contained information about demographic characteristics, history of underlying diseases, smoking status, drug history, clinical presentation, clinical signs and symptoms, baseline laboratory data, site of mucormycosis involvement, prescribed medications in the hospital, SARS-CoV-2 RT-PCR test result, length of hospital stay, history of SARS-CoV-2 infection, the time interval between initial mucormycosis clinical symptoms to diagnosis, and in-hospital mortality. Data gathering and extraction were performed by trained medical staff.

2.4. Statistical analysis

Data analysis was carried out using SPSS (IBM Corp, released 2017. IBM SPSS statistics for windows, version 25.0. Armonk, NY: IBM Corp.). The normality of data was assessed using Shapiro-Wilk test and Q-Q plot. Complete Case ("CC") analysis was used in the presence of missing data. Continuous variables are described using mean ± standard deviation or median and interquartile range (IQR). Categorical variables are reported as frequency and percentage. To compare continuous variables between groups, appropriate tests, including Student's t-test or Mann-Whitney U test, were used for normally and non-normally distributed variables, respectively. The distribution of categorical variables was evaluated between the groups using Chi-squared or Fisher's exact test (if more than 25% of the variables had a frequency below 5). Logistic regression was used to assess the association between in-hospital mortality and selected variables at univariate and multivariate levels. To select the potential factors for entering the multivariate model, we used a backward selection approach with p-value < 0.05. All calculations were performed at a significant level of less than 0.05 with a 95%

Table 1: Comparing the baseline characteristics of mucormycosis between COVID-19 and non-COVID-19 patients

Variables	Total (n=64)	COVID-19		p-value
		Yes (n=43)	No (n=21)	
Gender				
Female	30 (100)	20 (66.7)	10 (33.3)	0.934
Male	34 (100)	23 (37.6)	11 (23.4)	
Age (years)	53.40±10.32	52.16±10.63	55.95 ±9.38	0.170
Body mass index (kg/m2)	25.47±3.66	26.16 ±3.32	23.96 ±4.04	0.062
Length of stay Median (IQR)	16 (23.5)	20 (24)	15 (18)	0.710
Symptoms				
Sore eyes	41 (100)	27 (65.9)	14 (34.1)	0.760
Swelling of eyes and face	38 (100)	25 (65.8)	13 (34.2)	0.773
Blurred vision	23 (100)	16 (69.6)	7 (30.4)	0.762
Cough	19 (100)	19 (100)	0 (0)	<0.001
Weakness	15 (100)	11 (73.3)	4 (26.7)	0.403
Headache	13 (100)	9 (69.2)	4 (30.8)	0.507
Fever	12 (100)	7 (56.3)	5 (41.7)	0.570
Shortness of breath	12 (100)	12 (100)	0 (0)	0.006
Symptoms to diagnosis				
Median (IQR)	5 (4)	6 (6)	5 (3)	0.824
Presentation				
Acute	59 (100)	40 (67.8)	19 (32.2)	0.027
Subacute	5 (100)	3 (60)	2 (40)	0.534
Risk factors/ Underlying				
Smoking	31 (100)	23 (74.2)	8 (25.8)	0.247
Opium	4 (100)	1 (25)	3 (75)	0.099
Alcohol	2 (100)	1 (50)	1 (50)	1.000
Coronary artery disease	11 (100)	10 (90.9)	1 (9.1)	0.085
Diabetes mellitus	45 (100)	32 (71.1)	13 (28.9)	0.304
Dyslipidemia	18 (100)	14 (77.8)	4 (22.2)	0.259
Hypertension	26 (100)	17 (65.4)	9 (34.6)	0.799
Drug History				
Immunosuppressive	10 (100)	4 (40)	6 (60)	0.068
Anticoagulant	4 (100)	3 (75)	1 (25)	1.000
Antiplatelet aggregation	22 (100)	16 (72.7)	6 (27.3)	0.495
Antidiabetic	43 (100)	30 (69.8)	13 (30.2)	0.529
Antihypertensive	28 (100)	19 (67.9)	9 (32.1)	0.920
Laboratory tests				
ESR (sec)	56.34±33.50	60.32±31.74	47.94 ±36.38	0.187
Albumin (g/dL)	3.19±0.58	3.18±0.64	3.22 ±0.44	0.822
HbA1C (g/dL)	9.54 ±2.99	9.90±2.91	8.63 ±3.07	0.166
Blood urea nitrogen (mg/dL)	38.2 (31.8)	39 (36.7)	34.6 (27.45)	0.139
Blood sugar (mg/dL)	189 (211)	180 (210.75)	192 (310)	0.974

Data are presented as mean ± standard deviation (SD), frequency (%), and median (IQR). ESR: erythrocyte sedimentation rate; HbA1C: hemoglobin A1c.

Confidence Interval (CI).

3. Results

3.1. Baseline characteristics of studied cases

64 patients with the mean age of 53.40±10.32 (range: 33-74) years were studied (53.1% male). The most common underlying diseases were diabetes mellitus with 45 (70.3%), hypertension with 26 (40.6%), dyslipidemia with 18 (28.1%), and coronary artery disease with 11 (17.2%) cases. Nine (13.8%) patients were hospitalized due to malignancy. The most common chief complaints were sore eyes with 41 (64.1%), swelling of the eyes and face with 38 (59.4%), blurred vision with 23 (35.9%), and cough with 19 (29.7%) cases. Fifty-nine (92.2%) patients had the acute presentation of mucormycosis, and 5 (7.7%) had a sub-acute presentation. The most prevalent sites of fungal involvement were orbit with 60 (93.8%) and sinus with 38 (59.4%) subjects. The median duration of hospitalization was 16 days with an IQR of 23.5, the median time from onset of COVID-19 to the diagnosis

Table 2: Comparing the management and outcome of mucormycosis between COVID-19 and non-COVID-19 patients

Variables	Total (n=64)	COVID-19		p-value
		Yes (n=43)	No (n=21)	
Involvements				
Sinus	38 (100)	26 (68.4)	12 (31.6)	0.799
Orbit	60 (100)	39 (65)	21 (35)	0.294
Pulmonary	9 (100)	7 (77.8)	2 (22.2)	0.706
CNS	4 (100)	3 (75)	1 (25)	1.000
Managements				
Immunosuppressive	41 (100)	32 (78)	9 (22)	0.013*
Corticosteroid	33 (100)	32 (97)	1 (3)	<0.001
Outcomes				
Ventilation	21 (100)	18 (85.7)	3 (14.3)	<0.001
In-hospital mortality	22 (100)	19 (86.4)	3 (13.9)	0.018

CNS: central nervous system.

of COVID-19-associated mucormycosis (CAM) was 11 days with an IQR of 19.3, and the median time from onset of symptoms to diagnosis of CAM was six days with an IQR of 7.8.

3.2. COVID-19 vs. Non-COVID-19 cases

Forty-three (67.2%) out of 64 subjects had a positive COVID-19 PCR test. Table 1 and 2 compare the demographic, clinical, managements, and outcomes of mucormycosis between patients with and without COVID-19. Two groups had significant difference regarding symptom (cough (p < 0.001), shortness of breath (p = 0.006)), acute presentation (p = 0.027), using immunosuppressive (p = 0.013), using corticosteroid (p < 0.001) and outcome (in-hospital mortality (p = 0.018), and need for intubation (p < 0.001)).

3.3. Predictors of mortality

22 (34.3%) patients expired during hospital admission. Univariate analysis showed the association of in-hospital mortality with need for ventilation (p < 0.001), sinus involvement (p = 0.040), recent use of dexamethasone (p = 0.011), confirmed COVID-19 disease (p = 0.025), mean body mass index (BMI) (p =0.035), hemoglobin A1c (HbA1c) (p = 0.022), and median of blood urea nitrogen (BUN) (p =0.034). Based on the multivariate model, confirmed COVID-19 disease (OR = 5.01; 95% CI: 1.14-22.00; p = 0.033) and recent use of dexamethasone (OR= 4.08, 95% CI: 1.05-15.84, p = 0.042) were independent predictors of in-hospital mortality in this series.

4. Discussion

The mucormycosis cases with concomitant COVID-19 disease had higher frequency of cough and shortness of breath, higher frequency of acute presentation, higher need for immunosuppressive, corticosteroid, and ventilator support, and higher mortality rate. The two groups were similar regarding age, gender, BMI, risk factors, underlying diseases,

symptoms, and sites of involvement. COVID-19 was an independent predictor of mucormycosis in-hospital mortality.

The condition of mucormycosis, a rare invasive fungal infection, was previously a matter of concern in immunocompromised patients (13). These patients included those with hematologic malignancy, diabetes mellitus, transplant recipients, the receivers of immunosuppressive therapy and corticosteroid, and those with other immunodeficient conditions such as acquired immunodeficiency syndrome (14). With increase in the prevalence of COVID-19, and using corticosteroid and other immunosuppressive utilization to treat this disease, the number of cases has raised, significantly.

In this article, the most prevalent site of involvement was sinus and orbit. As previously reported, the site of involvement in mucormycosis patients is related to the predisposing condition. In patients with COVID-19, rhino-orbital involvement is the most prevalent (6). This is also the most common site of involvement in patients with mucormycosis due to uncontrolled diabetes (7). Involvement of other areas, such as pulmonary involvement are more commonly reported in patients with malignancy (7, 15, 16). Physicians should consider this phenomenon when they examine suspected mucormycosis patients.

Diabetes mellitus was recognized as an important risk factor for invasive mucormycosis. In 2019, Parakash H et al. reported 388 cases of mucormycosis, and diabetes was reported in 57% of these patients (17). It should be noted that the reported cases in the research had not been infected with SARS-CoV-2. As it was previously reported, diabetes mellitus and uncontrolled hyperglycemia are risk factors for more severe COVID-19 (17). In the present study, diabetes mellitus was the most prevalent underlying condition. We should consider that patients with severe COVID-19 will more often need to receive corticosteroid therapy and other immunosuppressive agents such as tocilizumab. All these factors together increase the rate of mucormycosis and a higher rate of

mortality is expected. Our study showed that corticosteroid therapy in these patients is linked to a higher mortality rate. Based on the recommendations of the latest guidelines, corticosteroids are the cornerstone of pharmacotherapy for the patients in severe stages of COVID-19 and hypoxia (18). The results of our study indicate that we should be careful about the administration of corticosteroids in high-risk patients for mucormycosis. The triad of COVID-19, corticosteroid, and diabetes put these patients at increased risk for opportunistic infections such as mucormycosis.

5. Limitations

In assessing the results of the present study, we should consider all the possible limitations. First of all, multicentric studies with a larger sample size evaluating different populations are needed. Risk factor evaluation in a population with various predisposing factors is of value. Second, although we evaluated the effect of pre-hospitalization glycemic control based on HbA1c, the role of glycemic control during hospitalization should be evaluated as it was shown that using insulin to control blood sugar during the hospital stay is important in COVID-19 patients (19). Third, we observed a higher rate of mortality in CAM patients. Both, severe COVID-19 and mucormycosis, could be lethal, and it is not possible to evaluate the net effect of each parameter on the outcome of the patients, separately, but a higher mortality rate is seen in mucormycosis patients with COVID-19. Fourth, we did not examine the association of the newer immunomodulators, such as baricitinib, anakinra, or tofacitinib, and CAM in high-risk patients or the effect of these agents on the outcome of CAM patients. These valuable agents are used in clinics for patients with severe COVID-19, but data about their association with increased risk of opportunistic infections is lacking. In this study, the diagnosis of mucormycosis was done based on clinical evaluation, and it could be proposed to confirm the diagnosis using organism identification via histopathology for further studies.

6. Conclusion

The mucormycosis cases with concomitant COVID-19 disease had higher frequency of cough and shortness of breath, higher frequency of acute presentation, higher need for immunosuppressive, corticosteroid, and ventilator support, and higher mortality rate. The two groups were similar regarding age, gender, BMI, risk factors, underlying diseases, symptoms, and sites of involvement. COVID-19 was an independent predictor of mucormycosis in-hospital mortality.

7. Declarations

7.1. Acknowledgments

7.2. Data availability

The data is at the disposal of the corresponding author of the article and it it can be made available to the researchers upon request.

7.3. Authors' contributions

MS and OM designed, reviewed the study, and revised subsequent drafts. MHA, MH, SHZ and SS were the medical consultants and participated in data acquisition. HA and NT prepared the first English draft of manuscript. AP analyzed data. All authors read and approved the final manuscript.

7.4. Funding and supports

7.5. Conflict of interest

There is none to declare.

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