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COMORBIDITIES AND ULTIMATE RESULTS OF RHINO-CEREBRAL AND ORAL MUCORMYCOSIS AMONG PATIENT WITH COVID-19: A CROSS-SECTIONAL STUDY CONDUCTED IN MOSUL CITY

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ABSTRACT

Background: Mucormycosis, often known as black fungus, is an aggressive and sometimes fatal fungal infection caused by phycomycetes, including Rhizopus and Mucor species. Angio-invasion and bad prognosis are hallmarks of mucormycosis. Given the difficulty in obtaining deep tissue samples, it is challenging to determine the precise diagnosis and extend of mucormycosis. **Objectives:** Is to assess the comorbidities and ultimate results of rhino-cerebral and oral mucormycosis among patient with COVID-19 in Mosul City. **Methods:** This retrospective cross-sectional study assessed 50 post-COVID-19 patients with rhino-cerebral and oral mucormycosis at Al Jamhoori Teaching Hospital in Mosul, Iraq**,** from the beginning of April 2021 to end of March 2023. The study included patients with rhino-cerebral or oral mucormycosis who on or had received corticosteroids and immunosuppressive drugs. Patients with gastrointestinal, pulmonary, cutaneous, and disseminated mucormycosis types were excluded from the study. The questionnaire includes five sections, section one for demographic information, section two for the patients' past history, section three for patients' treatment history and section four for response details of the infection and part five for complication and the final outcomes. **Results:** The study included 50 patients with rhino-cerebral and oral mucormycosis. Of them; 27[54%] patients were males and 23[46%] patients were females. With male to female ratio of 1.17:1. Moreover: the mean age ± standard deviation of the study participants was 53.21 ± 9.98 years. It's evident that uncontrolled diabetes was prevalent among 27[54%] patients, followed by hypertension which was prevalent among 20[40%] patients. Form the other hand; 7[14%] patient reported medical free history. Statistically significant difference was found between the patients who survive and those who passed regarding the presence of uncontrolled diabetes[P value <0.001], been medical free[P value = 0.037], central nervous system involvement[P value <0.001], eye involvement[P value <0.001], clinical picture of the disease presentation[P value <0.001], color of the mucosa[P value <0.001], perforation of the palate[P value <0.001] and perforation of the nose[P value <0.001]. **Conclusion:** The mortality rate for post-COVID-19 associated mucormycosis was very high, primarily as a result of delayed diagnosis and inadequate treatment. For a quicker diagnosis and better prognosis of such an aggressive illness, physicians must therefore be more knowledgeable about the clinical manifestations of mucormycosis in post-COVID-19 patients, particularly deep palatal ulcers and dentofacial pain with special caution for patients with uncontrolled diabetes.

KEYWORDS: Mucormycosis, Outcomes, COVID-19, Mosul, Iraq.

1- INTRODUCTION

Mucormycosis, often known as black fungus, is an aggressive and sometimes fatal fungal infection caused by phycomycetes, including Rhizopus and Mucor species.[1] Humans might get infection mostly by inhaling spores or by accidental inoculation or consuming of contaminated food.[2] Angio-invasion and bad prognosis are hallmarks of mucormycosis.[3] Given the difficulty in obtaining deep tissue samples, it is challenging to determine the precise diagnosis and extend of mucormycosis and the majority of cases are misdiagnosed.[3-4] Otorhinolaryngology has been involved in the pandemic since the beginning of first wave and had an essential role in diagnosing the condition using nasopharyngeal swab sampling. Otorhinolaryngology also identified ageusia and anosmia

as important symptom markers.[5-6] The pandemic was made worse during the second wave when rhino-cerebral mucormycosis, a more serious and potentially lethal form of invasive fungal sinusitis, appeared.[7]

A variety of symptoms, such as runny nose, facial edema, orofacial pain, and loosening of the teeth, can be present in the form of rhino-cerebral and oral mucormycosis.[8] Additionally, an oro-nasal/oro-antral fistula and a black necrotic ulcer or sequestrum in the palate, buccal vestibule, or maxillary alveolus may develop.[9] After the illness spreads to the brain, it can cause blindness, lethargy, seizures, and death.[9-10] However, a typical but not necessary hallmark of the disease is a necrotic black eschar that is often seen in the nasal cavity or on the hard palate region.[11]

Patients with SARS-CoV-2 infection who have hypoxia, hypoglycemia, hyperglycemia, and ketoacidosis due to immunological suppression, mechanical ventilation, steroids, antibiotics use and prolonged hospital stays may have a greater opportunity for mucorales spores to germinate.[12-13] Despite treatment, mucorales fungus-induced rhino-cerebral infection has a death rate of approximately 50%.[12-14] And since rhino-cerebral and oral mucormycosis still has a high overall death rate, subsequent studies must focus on developing new therapeutic alternatives, adopting rigorous multidisciplinary therapy, and figuring out how to acquire an early diagnosis.[14-15] Moreover; there are few studies dealt with complications of oral mucormycosis among patient with COVID-19, especially in Iraq. As a result, the purpose of this study was to assess the comorbidities and ultimate results of rhino-cerebral and oral mucormycosis among patient with COVID-19 in Mosul City.

2- PATIENT AND METHODS

This retrospective cross-sectional study assessed 50 post-COVID-19 patients with rhino-cerebral and oral mucormycosis at Al Jamhoori Teaching Hospital in Mosul, Iraq**,** from the beginning of April 2021 to end of March 2023. The study included patients with rhino-cerebral or oral mucormycosis who on or had received corticosteroids and immunosuppressive drugs. Patients with gastrointestinal, pulmonary, cutaneous, and disseminated mucormycosis types were excluded from the study.

Nineveh Health Directorate's responsible committee for continuing medical education accepted the study's protocol, which complied with the Declaration of Helsinki's principles. A modified questionnaire was used to collect data, including sociodemographic information, personal history, past and present medical and medication history, oxygen therapy and its type, mucormycosis clinical manifestations that mainly impact those patients. In order to determine whether an oral lesion was present, as well as its location, clinical presentation, and surrounding mucosal color, the patient who had oral mucormycosis in this study underwent an intraoral examination by a dentist using a simple dental mirror under artificial light. Then, the patients' radiographic findings; which included a computerized tomography scan of the paranasal sinuses and magnetic resonance imaging if central nervous system signs were presented, are evaluated by multidisciplinary team. To reach a definitive diagnosis, suspected cases did a biopsy specimen from tissue samples, such as nasal or sinus tissue, and excisional biopsies from ulcers site, to do microbiological and histopathological assessment. To evaluate the ultimate result, the patients with rhino-cerebral and oral mucormycosis were monitored for a maximum of 2 years.

Data analysis was done using SPSS[Statistical Package for Social Sciences] software version 26[IBM Corporation, USA]. The normality of the variables' distribution was verified using the Kolmogorov–Smirnov test. Frequencies and percentages were used to represent categorical characteristics like the patients' gender and clinical pictures of the lesions. A mean ± standard deviation was used to display continuous variables like the patients' age. The chi-square test [Fisher or Monte Carlo] was used to compare groups regarding to categorical variables. P value less than 0.05 was regarded as statistically significant.

3- RESULTS

The study included 50 patients with rhino-cerebral and oral mucormycosis. Of them; 27[54%] patients were males and 23[46%] patients were females. With male to female ratio of 1.17:1. Moreover: the mean age ± standard deviation of the study participants was 53.21 ± 9.98 years. As shown in figure 3.1.

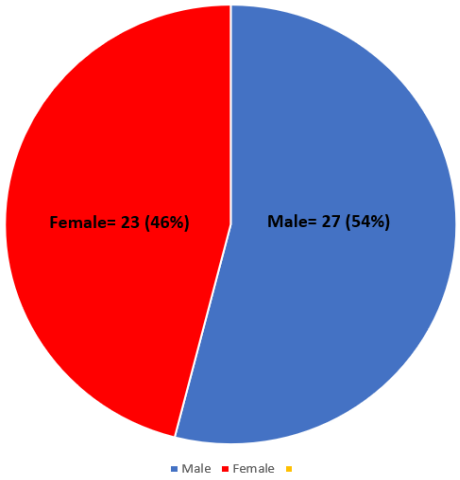

Figure 3.1: Distribution of the study participants according to the gender.

Table 3.1 shows patients' basic description according to their past medical history and treatment they received. It's evident that uncontrolled diabetes was prevalent

among 27[54%] patients, followed by hypertension which was prevalent among 20[40%] patients, while controlled diabetes, ischemic heart disease, chronic kidney disease and hypothyroidism were prevalent among 13[26%], 10[20%], 3[6%], 1[2%] patients respectively. Form the other hand; 7[14%] patient reported medical free history. Furthermore; all of the patients[100%] are received corticosteroid and antibiotics and 42[84%] patients received oxygen, 12[24%] patients were putted on CPAP. Lastly; 29[58%] patients had eye involvement and 21[42%] patients had central nervous system involvement.

Table 3.1: Patients' basic description according to their past medical history and treatment they received:[Number = 50 patients].

Medical History	Number = 50	Percent
Hypertension	20	40
Controlled diabetes	13	26
Uncontrolled diabetes	27	54
Chronic kidney disease	3	6
Ischemic heart disease	10	20
Medical free	7	14
Hypothyroidism	1	2
Corticosteroid use	50	100
Antibiotic use	50	100
Oxygen therapy	42	84
CPAP use	12	24
Central nervous system involvement	21	42
Eye involvement	29	58

Table 3.2 explores data description according to patient clinical findings of oral mucormycosis, all of the patient[100%] had palatal involvement with having deep necrotic ulcer among 22[44%] patients, superficial ulcer among 20[40%] patients and palatal fistula among 8[16%] patients. Moreover; with regard to the color of the affected palate, 22[44%] patients had black necrotic mucosa, 20[40%] patients had yellow exudate and normal color was present among 8[16%] patients. Furthermore; concerning the clinical presentation of the patients with oral mucormycosis; 48[96%] patients had oral manifestation, dental pain was present among 40[80%] patients, facial pain was present 35[70%] patients, while foul odor, loose tooth, headache, facial swelling and fever were present among 37[74%], 34[68%], 20[40%], 12[24%] and 3[6%] respectively.

Table 3.2: Data description according to patient clinical manifestations of oral mucormycosis:[Number = 50 patients].

Variable	Number = 50	Percent
Clinical picture:	**50**	**100**
Superficial ulcer	20	40
Deep necrotic ulcer	22	44
Fistula	8	16
Color of the mucosa:	**50**	**100**
Black necrotic mucosa	22	44
Yellow exudate	20	40
Normal	8	16
Symptoms of oral mucormycosis:	**48**	**96**
- - Facial pain	35	70
- - Dental pain	40	80
- - Swelling of the face	12	24
- - Headache	20	40
- - Fever	3	6
- - Loose tooth	34	68
- - Foul odor	37	74
- - Perforation of palate	25	50
- - Perforation of the nose	11	22

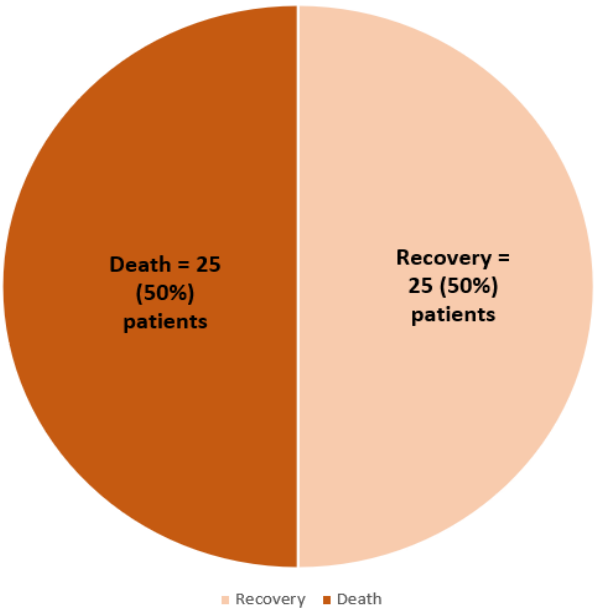

Figure 3.2 illustrates that among the 50 patients enrolled in the study; 25[50%] patients were recovered while unfortunately 25[50%] patients were died.

Table 3.3 shows comparison between patients who are recovered from mucormycosis and those who are died regarding different demographic and clinical manifestations. Statistically significant difference was found between the groups regarding the presence of uncontrolled diabetes[P value <0.001], been medical free[P value = 0.037], central nervous system involvement[P value <0.001], eye involvement[P value <0.001], clinical picture of the disease presentation[P value <0.001], color of the mucosa[P value <0.001], perforation of the palate[P value <0.001] and perforation of the nose[P value <0.001]. From the other hand; no statistically significant difference was found regarding patients' gender[P value = 0.589], patients' age[P value = 0.098], presence of hypertension[P value = 0.321], presence of controlled diabetes[P value = 0.835], presence of chronic kidney disease[P value = 0.241], presence of ischemic heart disease[P value = 0.124], presence of hypothyroidism[P value = 0.336], corticosteroid use[P value = 1], antibiotic use[P value =1], receiving of oxygen[P value = 0.168], CPAP use[P value = 1], facial pain[P value = 0.383], dental pain[P value = 0.269], facial swelling[P value =1], presence of headache[P value = 0.371], presence of fever[P value = 0.134], presence of loose teeth[P value = 0.189] and presence of foul odor[P value = 0.201].

Table 3.3: Comparison between recovered and died patients regarding different demographic and clinical manifestations[Number = 50 patients].

Variable	Recovery group [Number =25]		Death [Number =25]		P Value
	Number	Percent	Number	Percent	
Gender:					
Male	13	48.15	14	51.85	0.589
Female	12	52.17	11	47.83	
Age[years], mean ± standard deviation	51.24 ± 9.92		55.37 ± 10.23		0.098
Medical history:					
Hypertension	11	44	9	36	0.321
Controlled diabetes	6	24	7	28	0.835
Uncontrolled diabetes	8	32	19	76	**<0.001**
Chronic kidney disease	1	4	2	8	0.241
Ischemic heart disease	4	16	6	24	0.124
Medical free	6	24	1	4	**0.037**
Hypothyroidism	1	4	0	0	0.336
Corticosteroid use:	25	100	25	100	1
Antibiotic use:	25	100	25	100	1
Oxygen therapy:	20	80	22	88	0.168

CPAP use:	6	24	6	24	1
Central nervous system involvement	1	4	20	80	**<0.001**
Eye involvement	4	16	25	100	**<0.001**
Clinical picture: - Superficial ulcer - Deep necrotic ulcer - Fistula	 19 0 6	 76 0 24	 1 22 2	 4 88 8	**<0.001**
Color of the mucosa: Black necrotic mucosa Yellow exudate Normal	 0 17 8	 0 68 32	 22 3 0	 88 12 0	**<0.001**
Symptoms of oral mucormycosis: - - Facial pain - - Dental pain - - Swelling of the face - - Headache - - Fever - - Loose tooth - - Foul odor - - Perforation of palate - - Perforation of the nose	 16 22 6 8 1 16 16 0 0	 64 88 24 32 4 64 64 0 0	 19 18 6 12 2 18 21 25 11	 76 72 24 48 8 72 84 100 44	 0.383 0.269 1 0.371 0.134 0.189 0.201 **<0.001** **<0.001**

4- DISCUSSION

Mucormycosis is a potentially fatal infection, with rhino cerebral being the most prevalent manifestation. The opportunistic fungal infection is brought on by mucorales. Its spores are found in large quantities in nature and are dispersed by food, soil, air, and decomposing organic material. It may occasionally appear as a normal commensal in the nasal mucosa of healthy individuals due to its low virulence potential, but when a patient becomes immunosuppressed, the fungus has the chance to germinate in the paranasal sinuses and spread. It has a high risk for people with solid organ transplant recipients, hematological cancers, diabetes mellitus and ketoacidosis patients, and people taking high doses of steroids.

Fifty patients were enrolled in the current study with confirmed COVID-associated mucormycosis, which has a male incidence of 54% and a female incidence of 46%. Kirdak et al. conducted a similar study with comparable results[60 % for males versus 40 % for females].[16]

In the current study, 43[86%] of the patients with oral mucormycosis had more than one medical condition. However, just 7[14%] of these patients had no medical issues. Most often, mucormycosis is associated with patients who are medically compromised. By weakening the mucous membrane, chronic local damage alters the body's first line of defense and makes the victim more vulnerable to fungal infections. Thus, in immunocompetent people, these factors may decrease the possible of mucormycosis infection.[17, 18] However, uncontrolled diabetes mellitus was the most prevalent chronic medical condition among the study participants. Moreover; in patients with uncontrolled diabetes mellitus, immunological dysfunction such as neutrophil dysfunction, deterioration of the antioxidant system, and humoral immune system are affected. Reduced pH, reduced oxygen, higher glucose, increased ketone bodies, and high iron levels all speed up the fungal spores' germination and rapid growth.[19] This outcome was consistent with other studies that found a high rate of uncontrolled diabetic mellitus among the samples they studied.[20, 21]

In the current study, systemic corticosteroids and systemic antibiotics were administered to all patients with mucormycosis. This was expected given that corticosteroid medication is a recognized significant risk factor that increases a patient's vulnerability to mucormycosis by impairing neutrophil and macrophage activity and causing steroid-induced hyperglycemia. Although long-term corticosteroid use has frequently been linked to a variety of opportunistic fungal infections, including mucormycosis, even a short course of corticosteroids has recently been linked to mucormycosis, particularly in individuals with diabetes.[22] Comparable results were obtained from Michail S Lionakis et al.[23] These results urge for a reconsideration of the usage of corticosteroids during the COVID-19 treatment.

The majority of the patients in this study have dental pain, facial pain and loose tooth at early stage, but later on; three quadrants of the patients developed foul odor, half developed palate perforation and about a quarter developed nose perforation. This is going with Kumar Nilesh et al study results.[24] Furthermore; the study found that only half of the study participants were survived which parallel to Aastha Maini et al study findings.[25]

This study found that patients' death was significantly higher among those of brain or eye involvement, in case of black mucosa or in the presence of perforated palate or perforated nose. As the cribriform plate, blood vessels,

or orbital apex are three possible routes for infection to enter the brain, additionally; the paranasal sinus infection may result in a palatal perforation or quickly spread to the orbit and nasal cavity. The results of the study also supported those of earlier studies which was conducted by George Petrikkos et al.[26]

When interpreting the study findings, it is important to take into account the limitations of it. First, the results may not be as easily applicable to different populations due to the small sample size. Second, the study was only carried out at one center, which might limit the findings' external validity. However; the study strength is no previous Iraqi study about comorbidities and ultimate results of rhino-cerebral and oral mucormycosis among patient with COVID-19.

5- CONCLUSION AND RECOMMENDATION

The current study showed that the mortality rate for post-COVID-19 associated mucormycosis was very high, primarily as a result of delayed diagnosis and inadequate treatment. For a quicker diagnosis and better prognosis of such an aggressive illness, physicians must therefore be more knowledgeable about the clinical manifestations of mucormycosis in post-COVID-19 patients, particularly deep palatal ulcers and dentofacial pain with special caution for patients with uncontrolled diabetes.

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Conflict of Intertest

About this study, the authors disclose no conflicts of interest.

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