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COVID-19 coinfection with Mucormycosis

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Abstract

Objectives: We will try to present cases of coinfection with COVID-19 and mucormycosis in Kashan to increase the awareness of health-care providers and reduce the number of forgotten and neglected cases.

Methods: This is a descriptive cross-sectional study that patients infected with COVID-19 become vulnerable to a variety of opportunistic diseases. There are several studies of COVID-19 and mucormycosis, but an effort has been made to provide a collection of cases in Kashan (the center of Iran) to reduce morbidity and mortality by increasing the awareness of health-care providers.

Results: A total of 31 patients with mucormycosis following COVID-19 including 18 males and 13 females were included in the study. All reverse transcriptase-polymerase chain reaction patients were positive for severe acute respiratory syndrome-coronavirus-2. Twenty had a history of diabetes, eight had a history of hypertension, and three had no record of any underlying disease. The maxillary sinuses were the most common site of involvement. The maximum length of hospital stay was 52 dayss.

Conclusion: Patients with COVID-19 vulnerable to comorbidities, any facial involvement, or severe glucocorticoid and antibiotic treatment should be closely examined and monitored at the first encounter and during hospitalization for any signs of mucormycosis and start standard care and antifungal treatment as soon as possible.

Keywords: COVID-19, Comorbidity, Coinfection, Mucormycosis, SARS-CoV-2

Introduction

Fungal infections are on the rise due to the increase in patients with immunodeficiency, chemotherapy, long-term antibiotics, and greater patient survival.[1] Mucormycosis is a fatal fungal infection in humans[2] and is an opportunistic infection that most often occurs in people with immunodeficiency, including diabetes, hepatitis, kidney failure, blood disorders, leukemia, lymphoma, transplantation, malignancy, and neutrophil dysfunction.[3-6] This infection rarely occurs in healthy people.[6] This fungal infection is caused by the microorganisms of the zygomycete group.[7]

Mucormycosis usually occurs in the form of an acute infection with manifestations in the nasopharynx – brain, lungs, skin, and gastrointestinal tract– sometimes, it is manifested as a diffuse infection.[8] Mucormycosis is a rare but life-threateningdisease with high mortality (75%–80% of deaths) and morbidity.[9] Coronavirus disease-2019 (COVID-19), which is the cause of acute respiratory syndrome, is associated with a wide range of opportunistic bacteria and fungi.[10]

Both *Aspergillus* and *Candida* are major fungal pathogens in COVID-19 patients.[11] Recently, several cases of mucormycosis in people with COVID-19 have been reported increasingly worldwide. Hypoxia, high glucose (diabetes, new hyperglycemia, and steroid-induced hyperglycemia), acidic environment (metabolic acidosis and diabetic ketoacidosis), high iron levels

(increased ferritin), and decreased phagocytic activity of white blood cells due to the suppression of the immune system (severe acute respiratorysyndrome- coronavirus-2 [SARS-CoV-2]), steroids, or comorbidities, are associated with several other risk factors, including long-term hospitalization with or without mechanical respirators worldwide. The prevalence of mucormycosis varies from 0.005 to 1.7/million population. According to a recent estimate in 2019–2020, its prevalence is almost 80 times higher in India (0.14/1000) than in developed countries,[12-14] more so in the general population based on computational modeling.[15] There are large published studies on the clinical and preclinical manifestations of mucormycosis and COVID-19.[16-18] COVID-19 also shows a variety of clinical signs that can easily distort the presence of mucormycosis.

Objectives

Therefore, we will try to present cases of coinfection with COVID-19 and mucormycosis in Kashan to increase the awareness of health-care providers and reduce the number of forgotten and neglected cases.

Methods

This study is a cross-sectional study conducted from June to October 2021 during the fourth and fifth waves, based on collecting and reanalyzing the available data from the registration information in Shahid Beheshti Hospital affiliated with Kashan University of Medical Sciences.

In this study, all patients with COVID-19 with mucormycosis were evaluated using the information from the hospital registration system. This information is related to all patients who have been hospitalized or referred to Kashan hospitals (outpatient). The diagnostic test for COVID-19 was a reverse transcriptase-polymerase chain reaction (RT-PCR) assay. Mucormycosis diagnosis is based on clinical suspicion, followed by sinus endoscopy and biopsy. Tissue samples are given for histological examination and culture to confirm the diagnosis. This information is recorded in the hospital information system (HIS) and contains variables of age, sex, type of underlying disease, and accident outcome.

Data collection was performed in a single research environment (HIS) and the file was archived.

The study population consisted of the file of patients with coronavirus who were admitted to different wards of the hospital with mucormycosis. Sampling was done as available in the study period (June to October 2021 during the fourth and fifth waves).

After obtaining the approval of the ethics and receiving a letter of reference and presenting it to the relevant center, the consent of the relevant authorities was obtained and permission to attend the research environment was granted. Receiving the real information of the patients and the principle of confidentiality of the information was observed and the checklist did not contain names and surnames. The researchers were present at the collection site and then collected information from the files and entered them into the researcher-made checklists. After reviewing the inclusion criteria, the files of all patients with COVID-19 and mucormycosis could be reviewed. Furthermore, patients whose medical files were incomplete were followed and included in the study.

In this study, information was extracted from patients' files and entered into predesigned researcher-made checklists. This designed checklist includes demographic characteristics (age, sex, and race), underlying diseases (cardiovascular disease, diabetes, hypertension, chronic obstructive pulmonary disease, kidney disease, neurological disease, liver disease, glands diseases, blood disease, and active cancer), and clinical outcomes (total length of hospital stay, death, and discharge with recovery).

Ethical considerations

The study was conducted in accordance with the Declaration of Helsinki. This work was approved by the Research Ethics Committees of Kashan University of Medical Sciences (IR.KAUMS. NUHEPM.REC.1400.057). Receiving the real information of the patients and the principle of confidentiality of the information was observed and the checklist did not contain names and surnames.

Results

In this study, out of 31 definitively diagnosed cases of mucormycosis, 18 (54.5) were male and the rest were female. The mean age and standard deviation of patients were 61.9±10.9, with a minimum age of 41 and a maximum of 85 years old. Twenty of these patients recovered (64.5%) and 11 (35.5%) died.

All patients were RT-PCR positive for SARS-CoV-2. Twenty people had a history of diabetes and 11 people died. Eight patients had no history of any underlying disease. The maxillary sinuses were the most common site of involvement. All patients received amphotericin B and corticosteroids. The mean length of hospitalization was 17 days and the maximum length of hospitalization was 52

days. Corticosteroid intake for the treatment of COVID-19 was present in all cases. The most common organ involved with mucormycosis was the nose and sinus, sinus maxillary (27/31), ethmoid sinus (14/31), orbital (5/31), and brain (2/31) [Figure 1]. Overall mortality was noted in 35% of the cases.

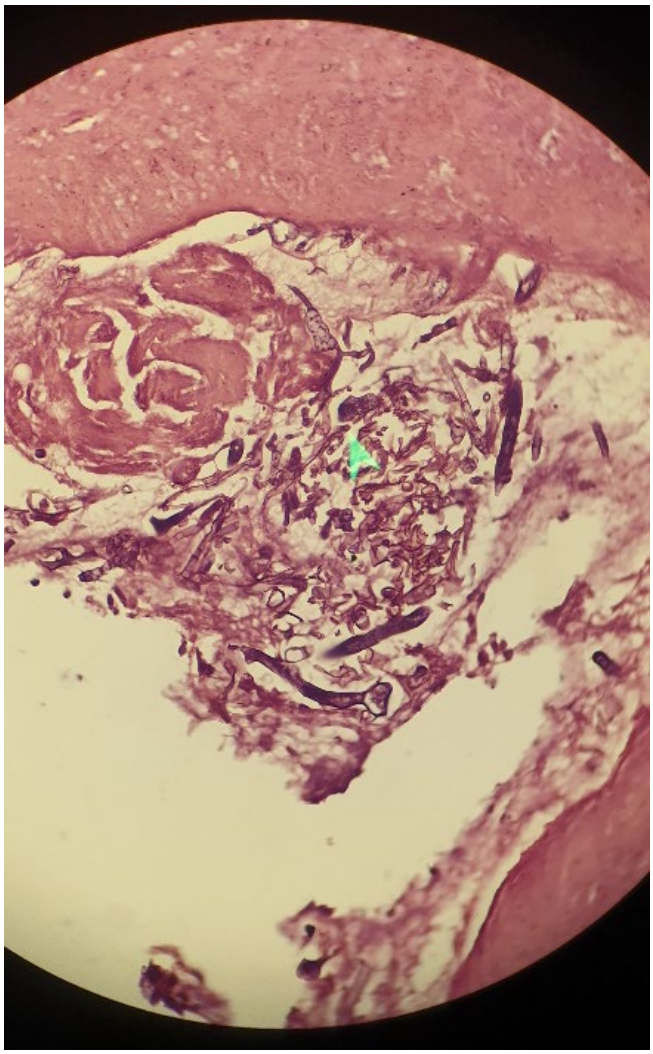

Figure 1. Endoscopic sinonasal biopsy

All included patients were treated with corticosteroids. For 1–28 days, 11 patients were treated with 1 type of corticosteroids, eight with 2 types of corticosteroids, 10 with 3 types of corticosteroids, and two with 4 types of corticosteroids. Prescribed corticosteroids include dexamethasone, methylprednisolone, prednisolone, and hydrocortisone. Twenty-six patients were treated with hydrocortisone, 14 with methylprednisolone, 14 patients with dexamethasone, and 12 patients with prednisolone. Based on the equivalent dose of corticosteroid (20 times hydrocortisone, five times prednisolone, four times methylprednisolone, and 0.75 times dexamethasone), the dose of corticosteroid received by each patient was calculated [Table1]. Rhino-orbito-cerebral mucormycosis was the most common presentation.

Surgical intervention was performed in all patients on 31/31 (100%). The time of diagnosis of COVID-19 and mucormycosis was between 2 days and 1 month; the mortality rate among patients with viral pneumonia and mucormycosis co-infection was 35% (11/31).

Discussion

The incidence of mucormycosis during the fourth and fifth waves of COVID-19 has increased as compared to previous waves in Kashan. The incidence of mucormycosis in the world varies in the range of 0.003–0.005/1.7 million of the population. The incidence became 80 times higher in India than in any other part of the world.[12-14]

Complex overlap of factors, including underlying diseases such as diabetes, previous respiratory illnesses, use of immunosuppressive therapies, risk of nosocomial infections, and systemic infection may lead to secondary infections in their own right that are increasingly increasing in COVID-19 and lead to increased morbidity and mortality.[19]

In one study, 62/806 (8%) patients admitted to the hospital reported secondary fungal and bacterial infections. The widespread use of broad-spectrum antibiotics in patients who reported no evidence of infection occurred in 1450/2010 (72%).[20]

Certain pathophysiological features of COVID-19 may cause secondary fungal infections. These include the tendency to develop extensive lung disease and subsequent alveolar-interstitial pathology that may increase the risk of invasive fungal infections. Second, disruption of the immune system associated with COVID-19 may alter innate immunity by reducing the number of T, CD4 + T, and CD8 + T-lymphocytes.[21]

Corticosteroid therapy and a history of chronic lung disease were associated with a higher risk of invasive fungal infections.[22] Furthermore, a high incidence was reported in Pakistan (23/147) at 15.6% and in Italy (30/108) at 27.7%. The spread of invasive fungi alters the natural history of the disease.[23,24]

A recent systematic study was conducted by John *et al.*[25] In this study, they found 41 confirmed cases of mucormycosis in people with COVID-19, with diabetes reported in 93% of cases, whereas 88% received corticosteroids. These findings are consistent with the findings of studies.[26] Overall, these findings suggest a clear association between mucormycosis, diabetes, and

steroids in people with COVID-19.

Song *et al*. proposed an algorithm for the early detection and management of common invasive fungal infections (*Aspergillus*, candidiasis, cryptococcosis, and mucormycosis).[11] It should be noted that diabetes can be well controlled at the beginning of the disease, but with the onset of COVID-19 and the use of corticosteroids, it quickly gets out of control.

Increased mucormycosis in patients with uncontrolled diabetes, overuse of corticosteroids to suppress the immune system, and prolonged stay in intensive care units[25] are among the causes of the disease, which is similar to our study. Seventy-one percent of cases of mucormycosis in COVID-19 patients have been reported from December 2019 to the beginning of April 2021.[25]

In various Indian states, measures were quickly taken to ensure control of the situation by setting up special forces, issuing urgent instructions, setting up separate wards in hospitals to manage mucormycosis cases, and providing medicine for treatment. Approximately 0.1 million vials of amphotericin B were used to manage mucormycosis. Amphotericin B deficiency has been considered in several cases and measures such as preparation and optimal drug allocation with increasing domestic production, and different methods of importing this drug were investigated.

Given that new diabetes occurs in 15% of patients admitted to COVID-19 and many patients develop stress-induced hyperglycemia,[27] based on current evidence, we recommend glycated hemoglobin (HbA1c) in all patients with COVID-19 be examined. Accurate blood sugar control (110–180 mg/dL) should be performed in diabetic patients.

One of the limitations of this study is that having a previous diagnosis of diabetes is a predisposing factor for mucormycosis infection. The etiology between COVID-19 and mucormycosis cannot be conclusively stated. However, there is a clear correlation between the two that cannot be ignored. Finally, while mucormycosis infection can be seen worldwide, it is more prevalent in the less developed regions of the world. Therefore, spread cases are most likely from these regions of the world.

In our sample, most patients had blood sugar above 120mg/dl. Rational use and avoidance of unnecessary doses of systemic corticosteroids, anti-interleukin-6 drugs in COVID-19 patients, recommendations during and after treatment with steroids, and immunomodulatory agents, as well as a daily examination of eyes and nasal and oral cavities in patients with COVID-19, should be monitored before and after discharge in patients with severe respiratory support, especially mechanical ventilation, history of corticosteroids or hyperglycemic conditions, hyperglycemia, and HbA1C.

Monitoring and analyzing the situation, disseminating information, educating the public, and committing to basic measures are essential to prevent further increase in the number of cases of mucormycosis in patients with COVID-19 and mortality. It is very likely that the reported cases of mucormycosis could be an underrepresentation of the actual burden due to the difficulty of making a specific microbiological or histopathological diagnosis Whereas certain case reports had all the details, others did not report any important parameters, for example, the duration of the diabetes mellitus and the lack of HbA1c baseline data in most cases. Second, the lack of a denominator value may not permit a true estimate of the incidence of mucormycosis in people with COVID-19, compounded by a lack of control.

Conclusions

The increase in mucormycosis in Kashan seems to be due to three factors: diabetes (high prevalence genetically), indiscriminate use of corticosteroids (increased blood glucose and opportunistic fungal infections), and COVID-19 (cytokine storm, lymphopenia, and endothelial damage). Every effort should be made to maintain optimal hyperglycemia, and only the wise use of evidence-based corticosteroids is recommended in patients with COVID-19 to reduce the burden of fatal mucormycosis.

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Competing interests

The authors declare that they have no competing interests.

Abbreviations

Coronavirus disease 2019: COVID-19;

Severe acute respiratory syndrome coronavirus 2: SARS-CoV-2;

glycated hemoglobin: HbA1c;

hospital information system: HIS;

reverse transcriptase-polymerase chain reaction: RT-PCR;

Rhino-orbito-cerebral mucormycosis: ROCM.

Table 1. Mucormycosis in COVID-19 – summary of 31 cases reported in Kashan- Iran

Variable	Case									
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Gender	male	male	male	male	female	male	female	female	male	male
Age	62	68	64	50	68	62	42	63	59	56
Underlying disease	MI	DM	DM	DM	Previous PCI HTN	DM	-	DM	DM	DM
Location	Maxillary Sinus	-	All paranasal sinuses	left Frontal	Left Maxillary Sinus	Maxillary left, left middle cornea, left ethmoid, left eye, *Esfenoide* left	Sphenoid Orbit	Maxillary left Com hard	*Esfenoide* left maxillary left Left middle cornea	sinus
Outcome	death	death	recovery	recovery	recovery	death	recovery	recovery	death	recovery
Lymphocytes	8-10	11.9-16.6	4.8-7	5.4-11.9	14.2-21.5	10.8	4-20.6	14.3-26.1	17.8	10.1-25.8
Neutrophils	85-85	84-77.8	90	89.2-84.5	83.2-61	82.1	85.1-60.3	92.3-57.1	78-77.1	84.5-70.3
Magnesium	2.2-2.5	4.9-2.4	3.13-2.5	2-1.9	1.6-1.7	1.7-2.6	11.7-1.9	2-1.38	2.58-1.8	1.73-2.38
Blood sugar	182	319-350	238-600	173	128	308	-	251-402	258	421
BS pre-mucor	182	325	462	200	120	288	187	304	258	380
Staying Time	11	27	14	37	17	12	45	19	34	30
Severity	severe	critical	moderate	severe	moderate	moderate	moderate	moderate	severe	moderate
Covid to mucor	50	17	7	16	40	15	11	14	21	20
Symptom to culture	6	7	5	9	8	8	9	10	9	11
Active covid	no	yes	yes	yes	no	yes	yes	no	yes	no
O2 (%)	86	75	94	88	93	90	89	90	77	94
Corticosteroid	Dexamethasone (4 days) Methylprednisolone (6 days) Hydrocortisone (2 day)	Prednisolone (3 days) Dexamethasone (2 days) Methylprednisolone (10 days)	Dexamethasone (5 days) Hydrocortisone (5 days)	Dexamethasone (13 days) Methylprednisolone (8 days) Hydrocortisone (4 days)	Prednisolone (4 days) Hydrocortisone (1 days)	Hydrocortison (9 days)	Hydrocortisone (9 days)	Hydrocortisone (1 days)	Methylprednisolone (5 days) Hydrocortisone (10 days)	Prednisolone (3 days) Hydrocortisone (7 days) Dexamethasone (1 days)
Corticosteroid Cumulative Dose	113	124.28	178.2	238.32	9	45	45	5	100	49

Table 1. Contd…

Variable	Case									
	11	12	13	14	15	16	17	18	19	20
Gender	female	female	female	male	male	male	male	male	female	male
Age	78	67	46	51	79	68	68	53	56	50
Underlying disease	DM	DM	-	DM	DM - cirrhosis Of Liver	DM-HTN	Asthma, DM	DM-HTN	DM	-
Location	Right Frontal Sinus	Right maxillary sinus	Lower left cornea Left middle cornea	Maxillary left left eye Left ethmoid	Right septum	Right ethmoid Sinus	Right middle cornea	-	-	Left stenoid Bilateral maxillary
Outcome	death	recovery	recovery	recovery	recovery	death	death	recovery	recovery	recovery
lymphocytes	11.4-5.4	10.3-11.3	9.7-20	19.7-18.7	7.7-21.1	5.1-14.1	28-14.9	13.2-16.5	3.5-11.2	29.6-13.8
Neutrophils	82-90	88.1-87.6	88.5-69.7	75-50.4	82.6-64.5	90.5-82.3	26-79.8	78.8-78.4	93.7-84.9	63.3-76.2
Magnesium	2-2.3	2-2.3	2.3-2.5	2.4-1.8	1.78-1.69	2.4-2.81	2.43-2	2.13-2.5	2.49-3.53	2.46-1.9
Blood sugar	383	128-238	115	422	351	443	286	139	200	347
BS pre-mucor	380	230	238	380	351	450	324	234	234	347
Staying Time	13	65	4	52	28	15	28	10	13	40
Severity	severe	severe	mild	severe	moderate	moderate	moderate	moderate	moderate	mild
Covid to mucor	30	48	20	18	15	10	20	45	27	16
Symptom to culture	7	9	8	10	10	10	11	11	9	11
Active covid	yes	yes	no	yes	no	yes	yes	no	no	no
O2	86	90	96	80	95	98	90	96	86	94
Corticosteroid	Prednisolone (3 days) Hydrocortisone (7 days)	Prednisolone (1 days) Hydrocortisone (12 days) Methylprednisolone (11 days)	Prednisolone (1 days)	Prednisolone (5 days) Dexamethasone (8 days)	Prednisolone (9 days) Dexamethasone (4 days) Hydrocortisone (19 days)	Methylprednisolone (1 days) Hydrocortisone (14 days)	Dexamethasone (15 days) Methylprednisolone (7 days) Hydrocortisone (10 days)	Hydrocortisone (8 days)	Methylprednisolone (5 days)	Hydrocortisone (22 days)
Corticosteroid Cumulative Dose	38	171	1	90.12	147	80	280	40	50	110

Table 1. Contd…

Variable	Case										
	21	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**	31
Gender	female	female	female	male	female	female	male	male	female	male	male
Age	68	76	54	56	41	68	73	52	85	68	68
Underlying disease	-	DM	DM	-	-	DM	DM	kidney Stone	-	-	DM
Location	Right maxillary sinus	-	Maxillary Sinus	Left middle cornea Maxillary left	Ethmod Maxillary Sinus	Maxillary Sinus	Maxillary Sinus on Both Sides	Maxillary Sinus	Right Maxillary	Ecimosparyorbit	Sino Orbital
outcome	recovery	recovery	death	recovery	recovery	recovery	recovery	recovery	death	death	death
Lymphocyte	27.2-23.6	1.30- 10	1.34- 7.5	8.4-18.1	9.4-23	27.2- 23.6	2.3-17	17.6-19.1	14.1-3.5	-	6.9-8.5
Neutrophils	63.9-70.2	82.4- 85	80.6- 83.5	89.1- 67	89.2- 70	70.2- 63.9	93.4- 80	73.7-75.6	82.5-92.9	-	90.6-84.4
Magnesium	2.2	1.9- 2.3	2.2	2.2- 2.36	2.4-2.46	2.2- 2.24	2.1- 2.52	2.4- 2.7	2- 2.25	-	2-2.1
Blood sugar	77	236	346	134	140	366	227	-	120	320	307
BS pre-mucor	162	250	335	120	150	210	227	-	230	320	300
O2	97	94	82	81	82	96	89	91	82	72	92
Staying Time	11	21	10	49	34	11	29	5	11	9	52
Severity	mild	moderate	severe	severe	severe	mild	moderate	moderate	severe	moderate	moderate
Covid to mucor	56	19	25	17	14	56	15	?	10	30	13
Symptom to culture	10	9	10	11	10	10	9	?	8	9	7
Active covid	no	yes	no	yes	yes	no	yes	yes	yes	yes	yes
Corticosteroid	Dexamethasone (4 days) Methylprednisolone (2 days)	Hydrocortisone (17 days)	Hydrocortisone (9days)	Prednisolone (8 days) Dexamethasone (5 days) Methylprednisolone (13 days) Hydrocortisone (10 days)	Dexamethasone (1 days) Methylprednisolone (25 days) Hydrocortisone (2 days)	Dexamethasone (4 days) Methylprednisolone (2 days	Hydrocortisone (28 days)	Hydrocortisone (6 days)	Hydrocortisone (6 days) Methylprednisolone (8 days) Dexamethasone (2 days)	Dexamethasone (3 days) Methylprednisolone (2 days) Hydrocortisone(6 days)	Dexamethasone (10 days) Methylprednisolone (10 days) Hydrocortisone (20 days) Prednisolone (8 days)
Corticosteroid Cumulative Dose	63	85	45	241	271	63	140	30	131.3	82	314

Authors' contributions

All authors read and approved the final manuscript. All authors take responsibility for the integrity of the data and the accuracy of the data analysis.

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Availability of data and materials

The data used in this study are available from the corresponding author on request.

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki. This work was approved by the Research Ethics Committees of Kashan University of Medical Sciences (IR.KAUMS.NUHEPM.REC.1400.057).

Consent for publication

By submitting this document, the authors declare their consent for the final accepted version of the manuscript to be considered for publication.

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